

Formulation and Evaluation of Effervescent Tablet of Analgesic and Antipyretic

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Abstract— Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose..

Index Terms— GRTs, GI, TD, ED, CRD, CR, IV, I.

1. INTRODUCTION^[1-22]

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose. Effervescent tablets are becoming increasingly popular in a variety of sectors including supplements and pharmaceutical use due to the ease in which they can be consumed. Effervescent tablets are designed to break in contact with liquid such as water or juice, often causing the tablet to dissolve into a solution. These buoyant delivery systems utilize matrices prepared with swell able polymers such as Methocel or poly saccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g. Ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained- release pills as seeds surrounded by double layers. The inner layer was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sublayer and tartaric acid was in the outer layer. When the system was immersed in a buffer solution at 37°C, it sank at once in the solution and formed swollen pills, like balloons, with a density much lower than 1 g/ ml. The reaction was due to carbon dioxide generated Patel et al by neutralization in the inner effervescent layers with the diffusion of water through the outer swellable membrane layers. The system was found to float completely within 10 min and approximately 80%remained floating over a period of 5 hr irrespective of pH and viscosity of the test medium. While the system was floating, a drug (p-amino benzoic acid) was released. A variant of this approach utilizing citric acid (anhydrous) and sodium bicarbonate as effervescing agents and HPC-H grade as a release controlling agent has also been reported. In vitro results indicated a linear decrease in the FT of the tablets with an increase in the amount of effervescing agents in the range of 10–20%. Attempts have also been made to

develop SR floating tablets using a mixture of sodium bicarbonate, citric acid and chitosan. Effervescent or carbon tablets are tablets which are designed to dissolve in water, and release carbon dioxide. They are products of compression of component ingredients in the form of powders into a dense mass, which is packaged in blister pack, or with a hermetically sealed package with incorporated desiccant in the cap. To use them, they are dropped into water to make a solution. The powdered ingredients are also packaged and sold as effervescent powders or may be granulated and sold as effervescent granules. Generally powdered ingredients are first granulated before being made into tablets. Effervescent tablets are becoming increasingly popular in a variety of sectors including supplements and pharmaceutical use due to the ease in which they can be consumed. Effervescent tablets are designed to break in contact with liquid such as water or juice, often causing the tablet to dissolve into a solution. This makes effervescent tablets the preferred choice of many, including people who are taking tablets medicinally as well as a dietary supplement. Here we look at 5 benefits of effervescent tablets over regular tablets. Pleasant Taste Compared to Regular Tablets Effervescent tablets are so popular due to the fact they can be dissolved in a liquid such as water or fruit juice, meaning that they often taste better than regular tablets. Conventional tablets dissolve slowly which can result in reduced absorption rates, effervescent tablets, in contrast, dissolve quickly and completely, meaning you get the full benefit from the ingredients.



FIGURE 1: EFFERVESCENT TABLETS

Factor Influencing the Formulation of Oral Controlled Release Drug Delivery System Physicochemical Factors

Solubility^[5]

Low aqueous solubility drugs have low oral bioavailability. Drugs having good solubility in stomach are poor choice for controlled/sustained oral dosage forms. The water solubility limits the loading efficiency of drug into a variety of carrier systems such as liposome and micro particles, where highly water-soluble drug tend to leach fast from the carrier. The pH dependent solubility particularly in the physiological pH range would be another problem for controlled release formulation because of the variation in pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system allow to estimate contribution of three major factors Solubility, Dissolution and Intestinal Permeability which affect oral absorption.

Class III (High solubility-Low permeability) and Class IV (Low solubility-Low permeability) drugs is poor candidate for controlled release dosage form.

Drug Stability^[6,7]

A drug in a solid state undergoes degradation at a much slower rate than a drug in suspension or solution. Drugs that are unstable in gastric pH can be developed as slow release dosage form and the drugs can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for oral controlled drug delivery systems.

Molecular Size and Diffusivity

Diffusivity defined as the ability of a drug to diffuse through membrane, is inversely related to molecular size. Diffusivity depends on size and shape of the cavities of the membrane.

More than 95% of drugs are absorbed by passive diffusion. The upper limit of drug molecular size for passive diffusion is 600 Dalton. The examples of the drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

Partition coefficients

Partition coefficient is defined as the fraction of drug in an oil phase to that of an aqueous phase.

It governs the permeation of drug particles through biological membrane. Drugs with high partition coefficient value easily permeate through biological membrane. The diffusion of drug molecules across rate controlling membrane or through the matrix system essentially relies on partition coefficient. Drugs that have lower partition coefficient are not suitable for oral controlled release drug delivery system and drugs that have higher partition coefficient are also not suitable for oral controlled drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidate for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption.

Biological factors Absorption

The aim of formulating controlled release product is to place a control on delivery system. The desirable quality of oral controlled delivery system is that it should release complete drug and the release drug should be completely absorbed. The fraction of drug absorbed from the system can be lower than the expected due to degradation of drug, protein binding, site- specific, dose-dependent absorption, poor water solubility and small partition coefficient.

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of drug, are poor candidate for oral drug delivery system. The apparent volume of distribution is one of the important parameter of drugs that describes the magnitude of distribution as well as protein binding within the body. The distribution of drug can be determined by the volume of distribution at steady state and T/P ratio.

$$T/P = K_{12} / (K_{21} - b)$$

T=Amount of drug in peripheral compartment, P=Amount of drug in central compartment, K₁₂=Constant for distribution of drug from central to peripheral compartment, K₂₁=Constant for distribution of drug from peripheral to central compartment, b=Slow disposition constant.

Metabolism

Metabolism of a drug is either an inactivation, of an active drug or conversion of an inactive drug to an active metabolite. There are two factors related to metabolism of drug which restrict the design of sustained/controlled drug delivery.

For chronic administration, drugs that are capable of either inducing or inhibiting enzyme synthesis, they are poor candidates for controlled delivery systems due to difficulty in maintaining uniform blood levels.

Drugs possessing variations in bioavailability due to first-pass effect or intestinal metabolism are not suitable for sustained/controlled drug delivery.

Half- life

The duration of action is dependent on the biological half- life. Drugs with short half-life (greater than 2 hrs) are most suitable for controlled drug delivery system. Factors influencing the half-life of a drug are elimination, metabolism, and distribution.

Therapeutic index

Margin of safety can be described by considering therapeutics index, which is the ratio of median toxic dose and median effective dose. Therapeutic index = TD_{50}/ED_{50} . Drugs with low therapeutics index are unsuitable for drug incorporation in controlled release formulation. The side effects can be minimized by controlling the concentration within therapeutic range.

Size of dose

If the dose of a drug in conventional dosage form is high, then it is less suitable candidate for CRDDS. This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty.

Absorption window

Certain drugs when administered orally are absorbed only from a specific part of GI tract. This part is known as 'absorption window'. These kinds of drugs are not suitable for CRDDS.

Plasma concentration response relationship

Plasma drug concentration is more responsible for pharmacological response than dose. But the drugs having pharmacological activity independent of plasma concentration are poor candidate for oral CR drug delivery system

Concentration dependency on transfer of drug ^[1,13]

If transfer of drug from one compartment to other follows zero order kinetic process then such drugs are poor candidate for oral CR delivery system. It should be first order kinetics. The following figure represents various formulation strategies for oral CR drug delivery system.

Drug administration

Drug administration is the giving of a drug by one of several means (routes). Drug kinetics (pharmacokinetics) describes how the body handles a drug and accounts for the processes of absorption, distribution, metabolism, and elimination. Drug treatment requires getting a drug to its specific target site or sites in tissues where the drug has its action. Typically, the drug is introduced into the body the process of administration, sometimes far from this target site. The drug must move into the bloodstream the process of absorption and be transported to the target sites where the drug is needed the process of distribution. Some drugs are chemically altered the process of metabolism by the body before they take effect, others are metabolized afterward, and still others are not metabolized at all. The final step is the removal of the drug and its metabolites (byproducts) from the body the process of elimination

.Many factors, including a person's weight, genetic makeup, and kidney or liver function, can influence these kinetic processes. Changes due to aging also affect how the body processes drugs. Drugs are introduced into the body by several routes. They may be

- Taken by mouth (orally)
- Given by injection into a vein (intravenously, IV)
- Into a muscle (intramuscularly, IM)
- Into the space around the spinal cord (intrathecally)
- Beneath the skin (subcutaneously, sc)
- Placed under the tongue (sublingually) or between the gums and cheek (buccally)
- Inserted in the rectum (rectally) or vagina (vaginally)
- Placed in the eye (by the ocular route) or the ear (by the otic route)
- Sprayed into the nose and absorbed through the nasal membranes (nasally)
- Breathed into the lungs, usually through the mouth (by inhalation)
- Mouth and nose (by nebulization)
- Applied to the skin (cutaneously) for a local (topical) or bodywide (systemic) effect
- Delivered through the skin by a patch (transdermally) for a systemic effect Each

route has specific purposes, advantages, and disadvantages.

Oral route

Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter metabolize many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect.

When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract. For example, aspirin and most other non steroidal anti-inflammatory drugs (NSAIDs) can harm the lining of the stomach and small intestine to

potentially cause or aggravate preexisting ulcers. Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Other routes of administration are required when the oral route cannot be used, for example:

- When a person cannot take anything by mouth
- When a drug must be administered rapidly or in a precise or very high dose
- When a drug is poorly or erratically absorbed from the digestive tract

Drug absorption

Absorption affects bioavailability—how quickly and how much of a drug reaches its intended target (site) of action. Factors that affect absorption (and therefore bioavailability) include

- The way a drug product is designed and manufactured
- Its physical and chemical properties
- Other ingredients it contains
- The physiologic characteristics of the person taking the drug
- How the drug is stored

A drug product is the actual dosage form of a drug a tablet, capsule, suppository, transdermal patch, or solution. It consists of the drug (active ingredient) and additives (inactive ingredients). The active ingredient is the chemical substance (the drug) that is taken to produce the desired effect (such as lowering blood pressure). The additives (inactive ingredients such as diluents, stabilizers, disintegrants, and lubricants) are mixed with the drug to make it easier to swallow or help break it up in the gastrointestinal tract. For example, to make tablets, the active/inactive ingredient mixture may be formed into small grains and compressed into tablet form. The type and amount of additives and the degree of compression affect how quickly the tablet disintegrates and how quickly the drug is absorbed. Drug manufacturers adjust these variables to optimize absorption. Because drug products that contain the same drug (active ingredient) may have different inactive ingredients, absorption of the drug from different products may vary. Thus, a drug's effects, even at the same dose, may vary from one drug product to another. Drug products that not only contain the same active ingredient but also produce virtually the same blood levels at the same points in time are considered bioequivalent. Bioequivalence ensures therapeutic equivalence (that is, production of the same therapeutic effect), and bioequivalent products are interchangeable.



FIGURE 2: FORMS OF TABLET

Tablets

If a tablet releases the drug too quickly, the blood level of the drug may become too high, causing an excessive response. If the tablet does not release the drug quickly enough, much of the drug may be eliminated in the feces without being absorbed, and blood levels may be too low. Drug manufacturers formulate the tablet to release the drug at the desired speed.

Capsules

Capsules consist of drugs and additives within a gelatin shell. The shell swells and releases its contents when it becomes wet. This usually occurs quickly. The size of the drug particles and the properties of the additives affect how quickly the drug dissolves and is absorbed. Drugs tend to be absorbed more quickly from capsules filled with liquid than from those filled with solid particles.

Enteric coatings

If an orally administered drug harms the stomach lining or decomposes in the acidic environment of the stomach, a tablet or capsule of the drug can be coated with a substance intended to prevent it from dissolving until it reaches the small intestine. These protective coatings are described as enteric coatings. For these coatings to dissolve, they must come in contact with the less acidic environment of the small intestine or with the digestive enzymes there. However, the coatings do not always dissolve as intended. The tablet or capsule may be passed intact in the feces, especially in older people.

Controlled-release formulations

Some drug products are specially formulated to release their active ingredients slowly or in repeated small amounts over time—usually for a period of 12 hours or more. This dosage form is called modified-release, controlled-release, sustained-release, or extended-release.

After a drug is absorbed into the bloodstream, it rapidly circulates through the body. The average circulation time of blood is 1 minute. As the blood recirculates, the drug moves from the bloodstream into the body's tissues.

Once absorbed, most drugs do not spread evenly throughout the body. Drugs that dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol, tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the antianxiety drug clonazepam, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland) because the tissues there have a special attraction for (affinity) and ability to retain that drug.

Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the antibiotic rifampin, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs can. For some drugs, transport mechanisms aid movement into or out of the tissues.

Drug metabolism

Some drugs leave the bloodstream very slowly because they bind tightly to proteins circulating in the blood. Others quickly leave the bloodstream and enter other tissues because they are less tightly bound to blood proteins. Some or virtually all molecules of a drug in the blood may be bound to blood proteins. The protein-bound part is generally inactive. As unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them. Thus, the bound drug in the bloodstream may act as a reservoir for the drug. Some drugs accumulate in certain tissues (for example, digoxin accumulates in heart and skeletal muscles), which can also act as reservoirs of extra drug. These tissues slowly release the drug into the bloodstream, keeping blood levels of the drug from decreasing rapidly and thereby prolonging the effect of the drug. Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug. Distribution of a drug may also vary from person to person. For instance, obese people may store large amounts of fat-soluble drugs, whereas very thin people may store relatively little. Older people, even when thin, may store large amounts of fat-soluble drugs because the proportion of body fat increases with age. Some drugs are chemically altered by the body (metabolized). The substances that result from metabolism (metabolites) may be inactive, or they may be similar to or different from the original drug in therapeutic activity or toxicity. Some drugs, called prodrugs, are administered in an inactive form, which is metabolized into an active form. The resulting active metabolites produce the desired therapeutic effects. Metabolites may be metabolized further instead of being excreted from the body. The subsequent metabolites are then excreted. Excretion involves elimination of the drug from the body, for example, in the urine or bile.

Most drugs must pass through the liver, which is the primary site for drug metabolism. Once in the liver, enzymes convert prodrugs to active metabolites or convert active drugs to inactive forms. The

liver's primary mechanism for metabolizing drugs is via a specific group of cytochrome P-450 enzymes. The level of these cytochrome P-450 enzymes controls the rate at which many drugs are metabolized. The capacity of the enzymes to metabolize is limited, so they can become overloaded when blood levels of a drug are high substances (such as drugs and foods) affect the cytochrome P-450 enzymes. If these substances decrease the ability of the enzymes to break down a drug, then that drug's effects (including side effects) are increased. If the substances *increase* the ability of the enzymes to break down a drug, then that drug's effects are decreased.

Because metabolic enzyme systems are only partially developed at birth, newborns have difficulty metabolizing certain drugs. As people age, enzymatic activity decreases, so that older people, like newborns, cannot metabolize drugs as well as younger adults and children do consequently, newborns and older people often need smaller doses per pound of body weight than do young or middle-aged adults.

Genetic variations in how certain drugs (for example, statins) are transported into and out of the liver may increase a person's risk of drug side effects or drug-related liver injury.

Drug elimination

All drugs are eventually eliminated from the body. They may be eliminated after being chemically metabolized, or they may be eliminated intact. Most drugs, particularly water- soluble drugs and their metabolites, are eliminated largely by the kidneys in urine. Therefore, drug dosing depends largely on kidney function. Some drugs are eliminated by excretion in the bile a greenish yellow fluid secreted by the liver and stored in the gallbladder.

Drug elimination in the urine

Several factors, including certain characteristics of the drug, affect the kidneys' ability to excrete drugs. To be extensively excreted in urine, a drug or metabolite must be water soluble and must not be bound too tightly to proteins in the bloodstream. The acidity of urine, which is affected by diet, drugs, and kidney disorders, can affect the rate at which the kidneys excrete some drugs. In the treatment of poisoning with some drugs, the acidity of the urine is changed by giving antacids (such as sodium bicarbonate) or acidic substances (such as ammonium chloride) to speed up the excretion of the drug.

The kidneys' ability to excrete drugs also depends on

- Urine flow
- Blood flow through the kidneys
- The condition of the kidneys

Kidney function can be impaired by many disorders (especially high blood pressure, diabetes, and recurring kidney infections), by exposure to high levels of toxic chemicals, and by age- related changes. As people age, kidney function slowly declines. For example, the kidneys of an 85-year-old person excrete drugs only about half as efficiently as those of a 35-year-old person.

In people whose kidney function has declined, the “normal” dosage of a drug that is eliminated primarily through the kidneys may be too much and may cause side effects. Therefore, health care practitioners sometimes must adjust the drug dosage based on the amount of decline in the person’s kidney function. People with impaired kidney function require lower drug doses than those with normal kidney function.

Health care practitioners have several ways to estimate the decline in kidney function. Sometimes they base an estimate solely on the person’s age. However, they can get a more accurate estimate of kidney function by using the results of tests that measure the level of creatinine (a waste product) in the blood and sometimes also the urine. They use these results to calculate how effectively creatinine is removed from the body (called creatinine clearance—see Kidney Function Tests), which reflects how well the kidneys are functioning.

Drug elimination in the bile

Some drugs pass through the liver unchanged and are excreted in the bile. Other drugs are converted to metabolites in the liver before they are excreted in the bile. In both scenarios, the bile then enters the digestive tract. From there, drugs are either eliminated in feces or reabsorbed into the bloodstream and thus recycled.

If the liver is not functioning normally, the dosage of a drug that is eliminated primarily by metabolism in the liver may need to be adjusted. However, there are no simple ways to estimate how well the liver will metabolize (and thus eliminate) drugs like there are for kidney function.

Other forms of drug elimination

Some drugs are excreted in saliva, sweat, breast milk, and even exhaled air. Most are excreted in small amounts. The excretion of drugs in breast milk is significant only because the drug may affect the breastfeeding infant. Excretion in exhaled air is the main way that inhaled anesthetics are eliminated.

Advantages ^[3-14]

Popular dosage forms that have several advantages over other methods of pharmaceutical delivery include effervescent formulations. The following are some advantages of effervescent formulations:

- **Faster onset of action:** In contrast with medicine types, effervescent formulations quickly dissipate in water and are absorbed by the body. This may lead to a quicker start to action and quicker symptom relief.
- **Better bioavailability:** Effervescent preparations may improve a drug’s bioavailability, which is the amount of the active component that is absorbed by the body and is readily available to have a therapeutic effect.
- **More feasible:** Patients who struggle to swallow will find effervescent formulations more convenient because they can be dissolved in water.
- **Better taste:** Effervescent formulations frequently have a tasty flavour, which can increase patient

compliance and drug adherence.

- Reduced gastrointestinal irritation: By buffering the stomach acid, effervescent formulations might lessen the gastrointestinal irritation brought on by some drugs.¹⁵
- Improved portability: When compared to liquid dose forms, effervescent tablets are easier to store and transport because of their compact form.
- Increased palatability: Flavouring agents are frequently used in the formulation of effervescent tablets to enhance their flavour and increase patient acceptability. This might be especially helpful for children and older people who may have trouble swallowing regular tablets or capsules.
- Good stability: Effervescent pills have good stability in general. This is a consequence of the tablet packaging shielding the active chemicals from the outside environment, preventing them from being exposed to oxygen or moisture, which may lead some medications to deteriorate and become ineffective.
- Improved absorption: Effervescent formulations have been prepared to dissolve fast in the water, which can help the active components be absorbed more readily. This is so that the medication will be spread more equally and have a larger surface area during the effervescence process, which will make it easier for the body to absorb it.
- Prevents first-pass metabolism: Effervescent tablets have the ability to prevent first-pass metabolism, which is the liver's breaking down of a drug before it enters the bloodstream. This is an instance of medication's direct bloodstream absorption from the digestive system, avoiding the liver.
- Can include a high amount of active ingredient: Effervescent formulations can contain lots of active compounds, which may be very helpful for drugs that need greater doses. This is so because, in comparison to other medicine forms, the effervescent tablets matrix may hold a greater volume of active chemicals.
- Exact dosing: Effervescent tablets deliver an exact quantity of active components on account of the available tablet dosage form.
- Possibility of a therapeutically-appropriate combination of numerous active ingredients: Effervescent tablets can combine more than one active component if doing so is therapeutically acceptable on account of the relatively large tablets.

Disadvantages ^(3, 4, 14)

- Unpleasant taste of some active ingredients.
- Larger tablets requiring special packaging materials.
- Relatively expensive to produce due to large amount of more or less expensive excipients and special production facilities.
- Clear solution is preferred for administration, although a fine dispersion is now universally acceptable
- Bigger tablets: Tablets that are effervescent are often larger in size than ordinary tablets, necessitating specific packaging.
- Complex process: when compared to traditional tablets, this requires correct temperature and humidity conditions, making it a difficult moreover pricey procedure.

- Sensitive packaging: because these tablets are prone to hygroscopicity, it requires sensitive packing that includes a desiccant.
- Some active compounds have off-notes: some active compounds have off-notes that cannot be disguised by flavourings or sweeteners. This will result in an unsatisfactory product.
- Required time for disintegration: the disintegration of tablets might take up to 5 minutes. This is mostly determined by the temperature of the water and active substances present.

FUNDAMENTALS OF EFFERVESCENTS: ⁽²⁰⁻²¹⁾

Effervescence consists of a soluble organic acid and an alkali metal carbonate salt, one of which is often the API. Carbon dioxide is formed if this mixture comes into contact with water. Typical examples of the acids and alkalis used include:

- Citric acid
- Tartaric acid
- Malic acid
- Fumaric acid
- Adipic acid
- Sodium bicarbonate
- Sodium carbonate
- Sodium sesquicarbonate
- Potassium bicarbonate
- Potassium carbonate

Effect of water on effervescent formulations ^(12, 13, 22)

When water is present, even in little amounts as a catalysing agent, this reaction begins. Because water is one of the reaction products, water will speed up the reaction rate, making it complicated to halt. Due to this, minimal water interaction is incorporated into the entire manufacture and storage of effervescent items.

Active ingredients that can be formulated in effervescent tablets:

Drugs that are challenging to digest or have stomach disturbances: Calcium carbonate tablets, the most popular type of calcium, are a prime illustration. The calcium salt of carbonate in a typical tablet or powder dissolves in the stomach's acidic pH and is then transported into the digestive tract for absorption. But when calcium carbonate dissolves in the digestive system, CO₂ is released, which typically results in gas within the stomach. However, as people get older, their stomach acid decreases, making it possible for a calcium carbonate tablet to pass through the stomach undissolved. Constipation may follow from that. However, calcium dissolves in water when taken as an effervescent formulation, making it easily accessible to the body. PH-sensitive medications, including antibiotics and amino acids. Active substances may get denatured, lose action, or remain inactive due to the stomach's low pH. However, effervescent substances can prevent the water-active solution from degrading or inactivating by buffering

it so that the stomach's pH rises to alkaline and becomes less acidic. The stomach is induced to empty quickly typically within 20 minutes into the small intestine resulting in optimum absorption of the active component because of this buffering effect due to carbonation.

Drugs that call for a high dose A normal effervescent tablet with a diameter of around 1 inch and a weight of 5 g contains over 2 g of water-based active ingredients in a single dose. If the necessary dosage is higher then, it can be delivered in powder dosage form. E.g., N-acetyl cysteine effervescent tablets. Those who are sensitive to oxygen, dampness, or light. This group includes a lot of vitamins. There is often less than 0.5 per cent free moisture in effervescent formulations. The material required for the packaging formulation should consist of aluminum with a thickness of 0.001 inches. It must be capable of completely blocking light, oxygen, and moisture to ensure the preservation of the contents and prevent any damage from the surrounding environment.

Preparation of effervescent tablets:

The effervescent tablet is made up of three primary parts:

- Active component;
- Acidic source;
- Alkaline substances (mainly carbonates/ bicarbonates).

The acids and alkalis are the crucial components that cause the tablet to effervesce and disintegrate when it comes in contact with water. Citric acid, both hydrated and anhydrous, is the most widely utilised acidic component, but other edible acids such as tartaric acid, fumaric acid, adipic acid and malic acid can also be employed. Acid anhydrides and salts of acids are also used as acidic sources.

The carbonate, which is the source of the carbon dioxide that causes effervescence, is often a water-soluble alkaline carbonate. The carbonate employed is critical since, in addition to causing effervescence, it can affect the tablet's stability. Because it is highly soluble and inexpensive, sodium bicarbonate is one of the most commonly utilised carbonates.

Other alkaline or alkaline earth metal carbonates that are physiologically appropriate may be employed, such as potassium carbonate or bicarbonate, calcium carbonate or bicarbonate, sodium carbonate, sodium glycine carbonate etc.

Diluents, buffering agents, ligands, sweeteners, colouring agents, flavouring agents, solubilizers, wetting agents, disintegrants, and other commonly used excipients may be included in the formulation or preparation of effervescent tablets.

Effervescent tablet formulations may also include a lubricant, which must be selected from totally water-soluble compounds that produce a clear solution. Sodium acetate, sodium benzoate, fumaric acid, polyethylene glycol (PEG) greater than 4000, glycine, and alanine are examples of this type of lubricant.

Effervescent tablets require the use of proper lubricants, even though formulations using tartaric acid are less adherent to tablet tools than those containing citric acid.

Effervescent products can contain natural watersoluble sweeteners like sucrose, lactose, xylitol, D-glucose, sorbitol, or mannitol, and approved artificial sweeteners such as saccharin, aspartame, Acesulfame K, or cyclamates.

Antifoaming agents are substances used to prevent foaming. They include alcohols like cetostearyl alcohol, insoluble oils such as castor oil, polydimethylsiloxanes, stearates, silicone derivatives, ethers, and glycols. However, because acidic and alkaline components add bulk to the tablets, other excipients should be maintained to a minimum and used only when necessary

FORMULATION METHODOLOGIES: [24-36]

Wet Granulation: The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Important steps involved in the wet granulation

- Mixing of the drug(s) and excipients
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass
- Drying of moist granules.
- Mixing of screened granules with disintegrant, glidant, and lubricant.

Advantages

- Permits mechanical handling of powders without loss of mix quality.
- Improves the flow of powders by increasing particle size and sphericity.
- Increases and improves the uniformity of powder density.
- Limitation of wet granulation
- The greatest disadvantage of wet granulation is its cost.
- It is an expensive process because of labor, time, equipment, energy and space requirements. Loss of material during various stages of processing.

Dry Granulation: [33-40]

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is recompressed and the resulting tablet or slug are milled to yield the granules. The other method is to recompress the powder with pressure rolls using a machine such as Chilosonator.

Rollar Compaction:^[40-44] The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules. Use: Use in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations. Advancement in Granulations Steam Granulation It is modification of wet granulation. Here steam is used as a binder instead of water. Its several benefits includes higher distribution uniformity, higher diffusion rate into powders, more favorable thermal balance during drying step, steam granules are more spherical, have large surface area hence increased dissolution rate of the drug from granules, processing time is shorter therefore more number of tablets are produced per batch, compared to the use of organic solvent water vapour is environmentally friendly, no health hazards to operators, no restriction by ICH on traces left in the granules, freshly distilled steam is sterile and therefore the total count can be kept under control, lowers dissolution rate so can be used for preparation of taste masked granules without modifying availability of the drug.

Melt Granulation / Thermoplastic Granulation^[46-48] Here granulation is achieved by the addition of moldable binder. That is binder is in solid state at room temperature but melts in the temperature range of 50 – 80°C. Melted binder then acts like a binding liquid. There is no need of drying phase since dried granules are obtained by cooling it to room temperature.

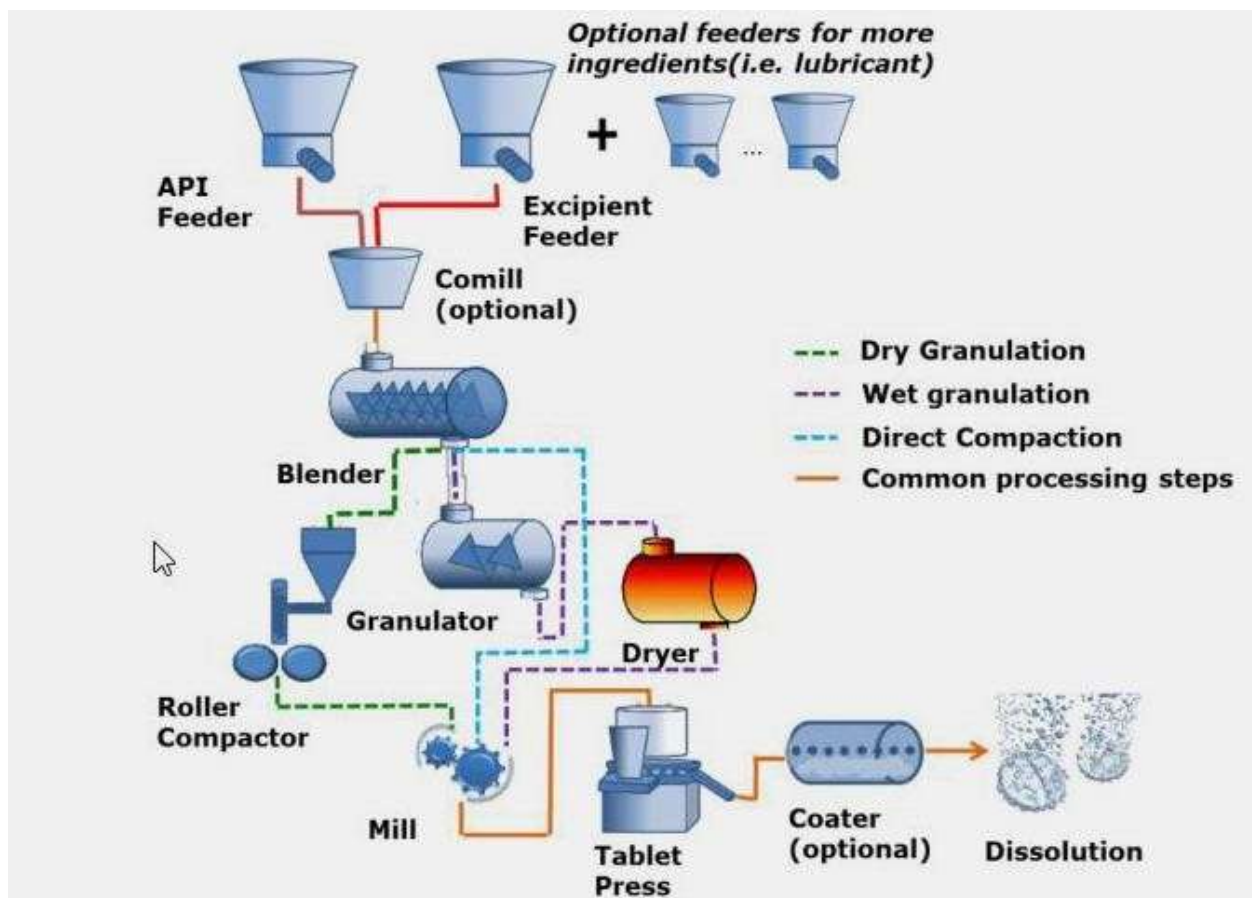


FIGURE 3: METHODS OF GRANULATIONS

Manufacturing of effervescent tablets: Effervescent tablet manufacturing is similar to regular tablet production but requires controlled environmental conditions. Temperature and humidity must be carefully regulated to prevent the raw materials from absorbing moisture and initiating the effervescent reaction. Low relative humidity (maximum of 25% or less) and moderate to cool temperatures (25°C) are necessary to prevent product degradation and sticking to machinery. The most popular method to produce tablets with desirable properties is granulation. There are many different granulation processes available, ranging from one- step granulation utilizing water or organic solvents to two-step granulation such as granulating the acid and alkali phases separately.

Wet granulation: The most recommended approach for effervescent granulation is still wet granulation, despite significant drawbacks. This process produces uniform tablets, either in terms of weight or the amount of active component, and produces homogeneous granules suited for compression.

Two-step granulation technique: Before adding lubricant for tableting, the acidic and basic components are separately granulated and then drily mixed using standard machinery like a fluid bed spray granulator, single pot, or high-shear granulator. Alternatively, one among the effervescent sources can be granulated and the other incorporated as a powder during final blending with additional chemicals like flavours and lubricants. This method boosts productivity and lowers costs by avoiding a full granulation stage.

One-step granulation technique: The one-step granulation technique involves granulating acidic and alkaline components together using a small amount of water or organic solvents like alcohol, isopropanol, or other solvents with a binder. This technique produces dry effervescent granules instantly, regulating the effervescent reaction and leading to granule formation. It is essential for the effervescent and other components to be insoluble in the organic solvent used.

Fluidised bed granulation: The components of an effervescent combination are all granulated in one step using fluid-bed granulator-dryer technology. With this technique, a fluidized bed is created by suspending a dry mixture of an acid source and a carbonate source in a heated air stream. When water, the most common granulating fluid, is injected in a little volume, it reacts briefly before being vaporised. When water is no longer sprayed and the drying phase is completed with warm dry air, the reaction is terminated.

To create effervescent granules a rotor fluid bed spraygranulator can be used as an alternate approach. This technique reduces contact between two effervescent system components. This is a continuous two- or three-step technique for making effervescent granules. Granulating alkaline components in the rotary fluid bed is the first stage. In the following step, the granulating solution is sprayed along with acidic powders onto the alkaline spheres. This results in the formation of an outer acidic layer on the spheres, which is separated from the binder by a neutral layer. Agglomeration is finished, and then drying is initiated.

High shear granulation-It is conceivable to quickly switch from the granulation phase to the drying phase in high-shear granulator-dryer technology by creating a vacuum inside the bowl. This causes the water boiling point to decrease rapidly and the bowl is heated up to provide energy for evaporation. Within seconds, water on the surface of the wet granules is removed and the effervescent reaction stops.

Microwave radiation combined with vacuum can also be applied to dry effervescent granules and stop the reaction. TOPO granulation can be utilised for this type of granulation, where a vacuum can be applied to stop the reaction.

Dry granulation: The effervescent reaction is sparked by the wet granulation process, which degrades the substance. As a result, other options have been developed. One of these is dry granulation by slugging, which involves compressing big tablets or slugs using roller compactors or directly compressed other forms. These are the most successful alternatives to the wet granulation process.

Slugging: To make slugs or large tablets, a roller compactor or chilsonator is often used to compress mixed powders between two counter-rotating rollers under higher pressure. The resulting slugs are then reduced to the appropriate size for tablet granulation. Lubrication may be necessary during the slug-making process. This technique is effective in producing effervescent tablets using dry granulation with acidic and basic substances. However, it involves the use of costly excipients and is only suitable for manufacturing small batches of tablets. The technique is simple, cost-effective, increase product throughput, and requires fewer operators and less space, but it also requires less air ventilation.

Direct compression: Making effervescent tablets with acetylsalicylic acid has successfully used direct compression as an alternative way to dry granulation. Addressing problems with the process's operational effectiveness and stability is helpful with this procedure. However, on account of the need for complex raw material combinations that are compressible, free-flowing, and non-segregating, this technology can only be used in the most perfect of manufacturing environments, which limits its application in real-world applications.

Granulation by heating ^[77-80] Dry granulation techniques, such as hot melt granulation, can be used as an alternative to wet granulation. In hot melt granulation, hydrated citric acid is melted to release the hydration water that serves as the granulating liquid, agglomerating the powder mixer's particles. The resulting granules are then chilled to achieve the required hardness and mechanical stability. Hot melt granulation can be accomplished using a high-shear granulator-dryer, or with low melting point polymers like PEGs as binders in a fluid bed spray-granulator. Hot melt extrusion is another unique technique that requires a hot-melt extrudable binder, extruders with temperature-controllable heating zones, and an extrusion die.

Evaluation tests of effervescent granules: ^[80-83]

1. **Angle of repose:** Pouring the effervescent granules down a funnel onto the flat surface, generating a cone-shaped pile, is one way for measuring the angle of repose. The pile's height and radius are then measured, and the angle of repose is determined using the formula below. Another approach is to use a digital or mechanical angle of repose tester, which automatically calculates the angle of repose depending on the pile's height and radius. The angle of repose can be calculated using the formula below:

$$\tan \theta = H/R$$

$$\theta = \tan^{-1}(H/R)$$

where,

θ is the angle of repose, h is

the pile's height,

r is radius of the pile's base. Flowability

Less than 250 Excellent Between 250 to 300 Good Between 300 to 400 Fair More than 400 Poor

2. **Bulk density:** This density can be obtained by dividing the mass of the powder by its total volume., including the spaces between particles. It is an important factor in the development of effervescent dosage forms as it affects flow properties, compressibility, and rate of dissolution. Measuring the bulk density ensures consistent dosing and optimal packaging.

$$D_f = M/V_p$$

Where ,

M is total mass of sample in grams

V_p is final volume of tablets in cm

3. **Tapped density:** The powder density following tapping or compression is known to be tapped density of effervescent granules. It mimics the settling of powder during storage or transportation. Compared to bulk density, it is a more accurate indicator of powder packing behaviour. Tapped density is a crucial factor to take into account when developing effervescent dosage forms since it has an impact on the powder's uniformity and rate of dissolution. Calculating the tapped density involves dividing the granule mass by the powder's tapped volume. To obtain precise and repeatable readings, a calibrated tapping instrument should be employed. The standardised tapping conditions are specified in the USP or EP.

$$D_o = M/V_p$$

Where ,

M is total mass of sample in grams

V_p is final volume of tablets in cm

4. **Carr's index:** Carr's Index, also known as Carr's compressibility index, is a method for measuring powder flow indirectly by using a bulk density. It was created by Carr, and it establishes a powder's percentage compressibility, which reveals its potential strength and stability in the formation of bridges or arches. Carr's index of a formulation can be calculated using a specific equation that compares the poured bulk or bulk density to the tapped or consolidated bulk density. The equation involves subtracting the tapped density from the poured density, dividing the result by the poured density, and multiplying by 100 to obtain the percentage compressibility.

$$\text{Carr's index} = \frac{D_f - D_o}{D_f} * 100$$

Where,

Df is the poured bulk intensity

Do is tapped or consolidated bulk density

5. **Hausner's ratio:** A measurement of a powder's flowability known as Hausner's ratio is obtained by dividing the tapped density by the bulk density. The powder is put through standardised tapping to determine the values, and the bulk density is calculated by measuring the powder's volume and dividing it by its mass.

Evaluation tests of effervescent tablets: Pharmacopoeial evaluation criteria for effervescent tablets are identical to those for conventional tablets, although they all place a strong emphasis on the disintegration test. They are evaluated using parameters such as disintegration time/effervescent time, dissolution time, weight variation, content uniformity, pH of the solution, hardness, friability, water activity, organoleptic properties, and carbon dioxide (CO₂) content.

1. **Organoleptic properties:** The organoleptic qualities of effervescent tablets are assessed using different procedures, including visual inspection for colour, shape, and uniformity; odour assessment for the distinctive aroma of active components; and taste evaluation for effervescent reaction and overall palatability. These tests guarantee that the tablets satisfy the required quality standards and give consumers a positive sensory experience.
2. **Weight variation:** The weight variation test is performed to make sure that each batch of effervescent tablets has weights that fall within a predetermined range. In this test, the weights of individual tablets are measured from a sample of tablets. The weights of the individual tablets are then contrasted with their combined weight. Typically, a percentage departure from the average weight is utilized to ascertain the allowable weight range. The test of weight variation is passed if the tablets fall within this range. If the tablets couldn't pass the test, additional analysis is needed to figure out what caused the variation and how to fix it. Standard values weight variation test as per IP/BP and USP Avg. weight of tablet as per IP/BP % deviation.
3. **Content of uniformity:** Evaluate the amount of the active ingredients in 10 units of a single-dose formulation to see if it is uniform. The composition of each unit should be between 85 and 115% of the average. The test is invalidated if one or more units fall outside of this range or outside of the range of 75 to 125%. Test 20 more units if one unit is between 75 and 125% but outside of the range of 85 to 115%. The test is considered acceptable if no more than one of the 30 total units falls outside of the range of 85-115% and no units fall outside of 75-125%.⁸⁵
4. **Disintegration time/ effervescent time:** As specified in IP, to test the disintegration of tablets, take a beaker with 250 ml of water at a temperature between 20°C to 30°C, add one tablet, and observe the release of CO₂ bubbles. The tablet should disintegrate within five minutes, leaving no clumps or particles. Repeat this process with five more tablets. The test is considered successful if all six tablets disintegrate within five minutes unless the specific rules of the tablet require otherwise.
5. **Friability test:** For tablets that weigh 0.65 g or less on average, a sample of 6.5 g of whole tablets is obtained for testing, and for that tablet weight 0.65 g or more on average, a sample of 10 entire

tablets is taken. The tablets are precisely weighed after being accurately dedusted, and then they are put in a drum and rotated 100 times. The tablets are cleansed of any loose dust after the rotation and precisely weighed one more. The test is run once, but if the weight loss exceeds the 1.0 % permissible limit, it is run twice, with the mean of the three tests being calculated. Following the test, if the sample has tablets that are clearly broken, chipped, or obviously cracked, the sample is considered a failure.

6. **Dissolution test:** In an effervescent tablet dissolution test, a tablet is drenched in a set amount of water at a specified temperature in dissolution equipment. The apparatus's paddle or basket rotates to induce agitation, and the drug concentration in the water is measured at regular intervals with a spectrophotometer or another technique. The test is carried out in triplicate, and the results are compared to the relevant quality and efficacy requirements.
7. **pH of the solution:** For quality control, the pH of effervescent tablet solution is critical. A stable pH throughout batches suggests that the raw ingredients are homogenous, whereas excessive fluctuation may indicate granulation or weighing difficulties. The taste of the tablet is also affected by the pH; acidic pH is preferable for antacids with citrus or berry flavours, whilst mint flavours are created at a neutral to slightly alkaline pH.¹⁹ Because effervescent tablets change pH on standing due to the breakdown of carbonic acid and the presence of slowly soluble ingredients, pH can be determined using proper apparatus i.e., a pH meter at a given period.
8. **Water activity:** The availability of unbound water for microbial growth is determined by water activity (aW), which is a crucial component in assuring food safety. Capacitance sensors and chilled-mirror dewpoint systems are utilised as the two measuring tools for aW. Hygroscopic polymer membranes are used in capacitance sensors whereas dewpoint sensors and infrared thermometers are used in chilled-mirror systems. Despite the advantages and disadvantages of each approach, both can measure aW precisely.
9. **Hardness and thickness:** Effervescent tablets must be strong enough to handle without chipping or breaking. Proper tool choices, like those with bevelled edges, can minimize these issues. A ratio of 1 between the thickness of the tablet and hardness is recommended for a strong tablet, though this can make packaging difficult due to increased thickness. Tablet height is also important for packaging, as it affects pack tightness. Hardness can be calculated with standard testers like Monsanto's or Pfizer's hardness testers, Strong Cobb, or Schleuengir. Thickness can be evaluated with a vernier caliper.
10. **Carbon dioxide content:** Various methods can be used to measure the carbon dioxide released from effervescent tablets, including gravimetric, barometric volumetric, gasometric, colorimetric, and balloon methods. Every technique possesses its advantages and disadvantages. The gravimetric method calculates CO₂ released by determining the difference in sample weight before and after the reaction but is not very precise. The barometric method measures pressure and volume in a closed system. The volumetric method involves acid-base titration and is time-consuming. The gasometric method directly determines gas volume but is limited in adaptation for pharmaceutical use. The colorimetric method uses indicators to change colour intensity. The balloon method measures CO₂ by passing it into a balloon containing sodium hydroxide solution and titrating it with HCl.

As per revised definition proposed to US FDA, Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. Effervescent tablets are uncoated tablets that generally contain acid or acid salts (Citric, tartaric, Malic acid or any other suitable acid or acid anhydride) and carbonates or bicarbonates Sodium, potassium or any other suitable alkali metal carbonate or hydrogen carbonate), which react rapidly in the presence of water by releasing carbon dioxide. Due to liberation in CO₂ gas, the dissolution of API in water as well as taste masking effect is enhanced. The reaction between Citric acid and Sodium bicarbonate & Tartaric acid and Sodium bicarbonate, which results in liberation of carbon dioxide shown as follows:

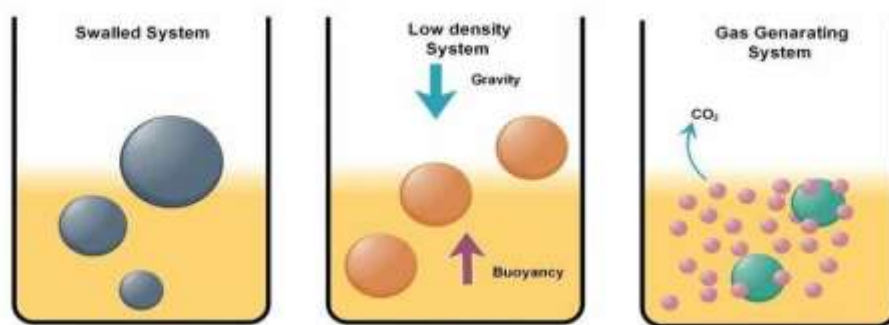
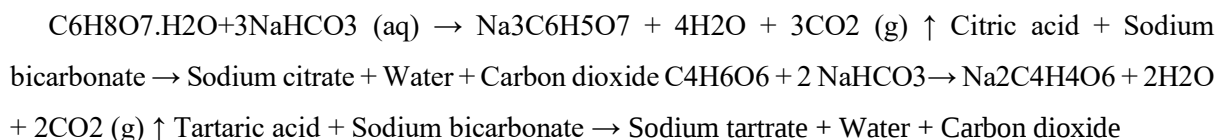


FIGURE 4: EFFERVESCENT REACTIONS

Analgesic drugs

Analgesics are medications that relieve pain. Unlike medications used for anesthesia during surgery, analgesics don't turn off nerves, change the ability to sense your surroundings or alter consciousness. They are sometimes called painkillers or pain relievers. The most common types of analgesics includes.

- Nonsteroidal anti-inflammatory drugs (NSAIDs): Such as ibuprofen, aspirin, and naproxen.
- These medications work by reducing inflammation, which often accompanies pain.
- Acetaminophen (paracetamol): This is another common analgesic that is effective for reducing pain and fever. Unlike NSAIDs, acetaminophen does not reduce inflammation.
- Opioids: Stronger pain relievers, such as codeine, morphine, oxycodone, and hydrocodone.
- These are usually prescribed for severe pain, but they come with a risk of dependence and should be used cautiously.
- Combination medications: Some analgesic tablets contain a combination of different active ingredients, such as acetaminophen with codeine or ibuprofen with paracetamol.

Advantages of analgesic drugs:

- **Pain Relief:** The primary advantage of analgesic tablets is their ability to relieve pain, whether it's mild, moderate, or severe. They provide relief from various types of pain, including headaches, muscle aches, joint pain, menstrual cramps, and pain from injuries or surgeries.
- **Convenience:** Analgesic tablets are often available over-the-counter (OTC), making them easily accessible without needing a prescription. This accessibility allows individuals to manage pain promptly without having to visit a healthcare provider for a prescription.
- **Versatility:** There are different types of analgesic tablets available, catering to various needs and preferences. For example, some people may prefer NSAIDs for their anti-inflammatory properties, while others may opt for acetaminophen for its fever-reducing effects. Having a variety of options allows individuals to choose the most suitable medication for their specific type of pain.
- **Ease of Administration:** Analgesic tablets are typically easy to administer, requiring only swallowing with water or another liquid. This ease of administration makes them convenient for self-medication at home or on-the-go.
- **Fast-Acting:** Many analgesic tablets are formulated for quick absorption and onset of action, providing rapid relief from pain symptoms.
- **Reduced Need for Invasive Treatments:** In many cases, analgesic tablets can effectively manage pain without the need for invasive procedures or stronger interventions. This can be particularly beneficial for individuals with chronic pain conditions who prefer non-invasive pain management options.
- **Affordability:** Compared to other forms of pain management, such as physical therapy or prescription medications, analgesic tablets are often more affordable, especially the OTC varieties.

Disadvantages

- **Side Effects:** Analgesic tablets can cause side effects, ranging from mild to severe, depending on the medication and individual factors. Common side effects may include stomach upset, nausea, gastrointestinal bleeding (with NSAIDs), liver damage (with acetaminophen), drowsiness, dizziness, constipation (with opioids), and allergic reactions.
- **Dependency and Tolerance:** Long-term use of certain analgesic tablets, particularly opioids, can lead to dependency and tolerance. This means that over time, higher doses may be needed to achieve the same level of pain relief, increasing the risk of addiction and withdrawal symptoms when stopping the medication.

- **Drug Interactions:** Analgesic tablets can interact with other medications, supplements, or substances, leading to adverse effects or reduced effectiveness. It's essential to consult a healthcare professional before taking analgesic tablets, especially if you're already taking other medications.
- **Masking Underlying Issues:** While analgesic tablets provide pain relief, they do not treat the underlying cause of the pain. Relying solely on pain medication without addressing the root cause can lead to delayed diagnosis and treatment of potentially serious medical conditions.
- **Overuse and Misuse:** Easy accessibility of analgesic tablets, especially OTC varieties, can lead to overuse or misuse. Taking higher doses than recommended or using them for non- medical purposes can increase the risk of adverse effects and dependency.
- **Organ Damage:** Prolonged or excessive use of certain analgesic tablets, particularly NSAIDs and acetaminophen, can lead to organ damage, such as kidney damage (with NSAIDs) or liver damage (with acetaminophen).
- **Risk of Overdose:** In cases of accidental or intentional overdose, analgesic tablets, especially opioids, can be life-threatening. Symptoms of overdose may include respiratory depression, coma, and death.
- **Not Suitable for Everyone:** Some individuals may have contraindications to certain types of analgesic tablets due to pre-existing medical conditions or allergies. It's essential to consult a healthcare professional to determine the appropriateness of specific analgesic medications for individual circumstances

Antipyretics

Antipyretics are medications used to reduce fever. They work by lowering the body's temperature, which can help alleviate discomfort and prevent complications associated with high fever. The most commonly used antipyretic medications include:

- **Acetaminophen (Paracetamol):** This is one of the most widely used antipyretic medications. It is available over-the-counter and is often the first choice for reducing fever, especially in children. Acetaminophen is available in various forms, including tablets, liquid suspensions, and suppositories.
- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):** NSAIDs such as ibuprofen, naproxen, and aspirin also have antipyretic properties in addition to their analgesic and anti- inflammatory effects. They work by reducing inflammation and inhibiting the production of prostaglandins, which are substances in the body that can cause fever. NSAIDs are available over-the-counter and are commonly used to reduce fever in adults and children.
- **Aspirin (Acetylsalicylic Acid):** Aspirin is another NSAID with antipyretic properties. It is effective in reducing fever but is less commonly used in children due to the risk of Reye's syndrome, a rare but

serious condition that can occur when aspirin is given to children with certain viral infections.

- **Combination Formulations:** Some antipyretic medications come in combination formulations that contain a combination of active ingredients, such as acetaminophen with an NSAID. These combination medications may provide more effective fever reduction in some cases.

Advantages

- **Fever Reduction:** The primary advantage of antipyretic medications is their ability to lower body temperature and reduce fever. By doing so, these medications help alleviate discomfort, malaise, and other symptoms associated with fever.
- **Symptom Relief:** Fever often accompanies various illnesses, such as infections and inflammatory conditions. By reducing fever, antipyretic medications can provide symptomatic relief, including relief from headache, muscle aches, and chills.
- **Improved Comfort:** Fever can make individuals feel uncomfortable, restless, and fatigued. By lowering body temperature, antipyretic medications can improve comfort levels, allowing individuals to rest and recuperate more effectively.
- **Prevention of Complications:** High fever can lead to complications, especially in vulnerable populations such as young children, the elderly, and individuals with certain medical conditions. By reducing fever, antipyretic medications can help prevent potential complications associated with elevated body temperature, such as dehydration, seizures, and delirium.
- **Facilitates Recovery:** Managing fever with antipyretic medications can help the body redirect energy and resources toward fighting the underlying cause of the fever, such as an infection. By reducing fever-related stress on the body, these medications may support the body's natural healing process and expedite recovery.
- **Versatility:** Antipyretic medications come in various forms, including tablets, liquid suspensions, suppositories, and dissolvable formulations, making them suitable for different age groups and preferences. This versatility allows for convenient administration and ensures that individuals can receive appropriate fever management based on their needs.
- **Readily Available:** Many antipyretic medications are available over-the-counter (OTC) without requiring a prescription, making them easily accessible for self-care at home. This accessibility allows individuals to promptly address fever symptoms without the need for a healthcare provider visit in many cases.
- **Safe and Well-Tolerated:** When used as directed, antipyretic medications are generally safe and well-tolerated by most individuals. Serious adverse effects are rare, especially when following recommended

Disadvantages

- **Masking Symptoms:** Antipyretic medications reduce fever but do not treat the underlying cause of the fever, such as an infection. By masking fever symptoms, these medications may obscure signs of illness, making it difficult to monitor the progression of the underlying condition. This could delay diagnosis and appropriate treatment.
 - **Potential Overuse:** Easy accessibility of antipyretic medications, particularly over-the-counter varieties, may lead to their overuse or misuse. Some individuals may use these medications unnecessarily for mild or transient fevers, which can contribute to antibiotic overuse (if fever is due to a bacterial infection) and may delay appropriate medical evaluation.
 - **Side Effects:** Antipyretic medications can cause side effects, although they are generally well-tolerated when used as directed. Common side effects may include gastrointestinal upset, allergic reactions, and skin rashes. Long-term or excessive use of certain antipyretics, such as acetaminophen, can lead to liver damage.
 - **Drug Interactions:** Antipyretic medications may interact with other medications, supplements, or substances, leading to adverse effects or reduced effectiveness. It's essential to consult a healthcare professional before taking antipyretic medications, especially if you're already taking other medications.
 - **Risk of Reye's syndrome:** Aspirin (acetylsalicylic acid), an antipyretic medication, is associated with the risk of Reye's syndrome, a rare but serious condition that primarily affects children and adolescents recovering from viral infections. Reye's syndrome can lead to liver and brain damage and can be fatal.
 - **Delay in Seeking Medical Attention:** While antipyretic medications can provide temporary relief from fever symptoms, they should not replace medical evaluation, especially if fever is persistent, high, or accompanied by other concerning symptoms. Relying solely on antipyretic medications to manage fever may delay appropriate medical care for underlying conditions that require treatment.
 - **Limited Effectiveness:** Antipyretic medications may not always effectively reduce fever, particularly in cases of severe infection or certain medical conditions. In such cases, other interventions may be necessary to manage fever and its underlying cause effectively. It also has an antiplatelet effect, which helps prevent blood clots. Aspirin works by inhibiting the enzyme cyclooxygenase (COX), which is involved in the synthesis of prostaglandins and thromboxanes. Prostaglandins are responsible for pain, fever, and inflammation, while thromboxanes play a role in platelet aggregation.
- ❖ **Waghmode, Atul A. et al. (2024):** In the present study Oral dosage forms are the most popular form of medication, although there are some problems compared to other methods such as the risk of drug absorption, which can be overcome by administering the drug in a liquid form, therefore, perhaps to allow for the use of low doses. However, the instability of many drugs in the liquid dosage form reduces their use. Formulation of Effervescent tablets can be used as an alternative to developing a dosage form

that can accelerate the dispersion and deterioration of drugs, usually used in quickrelease arrangements. The benefits of using this method of drug overdose and elimination can be accelerated. Immediate release of the preparation is an example of a product produced in this way. Pills are produced by a broadly effervescent process essential for drug delivery control, ongoing maintenance and control arrangements, drug delivery system, etc. are just a few products of this process. This review reflects the new use of the effervescent tablet.^[84]

- ❖ **Mahajan, Kiran C.et al (2024):**In the present study Floating tablets prolong the gastric residence time of drugs, improves bioavailability, and facilitate local drug delivery to the stomach. With this objective, floating tablets containing extract of Syzgium cumini seed extract as active ingredient was prepared for the treatment of antidiabetic. Material and method: Floating tablets of Syzgium cumini seed extract were prepared by direct compression method using Magnesium stearate, Microcrystalline cellulose, Citric acid and Sucrose. The formulations were evaluated for various physical parameters, floating lagtime. Result: The thickness was in the range 4.02-4.086 mm. The hardness ranged from 3.1-3.3 kg/cm², All formulations passed the USP requirements for friability and uniformity of weight. The buoyancy time of all tablet formulations was less than 5min and tablet remained in floating condition throughout the study. Conclusion: The optimized formulation was found to be F5 batch which released 98.13% of drug in 8hr invitro, while the floating lag time was 92 seconds.^[85]
- ❖ **Thatikonda, Nihari, et.al(2024):**In the present study after oral administration of Abacavir, rapid absorption occurs from upper part of gastro intestinal tract with peak concentrations occurring at 0.63 - 1 hr after dosing. Conventional drug therapy with tablets produce relatively rapid and high peak blood levels that requires frequent administration to maintain effective range of plasma drug levels. This conventional therapy leads to reduced effectiveness with poor therapeutic management. To overcome the inadequacy of conventional therapy with tablets, floating sustained release Abacavir tablets were developed.

Floating sustained release Abacavir Sulphate tablets were prepared by using direct compression method. Tablet were formulated using Ethyl Cellulose with hydrocolloids like Hydroxypropyl Methylcellulose (HPMC K4M) and Carbopol 974P as release retarding polymers, Sodium bicarbonate (NaHCO₃) and Citric acid as effervescent agents. Tablets were then evaluated for various physical parameters including hardness, thickness, weight variation, friability, drug content, in-vitro buoyancy, Swelling index and Invitro gastro retentive drug release were conducted. Drug and excipient compatibility studies show that they are compatible with each other. The optimized formulation (F9) shows the hardness of 5.7kg/cm², tablet thickness of 2.74mm, 0.45% of friability, in-vitro buoyancy was up to 6 hours and % drug release was 90.56% in 6 hours. Drug release kinetics was found to follow non-fickian diffusion. Hence, F9 is considered as optimized formulation based on invitro buoyancy and % drug release.^[86]

- ❖ **Uslu, İrem, et.al.(2024):**In the present study Multivitamin/mineral (MVM) supplements are the most commonly utilized dietary supplements by many populations. However, there is a severe concern about their adverse effects due to elemental impurities. In the present study, it was aimed to determine the levels of 11 elemental impurities (Cd, Pb, As, Hg, Co, V, Ni, Se, Mo, Cu, and Cr) by inductively coupled plasma-mass spectrometry (ICP-MS) and evaluate the human health risk associated with the consumption of 33 MVM effervescent tablet supplements available in Turkey. The precision of the

method in terms of relative standard deviation (RSD) was less than 4.6%. The accuracy of the method was tested with recovery experiments, and the results ranged between 86 and 107%. The impurity levels for Cd, Pb, As, Co, V, Ni, Se, Mo, Cu, and Cr were found between 0.011–0.050, 0.025–0.098, 0.018–0.056, 0.010–0.626, 0.027–0.290, 0.026–1.65, 1.92–21.83, 0.034–34.09, 0.140–183.9, and

0.033–13.10 µg/g, respectively, and Hg was not detected in any sample. The calculated concentrations for elemental impurities complied with EMA and USP guidelines, except one supplement for Se (21.83 µg/g) with a permitted limit of 15 µg/g. The hazard quotient (HQ) and hazard index (HI) levels were below 1 for all samples within the ranges of 3.4×10^{-1} –

1.4×10^{-6} for HQ and 7.8×10^{-1} – 1.4×10^{-6} for HI indicating that there is no risk for consumption. The carcinogenic risk (CR) of As was between 1.7×10^{-6} and 5.9×10^{-6} , below the threshold value of 1×10^{-4} . The results showed that there is no risk to human health.^[87]

- ❖ **Shaukat, Ayisha, et al. (2024):** In the present study homemade medicinal remedies used to treat both acute and chronic ailments for centuries need to be transformed into modern evidence-based dosage forms. Therefore, the present study aimed to develop buccal dispersible film, syrup and effervescent granules of an extemporaneous antigout homemade remedy. The dosage forms were prepared using holistic remedy (HR) as an active entity and excipients masking disagreeable features. The dosage forms and HR were subjected to physicochemical evaluation, and standardised by a reversed-phase HPLC method using chlorogenic acid, caffeic acid, vanillin, and ferulic acid as analytical standards. The standardised dosage forms were investigated for antigout activity using an appropriate model. The dosage forms were found to be physically elegant and phytochemically aligned with HR. The developed dosage forms contained the selected markers and possessed antigout activity. Hence, these standardised and evidence-based dosage forms may have wider acceptance in the market compared to HR.^[88]
- ❖ **Szulc-Musiol, Beata, et.al. (2024):** In the present study aimed to assess the changes occurring during the storage of tablets of three effervescent preparations available in Polish pharmacies containing calcium and quercetin from various manufacturers under stressful conditions (45 °C, UV radiation) using a hyperspectral Specim IQ camera (Finland), X-ray microtomography (Germany), and selected pharmacopoeial parameters. All measurements were made three times at the beginning of the experiment (day 0) and then on days 3 and 10. In general, for all analyzed preparations, the values of reflectance (within a range from visible light to near-infrared) were significantly higher on day 0 than after 10 days of heat and UV ($p < 0.001$ each). The hardness of the tablets of all analysed preparations was higher on days 3 and 10 compared to day 0. Significant differences were found in the density of the internal structure of the tested preparations ($p < 0.001$), but in Preparations 1 and 2 on day 10, the density was higher compared to the initial density. In contrast, the porosity was lower on day 10 than on day 0 for Preparations 1 and 2, while in Preparation 3, it remained the same. In conclusion, lower reflectance values indicate that more light passes through/into the tablet, and the increase in density and decrease in porosity may indicate changes in the microstructure of the tablets.^[89]
- ❖ **Nugraha, et.al.(2024):** In the present study the beginning of human history, bee honey has been used by humans. However, there are also other bee products such as bee pollen (BP), royal jelly, propolis, and beeswax. Previous research has identified that pollen contains amino acids, lipids, flavonoids, micronutrients and many fat-soluble vitamins such as vitamins A, E and D, as well as water-soluble vitamins such as vitamins B1, B2, B6 and C. The objective of this study is to formulate bee pollen as

effervescent tablet. The method in this study used alkaline granulation which requires an oven process for 24 hours and the use of a combination of sodium bicarbonate with citric acid. Three formulas were optimized in this study. The stability test results showed that formula number 3 has an average moisture content of $0.5696 \pm 0.6154\%$, and average flow rate of 0.67 ± 0.02054 g/sec, the average compressibility in formula number 1 is $0.046 \pm 0.0452\%$. Overall, it is also known that formula number 2 has the smallest dissolution time compared to other formulations. The effect of the combination of citric acid and sodium bicarbonate used in the formulation of effervescent tablets from bee pollen on the physical quality of the tablets, namely friability, hardness, and dissolving time, the higher levels of citric acid and sodium bicarbonate used do not have a significant effect on friability, hardness, and time dissolving effervescent tablets from bee pollen from kelulut bees.^[90]

❖ **Kamble, Siddaling, et.al.(2024):** In the present study the ongoing, interdependent tasks related to the departments of research and development, quality control, and quality assurance are the creation and validation of analytical methods. Analytical methods are essential for risk management and equivalency assessments. It aids in the development of acceptability standards unique to a product and the consistency of outcomes. Validations establish whether the analytical process is appropriate for the goal for which it was designed. A review of the literature indicates that paracetamol and caffeine can be determined individually or in combination with other medications using analytical techniques based on UV spectroscopy, RP-HPLC, and HPTLC. The parameters were checked for correctness, precision, robustness, and other aspects of analytical validation in accordance with ICH guidelines. The discovered techniques can be applied to the bulk and tablet dosage form analysis of paracetamol and caffeine in effervescent form since they are straight forward, sensitive, and repeatable. The review also outlines the applicability and constraints of numerous published analytical techniques for paracetamol and caffeine analysis. Stability studies have to be conducted on time and in compliance with the standards issued by the World Health Organization, International Conference of Harmonization, and other bodies. The capacity of a pharmaceutical product to meet the physical, chemical, microbiological, toxicological, protective, and informational requirements of a specific formulation in a particular container- closure system is known as its stability. It also ensures that a pharmaceutical product's effectiveness, safety, and performance will be maintained for the duration of its shelf life, which is seen as a need for approval and acceptability. The requirement for ongoing quality and purity monitoring of medications and products gave rise to various stability test techniques. This review covers the various drug substance stability categories as well as the applicability of various techniques for drug substances that are stable, the applicability of various methods used to test the pharmaceutical product's stability, guidelines released to test the pharmaceutical product's stability, protocols for stability testing that outline the essential elements of a well-managed and regulated stability test, and other aspects of stability are all covered in this review. The researcher working on paracetamol and caffeine in effervescent form will greatly benefit from this thorough review study.^[91]

❖ **Nadendla, Rama Rao, et.al.(2024):** In the present study investigation is concerned with the formulation and development of rivaroxaban (RN) effervescent granules using a dry granulation process. A 2^3 factorial design was employed using Design-Expert® software to develop an ideal formulation. Formulations were evaluated, and showed outstanding flow characteristics, compositions with low moisture content contributing to their stability, effervescence time of less than 180 seconds and in vitro profile of over 90% for 30 minutes.^[92]

- ❖ **Iwansyah, Ade Chandra, et al. (2023):** In the present study new product development of Moringa oleifera effervescent tablet was optimization of the acid-base in the formula by using the D-optimal mix design. Chemical profiling and antioxidant activity of Moringa oleifera extract was evaluated. The physicochemical and sensory characteristics of Moringa oleifera effervescent tablet was measured. The results shows that chemical compounds of aqueous and ethanol extracts of Moringa oleifera extracts were hydrocarbons, esters, alcohols, and fatty acids. Both extracts exhibited high antioxidant by the IC50 value at

240.27 µg/mL and 301.21 µg/mL respectively. The quadratic model was found to be the best fitted for evaluating the solubility time, colour, taste and aroma; meanwhile, the special cubic model appeared to be the best fitting model for assessing the hardness response. The optimization process suggested that citric acid (22.19% w/w), tartaric acid (11.17% w/w), and sodium bicarbonate (33.64% w/w) was the best solution for this combination of variables, with a desirability value of 0.798.^[93]

- ❖ **Lamkhade, Aniket Kandul, et.al. (2023):** The present study effervescent tablets were designed to produce solutions that release carbon dioxide simultaneously. Usually, these tablets are prepared by compressing the active ingredients. The main advantages of effervescent tablets are quick production of solution. Thus, it is faster and better to absorb. Effervescent tablets are produced and controlled same as conventional tablets. These controls are included physicochemical properties such as hardness, weight variation, friability, solution time, pH and content uniformity.^[94]

- ❖ **Dani, Danish Hassan, et al.(2023):** In the present study was to develop stable effervescent- tablets without controlling area relative humidity; temperature and no requirement of special packaging. Current 32 factorial-design experimental studies were conducted in the Research Laboratory of Pharmaceutics, Hamdard University. Duration of study is from December- 2021 to November-2022. Various paracetamol based effervescent formulations (F1-F9) were prepared with different molar ratio of citric-acid anhydrous and sodium-bicarbonate as independent variables. Design-Expert® software was used to graphically express the influence of each factor. By novel approach; tablets were compressed at ambient temperature and relative-humidity; acid components were kept on one-side and basic ingredients on another side; both sides were separated by an inert-layer. Tablets were kept at accelerated humidity and temperature in normal packing for six months; after six months, F6 formulation was found acceptable based on effervescence-time (120 sec), pH-value (5.5) and other quality criterion. Parameters of assay, effervescence-time, pH-value and carbon-dioxide content were found within the set-limit. Hence; novel approach for developing effervescent formulation by separating acid components at one-side and basic ingredients on another side of tablet through inert-layer is workable under room temperature and humidity. It is expected that commercial production of tablets by this technique may reduce cost of effervescent products and no requirement for special packaging.^[95]

- ❖ **Azahar, N. N., et.al.(2023)-** The present study radish is a vegetable high in nutritional and phytochemical contents that are beneficial to the human body, especially for managing kidney stone disease. However, it is less consumed as compared to other vegetables due to its pungent flavour and odour. Therefore, the objective of the present work was to formulate a radish effervescent tablet to enhance the palatability of the vegetable. The radish effervescent tablet was formulated by using Simplex Lattice Mixture Design where the percentages of sucralose and strawberry flavour were chosen as the factors. Five formulations were generated, and sensory acceptance test was conducted

on them. Next, the halalan toyyiban principle compliance was evaluated based on the Halal Control Points (HCPs), toxicity assay (brine shrimp lethality assay), anti-urolithiatic properties (turbidimetric assay), and nutritional composition (energy, total protein, total fat, total carbohydrate, and total sugar). Formulation 5 (F5) with 20% citric acid, 12% sodium bicarbonate, 58% radish powder, 2.5% sucralose, and 7.5% strawberry flavour was selected as the most acceptable formulation ($p < 0.05$). For the halalan toyyiban principle compliance, F5 was evaluated, and it complied with the halalan toyyiban principles. It is halal, non-toxic, and safe for consumption as the LC50 was greater than 1,000 $\mu\text{g/mL}$ (2,223.31 $\mu\text{g/mL}$) for toxicity test, and exhibited significant potential as an anti-urolithiatic agent (88.13% inhibition). In the future, prototype development of radish effervescent tablet with potential anti-urolithiatic and fast-dissolving properties can be carried out.^[96]

❖ **Huynh, Duyen Thi My, et al. (2023):** In the present study Azithromycin, a macrolide antibiotics, is one of the frequently used drugs in the children and elder. However, due to these population difficulty in swallowing and inefficient absorption, and azithromycin inherent poor solubility, bitter taste, and instability in the stomach acidic condition, it is a challenge to reach high oral bioavailability of this drug. To overcome these issues, we developed and characterized the effervescent granules containing azithromycin solid dispersion. Firstly, the solid dispersion was prepared, employing both wet grinding and solvent evaporation methods, with different types/amounts of polymers. The optimal solid dispersion with β -cyclodextrin at a drug:polymer ratio of 1:2 (w/w), prepared by the solvent evaporation method, significantly enhanced the azithromycin solubility 4-fold compared to the free drug, improved its bitterness from “bitter” to “normal”, possessed intermolecular bonding between the drug and polymer, and transformed the azithromycin molecules from crystalline to amorphous state. Secondly, the effervescent granules incorporating the solid dispersion were formulated with varied excipients of sweeteners, gas-generators, pH modulators, and glidants/lubricants. The optimal formula satisfied all the properties stated in the Vietnamese Pharmacopoeia. In summary, the final effervescent granules product could be further investigated in in-vivo and in clinical settings to become a potential azithromycin delivery system with high bioavailability for the children and elder.^[97]

❖ **Mang Sung Thluai, Lucy, et al (2023):** In the present study the objective of this study was to develop effervescent cleansing tablets that can be dissolved and turned into liquid soap, which can be used for bathing or soaking the body. The asiatic-acid-loaded solid lipid microparticles (AASLMs) were prepared via the hot emulsification method followed by cold re-solidification and then freeze-dried to obtain dry powder. The physicochemical properties such as morphology and % entrapment efficiency (%EE) were evaluated. The results revealed that AASLMs have an irregular shape, and the %EE for the resulting AASLMs was $92.04 \pm 3.43\%$. The tablets were manufactured via the direct compression technique. The compatibility test was conducted to ensure that the excipients are compatible with the active ingredient. The angle of repose, Carr's index, and Hausner's ratio were studied to evaluate the flowability of the powder blend before compression. The weight of each tablet was set to 1000 mg, and physicochemical characteristics, in vitro dissolution, ex vivo cleansing efficacy, and stability were evaluated. The results showed that the active ingredient was compatible with other excipients, as the results obtained from FTIR spectra indicated the absence of potential chemical interaction between the active ingredient and excipients used in this study. Additionally, all formulations had good flow properties. The effervescence times of selected formulations, F2 and F3, were <5 min, with favorable

pH and hardness values. The friability values of all formulations exceeded 1% because the excipients used in effervescent tablets are very fragile. The release of asiatic acid (AA) from the tablets was dependent on the concentration of SLS. In an ex vivo test, it was discovered that the developed products F2 and F3 showed much more effective cleansing efficacy than water. Nevertheless, brown spots appeared in the tablets and the AA content was significantly decreased in both tested formulations after 3 months' storage at 40 ± 2 °C/75% RH $\pm$ 5% RH. The stability study revealed that the developed products were not stable at high temperature and humidity. Therefore, it is recommended that the developed effervescent tablets are not stored at a high temperature.^[98]

- ❖ **Maharjan, Sajjan, et.al(2023):** In the present study research work attempts to design, formulate and optimize the floating pulsatile drug delivery system (FPPDS) intended to treat nocturnal hypertension. FPPDS was designed based on central reservoir system containing effervescent agent with rupturable coating and a buoyant layer on top of the coated core. This system consists of rapid release core that contains drug with disintegrants, osmogent (sodium chloride) and effervescent agent (sodium bicarbonate and tartaric acid) which was film coated by hydrophobic polymer Ethyl Cellulose(EC) with polyethylene Glycol(PEG) 6000 as a plasticizer for controlling membrane permeability to provide pulsatile drug release with the target lag time of 6 hours. This pulsatile release tablet was further press coated from one side with Sodium bicarbonate, HPMCK100 and Carbopol to produce buoyant layer for the high floating duration time and less floating lag time. Atenolol being absorbed in upper GI tract and used to treat chronological cardiovascular disease was used as a model drug. Total of 39 formulations were formulated and dissolution test were performed using USP type II at 50 RPM for 8 hours in 0.1N HCl. Results revealed that both coating composition were significant factors in affecting pulsatile lag time and cumulative percentage drug release. Similarly, HPMCK100 and sodium bicarbonate showed the significant role for determining floating lag time.^[99]
- ❖ **Rukaya, Benazir Evita, et.al.(2022):** In the present study Moringa leaves (*Moringa oleifera L.*) are a plant that is widely consumed by Indonesian people and has high nutrition and antioxidants. Utilization of Moringa leaves as a health supplement requires an innovative dosage form to make it practical to use, one of which is by making it in the form of effervescent tablets. The purpose of this study was to obtain an optimal formula for effervescent tablets of aqueous extract of Moringa leaves (*Moringa oleifera L.*). This study was an experimental study, by preparing effervescent tablets of aqueous extract of Moringa leaves using 3 different formulas using the wet granulation method. The physical stability of the effervescent tablets obtained was then evaluated. The evaluation results were analyzed to obtain the optimal formula from the 3 formulas. The research results obtained showed that F3 was a formula that had good physical stability of granules and tablets. Granules from F3 have an angle of repose of 22.45°, and a compressibility percentage of 12.67%. F3 effervescent tablets have a weight uniformity that does not exceed 5% or 10%, size uniformity that is not more than 3 times the thickness of the tablet, and a faster dissolving time compared to other formulas, namely 1 minute 22 seconds. Based on these results, it can be concluded that the optimal formula of the 3 formulas is F3 with an acid and base concentration of 20% each.^[100]
- ❖ **Uppara, Umadevi, et.al (2022):**In the present study the aim of the present study involved the formulation and evaluation of metformin hydrochloride effervescent floating tablets. Two hydrophilic polymers are used at various concentrations (10, 12.5, 15 and 17.5%), xanthum gum and

hydroxypropylmethylcellulose (HPMC) at three viscosity grades (K4M, K15M and K100M). The results have shown the effect of nature of hydrophilic polymer on the biopharmaceutical behavior of metformin HCl floating tablets. The prepared tablets were evaluated for number of parameters like Thickness, Hardness, Weight variation, Friability, Drug content uniformity, Floating lag time, Floating time and in vitro release studies. The drug release kinetic was found to be dependent on HPMC viscosity, particularly at the concentration 17.5%. The floating tablets F8 (HPMC K15M) and F12 (HPMC K100M) have exhibited extended release kinetics (>8 hours) with release rates of 92.18 ± 1.09 and $80 \pm 1.14\%$ respectively.^[101]

❖ **Soesanto, Loekas, et.al (2022):** In the present study *Fusarium oxysporum* f.sp *capsici*, which causes chili-fusarium wilt disease, may be regulated by a secondary metabolite of *Trichoderma harzianum*. Effervescent tablets are used because liquid formulations have some drawbacks. The purpose of this study is to qualitatively determine *T. harzianum*'s best crude secondary metabolites, growth and yield, and phenolic compound content in chili crops in foamed tablet formulations against *F. oxysporum* in vitro. The in vitro study used 6 replicates, a completely randomized design, and 4 treatments consisted of controls and 4, 6, and 8 tablets. Under in vivo conditions, the experiment used a randomized block designs with 4 replicates, eight treatments consisting of controls, fungicides (benomyl), and four, six, or eight tablets per day before or after inoculation. The variables observed were antagonist testing, incubation time, disease intensity, disease incidence, AUDPC, germination rate, plant height, root fresh weight, and qualitative phenolic composition. The results of the study showed that the best dose of *T. harzianum*'s crude secondary metabolite in vitro was 4 tablets. Medications in in-plant studies delayed the incubation period by 64.11%, suppressed disease outbreaks by 58.34%, reduced disease intensity by 80.45%, increased plant height by 50.4%, and harvested phenols (saponins, tannins, hydroquinone). The content of the compound has been qualitatively increased.^[102]

❖ **Taymouri, Somayeh, et.al.(2022):**In the present study valacyclovir (VA) displays antiviral activity against Herpes simplex virus (HSV) and Varicella zoster virus (VZV). The aim of this study was to design, formulate and evaluate the physicochemical properties of effervescent tablets containing VA in order to facilitate pill swallowing for the pediatric, elderly and bed-ridden patients. Sixteen formulations with different amounts of effervescent base were prepared by modified direct compression for the loading of 500 mg VA. The Design-Expert® software was then used to generate formulations using a full factorial design with four different variables: citric acid (A), sodium bicarbonate to citric acid molar ratio (B) 6000 (D). The prepared tablets were assessed for weight variation, hardness, thickness, friability, drug content, CO₂ content, effervescence time and pH. To improve the taste of formulations, several sweeteners and fruity essences such as raspberry and cherries were used. F2 formulation was selected as the optimized formulation with the desirability of 72.8%. The optimized formulation had an effervescent time of 98.33 ± 3.51 seconds, friability

% of 0.55, pH value of 4.67 ± 0.06 , CO₂ amount of 261.33 ± 20.26 mg and hardness of 77.23 ± 3.12 N. It, therefore, seems that optimized effervescent tablets may be helpful for the delivery of VA in the treatment of herpes simplex or herpes zoster and chickenpox.^[103]

❖ **Munirajalakshmi, K., et.al. (2022):** In the present study objectives is peptic ulcer causes lesions in the stomach and oesophagus. The present work is aimed to develop the effervescent granules of Ranitidine Hydrochloride to relieve the pain instantly. Materials and methods : Effervescent granules were

prepared by dry granulation technique using disodium citrate, sodium saccharin, polyvinyl pyrrolidone, glycine, sodium benzoate, sodium bicarbonate. The prepared granules were evaluated for angle of repose, bulk and tapped density, carr's index and hausner's ratio, in-vitro drug release studies and DSC. Results: The angle of repose for formulations F1-F6 was obtained in the range of $32.38^{\circ} \pm 0.34$ to $37.65^{\circ} \pm 0.53$ which indicates the passible flow property of the formulation. Bulk density and Tapped density for formulations F1-F6 was obtained in the range of 0.42 ± 0.01 to 0.46 ± 0.02 and 0.51 ± 0.02 to 0.58 ± 0.02 respectively. The Carr's Index and Hausners Ratio for the formulations F1-F6 was obtained in a range of 15.85 ± 2.97 to 22.4 ± 2.88 and 1.256 ± 0.05 to 1.196 ± 0.04 which indicates good flow property of the given formulation. Percentage release of the drug for the formulations F1-F6 was obtained in a range of 50% to 91%. Conclusion: Among all formulations F4 formulation has highest amount of drug release compared to other formulations. Hence it was considered as promising formulation for further studies. DSC of F4 formulation was found be at 184.5 which indicates that there is no incompatibility between the drug and excipients.^[104]

- ❖ **Agbam, E., et al.(2022):** In the present study the aim is this study was aimed to determine the effect of varying parameters on the properties of effervescent paracetamol tablets for paediatrics. Study Design: This analytical study was carried out on effervescent paracetamol tablets formulated with differing formulation parameters. Place and Duration of Study: This study was carried out in the Faculty of Pharmacy, Delta State University and Abraka from April 2017 to November, 2017. Methodology: Different formulations of effervescent paracetamol tablets were produced through wet granulation method using varied concentrations of citric acid (15, 20 and 25 %) and sodium bicarbonate (15, 20 and 25 %) as the major effervescent ingredients. The powder blends were evaluated for angle of repose, tapped and bulk density to determine its flow property. The prepared tablets were further evaluated using the unofficial test for hardness, friability and thickness as well as the official tests for weight uniformity, disintegration time, carbon dioxide (CO₂) content, water content and pH. Results: Angle of repose ranged from $23.96 \pm 1.97^{\circ}$ - $28.84 \pm 0.91^{\circ}$, Hausner's ratio ranged from 1.16 ± 0.02 - 1.25 ± 0.02 while Carr's index ranged from 14 ± 1.73 - 20 ± 1.15 . All the granules had good flow properties while granules for F3 was the optimized formulation. Friability values were from 0.38 - 0.39 %. Tablets disintegrated between $3 \pm$

43.06 to 5 ± 16.3 min. The effervescence time in all formulations was between 3 to 5 mins with batch F3 giving the best effervescence time. Conclusion: Granules made with Formulation F3 had the optimized flow characteristics. Effervescent paracetamol tablets containing 25% each of citric acid and sodium bicarbonate had the most desired properties as increase in both the concentration of the citric acid and sodium bicarbonate led to a decrease in the disintegration and effervescence time.^[105]

- ❖ **Waghmare,.et.al.(2022):** In the present study recent advances in Novel Drug Delivery System is aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. The controlled release drug delivery systems owning the capacity to be engaged in the stomach remains entitled as Gastro Retentive Drug Delivery Systems. One of the novel approaches for better patient compliance is floating drug delivery. Number of Gastro Retentive dosage forms has been designed to prolong gastric residence time. We are trying to overcome less gastric retention time and trying to reduce the dosing frequency. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence

time of drugs. Present study involves preparation of floating tablet of Guaifenesin with HPMC K10 and K15M floating tablet were designed to achieve the extended release or retention in GIT, which may result enhance in absorption and leads to increase in bioavailability. The aim of the present work is to develop safe, effective HPMC based gastro retentive drug delivery system of effervescent Guaifenesin tablet for dry cough with extended release profile.^[106]

- ❖ **Devi, Jyoti, et.al (2022):** The present study Oral Dispersible tablets (ODTs) constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The aim of the proposed work is to formulate fast dissolving tablets of Amphetamine for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of motion sickness. For this purpose the tablets of Amphetamine were prepared by Effervescent method, Super disintegrants addition method and Sublimation method. Amphetamine is an Antihistamines drug has been used for the treatment of motion sickness. Amphetamine is poorly soluble in water making it a potent candidate fast- dissolving drug delivery system.^[107]
- ❖ **Tambe, et.al.(2021):** In the present study oral dosage forms are the most popular way of taking medication, despite having some disadvantages compared with other methods like risk of slow absorption of the medicament, which can be overcome by administering the drug in liquid form, therefore, possibly allowing the use of a lower dosage. However, instability of many drugs in liquid dosage form limits its use. Effervescent technique can be used as alternate to develop a dosage form which can accelerate drug disintegration and dissolution, is usually applied in quick release preparations. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO₂ in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water. Due to liberation in CO₂ gas, the dissolution of API in water as well as taste masking effect is enhanced Along with the development of new pharmaceutical technique, effervescent tablet are more and more extensively to adjust the behavior of drug release, such as in sustained and controlled release preparations, pulsatile drug delivery systems, and so on. In present work an attempt has been made to formulate an effervescent tablet containing immediate release of paracetamol using various acids and bases. In present work we are used different acids and bases in different concentration. The formulation of tablets was done by using wet granulation as well as dry granulation in that technique wet granulation which was found acceptable. Then formulated tablets were evaluated for hardness, friability, weight variation, and disintegration time . From study it was concluded that F5 shows the better result than the F1, F2, and F3 & F4.^[108]
- ❖ **Korde, Apeksha B., et al. (2021):** In the present study the oral dosage forms are the furthestmost widespread way of taking medicine despite having around drawbacks like slow absorption and thus onset of action is delay. This can be overcome by administering the medication in liquid form but, many APIs consume limited level of constancy in liquid form. So, Effervescent Tablets turns as an alternate dosage form. The tablet is added into a glass of liquid just previously administration and the medication solution or dispersion is to be drunk instantly. The tablet is rapidly broken separately by internal release of CO₂ in water due to interface between tartaric acid and citric acid with alkali metal carbonates or hydrogen carbonate in existence of water. Due to release of CO₂ gas, the dissolution of API in water in addition to taste masking effect is enhanced. The advantages of effervescent tablets

associated with further oral dosage forms contains an prospect For formulator to expand taste, a added gentle action on patient's stomach and marketing characteristics. In present work an attempt has been made to formulate an effervescent tablet containing instant release of paracetamol by means of various acids and bases. In present work we are used different acids and bases in dissimilar concentration. In the preformulation study, compatibility evaluation was performed which implies that drug; acids, bases and other excipient are well-matched with each other. The formulation of tablets was done by using wet granulation technique. Then formulated tablets were evaluated for hardness, friability, weight variation, disintegration time and in-vitro drug release. From study it was concluded that F3 shows the better result than the F1 & F2.^[109]

❖ **Rajani, T.et al. (2021):** In the present study the purpose of this research was to develop gastro-retentive drug delivery system of Valacyclovir hydrochloride to prolong gastric residence time with desired in vitro release profile. Valacyclovir hydrochloride is an Anti- viral drug with high solubility in gastric pH. In the present study, Valacyclovir hydrochloride floating tablets were prepared by effervescence method using sodium bicarbonate and citric acid as a gas generating agent. The tablets were formulated using direct compression method using polymers like HPMC K15M, HPMC K100M, Xanthan gum and Sodium alginate. Pre- compression parameters such as for angle of repose, bulk density, tapped density and hausner's ratio whereas the prepared tablets were evaluated for weight variation, thickness, hardness, friability, drug content, floating lag time, total floating time, in vitro dissolution study and in vivo radiographic studies. FT-IR and DSC studies elucidated the compatibility of the drug with the polymers and other excipients used in the study. In Vitro release studies of the prepared tablets depicted to follow Zero order kinetics with R2 value of 0.941 and Fickian diffusion where n value is < 0.5 and found to be the main mechanism of drug release. The manufacturing procedure was found to be reproducible and formulations were stable after one month of accelerated stability studies.^[110]

❖ **Rahamathulla, Mohamed, et al.(2021):**In the present study Losartan potassium (LP) is an angiotensin receptor blocker used to treat hypertension. At higher pH, it shows poor aqueous solubility, which leads to poor bioavailability and lowers its therapeutic effectiveness. The main aim of this research was to develop a direct compressed effervescent floating matrix tablet (EFMT) of LP using hydroxyl propyl methylcellulose 90SH 15,000 (HPMC-90SH 15,000), karaya gum (KG), and an effervescent agent, such as sodium bicarbonate (SB). Therefore, an EFMT has been developed to prolong the stomach residence time (GRT) of a drug to several hours and improve its bioavailability in the stomach region. The blended powder was evaluated for pre-compression characteristics, followed by post-compression characteristics, in vitro floating, water uptake studies, and in vitro studies. The optimized formulation of EFMT was investigated for in vivo buoyancy by X-ray imaging and pharmacokinetic studies in Albino rabbits. The results revealed that the parameters of pre- and post-compression were within the USP limits. All tablets showed good floating capabilities (short floating lag time <1 min and floated for >24 h), good swelling characteristics, and controlled release for over 24 h. The Fourier-transform infrared (FTIR) and differential scanning calorimetry (DSC) spectra showed drug-polymer compatibility. The optimized formulation F3 (HPMC-90SH 15,000-KG) exhibited non-Fickian diffusion and showed 100% drug release at the end of 24 h. In addition,

with the optimized formulation F3, we observed that the EFMT floated continuously in the rabbit's stomach area; thus, the GRT could be extended to more than 12 h. The pharmacokinetic profiling in Albino rabbits revealed that the relative bioavailability of the optimized LP-EFMT was enhanced compared to an oral solution of LP. We conclude that this a potential method for improving the oral bioavailability of LP to treat hypertension effectively.^[111]

- ❖ **Pradana, et.al.(2021):** In the present study the research was conducted to analyze the effect of different types and concentrations of the acid source on the physical characteristics and chemical stability of black soybean (*Glycine max* (L.) Merr.) Detam I variety effervescent granules. Effervescent granules were made in three different acid sources, which are 15% citric acid for formula I, a mixture of 5% citric acid and 10% tartaric acid for formula II and a mixture of 8% citric acid and 16% tartaric acid for formula III, respectively. The granules' physical characteristics were obtained by particle size distribution, specific density, bulk density, moisture content, flow time, angle of repose, and effervescent time. Total phenolic content was evaluated for 28 days and the samples were collected at 0, 1, 4, 7, 14, 21, and 28

days. The sample was then measured using a visible spectrophotometric method at 505.5 nm wavelength. The results showed that granule effervescent with formula III was selected as the best formula in all parameters measured, except on the particle size distribution result. In addition, total phenolic in the formula I was the highest content with a better stability profile, compared to formula II and III. It showed that the formula with a combination of 8% citric acid: 16% tartaric acid is the most optimum formula physically, even for further research, adsorbent use or binder ratio in the formula, and moisture resistant of the primary packaging must also be considered.^[112]

- ❖ **Barhate, et.al.(2021):** In the present study hypertension is the commonest cause of high blood pressure in the elderly. The incidence increases with age advancement. Long acting dihydropyridines like amlodipine is very effective antihypertensive agent in management of ISH in elderly because of its vasodilatory as well as negative inotropic effect. The main Aim of Present work is to Formulate and Evaluate Amlodipine besylate Effervescent and direct compression tablets tablets in order to enhance its Bio-availability by using Amlodipine besylate are the main ingredients in effervescent Tablets and Fast Disintegrating agents like sodium starch glycolate, Crosscarmilose. Different batches of (F1-F6) immediate release tablets of Amlodipine besylate were prepared by using various concentrations of Citric acid & Sodium bicarbonate as effervescent agents and sodium starch glycolate, Cross cormilose as super disintegrates. Evaluation parameters like thickness, hardness, friability, weight variation and disintegration tests of the formulations were found to be satisfactory. Among all prepared formulations F6 was shown desired release pattern than others. Formulations F1- F6 did not show the optimum drug release .Hence effervescent technique is superior to direct compression by super disintegrates. And thus the F6 formulation was found to be the desired immediate release tablet for the treatment of Hypertension.^[113]

- ❖ **Rahamathulla, Mohamed, et.al (2021):** The present study Neratinib is a potent anticancer drug, used for the treatment of breast cancer. It is poorly soluble at higher pH, which tends to

minimize the therapeutic effects in the lower GIT leads to its poor bioavailability. An attempt has been made to prepare and develop a novel gastro-retentive system of neratinib to improve the drug bioavailability in the GIT by enhancing the gastric retention time. The floating matrix tablets were prepared by various proportions of carbopol 940, micro-crystalline cellulose (MCC) and ethyl cellulose (EC), sodium bicarbonate (NaHCO_3) as gas forming agent, by direct compression. The formulation mixture was assessed for pre and post compression test, lag time, in-vitro floating, FTIR, water uptake/swelling index, in vitro and kinetic release studies. The findings revealed that, the parameters of compression (pre and post) were within USP limits. The floating tablets swelled well and floated for more than 24h, with less than 120 seconds of buoyancy lag time. The optimized formulation F3 showed sustained release up to 12h; a non-Fickian mechanism. Therefore, all the results and findings have shown that developed neratinib floating matrix system is a promising approach as a drug delivery system and application in the treatment of breast cancer.^[114]

❖ **Zaman, Muhammad, et al. (2021):** In the present study the limitations of conventional type delivery systems to retain drug (s) in the stomach has resulted in the development of novel gastroretentive drug delivery system. We developed single-layer effervescent floating tablets of loxoprofen sodium for prolong delivery in the stomach using natural polymers xanthan gum, guar gum and semisynthetic polymer HPMCK4M. All the formulations (F1-F9) were developed by varying concentrations of xanthan gum and HPMCK4M while guar gum concentration was kept constant. Two gas generating agent (s) incorporated were sodium bicarbonate and citric acid. All compendial pre and post-compression tests results were in the acceptable limits. FTIR analysis confirmed drug-polymer compatibility. The in-vitro drug release in simulated conditions i.e., 0.1 N HCl for 12 h revealed orderly increase in total floating time, i.e., less than 6 h for F1 over 12 h for F9. Formulations F1 to F4 were not capable to retard drug release up to 12 h, whereas F5-F7 for 12 h, while F8 and F9 for more than 12 h. Data fitting in various kinetic models showed that drug release best fit in first order kinetic model and F9 in zero order. Based on results data, F7 was the best among all.^[115]

❖ **Ferrari, et.al (2021):** In the present study glutamine (GLN) used as a dietary supplement is practically insoluble in water, which reduces its bioavailability after oral administration. Here, effervescent GLN (EBGLN) was prepared by comminution with an effervescent base (EB) that enhances its water solubility. EB (80 mg/mL) composed of citric acid, tartaric acid, and sodium bicarbonate was used in the ratio 1:2:3. This formulation was characterized in the liquid state (solubility studies, pH, effervescence time, GLN content) and solid-state (size analysis, residual moisture, flow properties studies, differential scanning calorimetry, thermogravimetric analysis, powder x-ray diffraction, and Fourier transformed infrared Raman spectroscopy). *In vivo* studies were performed with adult overnight fasted (15 h) rats. The rats were euthanized 30, 60, and 120 min after the oral administration (gavage) of water

(vehicle of GLN), EB (vehicle of EBGLN), GLN (glutamine dissolved in water), or EBGLN (GLN dissolved in EB). Blood was collected and the plasma concentrations (nmol/mL) of GLN, glutamic acid, alanine, aspartic

acid, asparagine, histidine, serine, arginine, tyrosine, tryptophan, methionine, phenylalanine, valine, leucine, and isoleucine were obtained by high-performance liquid chromatography (HPLC) analysis. Physicochemical characterizations indicated that EBGLN was present as a physical mixture with lower crystallinity and higher solubility when compared with pure GLN. *In vivo* experiments demonstrated improved oral GLN bioavailability from EBGLN (500 mg/kg - 30 min and 60 min). Therefore, the solid effervescent system represents a new strategy for oral glutamine delivery with potential clinical relevance. ^[116]

- ❖ **Rosch, Moritz, et.al. (2021):** The present study hydrogen, as a medical gas, is a promising emerging treatment for many diseases related to inflammation and oxidative stress. Molecular hydrogen can be generated through hydrogen ion reduction by a metal, and magnesium-containing effervescent tablets constitute an attractive formulation strategy for oral delivery. In this regard, saccharide-based excipients represent an important class of potential fillers with high water solubility and sweet taste. In this study, we investigated the effect of different saccharides on the morphological and mechanical properties and the disintegration of hydrogen-generating effervescent tablets prepared by dry granulation. Mannitol was found to be superior to other investigated saccharides and promoted far more rapid hydrogen generation combined with acceptable mechanical properties. In further product optimization involving investigation of lubricant effects, adipic acid was selected for the optimized tablet, due to regulatory considerations. ^[117]
- ❖ **Singh, Mankaran, et.al.(2020):** In the present study the dental caries originate due to the localized dissolution of the hard tissues of teeth, mainly caused by acids, developed by the presence of microorganisms in the biofilm (dental plaque) on the surface of teeth causing “cavities”. Commercially available liquid mouthwashes containing synthetic active ingredients possess limitations like teeth staining, higher alcoholic content, taste disturbances, xerostomia, and stability issues. Objectives is to make the solid preparation for oral hygiene (US6428770B1) in the form of herbal effervescent mouthwash tablet (CN106619318A, US8728446B2) using *Azadirachta indica* and Curcumin having antimicrobial, antibacterial, antiplaque, and anti-inflammatory activity. Methods used the optimization study of effervescent granules was performed by 33 factorial design. A total of 27 preliminary

experimental batches were prepared by the fusion method, varying the amount of citric acid, tartaric acid, and sodium bicarbonate. A complex of curcumin was prepared with hydroxyl propyl β -cyclodextrin and further examined by scanning electron microscopy. The prepared tablets were evaluated for pre and post-compression parameters. The *in vitro* antimicrobial study was performed by Agar well diffusion method against *S. mutans*. Results: All the experimental batches of effervescent granules were evaluated for pH, effervescent time, and CO₂ content. Six batches were further selected for final tablet preparation. The results of the pre-compression parameters revealed excellent flow properties and post-compression parameters; the results were also significant. The antimicrobial study revealed the F3 as a final best formulation. Conclusion: The developed herbal formulation (F3) has a good potential to maintain oral hygiene as compared to alcoholic mouthwash and further studies may be necessary to confirm the efficacy of the formulation since only a single bacterial strain was assayed. ^[118]

- ❖ **Aklima, Aklima, et al.(2020):** In the present study targeted to formulate and prepare effervescent

tablets of Glipizide to provide more elegance, comfortability, and improved pharmacokinetics in diabetic treatment than the conventional dosage. Three formulations (F1, F2, and F3) of the effervescent tablet of Glipizide (5mg) were formulated with different amounts and ratios of excipients. By wet granulation technique, 60 tablets for every formulation were prepared with a weight of 700mg per tablet. Then, the features of both granules and tablets were evaluated by published methods. The angle of repose, Hausner ratio, Carr's index, Loss on drying (LOD), and Moisture Content (MC) used to measure granules property successfully proved right follow ability and compressibility. In contrast, physical and drug content related investigation failed to determine the perfectness of all three formulations. Friability on the formulations was around 0.70%, indicating the expected USP limit of friability (0.5 to 1%). The mean disintegration time of the formulations was from 95s to 105s. The tablet potency assay found 95.20% for F1, 88.80% for F2, and 97.40% for F3. The dissolution pattern of the drug followed a linear relationship with time. After one and a half hours, the highest amount of 59.20% cumulative dissolution was determined for F3 that revealed its strategic improvement of the drug solubility. As Glipizide is a poorly water-soluble drug, the effervescent tablet might mitigate disintegration and dissolution-related limitations and, consequently, enhance the drug's bioavailability.^[119]

❖ **Oktavia, et.al.(2020):** In the present study the application of RICA (Research Institute for Coastal Aquaculture) liquid probiotic bacteria proved to be able to prevent attacks of both types of vibriosis disease and White Spot Syndrome Virus (WSSV) through improved pond water quality. This RICA liquid probiotics is coated using maltodextrin with 3 variations of concentration which are then formed into probiotic effervescent tablets. Apart from making it easy to distribute, this solid probiotic is easily applied without fermentation such as the use of liquid probiotics. The aims of this study was to determine the physical characteristics of probiotic effervescent tablets from maltodextrin coatings with different concentration. The concentration maltodextrin as coating materials were is 20%, 30% and 40% (b/v). The parameters test are average weight, friability, hardness and disintegration time. The results showed that the effervescent tablets of probiotics with a concentration of maltodextrin 40% had a mean weight higher than other concentrations at 798.88 mg. While the effervescent tablets of probiotic with a maltodextrin concentration of 20% had a lower friability and disintegration time compared to other concentrations of 0.05% and 12.96 minutes. And has a higher level of hardness that is equal to 10.89 N compared to other concentrations that is 30% and 40% concentration maltodextrin. The concentration of 20% maltodextrin was the best treatment of this study.^[120]

❖ **Pagire, Sudhir K., et.al.(2020):** In the present study the major concern of the physical and chemical instability of effervescent products during manufacturing and storage is addressed through a co-crystallization strategy. Citric acid (CA) and sodium bicarbonate (SBC) are the essential components of effervescent products. CA is hygroscopic and led to an uncontrollable autocatalytic chain reaction with SBC in the presence of a small amount of moisture, causing product instability. The acid...amide dimer bond and layered structure of the citric acid-nicotinamide co-crystal restricts interaction of moisture with CA, making it nonhygroscopic, and improves the stability of effervescent products. The comparative study of effervescent products containing CA in its free form and as a co-crystal suggests a significant advantage of the use of co-crystal in effervescent products. This finding is supported by the mechanistic understanding developed through GAB and Y&N models obtained from moisture

sorption data along with the computational investigations into moisture interactions with different crystal surfaces. ^[121]

- ❖ **Begum, Shaik Asha, et al(2017):** In the present study Zolpidem Tartarate belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the

enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The pre-compression blend of Zolpidem Tartarate solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The pre-compression blend of all the batches indicates well to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F2 formulation containing, Drug and β cyclodextrin in the ratio of 1:2 showed good result that is 97.06 % in 20 minutes. Hence from the dissolution data it was evident that F2 formulation is the better formulation. By conducting further studies like *In vivo* studies, preclinical and clinical studies we can commercialize the product. ^[122]

- ❖ **Jalonya, Ravi, et al.(2018):**In the present study the present investigation concerns development of bilayer floating tablets of Diltiazem HCl is class I drug, though its reported bioavailability is only 40 %. It is having very short half life of 3 to 4 hr. Hence many sustained release formulations were developed for diltiazem HCl. But they take lag time to start the action. Hence a new approach is tried that gives one immediate release dose and a sustained release dose in single dosage form call bilayer tablets. Immediate release layer delivers the initial dose, it contains superdisintegrant which increase drug release rate whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period. A direct compression method was used to formulate 9 batches. Superdisintegrants like sodium croscarmellose, crospovidone was used for immediate release layer and HPMC K4 M, HPMC K 15 M, PVP K30 like polymers were used in floating layer. A simple visible spectrophotometric method was employed for the estimation of diltiazem at 236 nm and Beer's law is obeyed in the concentration range of 5-25 $\mu\text{g/ml}$. Preformulation studies were carried out to optimize the ratios required for various grades of polymers. The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index), and in vitro dissolution studies. Successful formulation was developed having floating lag time as low as 30 sec and drug release was sustained up to 12 hrs. A biphasic drug release can be obtained by using bilayer tableting technology which involved compression of immediate and sustained release layer together. Bilayered floating

tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption. ^[123]

- ❖ **Sh Mahmood, et.al(2018):**In the present study a simple, precise, and friendly environmental method for the determination of paracetamol and tramadol hydrochloride in pharmaceutical preparations has been worked out. The method is based on the determination of paracetamol at 242 nm and replaces its concentration in a multicomponent system equation for determination of both paracetamol and

tramadol at 227 nm. Beer's law for paracetamol was obeyed over the concentration range 8-25 ppm at 242 nm and 4-16 ppm at 227 nm, for tramadol it is obeyed over the range 2-14 ppm at 227 nm, water is used as a solvent for dissolution. The method is applicable to the determination of paracetamol and tramadol in their pharmaceutical preparations without prior separation steps from excipients as well as for determination of paracetamol in the presence of tramadol. The average recoveries for determination of mentioned drugs were 94.20-100.14%, and the average relative standard deviation of the method was better than $\pm 0.646\%$.^[124]

- ❖ **Velmurugan, S., et.al.(2015):**In the present study Objective is Levodopa is an immediate precursor of dopamine used in treatment of Parkinsonism disorders. The Levodopa effervescent floating tablets were prepared by direct compression technique, using different low density polymers (POLYOX different grades) in various drug polymer ratios. Methods: The Levodopa effervescent floating tablets were prepared by direct compression method. The floating tablets were evaluated for friability, thickness, hardness, weight variation test, drug content, in vitro release and floating properties. The drug excipients compatibility was evaluated by DSC and FT-IR study. Results: All the batches showed compliance with pharmacopoeia standards. Among all the formulation F4 containing PEO WSR 303 in 1:1 drug polymer ratio showed controlled drug release for 12h (99.15%) emerging as the best formulation and follow first order kinetics via, swelling, diffusion. An in vitro buoyancy study reveals that all batches showed good in vitro buoyancy. The DSC study revealed that there was no strong interaction between Levodopa and excipients. Stability studies were carried out for best formulation F4 (PEO WSR 303 in 1:1 drug polymer ratio) according to ICH guidelines. Stability studies ($40\pm 2^\circ\text{C}/75\pm 5\% \text{ RH}$) for 3 month indicated that Levodopa was stable in floating tablets. Conclusion: Hence different grades of low density polymer

(PEO) in various drug polymer ratios can be used to prepare Levodopa floating tablets for prolongation of gastric residence time with enhanced patient compliance.^[125]

- ❖ **Rani, P. Sobhita, et al. (2014):** In the present study the purpose of the present study was to develop floating matrix tablets for Curcumin using psyllium husk as release controlling polymer and to compare the release pattern with synthetic polymers like HPMC K15M and HPMC K100M. Formulations were prepared by wet granulation method and evaluated for floating lag time, swelling index, erosion, drug content and In-Vitro drug release profile. It was found that floating duration of the formulation containing psyllium husk alone was less than that containing similar concentration of HPMC K15M and HPMC K100M. Release rate of the formulation containing psyllium husk in combination with HPMC K15M more than the formulation containing similar amount of HPMC K100M. The In-Vitro release data and drug release mechanism of the optimized formulation followed the Higuchi kinetics and matrix type respectively. It can be concluded that psyllium husk can be a promising polymer for gastro retentive floating drug delivery systems in combination with synthetic polymers.^[126]
- ❖ **Thoke, Sagar B., et al. (2013):**In the present study Alendronate sodium is a bisphosphonates which has antiresorptive effect which is implicated in the prophylaxis and treatment of osteoporosis. The objective of this study was to formulate effervescent tablet of Alendronate sodium with Vitamin D3 against osteoporosis thereby improving patient compliance. As per revised definition proposed to US FDA, Effervescent tablet is a tablet intended to be dissolved or dispersed in water before

administration Effervescent tablets were formulated using citric acid and sodium bicarbonate as effervescent composition by wet granulation. The drug-excipient compatibility study done by DSC & FTIR analysis and it reveals absence of interaction between the drug and excipients. The flowability study of precompression blend shows good flow properties. Formulation was evaluated for weight variation, thickness, hardness, solution time, pH of solution & content uniformity. All the evaluation parameters were within the limit and complies specifications as per U.S.P. & B.P. From the Stability analysis may be inferred that there was no degradation and change in the formulation The Effervescent tablet of Sodium Alendronate and Vitamin D3 is a new pharmaceutical formulation to be taken orally and offering a considerable advantage: avoidance of gastro- intestinal disorders, to the limits of the possible. As compared to the pure drug and marketed

tablet, this formulation displayed significantly effective in the oral osteoporosis treatment in post menopausal women.^[127]

- ❖ **Aslani, Abolfazl, et.al.(2013):**In the present study the aim of this study was to design and formulation of potassium citrate effervescent tablet for reduction of calcium oxalate and urate kidney stones in patients suffering from kidney stones. **Methods:** In this study, 13 formulations were prepared from potassium citrate and effervescent base in different concentration. The flowability of powders and granules was studied. Then effervescent tablets were prepared by direct compression, fusion and wet granulation methods. The prepared tablets were evaluated for hardness, friability, effervescent time, pH, content uniformity. To amend taste of formulations, different flavoring agents were used and then panel test was done by using Latin Square method by 30 volunteers. **Results:** Formulations obtained from direct compression and fusion methods had good flow but low hardness. Wet granulation improves flowability and other physicochemical properties such as acceptable hardness, effervescence time ≤ 3 minutes, $\text{pH} < 6$, friability $< 1\%$, water percentage $< 0.5\%$ and accurate content uniformity. In panel test, both of combination flavors; (orange - lemon) and (strawberry - raspberry) had good acceptability. **Conclusion:** The prepared tablets by wet granulation method using PVP solution had more tablet hardness. It is a reproducible process and suitable to produce granules that are compressed into effervescent tablets due to larger agglomerates.^[128]
- ❖ **Eguvapattu,et.al (2013):** In the present study oral dosage forms are the most popular form of medication, although there are some problems compared to others methods such as the risk of drug absorption, which can be overcome by administering the drug in a liquid form, therefore, perhaps to allow for the use of low doses. However, the instability of many drugs in the liquid dosage form reduces their use. Formulation of Effervescent tablets/granules can be used as an alternative to developing a dosage form that can accelerate the dispersion and deterioration of drugs, usually used in quick-release arrangements. The benefits of using this method of drug overdose and elimination can be accelerated. Immediate release of the preparation is an example of a product produced in this way. Pills are produced by a broadly effervescent process essential for drug delivery control, ongoing maintenance and control arrangements, drug delivery system, etc. are just a few products of this process. This review reflects the new use of the effervescent tablet.^[129]
- ❖ **Shirsand, S. B., et al(2010):**In the present study fast disintegrating tablets of lorazepam were prepared by effervescent method with a view to enhance patient compliance. A 3^2 full factorial design was

applied to investigate the combined effect of two formulation variables: amount of crospovidone and mixture of sodium bicarbonate, citric acid and tartaric acid (effervescent material) on *in vitro* dispersion time. Crospovidone (2-8% w/w) was used as superdisintegrant and mixture of sodium bicarbonate, citric acid and tartaric acid (6-18% w/w) was used as effervescent material, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity and *in vitro* dispersion time. Based on *in vitro* dispersion time (approximately 13 s); the formulation containing 8% w/w crospovidone and 18% w/w mixture of sodium bicarbonate, citric acid and tartaric acid was found to be promising and tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short-term stability and drug-excipient interaction. Surface response plots are presented to graphically represent the effect of independent variables (concentrations of crospovidone and effervescent material) on the *in vitro* dispersion time. The validity of the generated mathematical model was tested by preparing two extra-design check point formulations. The optimized tablet formulation was compared with conventional marketed tablet for drug release profiles. This formulation showed nearly eleven-fold faster drug release ($t_{50\%}$ 2.8 min) compared to the conventional commercial tablet formulation ($t_{50\%}$ >30 min). Short-term stability studies on the formulation indicated that there were no significant changes in drug content and *in vitro* dispersion time ($P < 0.05$).^[130]

AIM

The aim of this study is to formulate and physicochemically evaluate the effervescent Tablets of analgesic and antipyretic of Aspirin to enhance the onset of action and increase the solubility of aspirin.

OBJECTIVES

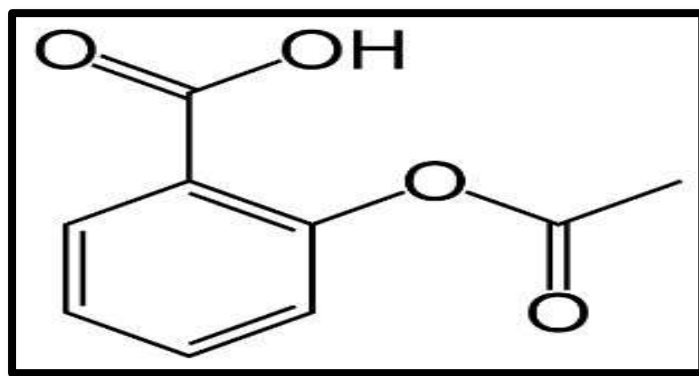
- To optimize the formulation for effervescent tablets
 - To prepare effervescent tablets
 - To evaluate various parameter for effervescent tablets
 - To generate information useful to the formulation in developing desired, stable and bioavailable dosage forms
 - To produce faster onset of action
 - To achieve better patient compliance.
 - To Avoid the First Pass Effect.
 - The Effervescent tablets should have satisfactory property.
 - Tablet having the greater bioavailability than other dosage form.
 - The stability of Effervescent tablets can be increased.
 - The effervescent tablets require strictly humid control area. The Effervescent tablets can be made in a normal area where the humidity and temperature Condition not maintained.
 - Tablet has a better patient compliance and rapid onset of action.
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PLAN OF WORK

1. Literature survey
2. Drug and Excipients Profile
3. Preformulation study of a drug
 - i) Determination of Melting point
 - ii) Determination of λ max
 - iii) Calibration curve
 - iv) Solubility of a drug
4. Method of preparation of effervescent tablets
5. Optimization of effervescent tablet of aspirin by central composite design
6. Pre compression parameter
 - i) Angle of repose
 - ii) Bulk density
 - iii) Tapped density
 - iv) Carrs index
 - v) Hausner ratio
7. Post formulation parameter
 - i) Organoleptic properties
 - ii) Weight variation
 - iii) Thickness
 - iv) Friability test
 - v) Hardness
 - vi) Drug content
 - vii) Dissolution study

DRUG PROFILE

ASPIRIN ^[132]**NAME** -Acetylsalicylic acid (ASPIRIN)**BRAND NAMES**-Bayer, Bufferin, Ecotrin, St. Joseph, Ascriptin

DRUG BANKACCSEION NUMBER- DB00945**CAS NUMBER-**50-78-2**IUPAC NAME-** 2-(acetyloxy) benzoic acid**CLASS-**No steroidal Anti-inflammatory Drug (NSAID)**STRUCTURE-****FIGURE 5: STRUCTURE OF ASPIRIN****MOLECULAR WEIGHT-**Average: 180.1574**CHEMICAL FORMULA** -C₉H₈O₄**MELTING POINT-**135-136°C, (275-277°F)

DESCRIPTION -Also known as Aspirin, acetylsalicylic acid (ASA) is a commonly used drug for the treatment of pain and fever due to various causes. Acetylsalicylic acid has both anti- inflammatory and antipyretic effects. This drug also inhibits platelet aggregation and is used in

the prevention of blood clots stroke, and myocardial infarction (MI). Interestingly, the results of various studies have demonstrated that long-term use of acetylsalicylic acid may decrease the risk of arious cancers, including colorectal, esophageal, breast, lung, prostate, liver and skin cancer . Aspirin is classified as a non-selective cyclooxygenase (COX) inhibitor and is available in many doses and forms, including chewable tablets, suppositories, extended release formulations, and others .Acetylsalicylic acid is a very common cause of accidental poisoning in young children. It should be kept out of reach from young children, toddlers, and infants.

PHARMACODYNAMICS-Effects on pain and fever

Acetylsalicylic acid disrupts the production of prostaglandins throughout the body by targeting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Prostaglandins are potent, irritating substances that have been shown to cause headaches and pain upon injection into humans. Prostaglandins increase the sensitivity of pain receptors and substances such as histamine and bradykinin. Through the

disruption of the production and prevention of release of prostaglandins in inflammation, this drug may stop their action at pain receptors, preventing symptoms of pain. Acetylsalicylic acid is considered an antipyretic agent because of its ability to interfere with the production of brain prostaglandin E1. Prostaglandin E1 is known to be an extremely powerful fever-inducing agent.

Effects on platelet aggregation

The inhibition of platelet aggregation by ASA occurs because of its interference with thromboxane A2 in platelets, caused by COX-1 inhibition. Thromboxane A2 is an important lipid responsible for platelet aggregation, which can lead to clot formation and future risk of heart attack or stroke.

A note on cancer prevention

ASA has been studied in recent years to determine its effect on the prevention of various malignancies. In general, acetylsalicylic acid is involved in the interference of various cancer signaling pathways, sometimes inducing or upregulating tumor suppressor genes. Results of various studies suggest that there are beneficial effects of long-term ASA use in the prevention of several types of cancer, including stomach, colorectal, pancreatic, and liver cancers. Research is ongoing.

PHARMACOKINETICS

Absorption: Rapidly absorbed from the gastrointestinal tract.

Distribution: Widely distributed in body tissues, crosses the placenta and enters breast milk.

Metabolism: Primarily metabolized in the liver.

Excretion: Excreted by the kidneys as metabolites

MECHANISM OF ACTION-Acetylsalicylic acid (ASA) blocks prostaglandin synthesis. It is non-selective for COX-1 and COX-2 enzymes. Inhibition of COX-1 results in the inhibition of platelet aggregation for about 7-10 days (average platelet lifespan). The acetyl group of acetylsalicylic acid binds with a serine residue of the cyclooxygenase-1 (COX-1) enzyme, leading to irreversible inhibition. This prevents the production of pain-causing prostaglandins. This process also stops the conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent inducer of platelet aggregation. Platelet aggregation can result in clots and harmful venous and arterial thromboembolism, leading to conditions such as pulmonary embolism and stroke. It is important to note that there is 60% homology between the protein structures of COX-1 and COX-2. ASA binds to serine 516 residue on the active site of COX-2 in the same fashion as its binding to the serine 530 residue located on the active site of COX-1. The active site of COX-2 is, however, slightly larger than the active site of COX-1, so that arachidonic acid (which later becomes prostaglandins) manages to bypass the aspirin molecule inactivating COX-2. ASA, therefore, exerts more action on the COX-1 receptor rather than on the COX-2 receptor. A higher dose of acetylsalicylic acid is required for COX-2 inhibition.

PROTEIN BINDING-50% to 90% of a normal therapeutic concentration salicylate (a main metabolite of acetylsalicylic acid) binds plasma proteins, particularly albumin, while acetylsalicylic acid itself binds negligibly. Acetylsalicylic acid has the ability to bind to and acetylate many proteins, hormones, DNA, platelets, and hemoglobin.

CLEARANCE-The clearance rate of acetylsalicylic acid is extremely variable, depending on several factors. Dosage adjustments may be required in patients with renal impairment. The extended-release tablet should not be administered to patients with eGFR of less than 10 mL/min.

DOSAGE FORMS-

- Tablets (81 mg, 325 mg)
- Chewable tablets
- Enteric-coated tablets
- Suppositories

DOSE-

Adult Dosage

Pain/Fever: 325-650 mg every 4-6 hours as needed.

Anti-inflammatory: 500-1000 mg every 4-6 hours as needed. Cardioprotection:

75-100 mg daily (typically 81 mg).

Pediatric Dosage:

Fever/Pain: Dosing varies, generally not recommended for children due to the risk of Reye's syndrome.

HALF LIFE-The half-life of ASA in the circulation ranges from 13 - 19 minutes. Blood concentrations drop rapidly after complete absorption. The half-life of the salicylate ranges between 3.5 and 4.5 hours

PH – Acidic PKA -3.5

SOLUBILITY- water soluble, soluble in methanol, ethanol. chloroform, ether and highly soluble in alkaline solutions

APPLICATIONS

- Used to reduce fever
- Used to relieve mild to moderate pain from headaches, menstrual periods, arthritis, toothaches, and muscle aches

ADVERSE EFFECTS

- Abdominal or stomach pain, cramping, or burning, headache
- Eaily decreased frequency of urination or amount of urine
- Weakness or heaviness of the legs
- Unusual drowsiness, dullness, tiredness, weakness, or feeling of sluggishness

EXCIPIENT PROFILE-

1. MICROCRYSTALLINE CELLULOSE ^[133]

Chemical formula

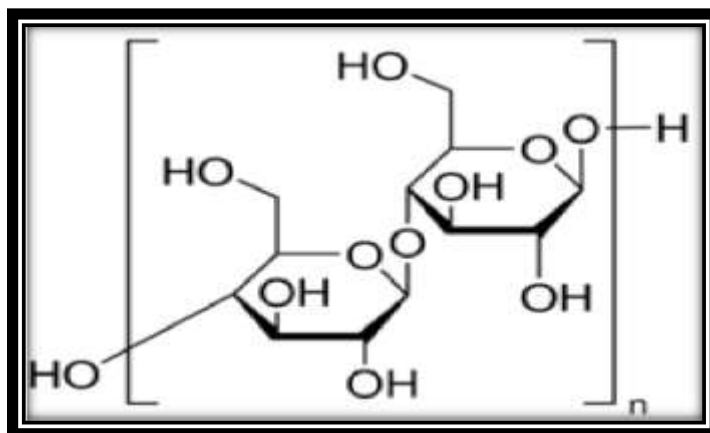


FIGURE 6 : STRUCTURE OF MICROCRYSTALLINE CELLULOSE

Molecular formula-(C₁₂H₂₀O₁₀)_n

Molecular weight-324.28

Solubility-Practically insoluble in water, dilute acid and most of organic solvents, Slightly soluble in dilute NaOH solution

Cas number- 9004-34-6

Physical appearance – White crystalline powder

Storage- Room temperature

Melting point- 76-78 °C(Solv: acetone (67-64-1); chloroform (67-66-3))

Description - Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder and diluent in tablet and capsule formulations where it is used in both wet granulation and direct compression processes. it is one of the strategic raw materials and an ideal excipient for pharmaceutical Formulations most importantly in Tablet. It exhibits excellent properties as an excipient for solid dosage forms

PH-5.0–7.5

Application- MCC has use in cosmetics as an abrasive, absorbent, anti-caking agent, aqueous viscosity increasing agent, binder, bulking agent, emulsion stabilizer, slip modifier, and texturizer which can be found in various hair and skin care products as well as makeup. used for direct compression tableting and wet granulation

Adverse effects- Adverse effect on the lung, depression, forgetfulness, lack of energy, and headaches.

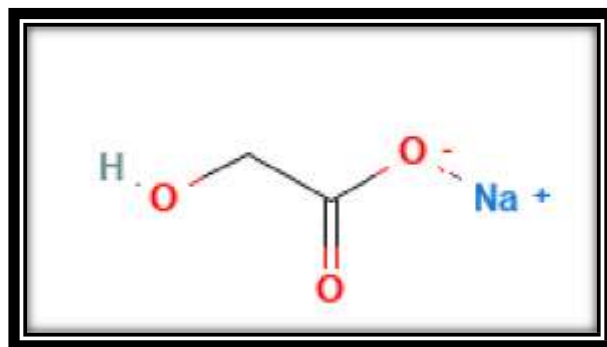
2. SODIUM STARCH GLYCOLATE ^[134]**Chemical formula**

FIGURE 7 : STRUCTURE OF SODIUM STARCH GLYCOLATE

Molecular formula- $(C_2H_4O_3)_x \cdot (Na)_x$ **Molecular****weight-**515.6862**Cas number-** 9063-38-1**Melting point-**Chars At About 200°C**Solubility-** insoluble in water and organic solvents.**Physical appearance** –white ,off white powder**Storage-**Preserve well in closed containers, it is preferred to keep away from wide variations in temperature and humidity.**Ph-**5.5-7.5**Description-**Sodium starch glycolate is a commonly used super-disintegrant employed to promote rapid disintegration and dissolution of IR solid dosage forms. It is manufactured by chemical modification of starch, i.e., carboxymethylation to enhance hydrophilicity and cross- linking to reduce solubility.**Application-**

- Sodium Starch Glycolate is used as rapid disintegrant that releases the medicine immediately when in contact with water.
- It can be used in a direct-compression or wet-granulation process.
- SSG can also be used as a suspending vehicle.
- It acts as a dissolution enhancing agent.
- SSG is used as a food stabilizer and as an anti-ageing agent for bread and in manufacturing of ice-creams.
- This is used as a component for manufacturing processes in pharmaceuticals, food, textiles, paper and adhesives.

Sodium starch glycolate absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules.

3. SODIUM BICARBONATE ^[135]

Chemical formula

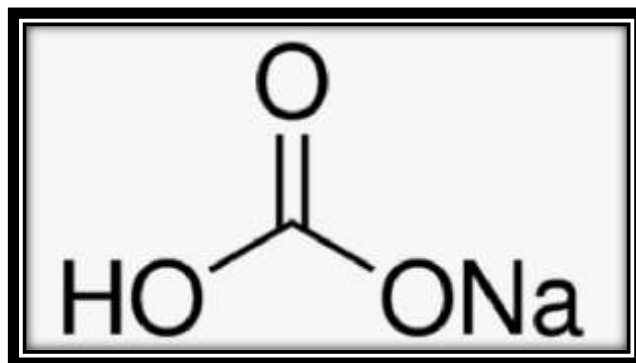


FIGURE 8 :STRUCTURE OF SODIUM BICARBONATE

Molecular formula- NaHCO

Molecular weight-84.0066 g mol⁻¹

Cas number-144-55-8

Melting point-Decomposes around 50 °C

Solubility- water soluble

Physical appearance- white crystalline.

Storage-Store in a well-ventilated place, Keep container tightly closed when not in use at room temperature.

Ph-8.5

Description-Sodium bicarbonate (IUPAC name: sodium hydrogencarbonate[9]), commonly known as baking soda or bicarbonate of soda, is a chemical compound with the formula NaHCO₃. It is a salt composed of a sodium cation (Na⁺) and a bicarbonate anion (HCO₃⁻). Sodium bicarbonate is a white solid that is crystalline but often appears as a fine powder. It has a slightly salty, alkaline taste resembling that of washing soda (sodium carbonate). The natural mineral form is nahcolite. It is a component of the mineral natron and is found dissolved in many mineral springs. sodium bicarbonate is an amphoteric compound.

Applications –

Used as a ph buffering agent, an electrolyte replenisher, systemic alkalizer and in topical cleansing solutions.

Mainly used in the composition of effervescent tablets, for neutralization of gastric acidity and hemodialysis

- Metabolic alkalosis.
- Headache.
- Muscle pain and twitching.
- Nausea or vomiting.
- Bradypnea.
- Nervousness or restlessness.
- Unpleasant taste.
- Increased frequency of urination.

4. CITRIC ACID ^[136]

Chemical formula

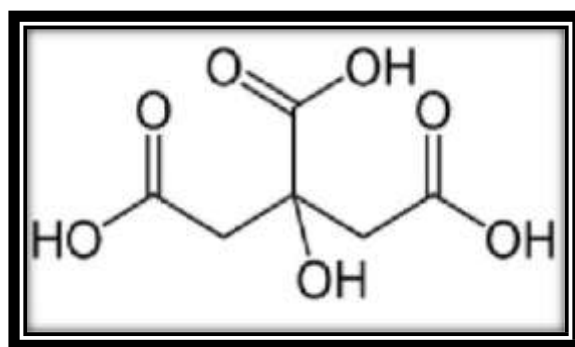


FIGURE 9 :STRUCTURE OF CITRIC ACID

Molecular formula- $\text{HOC}(\text{CO}_2\text{H})(\text{CH}_2\text{CO}_2\text{H})_2$

Molecular weight- 192.123 g/mol (anhydrous),
210.14 g/mol (monohydrate)

Cas number- 77-92-9

Iupac name -2-Hydroxypropane-1,2,3-tricarboxylic acid

Melting point- 153 °C

Solubility- Soluble in acetone, alcohol, ether, ethyl acetate, DMSO

Physical appearance- white crystalline solid

Storage- Store in a tightly closed container. Store in a cool, dry place at room temperature./

Ph-3-6

Description- Citric acid is an organic compound, it is a colorless weak organic acid. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which

occurs in the metabolism of all aerobic organisms. More than two million tons of citric acid are manufactured every year. Citric acid can be obtained as an anhydrous (water-free) form or as a monohydrate. The anhydrous form crystallizes from hot water, while the monohydrate forms when citric acid is crystallized from cold water

Application-

- It is used widely as an acidifier, as a flavoring, and a chelating agent.
- Citric acid is used with sodium bicarbonate in a wide range of effervescent formulae. Citric acid is an excellent chelating agent,
- The buffering properties of citrates are used to control pH.
- Citric acid is a versatile precursor to many other organic compounds

Adverse effects-

- skin and eye irritation.
- joint pain with swelling and stiffness,
- muscular and stomach pain, as well as shortness of breath

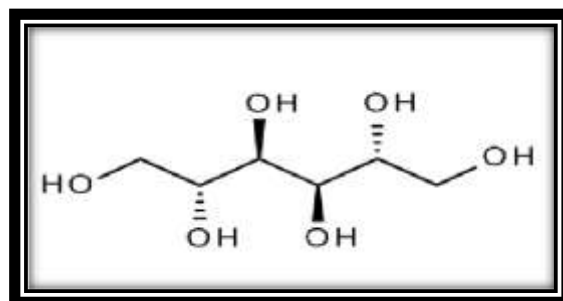
5. MANNITOL^[137]**Chemical formula**

FIGURE 10 : STRUCTURE OF MANNITOL

Molecular formula- (C₆H₈(OH)₆)**Molecular weight-** Average: 182.1718

Monoisotopic: 182.07903818

Cas number- 69-65-8**Melting point-** 168 °C**Physical appearance-** odorless white crystalline powder or free-flowing granules.**Storage-** Store at +15°C to +25°C.**Ph-**5-6.5

Description- Mannitol is available in different grades including crystalline, crystallized, spray- dried, and granulated, with each having distinct properties. Studies have shown that spray-dried mannitols with high surface areas have beneficial properties for solid dose formulation. Mannitol, a sugar alcohol (polyol), finds extensive use in the pharmaceutical industry due to its unique properties and diverse applications.

Applications-

- A solubilizing agent used to enhance the dissolution of the active ingredient..
- Meaning an increased protection against moisture in formulations, an improved chemical/physical stability of formulation and a protection of hydrolysable/moisture sensitive active.
- Used to improve tablet cohesion and provides binding properties and improves mouthfeel.

Adverse effects-

- Allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue.
- Confusion.
- Seizures.
- Signs and symptoms of electrolyte imbalance like severe diarrhea; unusual sweating; vomiting; loss of appetite; increased thirst.

6. SODIUM LAURYL SULPHATE ^[138]

Chemical structure

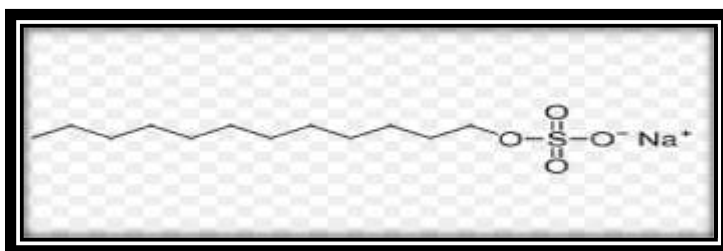


FIGURE 11 :STRUCTURE OF SODIUM LAURYL SULPHATE

Molecular formula-C₁₂H₂₅NaSO₄

Molecular weight-288.372 g/mol

Cas number-151-21-3

Melting point- 206 °C (403 °F; 479 K)

Solubility- It is highly soluble in water and non-volatile solvents.

Physical appearance- White or cream to pale yellow coloured crystals, flakes, or powder **Storage**- Store in cool place. Keep container tightly closed in a dry and well-ventilated place. **Ph**- 7-9.5

Description- It is an anionic surfactant used in many cleaning and hygiene products. This compound is the sodium salt of the 12-carbon organosulfate. Its hydrocarbon tail combined with a polar "headgroup" give the compound amphiphilic properties that make it useful as a detergent

Sodium Lauryl Sulfate (SLS) is an anionic surfactant naturally derived from coconut and/or palm kernel oil. It usually consists of a mixture of sodium alkyl sulfates, mainly the lauryl. SLS lowers surface tension of aqueous solutions and is used as fat emulsifier, wetting agent, and detergent in cosmetics, pharmaceuticals and toothpastes. It is also used in creams and pastes to properly disperse the ingredients and as research tool in protein biochemistry. SLS also has some microbicidal activity.

Applications-

Sodium lauryl sulfate is a widely used in the pharmaceutical field as an ionic solubilizer and emulsifier that is suitable for applications in liquid dispersions, solutions, emulsions and micro emulsions, tablets, foams and semi-solids such as creams, lotions and gels

Adverse effects

It is low to moderately toxic to humans but may cause allergic reactions of skin, eye or respiratory tract.

Materials**TABLE 1: DETAILS OF MATERIALS.**

MATERIALS	CATEGORY	SOURCE
Aspirin	Drug	Cipla Pvt.Ltd
Microcrystalline cellulose	Diluent	Cosmo Chem. Pvt. Ltd
Sodium bicarbonate	Alkalizing agent	Cosmo Chem. Pvt. Ltd
Citric acid	Acidifying agent	Cosmo Chem. Pvt. Ltd
Mannitol	Binding agent	Cosmo Chem. Pvt. Ltd
Sodium lauryl sulphate	lubricant	Cosmo Chem. Pvt. Ltd
Methanol	Solvent	Cosmo Chem. Pvt. Ltd
Ethanol	Solvent	Cosmo Chem. Pvt. Ltd
Distilled water	Solvent	Cosmo Chem. Pvt. Ltd

TABLE 2: LIST OF INSTRUMENTS

Sr. No.	Instrument / Equipment Name	Make
1	Fourier transform infrared spectroscopy (FTIR)	FTIR, Bruker, Germany
2	UV-Visible spectroscopy	Jasco V-630
4	Magnetic stirrer	Remi 1MLH Equipments, Mumbai, India
6	Dissolution apparatus	ELECTROLAB, TDT-06L, USP, India
9	Differential Scanning Calorimetry (DSC)	Shimadzu, Japan.
10	XRD	Carl Zeiss, supra55, German

TABLE 3: LIST OF SOFTWARES USED:

Name of Software	Version
Design of Expert	13.0.5

Ingredients – Aspirin, sodium bicarbonate, citric acid, mannitol, sodium lauryl sulphate, sodium starch glycolate. Microcrystalline cellulose.

TABLE 4: DETAILS OF EXCIPIENTS ROLE AND CATEGORY

Sr.no	Excipient name	Category	Use
1	Microcrystalline cellulose	Diluent	Use as a binder and filler in tablet formulations. It helps to provide structural integrity to tablets
2	Sodium bicarbonate	Alkalizing agent	Sodium Bicarbonate (NaCO_3), also known as baking soda, It can help adjust pH, create effervescence, aid disintegration, and potentially mask taste.
3	Citric acid	Acidifying agent	pH-adjustment, to improve the taste of pharmaceuticals such as syrups, solutions, elixirs
4	Mannitol	Binding agent	Mannitol is a sugar alcohol, it serves as a bulking agent, sweetener, and stabilizer.
5	Sodium lauryl sulphate	lubricant	It is a surfactant, and plays a role in wetting and dispersing the tablet ingredients upon contact with saliva.

METHOD OF PREPARATION OF EFFERVESCENT TABLET: [139,140]

- Drug (Aspirin), sodium bicarbonate were sieve through sieve No: 60#.
- Granules prepared with ethanol to form damp mass and it was passed through sieve no.40#. Citric acids, sodium bicarbonate, spray dried mannitol, sodium lauryl sulphate was blended & passes through sieve no: 40#.
- Granules prepared by using binding agent (ethanol) & dry at 60°C for 30 minutes.
- Both granules mix & dry at 60°C for 15 minutes.

- Granules were compressed into tablet by using single rotary tablet punching Machine.

EXPERIMENTAL DESIGN

In the current study, a Response Surface Methodology (RSM) known as Central Composite Design (CCD) was employed using Design Expert® software (Version 13.0.5.0). The CCD was applied with three independent variables: the amount of Sodium bicarbonate (mg), and Citric acid (mg) (B). The dependent variables under investigation in this study are Weight variation, Hardness and drug release. This CCD design incorporated factorial points, a center point, and axial points, resulting in a total of 9 runs. The details of the independent variables, their coded levels, and the scheme matrix of the CCD can be found in the provided table.

TABLE 5: FORMULATON TABLE

Formulation code	Aspirin (mg)	Sodium bicarbonate(mg)	Citric acid (mg)	Microcrystalline cellulose(mg)	Mannitol(mg)	Sodium lauryl sulphate(mg)
F1	300	92.0	100.0	49	5	4
F2	300	106.0	87.9	48	5	4
F3	300	120.0	90.0	31	5	4
F4	300	125.8	95.0	21	5	4
F5	300	86.2	95.0	60	5	4
F6	300	106.0	102.1	33	5	4
F7	300	106.0	95.0	40	5	4
F8	300	92.0	90.0	59	5	4
F9	300	120.0	100.0	21	5	4

PREFORMULATION STUDIES ^[141]

6.3.1 Identification of drug:

6.3.1.1 Appearance: Aspirin was observed visually by using watch glass for its physical appearance such as texture, color and odor.

6.3.1.2 Active pharmaceutical ingredient: Aspirin (Acetylsalicylic acid).

6.3.2 Melting Point

The melting point of Aspirin was determined using capillary tube method. Thieles tube containing liquid paraffin solution and then small amount of pure drug was filled in the capillary tube which is sealed at one end using flame. Sample filled in capillary is tied with thread to the thermometer and suspended into Thieles tube and heated till drug powder melts. The temperature at which the pure drug powder started melting was noted.

6.3.3 Solubility study of the Drug (Aspirin)

The solubility of Aspirin was performed in Methanol, ethanol, distilled water, phosphate buffer pH 7.4, Phosphate buffer pH 6.8, Acidic buffer pH 1.2 were taken in different 100 ml conical flask & 50 mg of Aspirin were added in it. The conical flask was stirred for 24 hrs. On mechanical shaker at 150 RPM. After

24 hrs. The flask was removed solutions were filtered and absorbance was measured at 265 nm.

6.3.3.1 Solubility of the drug in Distilled water

50 mg of the drug was dissolved in distilled water in 100 ml in a volumetric flask, and the volume was made to 100 ml with distilled water. 2 ml of this stock solution was further diluted to 100 ml to get the concentration of 10µg/ml. This solution was scanned in UV-spectrophotometer.

6.3.3.2 Solubility of the drug in Acidic buffer pH 1.2

50 mg of drug was dissolved in acid buffer, pH 1.2 in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 100 ml to get concentration of 10µg/ml. This solution was scanned in UV-spectrophotometer.

6.3.3.3 Solubility of the drug in Phosphate buffer pH 6.8

50 mg of drug was dissolved in phosphate buffer, pH 6.8 in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 100 ml to get concentration of 10µg/ml. This solution was scanned in UV-spectrophotometer.

6.3.3.4 Solubility of the drug in Phosphate buffer pH 7.4

50 mg of drug was dissolved in phosphate buffer, pH 7.4 in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 100 ml to get concentration of 10µg/ml. This solution was scanned in UV-spectrophotometer.

6.3.3.5 Solubility of the drug in Methanol

50 mg of drug was dissolved in methanol in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 100 ml to get concentration of 10µg/ml. This solution was scanned in UV-spectrophotometer.

6.3.3.6 Solubility of the drug in Ethanol

50 mg of drug was dissolved in ethanol in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 100 ml to get concentration of 10 μ g/ml. This solution was scanned in UV-spectrophotometer.

6.3.4 Spectrophotometric characterization of Aspirin in UV Spectroscopy

6.3.4.1 Detection of Absorption Maxima (λ max)

The sample of the standard solution were scanned between 200-400 nm regions on Shimadzu 1800 UV spectrophotometer. Aspirin sample was prepared by dissolving 25 mg of drug in 25 ml of methanol respectively. The absorption maximum for distilled water was found to be 265 nm.

6.3.4.2 Standard calibration curve

6.3.4.2.1 Standard calibration curve of Aspirin in Distilled water

❖ Preparation of stock solution in Distilled water

Standard stock solution was prepared by taking 25 mg in 25 ml of distilled water (1000 μ g/ml). The stock solution scanned in the range 400-200nm by UV spectrophotometer the solutionshowed maximum absorbance at 265 nm.

❖ Preparation of dilutions for the standard curve

From 1000 μ g/ml, diluted 10 ml to 100ml (100 μ g/ml), from this solution 2-12 μ g/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

6.3.4.2.2 Standard calibration curve of Aspirin in Methanol

❖ Preparation of stock solution in Methanol:

Standard stock solution was prepared by taking 25 mg in 25 ml of methanol (1000 μ g/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer. The solution showed maximum absorbance at 265 nm.

❖ Preparation of dilutions for the standard curve:

From 1000 μ g/ml, diluted 10 ml to 100ml (100 μ g/ml), from this solution 2-12 μ g/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

6.3.4.2.3 Standard calibration curve of Aspirin in Ethanol

❖ Preparation of stock solution in Ethanol

Standard stock solution was prepared by taking 25 mg in 25 ml of ethanol (1000 μ g/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer. The solution showed maximum absorbance at 265nm.

❖ Preparation of dilutions for the standard curve:

From 1000 μ g/ml, diluted 10 ml to 100ml (100 μ g/ml), from this solution 2-12 μ g/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

6.3.4.2.4 Standard calibration curve of Aspirin in Phosphate buffer pH 6.8

❖ Preparation of stock solution in Phosphate buffer pH 6.8:

Standard stock solution was prepared by taking 25 mg in 25 ml of Phosphate buffer pH 6.8 (1000 μ g/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer the solution showed maximum absorbance at 265 nm.

❖ Preparation of dilutions for the standard curve:

From 1000 μ g/ml, diluted 10 ml to 100ml (100 μ g/ml), from this solution 2-12 μ g/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

6.3.4.2.5 Standard calibration curve of Aspirin in Phosphate buffer pH 7.4

❖ Preparation of stock solution in Phosphate buffer pH 7.4

Standard stock solution was prepared by taking 25 mg in 25 ml of Phosphate buffer pH 7.4 (1000 μ g/ml). The stock solution scanned in the range 400- 200nmby UV spectrophotometer. The solution showed maximum absorbance at 265 nm.

❖ Preparation of dilutions for the standard curve:

From 1000 μ g/ml, diluted 10 ml to 100ml (100 μ g/ml), from this solution 2-12 μ g/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

6.3.4.2.6 Standard calibration curve of Aspirin in Acidic buffer pH 1.2

❖ Preparation of stock solution in Acidic buffer pH 1.2:

Standard stock solution was prepared by taking 25 mg in 25 ml of Acidic buffer pH 1.2 (1000 μ g/ml). The stock solution scanned in the range 400-200nm by UV spectrophotometer the solution showed maximum absorbance at 265 nm.

❖ Preparation of dilutions for the standard curve:

From 1000µg/ml, diluted 10 ml to 100ml (100 µg/ml), from this solution 2-12 µg/ml dilutions prepared. Absorbance was taken at 265 nm using water as a blank. The absorbance v/s concentration graph is plotted.

Evaluation of precompressed blend: ^[141]1. **Organoleptic Properties**

A small amount of sample is examined by simple visualization and colour, texture etc. were determined

2. **Solubility Studies**

A small quantity of the drug sample was taken in a test tube and the solubility was determined by European pharmacopoeia method.

3. **Angle of Repose (θ)** -The dry mixture powders were permitted to flow through the funnel immovable to a stand at certain height (h). The angle of repose was then considered by measure the height and radius of the heap of powders formed.

Procedure:

- The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone.
- A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity.
- From the cone formed on a graph sheet was taken to measure the area of pile, there by evaluating the flow ability of the granules. Height of the pile was also measured.
- Determine the angle of repose by measuring the height of the cone of powder and calculating the angle of repose, θ , from the following equation.

$$\tan \theta = \frac{H}{R}$$

$$\theta = \frac{(\tan^{-1} H) * R}{R}$$

Where,

θ called as angle of repose,

H is height

R is radius of the powder heap pleasingly.

TABLE 6: RELATIONSHIP BETWEEN ANGLE OF REPOSE (θ) AND FLOW PROPERTIES AS PER USP

Flow property	Angle of Repose
Excellent	<25
good	25-30
passable	40-30

Very poor	>40

4. **Bulk Density**- Apparent bulk density was resolute by pouring presieved drug excipient mixture into a graduated cylinder and measures the volume and weight “as it is”. It is expressed in g/ml

Procedure-

- Weigh accurately 25g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder.
- Carefully level the powder without compacting, and read the unsettled apparent volume.
- Calculate the apparent bulk density in gm/ml by the following formula.

$$D_b = \frac{M}{V_0}$$

Where,

M is mass of powder

V₀ is the Bulk volume of powder.

5. **Tapped density**- It is weight of granules divided by its tapped volume.

Procedure-

- Weigh accurately 25 g of granules, which was previously passed through 22# sieve.
- Transfer granules to 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

$$D_t = \frac{M}{V_t}$$

Where,

M is mass of powder

V_t is the tapped volume of the powder.

6. **Compressibility index**-The % compressibility is determined by Carr's compressibility index.

The % Carr's index is calculated by means of the following formula:

$$\% \text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulked density}}{\text{Tapped density}} \times 100$$

Where,

TD is tapped density

BD is bulk density.

TABLE 7: SCALE OF FLOW ABILITY AS PER USP

Compressibility index	Flow properties
5-15	excellent
12-16	Good
18-21-	Fair to passable
23-35	poor
33-38	Very poor
>40	Very very poor

7. **Hauser’s Ratio-** It was calculated by following formula:

Tapped density

Hauser’s ratio =

Bulk density

Hausner's ratio from 1.25 to 1.6 show moderate flowing properties. If ratio is more than 1.6 will show more cohesive powders.

TABLE 8 : RELATIONSHIP BETWEEN FLOW CHARACTER AND HAUSNER RATIO AS PER USP.

Flow Character	Hausner Ratio
Excellent	1.00–1.11
Good	1.12–1.18
Fair	1.19–1.25
Passable	1.26–1.34
Poor	1.35–1.45
Very poor	1.46–1.59
Very, very poor	>1.60

1. **Average thickness-** The thickness of the tablets was determined using vernier Calliper. According to report tablet thickness would be precise within a $\pm 5\%$ variation of average value.
2. **Hardness and friability-**For each formulation, the hardness and friability of 20 tablets were determined using the Monsanto Hardness Tester and Roche Friabilator resp. Percentage friability of tablets was measured by using following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

3. **Disintegration time-** This test performed on 6 tablets. For disintegration time, one tablet was positioned in the centre of the Petri dish (internal diameter 10 cm) comprising 10 ml of water and the time taken by the tablet to disintegrate totally was noted.
4. **Weight Variation-**Twenty tablets were selected casually. Tablets were weighed individually and mean weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was calculated.

Procedure -

- 20 tablets were selected and weighed collectively and individually.
- From the collective weight, average weight was calculated.
- Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not

Average weight = weight of 20 tablets/20

$$\% \text{ Weight variation} = \frac{\text{Average weight} - \text{Weight of each tablet}}{\text{Average weight}} \times 100$$

5. **Content Uniformity**-Used to ensure that every tablet contains the amount of drug substances certainly with little variation between tablets with in batch.
6. **In vitro drug release studies**-In vitro drug release studies were started using USP apparatus I (basket method). The dissolution media was 1000 mL of 0.1 N HCl at 37 °C for 30 minutes to signify the gastric medium where the tablets will disintegrate. In all experiments, 5 mL of sample was withdrawn at 5 min interval and replaced by means of fresh medium to keep sink condition. Samples were filtered and examined spectrophotometrically at 265 nm.

RESULT AND DISUSSION

7.1 PREFORMULATION STUDY

7.1.1 Identification of drug

7.1.1.1 Organoleptic studies

Powder of blend was found to be given in following table

TABLE 9: PHYSICAL APPEARANCE

Parameter	Results
Colour	White off.
Odour	Odour of acetic acid
Texture	Crystalline
Shape	Round

7.1.1.2 Active pharmaceutical ingredient: Aspirin (Acetylsalicylic acid)**7.1.2 Melting point**

FIGURE 12: MELTING POINT OF ASPIRIN

TABLE 10: OBSERVATION OF MELTING POINT

Drug name	Observed value	Reported value
Aspirin	135°C	133-137°C

7.1.3 Solubility study of Aspirin**TABLE 11: SOLUBILITY IN DIFFERENT MEDIUM**

Medium	Solubility(mg/ml)
Distilled water	38.20
Methanol	36.94
Ethanol	42.06
Phosphate buffer ph 6.8	32.76
Phosphate buffer ph 7.4	37.79
Acidic buffer ph 1.2	35.90

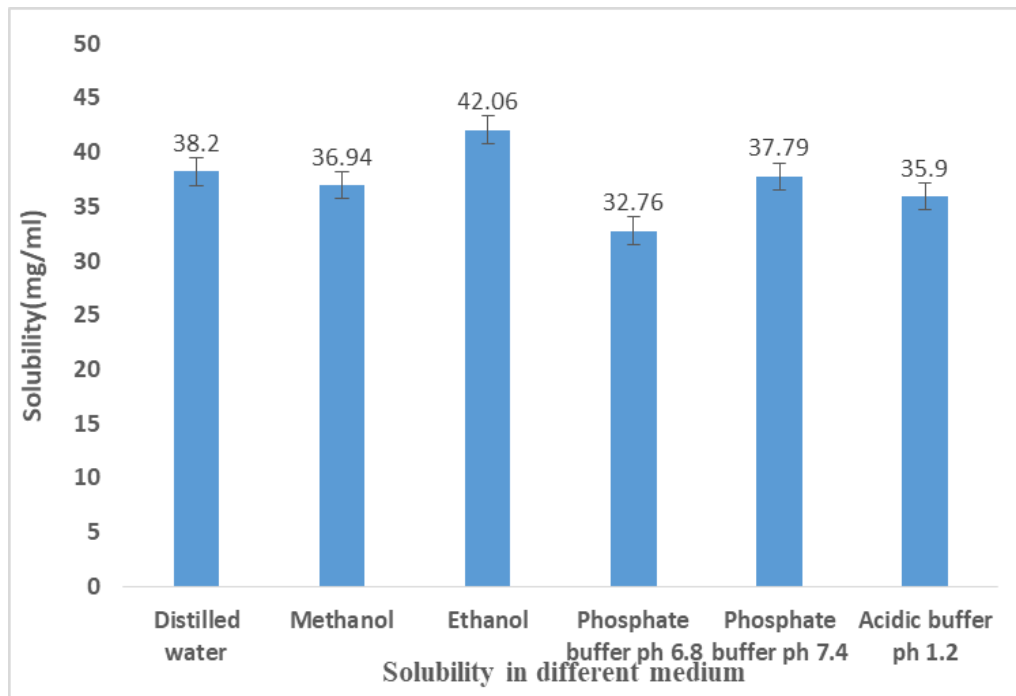


FIGURE 13: SOLUBILITY IN DIFFERENT MEDIUM

7.1.2 Spectrophotometric characterization of Aspirin in UV Spectroscopy

7.1.2.1 Detection of Absorption Maxima (λ max)

TABLE 12: OBSERVATION OF λ MAX

Drug name	Observed value(nm)	Reported value (nm)
Aspirin	265nm	263-266

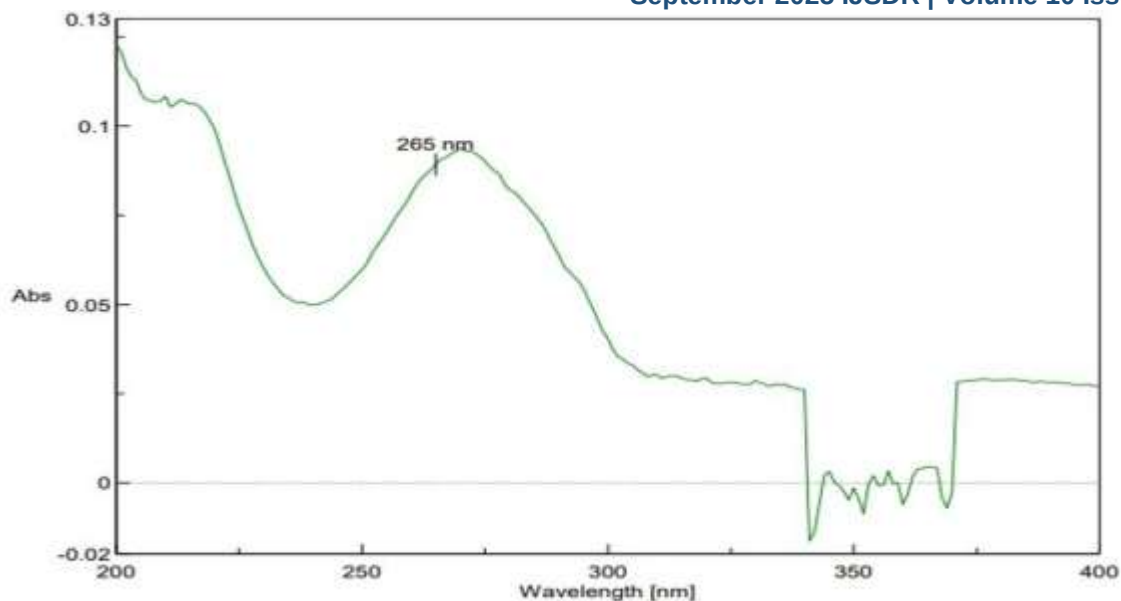


FIGURE 14: UV SPECTRA OF ASPIRIN IN ETHANOL

7.1.2.2 Standard Calibration curve

7.1.2.2.1 Calibration curve in Distilled water

The equation $y = 0.02x + 0.021$ and the correlation coefficient $R^2 = 0.987$ demonstrate a robust linear relationship between concentration (x) and absorbance (y) in a water medium. The high correlation coefficient suggests that the spectrophotometric method employed for analysis is dependable across the examined concentration range. Consequently, the derived equation can effectively determine the concentration of the analyte in water, highlighting the method's accuracy and suitability for precise measurements in this medium..

TABLE 13: CALIBRATION CURVE IN DISTILLED WATER

Concentration (µg/ml)	Absorbance
0	0
2	0.1267
4	0.2025
6	0.3252
8	0.4522

10	0.4912
12	0.628

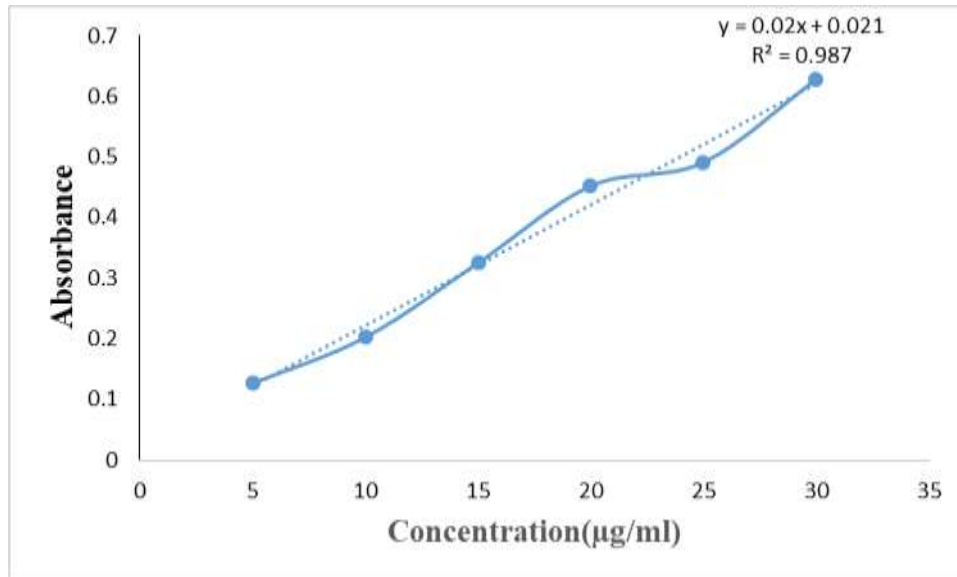


FIGURE 15: CALIBRATION CURVE IN DISTILLED WATER

Equation	$y = 0.02x + 0.021$
Correlation coefficient (R^2)	0.987

7.1.2.2.2 Calibration curve in Methanol

The equation $y = 0.0247x + 0.1523$ and the correlation coefficient $R^2 = 0.9768$ indicate a relatively strong linear relationship between concentration (x) and absorbance (y) in methanol. Although the correlation coefficient is slightly lower compared to some other solvents, it still suggests a good fit for the data within the tested concentration range. Therefore, the derived equation can be reasonably effective in quantifying the concentration of the analyte in methanol, implying the method's reliability for accurate measurements in this solvent medium.

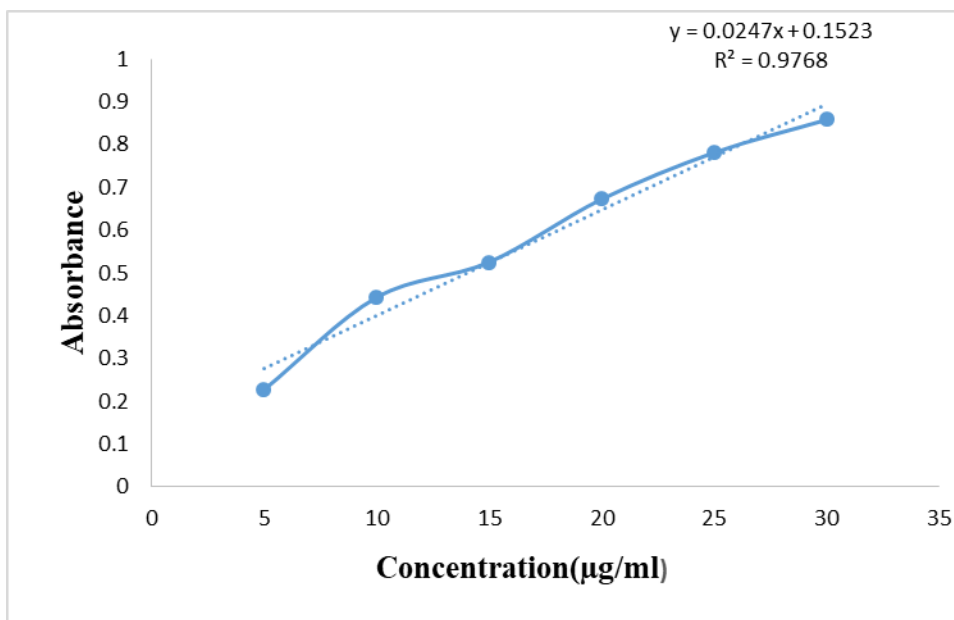


FIGURE 16: CALIBRATION CURVE IN METHANOL TABLE

14: CALIBRATION CURVE IN METHANOL

Concentration (µg/ml)	Absorbance
0	0
2	0.2267
4	0.4425
6	0.5252
8	0.6722
10	0.7812
12	0.858

Equation	$y = 0.0247x + 0.1523$
Correlation coefficient(R^2)	0.9768

7.1.2.2.3 Calibration curve in Ethanol

The equation $y = 0.0247x + 0.1423$ and the correlation coefficient $R^2 = 0.9925$ indicate a strong linear relationship between concentration (x) and absorbance (y) in ethanol. This high correlation coefficient suggests a good fit for the data within the tested concentration range. Therefore,

the derived equation can accurately quantify the concentration of the analyte in ethanol, demonstrating the reliability of the spectrophotometric method used for analysis in this solvent medium.

TABLE 15: CALIBRATION CURVE IN ETHANOL

Concentration (µg/ml)	Absorbance
0	0.0000
2	0.2367
4	0.4125
6	0.5352
8	0.6322
10	0.7512
12	0.878

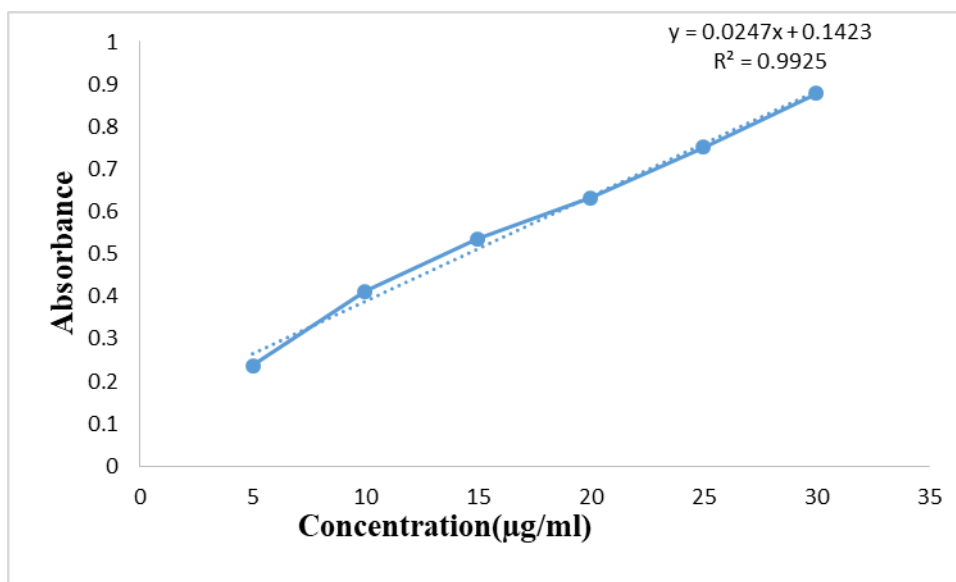


FIGURE 17: CALIBRATION CURVE IN ETHANOL

Equation	$y = 0.0247x + 0.1423$
Correlation coefficient(R^2)	0.9925

7.1.2.2.4 Calibration curve in Phosphate buffer pH 6.8

The equation $y=0.0213x+0.0357$ and the correlation coefficient $R^2=0.9741$ indicate a highly robust linear relationship between concentration (x) and absorbance (y) in phosphate buffer at pH 6.8. With such a high correlation coefficient, the data fit the linear model very well within the tested concentration range. Consequently, the derived equation can accurately determine the concentration of the analyte in phosphate buffer at pH 6.8, underscoring the reliability and precision of the spectrophotometric method utilized for analysis under these specific conditions.

TABLE 16: CALIBRATION CURVE IN PHOSPHATE BUFFER PH 6.8

Concentration (µg/ml)	Absorbance
0	0.0000
2	0.1567
4	0.2325
6	0.3552
8	0.4822
10	0.5112
12	0.7080

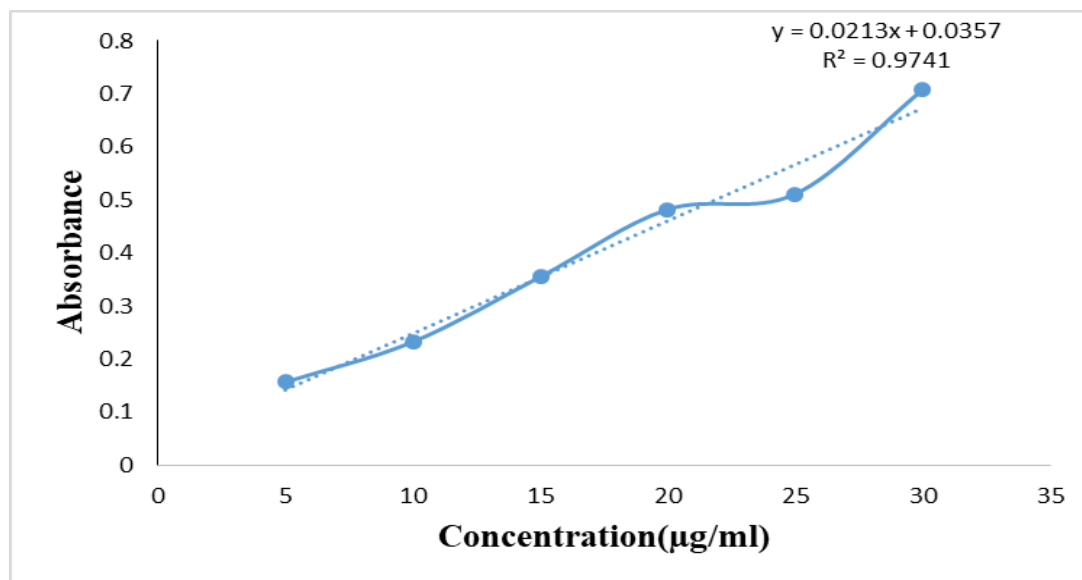


FIGURE 18: CALIBRATION CURVE IN PHOSPHATE BUFFER**PH 6.8**

Equation	$y = 0.0213x + 0.0357$
Correlation coefficient(R^2)	0.9741

7.1.2.2.5 Calibration curve in Phosphate buffer pH 7.4

In the phosphate buffer at pH 7.4, the equation $y=0.0206x+0.025$ = $0.0206x + 0.025$ and the correlation coefficient $R^2=0.9824$ signify a robust linear relationship between concentration (x) and absorbance (y). The high correlation coefficient indicates that the data closely adhere to the linear model within the examined concentration range. Consequently, the derived equation offers an accurate means of quantifying the analyte's concentration in phosphate buffer at pH 7.4. This underscores the reliability and precision of the spectrophotometric method employed for analysis under these specific buffer conditions.

TABLE 17: CALIBRATION CURVE IN PHOSPHATE BUFFER PH 7.4

Concentration (µg/ml)	Absorbance
0	0.0000
2	0.1467
4	0.2125
6	0.3152
8	0.4722
10	0.5112
12	0.6580

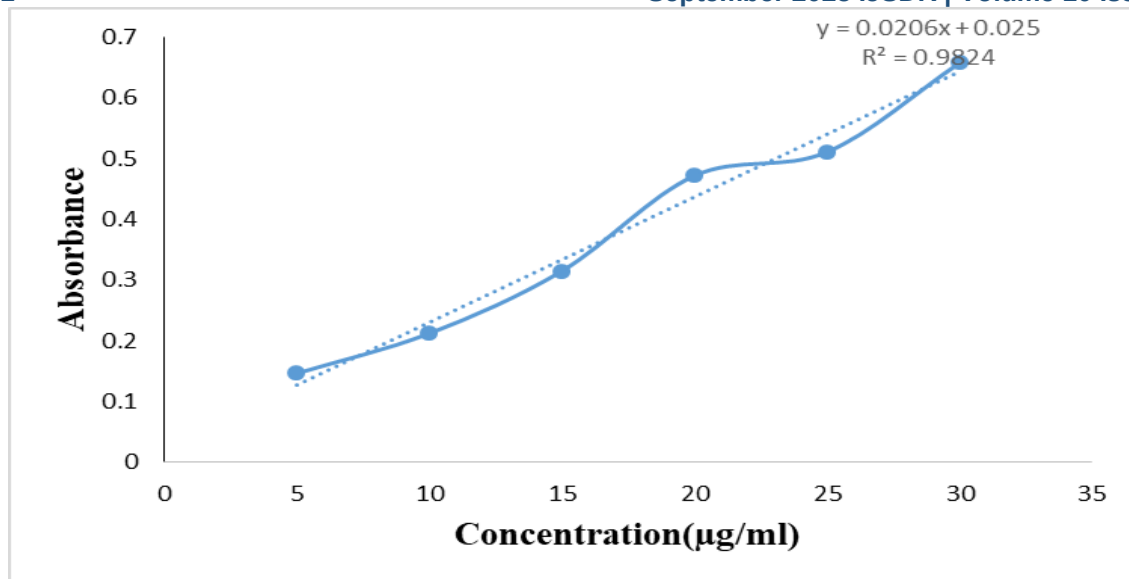


FIGURE 19: CALIBRATION CURVE IN PHOSPHATE BUFFER PH 7.4

Equation	Y=0.0206x+0.025
Correlation coefficient(R ²)	0.9824

7.1.2.2.6 Calibration curve in Acidic buffer pH 1.2

The calibration curve constructed in the acidic buffer at pH 1.2 exhibits a strong linear relationship between concentration and absorbance, as indicated by the equation $y = 0.0092x + 0.0095$ and a correlation coefficient of 0.9749. This linear correlation signifies the reliability of the spectrophotometric method employed for analysis within the tested concentration range. The equation derived from the curve fitting accurately quantifies the concentration of the analyte within this pH range, demonstrating the suitability of the method for precise and accurate measurements in acidic conditions

TABLE 18: CALIBRATION CURVE IN ACIDIC BUFFER PH 1.2

Concentration (µg/ml)	Absorbance
0	0.0000
2	0.0326
4	0.0442
6	0.0625
8	0.0722
10	0.1012
12	0.1228

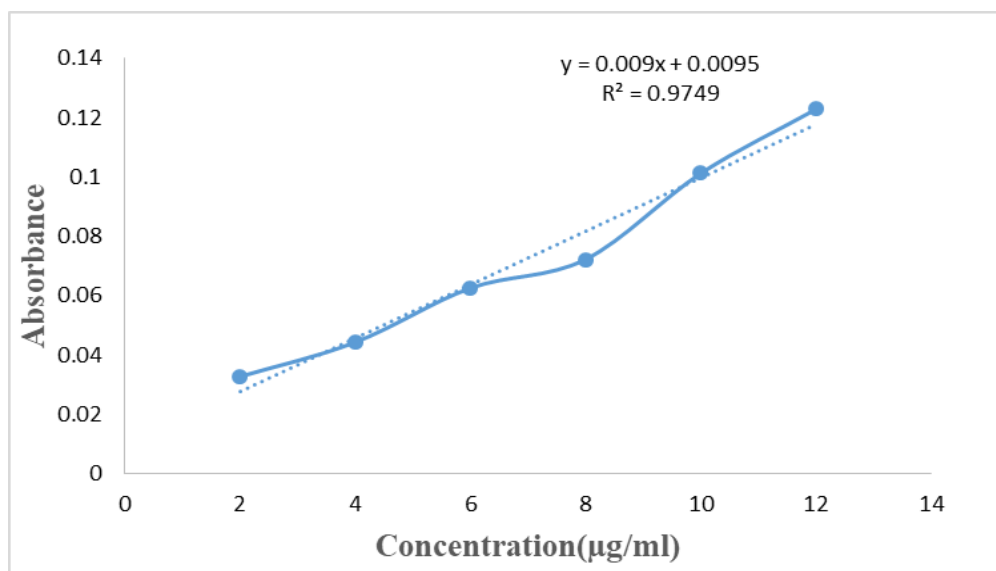


FIGURE 20: CALIBRATION CURVE IN ACIDIC BUFFER PH 1.2

Equation	$y = 0.009x + 0.0095$
Correlation coefficient(R^2)	0.9749

1. Angle of Repose-o

Batch F3 emerges as the optimized choice. It exhibits a mean angle of repose (θ) of 20.80 degrees, with consistent measurements across three trials and a standard deviation of ± 0.4 . While there is some variability indicated by the standard deviation, the mean angle falls within an acceptable range. Additionally, Batch F3 is labeled with a classification of "Excellent" for angle of repose, indicating highly desirable flow properties. Therefore, Batch F3 is recommended as the preferred option for ensuring optimal flow consistency during pre-compression processes, contributing to the overall quality and uniformity of tablet manufacturing.

TABLE 19: PRE COMPRESSION EVALUATION PARAMETERS ANGLE OF REPOSE
(θ)

Batch	Heig ht of pile (h) in cm	Radius (r) in cm			Angle of Repose (θ)			Mean θ	S.D (±)	Angle of repose
					θ1	θ2	θ3			
		r1	r2	r3						
F1	1.3	2.4	2.5	2.7	28.36	27.47	25.64	27.16	±1.3	Good
F2	1.1	2.6	2.4	2.5	22.78	24.7	23.74	23.74	±0.9	Excellent
F3	1.2	2.6	2.5	2.6	20.8	20.30	21.3	20.80	±0.4	Excellent
F4	1.5	2.8	2.7	2.6	28.36	29.24	30.11	29.24	±0.8	Good
F5	1.4	2.5	2.5	2.8	29.24	29.24	26.56	28.35	±1.4	Good
F6	1.4	2.8	2.7	2.7	26.56	27.47	27.47	27.17	±0.4	Good
F7	1.2	2.9	2.7	2.6	22.29	23.74	24.7	23.58	±1.1	Excellent
F8	1.1	2.4	2.6	2.8	24.7	22.78	21.30	22.93	±1.6	Excellent
F9	1.4	2.4	2.6	2.7	30.11	28.36	27.47	28.65	±1.2	Good

$\pm$ S.D. n=3

2. Bulk density

TABLE 20: PRE COMPRESSION EVALUATION PARAMETERS- BULK DENSITY

Batch	Mass of powder M (gm)	Bulk volume of powder V ₀			Bulk density Db			Mean Db	S.D. ±
					Db1	Db2	Db3		
		V01	V02	V03					
F1	25.003	65	64	61	0.38	0.39	0.41	0.40	±0.00
F2	25.002	65	64	62	0.38	0.39	0.40	0.39	±0.00
F3	25.004	61	62	62	0.41	0.40	0.40	0.41	±0.00
F4	25.003	63	60	62	0.40	0.42	0.40	0.41	±0.00
F5	25.002	61	62	61	0.41	0.40	0.41	0.41	±0.00
F6	25.002	68	65	62	0.37	0.38	0.40	0.39	±0.01
F7	25.04	63	65	64	0.40	0.39	0.39	0.39	±0.00
F8	25.002	64	63	61	0.39	0.40	0.41	0.40	±0.00
F9	25.002	65	64	62	0.38	0.39	0.40	0.39	±0.00

±S.D. n=3

1. Tapped density (TD):

TABLE 21: PRE COMPRESSION EVALUATION PARAMETERS- TAPPED DENSITY.

Batch	Mass of powder	Tapped volume of powder V_t	Tapped density Dt			Mean Dt	S.D. $\pm$
			Dt1	Dt2	Dt3		

	M (gm)	V_{t1}	V_{t2}	V_{t3}					
F1	25.003	55	58	57	0.45	0.43	0.44	0.44	± 0.00
F2	25.002	57	55	54	0.44	0.45	0.46	0.45	± 0.00
F3	25.003	58	59	57	0.43	0.42	0.44	0.43	± 0.00
F4	25.003	57	56	55	0.44	0.45	0.45	0.45	± 0.00
F5	25.001	57	57	56	0.44	0.44	0.45	0.44	± 0.00
F6	25.003	58	57	56	0.43	0.44	0.45	0.44	± 0.01
F7	25.04	54	55	56	0.46	0.46	0.45	0.46	± 0.00
F8	25.002	53	52	55	0.47	0.48	0.45	0.47	± 0.00
F9	25.002	51	53	55	0.49	0.47	0.45	0.47	± 0.00

$\pm$ S.D. n=3

2. Carr's Index:

Batch F3 demonstrates optimized characteristics with a tapped density (Dt) of 0.43 and a bulk density (Db) of 0.41. The Carr's Index, which measures the flowability of the batch, is calculated to be 5.7, indicating good flowability. Additionally, the flow character of F3 is labeled as "Excellent." These values suggest that Batch F possesses desirable properties in terms of density, flowability, and consistency, making it suitable for its intended application.

TABLE 22: PRE COMPRESSION EVALUATION PARAMETERS- CARR'S INDEX

Batch	Tapped Density (Dt)	Bulk Density (Db)	Carr's Index	Flow Character
			$100 \times (Dt) - (Db) / (Dt)$	
F1	0.44	0.40	10.5	Excellent
F2	0.45	0.39	13.1	Excellent
F3	0.43	0.41	5.7	Excellent
F4	0.45	0.41	9.2	Excellent
F5	0.44	0.41	7.6	Excellent
F6	0.44	0.39	12.2	Excellent
F7	0.46	0.39	14.1	Excellent
F8	0.47	0.40	14.9	Excellent
F9	0.47	0.39	16.8	Good

5. Hausner's ratio-

In the pre-compression evaluation parameters, batch F3 emerges as the optimized choice with a Hausner ratio of 1.06, indicating excellent flow properties compared to other batches. A low Hausner ratio suggests improved powder flowability, crucial for consistent tablet compression and uniformity in tablet quality. Batch F3's optimal flow characteristics signify efficient manufacturing processes, potentially leading to enhanced production yields and consistent tablet performance.

TABLE 23:PRE COMPRESSION EVALUATION PARAMETERS HAUSNER'S RATIO

Batch	Tapped Density (Dt)	Bulk Density (Db)	Hausner Ratio	Flow Character
F1	0.44	0.40	1.12	Good
F2	0.45	0.39	1.15	Good
F3	0.43	0.41	1.06	Excellent
F4	0.45	0.41	1.10	Excellent
F5	0.44	0.41	1.08	Excellent
F6	0.44	0.39	1.14	Good
F7	0.46	0.39	1.16	Good
F8	0.47	0.40	1.18	Good
F9	0.47	0.39	1.20	Good

Evaluation of Tablets (Post compression parameters)

1. Organoleptic properties

All batches (F1-F9) were assessed for organoleptic properties like color, odor, and taste and found to be acceptable in all aspect.

General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour and texture.

a. Shape- Round

b. Colour- off white

c. Texture- Crystalline.

From the results obtained it was found that F1-F9 formulations has hardness, weight variation & friability within IP limit.

2. Weight Variation

Formulations F1 to F9, F3 exhibits the lowest weight variation at 0.40%, indicating superior consistency in tablet weights compared to the others. Therefore, F3 is the optimized batch, ensuring better dosage accuracy and patient safety.

TABLE 24: WEIGHT VARIATION

Sr. No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Weight variation (%)	0.45	0.46	0.36	0.42	0.48	0.44	0.49	0.51	0.43

ANOVA for 2FI model

Response 2: Weight variation

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0124	3	0.0041	6.25	0.0382	significant
A-Sodium bicarbonate	0.0081	1	0.0081	12.29	0.0172	
B-Citric acid	0.0000	1	0.0000	0.0633	0.8114	
AB	0.0042	1	0.0042	6.40	0.0526	
Residual	0.0033	5	0.0007			
Cor Total	0.0157	8				

Factor coding is **Coded**. Sum of squares is **Type III – Partial**. The **Model F-value** of 6.25 implies the model is significant. There is only a 3.82% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.0257	R^2	0.7894
Mean	0.4489	Adjusted R^2	0.6631
C.V. %	5.73	Predicted R^2	0.3296
		Adeq Precision	7.5114

The **Predicted R^2** of 0.3296 is not as close to the **Adjusted R^2** of 0.6631 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.511 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Weight variation	=
+0.4489	
-0.0319	A
-0.0023	B
+0.0325	AB

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Weight variation	=
+5.40887	
-0.046383	Sodium bicarbonate
-0.049671	Citric acid
+0.000464	Sodium bicarbonate * Citric acid

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

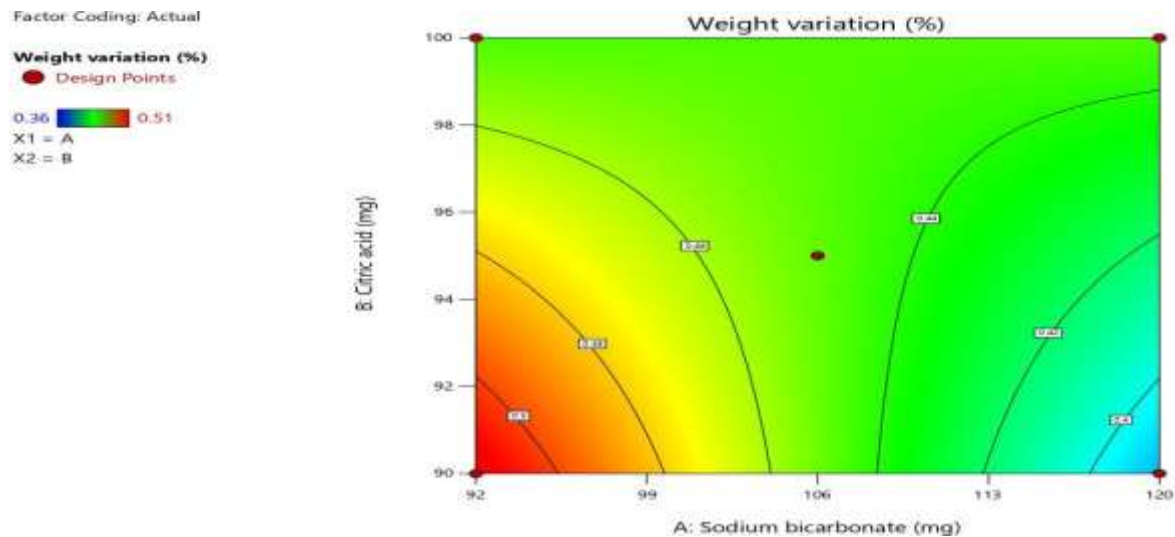


FIGURE 21: COUNTER PLOT

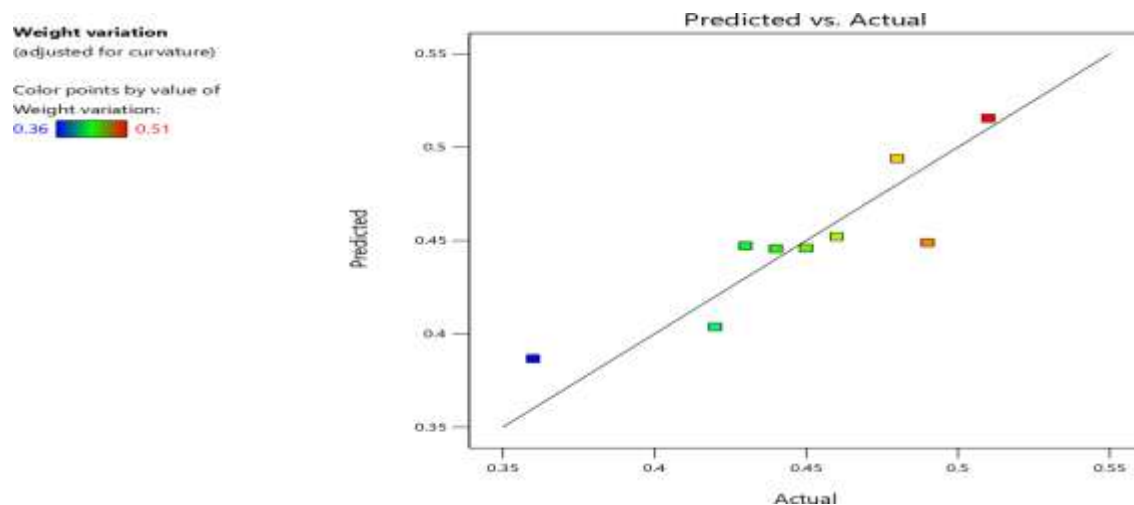


FIGURE 22 : PREDICTED VS. ACTUAL PLOT

Factor Coding: Actual

3D Surface

Weight variation (%)

Design Points:

● Above Surface

○ Below Surface

0.36 0.51

X1 = A

X2 = B

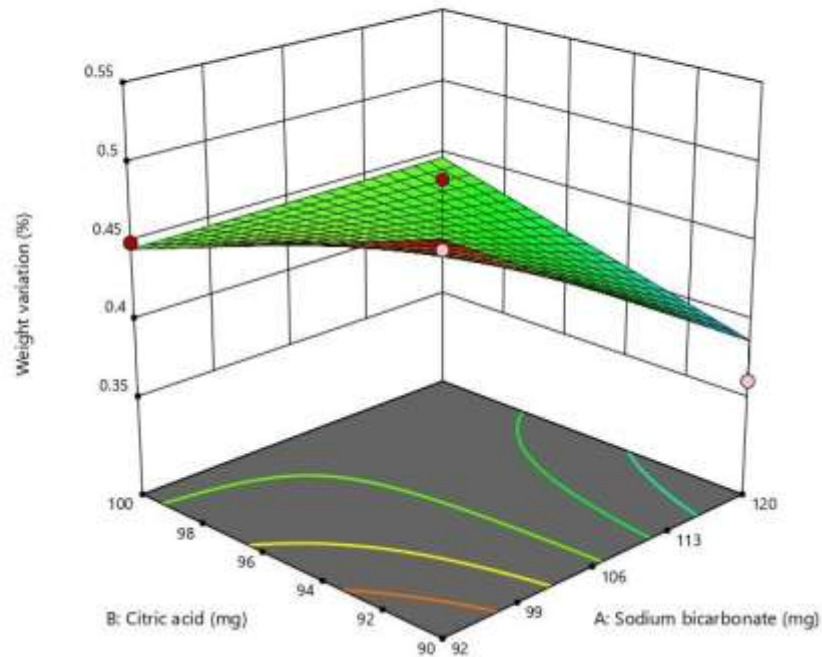


FIGURE 23: 3 SURFACE PLOT

3. Thickness

In the tablet thickness results provided for formulations F1 through F9, with batch F5 identified as the optimized batch, it's evident that F5 exhibits a thickness of 2.53 mm, which is one of the lowest among the batches. This indicates that tablets from batch F5 are relatively thin compared to the others. While a lower thickness can imply uniformity and precision in manufacturing, it's essential to ensure that this thickness falls within acceptable regulatory standards and formulation requirements. Therefore, batch F5's favorable thickness suggests good manufacturing practices and may contribute to consistent dosage delivery and patient experience. However, comprehensive evaluations considering various factors such as stability, dissolution rate, weight variation, and regulatory compliance are necessary before finalizing its suitability for large-scale production or commercialization.

TABLE 25: TABLET PARAMETERS (BATCH F1-F9) - THICKNESS.

Formulation code	Thickness(mm)	S.D. ±
F1	2.54	±0.12
F2	2.56	±0.23
F3	2.62	±0.156
F4	2.63	±0.02
F5	2.53	±0.03
F6	3.21	±0.45
F7	2.65	±0.34
F8	2.35	±0.44
F9	3.56	±0.46

5. Friability test:

The friability test results, where friability is calculated as the percentage of weight loss of tablets before and after the test, it is evident that batch F8 demonstrates the lowest friability at 0.06%. Therefore, F5 is identified as the optimized batch due to its superior resistance to crumbling or breakage during handling or transportation.

TABLE 26: TABLET PARAMETERS (BATCH F1-F9) - FRIABILITY TEST.

Batch	weight of tablets before test (W1)	weight of tablets after test (W2)	Friability % $\% \text{Friability} = [(W1 - W2)/W1] \times 100$
F1	301.2	300.2	0.33
F2	300.5	299.0	0.51
F3	300.0	299.2	0.28
F4	300.3	299.0	0.42
F5	300.0	299.8	0.06
F6	302.0	300.9	0.38
F7	301.0	300.0	0.33
F8	300.5	300.0	0.17
F9	299.9	298.5	0.47

7. Hardness

TABLE 27: TABLET PARAMETERS (BATCH F1-F9) - HARDNESS TEST

Formulation code	Hardness	S.D. ±
F1	4.4	±0.00
F2	4.7	±0.00
F3	4.1	±0.00
F4	4.8	±0.00
F5	4.4	±0.00
F6	4.9	±0.00
F7	5.1	±0.00
F8	5.2	±0.00
F9	5.3	±0.00

ANOVA for 2FI model Response 1:

Hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.08	3	0.3583	7.31	0.0282	significant
A-Sodium bicarbonate	0.0167	1	0.0167	0.3411	0.5845	
B-Citric acid	0.0583	1	0.0583	1.19	0.3252	
AB	1.0000	1	1.0000	20.41	0.0063	
Residual	0.2450	5	0.0490			
Cor Total	1.32	8				

Factor coding is Coded.Sum of squares is **Type III – Partial**

The **Model F-value** of 7.31 implies the model is significant. There is only a 2.82% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case AB is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.2214	R²	0.8144
Mean	4.77	Adjusted R²	0.7030
C.V. %	4.64	Predicted R²	0.5232
		Adeq Precision	7.9331

The **Predicted R²** of 0.5232 is in reasonable agreement with the **Adjusted R²** of 0.7030; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.933 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Hardness	=
+4.77	
+0.0457	A
+0.0854	B
+0.5000	AB

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Hardness	=
+74.72739	
-0.675306	Sodium bicarbonate
-0.740072	Citric acid
+0.007143	Sodium bicarbonate * Citric acid

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Factor Coding: Actual
Hardness ((kg/cm³))
 ● Design Points
 4.1 5.3
 X1 = A
 X2 = B

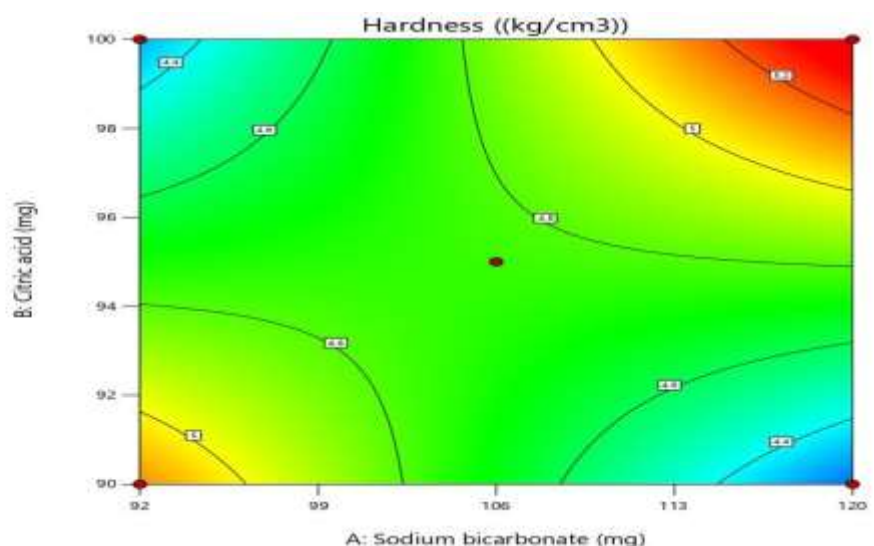


FIGURE 24 : HARDNESS

Hardness
(adjusted for curvature)

Color points by value of
Hardness:
4.1 5.3

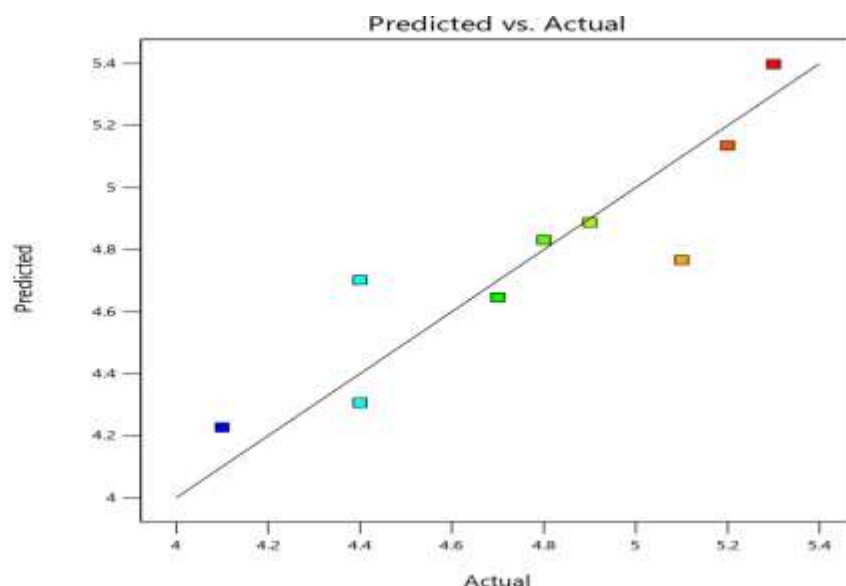


FIGURE 25: PREDICTED VS ACTUAL

Factor Coding: Actual

Hardness ((kg/cm3))

Design Points:

● Above Surface

○ Below Surface

4.1 5.3

X1 = A

X2 = B

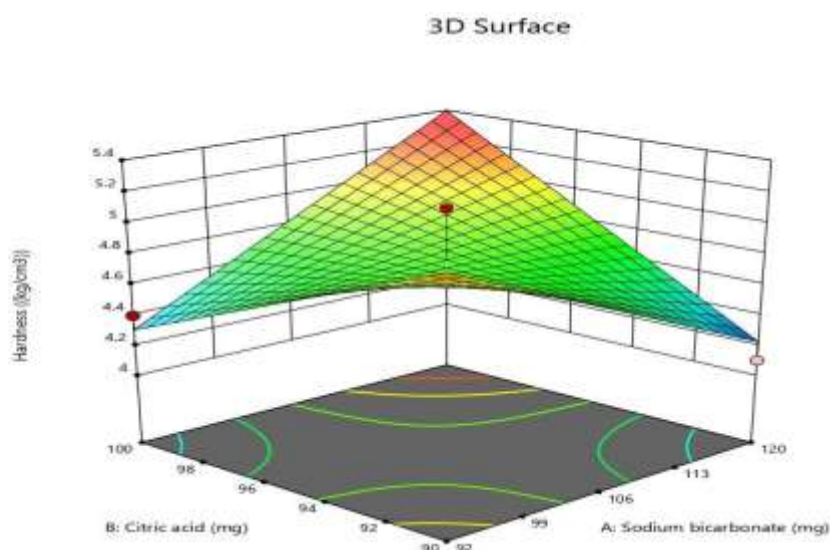


FIGURE 26 : 3D SURFACE

7. Drug Content (%)

Formulation F3 demonstrates a notably higher drug content percentage of 97.24%. This elevated drug content surpasses that of the other formulations, indicating a potentially superior potency and concentration of the active pharmaceutical ingredient (API) within the optimized batch. While other formulations, such as F8 and F9, also exhibit relatively high drug content percentages, they fall short of the exceptional level achieved by F3. The optimized formulation's significantly higher drug content suggests an effective formulation strategy, potentially involving optimized excipient selection, manufacturing processes, or dosage adjustments. However, it's crucial to recognize that high drug content alone does not necessarily guarantee optimal performance. Factors such as formulation stability, manufacturing

reproducibility, and overall product quality must also be carefully evaluated to determine the superiority of F3 over other batches comprehensively.

TABLE 28: DRUG CONTENT OF F1-F9

Formulation code	Drug content (%)
F1	90.15
F2	89.62
F3	97.24
F4	94.44
F5	93.99
F6	92.46
F7	94.41
F8	96.68
F9	96.12

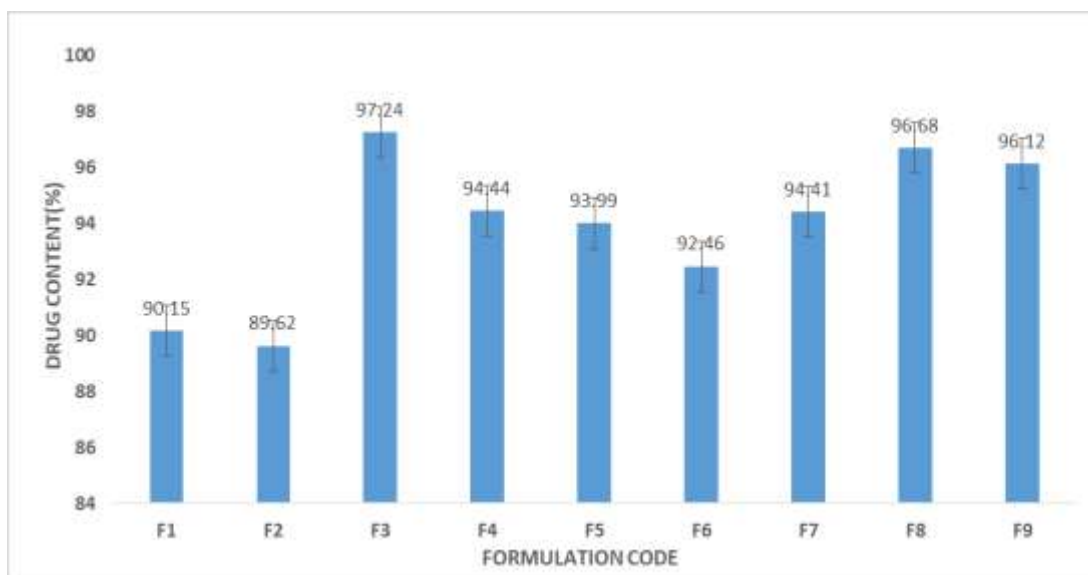


FIGURE 27: DRUG CONTENT OF F1-F9 BATCHES

8. Dissolution Study:-

The drug release profile of batch F3, reaching 96.5% drug is releases at the end of 8 hours, signifies its exceptional performance compared to the other batches tested. This achievement demonstrates batch F3's superior ability to release the drug compound within the specified timeframe, surpassing the drug release rates of the other batches. Consequently, batch F3 emerges as the leading candidate for pharmaceutical formulations, indicating its potential for efficient drug delivery.

TABLE 29: CUMULATIVE DRUG RELEASE (F1-F9)

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.5	10.0	14.5	10.1	12.3	13.7	11.8	10.6	15.4
2	20.6	18.2	20.5	22.3	25.8	24.7	23.5	22.9	25.9
3	30.8	36.3	29.5	30.6	35.8	38.4	33.7	32.8	35.6
4	40.5	39.5	45.8	46.3	44.8	42.7	48.6	45.2	47.6
5	50.7	50.3	65.6	54.8	62.7	58.9	57.5	56.2	57.9
6	60.1	76.5	63.8	68.1	72.2	64.8	77.5	62.8	61.3
7	78.6	88.8	77.9	78.7	83.0	75.8	89.3	75.8	79.8
8	90.5	82.2	96.5	85.5	84.5	89.6	87.8	90.4	87.1

Value are expressed as mean $\pm$ std

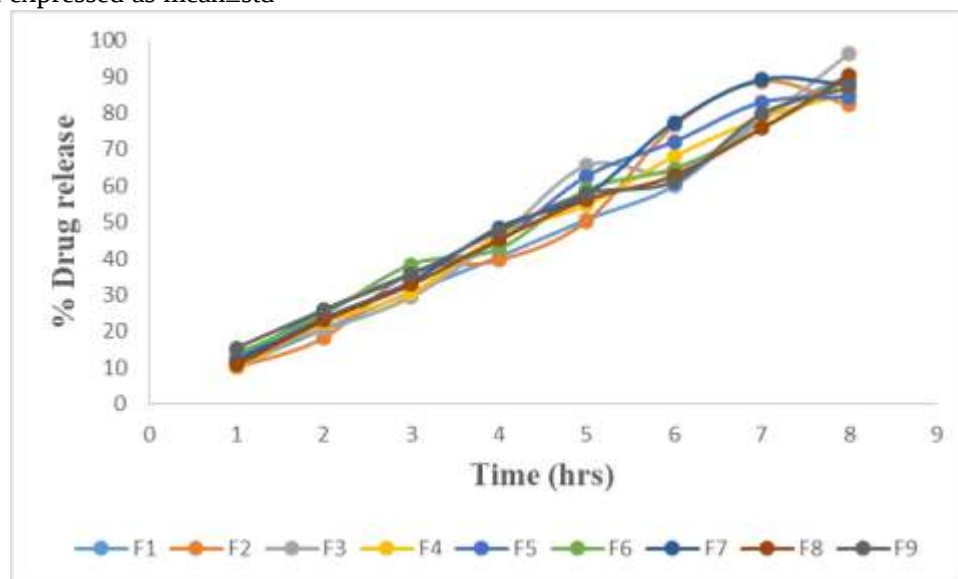


FIGURE 28: % DRUG RELEASE OF F1-F9

Kinetic analysis of drug release-

In order to define the release mechanism that gives the best description of the release pattern; the in vitro release data for all optimized batches were fitted to kinetic equations models.

The kinetic equations were used i.e., zero, first-order and Higuchi model. Both the kinetic rate constant (k) and the determination coefficient (R²) were calculated and presented in below graphs. The best fit model with the highest determination coefficient (R²) value for optimized batch was Higuchi model.

ANOVA for Quadratic model

Response 3: Drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	169.67	5	33.93	10.04	0.0432	significant
A-Sodium bicarbonate	3.44	1	3.44	1.02	0.3874	
B-Citric acid	37.55	1	37.55	11.11	0.0446	
AB	23.14	1	23.14	6.85	0.0792	
A ²	100.84	1	100.84	29.84	0.0121	
B ²	65.02	1	65.02	19.24	0.0219	
Residual	10.14	3	3.38			
Cor Total	179.81	8				

Factor coding is Coded. Sum of squares is **Type III – Partial**

The **Model F-value** of 10.04 implies the model is significant. There is only a 4.32% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B, A², B² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	1.84	R²	0.9436
Mean	91.44	Adjusted R²	0.8496
C.V. %	2.01	Predicted R²	NA ⁽¹⁾
		Adeq Precision	10.5542

⁽¹⁾ Case(s) with leverage of 1.0000: Pred R² and PRESS statistic not defined.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.554 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Drug release	=
+82.00	
+0.6556	A

CONCLUSION

The Preformulation study of aspirin included organoleptic evaluations, melting point determination, solubility analysis in various media, and UV spectrophotometric characterization. Organoleptic assessment indicated that the aspirin blend was off-white, with an acetic acid odor and a crystalline texture. The observed melting point of aspirin was 135°C, consistent with the reported range of 133-137°C. Solubility tests revealed varying solubility across different media, with the highest in ethanol (42.06 mg/ml) and the lowest in phosphate buffer pH 6.8 (32.76 mg/ml). UV spectrophotometric analysis confirmed an absorption maxima (λ_{max}) at 265 nm, and calibration curves in different solvents demonstrated strong linear relationships between concentration and absorbance, underscoring the reliability of the spectrophotometric method for quantifying aspirin. Additionally, pre-compression parameters, such as angle of repose, bulk density, tapped density, Carr's Index, and Hausner's ratio, indicated that batch F3 exhibited excellent flow properties, making it the optimal choice for tablet manufacturing. Post-compression evaluations, including weight variation, thickness, friability, and hardness, further identified batch F3 as having the most favorable characteristics, particularly in terms of thickness and friability, ensuring consistent dosage delivery and robustness of the final tablet product.

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