

Pediatric Oral Jelly Medications: A Comprehensive Review of Pharmaceutical Formulations

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Abstract- With the current advancements in medication delivery, administering a medicine orally is still the most convenient and favored method for achieving higher therapeutic benefits, which promotes patient compliance. The most appealing dose forms for children are medicated oral jellies, which may be consumed without water. It is a substitute for dose forms that are liquid and solid. The oral medicated jelly is made by heating several types of polymer in varying concentrations. Since the majority of pharmaceutical medications have an unpleasant taste, taste masking which is mostly accomplished by adding sugar and flavors is a crucial consideration when creating the dosage form. Numerous assessment metrics, such as viscosity, in vitro drug release, synergesis, and drug content, are used. - Oral, medicated jelly, pediatric, taste masking, gelling agent.

Key points: Oral, medicated jelly, pediatric, taste masking, gelling agent.

1.INTRODUCTION

Oral administration stands out as the foremost convenient and widely favored route for administering a wide array of pharmaceutical drugs. This preference stems from its inherent advantages in pharmacotherapy, primarily attributed to its cost-effectiveness and the straightforward nature of administration. This contributes to patients being more likely to follow their prescribed treatment.[1] Considered the most natural, uncomplicated, and convenient means of drug administration, oral dosage forms offer unparalleled flexibility in design, ease of production, and affordability. The simplicity of self-administration, coupled with their compactness and straightforward manufacturing process, underscores their widespread adoption. However, a notable drawback of conventional oral dosage forms, such as tablets, lies in the challenge of swallowing, leading to noncompliance among patients, particularly in pediatric and geriatric populations. This issue extends to individuals bedridden due to illness and those actively engaged in work or travel, especially in environments lacking access to water. In response to these medical challenges, pharmaceutical technologists have introduced a novel oral dosage form known as Oral Medicated Jellies (OMJs), which rapidly disintegrate in saliva, typically within seconds, without the need for water. This unique property facilitates swift drug dissolution, absorption, and onset of clinical effect, potentially enhancing drug bioavailability compared to conventional forms. Over the past decade, the demand for OMJs has surged significantly due to their profound impact on patient compliance, particularly among populations struggling with swallowing difficulties. OMJs have garnered appreciation from various segments of the population, particularly those with dysphagia (difficulty in swallowing). Dysphagia is prevalent across all age groups, with a higher prevalence among pediatric and geriatric populations, as well as institutionalized patients, psychiatric patients, and those experiencing complications like nausea, vomiting, and motion sickness. It's estimated that dysphagia affects approximately 35% of the general population, up to 60% of the elderly institutionalized population, and 18-22% of all patients in long-term care facilities. The incorporation of pleasing taste and flavors in OMJs enhances the acceptability of bitter drugs across different demographic groups. Jelly, characterized as a transparent or translucent non-greasy semisolid preparation, serves as a versatile vehicle for both external and internal applications. Over time, medicated jelly has garnered increasing acceptance as an effective drug delivery system. Incorporating various ingredients, including drugs necessitating rapid onset of action or those primarily absorbed in the stomach and small intestine, medicated jellies can be formulated from natural gums like tragacanth, pectin, and sodium alginates, or synthetic derivatives such as methyl cellulose and sodium carboxymethyl cellulose. Particularly appealing to children, jellies offer a preferred method of drug administration over oral liquids or tablets. The versatility of medicated jelly extends to both local treatments for oral cavity diseases and systemic conditions.

2. TYPES OF JELLIES:

2.1 Medicated jelly

Medicated jelly is a type of jelly that is used to cover mucous membranes and skin. It contains spermicides, local anaesthetics, and anti-inflammatory properties. It contains a sufficient amount of water that evaporates and provides local cooling, while the remaining film provides protection. Examples of medicated jelly include Ephedrine sulfate jelly, which is used to stop the bleeding of the nose due to its vasoconstriction properties.

2.2 Lubricating jelly:

These jelly beans are meant to lubricate instruments used in diagnostics, such as cytosopes, catheters, and surgical gloves.

2.3 Miscellaneous jelly:

These are intended for a number of uses, including electrocardiography and patch testing.

Jellies have an adequate amount of water. Water jelly evaporation produces a leftover film that offers protection as well as a localized cooling effect. Ephedrine sulphate jelly, for instance, is used as a vasoconstrictor to stop nasal bleeding. To set oral medicated jellies apart from more typical dosage forms, they should have a few perfect features. One of these dosage forms' key advantages is that it doesn't require water to be swallowed; instead, it should dissolve or disintegrate in the mouth in a matter of seconds.

After oral administration, the gelling agent should leave little to no residue in the mouth and be pleasant to the touch.

- Work well with flavor masking.
- Technologies that effectively disguise taste should be used for drugs with bitter tastes.
- Be transportable and unaffected by fragility.
- After oral delivery, leave very little to no residue in the mouth.
- Permit high drug loading.
- The oral disintegrating tablet shouldn't be impacted by the medicine or excipient properties.

3. CHALLENGES IN FORMULATING ORAL MEDICATED JELLY

- Palatability: Improving flavor and hiding the bitter taste of the medication are strongly linked to patient compliance.
- Hygroscopicity: Certain oral jelly dose forms require specific product packaging because they are hygroscopic and need to be protected from humidity.
- The drug's solubility, crystal shape, particle size, and bulk density all had an impact on the final jelly properties.
- Mouth feel: After oral treatment, medicated jelly leaves little to no trace in the mouth.

4. OBJECTIVES OF ORAL MEDICATED JELLIES

To create a formulation with a local or systemic impact that dissolves in the throat

1. To improve patient adherence
2. Using an insoluble medication in medicated jelly
3. Chipper dosage form formulation followed by standard formulation. [2,3]

The term "oral mucosa" refers to the delicate tissue that lines the inside of the mouth. It includes several key components:

- Mucosa
- Epithelium
- Lamina propria and
- Submucosa.

Saliva continuously cleanses the oral mucosal surface, which covers approximately 100cm². The turnover rate ranges from 0.5 to 2 liters daily. The dynamic structure of the oral mucosa serves important functions. [3]

4.1. The oral mucosa is classified into three main types, each serving distinct functions and exhibiting unique characteristics:

1. Lining Mucosa: This type of oral mucosa lines the inner surfaces of the cheeks, lips, and soft palate, providing protection and facilitating movement within the oral cavity. It is predominantly non-keratinized, featuring a moist surface that aids in speech, mastication, and swallowing.
2. Masticatory Mucosa: Found on the gingiva and hard palate, masticatory mucosa is specialized for withstanding the mechanical stresses of chewing and grinding food. It is primarily keratinized, featuring a tough outer layer that provides resilience against abrasion and friction.
3. Specialized Mucosa: This type of oral mucosa is found on the dorsum of the tongue and in the taste buds. It has unique structural and functional characteristics that are tailored to specific sensory and gustatory functions, such as taste perception and food manipulation during mastication.

The distinction between keratinized and non-keratinized oral mucosa further defines their structural properties and functional roles.

- **Keratinized Oral Mucosa:** This type is predominantly associated with masticatory mucosa and has a stratified squamous epithelium with a tough outer layer of keratin. It offers improved resistance to mechanical stress and abrasion while chewing.
- **Non-keratinized Oral Mucosa:** Similar to lining and specialized mucosa, this type lacks the tough, keratinized layer found in masticatory mucosa. Instead, it maintains a moist, pliable surface that allows for various oral functions such as speech and swallowing.

Despite its classification into these distinct types, the oral mucosa has similarities in composition and function, particularly in the production and role of mucus. Salivary glands secrete mucus into the oral cavity, and saliva contains roughly 70% mucin, a key component of mucus. At physiological pH, mucus has a crisscross structure with a negative charge, which promotes mucoadhesion—a process in which mucus forms a cohesive gel structure that adheres strongly to the epithelial cell surface. This gelatinous layer helps to lubricate, protect, and form barriers within the oral cavity, emphasizing the importance of mucus in maintaining oral health and function. [4]

4.2. The oral mucosa serves numerous functions that are essential for maintaining oral health and comfort:

1. Protection

The oral mucosa acts as a barrier, protecting the underlying tissues from abrasions caused by rough materials and chemical irritants. This function is dependent on saliva, which acts as a protective fluid.

2. Sensation

Sensory receptors in the oral mucosa detect a variety of stimuli, such as taste, temperature, and texture, which contribute to the sensory experience of eating and drinking.

3. Secretion

Saliva, a key secretion of the oral mucosa, lubricates food for easier swallowing, facilitates speech, and contributes to oral hygiene by rinsing away food particles and bacteria.

4. Thermal Regulation

The oral mucosa helps to keep the oral cavity at an optimal temperature, allowing food and beverages to be processed comfortably and regulating overall body temperature.

5. Permeability and Absorption

The oral mucosa is permeable, certain substances, such as medications administered orally, can be absorbed into the bloodstream, thereby facilitating therapeutic effects. Saliva flow rate and pH, which vary with stimulation levels, can influence absorption rate.

Saliva, which contains about 1% organic and inorganic materials, is essential for these functions. Its composition and flow rate, which are affected by a variety of factors such as the type and intensity of stimulation, play an important role in the oral mucosa's overall effectiveness in performing its various functions. Saliva's pH ranges from 5.6 to 7.9, with variations caused by factors such as saliva flow rate, which further influences its protective and regulatory roles in the oral environment. [5]

5. GASTROINTESTINAL TRACT :

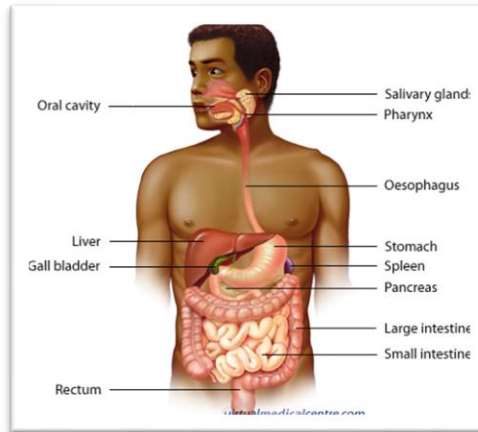


Figure 1: Gastrointestinal Tract [6]

It extends from the mouth to the anus and is divided into two sections:

1. Upper GIT.
2. Lower GI.

It measures about 9 meters (30 feet) and secretes various hormones to regulate the digestive process.

The GI is divided into layers:

1. Mucosa
2. Submucosa
3. Muscular Layer

Serosa and Adventitia FUNCTIONS OF GIT:

1. Digestion
2. Absorption.
3. Excretion.
4. Protection.

The pH of the upper portion is 4-6.5, while the pH of the lower portion is 1.5–4.

6. TASTE MASKING

For oral administration, a pleasant taste is preferred for children as it is a key pharmaceutical parameter. Taste buds play the role of taste, and there are approximately 10,000. Chemoreceptors send signals to the brain, allowing it to perceive taste. Because most pharmaceutical drugs have a bitter taste, taste masking is an important parameter in designing the dosage form, which is primarily accomplished by adding sweeteners and flavors.

Types of Taste:

Human tongue

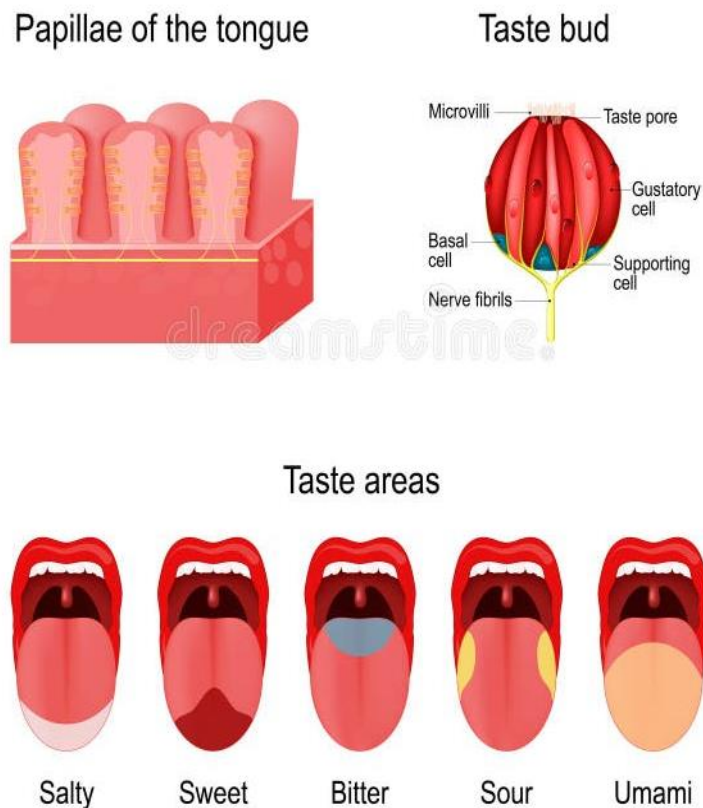


Figure 2: Different types of taste on the tongue. [7]

Types of Taste:

1. Sweet
2. Salty
3. Sour
4. Bitter.
5. umami.

The tongue is a muscular structure with a reddish pink color, V-shape, and grooves located inside the mouth.

Functions include:

1. Assistance with in taste
2. Assistance with speech.

Help with chewing and swallowing food. Tongue Parts:

1. Papillae
2. Sulcus terminalis.
3. Tonsils
4. Adenoids
5. Frenulum linguae

TASTE BUDS:

The taste buds are the small pores on the surface of the tongue called papillae.

It consists of three types:

1. Fungiform papillae
2. foliate papillae
3. Circumvallate papillae

Its structure is similar to that of an onion, with a group of receptor cells (50-100 cells) that transmit taste perception to the CNS via sensory neurons. There are four types of taste on the tongue in different regions, including sweet on top, sour on the sides, salty on the edges and upper portion, and bitter on the back. [8]

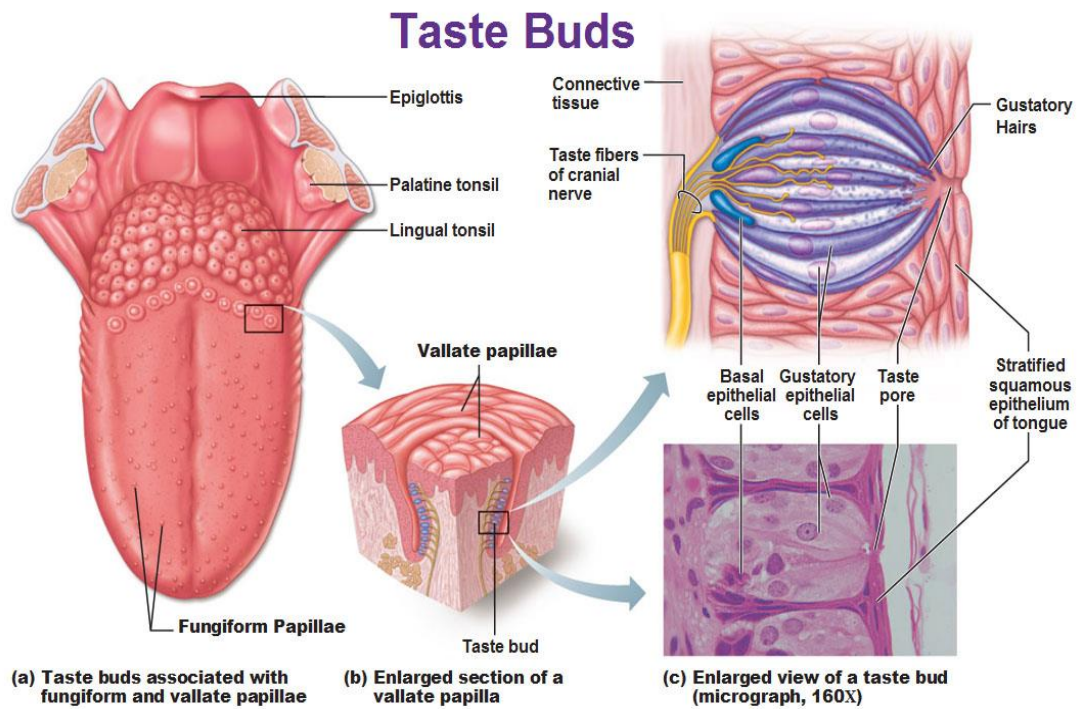


Fig. 3: Activity of taste buds. [9]

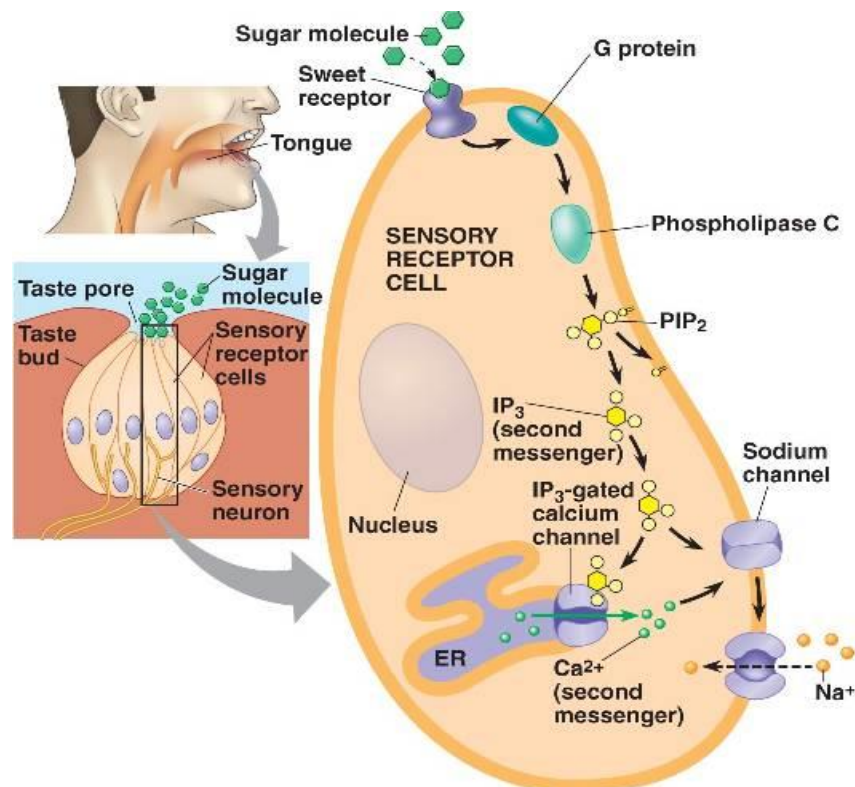


Fig.4: Mechanism of action. [10]

MECHANISM OF ACTION:

Molecular weight salts or compounds like free base. The stanza describes the complex process by which the sensation of taste is elicited, shedding light on the molecular mechanisms underlying this physiological phenomenon. Taste perception begins with the activation of taste buds, which are specialized chemoreceptors found on the tongue and other areas of the oral cavity. Chemicals, such as drugs, dissolved in saliva stimulate these taste buds. When these

chemicals bind to specific G-protein coupled receptors (GPCRs) on taste receptor cells' surfaces, a signaling cascade is initiated.

The binding of chemicals to GPCRs activates gustducin, a G-protein that acts as a key mediator in the taste transduction pathway. Gustducin, in turn, activates effector enzymes like phosphodiesterase IA and phospholipase C beta 2. These enzymes regulate the levels of intracellular second messengers such as cAMP, IP3, and DAG.

Changes in these second messengers' intracellular levels set off a chain reaction that eventually activates ion channels within taste receptor cells. This activation causes the cell membrane to depolarize, resulting in electrical signals transmitted as nerve impulses through sensory nerve fibers.

Nerve impulses travel to the brain, specifically to areas responsible for taste perception, where they are processed and interpreted. This neuronal activity culminates in the conscious perception of taste, which allows people to distinguish between sweet, sour, salty, bitter, and umami.

To summarize, the mechanism of taste perception involves a complex interplay of molecular events within taste receptor cells, which eventually leads to neural signal transmission to the brain and taste perception. This intricate process demonstrates the human gustatory system's remarkable sensitivity and specificity in detecting and discriminating between various tastants. [11]

7. INTERACTION BETWEEN TASTE AND COMPOUND ACCORDING TO CHEMICAL STRUCTURE:

Chemical structure and taste are interconnected. The degree of ionization, solubility, and types of ions produced in saliva undoubtedly influence the perception interpreted by the brain. The sweet taste is caused by polyhydroxy compounds, polyhalogenated aliphatic compounds, and amino acids. The positive effect is balanced by the presence of a negative group, amino and amide, which can produce a sweet taste. With an increase in the number of hydroxyl groups, solubility increases, and so does sweetness. Sour taste is caused by hydrogen ions and is directly proportional to the lipid solubility and hydrogen ion concentration of the compound. Salt taste results from the presence of both an anion and a cation, such as ammonium chloride, potassium bromide, and sodium salicylate. These are the characteristics of acids, alum, lactones, tannins, and phenols. Bitter taste is caused by high levels of alkaloids and amides. [12]

Specific area of tongue and threshold concentration for primary taste sensations (13)

Taste	Area of tongue	Threshold concentrations (%)
Sweet (sucrose)	Tip	0.5
Salt (NaCl)	Tip and sides	0.25
Sour (HCl)	Sides	0.007
Bitter (Quinine)	Back	0.00005

Several strategies are used to reduce the bitter taste associated with pharmaceuticals, thereby improving patient compliance and overall therapeutic experience:

1. Changing Drug Solubility: One approach is to reduce the drug's solubility in saliva at pH levels ranging from 5.6 to 6.8. By manipulating the drug's solubility profile, the bitter taste perception can be reduced.
2. Modifying Drug-Receptor Interaction: Another strategy involves changing the drug's inherent nature and affinity for taste receptors. The drug's bitter taste can be reduced by modifying the chemical properties that influence its interaction with taste receptors.

8. FACTORS THAT INFLUENCE THE EFFECTIVENESS OF TASTE MASKING TECHNIQUES

Active Pharmaceutical Dose:

The concentration of the active ingredient in the formulation influences taste perception. Adjusting the dosage to the optimal level can help reduce bitterness.

Particle Size and Distribution:

The size and distribution of drug particles in a formulation can affect taste perception. Finely dispersed particles may provide better taste masking.

Solubility Characteristics:

The drug's solubility in the formulation medium is critical for taste masking. Formulations with lower drug solubility may have reduced bitterness.

Dosage Forms:

The type of dosage form (tablets, capsules, or liquid formulations) can influence taste perception. Different dosage forms have varying levels of taste masking potential.

Ionic Characteristics:

The drug's ionic properties can affect its taste. Manipulating the drug's ionization state within the formulation can help to reduce bitterness.

To summarize, taste masking techniques include a variety of approaches aimed at reducing pharmaceuticals' bitterness. These strategies involve adjusting various formulation parameters to improve taste perception and patient acceptability.

There are various techniques for masking the taste to produce a pleasant taste. They are as follows.

1. Flavours and Sweeteners
2. Prodrug
3. Inclusion complexes
 1. Coating Polymer and Drug Particle
 2. By granulation.
 3. Ion Exchange Resin
 4. Micro-encapsulation
 5. Multiple emulsion technique.
 6. Gelation Technique
 7. Viscosity modification.
 8. Hot melt extrusion.
 9. pH Modifiers
 10. Various. [14]

Advantages of jelly:

1. Patient convenience and ease of administration.
2. Patient Acceptability.
3. The more palatable the formulation, the larger the dose volume that can be tolerated.
4. The choking hazard is reduced.
5. Consumed without water.

Disadvantages of jelly:

1. Stability and degradation issues.
2. Problem with dose measurement.
3. Interpatient variability occurs around the age of six years. [15]

9. EXCIPIENTS USED IN ORAL JELLY FORMULATIONS**A) GELLING AGENTS:**

Pectin, Tragacanth, Gelatine, Xanthan gum, Gellan gum, Carrageenans, and Guar gum. Sodium alginate is a cellulose derivative.

B) STABILIZERS:

- Propylene glycol
- Sorbitol

C) PRESERVATIVES:

- Methylparaben
- Propylparaben
- Benzalkonium chloride
- Sodium benzoate

D) SOLUBILIZERS:

- Cremophor RH40
- PEG 400

E) pH MODIFIERS:

- Citric Acid

F) SWEETENERS:

- Simple syrup
- Acesulfame potassium.

G) Flavors:

- strawberry
- vanilla
- orange

10. LIST OF CHOICE DRUGS ADDED TO ORAL JELLIES

- A) ANTI-HELMINTHICS: - Albendazole - Mebendazole A) ANALGESICS: - Ibuprofen - Paracetamol - Diclofenac
- B) ANTI-EMETICS: Domperidone, Ondansetron, Cetirizine
- C) ANTI-HISTAMINES: Cinnarizine, Cetirizine
- D) ANTAGONISTS OF LEUKOTRIENE: Zafirlukast, Montelukast
- E) ANTI-DIABETICS: - Metformin ,Glibenclamide ,Zafirlukast .

11. PREPARATION METHOD:

1. To make the jellies, various polymers are used in different ratios.
2. A separate recipe is made for sugar syrup.
3. After adding the gelling agent, the sugar syrup is heated and stirred continuously.
4. Stabilizers and solubilizers are added after the gelling agent has fully dissolved, and the mixture is boiled for a few minutes to ensure thorough mixing.
5. Preservatives are added to the mixture and stirred continuously after the mixture has completely dissolved.
6. Next, flavor and color are added, and the drug is added while the mixture is continuously stirred.
7. After allowing the mixture to settle, it is well combined.
8. Purified water is used to adjust the final weight.
9. To create the jelly, the mixture is subsequently poured into molds and left to cool at room temperature.

12. EVALUATIONS FOR ORAL JELLIES:**1) PHYSICAL APPEARANCE**

The oral jelly's texture, consistency, odor, and clarity are evaluated.

2) WEIGHT VARIATION

To ensure uniformity, the average weight of each ten jelly beans is measured after they are taken out of the molds.

3) STICKINESS AND GRITTIENESS

To visually evaluate stickiness and grittiness, rub the jelly between two fingers.

4) POURABILITY OF THE MIXTURE

Taking into account the addition of buffer salts to control gelation, the pourability of the jelly into molds is assessed.

5) pH DETERMINATION

After the jelly has been dissolved in distilled water, its pH is determined with a digital pH meter.

6) CONTENT UNIFORMITY

Crushing and mixing the sample, then extracting and quantifying the drug, ensures an equal amount of drug content in the jelly.

7) VISCOSITY

A Brookfield viscometer is used to measure viscosity, and a new sample is used each time.

8) SPREADABILITY

Spreadability is assessed by sandwiching a piece of jelly between two glass slides and timing how long it takes for the jelly to separate from the slide after a weight is applied.

9) STABILITY STUDIES

In accordance with ICH guidelines, stability is assessed over a 90-day period at room temperature while keeping an eye on physical appearance changes.

10) SYNERESIS

After a day at room temperature, the liquid separation caused by gel contraction is evaluated.

11) MICROBIAL STUDIES

By cultivating particular pathogens on appropriate media, the microbial profile of jellies is ascertained.

12) PERCENT DRUG CONTENT

The drug content is ascertained by utilizing UV spectroscopy to extract and quantify the drug from a gel that contains 50 mg of the drug.

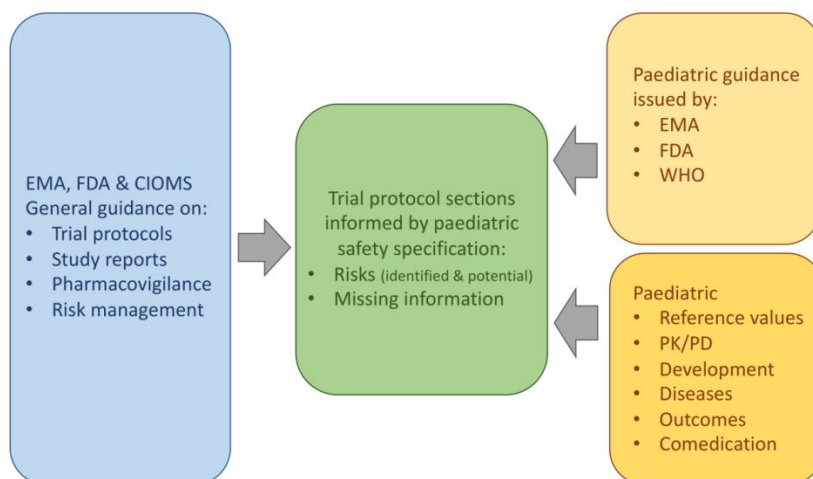
13) *IN VITRO* TASTE ANALYSIS

The jelly is placed in a pH solution that mimics saliva and the filterates are examined for the presence of drugs to determine taste competency.

14) DISSOLUTION STUDIES

Using a USP type 2 paddle apparatus, in vitro dissolution studies are carried out in a 900ml dissolution medium at 50 rpm and 37°C. [16]

Together, these factors guarantee the oral jelly formulations' acceptability, effectiveness, and quality.

13. ASPECTS FOR PEDIATRIC FORMULATION [17]**14. SAFE AND EFFECTIVE FORMULATION**

Important considerations include the creation of (novel) dosage forms, like jelly formulations, the security of excipients, their acceptability by children, and the significance of appropriate dosing equipment. Formulation scientists, physicians, pharmacists, and other caregivers can all benefit from the knowledge gained when prescribing, compounding, distributing, or giving medication to children.

15. CONCLUSION

Drugs that mask bitter tastes can be taken in a variety of ways. Medicated jelly has the potential to become the most widely used dosage form for children in the age group. With regard to the pediatric group, its special qualities enable us to improve patient compliance. By having a rapid onset of action and rapid drug absorption and dissolution, it can also offer notable therapeutic effectiveness. As an easy way to administer medication without ingesting water, oral

jelly is a good substitute for solid dosage forms because it has both liquid and solid properties. Oral medication jelly is therefore a recognized technology.

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