A Review on Solid dispersion- Solubility Enhancement of poorly soluble drug.

[1]Ranjodh Singh, [2]Mr. Lakshya Veer Singh.

[1]M. Pharma Student, [2]Assistant Professor
Department of Pharmacy
MJP Rohilkhand University Bareilly. U.P.

***Abstract*- The minimum 40 % of the novel drug from the pharmaceutical industries are poor ability of solubilization in water. To improve the solubility of poorly water -soluble drug enhancing their bio availabilities. the most challenging aspects in formulation development is solubility behavior of drugs.so solve these problems and increase dissolution development of solid dispersion with carriers having good water solubility is beneficiary. The solid dispersion procedures are found to be a current method to develop the solubility factor of the drug which showing poor solubility in water. Different types of polymers and surfactant are use in solid dispersion they increase the solubility of poor soluble drug.**

INTRODUCTION-

The most common and the most desirable route of drug administration is the oral route in which dosage forms such as tablets, capsules, or oral solution are generally used. One of the most difficult elements of medication development is improving the oral bioavailability of poorly water-soluble medicines 1. Therefore, compared to alternative modes of administration, oral drugs are more effective. At least 40% of innovative drugs produced by the pharmaceutical industry have poor solubilization properties in water due to sluggish release, slow dissolving, and poor bioavailability, necessitating the administration of high doses to provide desired pharmacological effects2. Efforts to boost medication dissolution are frequently required when a medicine has a low water solubility since the oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be a rate-determining step for therapeutic efficacy. The development of numerous techniques to enhance these qualities includes the production of salts, micronization, and solvent or surface-active agents3. the solutions to these issues the best choice is using the solid dispersion method to increase water solubility, improve solubility, and increase the rate of dissolution of poorly soluble pharmaceuticals. Consequently, solid dispersion is among the finest methods. for increasing the solubility, oral bioavailability, and dissolution rate of poorly water-soluble drugs. Enhancing the solubility and rate of dissolution of drugs that dissolve slowly in water and improving the permeability of drugs that are poorly permeable are the two fields of pharmaceutical research that are focused on increasing the active agent's oral bioavailability4,5.

TABLE 1 BCS CLASSIFICATION SYSTEM 6

Class	**Solubility**	**Permeability**
Class I	High Solubility	High Permeability
Class II	Low Solubility	High Permeability
Class III	High Solubility	Low Permeability
Class IV	Low Solubility	Low Permeability

Solubility-

When equilibrium is reached between the excess, or undissolved substance, and the solution at a specific temperature and pressure, that amount is said to have become soluble, or solubilized. The term "solute" refers to the substance that has to dissolve, while "solvent" refers to the liquid that carries out the dissolution, both of which combined make up.

Table No. 2; Definition of different solubility terms7

Description forms (solubility definition)	**Parts of solvent required for one part of solute**	**Solubility range (mg/ml)**	**Solubility assigned. (mg/ml)**
Very soluble	<1	>1000	1000
Freely soluble	1to 10	100-1000	100
Soluble	10-30	33-100	33
Sparingly soluble	30-100	10-33	10
Slightly soluble	100-1000	1-10	1
Very Slightly soluble	1000-10000	0.1-1	0.1
Practically insoluble	>10000	<0.1	0.01

Solid dispersion

To be considered a solid dispersion, a product must have at least two separate components, one of which must be a hydrophilic matrix and the other a hydrophobic medication. Both crystalline and amorphous matrixes are possible. And the medication is delivered as either crystalline or amorphous particles7.

Types of solid dispersion

1-Binary solid dispersion-A polymeric carrier and a medication are combined to form a binary solid dispersion.

2-Ternary solid dispersion-Drug, polymeric carrier, and surfactant are all present in a ternary solid dispersion.

3-Surface solid dispersion-Polymers and copolymers make up the surface solid dispersion.it is created using a fusion process to improve the solubility of a medicine that isn't very soluble

Types of solid dispersion

1-On the basis of carrier used 8

1-On the basis of carrier used-

First generation.

First generation solid dispersions were created utilizing crystalline carriers, the first to be used in solid dispersion. Examples of these carriers include sugars and urea. They are less effective than amorphous ones in terms of speed of drug release and have the drawbacks of generating crystalline solid dispersion**.**

Second generation.

Amorphous carriers are used in second generation solid dispersion in place of crystalline carriers, which are often polymers. Povidone (PVP), polyethylene glycols (PEG), and polymethacrylates are examples of synthetic polymers in this group. Other natural product-based polymers in this group include hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and hydroxypropyl cellulose, as well as starch derivatives such cyclodextrins.

Third generation

It has recently been demonstrated that the carrier's surface activity or self-emulsifying capabilities can improve the dissolution profile. Consequently, third generation solid dispersion emerged. High polymorphic purity and improved in vivo bioavailability have been demonstrated when surfactants such inulin, inutecSP1, compritol 888 ATO, gelucire 44/14, and poloxamer 407 are used as carriers.

Advantage of solid dispersion-

- To make wettability better
- TO increase the drug's porosity
- To alter medications' crystalline structure so they take on an amorphous shape in order to cover up their odor.
- To make oral tablets with fast disintegration
- Poorly water-soluble pharmaceuticals can be made more soluble and bioavailable by using the solid dispersion approach, which is simpler to make and more practical.

It causes a drug's extent and rate of absorption to rise, which causes a quick rate of breakdown.

- Transformation of liquid form of drug into solid form

Disadvantages of solid dispersion-

- It leads to the poor scale-up for the purpose of manufacturing.
- The polymers employed in solid dispersion can absorb moisture, resulting in phase separation, crystal development, and the transformation of amorphous form into crystallin form, which lowers solubility and slows the rate of dissolution.
- It is laborious method of preparation.
- It causes reproducibility of physicochemical characteristics.10

Application of the solid dispersion-

- It is mostly used to provide homogenous medication distribution in modest amounts of solid state.
- It aids in stabilizing the unstable medication.
- It is utilized to administer the substance in a solid dose condition whether it is liquid or gaseous.
- quick release Sustained dosage forms for primary doses are possible.
- Additionally, it is employed to create soluble drugs with sustained release by using a weakly soluble or insoluble carrier.
- In solid dispersion systems like solid solutions and eutectic mixtures, polymorph is shown.11/12.

Carriers used in solid dispersion-13.

S. No. Category Carriers

1 Sugars Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose

2 Acids Citric acid, succinic acid

3 Polymeric materials

Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan

4 Insoluble or enteric polymer

Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS

5 Surfactants Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans

6 Miscellaneous Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

Generations of Carriers: [14, 15]

- ***First generation carriers:*** Example: Crystalline carriers: Urea, Sugars, Organic acids
- ***Second generation carriers:***
  Example: Fully synthetic polymers include povidone (PVP), polyethylene glycols (PEG) and polymethacrylates. Natural product-based polymers are mainly composed by cellulose. Derivatives, such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins
- ***Third generation carriers:***
  Example: Surface active self-emulsifying carriers: Poloxamer408, Tween 80, and Gelu ire 44/

Techniques for Solid Dispersions:

Various methods of preparation solid dispersions are following.

A-Co-Melting method-

Co-melting technique in order to use this technique, a physical mixture of a medication and a water-soluble carrier must be prepared and heated until melting. The molten slurry is then vigorously stirred while swiftly solidifying in an ice bath. Crushed, ground, and sieved are used to create the final solid bulk. The co-melting approach has the advantages of being economical and solvent-free, but it is not appropriate for drugs or carriers that are unstable at fusion temperature or evaporate at higher temperatures16.

B-Fusion method-

It is a variation on the co-melting technique. The carrier is put inside a porcelain dish and cooked in a steam bath until it melts. Using a glass rod and a properly measured amount of medication, an organic solvent is dissolved in hydroxyl propyl methyl cellulose (used as a carrier) to create a clear, translucent gel. The medicine is then sonicated for a short period of time to dissolve it in the gel. Under vacuum, organic solvent evaporates. By using a mortar and pestle and a sieve, solid dispersions are condensed in size. Little amount is gradually injected into a molten carrier. After the medicine has been completely distributed throughout the carrier, the dish is taken out of the steam bath and set aside to cool at room temperature until its contents have solidified. The resultant solid dispersion is next ground and sieved. This technique helps prevent the heat degradation of drugs17.

C-Solvent evaporation method-

In a typical volatile solvent, both the medication and the carrier are dissolved, and the solvent is subsequently extracted under vacuum. Pulverized and sieved26 are applied to the produced solid dispersion18**.**

D-Kneading techniques-

This technique turns the carrier into paste by allowing water to permeate it. The drug is then added and mixed for a specific amount of time. The kneaded dough is then dried and, if necessary, put through a sieve. medicines that are moisture-sensitive cannot be processed using this technology; only thermolabile medicines can be processed using it19.

E-Co-precipitation method-

The necessary amount of medication is added to the carrier solution. The system is shielded from light and kept in magnetic agitation. By vacuum filtration, the precipitate is separated, then dried at room temperature20**.**

F-Gel entrapment technique-

An organic solvent is dissolved in hydroxyl propyl methyl cellulose (used as a carrier) to create a clear, translucent gel. The medicine is then sonicated for a short period of time to dissolve it in the gel. Under vacuum, organic solvent evaporates. By using a mortar and pestle and a sieve, solid dispersions are condensed in size21.

G-Spray drying method-

In this procedure, the medication and lipid carrier are carefully weighed out and then dissolved in methanol to produce a transparent solution. With the use of a lab-scale sprayer, this solution is applied there. Solid dispersion is created as a result of drying22.

H-Electrospinning method-

In this procedure, solid fibers are created from a polymeric fluid stream given through a millimeter-sized delivery device. nozzle scale. It mostly entails applying a high electrostatic field across a conductor attached to a reservoir that contains a polymer solution or melt and a catalyst.

screen for conductive I collection. Charge species that collected on the surface of a pendant drop destabilized the hemispherical shape into a conical shape with an increase in the electrostatic field strength up to but not surpassing a critical value. It is the simplest and least expensive method used to manufacture solid dispersion in subsequent research, and it has considerably more promise for producing nanofibers and controlling the release of medicines23,24, 25.

J-Supercritical fluid (SCF)method-

This method uses carbon dioxide to act as an anti-solvent for the solute and is known as the ultra-critical fluid anti-solvent approach. Drug particles may be recrystallized at greatly decreased particle sizes after being solubilized in supercritical fluid. The supercritical fluid technique' flexibility and precision enable for the micronation of medication particles within a constrained range of particle size, down to the sub-micron level26.

The current super critical fluid methods are capable of producing and demonstrating nano-particular suspensions of particles with a diameter of 5000 nm or less. Spraying the solution, which consists of the solute and the organic solvent, into the concurrently developing continuous super critical phase was done.

Characterization of solid dispersion

Fourier Transform infra-red spectroscopy (FT-IR)

Scanning Electron Microscopy (SEM)

X-ray Diffraction
Thermo-microscopic Methods
Differential Thermal Analysis (DTA)
Differential scanning calorimetry (DSC)

CONCLUSION-

One of the most efficient ways to improve the solubility of poorly water-soluble drugs and to boost their bioavailability is through the method of solid dispersion. Thus, it is necessary.to solve several issues with medication stability and flow. characteristics. As a results, the least poisonous, most biocompatible, and most widely accessible solid dispersion is the ideal option for increasing the solubility of the weakly water soluble BCS-II medication. The development of the oral bioavailability and release rate of weakly water-soluble medicines utilizing solid dispersion be careful carrier selection. It is also possible to alter the drugs release pattern by delaying or slowing it

REFERENCES:

1. Aulton, Aulton's Pharmaceutics, The Design and manufacture of medicine, 3rd ed, p 293-
2. haikh SN, Hifzur Rahman S, Athar MD, Dr. Khan GJ, Raza S, Mohd AA, "Review on solid dispersion of poor water-soluble drug by using natural polymers" The Pharma innovation Journal 2019; 8(1):631-636.
3. Shaikh SN, Hifzur Rahman S, Athar MD, Dr. Khan GJ, Raza S, Mohd AA, "Review on solid dispersion of poor water-soluble drug by using natural polymers" The Pharma innovation Journal 2019; 8(1):631-636.
4. Modasiya M and Patel V: Studies on solubility of curcumin. Int J of Pharm & Life Sci 2012; 3(3): 1490-97
5. Sultan A and Afzal H: Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble Drugs: newer formulation techniques, current marketed scenario, and patents. Drug Delivery 2020; 27(1): 1625-43.
6. Manpreet Walia, 2013, solubility enhancement by solid dispersion method, journal of drug delivery and therapeutics, 3(5): 148-155
7. Stegemanna S, Leveillerb F, Franchic D, Jongd de H, Lindéne H. When Poor Solubility Becomes an Issue: From
8. Early Stage to Proof of Concept. Euro J Pharm Sci**2007**;3(1):249-261. Dhirendra K., Lewis S., Udupan, Atin K., Solid dispersions: Review, Pak J Pharm Sci 2009; 22:2: 234-246
9. B, Kaur R, Behl H, Kour S. Solid Dispersion: An Evolutionary Approach for Solubility Enhancement of Poorly Water-Soluble Drugs. Int J Recent Adv Pharm Res**2012**;2(2):1-16.
10. Poovi Ganesan, et. al. -2015 Developed methods for characterization and solubility, Asian journal of pharmaceutics science, 10(5): 433-441
11. Karavas E, Georgarakis E, Sigalas MP, Avgoustakis K, Bikiaris D (2007) Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on the physical state of drug, particle size distribution, and drug–polymer interactions. Ear J Pharm BioPharma, 66(3): 334-347.
12. Kapoor B, Kaur R, Kaur S (2012) Solid Dispersion an Evolutionary Approach for Solubility Enhancement of Poorly Water-Soluble Drugs. Int J Rec Adv Pharm Res, 2(2): 1-16
13. D. Christopher Vimal's son, et, al. 2016, Enhance Solubility of Hydrophobic Drugs, Asian journal of pharmaceutics, 10(2): 67-74.
14. Manpreet Walia, 2013, solubility enhancement by solid dispersion method, journal of drug delivery and therapeutics, 3(5): 148-155.
15. Krishnamoorthy V, Nagalingam A, Priya Ranjan Prasad V, Parameswaran S, George N, et al. (2011) Characterization of Olanzapine-Solid Dispersions. Iran J Pharm Res, 10(1): 13-24.
16. Kalaiselvan R, Mohanta GP, Manna PK, Manavalan R. Studies on mechanism of enhanced dissolution of albendazole solid dispersions with crystalline carriers. Indian J Pharm Sci. 2006, 68(5), 599-607
17. Akiladevi D, Shanmugapandiyan P, Jebasingh D, Basak S. Preparation, and evaluation of paracetamol by solid dispersion technique. Int J Pharm Pharm Sci. 2011, 3(1), 188-191
18. Abd Alaziz DM, Sammour OA, Elshamy AA, Neseem DI. Formulation and evaluation of binary and ternary solid dispersions of domperidone by solvent evaporation method. Afr J Pharm Pharmacol. 2014, 8(3), 66-80
19. Ghareeb MM, Abdulrasool AA, Hussein AA, Noordin MI. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. AAPS Pharm Sci Tech. 2009, 10(4), 1206-1215.
20. Shah N, Iyer RM, Mair HJ, Choi DS, Tian H, Diodon R, Fahnrich K. A Pabst-Ravot, K Tang, E Scheubel et al. Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer-stabilized solid dispersion prepared by a solvent-controlled coprecipitation process. J Pharm Sci. 2013, 102(3), 967-981.
21. Bakatselo V, Oppenheim RC, Dressman JB. Solubilization and wetting effects of bile salts on the dissolution of steroids. Pharm Res. 1991, 8(12), 1461-1469
22. Shaikh SN, Hifzurrahman S, Athar MD, Dr. Khan GJ, Raza S, Mohd AA, "Review on solid dispersion of poor water-soluble drug by using natural polymers" The Pharma innovation Journal 2019; 8(1):631-636.
23. Singh J, Walia M, Harikumar SL, Solubility enhancement by solid dispersion method: A Review, Journal of drug delivery & therapeutics, 2013; 3(5):148-155.
24. Singh S, Baghel RS and Yadav L, "A review on solid dispersion" International journal of pharmacy & life science 2011; 2(9):1078-1095.

25. Dixit ND, Niranjan SK. “A review: Solid dispersion” World journal of pharmacy and pharmaceutical science.2014; 3(9):238-257
26. Singh S, Baghel RS and Yadav L, “A review on solid dispersion” International journal of pharmacy & life science 2011; 2(9):1078-1095.

.