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Bioavailability Enhancement Techniques for Poorly Soluble Drugs: A Review

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ABSTRACT

Bioavailability is defined as the rate and extent of absorption of unchanged drug from its dosage form. The oral bioavailability of drugs with poor solubility and reasonable permeability is limited by the drug dissolution step from drug products. Low aqueous solubility is the major problem encountered with formulation development of new drugs. The article briefly highlights traditional and novel techniques that are used for solubility enhancement of BCS Class II drugs are discussed in this article. The Traditional techniques include use of co-solvents, hydrotrophy, micronization, change in dielectric constant of solvent, amorphous forms, chemical modification of drug, use of surfactants etc. Novel technologies are size reduction technologies, lipid based delivery system, micellar technologies, solid dispersion and many more.

Keywords: Bioavailability; Micronization; BCS; Solid dispersion.

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INTRODUCTION

Bioavailability is one of the important pharmacokinetic properties of drugs which are used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a drug is administered intravenously, its bioavailability is 100%. However, if the drug is administered through oralroutes (such as), its bioavailability decreases because of incomplete absorption or first pass metabolism.[1]

Drugs are classified on the basis of their solubility and permeability characteristics. The Biopharmaceutical Classification System (BCS) categorizes drugs in four classes: Class I, Class II, Class III, and Class IV. Drugs belonging to BCS Class II are poorly soluble in water, with high permeability and thus are ideal candidates for enhancing bioavailability by simply enhancing solubility.[2, 3]

BIOAVAILABILITY ENHACEMENT TECHNIQUES

Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized as follows:

TRADITIONAL TECHNIQUES:

Use of Co-Solvents: The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a nonpolar drug. This process is known as cosolvencyand the solvents used in combination to increase the solubility of the drugs are known as co-solvents. The co-solvent system works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. [4,5]

Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parentally.[6]

Hydrotropy Method: Hydrotropy is a solubilization technique in which a large amount of second solute is added which results in an increase in the aqueous solubility of another solute. A hydrotropes is a compound that solubilizes hydrophobic compounds in aqueous solution. [7]

Hydrotropy leads to increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[8, 9]

Micronization: The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, rotor stator colloid mill etc. [10]

Use of Surfactants: Surfactants are amphiphilic in nature having a polar end and non-polar end. The surface-active agent enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. [11]

Use of metastable polymorphs: The crystalline state of a drug may affect its saturation solubility and hence it's dissolution

rate. A metastable polymorph is more soluble than the stable polymorph of a drug that exhibits polymorphism.[12]

Solvent deposition: In this method, the poorly aqueous soluble drug is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.[13]

Precipitation: In this method, the poorly aqueous soluble drug is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosizeparticles. The product so prepared is also called as "Hydrosol". Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water-soluble drugs for intravenous administration.[14]

Use of Salt forms: For compounds possessing functional group, the method of choice for improving absorption is through salt formation. Salts of poorly soluble compounds typically dissolve more quickly in the GIT, thus improving absorption.[15]

Use of Hydrates or Solvates: A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts, commonly referred to as "Solvate", and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as "Hydrate". A compound not containing any water within its crystal structure is termed "Anhydrous."[16]

Use of Prodrug:A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound.[17]

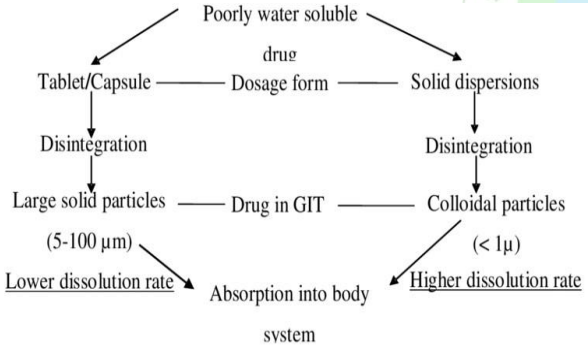

Figure: 1. A schematic representation of the bioavailability enhancement of a poorly water soluble drug by solid dispersion

NEWER TECHNIQUES:

Microemulsion Technology: A microemulsion is a fluid, transparent, thermodynamically stable oil and water system stabilized by a surfactant and co-surfactant mixture. These systems are generally formed over a narrow range of component concentration and can be prepared with either an oil or aqueous continuous phase. Microemulsion enhances bioavailability of poorly soluble drug through solubilization in the excipient matrix or interface and dispersion in the GIT. [18]

Size Reduction Technologies: Nano formulations are one of the more complex formulations. Not only must the drug particles be rendered into nano-sized but they must also be stabilized and formulated rigorously to retain the nature and properties of the nanoparticles.[19]

Porous Microparticle Technology: Poor water soluble drug is embedded in micro particles having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology applied as HDDS™ (Hydrophobic Drug Delivery System).[20]

Molecular encapsulation with cyclodextrin: Beta-cyclodextrin is used for molecular encapsulation of a variety of molecular to oligo saccharides produced from starch. As a result of their molecular structure and shape, they possess a unique ability to act as a molecular container by entrapping guest molecules in their internal cavity. For this reason cyclodextrin increases the water solubility of poorly soluble drug to improve their bioavailability.[21]

Solid Dispersion: The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix (carrier) and a hydrophobic drug. The matrix can be either crystalline or amorphous.[22]

Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanism.[23]

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles.

Thus the basic differerence between solid dispersion and solid solution/ eutectics is that the drug is precipitate out in an amorphous form in the former as apposed to crystalline form in the letter, e.g. amorphous sulfathiazole in crystalline urea. Such dispersions are often called as co-evaporates or co-precipitates. The method is suitable for thermolable substance but has a number of disadvantages like high cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent etc. The carriers used are same as for eutectics or solid solution with glassy materials, the dispersion or glass suspensions. Following figure show comparative dissolution rate of griseofulvin from PVP dispersion [23].

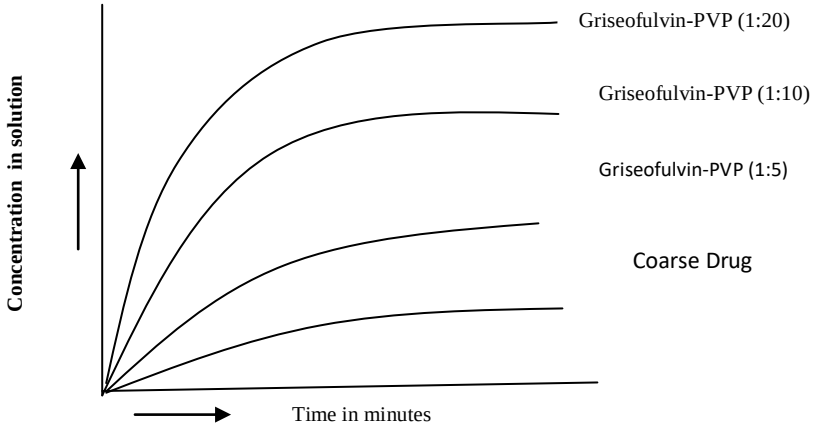

Figure: 1 Dissolution rate enhancement of griseofulvin by solid dispersion technique

Eutectic mixtures:- The systems are also prepared by fusion method. Eutectics melts differ from solid solutions in that the fused melt of solute solvent show complete miscibility but negligible such that systems are basically intimately blended physical mixture of two crystalline components. A phase diagram of two-component system is shown in figure11. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which solubilizes rapidly [22].

Two pharmaceutical examples of eutectic formation are these. The first concerns a mixture of two common antipyretic analgesic compounds Aspirin and acetaminophen. There has always been some "magic" associated with eutectic formation and, indeed, since such binary composition does melt at lower temperature than other combinations, the eutectic probably have weaker binding forces if any, and, being very fine grained also, it is more rapidly soluble. It is known that many drug compounds form eutectics and the aspirin-acetaminophen (APAP) eutectic (37 % APAP by weight) doses, dissolves more quickly than a simple mixture of the two of the same composition. Since a formed eutectic is created under equilibrium condition of intimate mixing as noted, the contact of the two compounds is much closer that achievable by simple the dry powder increases in dissolution rate obtained by using eutectics may result in a greater speed of physiological absorption.

The other example is urea and acetaminophen formed a eutectic containing approximately 46 % urea and 54 % acetaminophen which melted in the 110^0-115^0 ranges.

115^0 ranges.

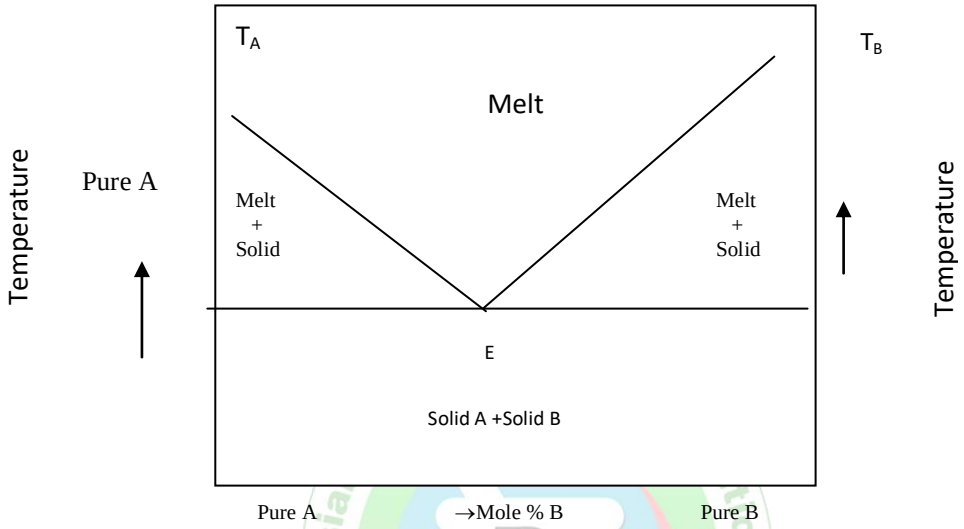

Figure: 2 Simple binary phase diagram showing eutectic point E . The eutectic composition at point E. of substance A. and B. represents the one having dose melting point. T_A and T_B are melting points of pure A pure B.

Solid solutions: - A solid solution is binary system comprising of a solid solute molecularly dispersed ion a solid solvent.

Since the two components crystallize together in a homogenous one phase system, solid solution are also called molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion[34].

They are generally prepared by fusion method where by physical mixture of solute and solvent are melted together followed by rapid solidification such system, prepared by fusion, are often called as melt e.g. griseofulvin-succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin. If the diameter of solute molecules is less than 60% of solvent molecules or it's volume less than 20% of volume of solvent molecule, the solute molecule can be accomodated within the intermolecular spaces of solvent molecules e.g. digitoxin-PEG 6000 solid solution. Such system shows faster dissolution.

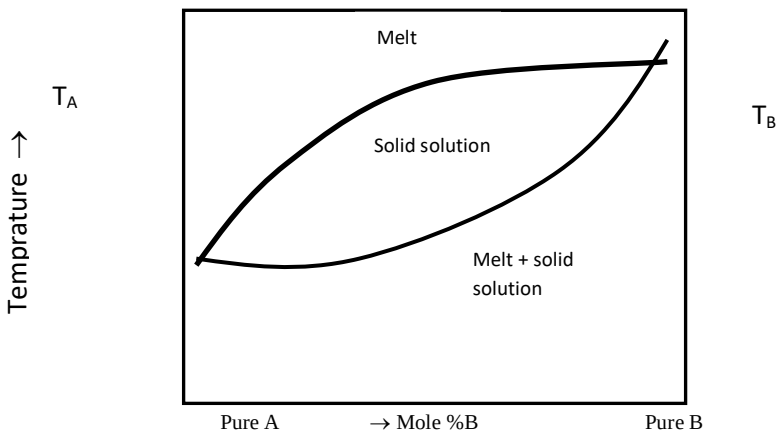

Figure: 3 Binary phase diagram for continuous solid solution of A and B. T_A and T_B are melting points of pure A and pure B respectively.

When the resultant solid solution is homogenous transparent and brittle system, it is called as glass solution. Two mechanisms suggested for enhance solubility and rapid dissolution of molecular dispersions are :

- When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles, and
- When the solid solution, which is said to be in a state of randomly arranged solute and solvent molecular in the crystal lattice, is exposed to the dissolution fluid the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.

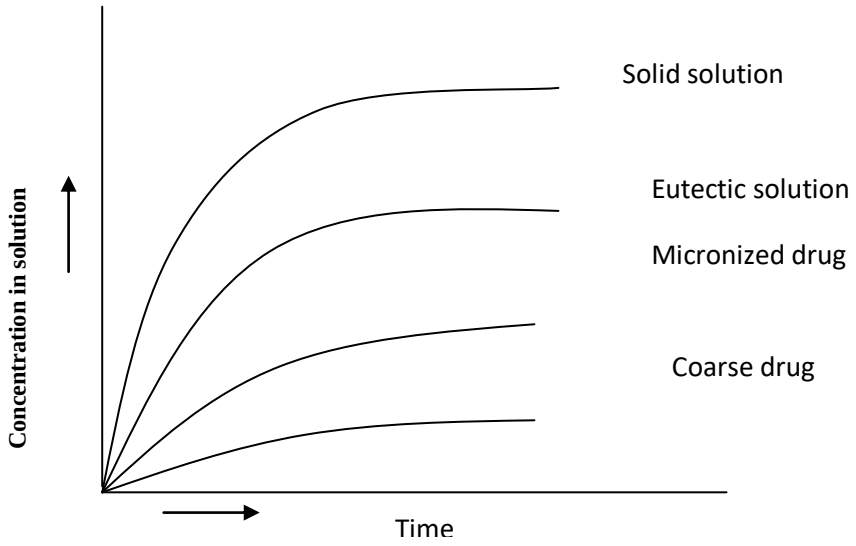

Figure: 4 Dissolution rates of griseofulvin as coarse particle, as micronized particle and as a eutectic and solid solution with succinic acid. This graph shows a comparison between the dissolution rates of different forms of griseofulvin

CONCLUSION

A pharmacological activity can only be observed above the minimum effective concentration, hence that concentration of the drug, which above MCE is required for drug.

The bioavailability studies are important because of the following reasons:

- Development of a suitable dosage form for a new drug entity.
- Development of new formulation of existing drug.
- Determination of influence various factors on the efficiency of absorption.

The various techniques described above alone or in combination can be used to enhance the bioavailability of poorly soluble drugs.

REFERENCES:

1. Shargel L, Yu AB, Applied biopharmaceutics & pharmacokinetics (4th edition),1999, New York, McGraw Hill. ISBN 0-8385-0278-4
2. R. Lobenberg and G. L. Amidon, "Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards," European Journal of Pharmaceutics and Biopharmaceutics, vol. 50, no. 1, pp. 3–12, 2000.
3. WHO Prequalification of Medicines Programme, "General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications," Guidance Document, 2011.
4. Amin, K., Dannenfelser, R.M., Zielinski, J., Wang, B., 2004. Lyophilization of polyethylene glycol mixtures, J. Pharm. Sci. 93, 2244-2249.
5. Yalkowsky, S.H., Roseman, T.J., 1981.Solubilization of drugs by cosolvents. In:Yalkowsky, S.H. Ed. Techniques of Soluhilization of Drugs. Dekker, New York.
6. Amit Kumar Nayak and PrachiPravaPanigrahi Solubility Enhancement of Etoricoxib by Cosolvency Approach ISRN Physical Chemistry Volume 2012.
7. Sajid MA, Choudhary V, Solubility enhancement methods with importance of hydrotropy, Journal of Drug Delivery & Therapeutics, 2012; 2(6):96-101
8. Rasool A.A., Anwar A. H., Lewis W.D. Solubility enhancement of some water- insoluble drugs in the presence of nicotinamide and related compounds, Journal of Pharmaceutical Sciences, 2002,80 (4), 387-393.
9. Badwana A.A., Khordaguib L.K., Saleh A.M., Khalil, S.A. The solubility benzodiazepines in sodium salicylate solution and a proposed mechanism for Bhydrotropic solubilization. International journal of Pharmaceutics, 1982, 13(1), 67-74. 94-97.
10. Chaumeil, J.C., 1998. Micronisation: a method of improving the bioavailability of poorly soluble drugs, Methods and Findings in Experimental and Clinical Pharmacology. 20, 211-215
11. DM.schachter J xiong, GC Tirol- international Journal of Pharmaceutics, 2011- Elsevier.
12. Treyble, R.E., "Mass Transfer Operation", 3rd Edition, McGraw Hill, New York, 1979.
13. Wiliams, Gardner, A., "Industrial Drying, The chemical Rubbr Co., Cleveland", Ohto 1971.
14. Gabmann, P., List, M., Schweitzer, A., Sucker, H., 1994. Hydrosols - Alternatives for the parenteral application of poorly water soluble drugs. Eur. J. Pharm. Biopharm. 40, 64–72
15. Perry, R.H., and Green, D.W.,"Perry's Chemical Engineers Hand Book", 6th Edition, McGraw Hill, New York,1984
16. Lachman, L., Lieberman, H.A., Kanig, J.L., 1990. The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing House, Bombay. 177.
17. Amidon, G.L, Lennemas, H., Shah, V.P. Crison, J.R, "A theoretical basis for a biopharmaceutics drug classification : correlation of in vitro drug product dissolution and in Vivo bioavailability" Pharmaceutical Research. 12(3): 413-420, 1995.
18. Zangenberg N.H., Mullertz. A, Kristenen H.G. Hougaard.: "A dynamic in Vito lipolysis model. I. Controlling the rate lipolysis by continuous addition of Calcium". European Journal of Pharmaceutical Sciences. 14(2) : 115-122 (2001). Kiellend, J:J. Amer Chem. S Aoc, 1972.
19. Bertucco, A., Vetter, G., 2001. High Pressure Process Technology: Fundamentals and Applications. Industrial Chemistry Library, Elsevier, Amsterdam. 9, 1-3.
20. Chowdary, K.P.R., Madhavi, B.L.R., 2005. Novel drug delivery technologies for insoluble drugs.Indian Drugs. 42(9), 557-564.
21. Mulley, B.A. : Solubility in Systems containing surface active agent. In advance in Pharmaceutical sciences Vol. 1. Edited by H.S. Bean. London 1964.
22. Dhirendra k, solid dispersions: a review, pak. j. pharm. sci., vol.22, no.2, April 2009, pp.234-246
23. Arise MJ, Gines JM, Moyano JR, Perez M. Influence of preparation method of solid dispersions their dissolution rate; Study of triamterene d-mannitol system. Int J Pharm. 1995; 123:25-31