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Editorial

Solid dispersions: A feasible technique to improve the aqueous solubility of poorly soluble drugs

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ABSTRACT

Solid dispersion technology deals with dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve enhanced dissolution rate and stability. Upon increasing the dissolution rate in the gastro intestinal tract, the rate of absorption is increased as long as the dissolution rate is still the rate-limiting step. Various carriers have been used in the formation of solid dispersion, which can facilitate in improving the dissolution rate of poorly soluble drugs to improve better bioavailability.

Key words: Solid dispersion, carriers, dissolution enhancement and applications.

INTRODUCTION

A drug must possess some aqueous solubility to exert its therapeutic effect[1]. Due to the advancement in chemistry lead to the effective discovery of new drugs. However, 35-40% of these newly discovered drugs suffer from poor aqueous solubility[2-3]. The solubility behavior of a drug is key determinant to its oral bioavailability, and rate-limiting step in absorption of drugs from gastro intestinal tract[4-6]. Poor aqueous solubility of drugs leads to low bioavailability, increase in the dosage and variability in blood concentrations. It is a unique approach to present a poorly soluble drug in an extremely fine state of subdivision in gastrointestinal fluids. This dispersion consists of a microcrystalline dispersion of a poorly soluble drug in a matrix consisting of physiologically inert, readily soluble carrier[7-10]. Exposure of this type of solid dispersion to the gastro intestinal fluids results in dissolution of water soluble carrier and exposes the dispersed poorly soluble drug. The solubility characteristics of the drug may be altered by reduction in particle size. Several insoluble drugs have been shown to improve their dissolution character when incorporated into solid dispersion. It releases the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed[11-13]. Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drug's[15-16]. The advantages of solid dispersion system includes:

- An increase in aqueous solubility of the drug because of its extremely small particle size.
- Possible solubilization effect on the drug by the carrier in the surrounding diffusion layer.
- Reduction or absence of agglomeration of drug particles.
- Excellent wettability and dispersibility of the exposed drug particles in the gastro intestinal fluids.
- Formation of metastable polymorphic forms.

However, solid dispersion does have certain disadvantages which include change in crystallinity and decrease in dissolution rate on aging. Moisture and temperature have more detoriating effect on these systems and handling is not easy due to tackiness.

PREPARATION TECHNIQUES OF SOLID DISPERSION

a. Solvent evaporation method: In this method, physical mixture of two components are dissolved in a common solvent and followed by the evaporation of solvent. This method has been used for a long time in the preparation of solid solution or mixed crystals of organic or inorganic compounds. The advantages of this method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented. The higher cost of production, incomplete removal of solvent, adverse effect of solvent on the chemical stability of the drug and selection of common solvent are the drawbacks of this method[14].

b. Melting method: The physical mixture of drug and water-soluble carrier was heated to melt and the molten mixture was then cooled and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratio's. Decomposition should be avoided due to fusion time and rate of cooling[15].

c. Kneading method: The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1 v/v). The slurry is kneaded for 45 minutes and dried at 45° C. The dried mass is pulverized and sieved through sieve no 60 and the fraction was collected. The advantages of this method are low temperature requirement for solid dispersion preparation and usage of organic solvent is less[16]. This method of preparation avoids thermal degradation of drug and employs less quantity of organic solvent.

d. Melting solvent method: This method involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. The solvent or drug may not be miscible with the carrier. The liquid solvent used may affect the polymeric form of the drug precipitated in solid dispersion. This method possesses the advantages of both solvent and melting methods. It has been reported that about 5-10% w/v of liquid component could be incorporated into the carrier without significant loss of the solid property[17].

e. Spray drying: Spray drying technique finds more important utility in the pharmaceutical industry due to rapid drying and specific physical characters such as particle size and shape of the product. It is a cost effective process as compared to that of freeze drying resulting in the production of fine solid particles. The operation conditions and design of the drier depends upon the drying characteristics of the product and powder specifications. This process enhanced the dissolution of drug 10 times more than that of pure drug[18-19]. Spray drying technique is useful to obtain spherical particles with narrow distribution. Materials such as calcium silicate, cellulose used to formulate solid dosage forms due to special characteristics like decrease in melting point and crystallinity of drug. Porous silica has been reported to improve the dissolution rate of indomethacin and tolbutamide.

f. Lyophillization technique: This technique was an alternative to solvent evaporation method. Here the drug and carrier are dissolved in common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

g. Melt agglomeration process: This technique has been used to prepare solid dispersion where a binder acts as a carrier. The solid dispersion is prepared by heating binder, drug and excipient to a temperature above the melting point or spraying the dispersion of drug in the molten binder on the heated excipient using a high shear mixer[20]. The effect of binder type, method of preparation and particle size are the critical factors influencing the solid dispersion preparation by this method. These parameters results in various dissolution rates, mechanism of agglomerate formation and growth, agglomerate size and distribution.

CONCLUSION

The solubility of drugs in aqueous media is an important factor in determining their dissolution rate and bioavailability. Solubility of these drugs remains one of the most challenging aspects in drug development. A variety of methods were developed over the past years to improve the solubility and dissolution of drugs. The solid dispersion method is one of the effective approaches to enhancement of solubility of poorly water soluble drugs to improve their dissolution rate and oral bioavailability.

Table 1. Physicochemical characterization of solid dispersions

Methods	Significance
Thermal analysis a. cooling curve method b. thaw melt method c. thermomicroscopic method d. zone melting method e. DSC studies f. DTA studies	To study the morphology and degree of crystallinity. To find out the interaction between drug and carrier and formation of inclusion complex
X-ray diffraction studies	to find out the crystalline or amorphous form of drug
FTIR, NMR, Raman Spectra	to find out the complex formation between drug and carrier
Scanning electron microscopy	to find out the particle size and shape
Dissolution rate/diffusion rate studies	rate and extent of dissolution
Thermodynamic study	degree of crystallinity

Table 2. Therapeutic applications of solid dispersion

Drug	Carrier	Method of Preparation	Purpose
Ketoprofen	PEG-6000	melting	to improve the bioavailability
Piroxicam	Hydroxypropyl β-cyclodextrin	kneading	to improve the dissolution rate of drug and to reduce irritations to stomach mucosa in rats
Glipizide	β-cyclodextrin and sodium CMC	kneading	significant reduction in blood glucose level as compared to pure drug in mice
Aceclofenac	β-cyclodextrin	kneading	higher intestinal absorption in rats
Meloxicam (Suppository)	β-cyclodextrin	solvent evaporation	improved dissolution rate of meloxicam and overcome gastric side effects.
Mebendazole	β-cyclodextrin	solvent evaporation	exhibited higher bioavailability to treat hepatic echinoccosis
Rifampicin	γ-cyclodextrin	solvent evaporation	maximum solubility and better *in vitro* antimicrobial activity
Tolbutamide	β-cyclodextrin	melting	to improve the process of absorption in rabbits

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