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SOLID DISPERSIONS: A METHOD TO IMPROVE BIOAVAILABILITY OF ORAL DRUG DOSAGE FORM

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ABSTRACT:

Presently only few percent of drugs having high aqueous solubility, Number of drugs are belonging to biopharmaceutical classification system class II that means possessing poor aqueous solubility eventually results in low level of drug in systemic circulation. To overcome this problem, various strategies have been come out into notion such as self emulsifying drug delivery system solid dispersions, use of surface active agents, complex formation. Solid dispersions is found to be promising approach to increase bioavailability by use of various polymers. This review focuses on the mechanism of drug release from solid dispersion with its method of preparation and applications.

Key words: dissolution, particle size, solid dispersion

INTRODUCTION

Enhancement of bioavailability of hydrophobic drugs is one of the major challenges in drug development; solid dispersion is one of the useful methods for the dispersion of the drug into an inert, hydrophilic polymer matrix[1]. Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability of a range of hydrophobic drugs. Although a large number of studies have been published but the mechanisms underpinning the observed enhancement of the rate of drug release are not yet understood [2].The use of solid dispersions as an effective source of improving the dissolution rate of poorly soluble drugs has been well studied and demonstrated. The poorly water soluble drugs are characterised by insufficient bioavailability (low dissolution rates) and absorption in the gastro-intestinal tract[3]. Different methods have been used to increase the dissolution and bioavailability of poorly water soluble drugs including micronisation , the use of surfactants and the formation of solid dispersions[4]. Solid dispersions display an enhanced solubility of drug because of the conversion of the drug's crystal lattice into an amorphous form particle size reduction and increased wettability by the hydrophilic polymer. Therefore, the same pharmacological results can be obtained from a reduced amount of drug given to the patient[5, 6].

Types of Solid Dispersion

(a) First generation solid dispersions

It has been shown by Sekiguchi and Obi in 1961 that the formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Solid dispersions systems developed by Levy (1963) and Kanig (1964), who made solid solutions by using molecular dispersions instead of using eutectic mixtures, with mannitol as carrier. These improvements were due to faster carrier dissolution, releasing particles of drug[7, 8].

These dispersions prepared using crystalline carriers were described as first generation of solid dispersions. Urea and sugars were the first crystalline carriers to be used in dispersions. The major drawback of first generation solid dispersion

is that they form crystalline solid dispersions which being thermodynamically more stable did not release the drug as quickly as amorphous ones[9].

(b)Second generation solid dispersions

It was noticed in the late sixties that solid dispersions with drug in the crystalline state are not as effective as amorphous because they are thermodynamically stable. Therefore, second generations of solid dispersions were introduced having amorphous carriers instead of crystalline. Formerly, the drugs were molecularly dispersed in amorphous carriers which are usually polymers in random pattern[10, 11].

(c) Third generation solid dispersions

Third generation of solid dispersions appeared as the dissolution profile could be increased by using carriers having surface activity and self-emulsifying characteristics. These contain surfactant carriers or a mixture of amorphous polymers and a surfactant as carrier[12, 13]. The third generation solid dispersions stabilise the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug. The use of surfactants such as poloxamer 407 as carriers resulted in high polymorphic purity and improved vivo bioavailability[13, 14].

Mechanisms for Drug Release from Solid Dispersions

Different factors influence the enhancement of dissolution rate of solid dispersions. The use of increased amount of urea enhances the dissolution rate of drug as was shown in a study with 20% chloramphenicol and 80% urea [15]. This was due to the reduction in particle size. However, it was later found that the dissolution rate could be improved without any change in the particle size. Non surface active carrier can enhance the wettability of a drug by reducing the contact angle and thus causing an increase in the surface area available for dissolution[16]. A drug can be retained in the solution by inhibiting it is precipitation with the addition of a polymer. The drug dissolves back into the solution, after precipitating out as metastable polymorph as this form is more soluble than the original polymorph of the drug, as highlighted in a study with indomethacin. Carrier-controlled or drug-controlled dissolution mechanisms were first proposed by Craig in which the drug release depends either on the carrier or the drug itself[17, 18]. This method is based on the models proposed by Higuchi et al. and Higuchi. The dissolution surface is non-disintegrating and the dissolution of both parts is diffusion controlled. The dissolution is controlled through a drug rich dissolving surface, formed only if the drug makes the larger component[19]. In high polymer loading there is insufficient drug to support the drug controlling layer formed at the dissolving surface. This causes the drug to disperse within the polymer resulting in a carrier-controlled drug release process. In high drug loading solid dispersions, the dissolution rate of the drug can be measured, by considering the polymer as faster dissolving component. Hence, the dissolution of the drug is controlled by polymer dissolution if the drug forms the minor component in the solid dispersion[20]. The carrier-controlled dissolution was further supported by another study investigating the incorporation of ten drugs into PEG 6000 solid dispersions where identical dissolution rates were reported. A linear relationship was shown when the dissolution rate was plotted against the drug content. Carrier-controlled dissolution works up to a limited concentration depending upon the drug evident from the differences in the linear relationships for various drugs. Currently, there is no mechanism that can predict the behaviour of a drug in solid dispersion, as various factors are pivotal in deciding drug release. Extensive work is required in order to fully understand the association of the carrier and drug in dispersion[20, 21, 22].

Advantages of Solid Dispersions

1. Particles with reduced particle size: Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug[23].

2. Particles with improved wettability: Carriers with surface activity, such as cholic acid and bile salts, when used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects[24].

3. Particles with higher porosity: Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. Linear structured polymers produces more porous particles when compared to reticular polymers.. More porous nature of the particle results higher dissolution rate[25].

4. Drugs in amorphous state: Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process[26].

Disadvantages of Solid Dispersions

1. Instability due to crystallinity and decrease in dissolution rate with. Some solid dispersion may not lend them to easy handling because of tackiness[27, 28].
2. Moisture and temperature effects
3. Laborious and expensive methods of preparation.
4. Reproducibility of physicochemical characteristics.
5. Difficulty in incorporating into formulation of dosage forms [29, 30].

Method of Preparation of Solid Dispersion

Various methods used for preparation of solid dispersion system. These methods are given below.

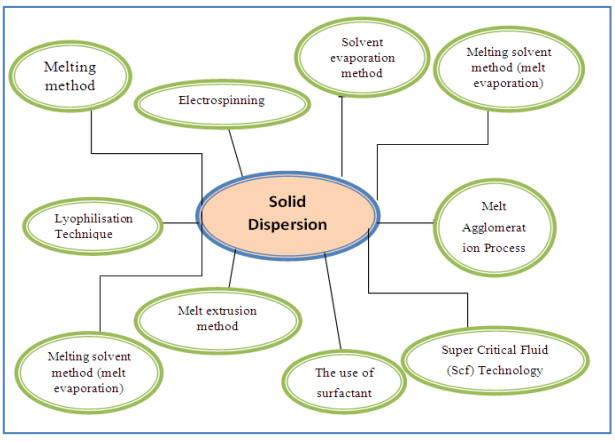

Figure 1: Different method of preparation of solid dispersion[31]

Applications of Solid Dispersions

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique be used[21]:

1. To obtain a homogeneous distribution of a small amount of drug in solid state.

2. To dispense liquid or gaseous compounds in a solid dosage.

3. To formulate a fast release primary dose in a sustained released dosage form.

4. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate absorption and bioavailabilty[9,10].

5. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

6. To reduce side effects of certain drugs.

7. Masking of unpleasant taste and smell of drugs.

8. To avoid undesirable incompatibilities[11, 12].

10. To obtain a homogeneous distribution of a small amount of drug in solid state.

11. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

12. To formulate a fast release primary dose in a sustained released dosage form.

13. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

14. To reduce pre systemic inactivation of drugs like morphine and progesterone[15,16,17].

Conclusions:

Delivery of poorly soluble drug is slowed down where dissolution is the rate limiting step, so, solid dispersion technique can be used to enhance the solubility of poorly soluble drugs by reducing the particle size,that will reduce the dosing frequency and improve the patient compliance.

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