CHAPTER I

INTRODUCTION

In biopharmaceutical classification system the drugs which come under class II are characterized by more membrane permeability, less dissolution rate and high per oral dose [1]. It was reported that most of the newly discovered drugs are comes under BCS class II category. But the dissolution is acting as a rate-limiting step for poorly aqueous soluble class II drugs. Hence, there is a need to increase the bioavailability of poorly water-soluble BCS class II drugs. In this regard, there are several methods have been reported for enhancement of dissolution rate of poorly aqueous soluble drugs. Among the different methods, micronization technique is the most common method to decrease size of the drug particle. But this method is limited by their agglomeration of particles which decreases the surface area and dissolution of the particles. Solid dispersion technology can be used as one of the best and simple, easily scalable technology to improve the bioavailability of poorly aqueous soluble drugs [2]. The solid dispersions (SD) consist of a hydrophilic carrier in which molecular dispersion of drug occurs. In SD technology, the drug particle size is reduced almost to a molecular level, and wettability of the drug is remarkably increased [3].

1.1 Solid dispersion system and its historical background

In formulation development process, increasing the oral bioavailability of the poor aqueous drug is a highly challenging aspect of drug delivery. Bioavailability may be described as the rate and amount of drug reaching the systemic circulation from the dosage form and reaches the site of action to produce the desired effect. A poorly water-soluble compound has classically been defined as one dissolving in less than 1 part per 10000 parts of the water will create a bioavailability problem and thereby affecting the therapeutic efficiency of a new drug. The bioavailability problem can be solved by increasing the water solubility of the drug [4].

Methods to enhance the water solubility of a drug are co-solvents and emulsified system, solubilization, particle size reduction, amorphous drug forms, molecular complexes, biorise technology. They have been commonly used to enhance
drug release rate and thereby oral bioavailability of such drugs. But it has been reported that there are practical limitations to these techniques. In 1961, Sekiguchi and Obi Proposed a new technology in which most of the problems mentioned above can be succeeded. Later this technology was termed ‘Solid Dispersion'. In solid dispersions, eutectic mixture of drug is formed with hydrophilic carrier in a microcrystalline state.

Following, Goldberg et al outlined there is a tiny part of drug would be molecularly distributed in the hydrophilic carrier and comprising a solid dispersion. In both cases, drug has released as fine colloidal particles thereby dissolution rate was expected to be high [5]. Amorphous phase formation of the drugs is desirable for enhancement of dissolution rate, which increases the oral bioavailability remarkably. Sorbed water into the amorphous regions increases molecular mobility. An amorphous phase is considered as a condensed solid state without three-dimensional molecular order in comparison to that observed in a crystal. The main expertise of formulation development is to enhance the drug dissolving capacity and drug release pattern of poorly aqueous soluble drugs. Amphorization of poorly aqueous soluble drugs which increases dissolution rate and can lead to remarkable enhancement in their bioavailability. In general, an amorphous form of drug always has much more enthalpy than its crystalline structure. Inhibition of crystallization is possible by converting the drug into amorphous molecular dispersion using hydrophilic carrier matrix.

1.2 Solid dispersions-Definition and methods

A SD is a multiparticulate delivery structure and is defined as a dispersion of one (or) more active ingredients in an inert carrier at a solid state prepared by melting (fusion), solvent or melting-solvent methods.

1.3 Methods of preparation

Basically there are three methods

- Melting or fusion method
- Solvent evaporation method
- Melting-solvent method
1.3.1 Melting method

The melting technique is less difficult method for preparing solid dispersions. In this method, the SDs are prepared by melting the drug and carrier, and the molten mixture is solidified immediately in ice bath. The mixture is stirred vigorously to get a final mass. The mass obtained is pulverized and passed through a suitable sieve to get a solid dispersion. In another method, the molten mixture is cooled by spray-drying technology [6]. The molten mixture is sprinkled on the chilled metal surface thereby forming pellets of solid dispersions. An important advantage of this method is there is no alteration of crystalline structure, and the SDs can be solidified at a controlled rate.

**Advantages**

- Simple and economical
- Less time consuming
- This technique can be convenient for that drug which cannot undergo thermal decomposition.

**Disadvantages:**

An important disadvantage of this technique includes thermal decomposition of the drug. The higher temperature required to melt the drug and solidification of dispersion can affect the crystallization rates. This may lead to tacky or glossy dispersion.

**Examples:** Solid dispersions of Sulphamethoxazole, Acetaminophen, Griseofulvin, Primidone, Chloropropamide, Chloramphenicol, Tolazamide, Steroids, Ketoprofen, Nimesulide.

1.3.2 Solvent Evaporation Method

In this method a suitable solvent is selected which can capable of solubilizing both drug and hydrophilic carrier. Then a respective amount of drug and hydrophilic polymer are dissolved in common solvent and the same is removed under reduced temperature. The obtained mass is dried in a desiccator, pulverized and sieved through a suitable sieve to get the solid dispersion. Another method of removing solvent is by spray drying technology [7].

The solvent can be removed very effectively by an alternative method called
spray drying technology. The freeze-drying method is also employed to develop SDs by the removal of water based solutions.

**Advantages**

1. The method is reliable for compounds that are thermo-labile.
2. The thermal degradation of drug compound can be avoided because the solvent can be removed under lower temperatures.
3. The aqueous systems can be evaporated by frozen systems in which the chemical integrity of the drug can be enhanced.

**Disadvantages:**

1. There is a difficulty in complete removal of the solvent.
2. There is a difficulty of choosing the solvent which can capable of dissolving both drug and polymer used.
3. Some solvents can cause plasticization of polymers like PVP.


**1.4 Classification and fast release mechanisms**

**1.4.1 Simple eutectic mixtures**

When the fused liquid of two components are rapidly solidified there is a formation of eutectic mixtures which often give greater aqueous solubility. If the mixture is kept in water the hydrophilic carrier dissolves quickly and releases tiny crystals of drug having larger effective surface area results in enhanced drug release rate of the drug [8].

**1.4.2 Solid solutions**

Solid solutions are prepared by dissolving a solid solute in a solid solvent. In these solid solutions two solid components crystallizes to form homogenous single phase system. In general, solid solutions give greater dissolution than eutectic mixtures. This is because of the reduction of particle size to almost molecular level.
Solid solutions are further classified into

1.4.2.1 Continuous Solid Solutions
In this system, the two constituents are having stronger bonding strength than molecules of each component.

1.4.2.2 Discontinuous Solid Solution
There is a limited solubility of a solute in a solid solvent in this group of solid solutions. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature.

1.4.2.3 Substitutional Crystalline Solid Solution
In this, the solute molecules substitutes for the solvent molecules in the crystal lattice of the solid solvent.

1.4.2.4 Interstitial Crystalline Solid Solution
The solute (guest) molecule occupies the interstitial space of the solvent (host) in the lattice.

1.4.3 Glass solutions
These systems are made by dissolving a solute in glassy solvent. Glass solutions are another important method to improve the drug release and absorption. The word glass may be utilized to narrate a pure chemical in a glossy state.

1.4.4 Amorphous preparations
The amorphous form of a drug always possess the greatest energy form. An amorphous structure is otherwise called as super cooled liquids which always give rapid dissolution and faster absorption rates than crystalline form. Novobiocin has been reported to have a ten-fold greater solubility than the crystalline form [9].

1.4.5 Complex formulations
The water soluble hydrophilic polymers are often used for formulating solid dispersion of poorly aqueous soluble drugs. The bioavailability of the drug based on the rate at which a drug absorbed from the complex.

1.5 Advantages of SDs
Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs. Many of the advantages claimed for SD are derived from their rapid dissolution rates.
The increased rate of nitrazepam from the citric acid dispersion produces an enhancement in the rate and amount of absorption.

- PEGs may protect certain drugs like cardiac glycosides against the decomposition by saliva.
- Various fast release solid dispersions can be prepared by solid dispersion technique. For ex: fast release solid dispersions of Lorazepam can be prepared by using urea, PEG 6000 or Mannitol as carriers.
- Solid dispersions may be a thermodynamically more active form of drug and directly influence the diffusion and release rate.
- An increased diffusion of steroid from the ointment was obtained. Ex: solid dispersion of prednisolone urea dispersion.
- Solid dispersion technology can be used to solidify liquid drugs. Ex: clofibrate and benzyl benzoate.

1.6 Disadvantages of solid dispersions

- Tackiness and decommission during preparation and formulation.
- The oral administration of solid dispersions without the concomitant reduction in dose may result in higher incidence of adverse effects eg: ulceration of Indomethacin–PEG 6000 dispersion.
- Reproducibility of its physicochemical properties.
- The scale-up of the manufacturing process.
- Its formulation into dosage forms.
- Difficulty in pulverization.
- Drug carrier incompatibility.
- Poor flow and mixing properties.
- There is a difficulty of sifting the solid dispersions because of tacky property.

1.7 Antihypertensive

1.7.1 Definition

Hypertension is usually defined as the presence of chronic elevation of systemic arterial pressure above the particular threshold value. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that
damage the heart, kidney, vasculature and other organs and leads to premature morbidity and death.

**Classification of Hypertension.**

Stage I hypertension:
- Elevations of blood pressure levels occasional or intermittent.

Stage II hypertension:
- Sustained blood pressure or progressive cardiovascular disease.
- It is moderate hypertension Systemic blood pressure 160-179mmHg.

Stage III hypertension:
- Advanced cardiovascular disease.
- It is severe hypertension Systemic blood pressure 180-209 mmHg

**1.7.2 Classification of antihypertensives.**

a) β- Blockers
- Propranolol
- Metoprolol
- Atenolol

b) Calcium channel blocker
- Verapamil
- Diltiazem
- Nifedipine
- Amlodipine

c) ACE inhibitors
- Enalapril
- Lisinopril
- Ramipril

d) Diuretics
- Thiazides- indapamide, hydrochlorothiazide
- High ceiling- Furosemide
- K+ sparing- spironolactone, triamterene

e) Sympatholytic and adrenergic blocker
- Clonidine, methyldopa
- Prazosin, terazosin

f) AT1 antagonist
- Losartan
- Candesartan

g) Direct arterial vasodilator
- Hydralazine
- Minoxidil
- Sodium nitroprusside

- **Contraindication**
  - Unstable angina, pre-existing hypotension
  - Liver failure, Aortic stenosis, Obstructive Cardiomyopathy.
  - Abrupt withdrawal of extended therapy of drug leads to precipitation of angina and MI.
Table 1.1 Pharmacokinetics of dihydropyridine

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of Action (hrs)</th>
<th>Dosage range (mg)</th>
<th>No. of doses</th>
<th>Metabolism/excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>24</td>
<td>5-10</td>
<td>1</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Verapamil</td>
<td>4-8</td>
<td>80-120</td>
<td>1</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Diltiazam</td>
<td>6-8</td>
<td>60-120</td>
<td>3</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>4-8</td>
<td>5-10</td>
<td>1-2</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Felodipine</td>
<td>24</td>
<td>5-10</td>
<td>1</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>4-5</td>
<td>60</td>
<td>1</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

- **Pharmacokinetics**
  - Well absorbed orally and 90% plasma bound.
  - Most of them are metabolized in the liver and excreted in urine.
  - They have substantially longer half-life.
  - Having a low and variable bioavailability because of extensive first-pass metabolism [10].

The incorporation of solid dispersions in fast dissolving tablets with superdisintegrants is another exciting method to improve the drug release rate of poorly aqueous soluble drugs. For preparing fast dissolving tablets the superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone were used. Nisoldipine and amlodipine besylate are calcium channel blockers which are employed in the treatment of hypertension, and it belongs to BCS Class II category. The poor aqueous solubility of these drugs leads to poor bioavailability. Hence, the drug release rate can be increased utilizing the solid dispersion technology. [11] Poloxamer407 (P 407) and poloxamer 188(P 188) were used as the carriers for the preparation of solid dispersions with nisoldipine and with amlodipine besylate. Poloxamer is a hydrophilic synthetic block copolymer widely used in pharmaceutical preparations as a solubility enhancer[12].