Solid dispersion a novel approach for enhancement of solubility and dissolution rate: a review

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ABSTRACT

The oral route is the most preferred route for the administration of various drugs because it is the most convenient and safest route for drug delivery. The researcher develops a recently fast dissolving tablet (FDT). This improved patient compliance and convenience. FDTs are defined as the solid dosage form, which disintegrates in saliva without the need for water. Solid dispersions attract considerable interest by increasing the dissolution rate and also enhance the bioavailability of poor water-soluble drugs. Pre-gastric absorption avoids first-pass hepatic metabolism, which increases the bioavailability of the drug. One part of the review article focus on solid dispersion, there advantages, disadvantages, and method of preparation. Later part of the review article focus on the evaluation of fast dissolving tablet.

INTRODUCTION

Drug delivery refers to the system transporting a pharmaceutical compound in the body to achieve its therapeutic effect. Various types of dosage forms are available such as tablets, capsules, syrups, injections, suspension, suppositories, transdermal, and patches having a different type of drug delivery mechanism.[1] These dosage forms have some advantages and disadvantages. So, the development of an ideal drug delivery system is a big challenge to manufacture. To get the desired effect, the drug should be delivered to its site of action at such a rate and extent to achieve the minimum adverse effect and maximum therapeutic effect. For the development of a suitable dosage form a thorough study about the physicochemical and biochemical properties that govern a specific dosage form of a drug should be obtained.[2] The oral route of drug delivery is the most preferred route of drug administration to get the systemic effect.[3] Overall, 90% of the drugs used to produce systemic effects are administered by the oral route. Tablet is the most popular dosage form among all dosage forms existing today because of its self-administration and easy manufacturing. But swallowing is a common phenomenon which leads to poor patient compliance. To overcome this drawback, fast dissolving tablet, which is also called a mouth dissolving tablet and orodispersible tablet is formulated.[4] Fast dissolving tablet disintegrates in saliva in less than a minute without the need of water. Their ideal property such as administration without water anywhere and anytime lead to their suitability to geriatric and pediatric patients. They are suitable for the bedridden and mentally ill patients and also suitable for patients who do not have easy access to water.[5, 6] According to European Pharmacopoeia, orodispersible tablets should disintegrate in less than three minutes, but according to USP, the disintegrating time of fast dissolving tablets approximately 30 seconds or less [7, 8]. The bioavailability of drugs those suffering from a high first-pass metabolism can be enhanced due to pre-gastric absorption and also reduce the drug dose from the formulation [9]. In order to increase the dissolution rate and bioavailability of poorly soluble drugs, various techniques have been introduced to enhance the dissolution rate such are micronization, solid dispersion and use of surfactant [10]. Solid dispersion attracts much of the researcher, this technology involves drugs that are
poor water soluble and high permeability through biological membranes also called as BCS Class II drugs. These drugs dissolution is the rate limiting step for absorption. Hence the rate of absorption will be increased by increasing the dissolution rate. Therefore, solid dispersion technologies are promising for improving the oral absorption by increasing the dissolution rate and also enhance the bioavailability of BCS Class II drugs [11].

Need for development of fast dissolving tablet

**Patient factor:** Fast dissolving tablet suitable for
- A schizophrenic patient, they try to hide a solid dosage form under his tongue to avoid daily dose.
- Patients having difficulty in swallowing or chewing a solid dosage form.
- Patient undergoing radiation therapy for breast cancer may be nauseous to swallow her H₂ blocker.
- Patient with persistent nausea, who may be journey, or has little or no access to water [12].

**Effectiveness factor**
- Fast dissolving tablet disintegrate in saliva in oral cavity cause pre-gastric absorption of drug.
- Pre-gastric absorption avoid first pass metabolism which increase bioavailability of the drug [13].

**Advantages of fast dissolving tablet**
- Can be easily administered to pediatric, geriatric and mentally disable patients.
- No need of water to swallow the tablet
- Increase dissolution rate and drug absorption.
- Increase bioavailability of the drug.
- Avoid first pass metabolism.
- Reduce dose and dose related side effect [14,15]

**Disadvantages of fast dissolving tablet**
- Tablet may leave unpleasant taste and grittiness in oral cavity if not formulated properly.
- Usually tablets have insufficient mechanical strength. So, careful handling is required during manufacturing.
- Drug with large doses are difficult to formulate into fast dissolving tablet [16].

**Solid dispersion**

Solid dispersion is define as the group of solid products consisting of at least two different components, in which one component is hydrophilic matrix and another one is hydrophobic drug. The matrix can be either crystalline or amorphous. And the drug is dispersed in crystalline particles or in amorphous particles [17].

**Types of solid dispersion**

1. **Binary solid dispersion** Binary solid dispersion consists of drug and a polymeric carrier.
2. **Ternary solid dispersion** Ternary solid dispersion contains drug, a polymeric carrier and a surfactant.
3. **Surface solid dispersion** Surface solid dispersion consists of polymers and copolymer. It is formulated by fusion method to increase the solubility of poorly soluble drugs.

**On the basis of molecular arrangement solid dispersion are of following types**

**Simple eutectic mixture**
Simple eutectic mixture formed by the fusion of two components which shows complete miscibility in liquid form.

**Solid solutions**
Solid solution are formed when two components are crystallize together to form a homogeneous mixture or one phase system. Particle size reduced into molecular size in the solid solution. Solid solution helpful to enhance the dissolution rate than the others eutectic mixture.

**Glass solutions and suspensions**
In glass solution a solute is dissolved in a glassy system to form a homogeneous glassy system. In the glass solution, precipitated particles are suspended in a glass solvent to form a glassy suspension. Glasses have not a sharp melting point and they become soft on heating. Glassy state is a transparency and brittleness below the glass transition state.

**Amorphous precipitations in a crystalline carrier**
Amorphous precipitation in a crystalline carrier is a type of solid dispersion in which, drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter.

**Compound or complex formation**
Compound is formed when a drug and matrix strongly interact with each other to form a complex in aqueous medium. Formation of a soluble complex takes place when low or intermediate fraction of carrier is helpful in the preparation of solid dispersion. Dissolution may be enhanced by using high friction carrier. Low association constant is necessary for dissolution enhancement [18, 19].

**Advantages of solid dispersion**
- Particles with reduced particle size and thus increase surface area which increase dissolution rate.
• Particles with improved wet ability which results in increase solubility thus increase bioavailability.
• A drug in amorphous form results in increase the solubility of the particles [20-22].

Disadvantages of solid dispersion
• Major disadvantage is their instability.
• Temperature and moisture have more deteriorating effect on solid dispersion.
• Difficulty in handling [23].

Method of preparation of solid dispersion

1. Fusion method
Fusion method is also called as melt method. The first solid dispersion prepared for pharmaceutical application was formulated by the fusion method. The dispersion consists of sulfathiazole and urea as a matrix. This was melted using a physical mixture and form eutectic composition of drug and urea. The eutectic composition used to obtained crystallization of drug and matrix during cooling. Poly ethylene glycol is a hydrophilic polymer which is also used to prepare solid dispersions with the fusion method.

2. Supercritical fluid method
this Method is also called as (RESS) Rapid Expansion of Supercritical Solution. Supercritical fluid method is mostly applied with carbon dioxide. In this method carbon dioxide is used as solvent for drug and matrix. Drug and matrix are dissolved in carbon dioxide and sprayed through a nozzle into an expansion vessel with lower pressure and particles are formed immediately. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of solvent so, called as solvent free technique [24-26].

3. Melting solvent method
In melting solvent method solid dispersion prepared by dissolving the drug in a liquid solvent than this solution is directly incorporating into the melted polyethylene glycol. After that this mixture is evaporated until a clear and solvent free film is obtained. Finally this film is further dried to constant weight.

4. Solvent evaporation method
Solvent evaporation method followed by two steps. In first step a solution is prepared which contain both matrix material and drug. So, in this step a mixture of drug and carrier is dissolved in a common solvent, than follow the second step. In second step this solution is evaporated until a clear and solvent free film is obtained. This film is further dried to constant weight. This Method avoids the thermal degradation of drug and polymer.

5. Hot melt extrusion
In hot melt extrusion method, drug and polymer are mixed by using extruder and followed by cooling step. Melt extrusion helpful to give shape in dosage form. For e.g. ophthalmic inserts, implants and oral dosage form.

6. Lyophilization technique
This technique is an alternative to solvent evaporation technique. It involves the transfer of heat and mass to form the product. Lyophilization is a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilizing molecular dispersion.

7. Electrospinning
In Electrospinning process a strong electrostatic field will be applied to a conductive capillary attaching to a reservoir containing a polymeric solution. Due to increase the electrostatic field it provides strength to the solution. But this electrostatic field not exceed to a critical point value. At the end of process fibers of submicron diameter are produce. Evaporate the solvent and collect the fibers on the screen.

8. Spray freeze drying
In a fix concentration dissolve the drug in solvent and carrier in water. Mix this solution in ration of 40:30. Than spray this solution in to the liquid nitrogen with the help of nozzle. Set the liquid feed rate and atomize the air flow. Also set the nozzle outlet at a position about 10cm above the liquid nitrogen. To avoid the freezing of solution inside the nozzle hot water is pumped through the jacket of nozzle. Finally, transfer this resulting suspension in to the lyophilizer. When all the nitrogen is evaporated than start the Lyophilization procedure [27-31].

9. Melt agglomeration technique
In melt agglomeration technique polymer act as a binder which is helpful for the preparation of agglomeration. In this process solid dispersions are prepared by heating the drug, excipient and polymer above the melting point of the
binder. Solid dispersion can also be prepared by spraying the drug in molten binder on the heated excipient by using a high shear mixer [32]. Rotary processor can be used for this technique. It is easier to control the temperature [33].

Conventional techniques used for the preparation of fast dissolving tablet

1. Disintegrant addition technique

This is a most popular technique used for the formulation of fast dissolving tablet. In this technique superdisintegrants are added in the formulation at optimum condition to achieve complete disintegration.

2. Moulding

In moulding method moulded tablets are prepared. Tablet is prepared by using water soluble ingredients. Due to the water soluble ingredient tablet dissolve completely.

3. Freeze drying lyophilization

In freeze drying Lyophilization, heat sensitive drugs and biological substance are drying under a low temperature condition and allow the removal of water by sublimation [34-38].

4. Sublimation

Due to low porosity, dissolution decreases in compressed tablet even containing high water soluble ingredients. The volatile material is removed by sublimation technique which helpful to generate pores in the tablet. And increase dissolution rate. Solvent like cyclohexane and benzene is used as a pore forming agent.

5. Direct compression

In this Method the drug diluents, superdisintegrants pass through the sieve #40. All the ingredients are mix properly. Talc and magnesium stearate are passé through the sieve #80 and mix properly in the above mixture and blended. The blended powder compressed into tablets.

6. Mass extrusion

In mass extrusion technique water soluble mixture of polyethylene glycol is used for the softening of active blend with the help of methanol.

7. Spray drying

In spray drying, formulation is incorporated by hydrolyzed and non hydrolyzed gelatin as supporting material. Bulking agent, super disintegrating agent and acidic or alkali material are used to enhance the disintegration. Spray drying process produce highly porous and fine powder which dissolve completely and increase disintegration and dissolution [39-43].

Pre compression evaluation of granules

- Compatibility study by Fourier Transform Infra-Red (FTIR) spectroscopy
- Bulk Density
- Tapped Density
- Compressibility Index
- Hausner’s Ratio
- Angle of repose

FTIR spectroscopy

FTIR of active drug and solid dispersion will be taking using FTIR Spectrophotometer. FTIR is helpful to study any chemical interaction between the drug and the polymeric material which occurs during the preparation of tablet.

Angle of repose

It is define as the maximum angle possible between the surface of pile and horizontal plane of the powder. It would determine by fixed funnel method. In this method funnel will secured at a height above the paper which is placed on the flat horizontal surface. It can be calculated by the following formula [44].

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( \theta \) = angle of repose
\( h \) = height of the pile
\( r \) = radius of cone base

Bulk density

Bulk density is defined as the tendency of the particles to adhere one another [45]. Bulk density is the density of powder which is poured into the measuring cylinder. It can be calculated by measuring the known mass of powder sample that will pass through a screen in to a graduated cylinder.

\[ \text{Bulk Density} = \frac{\text{Mass}}{\text{Bulk Volume}} \]

Tapped density

Tapped density determine by using measuring cylinder. It can be achieved by tapping the measuring cylinder which

| Table 1: Scale of Flowability for angle of repose |
|-----------------|------------------|
| Angle of repose | Flowability       |
| <25°            | Excellent flow    |
| 25°-30°         | Good             |
| 30°-40°         | Satisfactory or passable |
| 40°-50°         | Poor             |
| >50°            | Very poor or damp |

is filled with the sample powder. It will be calculated by filling the known mass of sample powder in the measuring cylinder and observe the volume of powder. Than cylinder is mechanically tapped and note the volume of powder after change in volume is observed [46].

It is calculated by the following formula,

\[
\text{Tapped Density} = \frac{\text{Mass}}{\text{Tapped Volume}}
\]

**Compressibility index**

Compressibility index calculated by the basis of bulk density and tapped density. It is calculated by using the following formula [47].

Compressibility index = \([\text{Tapped density} – \text{Bulk density}/\text{Tapped density}] \times 100\]

**Hausner ratio**

Hausner ratio also determined on the basis of bulk density and tapped density [48].

Hausner ratio calculated by using following formula,

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Table 2: Acceptance criteria of flowability for compressibility index and hausner's ratio**

<table>
<thead>
<tr>
<th>Compressibility index</th>
<th>Flowability</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15</td>
<td>Excellent</td>
<td>1.05-1.18</td>
</tr>
<tr>
<td>12-16</td>
<td>Good</td>
<td>1.14-1.20</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair-passable</td>
<td>1.22-1.26</td>
</tr>
<tr>
<td>21-33</td>
<td>Poor</td>
<td>1.30-1.54</td>
</tr>
<tr>
<td>33-37</td>
<td>Very poor</td>
<td>1.50-1.61</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Very-very poor</td>
<td>&gt;1.61</td>
</tr>
</tbody>
</table>

**POST COMPRESSION EVALUATION OF TABLET**

• Weight variation
• Thickness
• Hardness
• Friability
• Disintegration
• Dissolution
• Drug content

**Weight variation**

Weight variation calculated by using 20 tablets. Weigh 20 tablets individually and calculate the average weight of 20 tablets. Than calculate the upper limit and lower limit by using the formula.

For lower limit,

\[
\text{Minimum weight} – \text{Average weight}/\text{Average Weight} \times 100
\]

For upper limit,

\[
\text{Maximum weight} – \text{Average weight}/\text{Average Weight} \times 100
\]

**Table 3: IP and USP limits for weight variation**

<table>
<thead>
<tr>
<th>IP</th>
<th>%</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 85mg</td>
<td>±10%</td>
<td>130mg or less</td>
</tr>
<tr>
<td>85mg – 250mg</td>
<td>±7.5%</td>
<td>130mg-324mg</td>
</tr>
<tr>
<td>Greater than 250</td>
<td>±5%</td>
<td>324mg or more</td>
</tr>
</tbody>
</table>

**Thickneess**

Vernier caliper is used to determine the thickness of tablet.

**Hardness**

Harness is defined as the force required to breaks the tablet. It is used to determine the strength of tablet. Monsanto hardness tester is used to determine the hardness of tablet. Hardness is measured in kg/cm2.

**Friability**

Roche Friabilator is used to determine the friability. 10 tablets are required to calculate the friability. For friability pre-weighted 10 tablets than rotate at 25 rpm for 4 minutes. After the removal of fine particles re-weight the tablets. Than percentage of weight loss will be calculated by using following formula,

\[
\% \text{ Friability} = \frac{W1-W2}{W1} \times 100
\]

Where, \(W1 = \text{Initial weight of tablets}\)
\(W2 = \text{Final weight of tablets}\)

**In vitro dissolution study of tablets**

In vitro dissolution study carried out by using USP Type-2 apparatus (Paddle type) and IP Type-1 dissolution apparatus (Paddle type). For mouth dissolving tablet phosphate buffer pH 6.8 will be required as dissolution media. Drop the single tablet in 900ml dissolution media after maintained the temperature at 37.0 ± 0.5°C and rotate at 50rpm for 60 minutes. Collect the 10ml of sample after a time interval of 5, 10, 15, 30, 45, 60 minutes. And replace with fresh dissolution media after each interval. Filter the sample with the help of 0.45µm millipore filters and analysed using a UV-visible double beam spectrophotometer.

**Drug content**

For drug content, weigh 20 tablets accurately and crush all the tablets into fine powder. Weigh the sample equivalent to active drug (in mg) and dissolve in methanol. Filter the sample through 0.45µm millipore filters and analyse under UV Spectrophotometer [49-52].

**Disintegration time**

Tablet disintegration apparatus will used to study the disintegration time. Water will used as a disintegrating
media. To carry out the test fill the vessel with 900ml of disintegration media and maintained at temperature 37 ±0.2°C. Add 6 tablets in each 6 tubes and start the apparatus. Note the time when all the tablets are completely disintegrate [53].

Conclusion
Fast dissolving tablet formulated to overcome some problem that arises with conventional dosage form such as difficulty in swallowing of tablet in pediatric and geriatric patients, bedridden patient, psychiatric patients, patients with nausea vomiting and motion sickness. Fast dissolving tablet improve drug bioavailability by avoiding first pass metabolism, improve drug efficacy and rapid onset of action due to its fast absorption through mouth. Solid dispersion is a novel technique to formulate fast dissolving tablet. Solid dispersion helps to enhance the solubility of poorly soluble drug such as BCS Class-II drug. In future fast dissolving dosage forms mostly acceptable due to its fast onset of action.

Future Directions
Future holds lots of promises in fast dissolving tablet. By further study this will be developed efficient approach and novel ideas of drug delivery system.

Reference


