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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 drug because it is the most convenient and safest route for drug delivery. Recently fast dissolving tablet (FDT) is developed by the researcher. This improved patient compliance and convenience. Fast dissolving tablet are defined as the solid dosage form which disintegrates in saliva without the need for water. Solid dispersions attract considerable interest by increasing dissolution rate and also enhance the bioavailability of poorly 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.

KEYWORDS: Fast dissolving tablet, Oral route, Solid dispersion, Method of preparation.

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. These dosage forms have some advantage and disadvantage. So, the development of an ideal drug delivery system is a big challenge to the manufacturer. 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 formulation, a thorough study about the physicochemical and biochemical properties that govern a specific dosage form of a drug should be obtained ¹.

Oral route of drug delivery is the most preferred route of drug administration to get the systemic effect. Overall 90% of the drugs used to produce systemic effects

are administered by the oral route. Tablet is the most popular dosage formulation 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 are formulated ². Fast dissolving tablet disintegrates in saliva in less than a minute without the need for water. Due to their ideal property such as administration without water anywhere and anytime lead to their suitability to geriatric and pediatric patients. They are suitable for bedridden and mentally ill patients and also suitable for patients who do not have easy access to water ³⁻⁴. According to European Pharmacopoeia orodispersible tablet should disintegrate in less than three minutes but according to USP the disintegrating time of fast dissolving tablets approximately 30 seconds or less⁵⁻⁶. 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 ⁷.

In order to increase the dissolution rate and bioavailability of poorly soluble drugs, various techniques have been introduced to enhance the dissolution rate such as micronization, solid dispersion and use of surfactant⁸. Solid dispersion attracts much of the researcher, this technology involves drugs that are poorly 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 drugs⁹.

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.
- The patient undergoing radiation therapy for breast cancer may be nauseous to swallow her H₂ blocker.
- Patient with persistent nausea, who may be a journey, or has little or no access to water.

Effectiveness factor:

- Fast dissolving tablet disintegrates in saliva in the oral cavity cause pre-gastric absorption of the drug.
- Pre-gastric absorption avoids the first-pass metabolism which increases the bioavailability of the drug¹⁰.

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 the dissolution rate and drug absorption.
- Increase the bioavailability of the drug.
- Avoid the first-pass metabolism.
- Reduce dose and dose-related side effect^{11,12}.

DISADVANTAGES OF FAST DISSOLVING TABLET

- Tablet may leave unpleasant taste and grittiness in the oral cavity if not formulated properly.

- Usually, tablets have insufficient mechanical strength. So, careful handling is required during manufacturing.
- Drug with large doses is difficult to formulate into fast dissolving tablet¹³.

SOLID DISPERSION

Solid dispersion is defined as the group of solid products consisting of at least two different components, in which one component is hydrophilic matrix and another one is a hydrophobic drug. The matrix can be either crystalline or amorphous. And the drug is dispersed in crystalline particles or in amorphous particles¹⁴.

TYPES OF SOLID DISPERSION

1. **Binary solid dispersion:** Binary solid dispersion consists of a drug and a polymeric carrier.
2. **Ternary solid dispersion:** Ternary solid dispersion contains the drug, a polymeric carrier and a surfactant.
3. **Surface solid dispersion:** Surface solid dispersion consists of polymers and copolymer. It is formulated by the 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 is formed when two components are crystallized together to form a homogeneous mixture or one phase system. Particle size reduced into molecular size in the solid solution. The solid solution helps to enhance the dissolution rate than the other 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. The glassy state is 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, the drug is precipitated out in an

amorphous form in the former as opposed to a crystalline form in the latter.

Compound or complex formation: Complex is formed when a drug and matrix strongly interact with each other to form a complex in an aqueous medium. Formation of a soluble complex takes place when a low or intermediate fraction of carrier is helpful in the preparation of solid dispersion. Dissolution may be enhanced by using high friction carrier. The low association constant is necessary for dissolution enhancement¹⁵⁻¹⁶.

ADVANTAGES OF SOLID DISPERSION

- Particles with reduced particle size and thus increase surface area which increases dissolution rate.
- Particles with the improved wet ability which results in increased solubility thus increase bioavailability.
- A drug in amorphous form result increases the solubility of the particles¹⁷⁻¹⁹.

DISADVANTAGES OF SOLID DISPERSION

- Major disadvantage is their instability.
- Temperature and moisture have a more deteriorating effect on solid dispersion.
- Difficulty in handling²⁰.

METHOD OF PREPARATION OF SOLID DISPERSION

- 1. Fusion method:** Fusion method is also called a melt method. The first solid dispersion prepared for the 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 a eutectic composition of drug and urea. The eutectic composition used to obtained crystallization of drug and matrix during cooling. Polyethylene 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. The supercritical fluid method is mostly applied to carbon dioxide. In this method, carbon dioxide is used as a 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 a solvent-free technique²¹⁻²³.
- 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 poly ethylene 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 the 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 then follow the second step. In the 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 the 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 increasing the electrostatic field it provides strength to the solution. But this electrostatic field not exceed a critical point value. At the end of process fibres of submicron diameter are produced. Evaporate the solvent and collect the fibres on the screen.
- 8. Spray freeze drying:** In a fix, concentration dissolves the drug insolvent and carrier in water. Mix this solution in a ration of 40:30. Then spray this solution into the liquid nitrogen with the help of nozzle. Set the liquid feed rate and atomize the airflow. 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 the nozzle. Finally, transfer this resulting

suspension into the lyophilizer. When all the nitrogen is evaporated than start the Lyophilization procedure ²⁴⁻²⁸.

- 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 ²⁹. The rotary processor can be used for this technique. It is easier to control the temperature ³⁰.

CONVENTIONAL TECHNIQUES USED FOR THE PREPARATION OF FAST DISSOLVING TABLET

- Disintegrant addition technique:** This is the 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.
- 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.
- 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 ³¹⁻³⁵.
- 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. A solvent like cyclohexane and benzene is used as a pore forming agent.
- 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 blend. The blended powder compressed into tablets.
- Mass extrusion:** In mass extrusion technique water-soluble mixture of polyethene
- Spray drying:** In spray drying, the 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 produces highly porous and fine powder which dissolve completely and increase disintegration and dissolution ³⁶⁻⁴⁰.

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 defined 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 be secured at a height above the paper which is placed on the flat horizontal surface. It can be calculated by the following formula ⁴¹.

$$\theta = \tan^{-1} [h/r]$$

Where, θ = angle of repose

h = height of the pile

r = radius of the cone base

Table 1 Scale of Flowability for the 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

Bulk density

Bulk density is defined as the tendency of the particles to adhere to one another ⁴². 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 into a graduated cylinder.

$$\text{Bulk Density} = \text{Mass/Bulk Volume}$$

Tapped density

Tapped density determine by using a measuring cylinder. It can be achieved by tapping the measuring cylinder which 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 ⁴³.

It is calculated by the following formula,

$$\text{Tapped Density} = \text{Mass/Tapped Volume}$$

Compressibility index

Compressibility index calculated by the basis of bulk density and tapped density. It is calculated by using the following formula ⁴⁴.

$$\text{Compressibility index} = [\text{Tapped density} - \text{Bulk density}/\text{Tapped density}] \times 100$$

Hausner ratio

Hausner ratio also determined on the basis of bulk density and tapped density ⁴⁵.

Hausner ratio calculated by using the following formula,

$$\text{Hausner ratio} = \text{Tapped density/Bulk density}$$

Table 2 Acceptance criteria of flowability for compressibility index and Hausner's ratio.

Compressibility index	Flowability	Hausner's ratio
5-15	Excellent	1.05-1.18
12-16	Good	1.14-1.20
18-21	Fair-passable	1.22-1.26
21-33	Poor	1.30-1.54
33-37	Very poor	1.50-1.61
>40	Very-very poor	>1.61

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. Then 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.

IP	%	USP
Less than 85mg	±10%	130mg or less
85mg – 250mg	±7.5%	130mg-324mg
Greater than 250	±5%	324mg or more

Thickness

Vernier calliper is used to determine the thickness of a tablet.

Hardness

The 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 the 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 the following formula,

$$\% \text{ Friability} = W_1 - W_2 / W_1 \times 100$$

Where W_1 = Initial weight of tablets

W_2 = 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 $37.0 \pm 0.5^\circ\text{C}$ and rotate at 50rpm for 60 minutes. Collect the 10ml of the 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 0.45 μm 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 a fine powder. Weigh the sample equivalent to an active drug (in mg) and dissolve in methanol. Filter the sample through 0.45 μm millipore filters and analyse under UV Spectrophotometer⁴⁶⁻⁴⁹.

Disintegration time

Tablet disintegration apparatus will be used to study the disintegration time. Water will be used as a disintegrating media. To carry out the test fill the vessel with 900ml of disintegration media and maintained at temperature $37 \pm 0.2^\circ\text{C}$. Add 6 tablets in every 6 tubes and start the apparatus. Note the time when all the tablets get completely disintegrate⁵⁰.

Conclusion

Fast dissolving tablet formulated to overcome some problem that arises with conventional dosage formulation 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 improves 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 a 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 an efficient approach and novel ideas of drug delivery system.

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