1.1 DRUG DELIVERY

A drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man and animals. Drugs are rarely administered in their original pure state. They are administered in different dosage forms after converting them into a suitable formulation. Every dosage form is a combination of the drug and different kind of components called “additives”. The additives are used to give a particular shape to the formulation, to increase its stability, palatability and to give more elegance to the preparation.\(^1\)

The goal of drug formulation and delivery is to administer a drug at a therapeutic concentration to a particular site of action for a specified period of time. The design of the final formulated product for drug delivery depends upon several factors.\(^2\)

Parameters that define the therapeutic action of drug include the site of action either targeted to a specific region of the body or systemic, the concentration of the drug at the time of administration, the amount of time the drug must remain at a therapeutic concentration, and the initial release rate of the drug for oral/controlled release systems. Moreover, the drug must remain physically and chemically stable in the formulation. The choice of delivery method must reflect the preferred administration route for the drug, such as oral, parenteral, or transdermal. The physiochemical properties of the drug both in solution and in the solid state play a critical role in drug formulation. A full characterization of the drug in the solid state will often include a determination of its melting point and heat of fusion using differential scanning calorimetry, loss of solvent upon heating using thermogravimetric analysis, and a characterization of the molecular state of the solid using diffraction and spectroscopic techniques.\(^2\)

1.2 DRUG DELIVERY SYSTEMS

Drug delivery systems (DDS) are strategic tools for expanding markets and indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. An increasing number of systems are available for drug delivery.\(^3\) The drug delivery method is chosen on the basis of the physiochemical properties of the drug, the desired site of action, the duration of action and the biological barriers (including rapid drug
metabolism) that must be overcome to deliver the drug. Some of the most common delivery methods are oral (enteral), parenteral, transdermal, and aerosol.

1.3 DOSAGE FORMS

Based on different drug delivery systems drug is transformed into different dosage forms for the following reasons:

- To protect the drug substance from oxidation, hydrolysis, and reduction. e.g. coated tablets and sealed ampoules.
- To protect the drugs form the destructive effect of gastric juice of the stomach after oral administration. e.g. enteric coated tablets.
- To provide a safe and convenient delivery of accurate dosage.
- To conceal the bitter, salty or obnoxious taste or odor of a drug substance. e.g. capsule, coated tablets and flavored syrups etc.
- To provide for the optimum drug action through inhalation therapy. e.g. inhalation aerosols and inhalants.
- To facilitate for the insertion of the drug into one of the body cavities. e.g. rectal or vaginal suppositories.
- To provide form for the maximum drug action from topical administration sites. e.g. creams, ointments, ophthalmic preparation and E.N.T. preparation.
- To provide sustained released action through controlled released mechanism. e.g. sustained released tablets, capsules and suspensions.
- To provide liquid dosage form of the drugs soluble in a suitable vehicle. e.g. solution.

1.4 SOLUBILITY

The term ‘solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the pharmacopoeia
provides general terms to describe a given range. These descriptive terms are listed in table 1.1.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parts of solvent required for one part of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very Slightly soluble</td>
<td>1000-10000</td>
</tr>
</tbody>
</table>

Noyes-Whitney equation illustrates how dissolution rate of very poorly soluble compounds may be improved to minimize the limitations to oral bioavailability.

\[ \frac{dC}{dt} * h = AD \times (C_s - C) \]

Where, \( \frac{dC}{dt} \) is the rate of dissolution, \( A \) is the surface area available for dissolution, \( D \) is the diffusion coefficient of the compound, \( C_s \) is the solubility of the compound in the dissolution medium, \( C \) is the concentration of drug in the medium at time \( t \), \( h \) is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.9,10

Solubility enhancement occupies an important place especially in regard to poorly soluble drugs and in absence of proper water solubility the bioavailability of some useful and important drugs remains a problem.

1.5 SOLUBILITY ENHANCEMENT11,12

Co solvency

Weak electrolytes and nonpolar molecules frequently have poor water solubility. Their solubility usually can be increased by the addition of water miscible solvent in which
the drug has good solubility. This process is known as cosolvency and the solvents used in combination to increase the solubility of the drugs are known as cosolvents.

**Hydrotropy**

The term “hydrotropy” has been used to designate the increase in aqueous solubility of various poorly water soluble compounds due to the presence of a large amount of additives. Concentrated solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been employed to enhance the aqueous solubility and dissolution of a large number of drugs.

**Solid dispersions**

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products. Solid dispersions are prepared by using several methods including the fusion (melt) method and the solvent method. A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available.

**Micronization**

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).

**Nanonisation**

It is a process whereby the drug powder is converted to nanocrystals of sizes 200-600 nm. The nanocrystals yield as a dispersion of drug nanocrystals in a liquid, typically called “nanosuspension”.
Change in dielectric constant of solvent

The addition of a cosolvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant.

Amorphous forms

They have atoms or molecules randomly placed as in a liquid and have higher thermodynamic energy than corresponding crystalline forms. Solubilities as well as dissolution rates are generally greater.

Chemical modification of the drug

It is done by the addition of polar groups like carboxylic acids, ketones and amines increase solubility by increasing hydrogen bonding and the interaction with water.

Lipid based formulations

The formulations include lipid solutions, lipid emulsions, micro-emulsions and self dispensing lipid formulations (SDLF). Bioavailability enhancement with lipids occurs due to the solubilization of the poorly soluble drugs. Lipid solutions consist of drug dissolved in vegetable oil or medium chain triglycerides. The lipid emulsions and SDLF essentially comprise of lipid and surfactant mixture. These formulations are mainly employed for oral use.

Use of surfactant

Surfactants are amphipathic in nature, meaning they have polar end (the circular head) and non-polar end (the tail). When a surfactant (e.g. Tween-80, sodium lauryl sulphate, polyethylene glycol, propylene glycol, polyvinyl pyrrolidone K30) is placed in water, it forms micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubilize the complex.

Inclusion complexes or clathrates

Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. β- Cyclodextrins can solubilize water insoluble drugs.
Alteration of pH of solvent

pH of solvent when reduced causes solubility enhancement. A combined effect of pH and complexation on solubilization is also synergistic in nature.

Use of hydrates or solvates

A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. Stoichiometric adducts, commonly referred to as “Solvate”, is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as “hydrate”. A compound not containing any water within its crystal structure is termed “anhydrous”. Aqueous solubilities of anhydrous forms are higher than the hydrate forms.

Use of soluble prodrug

The physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility.

Application of ultrasonic waves

Solubility increase by use of ultrasonic vibrators is also possible. An oscillator of high frequency (100-500 KHz) is used and device is known as “Pohlman whistle”.

Functional polymer technology

Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, “resinate”, can be formulated as a suspension, dry powder or tablet. The functional polymers are DUOLITE™ AP 143 which is a cation exchange resin and AMBERLITE™ IPR69 which is anion exchange resin.
**Porous microparticle technology**

In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles.

**Controlled precipitation technology**

In this process, the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals.

**Supercritical fluid recrystallisation**

Another novel nanosizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid processes. Supercritical fluids (e.g.: carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas.

**Spray freezing into liquid (SFL)**

This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO₂, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluoroethers).

**Solvent deposition**

In this method, the poorly aqueous soluble drug is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose evaporation of solvent.

**Precipitation**

In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as “Hydrosol”.
1.6 SOLID DISPERSIONS\textsuperscript{13}

Two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.

1.6.1 ADVANTAGES OF SOLID DISPERSION\textsuperscript{13}

Reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

Improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties for instance; solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after
system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.

1.6.2 CLASSIFICATION OF SOLID DISPERSIONS

First generation solid dispersions

The first description of solid dispersions given from Sekiguchi and Obi in 1961 showed that formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. They have the disadvantage of forming crystalline solid dispersions, which are more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions

It was noticed in the late sixties, that solid dispersion with drug in the crystalline state is not as effective as amorphous because they are thermodynamically stable therefore, second generation of solid dispersions are introduced having amorphous carriers instead of crystalline.

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. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug. Surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility.
1.6.3 METHODS OF PREPARATION OF SOLID DISPERSIONS\textsuperscript{15-18}

**Fusion method**

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The dispersion consists of drug and carrier as a matrix which are melted using a physical mixture at the eutectic composition, followed by a cooling step. This method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. This method has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate.

**Melt extrusion method**

The drug and carrier mixture is typically processed with a twin-screw extruder. The drug and carrier mixture is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. Solid dispersion by this method is composed of active ingredient and carrier, and prepared by hot-stage extrusion using a co-rotating twin-screw extruder as shown in Fig.1.2 and 1.3.

![Fig.1.2 Screw and kneading elements\textsuperscript{17}](image)
Solvent method

Solid dispersion prepared by solvent method is termed by Bates as coprecipitates. In this method drug & carrier are dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve.

Melt agglomeration method

This technique has been used to prepare solid dispersions where in the binder itself acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer.

Supercritical fluid method

Super critical fluid technique can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. The physical and thermal properties of super critical fluids fall between those of the pure liquid and gas. Super critical fluids offer liquid-like densities, gas-like viscosities, gas-like compressibility properties and higher diffusivities than liquids.

Dropping method
It is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

**Direct capsule filling method**

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature. It is not until much later that the potential application of the technique for solid dispersions is fully realized.

**Surface active carriers (Surfactants)**

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/ dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Recently a new class of surfactant known as Gelucires is introduced which identify by melting points and HLB values.

**1.6.4 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 for the following:

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug and to dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form and to formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

1.6.5 NOVEL DRUG - DRUG SOLID DISPERSION

Earlier studies reveal that solid dispersion approach has been extensively used by the researchers for enhancing the dissolution characteristics of poorly soluble drugs and encouraging results have been reported by them. The enhanced dissolution of poorly soluble drugs such as griesiofulvin\textsuperscript{19}, prednisone\textsuperscript{20}, naproxen\textsuperscript{21} and triamterene\textsuperscript{22} from solid dispersion has been well documented. In the recent past, similar studies have been performed on glibenclamide\textsuperscript{23}, clofibrate\textsuperscript{24}, zolpidem\textsuperscript{25}, albendazole\textsuperscript{26}, allopurinol\textsuperscript{27} and promising results are reported. On careful analysis of the literature on the solid dispersion of several drugs, it look apparent that a physiologically inert carrier has been employed as a solid solvent which is incorporated in a solid drug to effect solid dispersion\textsuperscript{28}. In the modern clinical practice, single drugs are seldom prescribed for the treatment of acute or chronic ailment. Fixed dose combination of drugs has become a rule rather than exception in combating many clinical disorders; in all combination of drugs the therapeutic benefits have been justified. In other words, the relationships between the physiological interactions between the drugs that are used in combinations have been well explored. However, whether the pharmaceutical factors related to the drugs in combinations seems to have been given better consideration need to be examined. The fixed dose combination of drugs is effective in the treatment of essential hypertension and of systolic hypertension in the elderly patient\textsuperscript{29}. Considering the above factors a novel solid dispersion approach is now being researched by the scientists around the world wherein the poorly soluble drug can be solid dispersed in the water soluble drug (both type of drugs available in a fixed dose combination) that improves dissolution of the poorly soluble drug and hence its absorption.

1.7 TABLET\textsuperscript{30, 31}

A tablet is a solid dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients include diluents, binders or granulating agents, glidants and lubricants to ensure efficient tableting, disintegrants to promote tablet break-up in the digestive tract,
sweeteners and flavors to enhance taste and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment. About two-thirds of all prescriptions are solid dosage forms and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site. It is usually taken orally, but can be also administered by sublingually and buccally. Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified.

1.7.1 TYPES OF TABLET

Tablet may be uncoated or coated. Uncoated tablets are chewable tablet, effervescent tablet, lozenge tablet, soluble tablet, and sublingual tablet. Coated tablets are enteric coated tablet, film coated tablet, implant, sugar coated tablet, and modified-release tablet.

**Chewable tablet**

The tablet which is intended to be broken and chewed in between the teeth before ingestion. Antacid and vitamin tablets are usually prepared as chewable tablets.

**Effervescent tablet**

The tablet that contains acid substances and carbonate or hydrogen carbonate that react rapidly in the presence of water to release carbon dioxide. Sodium bicarbonate, citric acid and tartaric acid are added to the active ingredients to make the tablet effervescent.

**Lozenge tablet**

The tablet that is intended to produce continuous effect on the mucous membrane of the throat. There is no disintegrating agent. The quality of the binding agent is increased so as to produce slow dissolution. Suitable sweetening, coloring and flavoring agents must be included in this formulation. Gum is used to give strength and cohesiveness to the lozenge and facilitating slow release of the active ingredient.
Soluble tablet

The tablet that dissolves completely in liquid to produce solution of definite concentration. Mouth wash, gargle, skin lotion, douche, antibiotic, certain vitamins, and aspirin are given in this formulation.

Sublingual tablet

The drug which is destroyed or inactivated within the gastrointestinal tract can be absorbed through the mucosal tissue of the oral cavity is usually given in this formulation. The tablet is required to be placed below the tongue for the slow release of drug. But for immediate effect some medicaments are formulated in such a way to dissolve within 1 to 2 minutes.

Enteric coated tablet

Some drugs are destroyed by gastric juice or causes irritation to the stomach. These two factors can be overcome by coating the tablet with cellulose acetate phthalate. This polymer is insoluble in gastric contents but readily dissolves in intestinal contents. So there is delay in the disintegration of dosage form until it reaches the small intestine. Broken or crushed form of the enteric coated tablet causes destruction of the drug by gastric juice or irritation to the stomach.

Film coated tablet

The tablet that is covered with a thin layer or film of polymeric substance which protects the drug from atmospheric conditions and mask the objectionable taste and the odor of drug.

Implant

A small tablet that is prepared for insertion under the skin by giving a small surgical cut into the skin which is stitched after the insertion of the tablet. The drug used in this preparation is usually water insoluble and the tablet provides a slow and continuous release of drug over prolonged period of time ranging from 3 to 6 months or even more.
Sugar coated tablet

The tablet that contains active ingredient of unpleasant taste may be covered with sugar to make it more palatable. This type of tablet should be administered in whole form, otherwise the patient will experience the unpleasant taste of the active ingredient.

Modified release tablet

Modified-released tablet is either uncoated or coated. This contains special additives or prepared by special procedure which, separately or together, is intended to modify the rate of release of the drug into the gastrointestinal tract and also reduces the frequency of administration of drug.

1.8 DISADVANTAGES OF EXISTING ORAL DOSAGE FORM\textsuperscript{32}

- Patient who suffer from tremors therefore they have difficulty to take powder and liquids.
- In dysphasia physical obstacles and adherence to esophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system.
- Suspension and emulsion are packed in multidose container therefore achievement of uniformity in the content of each dose may be difficult.
- Buccal and sublingual formation may cause irritation to oral mucosa so patients refuse to use such medications.

Oral dosage forms have disadvantage of slow dissolution rate while this problem can be overcome with mouth dissolving tablets which contain super disintegrants in their formulation.

1.9 CRITERIA FOR FAST DISSOLVING DRUG DELIVERY SYSTEM\textsuperscript{33}

- It should not require water to swallow, but it should dissolve or disintegrate in the mouth within matter of seconds.
Be compatible with taste masking and be portable without fragility concern.

Have a pleasing mouth feel and leave minimal or no residue in the mouth after oral administration.

Exhibit low sensitivity to environmental condition as humidity and temperature.

Be manufactured using conventional processing and packaging equipment at low cost.

1.9.1 IDEAL CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEM

Mouth-feel

Mouth-feel is critical, and patients should receive a product that gives pleasant feeling. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. Certain flavors improve mouth-feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth-feel by reducing the “dryness” of a product.

Friability

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and brittle which are difficult to handle, often requiring specialized peel off blister packing.

1.9.2 ADVANTAGES OF FAST DISSOLVING DRUG DELIVERY SYSTEM

Improved compliance and cost effectiveness

Quick dissolution, disintegration and release

No water and no chewing needed

Better taste and improved stability

Suitable for controlled/sustained release actives

Allows high drug loading.
Ability to provide advantages of liquid medication in the form of solid preparation.

Adaptable and amenable to existing processing and packaging machinery.

1.9.3 TECHNIQUES USED IN THE PREPARATION OF FAST DISSOLVING DOSAGE FORM

- Freeze drying technique
- Tablet molding technique
- Spray drying technique
- Direct compression technique
- Sublimation technique
- Mass extrusion technique

**Freeze drying technology (Zydis technology)**

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.

**Tablet molding**

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet.
Spray drying\textsuperscript{35}

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly, spray drying can produce highly porous and fine powder. Spray drying can be used to prepare rapidly disintegrating tablets.

Direct compression method\textsuperscript{35}

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Sublimation technique\textsuperscript{35,46}

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

Mass-extrusion\textsuperscript{35}

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.

1.10 FUTURE PROSPECTS\textsuperscript{43,47,48,49}

One major focus of future research will be identification of new surface-active carriers and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion system may be the inadequate drug solubility in
carriers, so a wider choice will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention should also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipoidal in nature, so potential roles of such carriers on drug absorption, especially on their p-glycoprotein-mediated drug efflux, will require careful consideration. In addition to bioavailability enhancement, much recent research on solid dispersion systems is directed towards the development of extended-release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.
REFERENCES


