

Rapid Melts: A Review

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ABSTRACT

Oral drug delivery remains the most preferred route of administration of various therapeutic agents. Over a decade the demand for development of rapid melts has enormously increased as it has significant impact on the patient compliance. Rapid melts are solid unit dosage forms which dissolve or disintegrate in mouth without water or chewing. Prescription rapid melts are initially developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric and psychiatric patients with dysphasia. Technologies used for manufacturing of rapid melts are either conventional or patented technologies. Important ingredients that are used in the formulation of rapid melts should allow quick release of drug, resulting in faster dissolution.

Keywords: Rapid melts, superdisintegrants, oral route, excipients.

INTRODUCTION

Oral route of administration has wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. Oral dosage forms like tablets, capsules possessing great problem of swallowing mainly for pediatrics, geriatrics, nauseous, noncompliant and bedridden patients. Oral disintegrating dosage forms have to be placed in mouth and get dispersed in saliva without need of water. This is an innovative tablet technology where the dosage form containing drugs that disintegrates rapidly and dissolves in mouth without need of water, providing optimal convenience to the patient. Orally disintegrating tablet is a solid dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60sec or less. Drug absorption will take place through oral mucosa and through pre and post gastric parts of GIT.

USFDA defines orally disintegrating tablet as "a solid dosage form which contains a medicinal substance or active ingredient which disintegrates rapidly within matter of seconds when placed upon the tongue. European pharmacopeia described ODT as "uncoated tablets intended to be placed in the mouth where they disperse before being swallowed." After coming in contact with saliva ODS disintegrates immediately and produce a suspension that can be easily swallowed by the patient. The active ingredients in solution

are more rapidly absorbed through pregastric route from mouth, pharynx, and esophagus and through epithelium to produce the desired effect. Formulation of ODTs can be studied as one of the ways to improve the bioavailability of poorly water soluble drugs and it has been observed that ODT increase the bioavailability of such type of drugs.

Oral disintegrating tablets are also known as fast dissolving tablets, rapid melts, porous tablets, melt in mouth tablets, mouth dissolving tablets.

Significance of oral disintegrating tablets

Oral disintegrating tablets offer dual advantages of both solid and liquid dosage forms in terms of stability and bioavailability.

1. No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and don't have immediate access to water.
2. No risk of suffocation in airways due to physical abstraction when swallowed, thus providing improved safety and compliance.
3. Rapid dissolution and absorption of drug, which will produce quick onset of action. Bioavailability is enhanced due to absorption from mouth, pharynx and esophagus.
4. Being a solid dosage form it provides luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability.

5. Pregastric absorption can result in improved bioavailability and reduced dosage, improved clinical performance through a reduction of unwanted effects.
6. Good mouth feel character helps to change the perception of medication as better pill particularly in pediatric patients.
7. An increased bioavailability especially in hydrophobic drugs due to rapid disintegration and dissolution of these tablets.
8. Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.
9. Provide new business opportunities in the form of product differentiation, line extension and lifestyle management no specific packaging is required.
10. No specific packaging is required.
11. Minimum risk of suffocation in airways due to physical obstruction when ODT's are swallowed, thus they provide improved safety and compliance with their administrations.
12. Pregastric absorption result in improved bioavailability and because of reduced dosage form improved clinical performance through a reduction of unwanted effects.
13. An increased bioavailability particularly incase of insoluble and hydrophobic drugs, due to rapid dissolution and disintegration of these tablets.
14. Rapid onset of action.
15. Rapid drug therapy intervention.
16. Provide advantage of liquid medication in form of solid preparation.
17. Allow high drug loading.
18. Adaptable and amenable to existing processing and packaging machinery.
19. No chewing needed.
20. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Ideal characteristics of rapid melts

1. No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.
2. Provide pleasant feeling in the mouth.
3. Be compatible with taste masking.
4. Leave negligible or no residue in the mouth after oral administration.
5. Dissolve or disperse in the mouth within matter of seconds.
6. Exhibit low sensitivity to environmental conditions as humidity and temperature.
7. Allow the manufacture of tablet using conventional processing and packing equipments at low cost.
8. Less friable and should have sufficient hardness.

Advantages of rapid melts

1. Improved patient compliance.
2. Rapid onset of action and may offer an improved bioavailability.
3. Useful for pediatric, geriatric and psychiatric patients.
4. Suitable during travelling where water may not be available.
5. High drug loading is possible.
6. Leave minimum residue in the mouth after oral administration.
7. Cost effective.
8. Conventional manufacturing equipment.
9. Good chemical stability as conventional oral solid dosage form.
10. No specific packaging is required.

Selection of drug

The ideal characteristics of a drug for *in vivo* dissolution from an ODT include

1. No bitter taste.
2. Small to moderate molecular weight
3. Good stability in water and saliva.
4. Ability to diffuse and partition into the epithelium of the upper GIT(log P>1 preferably >2)
5. Dose should be as low as possible.(less than 50mg)
6. Ability to permeate the oral mucous tissue.
7. Partially nonionised at the oral cavities.

Unsuitable drug characteristics

1. Short half life and frequent dosing.
2. Very bitter or unacceptable odour and taste of drugs.
3. Drugs which require controlled or sustained release.

Challenges in the formulation of rapid melts

1. It is difficult to achieve sufficient mechanical strength.
2. It is a challenge to achieve rapid disintegration of the tablet.
3. Selection of polymer and it's concentration for the coating of drug

particle is a complicated task since the thickening of drug particle coating or h dependent solubility of coated polymer such as methacrylate of pvp effect the dissolution profile.

4. To achieve better patient compliance it is expected that no residue should remain in the mouth after swallowing.
5. Some API's have bitter taste and it is a big challenge for the formulation scientist to achieve acceptable taste masking for such ingredients.

Taste masking of rapidmelts

Taste masking is the first and foremost task in the preparation of ODT. A number of taste masking techniques is available. They are

1. Layering of drug onto the inert beads using a binder and its subsequent coating with a taste masking polymer.
2. Granulating the drugs and subsequent coating with a taste masking polymer.
3. Spray drying the drug disperses or dissolved in polymeric solution to get taste masked polymer.
4. Complexation by inclusion in cyclodextrins or drug resinsates complex formation.
5. Co-acervation to make the drug microencapsulated with a polymer.
6. Formation of pellets by extrusion spheronisation.
7. Taste masking can be done by lipophilic vehicles and ion exchange resins.

Excipients commonly used for rapid melts

ODT'S contain active drug, mixture of excipients comprising at least one disintegrant, a diluent, a lubricant, optionally sweetening agent, a permeabilising agent. Diluents most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starch, lactose and mannitol. The most common antistatic agents used are colloidal silica, β -cyclodextrins, magnesium stearate, stearic acid ...etc..

Ideal bulk excipients for orally disintegrating dosage forms should have the following properties.

1. Disperses and dissolves in the mouth within a few seconds without leaving any residue.
2. Masks the drug's offensive taste and offers a pleasant mouth feel.
3. Enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature.

The role of excipients is important in the formulation of fast-melting tablets. The

temperature of the excipients should be preferably around 30–35°C for faster melting properties.

Super disintegrants

Superdisintegrant plays a major role of in orodispersible tablet. The most commonly used Superdisintegrant are crosscarmellose sodium, crosspovidone, SSG.

Selection of super disintegrants

1. It should produce rapid disintegration, when tablet meets saliva in mouth.
2. It should be compatible enough to produce less friable tablets.
3. It should produce good mouth feel.
4. Small particle size is preferred to achieve patient compliance.
5. It should improve flow ability in mouth.

Mechanism of tablet disintegration

There are five major mechanisms for tablet disintegration as follows:-

1. Swelling
2. Porosity and Capillary Action (Wicking)
3. Deformation
4. Due to disintegrating particle/particle repulsive forces
5. Enzymatic reaction

1. Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down. .E.g. Sodium starch glycolate, Platago Ovata.

2. Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

3. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with "nonswellable" disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

4. Due to Deformation

Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.

5. By Enzymatic Reaction

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

Method of Incorporation of superdisintegrants

The incorporation of superdisintegrants in the dosage forms are mainly of three types:-

Intragranular or during granulation

In this process the superdisintegrants are blend with other powders and granulation is carried out. Thus the superdisintegrants are incorporated within the granules.

Extra granular or prior to compression

In this process superdisintegrants are mixed with reared granule before compression.

Incorporation of superdisintegrants at intra and extra granulation steps

In this process part of superdisintegrants are added to intragranular and a part to extragranules. This method usually produces better results and more complete disintegration than type I and type- II.

Types of superdisintegrants

Superdisintegrants are classified into two different types.

1. Natural superdisintegrants
2. Synthetic superdisintegrants

Natural Superdisintegrants

These superdisintegrating agents are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature. The natural materials like gums and mucilages have been extensively used in the field of drug delivery for their easy availability, cost effectiveness, Eco friendliness, emollient and non-irritant nature, non-toxicity, capable of multitude of chemical modifications, potentially degradable and compatible due to natural origin. There are several gums and mucilages are available which have superdisintegrating activity.

Plantago Ovata Seed Mucilage (Isapgula)

Isapgula consists of dried seeds of the plant plantagoovata and it contains mucilage which is present in theepidermis of the seeds. The seeds of Plantagoovatawere soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water. The material was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C.The mucilage of plantagoovatais a recent innovation for its superdisintegration property when compared with Crospovidone. It shows faster disintegration time than the superdisintegrant,Crospovidone

Lepidium sativum Mucilage

Lepidium sativum (family: Cruciferae) is known as asaliyo and is widely used as herbal medicine in India. It is widely available in market and has very low cost. Parts used are leaves, root, oil, seeds etc. Seeds contain higheramount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, Eand F and two new monomeric imidazole alkaloids semilepidinosideA and B. Mucilage of

Lepidium sativum has various characteristic like binding, disintegrating, gelling.

Gum Karaya

Gum Karaya is a negative colloid and a complex polysaccharide of high molecular weight. On hydrolysis it yields galactose, rhamnose and galacturonic acid. Gum Karaya occurs as a partially acetylated derivative. It is a dried exudation of *Sterculia urens* tree (Family-Sterculiaceae). Its synonyms are Karaya, *sterculia*, *Indiantragacanth*, *Bassoratrtragacanth*, *kadaya*, *Kadira*, *katila*. Gum Karaya is compatible with other plant hydrocolloids as well as proteins and carbohydrates.

Fenugreek Seed Mucilage

Trigonella foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family. It has found wide applications as a food, a food additive, and as a traditional medicine. The leaves and both the ripe and unripe seeds of *Trigonella foenum-graceum* are used as vegetables. Fenugreek has been used in treating colic flatulence, dysentery, diarrhoea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes. It is also used as gastro protective, antiurolithiatic, diuretic, antidandruff agent, Antiinflammatory agent and as antioxidant. The seed is stated to be a tonic. It also is used in post-natal care and to increase lactation in nursing mothers. Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage-containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids. The resulting soft mass is not absorbed by the body, but instead passes through the intestines and triggers intestinal muscle contractions.

Guar gum

Guar gum is a galactomannan, commonly used in cosmetics, food products and in pharmaceutical formulations. Guar gum is mainly consisting of the high molecular weight (approximately 50,000-8,000,000) polysaccharides composed of galactomannans and is obtained from the endosperm of the seed of the guar plant, *Cyamopsis tetragonoloba* (L) Taub. (Synonym-*Cyamopsis psoraloides*). It is used as thickener, stabilizer and emulsifier, and approved in most areas of the world (e.g. EU,

USA, Japan, and Australia). Its synonyms are Galactosol; guar flour; jaguar gum; meprogat; meyprodor. It has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, and in oral and topical products as a suspending, thickening, and stabilizing agent, and also as a controlled release carrier. Guar gum has also been examined for use in colonic drug delivery.

Cassia fistula gum

Seeds of *Cassia fistula* gum obtained from *Cassia fistula* tree. Gum obtained from the seeds of *Cassia fistula* comprises $\beta(1\rightarrow4)$ linked d-mannopyranose units with random distribution of $\alpha(1\rightarrow6)$ linked d-galactopyranose units as side chain having mannose:galactose ratio of 3.0). Carboxymethylation as well as carbamoylethylation of *Cassia* gum is reported to improve cold water solubility, improve viscosity and increase microbial resistance as compared to native gum. Therefore, an attempt was made to incorporate calcium or sodium salts of carboxymethylated or carbamoylethylated *C. fistula* gum as superdisintegrant in the formulation development of FDT.

Locust Bean gum

Locust bean gum is extracted from the endosperm of the seeds of the carob tree *Ceratoniasiliqua*, which grows in Mediterranean countries. It is also called Carob bean gum. Some other familiar polysaccharides are starch and cellulose, which are made of long chains of the sugar glucose. In locust bean gum, the ratio of mannose to galactose is higher than in guar gum, giving it slightly different properties, and allowing the two gums to interact synergistically so that together they make a thicker gel than either one alone. It shows as a binder and as a disintegrant property at different concentration. Pharmaceutical application of locust bean gum in various novel drug delivery systems. Locust bean gum has been widely used in food industry as a thickening and gelling agent. Locust bean gum has also been reported to have bioadhesive and solubility enhancement properties. There are various reports that Locust bean gum can be used in pharmaceutical and biotechnological purpose.

Hibiscus rosa-sinensis Linn. Mucilage

Hibiscus rosa-sinensis Linn of the Malvaceae family is also known as the shoe-

flower plant, China rose, and Chinese hibiscus. The plant is available in India in large quantities and its mucilage has been found to act as a superdisintegrant. The plant contains cyclopropanoids, methyl stercolate, methyl- 2-hydroxystercolate, 2-hydroxystercolate malvate and β -rosasterol. The leaves contain carotene (7.34 mg/100 g of fresh material) moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorus. Mucilage of Hibiscus rosa-sinensis contains L- rhamnase, D- galactose, D- galactouronic acid, and D- glucuronic acid.

Mango Peel Pectin

Dried mango peel powder is used for extracting pectin. Rather mango peel pectin cannot be used for promising the behaviour of superdisintegrants, but due to its good swelling index and good solubility in biological fluids it can be used to prepare fast dispersible tablets.

Synthetic Superdisintegrants

A group of superdisintegrants including croscarmellose sodium (Ac-Di-Sol) sodium starch glycolate (Primojel and Explotab) and crospovidone (Polyplasdone XL) alleviate most of these problems. Use of the superdisintegrants in fast dispersible tablet is possible as tablet shows optimum physical properties.

Advantages of Synthetic Superdisintegrants

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly.

Sodium Starch Glycolate: (Explotab, Primogel)

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is recommended to use in tablets prepared by either direct-compression or wet-granulation processes. The recommended concentration in a formulation is 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. The disintegrant efficiency of sodium starch glycolate is unimpaired in the presence of hydrophobic excipients, such as lubricants unlike many other disintegrants. Increasing the tablet compression pressure also appears to have no effect on disintegration time. These are modified

starches with dramatic disintegrating properties and are available as explotab and primogel which are low substituted carboxy methyl starches. Explotab consisting of granules that absorb water rapidly and swell. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration. The natural predried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water.

Cross-linked polyvinyl pyrrolidone: (crospovidone, PolyplasdoneXL, XL10)

Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, Crospovidone superdisintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in ODT formulations. Swells very little and returns to original size after compression but act by capillary action. Unlike other superdisintegrants, which rely principally on swelling for disintegration, Polyplasdone disintegrants use a combination of mechanisms to provide rapid disintegration. Although Polyplasdone polymers swell by 95% to 120% upon contact with water, swelling is not the only mechanism for tablet disintegration. Swelling or swell volume is mainly a measure of the change in volume of the disintegrant after it is introduced to an aqueous solution and the system has reached equilibrium. However, swell volume does not measure the rate at which a disintegrant absorbs water and swells or the pressure generated by swelling. Polyplasdone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed polyplasdone particles come in contact with water that is wicked into the tablet, the polyplasdone particles recover their normal structure and then swell, resulting in rapid volume expansion

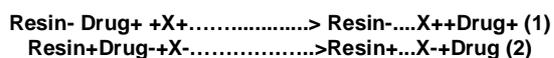
and high hydrostatic pressures that cause tablet disintegration.

Modified Cellulose (croscarmellose sodium, Ac-DiSol)

Croscarmellose sodium is described as a cross-linked polymer of carboxy methyl cellulose (CMC). This polymer is different in synthesis and structure as compare to Sodium starch glycolate. Most importantly, the degree of substitution using Williamson's ether synthesis of croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of crosslinking is also different. The chemistry of SSG is different that of cross carmellose sodium as some of the carboxymethyl groups themselves are used to cross-link the cellulose chains. For example, the cross-linking in Primogel are phosphate ester rather than carboxyl ester linksas compare to Cross carmellose sodium. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Resins

Resins although insoluble, have great affinity for water and hence, act as disintegrant. Moreover, because of their smaller particle size the rate of swelling is high making them Superdisintegrant. Like conventional disintegrant, they don't lump but additionally impart strength to the tablets. The use of ion exchange resins into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. Drug, molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins as shown below,



Where, X and Y are ions in the gastrointestinal tract.

OTHER INGREDIENTS

Diluents or fillers

Diluents are used to increase the bulkiness of the dosage form. Examples are mannitol, sorbitol, calcium carbonate, magnesium carbonate...etc.

Binders

Binders are used to maintain the integrity of dosage form before administration. Examples are poly vinyl alcohol, poly vinyl pyrrolidine, hydroxy propyl methyl cellulose.

Lubricants

Lubricant helps reduce friction and wear by introducing a lubricating film between mechanical moving parts of tablet punching machine.

Sweeteners and sugar based excipients

Sugar based excipients acts as bulking agents. These exhibits high aqueous solubility and sweetness and hence imparts taste masking property and pleasant mouth feel. Examples are mannitol, sorbitol, maltose, dextrose, and fructose....etc.

Surface active agents

They will reduce the interfacial tension and thus enhances the solubilisation of ODT. Examples are sodium lauryl sulphate, tweens...etc.

Flavors

Flavors increases the patient compliance and acceptability. Examples are peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil.

Colors

Enhances the appearance and organic properties of dosage form. Examples are Sunset yellow, Amaranth, Red iron oxide...etc.

Techniques for the prearation of raid melts conventional technologies

Freeze drying or lyophilization

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze- dried forms offer more rapid dissolution than other available solid products. The lyophilization processes imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristic of the formulation. The entire freeze drying process is done at nonelevated temperature to eliminate adverse thermal effects that may affect drug stability. The major disadvantages of lyophilization technique are that it is expensive and time

consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions and their limited ability to accommodate adequate concentration of drugs.

Direct compression

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescent agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble superdisintegrants like sodium starch glycolate and Crosscarmellose sodium show better disintegration property than the slightly water soluble agents like Crosspovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of Superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The Superdisintegrant may be used alone or in combination with other superdisintegrants.

Molding

Molded tablets, usually prepared from soluble ingredients, by compressing a powder mixture which is moistened with a solvent, into mould plates to form a wetted mass. Recently, molded forms have been prepared directly from a molten matrix, in which the drug is dissolved or dispersed or by evaporating the solvent from a drug solution or suspension at a standard pressure. Usually molded tablets are

compressed at a lower pressure than are conventional are conventional tablets, and possess a porous structure that hastens dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Unfortunately, molded tablets typically do not possess great mechanical strength. Erosion and breakage of the molded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases.

Mass extrusion Method

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with different super disintegrants. e.g. sodium starch glycolate, crosscarmellose sodium and crosspovidone.

Melt granulation method

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate@PEG-6-stearate).

Superpolystate@ is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues.

Phase transition process

Kuno et al proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, rapid Melts were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 - 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compatibility.

Sublimation

The slow dissolution of the compressed tablet containing even highly water soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When inert volatile solid ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane were added to along with other tablet excipients and the blend was compressed in to a table, which are finally subjected to a process of sublimation resulting in highly porous structures. Sublimation has been used to produce MDTs with high porosity. These compressed tablets exhibit good mechanical strength and have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

Patented technologies

Zydis technology

Zydis was the first marketed technology developed by R.P.Scherer, Inc. for formation of new generation tablets. Zydis, the best known of the fast dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolve in a matrix composed of two components, a saccharide e.g. mannitol and a polymer. When Zydis units are kept in the mouth the freeze dried structure disintegrates instantaneously and does not require water for swallowing. Polymers such as gelatin, dextran or are incorporated to impart strength during handling. Mannitol or sorbitols are incorporated, to obtain crystallinity, elegance and hardness. Flocculating agents (e.g. xanthan gum and acacia) to provide uniform dispersion of drug

particles; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulphate) to improve transmucosal permeability; pH adjusters (e.g. citric acid) to optimize chemical stability; flavours and sweeteners to improve patient compliance. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Gums prevent the sedimentation of dispersed particles in manufacturing process. Collapse protectants like gelatin prevents the shrinkage of Zydis units during freeze-drying process or on long term storage. The product is very light weight and fragile, and must be dispensed in a special blister pack.

OraSolv technology

OraSolv was Cima's first fast dissolving/disintegrating dosage form. In this system active medicament is taste masked, contains disintegrating agent. The disintegration of ODT in the mouth is caused by the action of an effervescent agent, activated by saliva. The amount of effervescent agent is in general about 20-25% of the total weight of the tablet. The widely used effervescent disintegration pair usually include an acid source (citric, tartaric, malic, fumaric, adipic and succinics) and a carbonate source (sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate). The microspheres are loosely compressed to maintain the integrity of the coating. The major disadvantage of the OraSolv formulations is its mechanical strength. For that reason, Cima developed a special handling and packaging system for OraSolv. Manufacturing requires a controlled environment at low relative humidity and protection of the final tablets with moisture impermeable blisters.

Durasolv technology

Durasolv is CIMA's second generation fast dissolving or disintegrating tablet formulation to produce stronger tablets for packing in conventional blisters or bottles. Durasolv has much higher mechanical strength due to use of the higher compaction pressure during tableting. One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to high pressure during compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting drugs to the patient taste buds. So this technology is good for tablets having low amount of active ingredients.

Wow tab technology

The WOW in the WOWTAB signifies the tablet is to be given without water. This technology utilizes sugar and sugar-like excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. The two different saccharides are those with high mold ability like maltose, mannitol, sorbitol, and oligosaccharides. (good binding property) and low mold ability like lactose, glucose, mannitol, xylitol (rapid dissolution). Tablets produced from this technology will have sufficient hardness to maintain the physical characteristics of the dosage form during production until it comes in contact with moisture such as saliva in mouth. Due to the significant hardness the WOWTAB formulation is more stable to the environment than the Zydis and Orasolv. Erythritol was found to be the best sugar for this type of formulation, showing rapid disintegration which is unaffected by tablet hardness.

Cotton candy process

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. The cotton candy process also known as the candy floss process. A mouth dissolving tablet is formed using candy floss or shear form matrix. It involves the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallised to have improved flow properties and compressability. This candy floss matrix is then milled and blended with active ingredients, excipients and subsequently compressed to ODT. This process can accommodate larger drug doses and offer improved mechanical strength. However, high process temperature limits the use of this process.

Oraquick technolog

The Oraquick fast dissolving/ disintegrating tablets formulation utilizes a patented taste masking technology. This taste masking process does not utilize solvents of any kind, so leads to faster and more efficient production. During processing low-heat is produced so this technique is suitable for heat sensitive drugs. KV pharmaceuticals also claim that the matrix that surrounds and protects the drug powder in microencapsulated particle is more pliable. This technique gives tablets with good taste masking and quick dissolution in matter of seconds.

Nanocrystal technology

NanoCrystal™ Fast dissolving technology provides for: Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix. Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded As Safe) ingredients, filled into blisters, and lyophilized. This method avoids manufacturing process such as granulation, blending and tableting which is more advantages for highly potent and hazardous drugs. For fast dissolving tablets, Elans proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase dissolution rate.

Shearform technology

In this technology, a shearform matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. This is followed by its exit through the spinning head that flings the floss under centrifugal force and draws into long and thin floss fibres, which are usually amorphous in nature. The floss so produced is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to rapid solubilisation of sugars in presence of saliva.

Pharmaburst technology

Pharmaburst technology is patented by SPI pharma. Pharmaburst technology uses off the shelf coprocessed excipients to create an ODT that, depending on the type of active ingredients and loading, dissolves within 30-40 seconds. The quantity of pharmaburst required in a formulation depends on the active ingredients in the tablet. The process involves a dry blend of a drug, flavor and lubricant that are compressed into a tablet on a standard tablet press with stock tooling. The manufacture process can be carried out under normal temperature and humidity conditions.

The tablets can be packaged in blister packs or bottle.

Frosta technology

Akina patents this technology. The core concept of Frosta technology is compressing highly plastic granules at low pressure to produce strong tablets with high porosity. The highly plastic granules comprise three classes of components: a porous and plastic material, a water penetration enhancer, and a binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The technology can be used for almost any drugs including aspirin, loratidine, caffeine, and folic acid, vitamins and dietary supplements. The highly plastic granule approach produces fast melting pharmaceutical tablets with excellent hardness and fast disintegration time ranging from several seconds to 30 seconds, depending on the size of the tablets.

Evaluation of rapid melts

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight of these selected tablets was calculated.

Hardness Test

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

Friability

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Disintegration test

The time for disintegration of ODTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The standard procedure of performing disintegration test for these dosage forms has several limitations and they are not suitable for the measurement of very short disintegration times. The method needs to be modified for ODTs as disintegration is required without water; thus the test should mimic

disintegration in salivary contents. A modified dissolution apparatus is applied to an ODT with a disintegration time that is too fast to distinguish differences between tablets when the compendial methods are used. A basket sinker containing the tablets is placed just below the water surface in a container with 900 mL of water at 37 °C, and a paddle rotating at 100 rpm is used. The disintegration time is determined when the tablet has completely disintegrated and passed through the screen of the sinker. Various scientists have developed new *invitro* methods that allow an accurate determination of disintegration test. The disintegration test is performed using a texture analyzer instrument. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, the instrument is set to maintain a small force for a determined period of time. The plots of some distance traveled by the probe generated with the instrument's software provide disintegration profile of the tablets as a function of time. The plots facilitate calculation of the start and endpoint of the tablet disintegration.

Dissolution test

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets.

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation

were kept in a dessicator over calcium chloride at 37°C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. [29] Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio, R can be determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

CONCLUSION

Rapid Melts offer numerous significant advantages over conventional dosage forms because of improved efficacy, greater first pass metabolism, bioavailability, rapid onset of action, better patient compliance and acceptance. The innovations in the arena of formulating rapid Melts are aimed at both increasing the performance of the dosage form by decreasing the disintegration time and increasing the patient compliance by masking the objectionable taste of the active ingredients. These can be prepared in several ways and product performance depends upon the drug stability and excipient selection in the delivery system. These rapidmelts are developed to overcome the difficulties in swallowing conventional tablets among paediatric, geriatric and psychiatric patients with dysphagia. The development of rapid Melts also provides an opportunity for a line

extension the market place: a wide range of drugs can be considered candidates for this dosage form. Pharmaceutical marketing is another reason for the increase in available fast dissolving/disintegrating products.

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