

Oral Disintegrating Tablets: A Future Compaction

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ABSTRACT

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is oral disintegrating tablets (ODTs). ODTs are solid unit dosage forms, which disintegrates or dissolves rapidly in the mouth without the general requirement for swallowing, the chewing and water. An oral disintegrating tablet provides an advantage particularly for pediatric and geriatric populations and is who have difficulty in swallowing conventional tablets and capsules. This review depicts the various formulation aspects, technologies developed, ingredients used, evaluation tests and marketed formulations

Keywords: Oral disintegrating tablets, patented technologies, superdisintegrants.

INTRODUCTION ORAL DRUG DELIVERY

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part due to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed along the gastrointestinal tract along with food stuff.

Tablets

Tablet may be defined as the solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding method. They have been in wide spread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by "JOHN WYETH". Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient.

Immediate release drug delivery system

Definition

Immediate release drug delivery system is also conventional type of drug delivery system as it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.⁷

Advantages of immediate release drug delivery systems^{12,13,14}

- Release the drug immediately.
- Unit dose system and Long shelf life.
- Cost effective.
- More flexibility for adjusting the dose.
- It can be prepared with minimum dose of drug.
- Tastelessness and Elegance.
- Improved stability, bioavailability.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease.
- At the particular site of action the drug is released from the system.

Disadvantages of immediate release drug delivery systems

- Posses swallowing difficulty.
- Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density
- Drugs having bitter taste, objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating of tablet Bioavailability problems.

Tablet Excipients¹⁵

An excipient is generally a pharmacologically inactive substance used as a carrier for the active ingredients of a medication. In many

cases, an "active" substance (such as acetylsalicylic acid) may not be easily administered and absorbed by the human body; in such cases the substance in question may be dissolved into or mixed with an excipient.

Properties of Excipients¹⁶

1. They must be physiological inert.
2. They must be acceptable to regulatory agencies
3. They must be physiologically and chemically stable.
4. They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
5. They must not interfere with the bioavailability of the drug.
6. They must be commercially available in the form and purity commensurate to pharmaceutical standards.
7. Cost must be relatively inexpensive.
8. They must conform to all current regulatory requirements.

Types of Excipients¹⁷

- Diluents and Fillers
- Binders
- Antiadherents
- Disintegrants
- Flavours
- Colours
- Lubricants
- Glidants
- Preservatives
- Sorbents
- Sweeteners

Diluents and Fillers

When the dosage of active pharmaceutical agent is inadequate to produce the bulk some inert substances are added to make the tablet and to make the bulk.

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling.

Examples: lactose, direct compressible starches, microcrystalline cellulose and sucrose.

Binders

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.

Examples: starch, cellulose, micro crystalline cellulose, gelatin, tragacanth, etc.

Antiadherents

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches. They are also used to help protect tablets from sticking. Most commonly used is magnesium stearate.

Disintegrants

Disintegrants help to break the tablet into granules and granules into powder favoring dissolution.

Examples: carboxymethyl cellulose (croscarmellose sodium), polyvinyl pyrrolidone etc.

Flavours

Flavours can be used to mask unpleasant tasted active ingredients and to improve the likelihood that the patient will complete a course of medication.

Examples: Mint, cherry, anise, vanilla, raspberry, peach, apricot, liquorice etc.

Colours

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall.

Examples: Talc, silica, magnesium stearate, stearic acid etc.

Glidants

Glidants are used to promote powder flow by reducing inter particle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.

Examples: Fumed silica, talc, and magnesium carbonate.

Preservatives

Some typical preservatives used in pharmaceutical formulations are:

- Antioxidants like vitamin A, vitamin E, vitamin C, retinylpalmitate and selenium
- The amino acids cysteine and methionine.
- Citric acid and sodium citrate.

- Synthetic preservatives like the parabens: methyl paraben and propyl paraben.

Sorbents

Sorbents are used for tablet/capsule moisture-proofing by limited fluid sorbing (taking up of a liquid or a gas either by adsorption or by absorption) in a dry state.

Sweeteners

Sweeteners are added to make the ingredients more palatable, especially in chewable tablets such as antacid or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant taste or smell.

SUPERDISINTEGRANTS

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

Advantages

1. Effective in lower concentrations
2. Less effect on compressibility and flowability

3. More effective intragranularly

Mechanism of disintegrants

- 1) High swellability
- 2) Capillary action
- 3) Chemical reaction

Superdisintegrants in immediate release tablets^{3,18}

Superdisintegrants are effective at low concentration and have greater disintegrating efficiency and they are effective intragranularly as well as extra-granularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. These superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or accelerate the absorption of water leading to an enormous increase in the volume of granules to promote disintegration as shown below fig. 1.

FACTORS AFFECTING DISINTEGRATION

Parameters influencing the swelling behavior of superdisintegrants are given in Table 1.

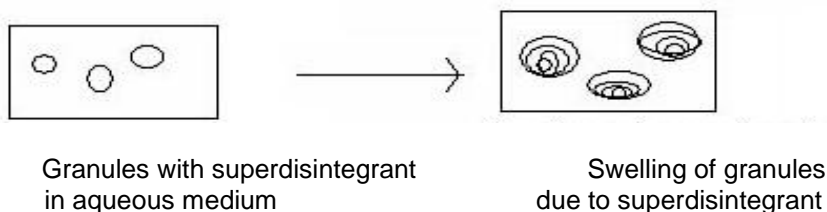


Fig. 1: Mechanisms of Superdisintegrants by swelling

PARAMETERS INFLUENCING THE SWELLING BEHAVIOUR OF SUPERDISINTEGRANTS

**Table 1: Factors affecting disintegration
METHODS OF ADDITION OF DISINTEGRANTS**

| PARAMETERS | EFFECTS |
|------------------------------|---|
| Amount of superdisintegrant | A minimum amount of superdisintegrant is necessary for the development of sufficient swelling to outer membrane |
| Additives (binders) | Polymeric binders can reduce swelling pressure by spacial separation of superdisintegrant particles or competition for free water |
| Ionic strength of the medium | Competition of the ions for free water |
| pH values | Swelling can be influenced for the superdisintegrants with ionizable groups (e.g:carboxylic groups in croscarmellose) |

Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at both processing steps.

Various steps involved in the manufacturing of tablets

various unit processes which are involved in making tablets (Fig. 2):

1. Dispensing
2. Sizing
3. Powder blending
4. Granulation
5. Drying
6. Tablet compression
7. Packaging

TABLET MANUFACTURING METHODS^{19, 20}

A) Direct compression

B) Granulation

A) Direct compression

- The term “direct compression” is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

B) Granulation²¹

- Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates.

Granulation Techniques

- (1) Dry Granulation
- (2) Wet Granulation

1. Dry granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, pre compression or double compression.

Two main Dry Granulation processes

a) Slugging process: Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b) Roller compaction: The compaction of powder by means of pressure roll can also be accomplished by a machine called Chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

2. Wet granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation.

Important steps involved in the Wet Granulation

- Mixing of the drugs and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve.
- Drying of moist granules.
- Screening of dry granules through a suitable sieve.
- Mixing of screened granules with disintegrant, glidant and lubricant.

Tablet compression²

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press).

The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge. The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply.

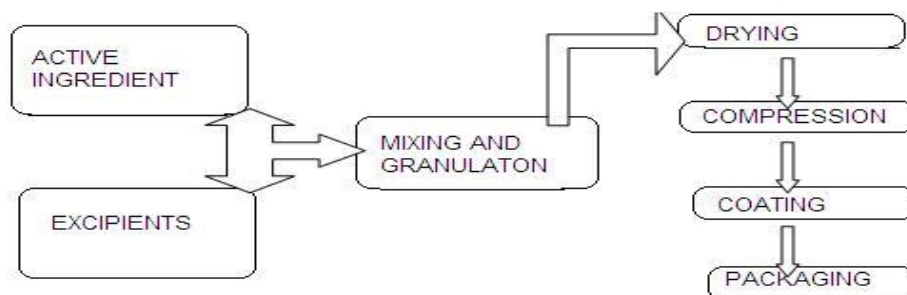


Fig. 2: Steps involved in manufacturing



Fig. 3: Rotary Punching Machine

COATING PROCESS²²

Types of coating²³

1. Enteric coating
2. Sugar coating
3. Film coating

Enteric coating

"An enteric coating is a coating system that resists disintegration or dissolution in gastric media but disintegrates or dissolves in intestinal fluid". An enteric protected dosage form is the most common type of delayed release product. Enteric protection relies on the use of a polymeric material, usually as a coating which has pH selective solubility, taking advantage of change in pH that occurs as the dosage form progress through the gastro-intestinal tract.

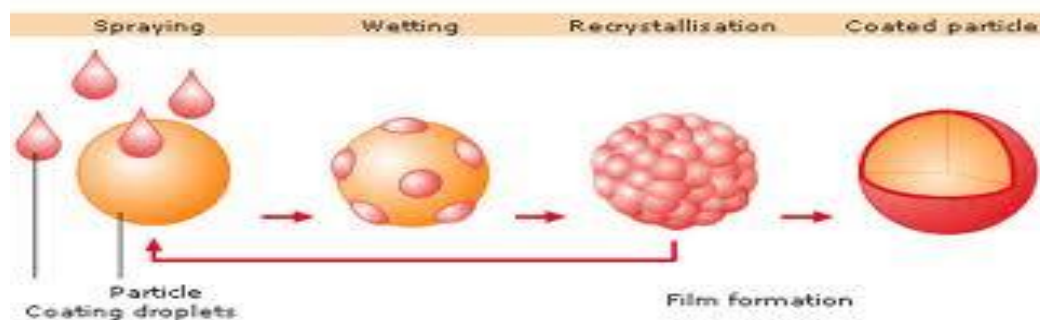
Sugar Coating

Sugar Coating is now rarely used in pharmaceuticals field because of it's Skillfull and tedious process. There are various steps of sugar coating:

1. Seal Coating
2. Sub Coating
3. Syrup (Smoothing/Color) Coating
4. Polishing

Film Coating:^{21,22}

Film Coating is widely used in pharmaceuticals to protect compressed tablets from Light, Heat and Moisture. A very even application of the coating material is an important feature of the coating process. Coatings must be dense and without mechanical damage and cracks.



Process of film-coating

The following are the most commonly used coating polymers

1. PVAP (Polyvinyl Acetate Phthalate)
2. HPMC-P (Hydroxy Propyl Methyl Cellulose Phthalate)
3. CAP (Cellulose Acetate Phthalate)

Polyvinyl acetate phthalate (PVAP)

PVAP is manufactured by esterification of partially hydrolyzed polyvinyl acetate with phthalic anhydride. It is less permeable to moisture and simulated gastric juice. It is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrate at pH 5.

Hydroxypropyl methylcellulose phthalate (HPMCP)

HPMCP is prepared by treating Hydroxypropyl methylcellulose with phthalic acid. The degree of substitution of the possible substituents determines the polymer characteristics, in particular the pH of dissolution.

It is available in two grades

- a) HP50
- b) HP55

Cellulose acetate phthalate (CAP)

CAP is manufactured by treating a partial acetate ester of cellulose with phthalic anhydride. Of the free hydroxyl groups contributed by each glucose unit of the cellulose chain in the resulting polymer, approximately half are acrylated and one-quarter esterifies with one of the two carboxylic acid groups of the phthalate moiety. The carboxylic acid group being free to form salts and thus serves as the basis of its enteric character.

Other Additives²³

Plasticizers

A plasticizer is a low molecular weight substance that, when added to another material usually a polymer makes the product

flexible, resilient and easier to handle. Modern plasticizers are synthetic organic chemicals, the majority of which are esters such as citrates and phthalates. Plasticizers are low molecular weight solids or liquids. They typically have low melting points ($<100^{\circ}\text{C}$) and can be volatile at ambient temperatures.

Solvents

The primary function of a solvent system is to dissolve or disperse the polymers and other additives and convey them to the substrate surface.

Colorants

Colorants are used to provide distinctive color and elegance to a dosage form. To achieve proper distribution of suspended colorants in the coating solution requires the use of fine-powdered colorants ($<10\ \mu$). The most common colorants in use are certified Food Drug and Cosmetic (FD&C) or Drug and Cosmetic (D&C) colorants.

Opaquant-Extenders

These are very fine inorganic powders used in the coating solution formulations to provide more pastel colors and increase film coverage. These opaquants can provide a white coating or mask the color of the tablet core. Colorants are much more expensive than these inorganic materials and effectively less colorant is required when opaquants are used.

COATING EQUIPMENTS²²

Coating Processes and equipment

The majority of tablet film coating is performed in perforated closed system pans. These provide the necessary controlled conditions of temperature and air flow which enable reproducible and efficient application of both appearance and functional coatings. In addition, they limit operator exposure.

Standard Coating Pan

It is also known as **Conventional Pan System**. The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.



Fig. 4: Standard coating pan

COATING DEFECTS²²

1. Picking and Sticking: Sticking is due to the improperly dried tablets, causing the tablet surface to stick to the coating pan. Picking is a form of sticking in which a small portion of tablet sticks to the coating pan and grows with revolution of pan picking out a cavity on the tablet face.

2. Bridging: This occurs when the coating fills in the lettering or logo on the tablet.

3. Capping: Capping is the term used to describe the partial (or) complete separation of the top (or) bottom crowns of a tablet from the main body of the tablet.

4. Erosion: This can be the result of soft tablets, an over-wetted tablet surface, inadequate drying or lack of tablet surface strength.

5. Peeling and Frosting: This is a defect where the coating peels away from the tablet surface in a tablet sheet.

6. Chipping: Chipping refers to tablets having pieces broken out (or) chipped, usually around the edges.

7. Mottling: It is unequal distribution of color (or) a tablet with light (or) dark areas standing out in a uniform surface.

8. Orange peel effect: Refers to a coating texture that resembles the surface of an orange.

9. Twinning: This is the term for two tablets that stick together.

OPTIMIZATION PARAMETERS FOR COATING

Process Parameters

- 1) Inlet Temperature
- 2) Product Temperature
- 3) Exhaust Temperature
- 4) Drive speed
- 5) Spray pump speed
- 6) Air flow
- 7) Operating air
- 8) Actual weight
- 9) Spray rate.

PROCESS CONTROLS

PAN VARIABLES:^{22,23}

Rotating speed of pan

Tablet motion, a factor influenced greatly by pan speed, can be a major issue in the cases of tablet breakage, edge wear, surface erosion. The uniformity of distribution of the applied coating i.e. higher the pan speeds being better in this regard. It is well documented that increasing the rotating speed of the pan improves the mixing of tablets. The pan speed affects the time spent on the spraying zone and subsequently, the homogenous distribution of the coating solution on the surface of each tablet throughout the batch. Increasing the pan speed decreases the thickness variation and increases the uniformity of coatings. Too much rotating speed of the pan will cause the tablet to undergo unnecessary attrition and breakage.

Pan Loading

It is defined in terms of volume fill rather than by weight. Thus optimum pan loading by weight will vary from product to product, depending on the apparent density of the product.

The difficulty arises for the following reasons:

1. On the laboratory scale, it is not difficult to ensure that a pan is appropriately loaded. Even when only a very small amount of product is available, this problem can be dealt with by bulking up active tablets with placebos to make a full charge.
2. When the pan is under loaded, the side walls of the coating pan, or even baffles, become more exposed to the spray, causing coating liquid to build up on the exposed metal surfaces, often with the result that tablets will stick to the surfaces.

This can be minimized by the following ways:

1. Changing the gun-bed distances.
2. Gun spacing

- The number of guns used can minimize the problem.

SPRAY VARIABLES

Gun-to-tablet- bed distance

With the help of rudimentary positioning tools, such as a ruler, the operator is left to set up the gun position. Gun positioning needs to be optimized to:

- Ensure that optimal and reproducible bed coverage is achieved.
- Facilitate broad coverage while providing maximum surface drying time.
- Achieve reproducible spray droplet characteristics as they arrive at the tablet surface.

Spray-gun variables

Quality attributes of film coating tablets that can be associated with spray gun performance include:

- Appearance:
 - Coating gloss
 - Coating roughness
 - Existence of defects (picking etc)
 - Color uniformity
- Functional:
 - Uniformity of distribution of coating
 - Coating uniformity
 - Solvent penetration into the tablet cores and hence product stability

Spray rate

The spray rate is a significant parameter since it impacts the moisture content of the formed coating and subsequently, the quality and uniformity of the film. A low coating liquid spray rate causes incomplete coalescence of polymer due to insufficient wetting, which could effect in brittle films. A high coating liquid spray rate may result in over wetting of the tablet surface and subsequent problems such as picking and sticking. If the spray rate is high and the tablet surface temperature is low, films are not formed during the spraying but the post drying phase and rapid drying often produces cracks in the films.

Atomizing air pressure

In general, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films. If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry

before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence. If spraying air pressure is inadequate, the film thickness and thickness variation are greater possibly due to change in the film density and smaller spray loss. In addition, with low spraying air pressure big droplets could locally over wet the tablet surface and cause tablets to stick to each other.

Inlet air temperature

The inlet air temperature affects the drying efficiency (i.e. water evaporation) of the coating pan and the uniformity of coatings. High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the tablet core decreases the core tablet porosity, tensile strength and residual moisture content of coated tablets. Too much air temperature increases the premature drying of the spray during application and subsequently, decreases the coating efficiency. Measuring the pan air temperature helps to manage the optimum conditions during the coating process and consequently, enables predicting possible drying or over wetting problems which may result in poor appearance of the film or may have unfavorable effects on the moisture and heat sensitive tablet cores.

Drying-air volume

Drying air volume is selected based on:

- The recommendations of the vendor of the equipment
- On the basis of optimum conditions designed for the air-handling system that has been installed.

The supply and exhaust air fan speeds should be set, based on the equipment used, to meet negative pressure pan settings that are usually recommended. Once the appropriate drying air volume has been established, this setting becomes a driver for other key processing.

CONCLUSION

The technologies depicted in this article demonstrate how recent advances in formulation development and processing technologies meet the efforts to achieve more sophisticated drug delivery system (Oral Disintegrating Tablets). ODT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in traveling, patients who are may not have access to water. Such products provide opportunity for the product line extension in

the market place and extension of patent term of innovator. Due to these wide significance of ODT, this drug delivery system may lead to better patient compliance and ultimate clinical output. Future might witness many more classes of drugs developed in the form of ODT.

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