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IMMEDIATE DRUG RELEASE DOSAGE FORM: A REVIEW

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ABSTRACT

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. There are novel types of dosage forms that act very quickly after administration. The basic approach used in development tablets is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Crosscarmellose), Sodium starch glycolate (Primogel), Kollidone CL etc. which provide instant disintegration of tablet after administration. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, immediate release formulations are similar to many sustained release formulations that are now commonly available.

KEYWORDS: Immediate release, Superdisintegrants. Direct compression, Wet Granulation.

INTRODUCTION

In the present study and research novel drug delivery systems are developed for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance. In these solid formulations do not require sterile conditions and are therefore, less expensive to manufacture**.** Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the

drug discovery such as genomics. The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

In this context, the term "release" includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1 to 3, especially at, or about, pH=1. In one aspect of the invention a formulation as described herein with a compound of formula (I), or an acid addition salt thereof, in crystalline form releases drug under a range of pH conditions. In another aspect of the invention a formulation as described here in with a compound of formula (I), or an acid addition salt thereof, releases drug under pH conditions such as pH=1 to 3, especially at, or about, pH=1. Thus, formulations of the invention may release at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes), of administration, whether this be oral or parenteral.

Bio-pharmaceutical Consideration

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion.

Pharmacokinetics: It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamics: Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.

1. Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
2. Decreased sensitivity of –adrenergic agonist and antagonist
3. Immunity is less and taken into consideration while administered antibiotics.
4. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.
5. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.

Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, antihypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

Problems with Existing Oral Dosage Form

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an oesophagus 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 and elderly patients suffer from dysphasia.
- Liquid medicaments (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 refused to use such medications.
- Cost of products is main factor as parenteral formulations are most costly and discomfort.

Desired Criteria for Immediate Release Drug Delivery System

Immediate release dosage form should-

- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not 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.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Merits of Immediate Release Drug Delivery System

- Improved compliance/added convenience
- Improved stability, bioavailability
- 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
- Cost- effective
- Improved solubility of the pharmaceutical composition;
- Decreased disintegration and dissolution times for immediate release oral dosage forms

Other Excipients: Excipients balance the properties of the actives in immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired Organolaptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking Materials: Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluents, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

Emulsifying Agents: Emulsifying agents are important excipients for formulating immediate release tablets they aid in rapid disintegration and drug release. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

Lubricants: Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Flavours and Sweeteners: Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the Organolaptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

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

Advantages

- Effective in lower concentrations
- Less effect on compressibility and flowability
- More effective intragranularly

Some super disintegrants are

1. **Sodium Starch Glycolate (Explotab, primogel)** used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

2. **Cross-linked Povidone or crospovidone (Kollidone)** used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants.

3. **Low-substituted hydroxyl propyl cellulose,** which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration capacity. Recommended concentration 1-5%

4. **Cross linked carboxy methyl cellulose sodium (Ac-Di-sol) Croscarmellose sodium**

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation.

Conventional Technique Used in the Preparation of Immediate Release Tablets

- Tablet molding technique
- Direct compression technique
- Wet granulation technique
- Mass extrusion technique
- By solid dispersions

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. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

Direct Compression Method: 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. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Wet Granulation Method: Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Procedure

- The active ingredient and excipients are weighed and mixed.
- The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, and cellulose derivatives such as methyl cellulose, gelatin, and povidone.

- Screening the damp mass through a mesh to form pellets or granules.
- Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
- After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

Mass-Extrusion (Mass-Extrusion): 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. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

By solid dispersions: When formulating such solid amorphous dispersions into immediate release solid dosage forms for oral administration to a use environment such as the GI tract of an animal such as a human, it is often desirable to maximize the amount of dispersion present in the dosage form. This minimizes the size of the solid dosage form required to achieve the desired dose. Depending on the drug dose, it is often desired that the solid amorphous dispersion comprise at least 30 wt %, preferably at least wt %, and more preferably at least 50 wt % or more of the solid dosage form. Such high drug loadings of dispersion in a solid dosage form minimize the dosage form's size, making it easier for the patient to swallow it and tending to improve patient compliance. The immediate release dosage forms containing a solid dispersion that enhances the solubility of a “low-solubility drug,” meaning that the drug may be either “substantially water-insoluble,” which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, “sparingly water-soluble,” that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous-solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL.

Evaluation of immediate release tablets

Evaluation of Blend

The prepared blend is evaluated by following tests.

1. Angle of repose
2. Bulk density
3. Tapped density
4. Carr's index
5. Hauser's ratio.

1. Angle of repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion) excipients blend was allowed to flow through the funnel Freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\theta = h/r}$$

2. Bulk Density (BD)

Weigh accurately 25 g of granules, which was previously passed through #20 sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0).Calculate the apparent bulk density in gm/ml by the following formula-

Bulk density = Weight of powder / Bulk volume

3. Tapped density (TD)

Weigh accurately 25 g of granules, which was previously passed through #20 sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2)to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2). Calculate the tapped density in gm/ml by the following formula-

Tapped density = Weight of powder / Tapped volume

4. Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below-

Carr's Index= [(TD-BD)*100]/ TD

5 Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular

Hausner's ratio = TD/BD

EVALUATION OF TABLETS

These tests are as following:

1. Appearance
2. Thickness
3. Hardness
4. Weight variation
5. Friability
6. Disintegration
7. Uniformity of dispersion
8. Wetting Time
9. Drug content
10. *In vitro* Dissolution.

1. Appearance

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance.

2. Thickness

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.

3. Hardness

The hardness of tablet is an indication of its strength against resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage.

Measuring the force required to break the tablet across tests it. Hardness of 10 tablets (randomly) from whole tablet batch was determined by Monsanto hardness tester. Hardness measured in kg/cm2.

4. Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

5. Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula:

$$\% \text{ friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} * 100$$

6. Disintegration test

The USP device to rest disintegration was six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 20C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

7. Uniformity of dispersion

Two tablets were kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered to pass the test if no residue remained on the screen.

8. Wetting Time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a Petridis containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time.

9. Drug content

10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media buffer or 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation carried out to determine drug content in one tablet.

10. In vitro drug release studies

The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 phosphate buffer or 0.1N HCl for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in dissolution test apparatus using specified volume 900ml of dissolution media maintained at 37±0.20C. The tablets are kept in the cylindrical basket or directly placed in medium with paddle then rotated at 100 rpm. 5ml of the sample from the dissolution medium are withdrawn at each time interval (5, 10, 15 & 30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml. These samples were analyzed spectrophotometrically and further calculation was carried out to get drug release. The drug released data were plotted and tested with zero order (Cumulative % drug released Vs time), First order (Log % Remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants, correlation coefficient and dissolution efficiency were calculated.

CONCLUSION

This is new enhanced oral product arising within this market segment and applicable to a wide range of therapeutic agents. Approximately one-third of the patients need quick therapeutic action of drug, resulting in poor compliance with conventional drug therapy which leads to reduced overall therapy effectiveness. A new dosage format, the immediate release pharmaceutical form has been developed which offers the combined advantages of ease of dosing and convenience of dosing. These tablets are designed to release the

medicaments with an enhanced rate. Due to the constraints of the current technologies as highlighted above, there is an unmet need for improved manufacturing processes for immediate release pharmaceutical form that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets. To fulfill these medical needs, formulators have devoted considerable effort to developing a novel type of tablet dosage form for oral administration, one that disintegrates and dissolves rapidly with enhanced dissolution. An extension of market exclusivity, which can be provided by immediate release dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations.

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