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Review Article

RECENT ADVANCEMENT IN IMMEDIATE RELEASE DRUG DELIVERY SYSTEMS: 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. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after adminstration. The basic approach used in development tablets is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmeliose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration. The development of immediate release tablets also provides an opportunity for a line extension in the market place. A wide range of drugs (e.g., cardiovascular drugs, analgesics, antihistamines, and drugs can be considered candidates for this dosage form. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. Immediate release dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. Now a day, immediate release formulations are similar to many sustained release formulations that are now commonly available.
Key**words:** Immediate release, Superdisintegrants. Direct compression, Wet Granulation.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool 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[1]. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture[2]**.** 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. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights[3].

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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 diluent or carrier, which diluent 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[6].

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 sensivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at lowcost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action[7].

Advantages of Immediate Release Drug Delivery System

An immediate release pharmaceutical preparation offers:

1. Improved compliance/added convenience
2. Improved stability
3. Suitable for controlled/sustained release actives
4. Allows high drug loading.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging machinery
7. Cost- effective
8. There is no dose dumping problem[8].

POTENTIAL CANDIDATE FOR IMMEDIATE RELEASE ORAL DOSAGE FORM

Analgesics and Anti-inflammatory Agents:

Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamicacid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac[9].

Anti-Arrhythmic Agents:

Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate[10].

Cardiac Inotropic Agents:

Amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin.

Diuretics:

Acetazolamideamiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, frusemide, metolazone, spironolactone, triamterene.

Nitrates and other Anti-anginal Agents:

Amyl nitrate, glyceryltrinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate[11].

Proteins, Peptides and Recombinant drugs:

Insulin, glucagon, growth hormone (somatotropin), polypeptides or their derivatives, calcitonins and synthetic modifications thereof, enkephalins, interferons , LHRH and analogues (nafarelin, buserelin, zolidex), GHRH, secretin, bradykin antagonists, GRF, THF,TRH, ACTH analogues, IGF (insulin like growth factors),CGRP(calcitoningene related peptide), a trial natriurecticpeptide, vasopressin and analogues(DDAVP, lypressin),factor VIII, G-CSF (granulocyte-colony stimulating factor), EPO (erythropoitin)[11,12].

OTHER EXCIPIENTS:-

Excipients balance the properties of the actives in immediate release dosage forms. Immediate release excipient demands a thorough understanding of the chemistry of these excipients are prevent interaction with the actives. The cost of these ingredients is another issue that needs to be addressed by formulators. Excipients role is Important in the formulation of fast-melting tablets. The excipient inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are common and can be used for a broad Range of actives, except some actives that require masking agents[13].

LUBRICANTS

Lubricants are the excipients which can further assist in making these tablets more palatable after they disintegrate in the mouth or stomach. Lubricants have ability to remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach[14,15].

SUPER DISINTEGRANTS

A superdisintegrants is major 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:

- Effective in lower concentrations
- Less effect on compressibility and flow ability
- More effective intragranularly[16]

Some super disintegrants are:

1) Sodium Starch Glycolate (Explotab, primogel)

SSG is used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: The sodium starch glycolate Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in optimum concentration from 2- 15% of tablet weight. And Water wicking[17].

2) Cross-linked Povidone (Crosspovidone) (Kollidone)

It is used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action: Crospovidone when contact with water it swelling and possibly some deformation recovery. It rapidly disperses and swells in water, but does not gel even after prolonged exposure. The greatest rate of swelling compared to other disintegrants and the Greater surface area to volume ratio than other disintegrant[18].

3) Low-substituted hydroxyl propyl cellulose,

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 conce ntration 1-5 %.

4) Cross linked carboxy methyl cellulose sodium (i.e. 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[19].

BULKING AGENTS

Bulking agents 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 .

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 organoleptic 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[20].

Technique Used In The Preparation Of Immediate Release Tablets

* Tablet molding technique
* Direct compression technique
* Wet granulation technique
* Mass extrusion technique

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[21].

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[22].

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[23].

Procedure

Step 1: The active ingredient and excipients are weighed and mixed.

Step 2: 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.

Step 3: Screening the damp mass through a mesh to form pellets or granules.

Step 4: Drying the granulation. A conventional traydryer or fluid-bed dryer are most commonly used.

Step 5: 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[25].

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[26].

Immediate release solid dosage forms prepared 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[27].

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.

The drug dispersions used in fabricating the high loading immediate release dosage forms of the present invention comprise solid dispersions of a drug and at least one concentration-enhancing polymer. The concentration-enhancing polymer is present in the dispersions used in the present invention in a sufficient amount so as to improve the concentration of the drug in a use environment relative to a control composition. At a minimum, the dispersions used in the present invention provide concentration enhancement relative to a control consisting of crystalline drug alone. Thus, the concentration-enhancing polymer is present in a sufficient amount so that when the dispersion is administered to a use environment, the dispersion provides improved drug concentration relative to a control consisting of an equivalent amount of crystalline drug, but with no concentration-enhancing polymer present[26].

Drug-excipient compatibility studies

The proper design and the formulation of a dosage form require consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product i.e. stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets. Compatibility studies are carried out by mixing definite properties of drug and excipient and kept in glass vials, which is stored at 55°C for onemonth[23].

EVALUATION OF IMMEDIATE RELEASE TABLETS

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 excipient 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.

Tan = h/r

Where h and r are the height and radius of the powder conc.

Figure: Measurement of angle of repose (Fixed Funnel method).

Bulk density

Apparent bulk density was determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

BD =Weight of the powder / Volume of the packing.

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight
onto a hard surface from the height of 10cm at 2- second intervals. The tapping was continued until no further change in volume was noted.

TBD =Weight of the powder / volume of the tapped packing.

Compressibility Index

The Compressibility Index of the blends was determined by Carr's compressibility index.

Carr's compressibility index (%) = *[(TBD-LBD) X 100] / TBD*

A similar index has been defined by Hausner

Hauser's ratio = Tapped density/ Poured density

Hausner's ratio <1.25 – Good flow = 20% Carr 1.25 – Poor flow =33% Carr

Compression
Mixed Blends is compressed by direct compression method using Cadmach single punch machine. Caput punches and die (8 mm.) were used in this study.

EVALUATION OF TABLETS
The tablets are subjected to the following quality control tests:

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 from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated[24].

Hardness:
The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test:
Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where,
W1= Weight of tablet before test
W2 = Weight of tablet after test

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± 2 oC, 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[27].

In vitro drug release studies
The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus using specified volume of dissolution media maintained at 37±10C. The tablets are kept in the cylindrical basket and rotated at 100 rpm 5ml of the sample from the dissolution medium are withdrawn at each time interval (2, 3, 5, 10, 15&30 minutes) and 5ml of fresh medium was replaced each time[25]. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml.

Dissolution Profile
The compositions of the present invention preferably are immediate release compositions from which about 50% of the micronized drug is dissolved in vitro within about 15 minutes, more preferably at least about 80% of the drug is dissolved in vitro within about 30 minutes, and still more preferably at least about 90% of the e is dissolved in vitro within about 45 minutes using 1% sodium dodecyl sulfate (SDS) in water as the dissolution medium at 37° C.

Conclusion
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.

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