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## **IMMEDIATE RELEASE DRUG DELIVERY SYSTEM: 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 administration. The basic approach used in development tablets is the use of superdisintegrants like Cross linked carboxymethylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration. Immediate release liquid dosage forms and parenteral dosage form have also been introduced for treating patients. The development of immediate release therapy also provides an opportunity for a line extension in the marketplace, a wide range of drugs e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines and other 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.

## **INTRODUCTION**

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral route is most common and popular route of administration of drug is oral route because of its systemic effect, patient compliance, less expensive to manufacture. Tablet provides high precision dosing. Tablet form is the most widely used dosage form because of self-administration and ease in manufacturing<sup>1</sup>. In most of the cases immediate onset of action is required as compared to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is now a days popular and used as an alternative oral dosage form. Immediate release tablets are very quickly after administration. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration<sup>1-3</sup>.

### **Type and Classes of Tablets :**

#### **A. Oral Tablets for Ingestion<sup>1-2</sup>**

- Compressed tablets
- Multiple compressed tablets
- Layered tablets
- Compression-coated tablets
- Repeat-action tablets
- Delayed-action and enteric-coated tablets
- Sugar and chocolate-coated tablets
- Film coated tablets
- Chewable tablets

#### **B. Tablets Used in the Oral Cavity<sup>1-3</sup>**

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

#### **C. Tablets Administered by Other Routes<sup>1,2,3-5</sup>**

- Implantation tablets
- Vaginal tablets

**D. Tablets Used to Prepare Solutions**<sup>2-5</sup>

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

**IMMEDIATE RELEASE**

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. 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. This term excludes formulations which are adapted to provide for “modified”, “controlled”, “sustained”, “prolonged”, “extended” or “delayed” release of drug. Release term 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 herein 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 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes), of administration, whether this be oral or parenteral<sup>7</sup>.

**MERITS AND DEMERITS OF IMMEDIATE RELEASE TABLETS****A. Merits:**

1. Unit dose system and Long shelf life.
2. Cost effective.
3. Improved stability, bioavailability.
4. Accuracy and uniformity of drug content.
5. More Economic and Ease of administration.

6. Tastelessness and Elegance.
7. Patient compliance.
8. They are in general the easiest and cheapest to package.
9. Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use<sup>2-3,7</sup>.

**B. Demerits:**

1. Posses swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density.
3. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet Bioavailability problems.
4. Chance of GI irritation caused by locally high concentrations medicaments<sup>2-3,7</sup>.

**PROBLEMS WITH EXISTING ORAL DOSAGE FORM**

1. Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration<sup>8</sup>.
2. 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.
3. Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.
4. Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications<sup>9</sup>.
5. 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 <sup>10</sup>.

### **BIOPHARMACEUTIC CONSIDERATION**

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

#### **Pharmacokinetics:**

In this consideration, study has done on 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 <sup>10-12</sup>.

#### **Pharmacodynamic:**

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 <sup>10-14</sup>.

## **POTENTIAL CRITERIA FOR IMMEDIATE RELEASE ORAL DOSAGE FORM**

The potential criteria for immediate release dosage form is as the following <sup>15-18</sup>:

### **Anti-bacterial Agents:**

Imipenem, nalidixic acid, nitro furantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim. Benethamine, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, demeclocycline.

### **Anti-Arrhythmic Agents:**

Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate.

### **Anti-depressants:**

Amoxapine, ciclazindol, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.

### **Anti-coagulants:**

Dicoumarol, dipyridamole, nicoumalone, phenindione.

### **Analgesics and Anti-inflammatory Agents:**

Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac.

### **Anthelmintics :**

Albendazole, bephenium, hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole.

### **Anti-fungal Agents:**

Amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid.

### **Anti-diabetics:**

Acetohexamide, chlorpropamide, glipizide, tolazamide, tolbutamide, sitagliptin.

### **Anti-epileptics:**

Beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, paramethadione, phenacetamide, phenobarbitone, phenytoin, primidone, sulthiame, valproic acid.

**Anti-hypertensive Agents:**

Amlodipine, carvedilol, benidipine, darodipine, diltazem HCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nifedipine, nimodipine, phenoxymethamine HCl, prazosin HCL, reserpine, terazosin HCl.

**Anti-gout Agents:**

Allopurinol, probenecid, sulphinpyrazone.

**Anti-malarials:**

Amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.

**Anti-migraine Agents:**

Dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate.

**Anti-muscarinic Agents:**

Atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mepenzolate bromide, orphenadrine, oxyphencyclimine HCl, tropicamide.

**Anxiolytic, Sedatives, Hypnotics and Neuroleptics:**

Alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clonazepam, clozapine, diazepam, droperidol, ethinamate, flunarisone, flunitrazepam, flupromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol.

**Anti-protazoal Agents:**

Benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, omidazole, tinidazole.

**Anti-thyroid Agents:**

Carbimazole, propylthiouracil.

**Anti-neoplastic Agents and Immunosuppressants:**

Aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone.

**Anti-protazoal Agents:**

Benznidazole, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, omidazole, tinidazole.

**Diuretics:**

Acetazolamide,amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid,frusemide, metolazone, spironolactone, triamterene.

**Corticosteroids:**

Beclomethasone, betamethasone , budesonide,cortisone acetate, desoxymethasone, dexamethasone, fludrocortisoneacetate, flunisolide, flucortolone,fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone,prednisone, triamcinolone.

**Cardiac Inotropic Agents:**

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

**Nitrates and other Anti-anginal Agents:**

Amyl nitrate, glyceryltrinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate.

**Nutritional Agents:**

Betacarotene, vitamin A, vitamin B2, vitamin D,vitamin E, vitamin K.Opioid .

**Analgesics:**

Codeine, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, pentazocine.

**Oral Vaccines:**

Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, AIDS, Measles, Lyme disease, Travellers Atrophic rhinitis, Erysipelas, Foot and Mouth disease, Swine, pneumonia, and other disease conditions and other infections and auto-immune disease conditions affecting companion and farm animals.etc.

**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 (calcitonin gene related peptide), atrial natriuretic peptide, vasopressin and analogues (DDAVP, lyspressin), factor VIII, G-CSF (granulocyte-colony stimulating factor), EPO (erythropoitin).

**Enzymes:** All the enzymes.

**Anti-parkinsonian Agents:** Bromocriptine mesylate, lysuride maleate.



**Gastro-intestinal Agents:**

Bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCL, ranitidine HCl, sulphasalazine .

**Histamine H<sub>1</sub>-Receptor Antagonists:**

Acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl,loratadine, meclozine HCl, oxatomide, terfenadine, triprolidine.

**Lipid Regulating Agents:**

Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

**Local Anesthetics :** Lidocaine

**Neuro-muscular Agents:** Pyridostigmine.

**Spermicides:** Nonoxynol.

**Stimulants:**

Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.

**Sex Hormones:**

Clomiphencitrate, danazol, ethinyloestradiol, medroxy progesterone acetate, mestranol , methyltestosterone, norethisterone, norgestrel, oestradiol, conjugated oestrogens, progesterone, stanozolol, stiboestrol, testosterone, tibolone.

**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 organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents<sup>19</sup>.

**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 starchhydrolystate 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<sup>20-21</sup>.

**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<sup>21-22</sup>.

**Super disintegrants :**

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<sup>19-23</sup>.

**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.

**2) Cross-linked Povidone (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<sup>23</sup>.

**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 (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<sup>19-22</sup>.

## **PRINCIPLES OF TABLET GRANULATION**

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. The objective of granulation is to improve powder flow and handling, decrease dustiness, and prevent segregation of the constituents. Granulation method can be broadly classified into two types There are three general methods of tablet preparation <sup>1-5</sup>.

1. Wet granulation method
2. Dry granulation method
3. Direct compression method

### **(i) Wet granulation:**

Wet granulation is a commonly used unit operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over-wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables <sup>1-3</sup>.

### **Important steps involved in wet granulation:**

1. Mixing of drug(s) and excipients.
2. Preparation of binder solution.
3. Mixing of binder solution with powder mixture to form wet mass.
4. Course screening of wet mass using a suitable sieve (6-12 screens).
5. Drying of moist granules.
6. Screening of dry granules through a suitable sieve (14-20 screen).
7. Mixing of screened granules with disintegrant, glidant, and lubricant.

### **Limitation of wet granulation:**

1. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labour, time, equipment, energy and space requirements.
2. Loss of material during various stages of processing.
3. Stability may be a major concern for moisture sensitive or thermolabile drugs.
4. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

**Special wet granulation techniques:**

High shear mixture granulation

Fluid bed granulation

Extrusion-spheronization

Spray drying

**(ii) Dry granulation**

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablets or slugs are milled to yield granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilosonator<sup>1-4</sup>.

**Advantages:**

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation.

Slugging can be used for advantages in the following situations:

- For moisture sensitive material
- For heat sensitive material
- For improved disintegration since powder particles are not bonded together by a binder

**Disadvantages:**

- It requires a specialized heavy duty tablet press to form slug.
- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
- The process tends to create more dust than wet granulation, increasing the potential contamination.

**Steps in dry granulation:**

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Compression into large, hard tablets to make slug
4. Screening of slugs
5. Mixing with lubricant and disintegrating agent
6. Tablet 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<sup>14-15</sup>.

### **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 to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules<sup>24-25</sup>.

### **(iii) 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 pre-treatment of the powder blend by wet or dry granulation procedure is required. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression, thus offering advantage particularly in terms of speedy production, as it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability<sup>11-15</sup>.

### **Advantages:**

- Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
- The most important advantage of direct compression is that it is an economical process. Reduced processing time, reduced labour costs, fewer manufacturing steps, and less number of equipments is required, less process validation, reduced consumption of power.
- Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
- Particle size uniformity.
- Prime particle dissolution.

□ In case of directly compressed tablets after disintegration each primary drug particle is liberated. While in the case of tablets prepared by compression of granules small drug particles with a larger surface area adhere together into larger agglomerates, thus decreasing the surface area available for dissolution.

**Disadvantages:**

**Excipients Related**

- Problems in the uniform distribution of low dose drugs.
- High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression for example, Aluminum Hydroxide, Magnesium Hydroxide.
- The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
- Many active ingredients are not compressible either in crystalline or amorphous forms <sup>1-4</sup>.

**Process Related**

- Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
- In some case it requires greater sophistication in blending and compression equipments <sup>3</sup>.

**TECHNIQUES USED IN THE PREPARATION OF IMMEDIATE RELEASE TABLETS**

- 1) Tablet molding technique <sup>26</sup>
- 2) Methods for tablet preparation <sup>26-27</sup>
- 3) Mass extrusion technique <sup>28</sup>
- 4) Melt granulation techniques <sup>28</sup>
- 5) By solid dispersions <sup>29-30</sup>

**1) Tablet molding technique:**

Molded tablets are generally prepared by mixing the active drug with lactose, dextrose, sucrose, mannitol, or some other appropriate diluent that can serve as the base. This base must be readily water soluble and should not degrade during the tablet's preparation. Lactose is the preferred base but mannitol adds a pleasant, cooling sensation and additional sweetness in the mouth.

**2) Methods for tablet preparation:**

**A. Granulation method:**

a. Wet granulation.

b. Dry granulation.

**B. Direct compression method**

**3) Mass extrusion technique:**

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. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

**4) Melt granulation technique:**

In this process, 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 Solublises rapidly leaving no residues.

**5) By solid dispersions:**

The immediate release dosage forms containing a solid dispersion that enhances the Solubility of a “lowsolubility 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 1to2 mg/mL, or even low to moderate aqueous- solubility, having an aqueoussolubility 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 <sup>1-3,5,14-18</sup> :

1. Angle of repose

2. Bulk density
3. Tapped density
4. Carr's index
5. Hauser's ratio

**Angle of repose:**

The angle of repose was determined using funnel method. Funnel that can be fit vertically with stand at 6.3 cm. height. The opening end of funnel are closed with thumb until drug are poured. The 5 gm of powder was poured into funnel that can be raised vertically until a maximum cone height (h). It was calculated using following formula.

$$\tan \theta = h/r$$

**Bulk Density:**

Apparent bulk density was determine by pouring the 5 gram of powder into a 100 ml granulated cylinder. The bulk volume (V) poured drug was determined. The bulk density was calculated using the formula.

$$V = V_b - V_p, \rho_b = M / V_b$$

Where :  $\rho_b$  - bulk density

M- is the weight of powder

V- is the volume of powder

**Tapped Density:**

Weight 5 gm of powder and placed in a measuring cylinder. Measuring cylinder containing known mass (5 gm) of powder was tapped for 100 times or fixed time. The minimum volume ( $V_t$ ) occupied was measured. The tapped density was calculated using following formula.

$$\rho_t = M / V_t$$

**Compressibility Index:**

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by Compressibility Index. The value below 15% indicates a powder with give rise to good flow properties, whereas above 25% indicate poor flowability. Which is calculated follows.

$$\% \text{ C.I.} = \rho_t - \rho_b \rho_t / \square 100$$

**Hausner ratio:**

Hausner ratio is an indirect index of ease of powder flow. Hosner ratio is the ratio of tapped density to bulk density. Lower the value of Housner ratio better is the flow property. Powder



with Hausner ratio less than 1.18, 1.19, 1.25, 1.3- 1.5 and greater the 1.5 indicate excellent, good, passable, and very poor, respectively. It is calculated by following formula.

$$\text{Hausner ratio} = \rho_t / \rho_b$$

**Void Volume:**

Void volume (V) was obtained by difference between bulk volume(V<sub>b</sub>) and tapped volume (V<sub>p</sub>).Void volume can be calculated by following formula.

$$V = V_b - V_p$$

**Evaluation of Tablets :**

The tablets are subjected to the following quality control tests<sup>1-3,5,14-18</sup> :

1. Weight variation
2. Friability
3. Hardness
4. Disintegration
5. Wetting Time
6. Water absorption Ratio
7. Taste / Mouth feel
8. In vitro Dissolution
9. Stability studies

**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.

**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/cm<sup>2</sup> 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 test 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 immersed in 1 liter beaker of distilled water at  $37 \pm 2^\circ \text{C}$ , such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker.

#### **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 eplerenone is dissolved in vitro within about 45 minutes using 1% sodium dodecyl sulfate (SDS) in water as the dissolution medium at  $37^\circ \text{C}$ . in the dissolution assay discussed hereinafter. More preferably, 0.1 N HCl in water at  $37^\circ \text{C}$ . is the in vitro dissolution medium in that assay, and about 50% of the micronized drug is dissolved in about 20 minutes, about 80% is dissolved at about 45 minutes and greater than about 90% is dissolved in about 90 minutes. More preferably, about 50% of the micronized eplerenone is dissolved in about 15 minutes, about 80% is dissolved at about 30 minutes and about 90% or more is dissolved in about 45 minutes.

#### **Stability study:**

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. Stability study of the dosage form must include a section for product

characterization and another section to study the product stability during storage. Formulations are evaluated for their appearance, possible weight gain in drug content thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, and in-vitro release study by keeping dosage form in different temperature and humidity condition after a specified time. The stability study indicates that the formulation is quite stable at different conditions of storage.

**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 petridish 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.

**Water Absorption Ratio:**

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper. The wetted tablet was then weighed.

**CONCLUSION**

Approximately most of the patients need rapid 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. 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.

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