



A REVIEW ON IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

*UTSAV PATEL¹, KHUSHBU PATEL¹, DARSHAN SHAH², RUSHABH SHAH²

1. K. B. Raval College of Pharmacy, Gandhinagar, Gujarat.
2. Kalol Institute of Pharmacy, Kalol, Gujarat.

Abstract

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Corresponding Author

Mr. Utsav Patel

K. B. Raval College of
Pharmacy, Gandhinagar,
Gujarat.

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. Liquid dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, AOT (dioctylsulfosuccinate) etc. 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 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. 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.

INTRODUCTION¹⁻⁴

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. Also solid oral delivery systems 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. Injections generally are not favored 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.

Type and Classes of Tablets¹⁻³

A. Oral Tablets for Ingestion

- 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

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

C. Tablets Administered by Other Routes

- Implantation tablets

- Vaginal tablets

D. Tablets Used to Prepare Solutions

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

DEFINITION⁴⁰⁻⁴⁶

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.

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 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.

Biopharmaceutic Consideration^{4, 11}

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.

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 α -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, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM^{5,7,8}

1. 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.
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.

5. Cost of products is main factor as parenteral formulations are most costly and discomfort.

DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM^{7, 8 &40}

Immediate release dosage form should-

In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form it should be compatible with taste masking.

2. Be portable without fragility concern.

3. Have a pleasing mouth feel.

4. It should not leave minimal or no residue in the mouth after oral administration.

5. Exhibit low sensitivity to environmental condition as humidity and temperature.

6. Be manufactured using conventional processing and packaging equipment at low cost.

7. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

POTENTIAL CANDIDATE FOR IMMEDIATE RELEASE ORAL DOSAGE FORM¹⁰

Analgesics and Anti-inflammatory Agents:

Auranofin, Azapropazone, Diflunisal, Fenbufen, Fenoprofen Calcim, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamicacid, Nabumetone, Oxyphenbutazone.

Anthelmintics

Albendazole, Dichlorophen, Mebendazole, Oxamniquine, Oxfendazole, Oxantel Embonate, Embonate, Thiabendazole.

Anti-Arrhythmic Agents:

Amiodarone Hcl, Disopyramide, Flecainide Acetate.

Anti-bacterial Agents

Benethamine, Penicillin, Cinoxacin, Ciprofloxacin HCl, Clarithromycin, Clofazimine, Doxycycline, Erythromycin, Nalidixic Acid, Nitrofurantoin, Rifampicin, Sulphabenzamide, Sulphadoxine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Trimethoprim.

Anti-coagulants

Dicoumarol, Dipyridamole

Anti-depressants

Amoxapine, Ciclazindol, Maprotiline HCl,
Mianserin HCl, Trazodone HCl.

Anti-diabetics

Acetohexamide, Chlorpropamide,
Glibenclamide, Gliclazide, Glipizide.

Anti-epileptics

Beclamide, Carbamazepine, Clonazepam,
Ethotoin, Methoin, Oxcarbazepine,
Paramethadione,
Phenobarbitone, Phenytoin, Primidone,

Anti-fungal Agents

Amphotericin, Butoconazolenitrate,
Clotrimazole, Econazolenitrate, Flucytosine,
Griseofulvin, Ketoconazole, Nystatin,
Sulconazole Nitrate, Terbinafine HCl,
Terconazole, Tioconazole.

Anti-gout Agents

Allopurinol, Probenecid, Sulphinpyrazone.

Anti-hypertensive Agents

Amlodipine, Carvedilol, Benidipine,
Darodipine, Dilitazem HCl, Diazoxide,
Guanabenz Acetate, Indoramin, Isradipine,
Minoxidil, Nicardipine HCl, Nifedipine,
Nimodipine, Reserpine.

Anti-malarials

Amodiaquine, Chloroquine, Chlorproguanil
HCl.

Anti-migraine Agents

Dihydroergotamine Mesylate, Succinate.

Anti-muscarinic Agents

Atropine, Benzhexol HCl, Biperiden,
Ethopropazine HCl, Tropicamide.

**Anti-neoplastic Agents and
Immunosuppressants:**

Aminoglutethimide, Amsacrine
Chlorambucil, Cyclosporin, Dacarbazine,
Estramustine, Etoposide, Lomustine,

Anti-protazoal Agents:

Benznidazole, Clioquinol, Decoquinolate,
Metronidazole, Nimorazole, Nitrofurazone,
Omidazole, Tinidazole.

Anti-thyroid Agents

Carbimazole, Propylthiouracil.

**Anxiolytic, Sedatives, Hypnotics and
Neuroleptics**

Alprazolam, Amylobarbitone, Barbitone,
Bentazepam, Bromazepam, Bromperidol,
Brotizolam, Chlormethiazole,
Chlorpromazine, Diazepam, Droperidol,

Ethinamate, Flunarisone, Flunitrazepam,
Fluopromazine,

Cardiac Inotropic Agents

Amrinone, Digitoxin, Digoxin, Enoximone,
Lanatoside C, Medigoxin.

Corticosteroids

Beclomethasone, Betamethasone,
Budesonide, Cortisone Acetate,
Desoxymethasone, Methylprednisolone,
Prednisolone, Prednisone, Triamcinolone.

Diuretics

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

Enzymes

All the enzymes.

Anti-parkinsonian Agents: Bromocriptine
mesylate, lysuride maleate.

Gastro-intestinal Agents: Bisacodyl,
cimetidine, cisapride, diphenoxylate
HCl, famotidine, loperamide,
mesalazine, nizatidine, omeprazole,
ondansetron HCl

Histamine H₁-Receptor Antagonists:

Acrivastine, astemizole, cinnarizine,
cyclizine, cyproheptadine HCl,
dimenhydrinate, flunarizine HCl.

Lipid Regulating Agents:

Bezafibrate, Clofibrate, Fenofibrate,
Gemfibrozil, Probucol.

Local Anaesthetics

Lidocaine

Neuro-muscular Agents

Pyridostigmine.

Nitrates and other Anti-anginal Agents

Amyl Nitrate, Glyceryltrinitrate, Isosorbide
Dinitrate, Isosorbide.

Nutritional Agents

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

Analgesics

Codeine, Dextropropoxyphene,
Diamorphine, Dihydrocodeine, Meptazinol.

Oral Vaccines

Vaccines designed to prevent or reduce the
symptoms of diseases of which the
following is a representative Influenza,
Tuberculosis, Meningitis, Hepatitis.

Proteins, Peptides and Recombinant drugs:

Insulin, Glucagon, Growth Hormone (Somatotropin), Polypeptides Or Their Derivatives, Calcitonins and Synthetic Modifications Thereof, Enkephalins, Interferons.

SexHormones

Clomiphencitrate, danazol, ethinyloestradiol, medroxyprogesterone acetate, mestranol, oestrogens, progesterone, stanozolol, stibioestrol, testosterone, tibolone.

Spermicides

Nonoxynol.

Stimulants

Amphetamine, Dexamphetamine, Dexfenfluramine, Fenfluramine, Mazindol, Pemoline.

Advantages of Immediate Release Drug Delivery System

^{10, 40, &41}

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

OTHER EXCIPIENTS ^{5, 6, 7, 8, 9, 10, 44, 45 & 46}

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.

SUPER DISINTEGRANTS ^{7, 8 & 35}

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:

1. Effective in lower concentrations
2. Less effect on compressibility and flowability
3. 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 (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 (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

Conventional Technique Used In The Preparation Of Immediate Release Tablets

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

Tablet Molding¹⁰

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

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. 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.

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 labor costs, fewer manufacturing steps, and less number of equipments are 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.

- * The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
- * Chemical stability problems for API and excipient would be avoided.
- * Provides stability against the effect of aging which affects the dissolution rates.

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, Aluminium 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.
- * Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
- * Non-uniform distribution of color, especially in tablets of deep colors.

Granulation^{1, 7, 9}

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 of the product. Granulation method can be broadly classified into two types:

- (i) Wet granulation and (ii) Dry granulation

Ideal characteristics of granules

The ideal characteristics of granules include spherical shape, smaller particle size

distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness.

The effectiveness of granulation depends on the following properties:

- * Particle size of the drug and excipients
- * Type of binder (strong or weak)
- * Volume of binder (less or more)
- * Wet massing time (less or more)
- * Amount of shear applied
- * Drying rate (Hydrate formation and polymorphism)

(i) Wet granulation^{8,10}

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. Hence, additional process monitoring techniques would be valuable.

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. Coarse 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

- * The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- * Loss of material during various stages of processing.
- * Stability may be a major concern for moisture sensitive or thermolabile drugs.

- * An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

It is a unique granulation technique that directly converts liquids into dry powder in a single step. This method removes moisture instantly and converts pumpable liquids into a dry powder.

Advantages

- * Rapid process.
- * Ability to be operated continuously.
- * Suitable for heat sensitive product.

(ii) Dry granulation^{7,10}

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 chilsonator.

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

Compression into large, hard tablets to make slug

3. Screening of slugs
4. Mixing with lubricant and disintegrating agent
5. 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.

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.

Mass-Extrusion (Mass-Extrusion) ¹²

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.

Immediate release solid dosage forms prepared by solid dispersions ⁴⁷

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.

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.

Evaluation of immediate release tablets

Evaluation Of Blend^{36, 37& 38}

The prepared blend is evaluated by following tests.

Angle of repose

Bulk density

Tapped density

Carr's index

Hauser's ratio

EVALUATION OF TABLETS^{36, 37}

The tablets are subjected to the following quality control tests:

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

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 assess 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 ± 2 °C, 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.

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.

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 (3ml). a tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color on the upper surface of the tablets was noted as the wetting time.

In vitro drug release studies^{21, 22, 24}

The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to assess 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 $37 \pm 10^\circ\text{C}$. 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. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml.

Dissolution efficiency¹⁰

DE is defined as the area under the dissolution curve upto the time "t" expressed as a percentage of the area of the trapezoid described by 100% dissolution in the same time.

$$DE = \frac{\int_0^t y \cdot dt}{Y_{100} \cdot t}$$

This has a range of values depending on the time interval chosen. For example, the index DE₃₀ would relate to the dissolution

of the drug from a particular formulation after 30 mins could only be compared with DE₃₀ of other formulations.

Dosage of Pharmaceutical Composition

The pharmaceutical composition contains micronized drug in an amount of about 10 mg to about 1000 mg. Preferably, the pharmaceutical compositions comprise micronized drug in an amount of about 20 mg to about 400 mg, more preferably from about 25 mg to about 200 mg, and still more preferably from about 25 mg to about 150 mg. It also has been found that the pharmaceutical compositions of the present invention provide a daily dosage of eplerenone sufficient to cause an average decrease in diastolic blood pressure in humans over an interval of about 12 to 24 hours, preferably about 24 hours, after ingestion of the composition of at least about 5%.

Unit Dosages

Dosage unit forms of the pharmaceutical compositions can typically contain, for example, 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg of drug. Preferred dosage unit forms contain about 25, 50, 100, or 150 mg of micronized

drug. The dosage unit form can be selected to accommodate the desired frequency of administration used to achieve the specified daily dosage. The amount of the unit dosage form of the pharmaceutical composition that is administered and the dosage regimen for treating the condition or disorder depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and thus can vary widely, as is well known.

Preparation of drug

The eplerenone of the novel pharmaceutical compositions of the present invention can be prepared using the methods set forth in Grob et al., U.S. Pat. No. 4,559,332 and Ng et al., WO 98/25948, particularly scheme 1 set forth in Ng. et al., WO 98/25948, both of whose disclosures are incorporated by reference.

Form of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise micronized drug in association with one or more non-toxic, pharmaceutically-acceptable carriers, excipients and/or adjuvants (collectively

referred to herein as "carrier materials"). The carrier materials are acceptable in the sense of being compatible with the other ingredients of the composition and are not deleterious to the recipient. The pharmaceutical compositions of the present invention can be adapted for administration by any suitable route by selection of appropriate carrier materials and a dosage of eplerenone effective for the treatment intended. For example, these compositions can be prepared in a form suitable for administration orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly (IM) or rectally. Accordingly, the carrier material employed can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 1% to about 95%, preferably about 10% to about 75%, more preferably about 20% to about 60%, and still more preferably about 20% to about 40%, by weight of micronized eplerenone. Such pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

Oral Administration

For oral administration, the pharmaceutical composition can contain a desired amount of micronized drug and be in the form of, for example, a tablet, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for oral administration. Such a pharmaceutical composition is preferably made in the form of a discrete dosage unit containing a predetermined amount of drug, such as tablets or capsules. Such oral dosage forms can further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with enteric coatings. Unit dosage tablets or capsules are preferred.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include, for example, lozenges comprising eplerenone in a flavored base, such as sucrose, and acacia or tragacanth, and pastilles comprising eplerenone in an inert base such as gelatin and glycerin or sucrose and acacia. Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing

inert diluents commonly used in the art, such as water. Such compositions can also comprise, for example, wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents. Examples of suitable liquid dosage forms include, but are not limited, aqueous solutions comprising eplerenone and β -cyclodextrin or a water soluble derivative of β -cyclodextrin such as sulfobutyl ether β -cyclodextrin; heptakis-2, 6-di-O-methyl- β -cyclodextrin; hydroxypropyl- β -cyclodextrin; and dimethyl- β -cyclodextrin.

Carrier Materials

As noted above, for therapeutic purposes, the pharmaceutical compositions of the present invention comprise micronized drug in a desired amount in combination with one or more pharmaceutically-acceptable carrier materials appropriate to the indicated route of administration. Oral dosage forms of the pharmaceutical compositions of the present invention preferably comprise micronized drug in a desired amount admixed with one or more carrier materials selected from the group consisting of diluents, disintegrants, binding agents and adhesives, wetting agents, lubricants, anti-adherent agents and/or

other carrier materials. More preferably, such compositions are tableted or encapsulated for convenient administration. Such capsules or tablets can be in the form of immediate release capsules or tablets, or can contain a controlled-release formulation as can be provided, for example, in a dispersion of drug in hydroxypropyl methylcellulose.

Injectable dosage forms preferably are adapted for parenteral injection. Preferably, these dosage forms comprise micronized drug in aqueous or non-aqueous isotonic sterile injection solutions or suspensions, such as drug suspended or dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

The selection and combination of carrier materials used in the pharmaceutical compositions of the present invention provides compositions exhibiting improved

performance with respect to, among other properties, efficacy, bioavailability, clearance times, stability, compatibility of drug and carrier materials, safety, dissolution profile, disintegration profile and/or other pharmacokinetic, chemical and/or physical properties. The carrier materials preferably are water soluble or water dispersible and have wetting properties to offset the low aqueous solubility and hydrophobicity of drug. Where the composition is formulated as a tablet, the combination of carrier materials selected provides tablets that can exhibit, among other properties, improved dissolution and disintegration profiles, hardness, crushing strength, and/or friability.

Disintegrants

The pharmaceutical compositions of the present invention optionally can comprise one or more disintegrants as a carrier material, particularly for tablet formulations. Suitable disintegrants can include, either individually or in combination, such disintegrants as starches; sodium starch glycolate; clays (such as Veegum™ HV); celluloses (such as purified cellulose, methylcellulose and sodium

carboxymethylcellulose, and carboxymethylcellulose); alginates; pregelatinized corn starches (such as National™ 1551 and National™ 1550); crospovidone USP NF; gums (such as agar, guar, locust bean, Karaya™, pectin, and tragacanth). Disintegrants can be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression. The present pharmaceutical compositions comprise one or more disintegrants in the range of about 0.5% to about 30%, preferably about 1% to about 10%, and more preferably about 2% to about 6%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet formulations, preferably in the range of about 1% to about 10%, preferably about 2% to about 6%, and more preferably about 5%, by weight of the composition.

Wetting Agents

Eplerenone, even micronized eplerenone, is largely insoluble in aqueous solution. Accordingly, the pharmaceutical compositions of the present invention optionally can comprise one or more

wetting agents as a carrier material, particularly for tablet formulations. Such wetting agents preferably maintain eplerenone in solution and improve the bioavailability of the pharmaceutical composition. Suitable wetting agents include, either individually or in combination, such wetting agents as oleic acid; glyceryl monostearate; sorbitan monooleate; sorbitan monolaurate; triethanolamine oleate; polyoxyethylene sorbitan mono-oleate; polyoxyethylene sorbitan monolaurate; sodium oleate; and sodium lauryl sulfate. Wetting agents that are anionic surfactants are preferred. The present pharmaceutical compositions comprise one or more wetting agents present at about 0.1% to about 15%, preferably about 0.25% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the composition. Sodium lauryl sulfate is a preferred wetting agent for tablet formulations. The compositions of the present invention preferably comprise sodium lauryl sulfate as the wetting agent at about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5 to about 2%, of the total weight of the composition.

Lubricants

The pharmaceutical compositions optionally comprise one or more lubricants and/or glidants as a carrier material. Suitable lubricants and/or glidants include, either individually or in combination, such lubricants and/or glidants as glyceryl behenate (Compritol™ 888); metallic stearates (e.g., magnesium, calcium and sodium stearates); stearic acid; hydrogenated vegetable oils (e.g., Sterotex™); talc; waxes; Stearowet™; boric acid; sodium benzoate and sodium acetate; sodium chloride; DL-Leucine; polyethylene glycols (e.g., Carbowax™ 4000 and Carbowax™ 6000); sodium oleate; sodium benzoate; sodium acetate; sodium lauryl sulfate; sodium stearyl fumarate (Pruv™); and magnesium lauryl sulfate. The present pharmaceutical compositions comprise one or more lubricants at about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition. Magnesium stearate is a preferred lubricant used to reduce friction between the equipment and granulation during compression.

Immediate Release Formulations

The immediate release compositions comprise micronized drug in an amount sufficient to provide the desired daily dosage, that is, an amount of about 10 mg to about 1000 mg, more preferably an amount of about 20 mg to 400 mg, still more preferably an amount of about 25 mg to 200 mg, still more preferably an amount of about 25 mg to 150 mg, and still more preferably an amount of about 50 mg to 100 mg. A once-a-day immediate release tablet or capsule contains drug in an amount, for example, of about 50 mg to about 100 mg. Preferably, the same batch can be used to prepare tablets (or capsules) of different strengths by compressing the formulation in different tablet sizes (or encapsulating the formulation in different capsule sizes or using different capsule fill weights). Although the amount of drug in such novel compositions preferably is within the ranges previously discussed, the formulations also can be useful for the administration of an amount of drug falling outside of the disclosed dosage ranges.

Dissolution Profile²³

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° C. in the dissolution assay discussed hereinafter. More preferably, 0.1 N HCl in water at 37° 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.

Disintegration Profile

Carrier materials for immediate release compositions preferably are selected to provide a disintegration time less than about 30 minutes, preferably about 20 minutes or less, more preferably about 18 minutes or less, and still more preferably about 14 minutes or less.

Hardness

For tablet formulations, the pharmaceutical composition in an amount sufficient to make a uniform batch of tablets is subjected to tableting in a conventional production scale tableting machine at normal compression pressure (for example, about 1 kN to about 50 kN). Any tablet hardness convenient with respect to handling, manufacture, storage and ingestion may be employed. Hardness in the range of about 3.5 kP to about 22 kP is typically acceptable, with about 3.5 kP to about 9 kP preferred for 25 mg tablets, about 5 kP to about 13 kP preferred for 50 mg tablets, and about 8 kP to about 22 kP preferred for 100 mg tablets. The mixture, however, is not be compressed to such a degree that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

Friability

For tablet formulations, tablet friability preferably is less than about 0.8%, more preferably less than 0.4%.

CONCLUSION

There is a clear opportunity for new enhanced oral products arising within this

market segment. This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. 'supergenerics' for veterinary or human application. 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 fulfil 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 a immediate release dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations.

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