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RECENT TRENDS ON IMMEDIATE RELEASE DOSAGE FORM: A REVIEW

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ABSTRACT

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy.To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. 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 thanconventional therapy. The basicapproach used in development tablets is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmeliose),Sodium starch glycolate (Primogel), Kollidon CL etc. which provide instant disintegration of tabletafter administration. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patientpopulation a more convenient dosage form or dosing regimen. In this regard, immediate release formulations are similarto many sustained release formulations that are now commonly available.

KEY WORDS: Immediate release, polymers, superdisintegrant.

INTRODUCTION[1, 2, 3, 4, 5, 6, 7, 8]

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 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. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance.

Definition:[9-14]

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.

Advantages of Immediate Release Drug DeliverySystem: [15,16]

1. Improved compliance/added convenience
2. Improved stability
3. Suitable for controlled/sustained releaseactives
4. Allows high drug loading.
5. Ability to provide advantages of liquidmedication in the form of solid preparation.
6. Adaptable and amenable to existingprocessing and packaging machinery
7. Cost- effective
8. More flexibility for adjusting the dose.
9. It can be prepared with minimum dose ofdrug.
10. There is no dose dumping problem.
11. Immediate release drug delivery systems used in both initial stage and final stage ofdisease 30.

Biopharmaceutic Consideration [4, 18]

When new drug delivery system put on, it ismust that to consider Biopharmaceuticalfactor like metabolism and excretion.

Pharmacokinetics

In this consideration, study has done onabsorption, 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 –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.

Criteria For Immediate Release Drug Delivery System [7,8]

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 sensivity 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

Immediate Release Drug Delivery Systems

Immediate release oral liquid dosage forms [11, 19]

Various dosage forms may exist for a single particular drug, since different medical conditions can warrant different routes of administration. For example, persistent nausea and emesis or vomiting may make it difficult to use an oral dosage form, and in such a case, it may be necessary to utilize an alternate route such as inhalational, buccal, sublingual, nasal, suppository or parenteral instead. A liquid formulation which shows immediate release is adapted to be suitable for oral administration. Immediate release oral liquid formulations may be in the form of suspensions of active ingredient in association with an aqueous solvent or, more preferably aqueous solutions (that is, solutions of active compound including water as a solvent). In this context, the term "aqueous solution" includes formulations in which at least 99% of active ingredient is in solution at above 5° C. and atmospheric pressure, and the term "suspension" means that more than 1% of active ingredient is not in solution under such conditions. Typical dispersion agents for suspensions are hydroxypropyl methylcellulose, AOT (dioctylsulfosuccinate), PVP and SDS. Other alternatives may be possible.The formulation provides an oral solution containing a pharmaceutically acceptable salt thereof, water and at least one additional agents. In another aspect formulation of a compound having formula comprising a solubilising agent such as a polyethylene glycol, β-cyclodextrin (such as hydroxypropyl-β-cyclodextrin), sorbitol or ethanol.

Immediate release parenteral dosage forms [12]

The term "parenteral" includes any mode of administration that does not comprise peroral administration to the gastrointestinal tract and includes administration subcutaneously, intravenously, intraarterially, transdermally, intranasally, intrabuccally, intracutaneously, intramuscularly, intralipomateously, intraperitoneally, rectally, sublingually, topically, by inhalation, or by any other parenteral route. Suitable formulations that are to be administered parenterally include those in which a pharmaceutically acceptable salt thereof is presented together with an aqueous carrier, such as water. A formulation contains an aqueous carrier may further comprise one or more excipients, such as an antimicrobial preservative; a tonicity

modifier (for example sodium chloride, mannitol or glucose); a pH adjusting agent (for example a common inorganic acid or base, including hydrochloric acid or sodium hydroxide); a pH controlling agents (that is, a buffer; for example tartaric acid, acetic acid or citric acid); a surfactant (for example sodium dodecyl sulphate (SDS) or Solutol™); a solubiliser which serves to help solubilise the active ingredient (for example ethanol, a polyethylene glycol or hydroxypropyl-β-cyclodextrin or polyvinyl chloride (PVP)); or an antioxidant. Formulations as parenteral formulations, comprising salts may be prepared by addition of diluent/carrier to the appropriate pre-prepared salt. Compositions including active ingredient may also be provided in solid form suitable for use in the preparation of a formulation of the invention (for example a solution, such as an aqueous solution, for example for parenteral adminstration) ex tempore. Such compositions may be in the form of a solid comprising active ingredient, optionally in the presence of one or more further excipients as hereinbefore defined and, optionally, up to 10% (w/w) of diluent and/or carrier.

Solid compositions of the invention may be made by removal of diluent/carrier (for example solvent) from a formulation of the invention, or a concentrated formulation of the invention, which may for example be in the form of a solution, such as an aqueous solution.Parenteral formulations may be in the form of suspensions of active ingredient in association with an aqueous solvent or, more preferably aqueous solutions (that is, solutions of active compound including water as a solvent). In this context, the term "aqueous solution" includes formulations in which at least 99% of active ingredient is in solution at above 5° C. and atmospheric pressure, and the term "suspension" means that more than 1% of active ingredient is not in solution under such conditions. Typical dispersion agents for suspensions are hydroxypropyl methylcellulose, AOT, PVP and SDS, but other alternatives are possible.

The number of excipients employed in the peroral and parenteral formulations of the invention depends upon many factors, such as the nature and amount of active ingredient present, and the amount of diluent/carrier (aqueous solvent or otherwise) that is included. A parenteral formulation contains a pharmaceutically acceptable salt thereof, water and at least one additional agents. The additional agents include:

1. polyethylene glycol (PEG) and optionally also ethanol and/or tartaric acid and/or hydrochloric acid; or
2. sodium chloride (which will be dissolved in the formulation), and optionally also ethanol; or
3. hydrochloric acid and/or sodium hydroxide to bring the pH to a suitable value (preferably in the range 3-8 ; or preferably in the range 3.5-8); or

4. DMA (dimethyl acetamide) and optionally also a medium chain triglyceride (such as miglyol); or
5. a β-cyclodextrin (such as hydroxypropyl-β-cyclodextrin);
6. a tonicity modifier such as sodium chloride and/or mannitol.

Immediate release micronized pharmaceutical dosage form[12]

It has been discovered that pharmaceutical compositions comprising micronized drug as the active ingredient in a daily dosage amount about 10 mg to about 1000 mg along with a pharmaceutically acceptable carrier material are unique compositions exhibit superior performance. Such pharmaceutical compositions exhibit superior activity, potency, safety and therapeutic effectiveness at this dosage range. These compositions provide drug to a patient at a dosage that is sufficient to provide prolonged and quick action and thus confer the desired therapeutic benefit, while maintaining a safe clearance time. Besides being useful for human treatment, these compositions are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents and the like. More preferred non-human animals include horses, dogs, and cats.Unformulated drug administered in capsule form is not well absorbed in the gastrointestinal tract. Accordingly, a need exists for suitable dosage forms. The pharmaceutical compositions of the present invention provide these dosage forms and exhibit one or more superior properties relative to unformulated drug and/or other compositions comprising drug. These superior properties include, but are not limited to, one or more of the following:

1 Improved bioavailability

2 Improved solubility of the pharmaceutical composition;

3 decreased disintegration times for immediate release oral dosage forms;

4 decreased dissolution times for immediate release oral dosage forms;

5 improved dissolution profiles for controlled release oral dosage forms;

6 decreased tablet friability;

7 increased tablet hardness;

8 improved safety for oral dosage forms;

9 reduced moisture content and/or hygroscopicity for oral dosage forms;

10 improved composition wettability;

11 improved particle size distribution of eplerenone;

12 improved composition compressibility;

13 improved composition flow properties;

14 improved chemical stability of the final oral dosage form;

15 improved physical stability of the final oral dosage form;

16 decreased tablet size;

17 improved blend uniformity;

18 improved dose uniformity;

19 increased granule density for wet granulated compositions;

20 reduced water requirements for wet granulation;

21 reduced wet granulation time; and/or

22 reduced drying time for wet granulated mixtures.

Immediate Release Tablet dosage form

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. Immediate release may be provided for byway 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

Potential Candidate For Immediate Release Oral Dosage Form [15].

Analgesics and Anti-inflammatory Agents

Aloxiprin, auranofin,azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofencalcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamicacid, nabumetone, naproxen, oxaprozin,oxyphenbutazone, phenylbutazone, piroxicam, sulindac.

Anthelmintics

Albendazole , bephenium, hydroxynaphthoate , cambendazole, dichlorophen,ivermectin, mebendazole, oxamniquine, oxfendazole, oxantelembonate, praziquantel, pyrantelembonate, thiabendazole.

Anti-ArrhythmicAgents

AmiodaroneHCl, Disopyramide, flecainideacetate, quinidinesulphate.

Anti-bacterial Agents

Benethamine penicillin, cinoxacin,ciprofloxacinHCl, clarithromycin,clofazimine, cloxacillin, demeclocycline, doxycycline,erythromycin, ethionamide, Imipenem ,nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine ,sulphamerazine ,sulphacetamide,sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim.

Anti-coagulants

Dicoumarol,dipyridamole, nicoumalone, phenindione.

Anti-depressants

Amoxapine, ciclazindol, maprotilineHCl, mianserinHCl, nortriptylineHCl, trazodoneHCl, trimipramine maleate.

Anti-diabetics

Acetohexamide,chlorpropamide, glibenclamide,gliclazide, glipizide, tolazamide, tolbutamide.

Anti-epileptics

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

Anti-fungal Agents

Amphotericin, butoconazolenitrate, clotrimazole, econazolenitrate, fluconazole, flucytosine,griseofulvin, itraconazole,ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafineHCl, terconazole, tioconazole, undecenoic acid.

Anti-gout Agents

Allopurinol,probenecid, sulphinpyrazone.

Anti-hypertensive Agents

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

Anti-malarials

Amodiaquine, chloroquine, chlorproguanilHCl, halofantrineHCl, mefloquine HCl, proguanilHCl, pyrimethamine, quinine sulphate.

Anti-migraine Agents

Dihydroergotaminemesylate,ergotamine tartrate, methysergidemaleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinicAgents

Atropine, benzhexolHCl,biperiden, ethopropazineHCl, hyoscine butyl bromide, hyoscyamine, mepenzolatebromide, orphenadrine, oxyphencylcimine HCl, tropicamide.

Anti-neoplasticAgents and Immunosuppressants

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

Anti-protazoal Agents

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

Anti-thyroid Agents

Carbimazole, propylthiouracil.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics:

Alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxidechlormethiazole, chlorpromazine, clobazam, clotiazepam,clozapine, diazepam, droperidol,ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixoldecanoate, fluphenazinedecanoate, flurazepam, haloperidol,

Cardiac InotropicAgents:

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

Corticosteroids

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

Diuretics

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

Enzymes

All the enzymes.

Anti-parkinsonianAgents

Bromocriptinemesylate, lysuride maleate.

Gastro-intestinal Agents

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

Histamine H,-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 Anaesthetics

Lidocaine

Neuro-muscular Agents

Pyridostigmine.

Nitrates and otherAnti-anginal Agents

Amyl nitrate, glyceryltrinitrate, isosorbidedinitrate, isosorbidemononitrate, pentaerythritoltetranitrate.

NutritionalAgents

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

Analgesics

codeine, dextropropyoxyphene, diamorphine,dihydrocodeine, meptazinol,methadone, morphine, nalbuphine, pentazocine.

Oral Vaccines

Vaccines designed toprevent 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 diseaseconditions affecting companion and farm animals.etc.

Proteins,Peptides and Recombinant drugs

Insulin, glucagon, growth hormone (somatotropin),polypeptides or their derivatives, calcitonins and synthetic modifications there of,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).

SexHormones

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

Spermicide

Nonoxynol.

Stimulants

Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline

Conventional Technique Used In The Preparation Of Immediate Release Tablets:

Tablet molding technique

Direct compression technique

Wet granulation technique

Mass extrusion technique

Tablet Molding [15]

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 [20,21,22,23]

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.

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

1. Problems in the uniform distribution of low dose drugs.
2. High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression for example, Aluminium Hydroxide, Magnesium Hydroxide.
3. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
4. Many active ingredients are not compressible either in crystalline or amorphous forms.
5. 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,
6. which may lead to unblending.
7. Non-uniform distribution of color, especially in tablets of deep colors.

Wet Granulation Method [24,25,26]

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

Procedure

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, 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 tray-dryer 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.

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

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

By solid dispersions

When formulating such solid amorphous dispersions into immediate release solid dosage forms for oral administration to a use environment such as the GI tract of an animal such as a human, it is often desirable to maximize the amount of dispersion present in the dosage form. This minimizes the size of the solid dosage form required to achieve the desired dose. Depending on the drug dose, it is often desired that the solid amorphous dispersion comprise at least 30 wt %, preferably at least wt %, and more preferably at least 50 wt % or more of the solid dosage form. Such high drug loadings of dispersion in a solid dosage form minimize the dosage form's size, making it easier for the patient to swallow it and tending to improve patient compliance. The immediate release dosage forms containing a solid dispersion that

enhances the solubility of a "low-solubility drug," meaning that the drug may be either "substantially water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, "sparingly water-soluble," that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous-solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL. 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.

Excipients Use For Immediate Release Tablet [5, 6, 7, 8, 26, 15, 13,14& 20]

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.

Bulking Materials

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

perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition .

Emulsifying Agents

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

Lubricants

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

Flavours And Sweeteners

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the 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.

Super Disintegrants [7, 8& 28]

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

Gas producing disintegrants

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tab letting, particularly on moisture level. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates. In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.

Evaluation Of Immediate Release Tablets [29]

Evaluation of powder blend

The prepared blend is evaluated by following tests.

1. Angle of repose
2. Bulk density

3. Tapped density

4. Hauser's ratio

5. Carr's index

1. Angle of repose

Angle of repose was determined by using fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blend were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile. Angle of repose was calculated using the following equation

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Here, **h** = Height of pile

r = Radius of pile

θ = Angle of repose

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

2. Bulk density

Bulk density was determined by pouring a weighed quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume.

$$\text{Bulk density} = \frac{m}{v} = \frac{m}{\pi r^2 h}$$

Here; **m** = weight of powder or granules (gm.)

v = Bulk Volume (cm.3)

π = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder (cm.)

3. Tapped Density

Tapped density is ratio of mass of tablet blend to tapped volume of tablet blend. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100 tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

Bulk density = $\frac{m}{v}$ $= \frac{m}{\pi r2h}$

Here; **m** = weight of powder or granules (gm.)

v = Bulk Volume (cm.3)

$\boldsymbol{\pi}$ = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder (cm.)

4. Hausner's Ratio

Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula

Hauser's ratio = Tapped density/ Poured density

5. Carr's Index (Compressibility Index)

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula

Carr's compressibility index (%) = [(TBD-LBD) X100] / TBD

Evaluation Of Tablets

These tests are as following:-

1. Appearance
2. Thickness
3. Hardness
4. Weight variation
5. Friability
6. Disintegration
7. Uniformity of dispersion

8. Wetting Time
9. Water absorption ratio
10. Drug content
11. *In vitro* Dissolution
12. Stability studies

1. Appearance

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

2. Thickness

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

3. Hardness

The hardness of tablet is an indication of its strength against resistance of tablets to capping**,** abrasion or breakage under conditions of storage, transportation and handling before usage. Measuring the force required to break the tablet across tests it. Hardness of 10 tablets (randomly) from whole tablet batch was determined by Monsanto hardness tester. Hardness measured in kg/cm2

4. Weight variation

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

5. Friability test

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

minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula

% Friability = [(W1-W2)100]/W1

Where,W1= Weight of tablet before test

W2 = Weight of tablet after test

6. Disintegration test

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 20^0 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.

7. Uniformity of dispersion:

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

8. Drug content

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

9. In vitro drug release studies [31,32]

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±10^0C. 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 Profile [28]

The compositions of the present invention preferablyare immediate release compositions from whichabout 50% of the micronized drug is dissolved invitro within about 15 minutes, more preferably atleast about 80% of the drug is dissolved in vitrowithin about 30 minutes, and still more preferably atleast about 90% of the e is dissolved in vitro withinabout 45 minutes using 1% sodium dodecyl sulfate(SDS) in water as the dissolution medium at 37 ^{0}C.

In vitro dissolution kinetic studies [32]

The drug released data were plotted and tested withzero order (Cumulative % drug released Vs time),Firstorder (Log % Remained Vs time).The zero order release kinetics was shown in Figures The First order release kinetics were shown in figures. The in vitro dissolution kinetic parameters, dissolution rate constants (K),correlation coefficient ® , the times (t50) for50% drug released (half life) and dissolution efficiency were calculated and presented in the tables of following chapters.From the slopes of linear plots, the dissolution rates were calculated. First – order release kinetics[17] log Q1 = logQo + k1t 2.303 The First order equation describes the release from systems where release rate is concentration dependent. Where Qo is the initial amount of the drug,t is in minutes and k1 describes the dissolution rate constant for first-order release kinetics.A plot of the logarithm of the percent drug remained against time will be linear if the release obeys first-order release kinetics.values of release rate constant k1 were obtained in each case from the slope of the log % drug remained versus time plots

Dissolution efficiency [10]

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 = t d y.dt Yidd.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**.**

One way ANOVA

One way analysis of variance (ANOVA) compares the means of three or more groups. The null hypothesis is that all column means are equal, and P value testing this null hypothesis. The one way ANOVA test assumes that data are randomly sampled from larger populations (or at least are representative of those populations) , that each value was obtained independently of others, that the populations are scattered accordingly to a Gaussian

distribution, and that the SD of the two populations are equal. It shows intermediate calculations that laid to calculate F value. If the calculated value is less than tabulated value, it can be concluded that the data are unlikely to be sampled from populations with equal means

Two ways ANOVA

When it is believed that two independent factors might have an effect on the response variable of interest, it is possible to design the test so that an analysis of variance can be used to test for the effects of the two factors simultaneously. Such a test is called a Two-Factor analysis of variance. With this we can test two sets of hypothesis with the same data at the same time. In this the data are classified according to two different criteria of factors. The procedure for analysis of variance is somewhat different than the one followed while dealing with problems of one-way ANOVA.(statistical methods –S.P.Gupta,34th edn,2005-pg no.-1019).

Similarity and Dis-similarity factor[33]

Purpose of dissolution profile comparison

1. For accepting product sameness under SUPAC-related changes.
2. To waive bioequivalence requirements for lower strengths of a dosage form.
3. To support waivers for other bioequivalence requirements.

Dissolution profiles may be considered similar by virtue of

(1) overall profile similarity and

(2) similarity at every dissolution sample time point. The dissolution profile comparison may be carried out using model independent or model dependent methods

Model Independent Approach Using a Similarity Factor

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles. The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves: where n is the number of time points, Rt is the dissolution value of the reference (prechange) batch at time t, and Tt is the dissolution value of the test (postchange) batch at time t.The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. A specific procedure to determine difference and similarity factors is as follows:

1. Determine the dissolution profile of two products (12 units each) of the test (postchange) and reference (prechange) products.

2. Using the *mean dissolution values* from both curves at each time interval, calculate the difference factor (f1) and similarity factor (f2) using the above equations. For curves to be considered similar, f1 3.values should be close to 0, and f2 values should be close to 100. Generally, f1 values up to 15 (0-15) and f2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and reference (prechange) products. This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. As further suggestions for the general approach, the following recommendations should also be considered:

1. The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both the profiles should be the same (e.g., 15, 30, 45, 60 minutes). The reference batch used should be the most recently manufactured prechange product.

2. Only one measurement should be considered after 85% dissolution of both the products.

3. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The mean dissolution values for Rt 4. can be derived either from (1) last t prechange (reference) batch or (2) last two or more consecutively manufactured prechange batches.

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.

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