IMMEDIATE RELEASE DRUG DELIVERY SYSTEM (TABLETS): AN OVERVIEW

Rishikesh*, Mohiuddin Ahmed Bhuyian, Ms. Irin Dewan, Drishti Rani Ghosh & Md. Asraful Islam
Department of Pharmacy, The University of Asia Pacific, Dhaka-1209, Bangladesh.
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Corresponding Author’s email: rishibd@gmail.com

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

Key words: Immediate release, Superdisintegrants, Direct compression, Wet Granulation

INTRODUCTION

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 development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriately 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.

DIFFICULTIES

- Patient may suffer from tremors therefore they have difficulty to take tablet, powder and liquids. In dysphasia physical obstacles and adherence to an oesophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.
CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM 7,8

Immediate release dosage form should:
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

CANDIDATE FOR IMMEDIATE RELEASE ORAL DOSAGE FORM

Analgesics and Anti-inflammatory Agents:
Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac.

Anthelmintics:
Albendazole, bephenium, hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel pamoate, praziquantel, pyrantel pamoate, thiabendazole.

Anti-arrhythmic Agents:
Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate.

Anti-bacterial Agents:
Benethamine penicillin, ciprofloxacin HCl, 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, dipyriramole, nicoumalone, phenindione.

Anti-depressants:
Amoxapine, clacizindol, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.

Anti-diabetics:
Acetohexamide, chlorpropamide, glimeclamide, gliclazide, glipizide, tolazamide, tolbutamide.

Anti-epileptics:
Beclamide, carbamazepine, clonazepam, ethotoin, methion, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbital, phenytoin, primidone, sulthiame, valproic acid.

Anti-fungal Agents:
Amphotericin, butoconazol, clotrimazole, econazol, fluconazole, fluconazole, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, triocainazole, undecenoic acid.

Anti-gout Agents:
Allopurinol, probenecid, sulphinpyrazone.

Anti-hypertensive Agents:
Amlodipine, carvedilol, benidipine, daropidine, dilazem HCl, diazoxide, feldopidine, guanabenz acetate, indoramin, iradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxymethazine HCl, prazosin HCl, reserpine, terazosin HCl.

Anti-malarials:
Amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.

Anti-migraine Agents:
Dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinic Agents:
Atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscymine, mefenolate bromide, orphenadrine, oxyphencycline HCl, tropicamide.

Anti-neoplastic Agents and Immunosuppressants:
Aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, procarbazine HCl, tamoxifen citrate, testolactone.

Anti-protozoal Agents:
Benznidazole, clindamycin, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, omeprazole, tinidazole.
Anti-thyroid Agents: Carbimazole, propylthiouracil.
Anxiolytic, Sedatives, Hypnotics and Neuroleptics:
Alprazolam, amylobarbitone, barbitone, benzepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide chloromethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate, flunisone, flunitrazepam, fluromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol.
Cardiac Inotropic Agents:
Amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin.
Corticosteroids:
Beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flunisolide, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.
Diuretics:
Acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.
Anti-parkinsonian Agents:
Bromocriptine mesylate, lysuride maleate.
Gastro-intestinal Agents:
Bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCl, ranitidine HCl, sulphasalazine.
Histamine H1-Receptor Antagonists:
Acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl, loratadine, meclozine HCl, oxatomide, terfenadine, triprolidine.
Stimulants:
Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol, pemoline.

Advantages of Immediate Release Drug Delivery System:

- Immediate release drug delivery systems used in both initial stage and final stage of disease.

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

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

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.

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

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

Some super disintegrants are:
1) Sodium Starch Glycolate (Explotab, primogel) used in concentration of 2-8 % & optimum is 4%.
**Mechanism of Action:** Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking
2) Cross-linked Povidone (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.

**Method Used In the Preparation of Immediate Release Tablets:**

* Direct compression
* Wet granulation

**Direct Compression Method**

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

**Wet Granulation Method**

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

**Procedure**

**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.

**Drug-excipient compatibility studies**

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

**EVALUATION OF IMMEDIATE RELEASE TABLETS**

**Angle of repose**

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug excipient blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.
Tan = h/r
Where h and r are the height and radius of the powder conc.

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

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

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

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

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

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

Carr’s compressibility index (%) = [(TBD-LBD) X 100] / TBD
A similar index has been defined by Hausner

Hauser’s ratio = Tapped density / Poured density
Hauser’s ratio <1.25 – Good flow = 20% Carr 1.25 – Poor flow =33% Carr

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

EVALUATION OF TABLETS

1. Weight variation
2. Friability
3. Hardness
4. Disintegration
5. In vitro Dissolution

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

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

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

% Friability = [(W1-W2)100]/W1
Where,
W1= Weight of tablet before test
W2 = Weight of tablet after test

Disintegration test:
The USP device to rest disintegration was six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 oC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.
In vitro drug release studies

The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus using specified volume of dissolution media maintained at 37±0.1°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 Profile

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

Conclusion

A new dosage format, the immediate release pharmaceutical form has been developed which offers the combined advantages of ease of dosing and convenience of dosing. These tablets are designed to release the medicaments with an enhanced rate. Due to the constraints of the current technologies as highlighted above, there is an unmet need for improved manufacturing processes for immediate release pharmaceutical form that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets.

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