RECENT ADVANCEMENT OF IMMEDIATE RELEASE DRUG DELIVERY SYSTEM: AN OVERVIEW

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Abstract-

Due to its ease of self-administration, compactness, and simple production, the tablet is the most widely used dosage form currently in use. In many situations, urgent action is necessary rather than conventional therapy. As an alternative oral dose form to address these limitations, instant release dosage forms have arisen. After ingestion, immediate medication release dosage forms dissolve more quickly than regular dose forms.

Superdisintegrants like Cross linked Polyvinylpyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croskarnellose), etc. are the fundamental method utilised in the production of tablets. After administration in the stomach, these superdisintegrants allow fast tablet disintegration. Parenteral dose forms and quick release liquid dosage forms have also been introduced in this field to treat patients.

Suspensions using common dispersion agents, such as hydroxypropyl methylcellulose, AOT (dioctyl sulfosuccinate), etc., can be administered in liquid dose form. A line extension in the market is made possible by the introduction of immediate release therapy; a variety of medications, including neuroleptics, cardiovascular medications, analgesics, antihistamines, and other medications, can be considered candidates for this dose form. Pharmaceutical companies frequently create a specific therapeutically entity in a new and enhanced dosage form as a drug entity approaches the end of its patent life. A novel dosage form enables a producer to maintain market exclusivity while providing a more practical dosage form or dosing schedule to its patient base.

Keywords: Superdisintegrant, polymers, Immediate release, Direct Compression, Novel Dosage
Introduction-

The most practical and often used method of drug administration is oral. Due to its simplicity, lack of discomfort, avoidance, adaptability, and most significantly, patient compliance appropriate for industrial production, enhanced stability, and bioavailability, oral administration is the most favoured route for systemic effects. Solid oral delivery methods can be produced at a reasonable cost because sterile conditions are not required.

In order to give patients more traditional ways to take their medications when receiving emergency care, the idea for instant release tablets is developed. Immediate release tablets have recently acquired popularity as a new medicine administered rapidly and effective.\footnote{1}

Because immediate release tablets are designed to dissolve and release their medications without any unique rate-controlling features, such as special coatings and other procedures, immediate release drug delivery systems are also standard types of drug delivery systems.\footnote{2}

Solid dosage forms that are meant to be taken whole dissolve and release their medications quickly and fiercely into the gastrointestinal tract, despite increased focus and interest in controlled release and targeted drug delivery systems in recent years.

An optimum drug therapy dose regimen is one that consistently maintains the desired therapeutic drug concentration in plasma \(\text{or at the site of action}\) throughout the course of treatment. Recently, the experts have concentrated their efforts on the quickly released tablet formulation. Choosing the right diluents and super disintegrants allows for the development of a fast-disintegrating tablet.

Immediate Release Tablets Definition:

The term "Immediate release tablets" refers to those that dissolve quickly and release the medication. An appropriate pharmaceutically acceptable diluent or carrier that doesn't significantly slow down the rate of drug release and/or absorption can be used to deliver immediate release. This term does not include drug formulations that have been adjusted to provide for "controlled," "sustained," "prolonged," "extended," or "delayed" drug release. The term "release" refers to the delivery (or presentation) of a drug from its formulation to the gastrointestinal tract, to body 's tissues, and/or into the systemic circulation. For gastrointestinal tract release, pH values such as pH=1 to 3 are ideal, particularly at or around pH=1. An element of the invention that involves a formulation with a under a variety of pH circumstances, the compound of formula (I) or an acid addition salt thereof releases the medicine.

A formulation of the invention as described here that contains a compound of formula (I) or an acid addition salt of it releases the medicine under conditions of pH ranging from 1 to 3, particularly at, or near, pH=1.

Thus, whether administered orally or parenterally, formulations of the invention may release at least 70\% (preferably 80\%) of the active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and particularly within an hour (such as within 30 minutes).\footnote{3}
Pharmacokinetics\(^{(2)}\).

It is the investigation of absorbing, distributing, metabolism, and excretion. Both the rate and extent of absorption are crucial since it determines when a drug reaches a therapeutic level and, consequently, when it produces a pharmacological effect. Dissolution is quick in conventional dose forms because there is a delay in disintegration. Numerous variables, such as tissue permeability, perfusion rate, drug binding to tissue, illness status, drug interaction, etc., affect medication distribution. The rate of drug clearance from the body or the site of action, or bioavailability, determines the duration and intensity of effect. Reduced regional blood flow to the liver and decreased liver volume may inhibit drug bioavailability by oxidation, reduction, and hydrolysis. Drugs excreted by the kidneys have a longer half-life because renal clearance is slower.

Pharmacodynamic\(^{(2)}\).

Drug interactions are impaired in both elderly and young adults due to abnormal organ development. When taking an antihypertensive drug like prazosin, side effects include decreased cardiac output, orthostatic hypotension, and decreased reflex response may occur. A reduction in the CVS's sensitivity to -adrenergic agonist and antagonist.

Immunity is diminished and taken into account when administering antibiotics. Elderly people exhibit reduced theophylline's bronchodilator action and higher susceptibility to barbiturates, indicating altered responses to pharmacological therapy. Elderly people frequently have concurrent ailments, which is taken into account when numerous pharmacological therapies are recommended. Researchers have clinically assessed medication combinations for quick release dosage forms of many kinds of cardiovascular medicines, diuretics, anti-hypertensive, etc. The patient's illness state will determine the best combination. Many pharmacological treatments are advised for elderly patients who frequently have co-occurring illnesses, which is taken into account.

**DESIRED CRITERIA FOR A DRUG DELIVERY SYSTEM WITH IMMEDIATE RELEASE:-**

**Dosage form for immediate release should**-

1. If a dose is given as a solid, it should quickly dissolve or disintegrate in the stomach.

2. Be produced at a minimal cost utilising standard processing and packaging equipment.

3. Feel good in the mouth.

4. After oral administration, it should not leave any, little, or no residue in the mouth.

5. Quick drug solubility and absorption, which could result in a quick start of action.

6. Have no fragility issues and be transportable.
IMMEDIATE RELEASE TABLETS:

Important Requirements For Immediate Release Tablet-

![Diagram of Immediate Release Tablet Requirements]

FIG. 1: IMPORTANT REQUIREMENTS FOR IMMEDIATE RELEASE TABLET.

A. Advantages

1. Extended shelf life and unit dosing method are merits.
2. Reasonably priced.
3. Enhanced bioavailability and stability.
4. The consistency and accuracy of the medication composition.
5. More economical and simpler to administer.
6. Elegance and a lack of taste.
7. Patient adherence.
8. They are typically the cheapest and easiest items to package.
9. The best possible medication breakdown and availability from the dosage form for absorption in line with intended usage.

B. Disadvantages

1. Has trouble swallowing.
2. The motion begins gradually and is reliant on dissolution and disintegration. Certain medications are resistant to compression because they are low-density or amorphous.
3. Tablets that have an offensive odour, a bitter taste, or are oxygen-sensitive may need to be coated or encapsulated issues with bioavailability.

4. The possibility of GI discomfort brought on by medications with locally high doses.

**EXCIPIENTS USED IN DRUG DELIVERY SYSTEMS FOR IMMEDIATE RELEASE**

In immediate release dosage forms, excipients maintain the characteristics of the actives in balance. To avoid contact with the active ingredients, it is imperative to fully comprehend the chemistry of these excipients.

Another problem that formulators must deal with is figuring out the price of these components.

Excipients play a crucial role in the manufacturing of tablets that melt quickly.

When used in the formulation, these inert substances of food grade provide the appropriate organoleptic qualities and product efficacy.

With the exception of some actives that require masking agents, excipients are generic and can be used with a wide variety of actives.

1. **Super Disintegrant**

An excipient called a disintegrant is added to a tablet blend to help the compacted mass break down when it is deposited in a fluid environment.

**ADVANTAGES**

1. They work more effectively in smaller amounts

2. These excipients have less of an influence on flow and compressibility.

3. Intrgranular disintegrants are more potent.

Sodium Starch Glycolate (Explotab, Primogel), used in concentrations of 2-8%, with 4% being ideal, is the most widely used super disintegrant.

**Mechanism of Action of different types Superdisintegrants** –

(A) Microcrystalline cellulose:

   Rapid and widespread swelling and little gelling.
Microcrystalline cellulose is utilised in concentrations of 2-15% of the required tablet weight (synonyms: Avicel, celex). Water absorption.

(B) Crosslinked Povidone (crospovidone) (Kollidone):

It is utilised in concentrations ranging from 2 to 5 percent of the required tablet weight. Not soluble at all in water.

Water wicking, swelling, and possibly some deformation recovery are the mechanisms of action. Quickly disperses and expands in water, yet even after prolonged exposure, it does not gel. Highest swelling rate when compared to other disintegrants. Superior surface-to-volume ratio compared to other disintegrants.

(C) Hydroxyl propyl cellulose:

With little substitution which water cannot dissolve. Quickly expands in water. LH-11 and LH-21 grades display possess the highest level of swelling. In addition to having some binding qualities, some grades can also disintegrate. 1–5% is the advised concentration in Conventional Methods for Making Tablets for Immediate Release.

2. Bulking components-

Bulking components play a major part in the manufacturing of immediate releases tablets. The substance provides diluent, filler, and cost-cutting properties.

Moreover, increasing bulk also lowers the concentration of the active ingredient in the composition. Bulking agents enhance the textural qualities, which in turn promote the disintegration.

For increased aqueous solubility and good sensory perception, more sugar-based bulking agents are advised for this delivery system, such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose), and starch hydrolystate.

In instance, mannitol has a high degree of water solubility and is well absorbed by the body.

Bulking agents are incorporated into the final composition in amounts ranging from 10% to 90% by weight.

3. Emulsifying Agents-

Emulsifying agents are essential excipients for making instant release tablets since they enhance the drug's release and breakdown.

Emulsifying chemicals are also helpful in stabilising immiscible blends and improving bioavailability.

For the creation of immediate releases tablets, a variety of emulsifiers are advised, including alkyl sulphates, propylene glycol esters, lecithin, sucrose esters, and others.

These substances can be included in the final composition in amounts varying from 0.05 to 15 percent by weight.
4. **Lubricants**-

Although they are not necessary excipients, lubricants can help make these tablets taste better once they dissolve in the mouth.

Lubricants eliminate gritty sensations and help the drug substances pass from the mouth into the stomach.

5. **(a) Flavours and Sweeteners:**

The products become more pleasant and pleasing for patients by the addition of flavours and sweeteners.

These substances help to mask the bitterness and unpleasant tastes of some active compounds.

Immediate releases tablets organoleptic properties can be improved by adding both natural and artificial flavours.

Sugar, dextrose, and fructose are just a few of the many sweeteners available to formulators. Non-nutritive sweeteners including aspartame, sodium saccharin, sugar alcohols, and sucralose are also options.

**(b) Sweeteners:**

Sweeteners are added to the recipe to enhance bulk and a pleasant flavour.

> **Conventional Methods Used in the Manufacturing of Immediate Release Tablets:**

For the production of immediate-release tablets, several technologies are available.

Moulding, lyophilization or freeze drying, direct compression, spray drying, and sublimation are the most popular preparation techniques.

![Conventional Methods Used in the Manufacturing of Immediate Release Tablets](image)

**FIG.2 CONVENTIONAL METHODS USED IN THE MANUFACTURING OF IMMEDIATE RELEASE TABLET.**
(1) Method of Direct Compression:

Without any prior processing, tablets are directly compressed from a mixture of the medicine and excipients. Pre-treatment as wet granulation is not necessary because the mixture to be crushed must have acceptable flow characteristics and maintain cohesion under pressure.

Few medications can be directly crushed into acceptable-quality tablets. The kind of disintegrant and its quantity are crucial factors. Particle size distribution, contact angle, pore size distribution, tablet hardness, and water absorption capacity are other aspects to be taken into account. (3)

Since it involves less equipment, fewer workers, fewer unit activities, and much shorter processing time in addition to improved product stability, it primarily benefits quick production (4).

These variables collectively control the disintegration. At the industrial level, the disintegrant addition method is inexpensive and simple to use. (3)

(2) Granulation Technique:

This size-enlargement process turns small particles into larger agglomerates, strengthening them physically. Avoiding product component segregation, improving powder flow and handling, and reducing dustiness are all advantageous.

Using the granulation technique, small particles are made into larger agglomerates, which strengthens them physically.

FIG 3. TYPES OF GRANULATIONS TECHNIQUES.
Steps In Direct Compression -

(A) Wet Granulation -

The process of wet granulation involves mildly agglomerating the powder combination using a liquid binder. A correctly controlled amount of liquid is required since an excessive amount will make the granules too hard and an insufficient amount will make them too soft and friable. Compared to solvent-based systems, aqueous solutions have the advantage of being safer to handle, but they might not be appropriate for medicines that are hydrolysed. It is perfectly spherical, and the smaller particles effectively cover the gaps between the granules. There are two categories in which this technique comes.
Steps Involved In Wet Granulation:

![Diagram of wet granulation process]

**Raw Material** → **Weighing** → **Screening** → **Drying** → **Sieving/Milling** → **Wet Massing** → **Screening** → **Mixing** → **Compression**

**B) Dry Granulation** -

The powder mixture is crushed without the use of heat or solvents during the dry granulation process. The two fundamental steps are to compress the material into a compact, and then to mill the compact to produce granules. For dry granulation, there are two techniques.

a) Slugging technique -

Granulation by slugging is the compression of dry powder used in tablet formation using a tablet press with a die chamber with a large enough diameter to fill quickly. It is not crucial that the slug is accurate or in good condition. Use a pressure that will condense the powder into even slugs. After slugs are created, they are milled and screened to a sufficient granule size for final compression.

(b) Rolling compaction –

A device known as a chilsonator can also be used to condense powder using pressure rolls. In contrast to a tablet machine, a chilsonator produces a compressed material in a steady, uninterrupted flow.

The hopper's powder is transferred between the rollers, in order to feed the powder into the compaction zone, which has a spiral auger. The aggregates are screened or processed to create granules, just like slugs.
(3) Tablet Moulding Technique-

The active substance is typically combined with lactose, dextrose, sucrose, mannitol, or another suitable diluent that can act as the foundation to create moulded tablets. This foundation shouldn't break down during making the tablet and should be freely soluble in water. Mannitol offers a pleasant, cooling sensation as well as added sweetness in the mouth, however lactose is the preferred basis.

(4) Mass Extrusion-

In this method, methanol, polyethylene glycol, and a softened mixture of the active medication are combined with a water-soluble solvent to make a cylinder-shaped product that is segmented with the help of a heated blade to create a dosage form known as tablets.

(5) Solid Dispersion-

Products that are solid and have two or more distinct ingredients, primarily a hydrophilic matrix and a hydrophobic medication. Either the matrix is crystalline or amorphous. This method deal with the challenge of mixing a matrix and drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. It is frequently desirable to enhance the degree of dispersion that occurs in the dosage form when creating instant release solid dosage forms from solid amorphous dispersion for oral administration to effective use in an environment like a human GI tract.

(6) Lyophilization-

It depends on the straightforward concept of sublimation. A substance is transformed by the sublimation process from a solid state to a vapour state without transitioning into the liquid phase. Under pressure and temperature conditions that are below the triple point, lyophilization is carried out. The entire procedure is carried out under low pressure and temperature while using vacuum, making it appropriate for drying thermolabile substances.

Evaluation Of Immediate Releases Tablet – (3)

- Preformulation Study-

Evaluation of powder mixture: The created blend is examined in the tests that follow.

1. The angle of repose
2. Bulk density.
3. Tapped density
4. Hauser ratio.
5. Carr's index.
1. **Angle of repose:** The fixed funnel method was used to calculate the angle of repose. In the fixed funnel method, graph paper was placed on a level, horizontal surface with a funnel propped up with its tip at a predetermined height (2 cm). The mixture of granules or tablets was gently poured through the funnel until the top of the conical pile barely touched the funnel's tip. Consequently, where \( r \) is the radius of the conical pile's base. The equation below was used to determine the angle of repose.

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

In this case, \( h \) = Height of pile.

\( R= \) radius of pile,

\( \theta= \) is the angle of repose.

2. **Bulk density:** A weighted amount of the tablet mixture was poured into a graduated cylinder, and the height was measured. The mass of the tablet mix to the bulk volume is measured by bulk density.

\[
\text{Bulk Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}
\]

Here; \( m \) = weight of granules or powder (gm). Bulk Volume (cm.3) = \( v \) Radius of Cylinder (cm) = \( \frac{22}{7} \approx 3.14 \)

\( h \) = Height of powder in cylinder, in centimetres.

3. **Tapped Density:** The ratio of a tablet blend's mass to its tapped volume is known as tapped density. A precisely weighed quantity of the tablet mixture is poured into the graduated cylinder, and the height is recorded. Then the cylinder was permitted to 100 tap onto a solid surface while bearing its own weight. The tapping continued until there was no longer any height change was noted.

\[
\text{Tapped Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}
\]

Here, \( m \) is the weight in grammes of the powder or granules. Tapped Volume = (v) (cm.3) Radius of Cylinder (cm) = \( \frac{22}{7} \approx 3.14 \)

\( h \) = Height of powder in cylinder after tapping (in centimetres).

4. **Hausner’s Ratio:** Defined as the ratio of tapped density to bulk density, the Hausner's Ratio describes the flow characteristics of powder. The formula provided was used to determine Hausner's ratio.

5. **Carr's Index (Compressibility Index):** Carr’s compressibility index measures the percentage compressibility of powder, which is defined as the ability of powder to decrease in volume under pressure using bulk density and tapped density.

It has a tangential connection to relative flow rate. The provided formula was used to determine Carr's compressibility index.
Carr’s Index = (1 - Bulk Density/Tapped Density) x 100

- Post Compression Study

Evaluation Of Tablet-

The following tests are included:

1. Appearance
2. Thickness
3. Hardness
4. Weight variation
5. Friability
6. Disintegration
7. Dispersion uniformity
8. Wetting Period
9. Ratio of water absorption
10. Drug Content
11. In vitro Dissolution

(a). Appearance:

The overall elegance, shape, colour and surface textures of a tablet define its visual identity. All of these factors are necessary for consumer approval.

(b). Thickness:

Vernier callipers were used to measure the thickness of the tablets. 10 tablets were chosen at random and their thickness was measured in mm and represented as mean ± SD and unit is mm.

(c). Hardness:

The strength of a tablet is determined by how resistant it is to capping, abrasion, or breakage under conditions of storage, transportation, and handling prior to use. It is tested by measuring the amount of force needed to break the pill in two. A Monsanto hardness tester was used to measure the hardness of 10 tablets chosen at random from the entire batch. In kg/cm2, hardness is measured.
(d). Weight variation:

To make sure that the weight of tablets in a batch is uniform, a weight variation test is performed. The average was computed after determining the total weight of 20 tablets chosen at random from the entire batch. Additionally, the precise weights of the individual tablets were ascertained, and the weight variation was determined.

(e). Friability test:

When a tablet loses weight in a container during handling or transit, it is due to the removal of tiny particles from the surface. The friability of the tablets was determined using the Roche friabilator. Take a sample of 10 whole tablets for tablets with an average weight of more than 0.65 g and a sample of entire tablets for tablets with an average weight of 0.65 g or less. 100 rounds of the Roche friabilator are cycled at 25 rpm for 4 minutes. The tablets were cleaned, then weighed once more. The formula \(\% f = \frac{W_0 - W_1}{W_0} \times 100\) was used to get the percentage of weight reduction.

\[\% f = \frac{W_0 - W_1}{W_0} \times 100\]

Here, \(\% f\) stands for percent friability.

\(W_0 = \) Initial weight (before testing)

\(W_1 = \) final weight (After Test)

(f). Disintegration test:

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 were the USP device to rest disintegration. One tablet is placed in each tube, and the basket rack becomes toxic in a 1 litre beaker of distilled water at a temperature of 37°C so that the tablets rise over the liquid's surface but don't go any closer than 2.5 cm to the beaker's bottom.

(g). Uniformity of dispersion:

Two tablets were held in 100 ml of water for two minutes while being gently swirled. 22 meshes were used to filter out the dispersion. If there was no trace of anything on the tablet's screen, it was deemed to have passed the test.

(h). Wetting Time:

The tablet’s wetting time was determined using a straightforward approach. A Petridish containing 10ml of a 0.2% w/v amaranth solution and five circular tissue papers each measuring 10cm in diameter was used. One tablet was delicately placed on the tissue paper's surface. The amount of time needed for the amaranth water-soluble dye to develop its blue colour on the top surface of the tablets was recorded as the wetting time.
(i). Water Absorption Ratio:

6ml of water was placed in a small petridish, and a little piece of tissue paper that had been folded twice was placed within. On the page was a tablet. After that, the wet tablet was weighed. R, the water absorption ratio, was calculated using the formula below.

\[ R = \frac{W_a - W_b}{W_b} \times 100 \]

Here, \( R \) = Water absorption ratio

\( W_b \) = Weight of tablet before water absorption

\( W_a \) = Weight of tablet after water absorption.

(j). Drug content:

10 tablets were crushed, and 100 mg of drug equivalent powder was dissolved in 0.1N HCl or an appropriate media buffer. By using that media, the volume of the solution reached 100ml. To quantify the amount of medication in one pill, the solution was filtered, dilute it 100 times, and then analyse it spectrophotometrically.

(k). In vitro drug release tests:

To determine if the formulation is capable of delivering immediate drug delivery, the immediate release tablets are put through in vitro drug release studies in pH 6.8 phosphate buffer or 0.1N HCl for 30 minutes. In dissolve test equipment with a predetermined volume of 900ml of dissolving media kept at 370.20C, drug release tests were conducted. The tablets are either held in the cylindrical basket or placed directly in the medium using the paddle, and then rotated at a speed of 100 rpm. At each interval of time (5, 10, 15 & 30 minutes), 5ml of the sample from the dissolving medium was removed, and 5ml of new medium was added. After filtering the samples, 1 ml of the filtrate was taken and diluted to 10 ml. These samples underwent spectrophotometric analysis, and additional calculations were made to determine drug release. The cumulative percent of drug released versus time and the log percent of drug remaining vs time were tested and plotted for the drug released data. The kinetics of in vitro dissolution Calculations were used to determine parameters, dissolution rate constants, correlation coefficients, and dissolving efficiency.

(l). Stability analysis:

The capacity of a given medication or dosage form to maintain its physical, chemical, therapeutic, and toxicological requirements in a particular container is known as stability. Drug decomposition or deterioration happens during storage due to a chemical change in the active ingredient or because of product instability, a decrease in the drug's concentration in the dose form.

A portion for product characterization and another section for studying the product stability during storage must be included in the stability study of the dosage form. By exposing dosage forms to various temperature and humidity conditions for a predetermined amount of time, formulations are assessed for their appearance, potential weight gain in drug content thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, and invitro release study. The stability research shows that the formulation is fairly stable under various storage circumstances.
CONCLUSION:

This is a brand-new, improved oral product that has emerged in this market sector and is adaptable to a variety of therapeutic agents. A third of the patients require immediate therapeutic action from their medications, which results in poor adherence to conventional drug therapy and decreased total therapeutic efficacy. A brand-new dosage form called the quick release pharmaceutical form has been created, and it combines the benefits of convenience and ease of administration. These tablets are made to release the medications more quickly. Due to the limitations of current technologies, which have been mentioned above, there is an unmet demand for improved manufacturing techniques for pharmaceutical products with instant release that are mechanically robust, easy to handle and package, and have production costs comparable to similar to that of standard tablets. Formulators have worked hard to create a novel type of tablet dosage form for oral administration that dissolves and disintegrates quickly with improved solubility in order to meet these medical needs. Immediate release dosage forms, which can extend market exclusivity, enhance sales while also focusing on underserved and undertreated patient populations.

References


