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A Review: Immediate Release Dosage Forms and Legislative Guidelines

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ABSTRACT

Most popular drug delivery in current days was solid drug delivery system it was more suitable in term of manufacturing and testing. In solid oral dosage forms different grade of filler, binder, disintegrating agent, sweetener, lubricant, glident are used, which play important role in tablet hardness, disintegration and dissolution. Filler, binder, and disintegrating agent, were found to influence tablet dissolution and disintegration, with the filler and disintegrating agent exerting the most significant influence. Slower dissolution was observed with increasing disintegration time when either the filler or the disintegrating agent was kept constant. Generic formulation cover app 90% of all over market. Lots of regulatory body was developed guidelines for industry to develop and testing prepared genric formulation. Generic formulation same in term of strength, shape, release rate, colour, etc. Lot of generic formulation in market for one molecule with same effect in term which show more significant in term of cost and availability.

Keywords: Solid Dosage forms, Immediate Release, Disintegration, Generic Formulation.

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INTRODUCTION

Oral Solid dosage forms (Tablets and Capsules) are some of the most popular and convenient methods of drug delivery[1]. They can be produced in a non-sterile environment and the process, equipment and technology is well defined and known after more than 100 years of development[2]. Dosage forms (also called unit doses) are essentially pharmaceutical products in the form in which they are marketed for use, typically involving a mixture of active drug components and non drug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example)[3]. The term unit dose can also sometimes encompass non-reusable packaging as well (especially when each drug product is individually packaged), although the FDA distinguishes that by unit-dose "packaging" or "dispensing". Depending on the context, multiple unit doses can refer to distinct drug products packaged together, or to a single drug product containing multiple drugs and/or doses[4]. The term dosage form can also sometimes refer only to the chemical formulation of a drug product's constituent drug substance(s) and any blends involved, without considering matters beyond that (like how it's ultimately configured as a consumable product such as a capsule, patch, etc) [5]. Because of the somewhat vague boundaries and unclear overlap of these terms and certain variants and qualifiers thereof within the pharmaceutical industry, caution is often advisable when conversing outside of one's typical discourse community [6].

Depending on route of administration, several type dosage forms. These include of liquid, solid, and semisolid dosage forms. Common dosage forms immediate release include pill, tablet, or capsule, drink or syrup, and natural or herbal form such as plant or food of sorts, among many others [7].

Immediate Release Dosage Forms

Among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self-administration, compactness and easy manufacturing; sometimes-immediate onset of action is required than conventional therapy in many cases[7]. So that to overcome these drawbacks, immediate release dosage form has emerged as alternative oral dosage forms [8]. Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution [9]. The basic approach used in development tablets is the use of super disintegrant[10] like Cross linked Polyvinylpyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croscarmellose) etc [11]. These superdisintegrants provide instantaneous disintegration of tablet after administration in stomach. In this field

immediate release liquid dosage forms and parenteral dosage form have also been introduced for treating patients [12]. The development of immediate release therapy also provides an opportunity for a line extension in the marketplace, a wide range of drugs e.g., neuroleptics [13], cardiovascular drugs [14], analgesics [15], antihistamines [16] and other drugs can be considered candidates for this dosage form[17]. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen [18].

GENERIC DRUG

Medicines those original patent has expired and lots of manufacturer now be produced as same as original innovator (patent-holding) company[19]. A drug patent gives a drug company the sole right to sell a new drug. The company sells its new drug under its own brand name. By law, other companies cannot sell this drug until the term of the patent is over. These types of drugs are called generics, or generic drugs [20]. The generic drug has the same active ingredient as the brand name drug, but it may not look like the brand name drug. The generic drug usually has its own shape or color [21]. This does not affect how it works. For example, Cipro is the brand name drug containing the active ingredients, ciprofloxacin. The generic version is also sold as ciprofloxacin**.** Approximate 63 generic drug of ciprofloxacin are available in market [22].

Legislative History

1906: Pure Food and Drug Act - Establishes regulation of Food and Drugs [23].

1938: Food, Drug and Cosmetic Act - Introduced safety standards [24].

1962: Kefauver-Harris Amendments to the FDA&C Act - tightened safety standards and introduced requirement that drugs must be effective [25].

1984: Hatch-Waxman Act - created an abbreviated mechanism for approval of generic copies of all drugs originally approved after 1962 by stating that preclinical and clinical testing does not repeated for generic [26]**.**

ROLL OF EXCIPIENTS AND ITS EFFECT IN IR TABLET

Process of selection of excipients especially for generic formulation has been based on the available information on reference product composition in patient information leaflet (PIL)/pack insert and other literature review[27]. The PIL was attached with references product or its was give in different authenticated website [28]. IR product consists of the following inactive ingredients- Mannitol, colloidal silicon dioxide (NF), ethylcellulose (NF), hydrogenated castor oil (NF),

hydroxypropyl methylcellulose (USP), magnesium stearate (NF), mannitol (USP), microcrystalline cellulose (NF), povidone (USP), and yellow ferric oxide (NF) [29-30].

Diluent:

The recommended Diluent for this delivery system should be more sugar-based such as Mannitol, Lactose, DCP, Starch, Polydextrose, lactitol, DCL (direct compressible lactose) for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Diluent agents are added in the range of 10 percent to about 90 percent by weight of the final composition [31].

Binder:

Binders act as an adhesive to 'bind together' powders, granules and tablets to result in the necessary mechanical strength [32].

- As a dry powder with other excipients in dry granulation (roller compaction, slugging) or as an extra-granular excipients in a wet granulation tablet formulation.
- As a dry powder with other intra-granular excipients in wet granulation. When the granulating fluid is added, the binder may dissolve partially or completely then exhibit adhesive binding properties in helping granules to form.
- Most commonly in wet granulation, the binder is added already dissolved in the granulating fluid to enable a more effective and controllable granule formation.

Commonly used formulation in IR tablet as a binder: cellulose derivative [33],

Lubricants:

lubricant used to ease tablet compression. 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 [34].

Flavors and Sweeteners:

Flavors 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 flavors 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 in to the composition [31].

Disintegrant:

Disintegrants are substances or mixture of substances added the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly. Some super-disintegrants like

Sodium Starch Glycolate (Synonyms: Explotab, Primogel) was widely used in oral pharmaceuticals preparation as a disintegrant . It was commonly used in tablets prepration by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is Sufficient. Mechanism of Action: Rapid and extensive swelling with minimal gelling.

S.No	Disintegrants	Conc. in granules	Properties
1	Ac-Di-sol	1-3	Directly Compressible
2	CMC	5-10	Binder, Disintegrant
3	Polyplasdone	0.5-5	Crosslinked PVP
4	Explotab	2-8	Superdisintigrant
5	MCC	10-20	Lubricant properties,
6	Starch	5-20	Higher amount is required, poorly compressible

Microcrystalline cellulose (**Synonym**: **Avicel**): used in concentration of 2-15% of tablet weight.

Cross-linked Povidone or crospovidone (Synonyms: Kollidon): 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 disintegrant. Greater surface area to volume ratio than other disintegrant.

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%.

Cross-linked carboxy methylcellulose sodium (Synonyms: Ac-Di-sol, Croscarmellose sodium): Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

Effective Concentrations[35]:

1-3% Direct Compression,

2-4% Wet Granulation

BIO WAVIER OF IR TABLET [36-41]

In recent years the necessity to provide a scientific basis for biowaiver for individual substances

has met considerable interest. A biowaiver implies that bioequivalence (BE) assessment studies are waived for marketing authorizations (MA) by Health Authorities for a new tablet or capsule, or a new formulation of an existing immediate release (IR) dosage form, and hence the product is considered bioequivalent to its reference product, without carrying out a BE study. In this case the comparative in vitro study assures BE of the test product. FDA - Guidance for Industry: "Waiver of in vivo bio-equivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a Bio-pharmaceutics Classification System" (2000). In BCS based bio waiver we evaluated the drug substance and drug product

In drug substance evaluation

- Pharmacodynamics / therapeutic aspects
- physicochemical aspects

In Drug product evaluation

- in vitro dissolution

QBD AND PAT IMPLEMENTATION IN PREPARATION OF TABLET [42-47]

In the future, manufacturing of solid dosage forms Process Analytical Technology (PAT), play important role for better assessment and understanding of the effect of process parameters on product quality attributes. With the help of PAT and QBD analysis of multiple variables such as qualitative and quantitative product manufacturing process parameter and critical quality attributes (CQAs) linked to clinical activity relationships. Through this we assuming this becomes possible, then safety and efficacy of a pharmaceutical product could be linked, in part, to product components and manufacturing process parameters. Ideally, according to Janet Woodcock, this new vision should create "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight". Analyze the reference listed drug (clinical, pharmacokinetic properties, drug release, physicochemical characterization, study of different composition). Study and optimized the targeted drug. Developed a dissolution method for bioequivalence study for all BCS class (IR product must give 85% release of drug in 30 min). Study of drug product (physicochemical properties, biological properties, risk assessment, drug compatibility study). Formulation Development (Initial Risk Assessment of the Formulation Variables, selection of particle size, process selection, formulation development study). Manufacturing process development.

QbD Methodology

- The evolution of process understanding
- Target Product Profiles, Critical Quality Attributes and Critical Process Parameters
- Knowledge space and design space as applied to solid dosage forms
- The excipients problem-a major challenge to adoption of QbD in solid dosage forms
    - variability
    - linking properties to behaviour and functionality testing
- PAT principles, levels of PAT implementation
- Control strategies such as at-line and on-line analytics
- Real time release

GUIDANCE FOR IR TABLET [49-51]

Lots guidance is available for industry in manufacturing and testing of IR tablet

- Guidance for industry immediate release solid oral dosage forms
    - This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the post approval period, to change:
        - the components or composition;
        - the site of manufacture;
        - the scale-up/scale-down of manufacture; and/or
        - the manufacturing (process and equipment) of an immediate release oral formulation.
- Guidance for industry dissolution testing of immediate release solid oral dosage forms
    - This guidance is developed for immediate release (IR) dosage forms and is intended to provide general recommendations for dissolution testing;
    - Approaches for setting dissolution specifications related to the biopharmaceutical characteristics of the drug substance;
    - Statistical methods for comparing dissolution profiles;
    - Process to help determine when dissolution testing is sufficient to grant a waiver for an in vivo bioequivalence study.

Three categories of dissolution test specifications for immediate release drug products are Described in the guidance:

- **Single-point specifications**
    - As a routine quality control test (For highly soluble and rapidly dissolving drug products).
- **Two-point specifications**
    - For characterizing the quality of the drug product.
    - As a routine quality control test for certain types of drug products (e.g., slow dissolving or poorly water soluble drug product like carbamazepine).
- **Dissolution profile comparison**
    - For accepting product sameness under SUPAC-related changes.
    - To waive bioequivalence requirements for lower strengths of a dosage form.
    - To support waivers for other bioequivalence requirements.

In the future, a two-time point approach may be useful, both to characterize a drug product and to serve as quality control specification.

DISSOLUTION SPECIFICATIONS FOR GENERIC PRODUCTS [52-54]

The approaches for setting dissolution specifications for generic products fall into three categories:

- USP Drug Product Dissolution Test Available
    - In this instance, the quality control dissolution test is the test described in the USP. The Division of Bioequivalence, Office of Generic Drugs, also recommends taking a dissolution profile at 15-minute intervals or less using the USP method for test and reference products (12 units each). The Division of Bioequivalence may also recommend submitting additional dissolution data when scientifically justified. Examples of this include (1) cases in which USP does not specify a dissolution test for all active drug substances of a combination product and (2) cases in which USP specifies use of disintegration apparatus.
- USP Drug Product Dissolution Test Not Available (Publicly Available);
    - In this instance, a dissolution profile at 15-minute intervals of test and reference products (12 units each) using the method approved for the reference listed product is recommended. The Division of Bioequivalence may also request.
- USP Drug Product Dissolution Test Not Available (Publicly not Available);
    - In this instance, comparative dissolution testing using test and reference products under a variety of test conditions is recommended. The test conditions may

include different dissolution media or multimedia dissolution test (pH 1 to 6.8), addition of surfactant, and use of apparatus 1 and 2 with varying agitation

In Special Case:

- **Two-Point Dissolution Test-** For poorly water soluble drug products (e.g., carbamazapine), dissolution testing at more than one time point for routine quality control is recommended to ensure in vivo product performance. Alternatively, a dissolution profile may be used for purposes of quality control.
- **Two-Tiered Dissolution Test-** To more accurately reflect the physiologic conditions of the gastrointestinal tract, two-tiered dissolution testing in simulated gastric fluid (SGF) with and without pepsin or simulated intestinal fluid (SIF) with and without pancreatin may be employed to assess batch-to-batch product quality provided the bioequivalence is maintained.

EFFECT OF FOOD ON RELEASE OF IR TABLET

FDA have been provide some guideline about effect of Food will on the bioavailability of drug, so we have doing in-vivo testing in both case in fed or without fed condition Potential[55]. Mechanisms of Food Effects on BA are –

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Some interesting case shows that effect of food in bioavailability of drug-

Tulpule, K. Krishnaswamy was study effect of food on Effect of food on bioavailability of Chloroquine and found that AUC and peak plasma levels were significantly higher when chloroquine was administered together with food, although the rate of absorption was not different[56]. G. Foulds', D. R. Luke review that two dosage form of Azithromycine tablets and suspension and they found that in the absence of food effect on the bioavailability of azithromycin not significantly affected by administration immediately following a high-fat breakfast. Thus, these tablet, sachet and suspension formulations of azithromycin may be administered without regard to meals, increasing the convenience of once-daily dosing regimens[57]. Sheldon Preskorn, et.al. study the effect of food on the pharmacokinetics of

Lurasidone, and concluded that Lurasidone should be administered with food—at least 350 kcal—to ensure maximum exposure[58]. Joachim Brouwers et.al present study demonstrated the value of two advanced tools in evaluating food-dependent tablet disintegration. Using MRI, they clearly illustrated the impaired water ingress into HPMC-coated fosamprenavir tablets immersed in a nutritional drink[59]. David Fleisher et.al. review of Drug meal and formulation Interaction Influencing Drug absorption n after oral administration and its clinical implication and he was present the current status of information regarding interaction which may influence GI absorption of orally administration drug[60]. Barbara Myers Davit et.al. review how the food effect on drug bioavailability:, food interaction with drug substance, rate of absorption in the presence of food and it Implication for New and Generic Drug development[61]. Kevin M. Koch et.al. study was conducted on the effect of food on relative bioavailability of Lapatinib and found that increases the Lapatinib bioavailability on fasted condition[62]. Ian R Welshman et.al. study the Linezolide absolute bioavailability and the effect of food on oral bioavailability and they are compaire the absorption of Linezolide tablet oral after high fat meal and in fasting condition[63]. R. Teng et.al determine the oral bioavailability of Trovafloxacine with and without food in healthy volunteers under fed and fasted condition in randomized and cross over study and found that food reduced mean Cmax by 12% but had no appreciable effect on mean AUC. Result shows that Trovafloxacin has good oral bioavailability and with food it clinical impact on bioavailability of drug [64]. Susan K. Paulson et.al. found that absorption of celecoxib is minimal affect when administered with food in human so Celecoxibe has been prescribed in chronic arthritis condition with or without food if Celecoxibe may be preferable given under fasting because food effect its absorption due to lag time of food [65].

CURRENT APPROACH IN IR TABLET

Press-coating of immediate release powders onto coated controlled release tablets with adhesives[66]. Develop an immediate release tablet of Cetirizine Dihydrochloride (Cetirizine HCl) for immediate release and 240 mg of pseudoephedrine hydrochloride (pseudoephedrine HCl) for extended release. The Cetirizine HCl is contained within an outer layer of the tablet while a semi permeable membrane of cellulose acetate and polyethylene glycol controls the rate at which pseudoephedrine HCl is released from the tablet core[67]. Coating of Immediate release tablet with dry powder applying a novel approach electrostatics dry powder coating process. In which plasticizer sprayed on surface of tablet core due to which conductivity of tablet core enhance particle deposition, electrical resistivity reduced then followed by coating polymer sprayed on tablet surface due to spray of coating polymer enhance the distribution of polymer on tablet

equal and found to be smooth surface of tablet. In this technique monitored the improvement in number and size of particle enter the dissolution media (was developed in combination with a population balancing model), through this model we able to understand the description of the dissolution behaviors of the tablets in terms of the rate that they release particles into solution. This was then successfully model in terms of a tablet erosion rate[68]. Linking dissolution was a new approach in which we analysis the description of the dissolution behaviors of the tablets in terms of the rate that they release particles into solution[69].

RESULTS AND DISCUSSION

Most valuable market for IR tablet was US, USFDA, MHRA and other regulatory authority was developed guidelines for manufacturing and testing of excipient, API and developed product. Main concern of these regulatory body was release profile and impurity of drug. Dissolution of tablet play important role in release of API form granules and tablet. Role of food was found to be important in release and absorption of drug. New approach was developed for manufacturing of tablet and increases the efficiency of formulation; all those things are enhance the importance of immediate release tablet in worldwide market.

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