



A REVIEW ON IMMEDIATE RELEASE DRUG DELIVERY SYSTEM BY USING DESIGN OF EXPERIMENT

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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; Sometimes immediate onset of action is required than conventional therapy in many cases. Tablets are the most popular dosage form because of its unique properties such as ease of administration, low cost and non-invasive therapy etc. Therapeutic success of any therapy depends on the patient's compliance toward the therapy. 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. To provide the patients with the most convenient mode of administration, there was a need to develop immediate release dosage form, particularly one that disintegrates rapidly and disperses and helps in enhancing stearate. Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. Direct compressed method was adapted to prepare the tablets by using different excipient microcrystalline cellulose, lactose, pregelatinized starch, croscarmellose sodium, talc, sodium starch glycolate, magnesium. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.

Key Words: Immediate release, direct compression, super-disintegrants

INTRODUCTION:

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in

which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.

ROLE OF DESIGN OF EXPERIMENTS IN PROCESS IMPROVEMENT:^{1, 2, 3, 4, 5}

The term "design of experiments" was originated around 1920 by Ronald A. Fisher, a British scientist who studied and proposed a more systematic approach in order to maximize the knowledge gained from experimental data. DOE is a formal mathematical method for systematically planning and conducting scientific studies that change experimental variables together in order to determine their effect of a given response.

Design-Expert software version 7 was used to optimize the quantity of superdisintegrants. The best-fitting mathematical model was selected based on the comparisons of several statistical parameters including the determination coefficient (R^2), the adjusted

determination coefficient ($\text{adj-}R^2$) and the F -value provided by analysis of variance (ANOVA). Subsequently, grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs were drawn in MS-Excel using the output files generated by the Design Expert Software. Experimental designs have long been employed to optimize various industrial products and/or processes such as the factorial designs (FDs) since 1926, ¹ the screening designs since 1946, the central composite designs (CCDs) since 1951, and mixture designs (SMDs) since 1958. The use of optimization techniques employing design of experiments (Doe), however, permeated the field of pharmaceutical product/process development around four decades ago. DOE makes controlled changes to input variables in order to gain maximum amounts of information on cause and effect relationships with a minimum sample size. DOE is more efficient than a standard approach of changing "one variable at a time" in order to observe the variable's impact on a given response. This is initial planning stage of process development. During this stage, technical Operation in both the manufacturing and quality-control departments should be consulted and provide the flow diagram for a convenient basis on which to develop a detailed list of variables and responses. Initially the working documents are critical, but they should never be "cast in stone", since new experimental data may drastically alter them. The final version will eventually be an essential part of the process characterization as the development program progresses; new discoveries will provide an update of the variable and responses: A full factorial design was used for optimization procedure.

USE OF EXPERIMENTAL DESIGN:

Experimental designs are used so that the treatments may be assigned in an organized manner to allow valid statistical analysis to be carried out on the resulting data. Different designs isolate different known or suspected sources of variation so that the treatments effects can be evaluated free of extraneous environmental or other influences. Statistical theory also requires that certain conditions be met during the execution of the experiments to permit valid probability statements to be made.

COMPLETELY RANDOMIZED DESIGN:

Completely randomized designs are the simplest in which the treatments are assigned to the experimental units completely at random. This allows every experimental unit, i.e., plot, animal, soil sample, etc., to have an equal probability of receiving a treatment. An example of a

completely randomized design is shown on the attached figure. Note that the 4 replicates of the 4 treatments are assigned at random to the 16 experimental units. This may be done by a table of random numbers, or by pulling numbered slips out of a hat. This analysis of variance table is also shown for this design.

ADVANTAGES OF COMPLETELY RANDOMIZED DESIGNS:

1. Complete flexibility is allowed - any number of treatments and replicates may be used.
2. Relatively easy statistical analysis, even with variable replicates and variable experimental errors for different treatments.
3. Analysis remains simple when data are missing.
4. Provides the maximum number of degrees of freedom for error for a given number of experimental units and treatments.

DISADVANTAGES OF COMPLETELY RANDOMIZED DESIGNS:

1. Relatively low accuracy due to lack of restrictions which allows environmental variation to enter experimental error.
2. Not suited for large numbers of treatments because a relatively large amount of experimental material is needed which increases the variation.

APPROPRIATE USE OF COMPLETELY RANDOMIZED DESIGNS:

1. Under conditions where the experimental material is homogeneous, i.e., laboratory, or growth chamber experiments.
2. Where a fraction of the experimental units is likely to be destroyed or fail to respond.
3. In small experiments where there is a small number of degrees of freedom.

The completely randomized design is seldom used in field experiments where the randomized complete block design has been consistently more accurate since there are usually recognizable sources of environmental variation.

TYPES AND CLASSES OF TABLET: ^{7, 8, 9, 10, 11}

A. Oral Tablets for Ingestion:

1. Compressed tablets
2. Multiple compressed tablets
3. Layered tablets
4. Compression-coated tablets
5. Repeat-action tablets
6. Delayed-action and enteric-coated tablets
7. Sugar and chocolate-coated tablets
8. Film coated tablets
9. Chewable tablets

B. Tablets Used in the Oral Cavity:

1. Buccal tablets
2. Sublingual tablets
3. Troches and lozenges
4. Dental cones

C. Tablets Administered by Other Routes:

1. Implantation tablets
2. Vaginal tablets

D. Tablets Used to Prepare Solutions:

1. Effervescent tablets
2. Dispensing tablets
3. Hypodermic tablets
4. Tablet triturates

IMMEDIATE RELEASE TABLETS:

Definition: Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. The term "release" includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.

It also finds applications in the field of local delivery of drug to the stomach and proximal small intestine and importantly in treating microorganisms (*Helicobacter pylori*) in immediate release tablets, disintegration is one of the important parameter. With the help of design of experiment (DOE) approach, process variables are first 'screened' to determine which are important to the outcome (excipients type, percentage, disintegration time (DT), etc. Next step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture. Immediate release tablets have gained prominence of being new drug delivery systems. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic.

DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM:

Immediate release dosage form should

1. In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
2. Be manufactured using conventional processing and Packaging equipment at low cost.
3. Have a pleasing mouth feel.
4. It should not leave minimal or no residue in the

mouth after oral administration

5. Rapid dissolution and absorption of drug, which may produce rapid onset of action
6. Be portable without fragility concern.

MERITS AND DEMERITS OF IMMEDIATE RELEASE TABLETS:

A. Merits:

1. Unit dose system and Long shelf life.
2. Cost effective.
3. Improved stability, bioavailability.
4. Accuracy and uniformity of drug content.
5. More Economic and Ease of administration.
6. Tastelessness and Elegance.
7. Patient compliance.
8. They are in general the easiest and cheapest to package.
9. Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use

B. Demerits:

1. Posses swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density
3. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet Bioavailability problems.
4. Chance of GI irritation caused by locally high concentrations medicaments

PHARMACOKINETICS:

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

PHARMACODYNAMIC:

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.

1. Decreased ability of the body to respond reflexive

stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Immunity is less and taken into consideration while administered antibiotics

2. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates

3. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.

EVALUATION OF POWDER BLEND:^{12, 13, 14,6,7,8}

1) **Angle of repose:** The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

$$\theta = \tan^{-1} (h/r)$$

Where, 'θ' is the angle of repose, 'h' is height of pile; 'r' is radius of base of the pile

2) **Bulk Density (D_b):** It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume.

From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$D_b = M / V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively

3) **Tapped Density (D_t):** It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given

$$\text{by } D_t = M / V_t$$

Where, M and V_t are mass of powder and tapped volume of the powder respectively

The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas:

LBD = Weight of the powder/volume of the packing.

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

4) **Compressibility index:** The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD-LBD) * 100] / TBD$$

Where, LBD = Weight of the powder/volume of the packing.

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

5) **Hausner's ratio:** Hausner's ratio can be determined by the following equation,

$$\text{Hausner's ratio} = TBD / LBD$$

Where, TBD: Tapped bulk densities and LBD: Loose bulk densities.

TECHNIQUES OF PREPARATION:^{15, 16,9,10, 11, 12}

- Tablet molding technique
- Direct compression technique
- Wet granulation technique
- Melt granulation techniques
- By solid dispersions

1)**Tablet molding technique:** Molded tablets are generally prepared by mixing the active drug with lactose, dextrose, sucrose, mannitol, or some other appropriate diluent that can serve as the base. This base must be readily water soluble and should not degrade during the tablet's preparation. Lactose is the preferred base but mannitol adds a pleasant, cooling sensation and additional sweetness in the mouth.

2)**Methods for tablet preparation:**

- A. Granulation method.
 - a. Wet granulation.
 - b. Dry granulation.
- B. Direct compression method

Table 1: Steps involved in this process:

Wet Granulation	Dry Granulation	Direct compression
Blending	Blending	Blending
Wet massing and screening	Slugging /roller compression	-
Drying	-	-
Dry screening	Screening	-
Blending (with lubrication)	Blending (with lubrication)	Blending (with lubrication)
Compaction	Compaction	Compaction

3) Mass extrusion technique:

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder shaped extrude which are finally cut 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.

4) Melt granulation technique:

In this process, pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity, involves

the use of a hydrophilic waxy binder (Superpolystate®, PEG-6-stearate). Superpolystate® is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and Solublises rapidly leaving no residues.

5) By solid dispersions:

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 1to2 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.

Table 2: Some superdisintegrants used in immediate release tablets

Examples	Super disinter grants	Mechanism of action	Special comment
Cross Linked Starch	Sodium Starch Glycolate	Swells 7-12 folds in <30 seconds.	Swells in 3-dimensions & high level serve as sustained release matrix
Cross linked cellulose	Crosscarmellose [®] Ac-Di-Sol [®] Primellose [®] Vivasol [®]	Swells 4-8 fold in <10 seconds. Swelling and wicking both.	Swelling is in the two Dimensions. Direct Compression or Granulation
Cross linked PVP	Crosspovidone Kollidon Polyplasdone	Swells 7-12 folds in <30 seconds. Swells very little & rectum to original size after Compression but act by Capillary action.	Swells in 3 dimensions & high level serves as Sustained release matrix.
Cross linked alginic acid	Alginic acid NF satialgine	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or but granulation.
Natural super disintegrats	Soly-Polysaccharides emcosoy	Rapid Dissolving	Does not contain any starch or sugar. Used in Nutritional product.

EVALUATION OF TABLETS: 17, 18, 19, 3,4,5, 9

1) Tablet Thickness:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using digital vernier calipers.

2) Weight variation:

Drug content, of tablet were representing as mean ± SD. Tablet weight variation friability were measured using the

USP methods and criteria. Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Weight, of tablet were representing as mean ± SD.

3) Friability:

Tablet friability was measured using friability tester (Roche friabilator).

4) Hardness:

Hardness of tablet was measured by Monsanto hardness tester. Hardness of tablet were representing as mean \pm SD.

5) In vitro Disintegration test:

The various core tablet formulations prepared by wet granulation method are subjected to disintegration studies using 900ml water (as a disintegrating medium) and the time taken for disintegration is noted.

6) In vitro Dissolution test:

In vitro dissolution test was carried out by triplicate method using USP Type II (Paddle type) Apparatus. 900ml of distilled water was used as dissolution medium, and the paddle was rotated at 50rpm for 1 hr at a temperature of 37°C. Sampling was done at regular intervals and was replaced by water after each sampling interval. The samples are then analyses spectrophotometrically at 315nm.

7) Wetting time and water absorption ratio:

A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 6 ml of distilled water, a tablet was put on the paper, and the time required for complete wetting was measured. The wetted tablet was then weighed. Three trials for each batch were performed and standard deviation was also determined. Water absorption ratio, R, was determined using equation.

$$R = 100 \times (W_a - W_b) / W_b$$

Where,

W_b = weight of the tablet before water absorption, W_a = weight of the tablet after water absorption

8) Stability studies:

Accelerated stability studies were conducted for the optimized formulation (S-II) as per ICH guidelines for one month

9) Statistical analysis:

All statistical calculations were performed using Sigma Stat 3.5 demo version software. Data were analyzed using student's t test and one way analysis of variance (ANOVA). Differences were considered statistically significant at $P < 0.05$.

10) Mathematical Modeling of Drug Release Profile:

The cumulative amount of drug release at different intervals fitted to zero order kinetics, Higuchi model and Koremeyer – Peppas model to characteristics mechanism of drug release.

Zero Order Kinetics:

It describes the system in which the drug release rate is independent of its concentration.

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = Amount of drug dissolved in time t and the Q_0 = Initial amount of drug in the solution, which is often zero order and K_0 is the zero order release constant.

If the zero drug release kinetic is obeyed, then a plot of Q_t versus t will give a straight line with a slope of K_0 and an intercept at zero.

First Order Kinetics:

It describes the drug release from the synthesis in which the release rate is concentration dependent.

$$\log Q_t = \log Q_0 + Kt / 2.303$$

Where, Q_t is the amount of drug released I time t , Q_0 is the initial amount of drug in the solution and k is the first order release constant.

If the first order drug release kinetic is obeyed, then a plot of $\log (Q_0 - Q_t)$ versus t will be straight line with a slope of $kt/2.303$ and an intercept at $t = 0$ of $\log Q_0$.

Higuchi Model:

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$M_t / M_\infty = k_H t^{1/2}$$

Where M_t and M_∞ are cumulative amounts of drug release at time t and infinite time, and k_H is the Higuchi dissolution constant reflection formulation characteristics. If the Higuchi model of drug release (i. e Fickian diffusion) is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will be straight line with slope of k_H .

Korsmeyer – Peppas model (Power Law):

The power law describes the drug release from the polymeric system in which release deviates from Fickian Diffusion, as expressed in following equation.

$$M_t / M_\infty = k t^n$$

$$\log [M_t / M_\infty] = \log k + n \log t$$

Where, M_t and M_∞ are cumulative amounts of drug release at time t and infinite time (i.e . fraction of drug release at time t) , k is the constant incorporating structural and geometrical characteristics of CR device , and n is a diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

CONCLUSION:

Most of the patients need quick therapeutic action of drug, resulting in poor compliance with conventional drug therapy which leads to reduced overall therapy effectiveness. Immediate release 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. An extension of market exclusivity, which can be provided by immediate release dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations.

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