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Design, Development and Characterization of Immediate Release Tablet of Pioglitazone

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ABSTRACT:

Pioglitazone, a Class II BCS drug having poor water solubility and slow dissolution rate may have a negative impact on its bioavailability, subtherapeutic plasma drug levels and thus may lead to therapeutic failure. In order to improve its solubility and thus dissolution rate, IR tablet of Pioglitazone is formulated using fluidized bed granulation by using carmellose Ca as super disintegrant. For the process parameter selected was effect of bed temperature, Atomization, Intragranular, Extragranular and effect of hardness and thickness. The effect of selected process parameters on critical properties of IR tablets were studied, like effect of disintegration time, friability, dissolution profile.Dissolution studies using the USP paddle method were performed for solid dispersions of Pioglitazone at 37 ± 0.50c and 50 rpm in pH 1.2,2.0,5.5 and 7.5 .

Keywords: Pioglitazone, spray drying, superdisintegrants, fast- dissolving tablets.

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INTRODUCTION:

Introduction to Immediate Release Dosage Form [1,2]

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption.

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants.

> Mechanism of Disintegrants:

1) High swellability
2) Capillary action and high swellability
3) Chemical reaction

When introduced to an aqueous environment of use, the tablet rapidly takes up water, leading to swelling of the disintegrant and rapid disintegration of the tablet before the dispersion polymer can form a hydrogel. The disintegrant should be chosen such that it (1) swells rapidly when introduced into the use environment and (2) has a low tendency to form or promote formation of a hydrogel. The rate of swelling of the disintegrant is directly correlated to tablet disintegration times. Tablets containing disintegrants cause more rapid swelling have faster disintegration times at comparable disintegrant levels.

The amount of work, W, or swelling energy, due to swelling can be measured using a dynamic mechanical analyzer (DMA). The swelling energy attributable to swelling of the disintegrant in the compact may be calculated from the following equation: W=PAV

Where W is the work or swelling energy of the disintegrant,
P is the pressure applied by the probe, and AV is the volume change of the sample.
To compare disintegrants, the swelling energy per mass of disintegrant is used. Preferably, the disintegrant generates a swelling energy of at least 0.05 J/g within about 10 minutes following addition of water to the liquid reservoir.

The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Classification of "Superdisintegrant" may be organized into three classes based on their chemical structure. As shown in Table below.

1) Modified starches (Sodium starch glycolate) and trade name is Explotab Primojel
2) Modified cellulose(Croscarmellose NF) and trade name is Ac-Di-Sol Nymcel
3) Cross-linked polyvinylpyrrolidone (Crospovidone) and trade name is Crospovidone Kollidon Polyplasdone

Incorporation into Immediate Release Dosage Forms

The immediate release dosage form comprises the dispersion, a porosigen, and a disintegrant. The dosage form is in the form of a compressed tablet or other solid dosage form. Other conventional formulation excipients may be employed in the dosage forms including surfactants, pH modifiers, fillers, matrix materials, complexing agents, solubilizers, pigments, lubricants, glidants, flavorants, may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions.

> Solid Dispersion:

The dosage forms contain a high loading of the solid amorphous dispersion. High loadings of dispersion in the dosage form minimize the size of the dosage form, making it easier for the patient to swallow it and improving patient compliance. Depending on the drug dose, the immediate release dosage form comprises at least 30-50 wt % of the dispersion. This type of dosage forms disintegrates within 10 minutes following introduction to a disintegration medium. The dosage form of the present invention releases at least 70 wt %, more preferably at least 80 wt % and most preferably at least 90 wt % of the low solubility drug within 35 minutes following introduction to a dissolution medium.

> Concentration-Enhancing Polymers:

Concentration enhancing polymers suitable for use in the solid drug dispersions in the sense that they do not chemically react with the drug in an adverse manner. The polymer can be neutral or ionizable, and should have an aqueous solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8.It is preferred that the concentration-enhancing polymer be "amphiphilic" in nature, meaning that the polymer has hydrophobic and hydrophilic portions. It is believed that such polymers have relatively strong interactions with the drug and may promote the formation of various types of polymer/drug assemblies in solution. A particularly preferred class of amphiphilic polymers is those that are ionizable non-cellulosic polymers. Exemplary polymers include: carboxylic acid-functionalized vinyl polymers, such as the carboxylic acid-functionalized polymethacrylates and polyacrylates such as the Eudragit; amine-functionalized polyacrylates and polymethacrylates; proteins, such as gelatin and albumin; and carboxylic acid-functionalized starches such as starch glycolate. Another class of polymers suitable for use comprises non-ionizable or neutral non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; polyvinyl alcohols; polyvinyl alcohol polyvinyl acetate copolymers; polyvinyl pyrrolidone; polyethylene polyvinyl alcohol copolymers. The amount of concentration- enhancing polymer relative to the amount of drug present in the solid drug dispersions depends on the drug and concentration-enhancing polymer and may vary widely from a drug-to-polymer weight ratio of 0.01 to 5, or from about 1 to about 80 wt % drugs. However, in most cases, except when the drug dose is quite low, i.e., 25 mg or less, it is preferred that the drug-to-polymer ratio is greater than 0.05 and less than 2.5. The maximum drug: polymer ratio that yields satisfactory results varies from drug to drug and is best determined in the in vitro and/or in vivo dissolution tests.

> Preparation of Dispersions:

Different methods are also been used for preparation of solid dispersions such as Melting method, Solvent method, Melting

solvent method (melt evaporation), Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, The Use Of Surfactant, Electrospinning and Super Critical Fluid Technology.

> **Disintegrants:**

As disintegrants sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, Crospovidone, polyvinyl polypyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch, sodium alginate, and mixtures thereof. The amount of disintegrant included in the dosage form will depend on several factors, including the properties of the dispersion, the properties of the porosigen and the properties of the disintegrant selected. Generally, the disintegrant will comprise from 1 wt % to 25 wt % of the dosage form.

> **Surfactants:**

One very useful class of excipients is surfactants, preferably present from 0 to 10 wt %. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzalkonium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene sorbitan fatty acid esters, natural surfactants such as sodium taurocholic acid, lecithin, and other phospholipids and mono- and diglycerides; and mixtures thereof. Such materials can advantageously be employed to increase the rate of dissolution by, for example, facilitating wetting, or otherwise increase the rate of drug release from the dosage form.

> **pH Modifiers:**

Inclusion of pH modifiers such as acids, bases, or buffers may also be beneficial in an amount of from 0 to 10 wt %. Acidic pH modifiers (e.g., acids such as citric acid or succinic acid) retard the dissolution of the pharmaceutical composition when the dispersion polymer is anionic. Alternatively, basic pH modifiers (e.g., sodium acetate or amines) enhance the rate of dissolution of the same types of pharmaceutical composition.

> **Diluents:**

Examples of other matrix materials, fillers, or diluents include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers, polyethylene oxide, hydroxypropyl methyl cellulose and mixtures thereof.

> **Surface Active Agents:**

Sodium lauryl sulfate and polysorbate 80. Drug-complexing agents or solubilizers include the polyethylene glycols, caffeine, xanthene, gentisic acid and cylodextrins.

> **Lubricants:**

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

> **Glidants:**

Examples of glidants include silicon dioxide, talc and corn starch. Preferably from 10 to 50 wt % of the dosage form Tablets are generally formed by blending the dispersion, disintegrant, and porosigen with optional excipients and then compressing the powder to form tablets. Often it is desirable to granulate the compositions, with or without the addition of excipients prior to compression. For example, the dispersion, disintegrant, and porosigen may be granulated by mechanical means for example, roller compaction or "slugging," followed by milling to form granules. The granules typically have improved flow, handling, blending, and compression properties relative to the ungranulated materials. Wet granulation techniques may also be employed, provided the solvents and process selected do not alter the properties of the solid amorphous dispersion. Improved wetting, disintegrating, dispersing and dissolution properties may be obtained by the inclusion of other excipients. After the tablet is formed by compression, it is desired that the tablet has "strength" of at least 5-10 Kp/cm^2. Here, "strength" is the fracture force, also known as the tablet "hardness," required to fracture a tablet formed from the materials. The fracture force may be measured using a Schleuniger Tablet Hardness Tester. Friability is a well- known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability.

- The methods used for development of batches are direct compression,wet granulation by intragranular and extragranular,top spray granulation methods using different excipients,super disintegrantsand lubricants with API.

Tablet Manufacturing[13,41]

The manufacturing of oral solid dosage forms such as tablets is a complex multi-stage process under which the starting materials change their physical characteristics a number of

times before the final dosage form is produced. Traditionally, tablets have been made by granulation. Both wet granulation and dry granulation or direct compression is used.

Following are the various unit processes which are involved in making tablets

1. Dispensing
2. Sizing
3. Powder blending
4. Granulation
5. Drying
6. Tablet compression
7. Packaging

Various factors associated with these processes can seriously affect content uniformity, bioavailability or stability.

MATERIALS AND METHODS:

Pioglitazone was obtained from Cadila healthcare ltd. Ahmedabad,India.Lactose monohydrate (Pharmatose 200) and lactopress 250 was purchased from Fonterra excipients, Netherland.Hydroxyl propyle cellulose- Lf (Klucel), HPC- SSL, HPC EF was purchased from lucid colloids, Mumbai. Carmellose-Ca (E.C.G-505) and Magnesium stearate used in the research from Roquette, france and Dr. Paul Lohman, Germeny. All other chemicals and solvents used are of analytical reagent grade.

Preparation of Pioglitazone immediate release tablets:

1) **By Direct Compression:**

> ADD and excipients sifted through sieve no 40 # and thoroughly mixed in a blender approximately for 5 min.

> Above mixer was lubricated for 2 min. with Magnesium Stearate which was already passed through sieve 60.

> The lubricated granules were then compressed in to tablets on a 16 station rotary machine.

2) **By Rapid Mixture Granulation:**

> ADD and excipients sifted through sieve 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) approximately for 10 min.

> HPC EF dissolved in sufficient quantity of water, and used as a binder solution.

> Granulation was done in Rapid Mixer Granulator using HPC EF binder solution .

> Wet granules were dried in fluid bed dryer (FBD) at 60-65^{0}C till a LOD of dried granules obtained NMT 1.5 % w/w.

> Dried granules were passed through sieve 20.

> The dried granules were blended in a blender for 5 m

Above mixer was lubricated then compressed in to tablets on a 16 station rotary machine.

By Fluidized Bed Processor:

Granulation was done in Fluidized bed Processor by Top Spray Granulation using HPC binder solution.

> Wet granules were dried in Fluidized bed Processor (FBP) till a LOD of dried granules obtained NMT 1.0 % w/w.

> Dried granules were passed through sieve 30.

The dried granules were blended in a blender for 5 min. with Extragranular which was passed through sieve 40.

Above mixer was lubricated for 3 min. with Magnesium Stearate which was already passed through sieve 60.

The lubricated granules were then compressed in to tablets on a 16 station rotary machine.

Evaluation of Tablets: [151]

Prepared immediate release tablets were evaluated for the following parameters.

a) **Physical characterization**

Hardness.

$$\% \text{ Friability} = \frac{(\text{Initial Weight} - \text{final weight})}{(\text{Initial weight})} \times 100$$

> Thickness: Ten Tablets were selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement.

> Weight variation: Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

Table: 6.16 Weight variation for uncoated tablets

Avg. Weight	Maximum % difference allowed
130 or less	10
130-324	7.5
More than 324	5

> **Disintegration time:** The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

I. **P. Specifications:** Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 7.4 (simulated saliva fluid) maintained at 37°C ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 7.4 maintained at 37°C ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

b) **Physico-mechanical characterization:**

> **Bulk Density(BD):**[6,7]

> Weigh accurately 25 g of drug (M), which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0).

• Calculate the apparent bulk density in gm/ml by the following formula, Bulk

$$\text{Density} = \text{Weight of powder} \backslash \text{Bulk Volume}$$

> **Tapped density(TD):** [6,7] 25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and tapped volume (V_1) was measured to the nearest graduated units.

Tapping was repeated an additional 750 times and the tapped volume (V_2) was measured to the nearest graduated units.

The tapped bulk density was measured in gm/ml by the following formula

Tapped density = Weight of powder/Tapped Volume

> Carr's Index:[8] The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below

Carr's Index= [(TD-BD)*100]/ TD

> **Hausner's Ratio**:[9] The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio = TD/ BD

> **Moisture content:**1101 Moisture content was determined by halogen moisture analyzer.Moisture content should not exceed 1.0 % w/w

> ***In vitro*** dissolution studies:151 Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH (7.4) as dissolution medium. Temperature of the dissolution medium was maintained at 37± 0.5°C, aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223 nm and concentration of

> the drug was determined from standard calibration curve.

RESULTS AND DISSCUSSION:

> The aim of dissertation entitled "Design, Development and Characterization of immediate release tablet of Pioglitazone" was to formulate a stable as well as robust dosage form.

> The basic objective was to develop a generic version of Pioglitazone tablets in line with the innovator. A generic version of Tablets was developed that is safe, efficacious and bioequivalent to the reference product.

> The compatibility parameters characterization of Pioglitazone and excipients were done by DSC method and found no interaction between Pioglitazone and excipients.

> Blend ready for compression was evaluated for bulk density, tapped density, Carr's index and Hausner's Ratio. It was found that blend had Carr's index from 11% to 15% and Hausner's Ratio from 1.12 to 1.18, which indicate that ready for compression blend was good flow property and compressibility property.

> The formulation of immediate release tablet was done by direct compression, wet granulation by RMG and FBG. From all of these formulation technique wet granulation by fluidize bed granulation was effective method and its shows good drug release profile that was inline with innovator.

> Formulations were prepared using different grade of hydroxypropyl cellulose and croscarmellose ca in different ratios along with lubricant and diluent. The tablets were evaluated for thickness, disintegration, hardness, friability, drug release, wt. variation and assay. The thickness of the tablet varied from 2.50 ± 0.05 mm. The disintegrating time was found to be between 60 sec to 90 sec. The hardness was in range of 5-6 Kp. Assay for different batches were found to be varied from 98.2 ± 0.5 to 101.7 ± 0.5 indicating the uniformity in drug content within tablets.

> All formulations were evaluated for ***in vitro*** drug release in pH 1.2, for 60 min followed

by pH2.0, 5.5, 7.5 buffers over a period of 2-3 hours using USP type II dissolution apparatus at 50 rpm. The dissolution profiles of the batches were compared with that of innovator product. Among all formulations F10 batch showed matching ***in vitro*** drug release to that of innovator.

> Batch F10 was charged for stability. After 3 months of accelerated study, samples were withdrawn and tablet showed no change physical appearances, assay, drug

> release which indicate that the tablet was stable.

> Immediate release tablets formulated By FBG showed comparable result with innovator. The techniques employed were practically simple and commercial exploited. From the results it can be concluded that batch F10 showed matching result with innovator. Hence Pioglitazone can be successfully formulated as an immediate release tablet.

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TABLES AND FIGURES:

Table 1: Composition of Pioglitazone immediate release tablets

Ingredients	**Quantity**									
Batch No.	F-01	F-02	F-03	F-04	F-05	F-06	F-07	F-08	F-09	F-10
				Intra-Granular						
API	33.12	33.12	33.12	33.12	33.12	33.12	33.12	33.12	33.12	33.12
Lactose	86.75	85.57	-	-	-	-	-	-		
Lactopress 250	86.75	-	-	-	-	-	-	-	-	
Pharmatos 200M	-	-	-	85.45	84.53	82.91	83.78	84.86	84.21	
Crosscarmellose	6.5	3	3.9	3.9	3.9	6.24	4.68	3.12	4	
HPC-SSL	3.25	3.25	-	-	-	-	-	-	-	-
HPC-EF	-	-	3.25	2.6	-	-	-	-	-	-
HPC-LF	-	-	-	-	3.25	3.25	2.6	4.33	3.25	3.25
P.Water	-	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
				Extra-Granular						
Croscarmellose	-	3.5	3.9	3.9	3.9	4.16	3.12	4.68	4.45	
Mg. Stearate	0.38	0.38	0.91	0.38	1.3	0.97	0.97	0.97	0.97	
Total	130	130	130	130	130	130	130	130	130	130

Table 2: Pre-compressional Parameters of Pioglitazone immediate release tablets.

Powder	Bulk Density	Tapped	Carr's Index (%) (gm/ml)	Hausner 's Ratio (gm/ml)
F-01	-	-	-	-
F-02	-	-	-	-
F-03	0.4	0.519	23	1.29
F-04	0.526	0.591	11	1.12
F-05	0.541	0.612	11.6	1.13
F-06	0.579	0.682	15.1	1.17
F-07	0.552	0.647	14.6	1.17
F-08	0.553	0.678	18.4	1.22
F-09	0.549	0.662	17.06	1.2
F-10	0.571	0.66	13.4	1.15

Table 3: Evaluation of Pioglitazone Immidiate release tablets

	Quantity(mg/tab)									
	F-01	**F-02**	**F-03**	**F-04**	**F-05**	**F-06**	**F-07**	**F-08**	**F-09**	**F-10**
	Parameters									
Avg tablet weight(mg)	128	130	127	129	129	127	128	130-134	128-132	128-131
Thickness(mm)	2.48	2.49	2.50	2.48	2.49	2.50	2.48	2.47	2.52	2.47
Hardness in kp	5.5-6.1	5.7-5.9	5.7-6.1	5.5-6.0	6.3-7.4	5.5-6.0	5.2-6.1	6.5-7.7	5.4-6.2	5.1-6.5
% Friability	0.22	0.12	0.18	0.26	0.22	0.15	0.21	0.28	0.19	0.16
D.T(sec)	20-25	20-25	45-50	40-45	48-53	50-55	53-59	71-75	53-59	55-60
Assay	93.10%	92.08%	91.40%	95.00%	98.20%	99.90%	99.60%	100.30%	101.70%	101.50%

Table 4: ***In-vitro*** drug release of F5-F10 batches in pH 1.2

Time (Min) 0	**Innovator**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	74.7	67.5	69.8	80.2	65.1	70.9	71.5
10	92.4	72.7	74.2	94.6	68.7	88.4	90.1
15	98.1	79.1	82.5	100.7	74.9	92.5	96.2
30	101.2	86.0	91.3	101.1	79.8	99.1	100.0
45	100.4	94.2	96.0	101.3	86.2	100.4	101.0
60	100.1	93.1	98.1	100.4	90.4	99.7	100.4
F2	-	51	55	84	45	79	89

Table 5: *In-vitro* drug release of F5-F10 batches in pH 2.0

Time (Min) 0	Innovator	F5	F6	F7	F8	F9	F10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	63.9	54.1	56.1	61.6	54.1	56.1	61.6
10	74.4	58.8	61.8	70.2	58.8	61.8	70.2
15	83.0	63.2	66.5	82.0	63.2	66.5	82.0
30	86.6	69.1	69.0	85.4	69.1	69.0	85.4
45	89.7	74.5	74.1	87.8	74.5	74.1	87.8
60	91.8	77.0	78.3	90.3	77.0	78.3	90.3
90	93.3	80.4	80.7	92.1	80.4	80.7	92.1
120	95.8	83.8	85.1	93.8	83.8	85.1	93.8
F2	-	46	47	84	46	47	84

Table6: ***In-vitro*** drug release of F5-F10 batches in pH 5.5

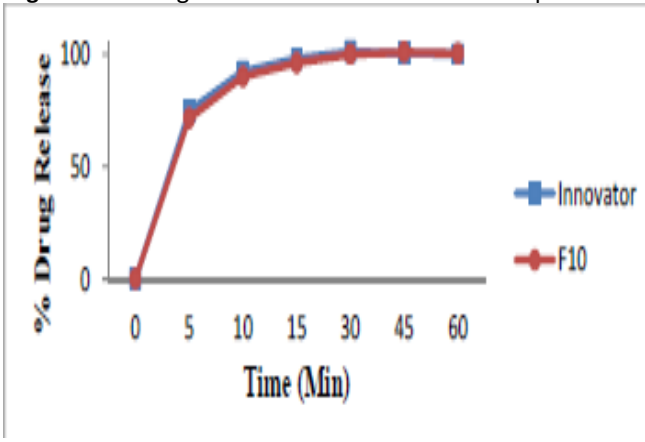
Time (Min) 0	Innovator	F5	F6	F7	F8	F9	F10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15	2.4	0.00	1.0	1.4	0.00	0.00	1.8
30	3.0	0.8	1.3	2.4	1.1	1.0	2.8
45	3.2	1.2	1.8	2.5	1.4	1.5	3.4
60	3.7	1.9	2.1	2.9	1.7	1.8	3.6
90	4.0	2.1	1.9	3.3	1.4	1.9	4.0
120	3.9	2.4	2.3	4.1	2.1	2.1	4.2
135	4.3	2.3	2.5	4.6	2.5	2.4	4.1
180	4.2	2.8	2.8	5.3	2.8	2.9	4.3
240	5.2	3.0	2.9	5.8	3.1	3.2	4.9
270	5.1	3.2	3.1	5.1	3.4	3.7	5.2
360	5.6	3.7	4.0	5.7	3.9	4.1	5.1
F2	-	83	85	96	83	84	99

Table 7: *In-vitro* drug release of F5-F10 batches in pH 7.5

Time (Min) 0	Innovator	F5	F6	F7	F8	F9	F10
0	0.00	0	0	0	0	0	0
15	0.7	0	0	0	0	0	1.3
30	1.2	0	0	0.6	0	0.3	2.2
45	1.5	0.4	0.6	1.1	0.5	0.5	2.3
60	1.6	0.7	0.6	1.3	0.9	0.7	2.4
90	1.7	0.7	0.9	1.1	1.1	1	2.4
120	1.9	0.9	1	1.8	1.1	1.3	3
135	1.9	1.1	1.1	1.5	1.3	1.4	2.7
180	1.7	1.4	1.2	2	1.8	1.8	2.9
240	2.2	1.2	1.7	1.8	1.9	1.5	2.8
270	2.6	1.5	1.6	2.1	1.9	2.2	2.8
360	3.7	1.5	1.7	2.4	1.9	2.4	3.6
F2	-	91.4	92.78	96.99	94.12	95.26	95.1

FIGURES:

Figure 1: % drug relrase of F05-F09 batches in pH1.2



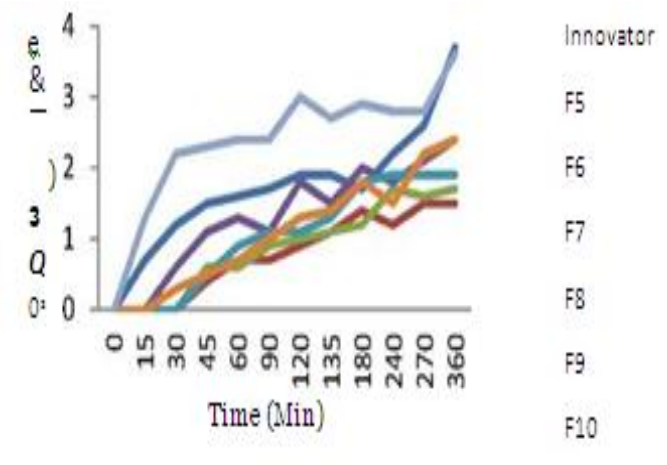


Figure 2: % drug relrase of F10 batch in pH1.2

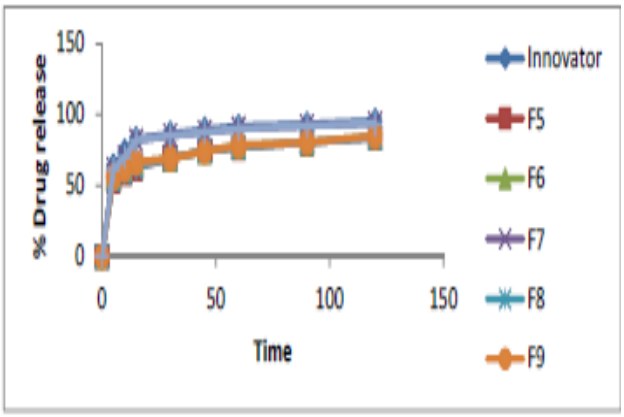


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Figure 3: % drug relrase of F05-F10 batches in pH2.0