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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF PIOGLITAZONE HYDROCHLORIDE BY EMPLOYING MODIFIED SUPERDISINTEGRANTS

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ABSTRACT: The aim and objective of the present work is to design and develop immediate release tablets of pioglitazone hydrochloride to improve the patient compliance and desired bioavailability by selected delivery system by following immediate release mechanism. In the present investigation, super disintegrants used in the combination of 1:1 ratio were modified using co-processed technology with the solvents like acetone and methanol using solvent evaporation technique. The dissolution rate of the drug was significantly increased which reaches closer to the dissolution profile of marketed product. This was due to an increase in surface area of drug available for dissolution. The physical modification of super-disintegrants using co processing technique and selection of processed material with particle size specificity made the drugs to possess required characteristics as fast dispersible. The pre compression and post compression properties are determined as per the procedure prescribed. The drug release studies and kinetics indicate that the prepared tablets with co-processed superdisintegrants were best at its release in the entire tract of GIT due to their change in bio pharmaceutical property like dissolution. Optimized formulations were selected for stability concern and *in-vivo* performance. The best formulations retain its properties within the stability period of 3 months. The *in-vivo* properties evaluated confirmed the approach of good bioavailability by the drug with the help of the design of drug into immediate release product.

INTRODUCTION: A drug delivery system which dissolves FPst, in extreme cases, is a solid tablet that dissolves or disintegrates in oral cavity without water or chewing". Many of FPst-dissolving drug delivery system like films should include other excipients to mask the bad taste of the active compounds.

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All these are called as melt-in-mouth tablets, repi melts, porous tablets, oro - dispersible, quick dissolving or rapid disintegrating tablets [1] or immediate release tablets which makes to overcome the disadvantages of tablets like hand tremors, dysphasia occurrence in geriatric patients, the semi developed muscular systems in children and in case of bedridden, the problem of swallowing is very common phenomenon leads to very poor patient compliance [2].

Direct compression is selected as the technique where a group of ingredients can be blended, placed onto a tablet press, and made into a perfect tablet without any of the ingredients having to be

changed. Powders that can be blended and com pressed are commonly referred to as directly compressible or as direct-blend formulations. The method selected is much suitable in development of solubility of poorly water soluble drugs and in improving the bioavailability of many drugs [3]. Pioglitazone Hydrochloride is used for the treatment of diabetes mellitus type 2. Pioglitazone Hydrochloride selectively stimulates nuclear receptor peroxisone proliferator-activated receptor gamma (PPAR-gamma). It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the lipidic, muscular tissues and in the liver [4].

MATERIALS AND METHODS:

Materials: Pioglitazone Hydrochloride is purchased from Yarrow Chem Products, Mumbai. All the used other chemicals included are off to be Laboratory grade.

Methods:

Formulation of Tablets using Co processed Super Disintegrants by Direct Compression Method: Tablets were prepared by using Direct Compression method consisting super disintegrants collected from different sieves co processed using different solvents in suitable concentration and ratios as shown in the given table. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg using 7 mm round flat punches on Single-station rotary tablet machine.

TABLE 1: TABLETS PREPARED BY CO PROCESSED SUPER DISINTEGRANTS

Ingredients (mgs)	Weight taken (mg)											
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12
Pioglitazone HCl	15	15	15	15	15	15	15	15	15	15	15	15
CCS: CP (1:1) (6%)	9	9	-	-	-	-	9	9	-	-	-	-
CP: SSG (1:1) (6%)	-	-	9	9	-	-	-	-	9	9	-	-
SSG: CCS (1:1) (6%)	-	-	-	-	9	9	-	-	-	-	9	9
MCC	88	88	88	88	88	88	88	88	88	88	88	88
Lactose	34	34	34	34	34	34	34	34	34	34	34	34
Talc	2	2	2	2	2	2	2	2	2	2	2	2
MgO	2	2	2	2	2	2	2	2	2	2	2	2

- FP1-FP6 consists of Super Disintegrants Co processed using Acetone as solvent.
- FP7-1P2 consists of Super Disintegrants Co processed using Ethanol as solvent
- FP1, FP3, FP5, FP7, FP9, FP11 - Co Processed Super Disintegrants collected from sieve no 24 where large amount retained
- FP2, FP4, FP6, FP8, FP10, FP12 - Co Processed Super Disintegrants collected from sieve no where large amount retained 66.

Determination of Precompression Characteristics: [5 - 6] The following Preformulation studies were performed for Pioglitazone Hydrochloride formulations:

Angle of Repose: For a burette stand a funnel was fixed upto a particular height. A graph sheet was placed under the funnel which was on the table. The powdered form of the drug was passed through funnel up to it forms a pile. The pile radius was noted. The Angle of repose of the material was calculated by using the formula.

$$\text{Angle of repose } \theta = \tan^{-1} H/r$$

Where; H = height of the pile, and r = radius of the pile.

Determination of Densities:

Apparent Bulk Density: The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Tapped Density: Weighed powder sample was transferred to a graduated cylinder and was placed on the tapped density test apparatus, was operated for a fixed number of taps (100). The tapped density was determined as the ratio of weight of sample to tapped volume.

$$\text{Density} = \text{Mass} / \text{Volume}$$

Carr's Index (% Compressibility): Based on the apparent bulk and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

% compressibility = Tapped density – Bulk density / Tapped density

Hausner's Ratio: The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio.

Dispersibility: Weigh approximately about 1g of sample. the material was dropped from a total height (610 mm) on to a tarred watch glass (dia-120 mm) through a hallow cylinder placed vertically 102 mm above the watch glass. The cylinder was secured to a support-stand by using support rings above and below the cylinder. The drop point is approximately 178 mm vertically above the top of cylinder. The material lanned within the watch glass is weighed. Any loss of powder during the FPll was the result of dispersion. The percent dispersibility was calculated using the formula;

Dispersibility (%) = Weight of power in watch glass × 100 / initial weight of sample

Porosity (€): Porosity of the compound is determined by liquid dispersion method

(€) = bulk volume – true volume / bulk volume

Evaluation Tests: [7 – 8] All the formulations are subjected to evaluation for Hardness, Friability, Weight Variation Uniformity of Disperssion, Thickness, Disintegration Time, Wetting Time, Drug Content and *in-vitro* Drug Release.

Hardness: Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded.

Friability: Two tablets were accurately weighed and placed in the friabilator (Electrolab. EF-2 Friabilator) and operated for 100 revolutions. The tablets were de-dusted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.

Weight Variation: 10 tablets were selected randomly from the lot and weighed individually to check for weight variation.

Thickness and Diameter: The thickness and diameter of 4 tablets were recorded during the process of compression using Vernier calipers.

Uniformity of Dispersion: 2 tablets were placed in 100 ml water and stirred gently until completely dispersed. A smooth dispersion was obtained which passed through a sieve screen 710 mcm (sieve number 22).

Wetting Time: A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

Disintegration Test: Tablets were taken and introduced one tablet in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

Drug Content: Analytical methods for the estimation of Pioglitazone Hydrochloride:

Determination of λ_{max} for Pioglitazone Hydrochloride: A 10 mcg/ml solution of Pioglitazone Hydrochloride in pH 6.8 phosphate buffer was scanned in UV range between 200 to 400 nm. Pioglitazone Hydrochloride showed maximum absorbance at 269.0 nm in buffer solution.

Preparation of calibration curve of Pioglitazone Hydrochloride: 100 mg of Pioglitazone Hydrochloride was accurately weighed and dissolved in 100 ml of pH 6.8 Phosphate buffer and suitable dilution were made to get 2, 4, 6, 8, 10 µg/ml of the solution. Absorbances of various concentrations were measured by U.V spectro-photometer at 269 nm using buffer solution as blank. Ten tablets from each formulation were taken, crushed and mixed. From the mixture 10 mg of pioglitazone hydrochloride equivalent of mixture

was extracted thoroughly with 100 mL of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 269 nm. This procedure was repeated thrice and this average was chosen.

***In-vitro* Drug Release studies of Pioglitazone Hydrochloride:** The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (EDISON-[ESI-06] Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium pH 6.8, phosphate buffer) was taken in covered vessel and the temperature was maintained at 37 ± 0.5 ºC. The speed of the paddle was set at 75 rpm. Sampling was done every one min interval. For each sample 5 ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37 ºC was replenished to the dissolution medium. The % absorbance was determined

For the best Formulations as per the FDA Dissolution criteria for medium.

The *in vitro* dissolution study was carried out in USP dissolution test apparatus type 2 M (paddle)

Dissolution Medium: 900 ml
0.1N HCL: To stimulate gastric environment.
pH 4.5 Acetate Buffer: To stimulate drug release in the upper part of Duodenum.
pH 6.8 phosphate Buffer: To stimulate drug release in the intestinal Environment.
Purified Water Temperature: 37 ± 0.5 ºC
RPM: 75
Tablets taken: 6 tablets were weighed and taken for study.
Volume withdrawn and replaced: 5 ml every five minutes.
Max: 269 nm.

Stability Studies: Stability studies were performed with and FP11 as per ICH guidelines for 3 months at 40 °C ± 2 °C / 75% RH ± 5%. Samples were withdrawn at regular intervals and evaluated for change in *in vitro* drug release pattern, hardness, and disintegration time.

***In-vivo* Safety and Pharmacokinetic Study of Tablets:** [9]

Chromatographic System: High pressure Liquid chromatography (Schemadzu HPLC Class VP series) and C-18 Column (250 mm × 4.6 mm) particle size 5 µm. The HPLC system was equipped with the soft ware Class-VP series version 5.03.

Preparation of Mobile Phase for Pioglitazone Hydrochloride: HPLC grade Water, Ethanol and acetonitrile were filtered through 0.2 m membrane filter and de aerated with the helium spurge for 15 minutes before use pumped through solvent reservoir to column at flow rate of 0.8ml/min yielded a column back pressure 200 - 225 kg/cm [74, 75]. The column temperature was maintained at 40ºC. The volume of 20 µl was injected in to loop.

Extraction Procedure and Analytical Method Validation in Rat Plasma for Pure Drug: 10 mg of drug was dissolved in methanol. The prepared serial dilutions (2, 4, 6, 8, 10 µL) were used to establish a calibration curve (RPHPLC) using blank plasma as a standard. The samples were evaluated for linearity statistically for its best fit [76].

Study Design: The present study was agreed by the Institutional Animal Ethical Committee (IAEC) license no: (1032/AC/07/CPCSEA). Wistar rats weighing 150 - 200 g and maintain normal temperature at 25 ºC and three rats per cage and stabilized for one week. The rats were allowed to approach to water for 12 hr before and during experiment.

Extraction of Procedure and Analytical Method Validation in Rat Plasma: Rats were classified into two groups with 6 rats in each group.

Group I: control was treated with distilled drinking water followed by normal saline daily by oral gavage.

Group II: Up to treatment with drug these were treated in a manner similar to Group I thereafter treated with Pioglitazone Hydrochloride tablets from the following time points: 0, 2, 5, 7, 9, 11, 14, 16, 18, 21 and 24 h. Centrifuged the heparinized blood samples at 1000 g for 10 min in a cooling centrifuge, and the plasma separated and transferred to micro centrifuge tubes for storage at -20ºC. Frozen plasma samples were thawed. A sample 0.2 mL was transferred into a glass tube lined with a Teflon cap, to it and add 0.2 mL of methanol. The mixture was vortexed for10 min and then centrifuged at 1000 g for 15 min. Dry the supernatant under a stream of nitrogen and

resuspended in 0.1mL mobile phase, vortexed for 3 min and centrifuged at 1000 g for 5 min; 0.02 mL of the subsequent supernatant was used to HPLC for analysis of Drugs as described below [80, 81, 82].

Pharmacokinetic Analysis: Pharmacokinetic parameters were calculated by noncompartment analysis based on the statistical moment theory using PK1, PK2 MS excel function such as maximum plasma concentration (C_{max}), and time of maximum concentration (T_{max}) were obtained directly from the Plasma concentration-time plots. Half life ($t_{1/2}$), Elimination rate constant (h^{-1}), AUC $_{0\text{-}t}$, AUC $_{0\text{-}inf}$, AUMC $_{0\text{-}t,}$ AUMC $_{0\text{-}inf}$, and MRT mean residence time (MRT) was calculated as AUMC/AUC. All the results were expressed in mean ± SD.

Experimental Results:

Construction of Calibration Curves:

TABLE 2: CALIBRATION CURVE OF PIOGLITAZONE HCl

Vol. made upto (ml)	Concentration (mcg /ml)	Absorbance Mean (± SD), n=3
50	0	0 ± 0.00
50	2	0.0143 ± 0.0011
50	4	0.0478 ± 0.0028
50	6	0.0737 ± 0.0028
50	8	0.0961 ± 0.0011
50	10	0.1305 ± 0.0046

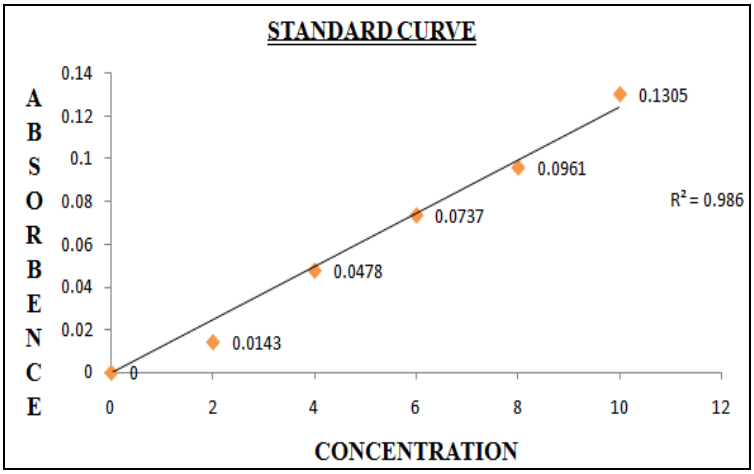

FIG. 1: CALIBRATION CURVE OF PIOGLITAZONE HYDROCHLORIDE

TABLE 3: PRE COMPRESSION RESULTS FOR FP1 TO FP12 (FORMULATIONS CONTAINING CO-PROCESSED SUPERDISINTEGRANTS IN MIXTURE AND COMPRESSED BY DIRECT COMPRESSION TECHNIQUE)

Parameters	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations					
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12
Angle of repose (degrees)	32.13 ±0.034	33.36 ±0.212	34.35 ±0.012	35.41 ±0.035	34.19 ±0.024	36.82 ±0.143	32.8 ±0.052	35.41 ±0.037	31.86 ±0.051	35.65 ±0.13	31.25 ±0.02 5	32.56 ±0.032
Bulk density (gm/cc)	0.39 ±0.39	0.36 ±0.065	0.41 ±0.086	0.33 ±0.008	0.32 ±0.004	0.38 ±0.07	0.24 ±0.02	0.27 ±0.03	0.30 ±0.03	0.27 ±0.02	0.29 ±0.03	0.28 0.01
Tapped Density (gm/cc)	0.45 ±0.32	0.42 ±0.16	0.48 ±0.09	0.39 ±0.11	0.38 ±0.21	0.44 ±0.43	0.25 ±0.04	0.26 ±0.026	0.32 ±0.15	0.29 ±0.02	0.316 ±0.0202	0.29 ±0.017
Porosity (%)	21 ±0.577	32.33 ±0.666	28 ±0.288	35.66 ±0.141	35.3 ±0.230	25.33 ±0.34	26.6 ±0.05	21.6 ±0.07	24.7 ±0.01	26.2 ±0.01	26.2 ±0.32	23.0 ±0.45
Carr's index	1.15 ±0.45	1.16 ±0.66	1.17 ±0.38	1.14 ±0.54	1.14 ±0.65	1.15 ±0.017	1.07 ±0.01	1.07 ±0.01	1.06 ±0.030	1.07 ±0.02	1.06 ±0.01	1.03 ±0.021
Hausners Ratio	14.6 ±0.066	20.66 ±0.664	10.33 ±0.333	12 ±0.318	11.16 ±0.118	20.33 ±0.331	17.14 ±0.015	15 ±0.321	16.5 ±0.160	16.66 ±0.160	13.125 ±0.160	12 ±0.318
Dispersibility (%)	78.30 ±0.011	82.33 ±0.021	90.13 ±0.027	88.10 ±0.025	89.59 ±0.022	85.40 ±0.13	88.30 ±0.03	89.12 ±0.07	93.14 ±0.05	84.50 ±0.02	83.87 ±0.013	95.40 ±0.023

TABLE 3: POST COMPRESSION RESULTS FOR FP1 TO FP12 (FORMULATIONS CONTAINING CO-PROCESSED SUPERDISINTEGRANTS IN MIXTURE AND COMPRESSED BY DIRECT COMPRESSION TECHNIQUE)

Parameters	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations					
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12
Hardness(kg/cm^2)	3.6	3.5	3.9	4.1	4.2	4.1	3.3	3.6	3.7	4.4	4.2	4.1
(± SD), n=3	±0.101	±0.074	±0.321	±0.122	±0.322	± 0.51	± 0.01	± 0.01	± 0.20	± 0.01	±0.027	± 0.16
Friability (%)	0.83	0.96	0.82	0.95	0.90	0.93	0.93	0.96	0.86	0.82	0.92	0.86
(±SD), n=3	±0.05	±0.08	±0.03	±0.16	±0.18	±0.02	±0.13	±0.44	±0.31	±0.018	±0.212	±0.54
Weight variation (mg) (±SD), n=20	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Uniformity of Dispersion	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Thickness (mm)	3.2	3.3	3.4	3.3	3.1	3.4	3.22	3.3	3.1	3.2	3.2	3.5
(±SD), n=4	± 0.03	± 0.08	±0.079	±0.089	±0.086	±0.084	± 0.30	±0.031	± 0.37	± 0.38	± 0.40	± 0.33
Disintegration	23	21	20	22	21	21	22	20	21	23	19	24
Time(sec)	±1.3	±1.21	±1.10	±1.26	±1.39	±1.28	±1.24	±1.42	±1.36	±1.65	±1.63	±1.17
Wetting Time (Sec)	45	47	41	44	42	43	43	41	42	44	40	41
	±0.23	±0.63	±0.32	±0.37	±0.78	±0.32	±0.47	±0.65	±0.41	±0.32	±0.21	±0.14
Drug content (%)	98.3	98.7	99.2	98.4	99.7	99.4	98.5	99.5	99	98	98.7	98.5
	±1.78	±1.76	±1.83	±1.77	±1.86	±1.91	±1.2	±0.7	±0.7	±0.84	±0.102	±0.60

TABLE 5: DRUG RELEASE STUDIES FOR FP1 TO FP12 IN WATER (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Time	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations						Market	Similarity
(min)	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula	factor *f2*
5	19.02	15.04	14.21	19.82	17.67	22.23	16.18	19.5	16.02	17.7	21.5	18.4	11.2	
	±0.13	±0.21	±0.14	±0.62	±0.56	±0.54	±0.65	±0.49	±0.23	±0.41	±0.27	±0.32	±0.23	
10	21.21	17.25	16.11	26.23	26.84	25.30	19.53	25.17	24.3	25.3	26.4	27.4	18.34	
	±0.22	±0.18	±0.23	±0.19	±0.43	±0.24	±0.34	±0.35	±0.41	±0.44	±0.27	±0.23	±0.39	
15	27.0	25.13	28.07	28.18	28.27	28.6	27.12	27.8	29.1	28.17	31.3	34.3	29.20	
	±0.21	±0.19	±0.15	±0.34	±0.19	±0.42	±0.26	±0.37	0±0.33	±0.67	±0.34	±0.31	±0.34	42.45
20	31.5	26.17	32.15	33.18	32.42	32.9	32.4	34.1	37.07	30.02	34.2	37.8	36.69	
	±0.41	±0.26	±0.32	±0.31	±0.46	±0.31	±0.37	±0.39	±0.54	±0.42	±0.23	±0.22	±0.39	
25	33.23	37.14	37.23	36.13	37.53	39.3	36.18	35.6	44.5	33.6	37.8	38.5	39.23	
	±0.14	±0.17	±0.34	±0.24	±0.39	±0.39	±0.47	±0.44	±0.37	±0.56	±0.43	±0.35	±0.64	
30	36.19	39.23	39.32	43.12	41.28	41.2	40.05	38.4	46.3	38.9	42.12	40.9	42.12	
	±0.26	±0.14	±0.23	±0.15	±0.46	±0.36	±0.46	±0.25	±0.39	±0.43	±0.23	±0.45	±0.325	

Note: No Similarity exists between Market formula and Formulations

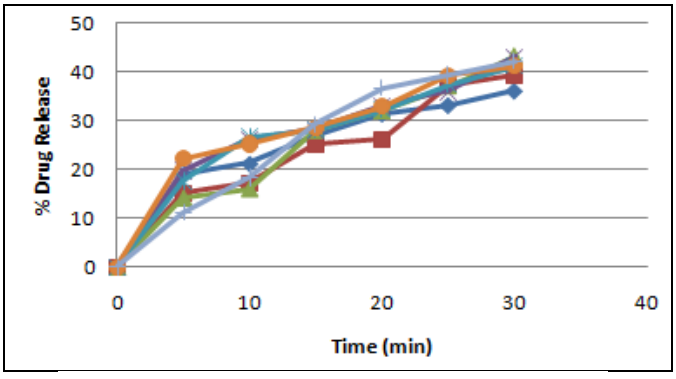

FIG. 2: DRUG RELEASE STUDIES OF FP1 TO FP6 IN WATER

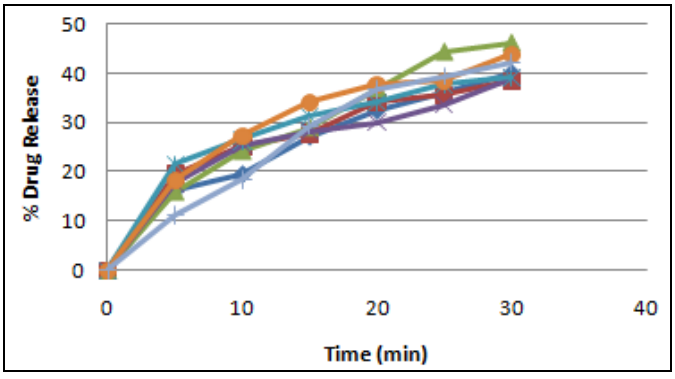

FIG. 3: DRUG RELEASE STUDIES OF FP7 TO FP12 IN WATER

TABLE 6: DRUG RELEASE KINETICS FOR FP1 TO FP12 IN WATER (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Parameters	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations						Marketed
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula
T50 (min.sec)	4.23	5	5	3.8	4.46	4.3	4.43	4	4.16	4.11	4	3.65	4.08
T90 (min.sec)	48.65	41.15	41.15	48.65	38.6	34.9	46.7	40.9	47.1	42.9	48.6	42.9	30.29
K µg/ml	2.303	1.84	2.7	1.01	1.84	9.5	0.23	0.59	0.32	2.98	1.01	1.28	1.32

TABLE 7: DRUG RELEASE STUDIES FOR FP1 TO FP12 IN 0.1N HCl (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Time	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations						Market	Similarity
(min)	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula	factor *f2*
5	37.24	28.71	13.83	22.08	14.14	25.47	18.3	24.2	13.9	23.23	15.52	6.9	34.6	
	±0.25	±0.15	±0.14	±0.58	±0.36	±0.25	±0.36	±0.58	±0.69	±0.45	±0.36	±0.58	±0.356	
10	43.25	39.56	25.3	27.57	23.8	48.57	30.3	31.7	34.7	36.74	30.39	18.3	42.34	
	±0.25	±0.89	±0.56	±0.45	±0.63	±0.96	±0.45	±0.36	±0.56	±0.85	±0.45	±0.58	±0.356	
15	54.80	48.28	39.4	29.61	35.8	60.2	46.2	56.6	46.8	47.78	51.18	35.8	51.34	
	±0.36	±0.69	±0.56	±0.45	±0.69	±0.96	±0.69	±0.75	±0.35	±0.25	±0.75	±0.65	±0.369	57.85
20	56.09	56.06	54.34	44.19	54.5	61.7	60.1	70.2	65.07	50.16	73.28	46.73	67.21	
	±0.14	±0.25	±0.47	±0.56	±0.58	±0.54	±0.85	±0.14	±0.25	±0.32	±0.39	±0.45	±0.569	
25	61.86	76.09	67.60	64.3	71.9	86.1	81.5	80.61	80.13	65.03	88.7	61.33	79.69	
	±0.25	±0.28	±0.85	±0.54	±0.69	±0.65	±0.21	±0.28	±0.64	±0.54	±0.94	±0.85	±0.789	
30	82.87	90.21	93.66	89.7	90.3	92.6	90.1	91.0	89.99	88.96	94.03	88.69	93.2	
	±0.52	±0.25	±0.45	±0.47	±0.54	±0.25	±0.21	±0.54	±0.54	±0.25	±0.45	±0.58	±0.654	

Note: Similarity exists between Market formula and Formulations

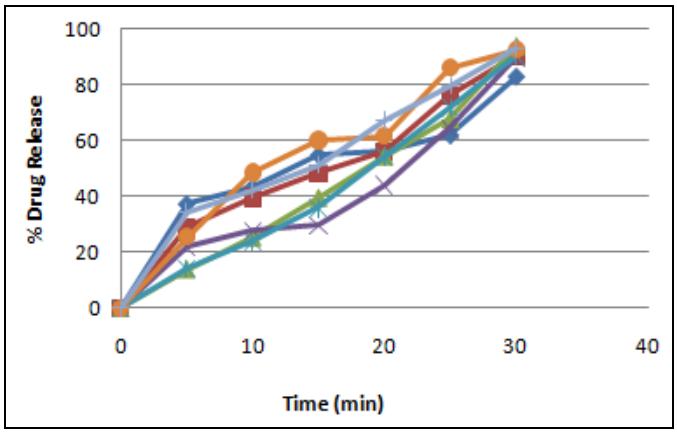

FIG. 4: DRUG RELEASE STUDIES OF FP1 TO FP6 IN 0.1N HCl

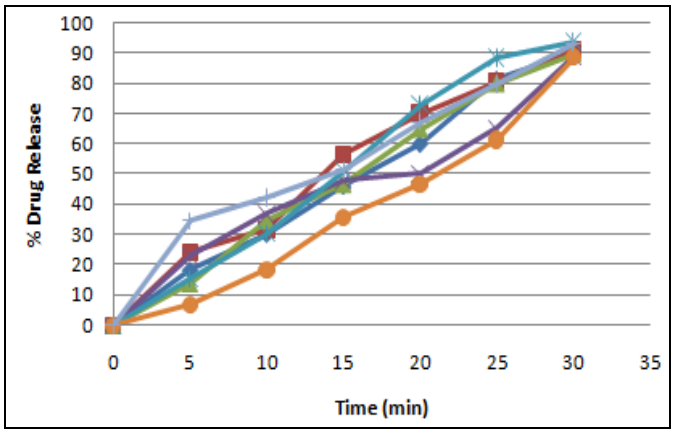

FIG. 5: DRUG RELEASE STUDIES OF FP7 TO FP12 IN 0.1N HCl

TABLE 8: DRUG RELEASE KINETICS FOR FP1 TO FP12 IN 0.1N HCl (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Parameters	Acetone Co- Processed Formulations						Methanol Co- Processed Formulations						Marketed
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula
T50 (min.sec)	5.8	6.7	8.3	9.7	11.1	11.9	15.4	15.43	8.9	5.1	8.38	5.7	3.86
T90 (min.sec)	20.6	23.7	29.1	29.8	33.1	28.7	30.4	23.1	26.4	31.9	25.1	25	29.28
K µg/ml	0.91	0.3	6.9	2.6	1.4	10.3	4.7	10.03	4.10	2.42	3.9	2.27	2.38

TABLE 9: DRUG RELEASE STUDIES FOR FP1 TO FP12 IN ACETATE BUFFER pH 4.5 (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Time	Acetone Co- Processed Formulations						Methanol Co- Processed Formulations						Market	Similarity
(min)	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula	factor *f2*
5	45.8	11.38	30.15	22.7	20.5	15.36	25.2	40.2	19.4	21.7	45.3	15.47	43.60	
	±0.182	±0.214	±0.21	±0.37	±0.22	±0.37	±0.41	±0.51	±0.21	±0.37	±0.21	±0.28	±0.356	
10	50.15	20.76	48.9	50.7	33.1	29.5	38.06	49.3	33.4	42.9	64.8	33.09	52.34	
	±0.19	±0.58	±0.37	±0.4	±0.18	±0.21	±0.05	±0.19	±0.34	±0.21	±0.37	±0.34	±0.369	
15	55.92	50.25	64.86	56.0	50.9	48.3	49.5	64.9	66.02	49.3	79.9	40.7	79.24	
	±0.25	±0.45	±0.24	±0.21	±0.11	±0.12	±0.21	±0.23	±0.78	±0.58	±0.24	±0.27	±0.569	75.53
20	65.29	63.5	80.59	69.8	65.1	54.43	51.95	82.5	85.5	66.2	81.9	69.3	88.63	
	±0.55	±0.56	±0.96	±0.32	±0.56	±0.23	±0.63	±0.32	±0.47	±0.63	±0.32	±0.45	±0.789	
25	79.7	86.28	81.43	84.9	85.5	73.02	84.5	84.8	87.9	88.5	88.7	80.4	90.21	
	±0.21	±0.32	±0.35	±0.88	±0.85	±0.12	±0.85	±0.63	±0.45	±0.52	0±.23	±0.32	±0.654	
30	88.5	89.2	87.93	86.8	89.4	87.8	86.7	88.5	88.3	89.9	90.3	88.2	90.42	
	±0.32	±0.32	±0.12	±0.55	±0.14	±0.66	±0.44	±0.47	±.17	±0.63	±0.58	±0.25	±0.63	

Note: Similarity exists between Market formula and Formulations

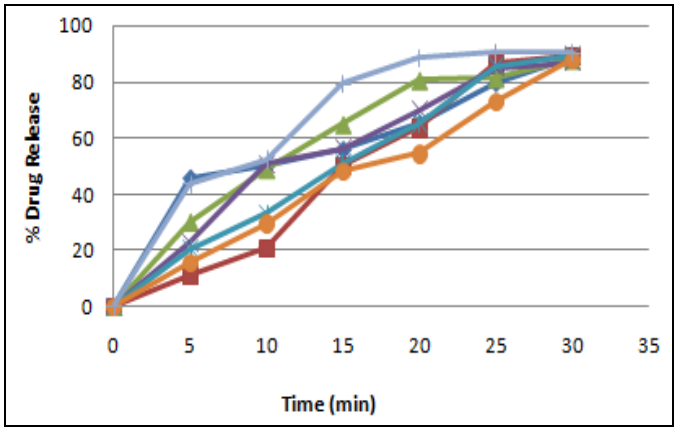

FIG. 6: DRUG RELEASE STUDIES OF FP1 TO FP6 IN ACETATE BUFFER pH 4.5

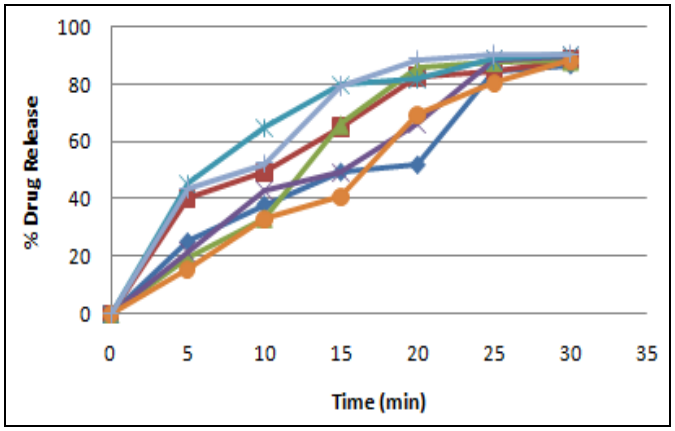

FIG. 7: DRUG RELEASE STUDIES OF FP7 TO FP12 TO FP6 IN ACETATE BUFFER pH

TABLE 10: DRUG RELEASE KINETICS FOR FP1 TO FP12 IN ACETATE BUFFER pH 4.5 (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Parameters	Acetone Co- Processed Formulations						Methanol Co- Processed Formulations						Marketed
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula
T50 (min.sec)	5.45	21.96	8.29	11.01	12.19	16.27	10.2	6.21	12.88	11.52	5.51	16.16	5.73
T90 (min.sec)	28.23	26.07	23.09	26.50	26.3	30.8	23.75	23.98	22.75	25.13	22.7	27.98	24.67
K µg/ml	4.31	0.11	7.24	6.35	1.93	2.39	3.43	8.01	8.96	7.78	4.60	4.06	1.95

TABLE 11: DRUG RELEASE STUDIES FOR FP1 TO FP12 IN PHOSPHATE BUFFER pH 6.8 (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Time	Acetone Co- Processed Formulations						Methanol Co- Processed Formulations						Market	Similarity
(min)	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	Formula	factor *f2*
5	51.21	37.04	28.58	34.63	36.74	35.27	36.11	21.36	44.82	49.10	49.28	49.7	68.4	
	±0.21	±0.25	±0.14	±0.47	±0.44	±0.36	±0.63	±047	±0.32	±0.41	±0.45	±0.99	±0.356	
10	65.23	65.05	58.01	50.42	47.48	44.03	49.35	47.93	55.89	54.4	59.6	60.8	78.34	
	±0.31	±0.25	±0.36	±0.69	±0.53	±0.35	±0.13	±0.93	±0.77	±0.36	±0.25	±0.39	±0.369	
15	88.38	78.68	67.97	66.55	59.50.	53.92	51.49	51.97	64.95	59.30	75.6	69.9	89.2	99.45
	±0.41	±0.36	±0.29	±0.49	±0.33	±0.69	±0.92	±0.44	±0.39	±0.26	±0.69	±0.11	±0.569	
20	97.5	84.27	68.6	75.94	79.24	56.82	55.93	61.26	75.68	64.8	84.6	82.6	90.69	
	±0.69	±0.92	±0.61	±0.25	±0.65	±0.36	±0.19	±0.81	±0.36	±0.22	±0.91	±0.33	±0.789	
25	98.49	85.04	82.20	83.96	82.35	78.59	66.28	82.79	84.6	70.7	89.5	89.9	92.2	
	±0.62	±0.35	±0.69	±0.56	±0.36	±0.44	±0.66	±0.63	±0.99	±0.70	±0.39	±0.21	±0.654	
30	97.9	96.81	97.58	98.2	98.02	96.3	97.34	97.48	96.3	97.2	99.3	98.5	96.4	
	±0.25	±0.36	±0.69	±0.36	±0.15	±0.63	±0.75	±0.39	±0.24	±0.31	±0.33	±0.99	±0.325	

Note: Similarity exists between Market formula and Formulations

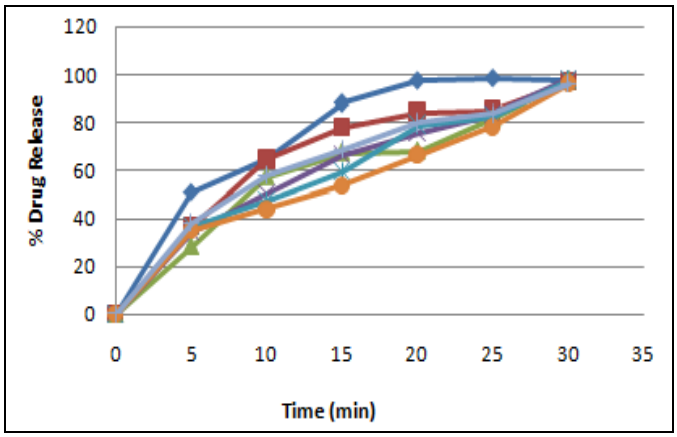

FIG. 8: DRUG RELEASE STUDIES OF FP1 TO FP6 IN PHOSPHATE BUFFER pH 6.8

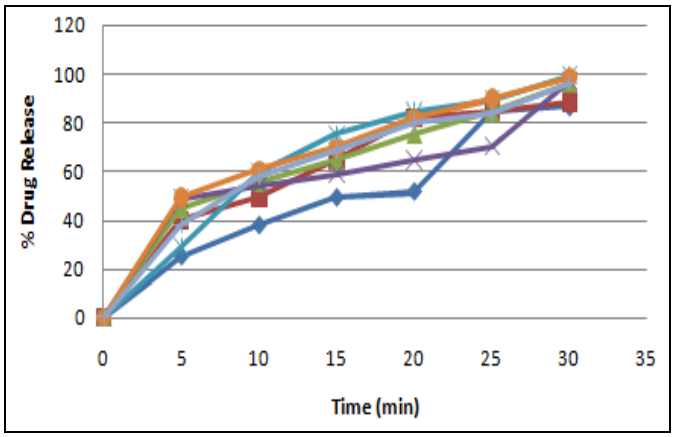

FIG. 9: DRUG RELEASE STUDIES OF FP7 TO FP12 IN PHOSPHATE BUFFER pH 6.8

TABLE 12: DRUG RELEASE STUDIES FOR FP1 TO FP12 IN PHOSPHATE BUFFER pH 6.8 (FORMULATIONS CONTAINING CO PROCESSED SUPERDISINTEGRANTS IN MIXTURE)

Parameters	Acetone Co- Processed Formulations						Methanol Co- Processed Formulations						Marketed Formula
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8	FP9	FP10	FP11	FP12	
T50 (min.sec)	4.8	6.74	8.6	9.9	12.6	13.9	14.5	14.43	8.94	9.19	8.38	5.03	3.65
T90 (min.sec)	19.6	28.7	29.6	30.8	33.0	28.8	33.4	29.1	28.4	31.9	25.1	25.0	15.13
K µg/ml	0.91	0.35	6.25	3.60	1.43	10.02	4.76	10.73	4.10	2.42	2.25	3.36	2.38

Stability Data:

TABLE 13: STABILITY DATA OF BEST FORMULATION AFTER ONE MONTH

S. no.	FP11
Colour and Appearance	No change
Hardness (kg/cm^2)	4.2 ± 0.021
Disintegration time (sec)	41 ± 0.3
In vitro drug release	99.3 ± 0.018

TABLE 14: STABILITY DATA OF BEST FORMULATION AFTER TWO MONTHS

S. no.	FP29
Colour and appearance	No change
Hardness (kg/cm^2)	4.2 ± 0.02
Disintegration Time (sec)	40 ± 0.4
In vitro drug release	99.5 ± 0.02

TABLE 15: STABILITY DATA OF BEST FORMULATION AFTER THREE MONTHS

S. no.	FP29
Colour and appearance	No change
Hardness (kg/cm^2)	4.2 ± 0.03
Disintegration Time (sec)	41 ± 0.2
In vitro drug release	99.4 ± 0.02

Calibration Curve of Pioglitazone Hydrochloride by HPLC in Rat Plasma: Calibration curve was done by repeated five injection continued for three days repeated for three days, an average of fifteen injections. Concurrently stability of the plasma in sample was analyzed. Plasma was kept at -20 ºC. 2 to 10 µg/ml concentrations were used to develop the standard curve and was linear. The regression equation and correlation coefficient R^2 was obtained to be 0.998.

TABLE 16: CALIBRATION CURVE DATA OF PIOGLITAZONE HYDROCHLORIDE BY HPLC IN RAT PLASMA

S. no.	Concentration ug/ml	Peak area 1	Peak area 2	Peak area 3	Mean peak area	Std. Deviatation	% RSD
1	0	0	0	0	0	0	0
2	2	10750	10280	10270	10275	10275 ± 5	0.275
3	4	18873	18890	18880	18881	18881 ± 8.544	0.506
4	6	27171	27180	27160	27170	27170 ± 10.016	0.728
5	8	36927	36930	36920	36926	36926 ± 3.5118	0.989
6	10	45151	45145	45155	45150	45150 ± 5.0332	1.2104

All the values were calculated as (Mean ± SD, n=3)

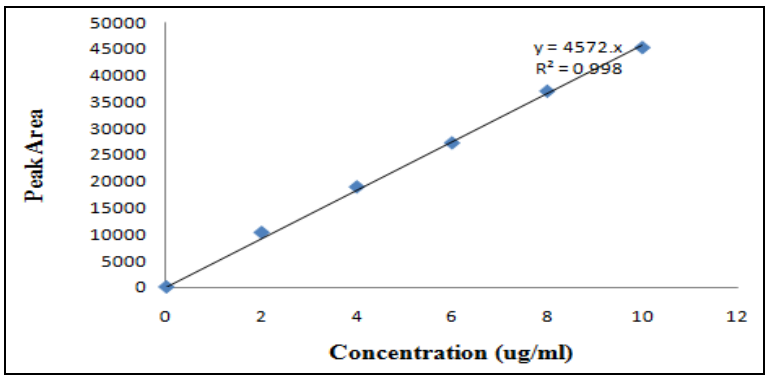

FIG. 10: CALIBRATION CURVE OF PIOGLITAZONE HCl BY HPLC IN RAT PLASMA

TABLE 17: CONCENTRATION OF DRUG AND PEAK AREA FOR PIOGLITAZONE HYDROCHLORIDE IN RAT PLASMA

Parameter	Pioglitazone Hydrochloride
Linearity (µg/mL)	2-10 (µg/ mL)
Slope (m)	4485.6
Regression (r^2)	0.998
LOD (µg/ mL)	0.0033
LOQ (µg/ mL)	0.01028

Pharmacokinetic Analysis: All the Pharmaco-kinetic required parameters were determined by using non compartment analysis based on the statistical moment theory using PK1, PK 2 excel function. The results was observed that C_{max} was (26 ± 0.5) FP 11.

Statistical Analysis: Difference in Pharmaco-kinetic parameters was analyzed using analysis of variance. Variation in mean PK Parameters of FP11 related to t-test and value of $P < 0.05$ was considered significant.

TABLE 18: PHARMACOKINETIC PARAMETER LOADED WITH PIOGLITAZONE HYDROCHLORIDE

S. no.	Pharmacokinetic parameters	FP11
1	C_{max} (µ g/ml)	26 ± 0.5
2	t_{max} (h rs)	4.5 ± 0.251
3	Elimination rate Constant(hr^{-1})	0.13515 ± 0.002
4	Half Life (hrs)	6.1285 ± 0.264
5	AUC_{0-t}	163 ± 1
6	AUC_{0-inf} (µg. hr/ml)	28.875 ± 0.1726
7	$AUMC_{0-t}$ (µg.hr/ml)	2922 ± 2
8	AUMC0-inf (µg. hr/ml)	37.415 ± 0.3066
9	MRT (days)	7.4054 ± 1

RESULTS AND DISCUSSION:

General Discussion: A oral pharmaceutical Tablets has long been one of the most favourable dosage forms for all types of patients unable to tolerate parenteral dosage form .The Solid form is preferred because of ease of flexibility in the administration of dose, and importance in stability maintenance and economical. More therapeutic and commercial advantages *i.e*.

1) High patient compliance, 2) Reduction in side effects 3) Non Invasive method.

In this work a new method of system "Combinational effect of co-processed super disintegrants" were developed and leads to improved bioavailability, present work explain the mechanism of improved bioavailability. 1) incorporation of coprocessed superdisintegrants with various solvents, step 2) Effect of particle size on bioavailability 3) Release of drugs in different mediums.

Evaluation of Powders:

Pre - compression Parameters: All the powders and granules prepared as per the formulations required were subjected to evaluate the precompression properties. The powders prepared with coprocessed superdisintegrants showed equal values as that of granules flow properties due to change in the shape and particle size by dissolving in solvents like acetone and methanol and passing through the sieves arranged in chronological order based on the size of the sieve or (sieve number). The powder changed to the form of granules made them specific to achieve good flow properties. The density of the materials have changed which maintained to regulate the granules in specific volume of die cavity of the punching machine. Compared to Amlodipine Besylate. All the results were tabulated in **Table 3**.

Post Compression Parameters: All the results were tabulated in **Table 4**. Fast disintegrating tablets are prepared in a single-station rotary compression mission shows the post-compressional parameters, hardness (3.4- 4.4 Kg/cm^2), friability (≤ 0.75 %), weight variation (Passes) values of the tablets. It indicates that with the change in use of superdisintegrants mixture and concentration, the tablets obtained with thickness (3.28 - 4.48 mm), for all the prepared tablets and all the specified values are in acceptable range. All the formulations

passed the uniformity of dispersion test. All the results were tabulated in **Table 4**.

Disintegration Time: The most important parameter that is needed to be optimized during the development of a fast disintegrating tablets is disintegrating time of the tablets. The disintegration test of the tablets was conducted in purified water. Disintegrating study showed that the disintegrating times of the tablets (from 21 sec to 28) with mixture of modified super disintegrants. The research work carried out selecting 6% concentration to be added in the mixture that is in the specified ratios. However, disintegration time of the tablets prepared with mixture of co processed superdisintegrants (1:1) are in the acceptable range with no much deviations due to conditional effect of superdisintegrant mixture.

The results are in consistent with other results. Tablets prepared by direct compression technique showed better disintegration as the mechanism of hydration worked out here. Anhydrates are having much better capacity in absorbing water compared to hydrates. Comparatively, the disintegration times of the prepared tablets with co-processed super disintegrants were much better and made the approach of fast disintegration and the objective was fulfilled and justified.

The super disintegrants co-processed with the solvents acetone and ethanol made the drugs to change in the property of solubility and the effective selection of particle size which were retained on the sieve collected more made the selection of drug particles with uniform size and the basic literature showed that the decrease in particle size improved solubility was once again proved by the method developed for the decrease in disintegration time of the tablets along with decrease in wetting time of the tablets of both the drugs.

Wetting Time: As per the change in surface area by maintaining effective particle size with the modified process of co-processing the super-disintegrants justified the decreased in wetting time. The co-processing technique achieved the objective of faster disintegration which is prior depended on wetting capacity of the material in the particular solvent.

***In-vitro* Release Studies of Pioglitazone Hydrochloride:** The dissolution data and kinetics of Pioglitazone Hydrochloride tablets prepared with various techniques and methods were shown in the **Table 6 - 12**. From the results it is evident that the tablets prepared with the co processed superdisintegrant mixture in the ratio of (1:1) by direct compression technique showed good release of drug compared to the tablets prepared by wet granulation technique. The rapid increase in dissolution of drug may be due to rapid swelling of Crosscarmellose sodium and sodium starch glycolate. The increase in the concentration of Crosscarmellose and sodium starch glycolate increased the swelling and disintegrating tablets rapidly into apparently primary particles. While tablets formulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more fastly due to the change in viscous gel layer of sodium starch glycolate by crosspovidone.

The further studied was carried out for the tablets prepared by co processing of super disintegrants using acetone and ethanol as solvents. The tablets prepared by selecting the materials retained more on the sieve no 44 gave the visionary and statistical evidence that the tablets were released the drug effectively and completely rather than the tablets prepared by acetone co-processed super-disintegrants and material retained less on the sieve no 66. The effective control of particle size and the solvation mechanism carried a way for enhancement of drug release and complete release (99.3%).

The drug release tested in various mediums for the tablets as per the FDA dissolution acceptance criteria revealed that the drug has possible release in water and effective release through the entire length of GIT. The drug release was very effective in oral cavity pH and upper area of the stomach that is slightly acidic pH. The formulations drug release was compared with the market formulation (Diavista from Dr. Reddy's- dose 15 mg). There exists similarity between market formulation and best formulation in the two mediums 0.1 N HCl and phosphate buffer pH 6.8. All the evidences proved to be the techniques and methods adopted made the drug release effectively which intended to have good bioavailability.

Stability Studies: The accelerated stability studies conducted for the best formulation as per the guidelines of ICH showed the consistent results for the period of three months. There are no changes in colour and appearance. The evaluated parameters like hardness, disintegration time and drug release was consistent in every month of study and even after 3 months. The studies showed FA3 were stable and effective in retaining their properties throughout their shelf life period.

Bioanalytical Study: Comparative pharmaco-kinetic study carried out using the previously developed HPLC method on wistar rats suggest that no reaction with the rat plasma, from the results it was shown that C_{max} was (26 ± 0.5 for Pioglitazone Formulation FP11. The t_{max} values are like 17 min for FP11. The MRT was 7.405 ± 1 (h) in the optimized F3 formulations. Thus the formulation is best in release of the drug immediately.

CONCLUSION: The present investigation of this work "Design and development of immediate release tablets by employing modified super-disintegrants" were developed and leads to improvement of bioavailability, present work explain the mechanism of drug release from tablets using modified superdisintegrants. In this work tablets were prepared by using crosscarmellose, sodium starch glycolate and crosspovidone as superdisintegrants in various ratios and various methods. The influence of tablet compression technique on the manufacturing of tablets was evaluated. The physical modification of super-disintegrants using co processing technique and selection of processed material with particle size specificity made the drugs to possess required characteristics as fast dispersible. The pre compression and post compression properties are determined as per the procedure prescribed. The drug release studies and kinetics indicate that the prepared tablets with co-processed superdisintegrants were best at its release in the entire tract of GIT due to their change in bio pharmaceutical property like dissolution. Optimized formulations were selected for stability concern and *in- vivo* performance. The main aim of the work is to prepare, evaluate *in vivo* performance and safety study of Pioglitazone Besylate tablets. The optimized formulation of tablets were identical possess similarity between marketed formulation. *In-vivo* study was randomly designed to evaluating tablets of Pioglitazone Besylate, best formulations, rat was chosen as animal models for *in-vivo* absorption study. Analytical method used was for pharmacokinetic profile. The pharmacokinetic parameters t_{max}, $t_{1/2}$, AUC, MRT were significant.

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CONFLICT OF INTEREST: Nil

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