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DESIGN AND EVALUATION OF PULSATILE PRESS COATED CORE-IN-CUP TABLETS OF ATENOLOL

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Abstract:

Aim of the present research was to formulate and evaluate an oral pulsatile press coated core-in-cup tablets of atenolol.

Pulsatile drug delivery system can deliver drug when and where it is required.

The Basic design consists of a core tablet prepared by wet granulation method using various ratios of HPMC E-15 and HPMC 50 cps. The tablet core was surrounded by two layers, a hydrophilic polymeric layer consisting of maltodextrin and an impermeable layer consisting of ethyl cellulose. The prepared press coated pulsatile tablets were evaluated for various pre and post formulation parameters such as pre compression characteristics of granule bed viz., rheological/micromeritic properties like bulk density, tapped density, compressibility index, Hauser's ratio, flow properties, thickness, diameter, weight uniformity , hardness, friability, disintegration and dissolution profiles by using standard procedures

In vitro release profiles of pulsatile device during 24 h studies were found to have very good sustaining effect. During the first five hours it shows minimum drug release. From the kinetic model fitting studies it concludes that in all the core-in-cup formulations the fit model was found to be first order kinetics with regression values 'r'>0.9000 and koresmayer peppas exponential value 'n' was found to be greater than 0.5 indicating the drug release mechanism follows non fickian diffusion

The programmable pulsatile release has been achieved from a press coated tablet over a 6 h period of lag time and drug release for 24 h.

Keywords: *Core-in-cup, pulsatile, atenolol.*

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INTRODUCTION:

During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide an immediate or rapid medication release, and supply a given concentration or quantity of the drug to the body's systemic circulatory system without any rate control.

To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second generation, modified drug release dosage forms. Treatments of numerous diseases using traditional drug products are often inconvenient and impractical if disease symptoms occur during the night or early morning.

Modified release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second generation modified release dosage forms include slowed release, delayed release, prolonged release, extended release, repeated release, sustained release, and controlled release drug preparations[1,2].

Since many diseases exhibit predictable cyclic rhythms, the timing of medication regimens can be used to improve the outcome of the chronic conditions for patients[3,4]. Thus, after understanding the disease physiology an advanced DDS with pulsatile hormone secretion function may be applied as a part of the treatment. The pulsatile drug delivery system (PDDS) is intended to deliver a rapid, or transient, and quantified medication release after a pre determined off release period (lag time)[5-6]. PDDS can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance.

PDDS avoids problems with degradation of drugs in the stomach or first pass metabolism, enables the simultaneous administration of two different drugs, allows the release drugs at different sites within the gastro intestinal tract, and can deliver a drug release burst at one or more predetermined time intervals, according to patient requirements.

The advantages of PDDS extend to drugs with chronopharmacological behaviors, where night time dosing is required, and for various diseases that are influenced by circadian rhythms[6-7].

Since PDDS has a unique mechanism of delivery, whereby a drug releases rapidly after a lag time, various PDDSs have appeared on the markets that replace modified release dosage forms. [8]

The PDDS is formulated to release a drug after a predetermined lag time in a specific region of the gastrointestinal tract, or as a chronotherapeutic time dependent release. Pulsatile drug release should occur independently of the environment (e.g. pH, enzymatic activity, intestinal motility) or other stimuli; lag time prior to the release of the drug is primarily determined by the formulation's design[25]. PDDS is a type of time-controlled DDS; it may be classified as a single unit or multiple unit system by application of different coating systems[26]. The single unit PDDS is applied for rapid dissolution after a designated lag time, and it is possible to avoid deviation in dissolution lag time for each unit. The single unit PDDS can be further sub divided into capsule based or tablet-based systems. The single unit PDDS is fabricated by coating the system with an eroding or soluble polymer, or a polymer coating that may be ruptured. Multiple unit PDDS can provide precise time control over drug release, though it requires more complex and expensive manufacturing techniques. Multiple unit PDDS units can be fabricated by coating multi particulates with a pH dependent barrier membrane, then, by blending variously coated multi particulates the desired release profile is obtained. Moreover, pulsatile release may be monitored by altering membrane permeability, or by coating the unit with a soluble, erodible, or rupturable membrane.

MATERIALS AND METHODS:

Atenolol was a complimentary sample from Divine Laboratories, Hyderabad. HPMC E-15 and 50CPS were procured from Sd Fine Chemical Mumbai, PVP K-90 and Propan-2-ol was procured from Arrow Chem, Mumbai and Qualigens Chemicals Mumbai respectively. All the other Chemicals were of analytical/ pharmacopeial grade from commercial suppliers and were used as received without any purification.

Method of preparation of core tablet

Preparation of granules: Granules of atenolol were prepared by wet granulation technology. All the ingredients as per the formulae were weighed and

grinded to fineness in a mortar and pestle. The powder blend was then passed through sieve # 120. The powder was then shaken in a polybag for uniform mixing then transferred into a glass mortar. To this add PVP K90 solution which was previously prepared in distilled water until a damp mass was obtained, further damp mass was passed through mesh # 22. The obtained granules are dried in oven at 60° C for 1h, further these dried granules were passed through mesh #16/20 and blend with an extent of 20% fine particles. This blend is subjected for Preformulation studies prior to compression.

Compression: After adding lubricant (talc) and anti-adherent (magnesium stearate) to the dry granule bed and subsequent blending, the granules were compressed into tablets on a pilot press machine using 10 mm diameter, convex, flat faced punches at a pressure of approximately 4&16 kg /cm^2.

Method of preparation of core-in-cup tablets: Formulation compositions of coating layer (F1 to F9) are shown in **Table-1** describes varying percentage of polymers were weighed and passed through desired numbered sieve. The ingredients of coating layer were mixed in a mortar. Required weight of coating powder was weighed and used in two steps for the upper and lower shell.

An impermeable coating cup material was applied under the bottom and core tablet was placed in the center of die.Core tablet was slightly pressed to fix the coating around and under the core tablet, above it the hydrophilic polymer was filled and manually lowered the lower punch slowly and compressed by using 13 mm flat faced punch.

The nine formulations viz., F-1 to F-9 press coated pulsatile release core-in-cup tablets of atenolol were prepared with varied concentration of HPMC E15: HPMC 50 cps: MCC keeping drug, maltodextrin and ethyl cellulose concentration constant and were presented in **Table No**.1. The evaluation was carried out in two steps preformulation and post formulation parameters.

Table 1: Formulae for F-1 to F-9 formulations

S.No	Drug/Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**CORE** Atenolol	25	25	25	25	25	25	25	25	25
2	HPMC E15	50	75	10	25	50	75	10	25	75
3	HPMC 50 cps	25	25	50	50	50	50	75	75	75
4	MCC	100	75	115	100	75	50	90	75	25
5	**CUP** EC	200	200	200	200	200	200	200	200	200
6	MD	100	100	100	100	100	100	100	100	100

HPMC-Hydroxy propyl methyl cellulose; **MCC**-Micro crystalline cellulose; **EC**- Ethyl cellulose; MD-Maltodextrin

Evaluation of Pulsatile Drug Delivery System
Preformulation studies
The prepared granules were subjected for various pre formulation studies such as pre-compression characteristics of granule bed viz., rheological /micromeritic properties like bulk density, tapped density, compressibility index, flow properties (angle of repose).
The results were presented in **Table -2**.

FTIR

The compatibility between pure drug and polymers and physical mixture at 1:1 ratio of drug with all

polymers were detected by FTIR spectra obtained on Perkin Elmer 1600 series, (USA). The pellets were prepared on KBr–press. To prepare the pellets, a few mg of the pure drug were ground together in a mortar with about 100 times quantity of KBr. The finely ground powder was introduced into a stainless-steel die. The powder was then pressed in the die between polished stainless-steel anvils at a pressure of about 10t/in2. The spectra were recorded over the wave

number range of 4000 to 500 cm^{-1} and shown in Figure 1 to 4.

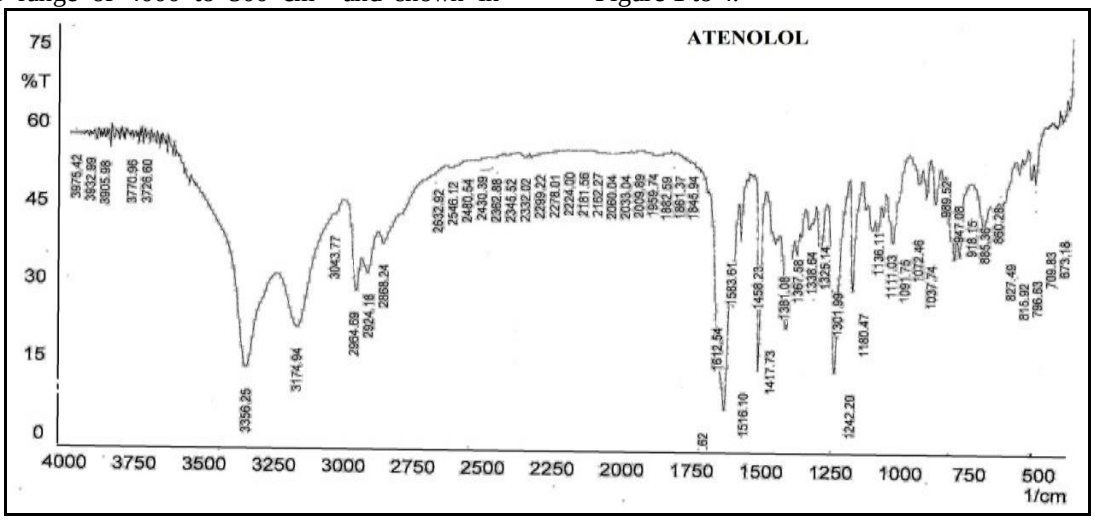

Figure -1: FTIR Spectrum of Atenolol

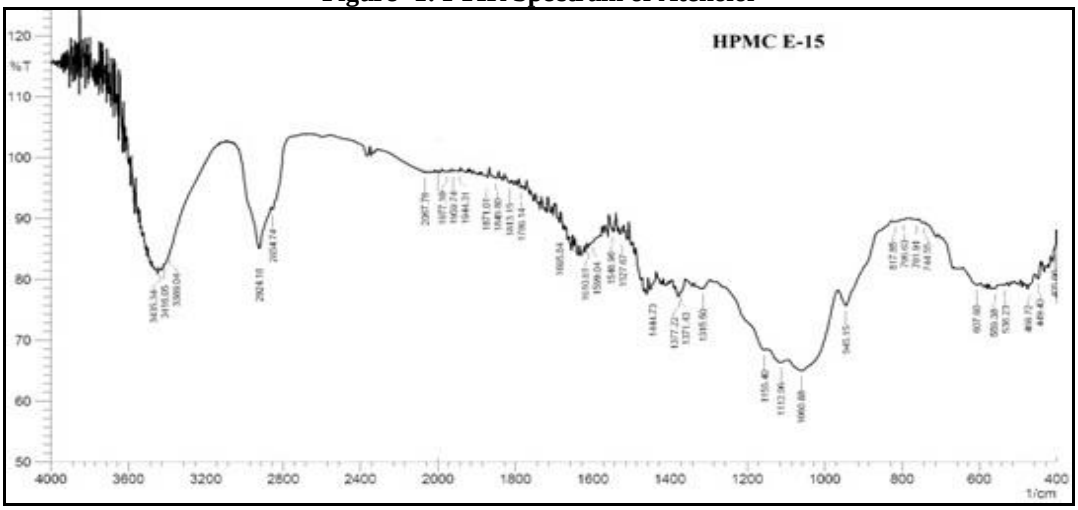

Figure -2: FTIR Spectrum of HPMC E-15

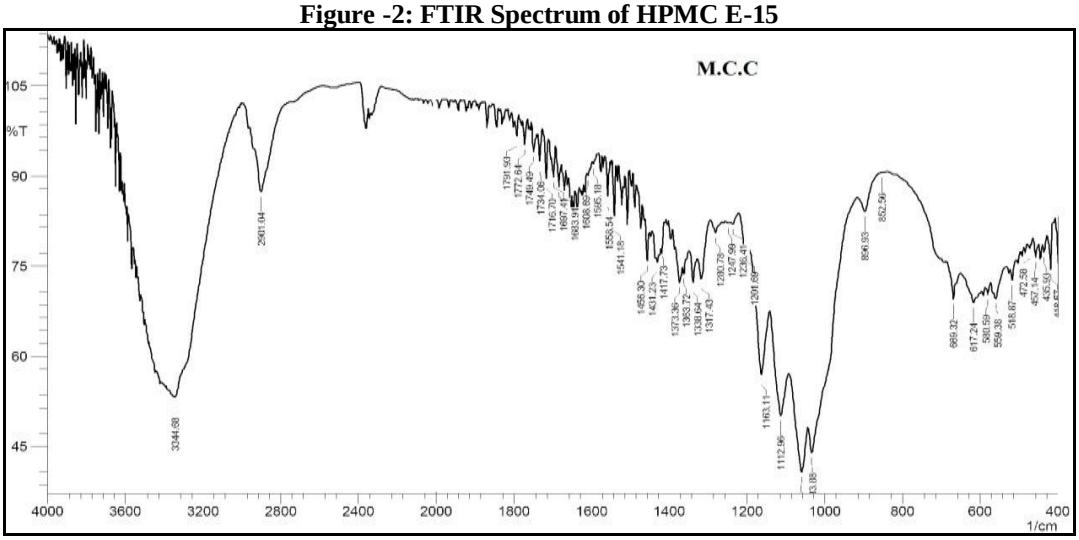

Figure -3: FTIR spectrum of MCC

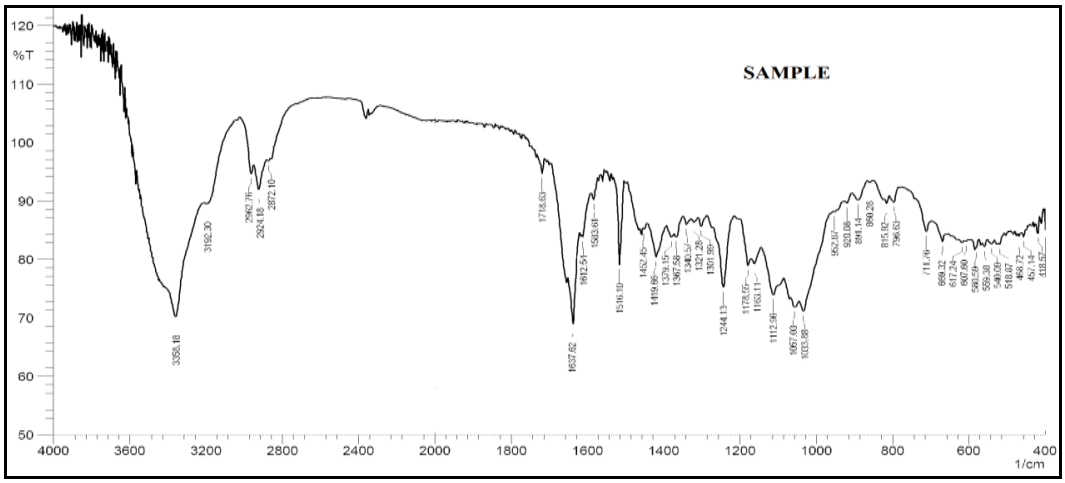

Figure-4: FTIR spectrum of physical mixture at 1:1 ratio of drug: polymers

Evaluation of post compression studies: Tablets were evaluated for their thickness, weight uniformity, hardness, friability, disintegration time and dissolution profiles by using standard procedures.

Post compression evaluation of core and core-in-cup tablets

Core tablets were subjected for drug content. Core tablets and core-in-cup tablets were evaluated for their thickness, diameter, weight uniformity, hardness, friability, drug content, disintegration time and dissolution profiles by using standard procedures and the data were presented in **Tables3 to 6**.

Dissolution studies

In vitro drug release studies were carried out in 900 ml of 0.1 N HCl using USP XXII dissolution apparatus type II. The press coated core-in-cup pulsatile system developed in the present study consist of three components, the central core tablet made up pure drug atenolol and different concentrations of HPMC E15, HPMC 50cps and MCC, the impermeable surrounding (lateral) consist of ethyl cellulose and the top layer consist of hydrophilic polymer maltodextrin. Both the external layers are intended to regulate the function of the system and modify the release of drug. The polymer materials present in the core tablet regulate drug release in controlled manner. This type of tablet could be described as a hybrid system in which the top cover layer consists of a fast-dissolving polymer layer and the inner part of a conventional tablet acting as a drug reservoir.

RESULT AND DISCUSSION:

The pulsatile press coated core-in-cup tablet system is developed in the present study, where the tablet core was surrounded by two layers, a hydrophilic polymeric layer consists of maltodextrin and an impermeable layer consists of ethyl cellulose. The nine formulations viz., F-1 to F-9 press coated pulsatile release core-in-cup tablets of atenolol were prepared with varied concentration of HPMC E15: HPMC 50 cps: MCC keeping drug, maltodextrin and ethyl cellulose concentration constant and investigate the influence of varied grade of HPMC on release rate and other parameters were investigated.

The prepared granules were subjected for various preformulation studies**Table-2**. The bulk density values were found to be in the range of 0.294 ± 0.002 gm/ml to 0.364 ± 0.005 gm/ml for F-1 to F-9 formulations. The tapped density values were found to be in the range of 0.344 ± 0.001 gm/ml to 0.413 ± 0.006 gm/ml for F-1 to F-9 formulations and the results obtained were within the acceptable range of the prepared granule mixture for core tablet.

The Carr's index (compressibility values) were found to be in the range of 7.80% ± 0.352 to 20.72% ± 0.171 for F-1 to F-9 formulations and the results obtained were within the acceptable range indicates acceptable flow property of the prepared granule mixture for core tablet. The Hausner's ratio were found to be in the range of 1.08 ± 0.005 to 1.23 ± 0.006 for F-1 to F-9 formulations and the results obtained were within the acceptable range indicates acceptable flow property and good packing ability of the prepared granule mixture for core tablet.

The angle of repose were found to be in the range of 21.08º ± 0.616 to 28.61º ± 0.751 for F-1 to F-9 formulations and the results obtained were within the

acceptable range indicates good flow property of the prepared granule mixture for core tablet.

The thickness of the core, core-in-cup tablet were found to be in the range of 2.91 ± 0.035 to 2.99 ± 0.021 mm and 3.67 ± 0.006 to 3.79 ± 0.01mm for F-1 to F-9 indicated proper relation with coating amount and was maintained properly. The diameter of the core, core-in-cup tablet were found to be in the range of 10.02 ± 0.042 to 10.05 ± 0.024 mm and 13.00 ± 0.047 to 13.06 ± 0.021 mm for F-1 to F-9 formulations indicated proper relation with coating amount and was maintained properly.

The weight of core, core-in-cup tablets was found to be uniform ranging between 0.19 ± 0.002 to 0.20 ± 0.007 gm for a 200 mg tablet and 0.49 ± 0.008 to 0.50 ± 0.011 gm for 500 mg tablet.

The drug content**(Table-3)** of all the formulations equivalent to 20 mg were found to be fairly uniform, reproducible and consistent, ranging between 19.53 ± 0.070 mg to 20.16 ± 0.055 mg per tablet of 500 mg.

The disintegration time **(Table-4)** for core tablets were ranging from 145 to 220 minutes, owing to the variation in amount of polymers incorporated.

The post compression data **(Table-5 and 6)** the hardness of core, core-in-cup tablets found to be fairly consistent and uniform, ranging between 2.16 ± 0.351 Kg/cm^2 to 4.06 ± 0.115 Kg/cm^2 and 4.63 ± 0.153 to 7.96 ± 0.057 Kg/cm^2. The friability of all the formulations of core, core-in-cup tablets were determined in a friabilator operated for 4 min at 25 rpm, and the percent friability was found to be ranging 0.19 % to 0.74% and 0.83% to 1.76 % respectively.

The cumulative percentage release of drug from F-1, F-2 and F-3 were found to be 98.52% (lag time of 5h), 97.24% (lag time of 5h) and 97.23 % (lag time of 4h) within 18 h, 18 h and 20 h of study respectively. The cumulative percentage release of drug from F-4, F-5 and F-6 were found to be 97.39% (lag time of 3h), 97.45% (lag time of 6h) and 98.56 % (lag time of 6h), within 16 h, 24 h and 24 h of study respectively. The cumulative percentage release of drug from F-7, F-8 and F-9 were found to be 99.03 % (lag time of 4h), 98.99% (lag time of 3h) and 99.21% (lag time of 6h) within 18 h, 16 h and 24 h of study respectively**Table-7**.

Dissolution study revealed that the formulations F-5, F-6 and F-9 showed good release property with increased lag time, better post compression property which was ideal and considered as optimum formulations **Fig- 9 to 10**.

From the kinetic model fitting studies (**Table-8**) it concludes that in all the core-in-cup formulations the best fit model was found to be first order kinetics with regression values 'r'> 0.9000 and koresmayer peppas exponential value 'n' was found to be greater than 0.5 indicating the drug release mechanism follows non fickian diffusion.

These findings indicate that in atenolol pulsatile core-in-cup tablets, drug molecules are released by diffusion out of the core tablet once the polymer top layer has being fully removed and the liquid molecules come in contact with the core tablet. The dissolution apparently starts when the polymer layer is nearly fully eroded or removed and the core tablet fully exposed to the dissolution liquid. The release starts at a later stage since the poor solubility of the drug delays further its dissolution and increases the time required for its complete release.

Table-2: Rheological and micromeritic data of prepared granule mixture for core tablet

Batch No	Bulk density gm/ml ± SD	Tapped density gm/ml ± SD	Carr's index % ± SD	Hausner's ratio % ± SD	Angle of repose θ ± SD
F-1	0.317 ± 0.034	0.382 ± 0.005	20.69 ± 0.170	1.13 ± 0.118	21.72 ± 0.682
F-2	0.364 ± 0.005	0.413 ± 0.006	11.03 ± 0.137	1.21 ± 0.074	21.59 ± 0.542
F-3	0.357 ± 0.015	0.371 ± 0.001	7.80 ± 0.352	1.08 ± 0.005	22.12 ± 0.103
F-4	0.312 ± 0.002	0.385 ± 0.003	18.74 ± 0.006	1.23 ± 0.006	28.61 ± 0.751
F-5	0.294 ± 0.002	0.355 ± 0.003	16.99 ± 0.596	1.21 ± 0.008	24.97 ± 0.278
F-6	0.355 ± 0.003	0.396 ± 0.002	10.23 ± 0.296	1.11 ± 0.004	21.08 ± 0.616
F-7	0.306 ± 0.001	0.358 ± 0.002	14.12 ± 0.003	1.16 ± 0.003	23.81 ± 0.694
F-8	0.315 ± 0.001	0.402 ± 0.007	20.72 ± 0.171	1.26 ± 0.002	24.61 ± 0.651
F-9	0.312 ± 0.002	0.344 ± 0.001	9.37 ± 0.005	1.11 ± 0.002	26.53 ± 0.104

Table 3: Drug content data of F-1 to F-9 core tablets

Batch No	Amount of drug recovered (drug equivalent to 20 mg) Mean* ± SD	Percentage drug content Mean* ± SD	Coefficient of Variation
F-1	19.68 ± 0.039	98.41 ± 0.196	0.199
F-2	20.06 ± 0.024	100.34 ± 0.119	0.118
F-3	19.53 ± 0.070	97.63 ± 0.352	0.360
F-4	19.98 ± 0.031	99.84 ± 0.213	0.213
F-5	19.98 ± 0.050	99.95 ± 0.251	0.251
F-6	20.05 ± 0.148	100.26 ± 0.742	0.740
F-7	20.11 ± 0.055	100.57 ± 0.274	0.272
F-8	20.16 ± 0.055	100.81 ± 0.274	0.271
F-9	19.98 ± 0.072	99.92 ± 0.358	0.358

*** Average of five readings**

Table 4: Disintegration time of F-1 to F-9 core tablets

Batch No	Disintegration time (minutes)
F-1	150
F-2	155
F-3	180
F-4	175
F-5	210
F-6	218
F-7	180
F-8	145
F-9	220

Table 5: Post compression evaluation data for core and core-in-cup tablets

Batch No	Thickness (mm) ± S.D		Diameter (mm) ± S.D		Weight variation (mg) ± S.D)	
	Core	Core-in-cup	Core	Core-in-cup	Core	Core-in-cup
F-1	2.99 ± 0.021	3.74 ± 0.017	10.03 ± 0.036	13.02 ± 0.022	0.19 ± 0.006	0.50 ± 0.011
F-2	2.99 ± 0.010	3.76 ± 0.005	10.04 ± 0.010	13.03 ± 0.011	0.19 ± 0.004	0.50 ± 0.007
F-3	2.97 ± 0.015	3.79 ± 0.010	10.04 ± 0.023	13.03 ± 0.011	0.19 ± 0.002	0.50 ± 0.006
F-4	2.95 ± 0.053	3.76 ± 0.010	10.02 ± 0.042	13.00 ± 0.047	0.19 ± 0.004	0.49 ± 0.012
F-5	2.95 ± 0.055	3.76 ± 0.025	10.04 ± 0.023	13.06 ± 0.021	0.19 ± 0.008	0.49 ± 0.008
F-6	2.92 ± 0.081	3.74 ± 0.010	10.05 ± 0.011	13.04 ± 0.030	0.19 ± 0.007	0.50 ± 0.003
F-7	2.98 ± 0.006	3.71 ± 0.021	10.04 ± 0.021	13.07 ± 0.010	0.19 ± 0.005	0.50 ± 0.005
F-8	2.98 ± 0.010	3.67 ± 0.006	10.03 ± 0.005	13.06 ± 0.021	0.20 ± 0.007	0.50 ± 0.005
F-9	2.91 ± 0.035	3.73 ± 0.010	10.05 ± 0.024	13.06 ± 0.015	0.20 ± 0.004	0.50 ± 0.006

Table 6: Post compression evaluation data for core and core-in-cup tablets

Batch No	Hardness(kg/cm^2) ± S.D		% Friability ± S.D	
	Core	Core-in-cup	Core	Core-in-cup
F-1	4.03 ± 0.057	7.73 ± 0.115	0.19 ± 0.001	1.16 ± 0.011
F-2	2.90 ± 0.100	7.66 ± 0.115	0.74 ± 0.007	0.83 ± 0.002
F-3	3.20 ± 0.201	7.90 ± 0.101	0.21 ± 0.014	1.03 ± 0.002
F-4	3.96 ± 0.153	7.93 ± 0.115	0.51 ± 0.014	1.76 ± 0.002
F-5	4.06 ± 0.115	4.63 ± 0.153	0.71 ± 0.002	1.76 ± 0.001
F-6	2.66 ± 0.115	7.86 ± 0.115	0.19 ± 0.007	1.07 ± 0.001
F-7	4.00 ± 0.115	7.86 ± 0.115	0.21 ± 0.014	0.84 ± 0.001
F-8	4.03 ± 0.057	5.01± 0.201	0.51 ± 0.007	1.42 ± 0.020
F-9	2.16 ± 0.351	7.96 ± 0.057	0.47 ± 0.007	1.39 ± 0.002

Table -7: Dissolution data of all the formulations F-1 to F-9

Time in hours	Cumulative percentage drug released								
	F-1	F-2	F-3	F-4	jF-5	F-6	F-7	F-8	F-9
1	27.04 ± 0.11	26.13 ± 0.10	26.20 ± 0.11	26.20 ± 0.02	21.91 ± 0.14	25.44 ± 0.13	28.67 ± 0.09	25.21 ± 0.11	26.57 ± 0.11
2	31.11 ± 0.10	32.76 ± 0.11	31.75 ± 0.10	31.75 ± 0.11	29.85 ± 0.10	31.02 ± 0.11	33.45 ± 0.05	30.53 ± 0.07	33.43 ± 0.09
3	33.54 ± 0.17	34.03 ± 0.11	33.23 ± 0.13	33.23 ± 0.10	30.98 ± 0.12	32.20 ± 0.11	35.89 ± 0.01	35.65 ± 0.10	34.89 ± 0.07
4	35.57 ± 0.12	36.90 ± 0.13	34.78 ± 0.09	36.03 ± 0.12	34.89 ± 0.11	35.57 ± 0.10	35.56 ± 0.21	37.28 ± 0.11	36.66 ± 0.08
5	37.24 ± 0.15	37.26 ± 0.14	37.24 ± 0.09	85.18 ± 0.15	36.98 ± 0.11	37.80 ± 0.09	38.32 ± 0.15	83.86 ± 0.11	38.40 ± 0.01
6	37.54 ± 0.23	38.59 ± 0.22	83.31 ± 0.08	87.01 ± 0.05	39.24 ± 0.09	38.78 ± 0.05	84.12 ± 0.11	86.80 ± 0.07	40.34 ± 0.02
7	84.99 ± 0.07	83.89 ± 0.10	84.99 ± 0.11	89.14 ± 0.01	40.10 ± 0.01	39.42 ± 0.11	86.89 ± 0.10	90.67 ± 0.17	41.23 ± 0.21
8	86.82 ± 0.11	85.05 ± 0.07	86.82 ± 0.10	90.55 ± 0.09	79.89 ± 0.06	84.50 ± 0.23	88.76 ± 0.13	92.78 ± 0.10	82.98 ± 0.11
9	88.94 ± 0.12	86.72 ± 0.08	88.94 ± 0.11	90.94 ± 0.11	82.98 ± 0.11	86.42 ± 0.32	90.23 ± 0.22	93.67 ± 0.11	84.36 ± 0.11
10	90.35 ± 0.15	88.84 ± 0.10	90.35 ± 0.07	91.96 ± 0.11	84.36 ± 0.27	88.00 ± 0.11	92.78 ± 0.11	94.45 ± 0.13	86.45 ± 0.10
11	91.86 ± 0.09	90.25 ± 0.11	91.86 ± 0.06	93.40 ± 0.11	86.45 ± 0.22	90.67 ± 0.11	93.45 ± 0.10	95.34 ± 0.14	89.17 ± 0.17
12	94.46 ± 0.13	91.76 ± 0.12	93.29 ± 0.02	94.46 ± 0.09	89.17 ± 0.17	92.76 ± 0.10	94.46 ± 0.09	96.58 ± 0.11	91.31 ± 0.21
14	95.59 ± 0.14	93.55 ± 0.21	94.35 ± 0.10	95.59 ± 0.10	90.67 ± 0.11	93.01 ± 0.12	96.00 ± 0.08	97.78 ± 0.10	92.22 ± 0.11
16	97.39 ± 0.18	95.67 ± 0.14	95.48 ± 0.11	97.39 ± 0.11	91.87 ± 0.12	95.56 ± 0.09	97.34 ± 0.12	98.99 ± 0.11	93.58 ± 0.11
18	98.52 ± 0.22	97.24 ± 0.11	96.54 ± 0.05	--	93.58 ± 0.15	96.87 ± 0.11	98.56 ± 0.34	--	94.56 ± 0.14
20	--	--	97.23 ± 0.06	--	95.26 ± 0.22	97.62 ± 0.12	99.03 ± 0.11	--	95.94 ± 0.21
22	--	--	--	--	96.35 ± 0.11	98.00 ± 0.10	--	--	98.34 ± 0.10
24	--	--	--	--	97.45 ± 0.10	98.56 ± 0.09	--	--	99.21 ± 0.11

Table 8: Model fitting data for F-1 to F-9 formulations

Batches	KINETIC MODELS										
	Zero order		1ST order		Matrix		Hix. Crow		Koresmayer peppas		
	r-value	k-value	r-value	k-value	r-value	k-value	r-value	k-value	r-value	k-value	n-value
F-1	0.8273	7.3988	0.9677	-0.2259	0.9276	25.362	0.9504	-0.0475	0.9025	20.6757	0.5772
F-2	0.8274	7.2735	0.9661	-0.2017	0.9307	24.9422	0.9447	-0.0446	0.9086	20.4185	0.5763
F-3	0.6841	6.9510	0.9663	-0.2083	0.9241	25.4875	0.9087	-0.0445	0.9106	22.5567	0.5491
F-4	0.7220	8.5531	0.9531	-0.2485	0.9245	28.1868	0.8991	-0.0540	0.9096	23.6178	0.5790
F-5	0.7407	5.5835	0.9689	-0.1576	0.9356	22.3588	0.9291	-0.0346	0.9332	19.4388	0.5510
F-6	0.7429	5.6047	0.9743	-0.1646	0.9343	22.4284	0.9392	-0.0353	0.9190	20.4359	0.5303
F-7	0.6922	6.9781	0.9714	-0.2156	0.9248	25.5706	0.9168	-0.0453	0.9104	22.3805	0.5536
F-8	0.7221	8.5532	0.9440	-0.2451	0.9282	28.1984	0.8923	-0.0537	0.9205	23.3733	0.5853
F-9	0.7377	5.6086	0.9728	-0.1656	0.9320	22.4516	0.9375	-0.0354	0.9156	20.5937	0.5275

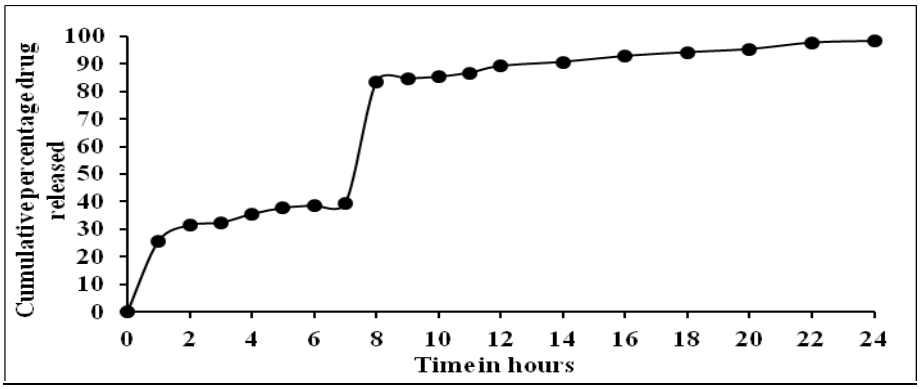

Figure-5: Dissolution profile of F-5 formulation without model fitting

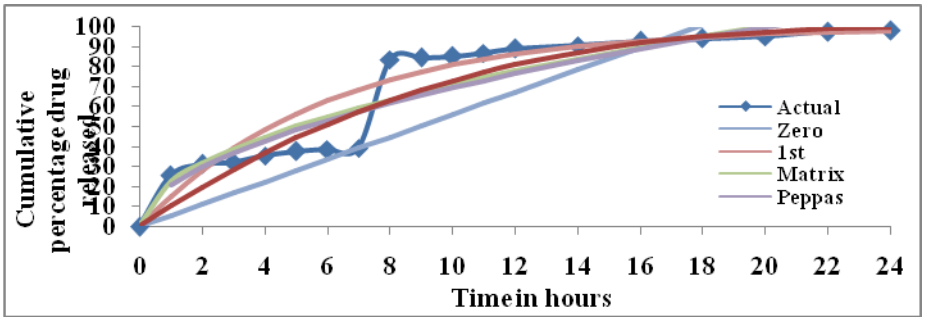

Figure 6: Dissolution profile of F-5 formulation without model fitting

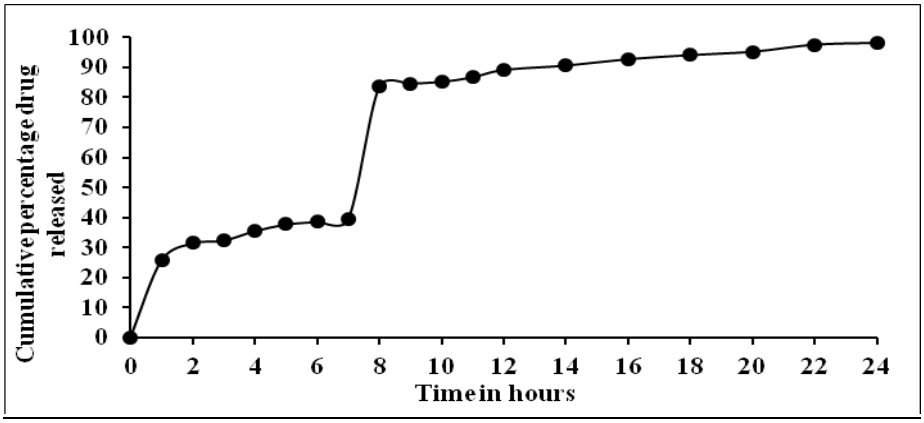

Figure-7 Dissolution profile of F- 6 formulation without model fitting

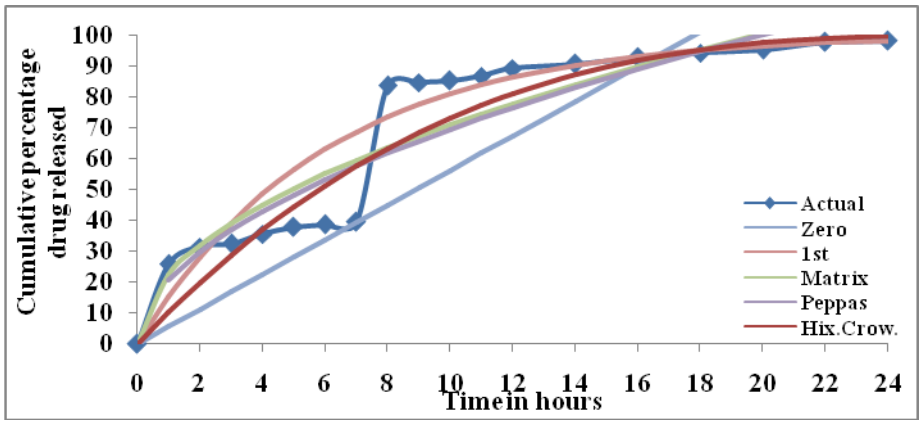

Figure- 8: Dissolution profile of F- 6 formulations with model fitting

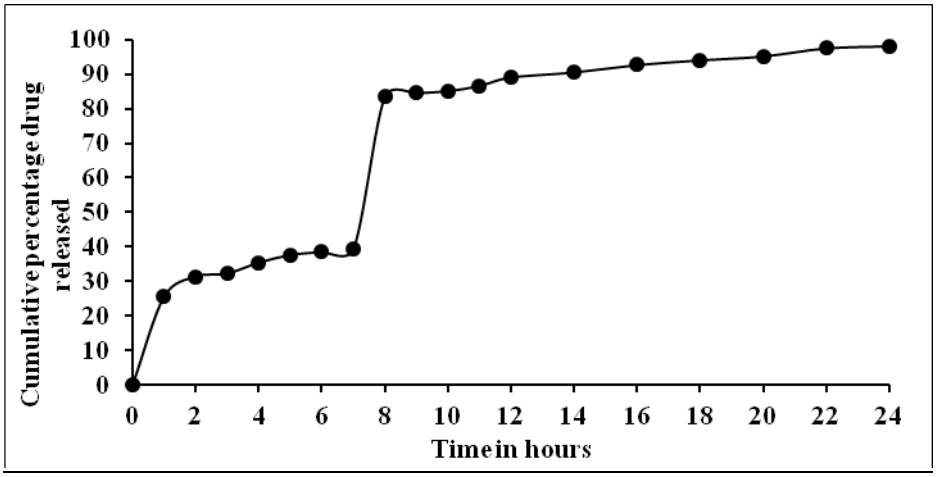

Figure -9: Dissolution profile of F- 9 formulations without model fitting

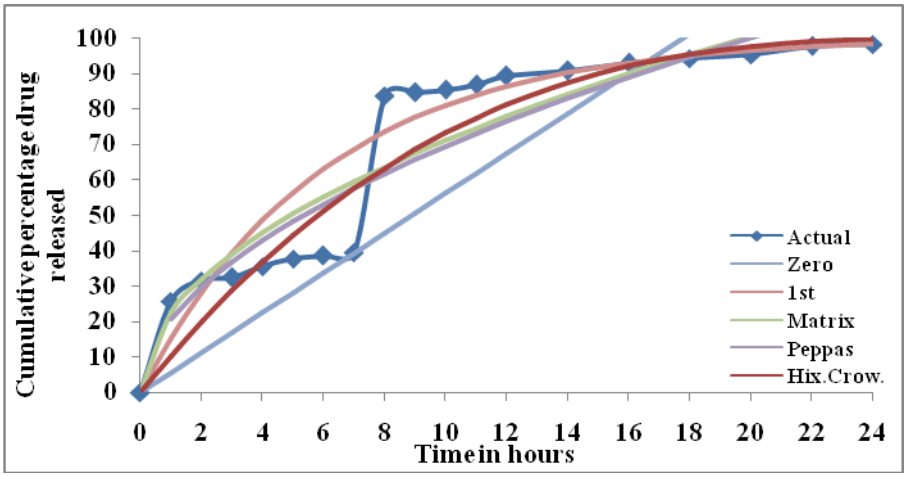

Figure 10: Dissolution profile of F- 9 formulation With model fitting

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