Formulation And Evaluation Of Compression Coated Tablets Of Cefpodoxime Proxetil

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ABSTRACT:

The purpose of this study was to formulate Cefpodoxime Proxetil compression-coated tablets for gastroretentive drug delivery. In this the core tablet is formulated to be retained in the stomach for a period of approximately 12 hrs using different polymer blend. The core tablet has half the amount of the drug and the rest of the drug in the coating layer. This outer layer is so formulated to release its drug content in a period of 15mins so as to achieve the initial burst release and then after 2 hours as the plasma concentration of the drug decreases then the core layer starts releasing its drug content so that the plasma concentration of the drug is maintained in the therapeutic window for the duration of 12 hrs. Thus the dosing interval is increased from 4 hrs to 12hrs. The batches are optimized using the factorial designing. Also the formulation is evaluated for its release profile and compared with the other standard release profiles.

Key words: Floating tablet, Fast disintegrating tablet, Factorial design, Xanthan gum, Hydroxypropyl methyl cellulose.

INTRODUCTION:

The oral drug delivery is by far the most preferable route of drug delivery system, due to ease of administration, patient compliance, and flexibility in formulation etc. Tablets are indeed the most popular solid dosage form for oral administration. One category of tablet formulations that has gained remarkable importance in drug therapeutics owing to various benefits it offers is controlled or modified release formulations. An ideal drug delivery system should deliver the drug at a rate dictated by the needs of the body during the period of treatment. These prerequisites lead to development of modified release technologies, which can improve the therapeutic efficacy and safety of a drug by targeting the drug to specific site in the body, thereby reducing both the size and number of doses required. The various modified release dosage forms available, include: extended release dosage forms that are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time. Delayed release dosage form is designed to release the drug at a time other than promptly after administration. Gastric retentive drug delivery devices (1,2) can be useful for the spatial and temporal delivery of many drugs.

Need of gastro retention arises because of two reasons, viz

- To improve bioavailability of drugs such as cyclosporin, ciprofloxacin, ranitidine, metoprolol tartarate, cefuroxime axetil etc. which are mainlyabsorbed from upper part of GIT or get degraded in basic PH.
- For local action in case of pathologies of stomach.

Furthermore, for drugs with poor solubility in the intestine and those with site-specific absorption limitations, gastric retention may increase the overall gastrointestinal absorption. Gastrointestinal retention depends on many factors such as density and size of the dosage form, the fasting or fed condition of the patient, the nature of the meal as well as posture. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time. The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several types of gastroretentive drug delivery systems, such as intragastric floating systems, swelling and expandable systems, bioadhesive systems, modified shape systems, high density systems, delayed gastric emptying systems and low density super porous systems. While the system is floating on the gastric contents, the drug is released slowly. A gastric floating device is useful for drug delivery to the upper part of the GI tract. The various approaches that have been studied for targeting orally administered drugs include use of pro-drugs, pH-sensitive polymers and time-dependent dosage forms.

A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and immediate release tablet in one dosage form. Such a system is known as compression coated tablets. Compression-coated tablets function like sugar-coated or film-coated tablets in that

the coating may cover a bitter substance. conceal an unpleasant or mottled appearance, or provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice. Another application of the compression-coated dosage form is in sustained- release preparations. A coating containing the immediate-release portion is compressed around a slowly releasing core. This gives a far more accurate dose than is the case with sugar coating.(3,4,5)

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic β- lactum antibiotic of cephalosporin class. Cefpodoxime proxetil is prodrug; its active metabolite is cefpodoxime. After oral administration cefpodoxime proxetil is absorbed from the gastrointestinal tract and de-esterifies to active metabolite cefpodoxime.(10,15) Over the recommended dosing range (100 to 400 mg) only the 50% of administered cefpodoxime dose was absorbed systemically. Also the drug has only 2 to 3 hours half life. Its action is by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes. Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil.(9)

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS:

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT.

2) For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

3) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

4) Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

5) The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs

6) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be avoided. This feature is of special importance for drug with a narrow therapeutic index.

7) Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

8) Reduction or fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

9) The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects.

In the present investigation it is intended to formulate and evaluate tablet in tablet (compression coated tablets) of the drug in which the inner core tablet is formulated to be as gastroretentive floating system while the coating tablet is for immediate release of the initial dose.

MATERIAL AND METHOD:

MATERIAL:

CEFPODOXIME PROXETIL was provided as a gift sample from CIPLA Pvt. Ltd, Mumbai, India. The Polymers Hydroxypropyl methyl cellulose K 15 M (HPMC K15 M) and Ethyl Cellulose (EC) was obtained as gift sample from Colorcon Pvt.Ltd, Goa. Microcrystalline cellulose (MCC) and Crosscarmellose Sodium (CCS) was supplied by JRS Pharma, Germany. All other ingredients were of Pharmaceutical grade and was obtained from S.D. Fine Chemicals.

PREPARATION OF CORE TABLET OF CEFPODOXIME PROXETIL:

The gastroretentive floating core tablets of Cefpodoxime Proxetil were prepared by direct compression method (Table 1). The drug, polymers (8) and sodium bicarbonate were weighed and mixed thoroughly for 10 min. Then the lubricant talc was added and the blend was again mixed well for another 5min. (4,5) and then the powdered blend was compressed on a single station tablet punching machine (Royal Artist, India.) using a 5mm flat punch.

BATCHES	DRUG	HPMC	EC	XANTHAN GUM	CARBOPOL	SODIUM BICARBONATE	Talc
A1	50	25				25	1%
A2	50		25			25	1%
A3	50	12.5	12.5			25	1%
A4	50			25		25	1%
A5	50	12.5		12.5		25	1%
A6	50	8.3	8.3	8.3		25	1%
A7	50				25	25	1%
A8	50	12.5			12.5	25	1%
A9	50	8.3	8.3		8.3	25	1%

Table.1: Different formulations of the core tablets: (All quantities are in mg)

PREPARATION OF FAST DISSOLVING COATING MATERIAL AND COMPRESSION COATED TABLETS:

The core tablets were compression coated with the coat mixture (Table 2). All the constituents of the coating mixture were uniformly mixed and then used for the compression coating. MCC was added in the coating formulation as a cushioning agent so as to protect the core tablet from any damage during the compression coating procedure. 50% of the drug dose was added in the coating fast dissolving layer so as to achieve an initial burst effect so that the drug plasma concentration reaches the therapeutic window. (6,7)

About 50% of the coating mixture was placed in the die cavity (9mm diameter). The core tablet was then placed in the centre of the die cavity, which was filled with the remainder of the coat formulation. Then, it was compressed around the core tablets to give a tablet in tablet formulation of Cefpodoxime Proxetil.

Table.2: Formulation of coating tablet:

Ingredients	Quantity
Drug	50mg
CCS	4%
MCC	q.s
Talc	1%

Factorial Design:

Based on the results of preliminary trial formulations obtained from the above 9 batches of the different polymers and polymer combinations; the combination of Xanthan gum and HPMC was found to give the desired floating time and swelling ratio and thus was used for the optimization of drug release with factorial design. A randomized 2^2 full factorial design was adopted to optimize the variables. In this design two factors were evaluated, each at two levels, and experimental trials were performed at all 4 possible combinations. The concentration of Xanthan gum and HPMC was selected as the 2 independent variables and the time required to release 80% of the drug as the response variable. (12, 13, 14)

Batches -	F1	F2	F3	F4
Factor A -	8.3	25	8.3	25
Factor B -	8.3	8.3	25	25

Factor A- Concentration of Xanthan gum

Factor B- Concentration of HPMC

EVALUATION OF THE COMPRESSION COATED TABLETS:

1. PREFORMULATION PARAMETERS:

a. Drug excipient interaction:

The pure drug and its formulation along with excipient were subjected to IR studies. The excipient compatibility was established by conducting a one month compatibility study at 40^0C and 75% Relative humidity. In the present study, potassium bromide pellet was employed using Shimadzu FTIR Spectrometer.

b. Standard calibration curve:

The spectrum of the drug was determined using Shimadzu UV-1800 instrument.

Then the concentration curve of the same was obtained within a range of 1ppm to 25ppm.

Accurately 10mg of Cefpodoxime proxetil was dissolved with 2ml ethanol and then made up to 10ml with distilled water. Then 1ml was pipette out and diluted to 10ml to prepare a stock solution of 100ppm. From the stock solution further solutions of 1, 5, 10, 15, 20, 25 ppm was prepared and the absorbance was measured at 263.2 nm.

2. EVALUATION OF CORE TABLETS:

a. Thickness:

Ten tablets from each formulation were taken randomly and their thickness was measured with a vernier calliper as per pharmacopeial specification.

b. Hardness and Friability:

Hardness of the tablets was measured using the Monsanto Hardness Tester. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving for100 rotation. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

c. Weight variation:

Twenty tablets were selected randomly. Tablets were weighed individually and average weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was computed.

d. Drug content:

For the content uniformity test, ten tablets were weighed and powdered and a quantity of powder equivalent to 10 mg of cefpodoxime proxetil was extracted into methanol. The drug content was determined by measuring the absorbance after appropriate dilution with methanol. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of six determinations.

e. Floating property: (9)

The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl.

i. Floating Lag Time: The time required for the tablet to rise to the surface of the medium and float was determined as floating lag time

ii. Floating Duration Time: The time for which the tablet remained floating on the surface of medium was determined as floating duration time.

3. EVALUATION OF COMPRESSION COATED TABLETS:

a. Thickness:

Ten tablets from each formulation were taken randomly and their thickness was measured with a vernier calliper.

b. Friability:

The friability of a sample of twenty tablets was measured using a USP type Roche friabilator.

c. Weight variation:

Studies were done on 20 tablets and the average was calculated to check the weight variation in individual batches.

d. Drug content:

The above method of drug content determination was again followed for the compression coated tablets.

e. Disintegration time of coating tablet:

In-vitro disintegration time was determined for core tablets using disintegration test apparatus. The buffer of pH 1.2 was maintained at a temperature of 37 ± 0.50 C and time taken for complete disintegration of the tablet was measured in seconds. (7)

4. RELEASE KINETICS

The in- vitro dissolution data was fitted in to different kinetic models like zero and first order, Korsemeyer peppas and Higuchi model to find out the drug release profile.

Also the formulation was compared with marketed formulation for its in vitro drug release property.(11)

RESULTS:

Drug excipient interaction with FTIR Determination: The compatibility study of 30 days at 40^0C and 75% RH showed no signs of incompatibility. As seen in the images below the prominent peaks of drug is seen in all the curves. This signifies that Cefpodoxime Proxetil is stable with the polymers like HPMC, EC, Carbopol and Xanthan gum. (Figure 1)
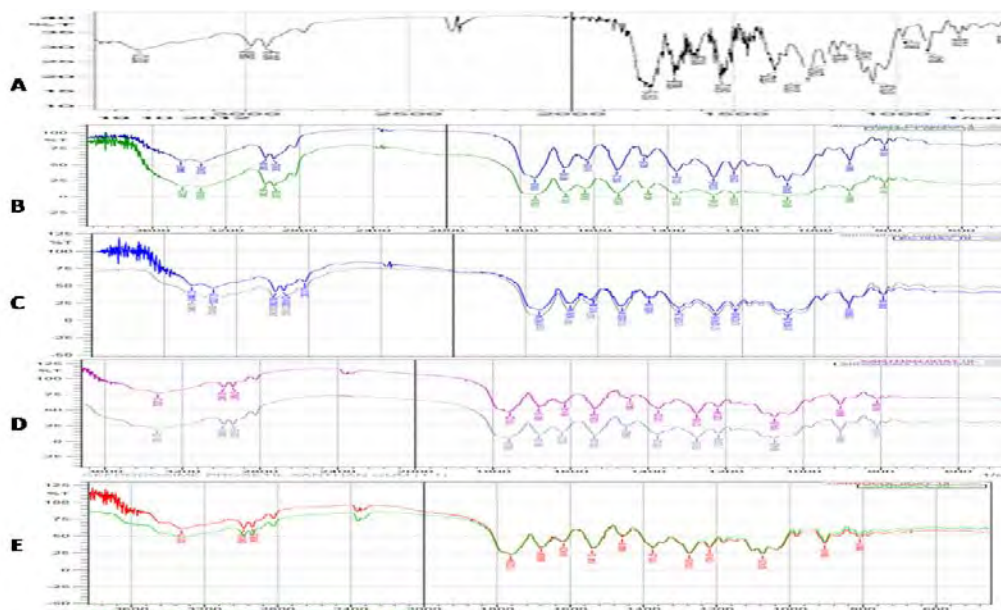
Figure.1: IR curve of Cefpodoxime Proxetil and compatibility with excipients.
(A) Plain Cefpodoxime Proxetil (B) Drug with HPMC K15M (C) Drug with EC (D) Drug with Xanthan Gum (E) Drug with Carbopol.

Concentration curve data:

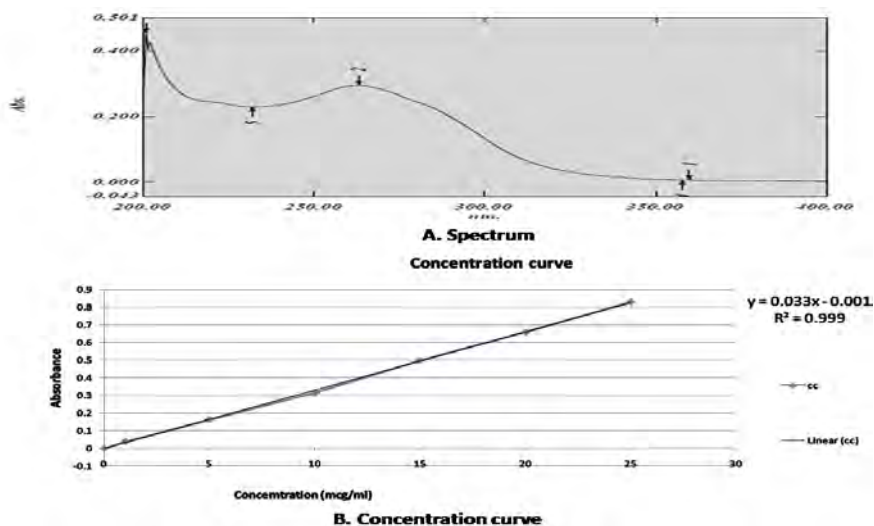The λ max of Cefpodoxime proxetil was found to be 263.2 nm. (Figure 2)

Figure 2: UV data of the drug

Evaluation of core tablet:

The Thickness, Hardness, Friability, Weight variation and drug content of all the batches were found to be in the range. The optimization batch was selected on the floating lag time and total duration of floating of the tables. The batches A3, A5, A6 gave a floating time of around 12hrs. (Table 3)

Batches	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Drug content (%)	Floating lag time (sec)	Floating duration (hrs)
A1	2.566±0.05	5.0 ± 0.02	0.35	103±1.3	99.12 ± 0.04	60±2.08	10
A2	2.533±0.05	4.9 ± 0.02	0.43	100±1.1	99.44 ± 0.02	120±2.45	5
A3	2.566±0.05	5.0 ± 0.04	0.56	100±1.5	99.44 ± 0.02	78±37	12
A4	2.533±0.05	4.8 ± 0.02	0.63	104±1.4	98.92 ± 0.07	38±21	8
A5	2.6±0.1	5.0 ± 0.02	0.37	99±1.3	99.12 ± 0.04	60±2.08	14
A6	2.6±0.1	4.9 ± 0.02	0.53	100±1.6	98.92 ± 0.07	120±34	12
A7	2.633±0.05	5.0 ± 0.04	0.55	100±1.3	100.224±0.449	126±63	4
A8	2.6±0.0	5.0 ± 0.04	0.37	101±1.4	99.44 ± 0.02	95±24	9
A9	2.6±0.0	4.9 ± 0.02	0.32	103±1.6	100.224±0.449	60±2.08	12
F1	2.6±0.0	5.0 ± 0.02	0.65	100±1.5	98.92 ± 0.07	67±1.45	9
F2	2.533±0.05	5.0 ± 0.04	0.46	103±1.2	99.12 ± 0.04	60±2.08	14
F3	2.566±0.05	4.9 ± 0.02	0.63	101±1.5	99.44 ± 0.02	60±2.08	15
F4	2.6±0.0	4.8 ± 0.02	0.47	100±1.4	99.12 ± 0.04	69±2.53	18

Table.3: Evaluation of core tablets of Cefpodoxime proxetil:

Also the batch A5 gave the least lag time among the above 3 batches, about 60sec . Due to this it was selected for the further optimization studies. Then the batches F1-F4 were formulated by varying the concentration of HPMC and concentration of Xanthan gum.

The batches of the compression coated tablet was evaluated and compared with marketed tablet on the parameters of thickness, friability, weight variation and drug content. It gave the satisfactorily comparable results. Also the disintegration time of the coating layer tablet of all the batches was around 60-70 mins. This signifies that around 50% of the drug will be released in the first 2 hrs after administration . (Table 4)

Batches	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content (%)	Disintegration time of coating tablet (mins)
A1	4.27±0.01	0.2134	303.4±0.76	98.13 ± 0.12	68
A2	4.173±0.02	0.3513	302.7±0.46	97.36±0.15	64
A3	4.16±0.045	0.2895	304.63±0.3	102.5±0.46	76
A4	4.27±0.01	0.197	304.7±0.75	100.4±0.45	63
A5	4.27±0.01	0.499	302.43±0.5	100.64±0.5	68
A6	4.16±0.045	0.375	304.43±0.54	102.32±0.343	67
A7	4.173±0.02	0.436	302.53±0.47	99.56±0.45	65
A8	4.086±0.04	0.3427	303.72±0.54	98.4±0.27	59
A9	4.086±0.04	0.432	302.46±0.74	99.3±0.5	71
F1	4.27±0.01	0.2895	302.25±0.35	100.3±0.45	59
F2	4.16±0.045	0.2654	304.28±0.5	102.6±0.5	66
F3	4.16±0.045	0.235	303.75±0.53	99.5±0.54	68
F4	4.173±0.02	0.653	303.56±0.6	98.35±0.5	58
Marketed	2.56±0.02	0.265	303.37±0.5	99.56±0.5	---

Table.4: Evaluation of compression coated tablets and marketed tablet:

Batches	First order		Zero order		Higuchi matrix		Korsmeyer-peppas	
	Equation	R^2	Equation	R^2	Equation	R^2	Equation	R^2
A5	y = 0.059x + 1.364	0.838	y = 6.685x + 19.83	0.986	y = 25.51x + 2.538	0.963	y = 0.52x + 1.400	0.979
F1	y = 8.822x + 19.48	0.983	y = 0.080x + 1.382	0.994	y = 22.92x + 11.74	0.836	y = 0.563x + 1.407	0.949
F2	y = 0.063x + 1.353	0.958	y = 6.700x + 18.17	0.998	y = 22.26x + 6.205	0.913	y = 0.548x + 1.350	0.977
F3	y = 0.062x + 1.266	0.918	y = 5.930x + 14.01	0.998	y = 22.18x - 0.322	0.936	y = 0.604x + 1.246	0.985
F4	y = 0.061x + 1.193	0.881	y = 4.780x + 12.74	0.992	y = 18.10x + 0.696	0.953	y = 0.592x + 1.180	0.990

Table5: Correlation coefficients (r^2) values of different kinetic models:

Comparision of the Floating time of the different Batches:

The comparative floating time of the different batches are given in Figure. 3.
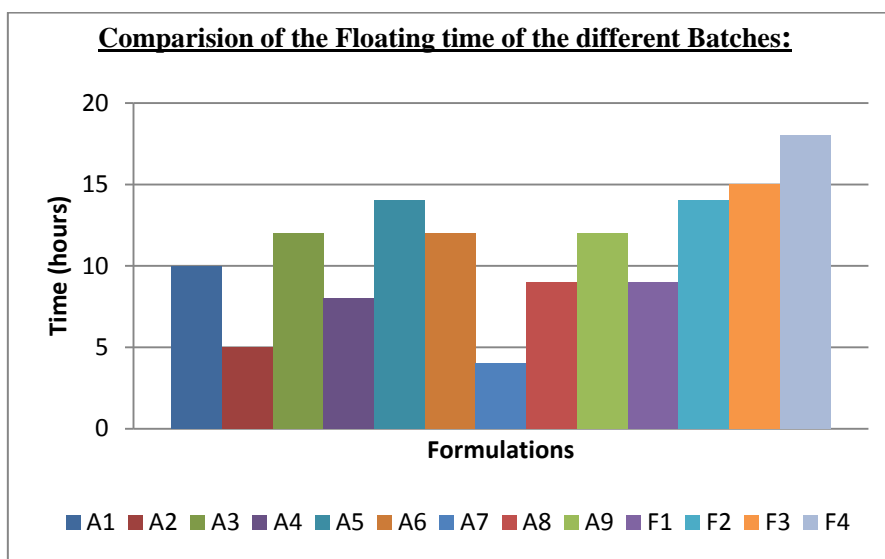

Figure.3: Comparative study of the duration of tablet floating

Drug release kinetics of compression coated formulations.

The release kinetics was estimated by fitting the in-vitro dissolution data the different kinetic models. Figure 4.
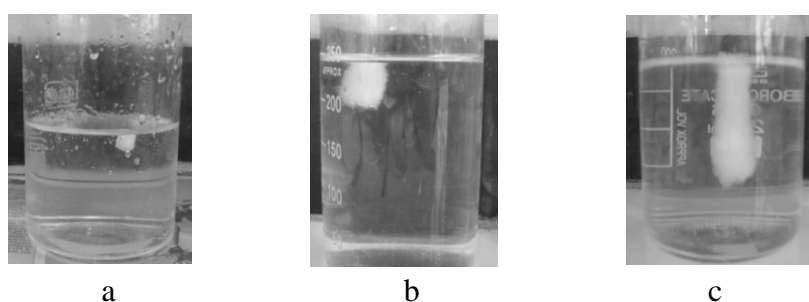

Figure.4: Floating of tablet at a) 0min; b) 6hrs; c) 12hrs

All the above batches show good regression analysis (R^2) value for zero order kinetics. This suggests that the formulation follows zero order model for the drug release.

The Batch F3 gave the most satisfactory result with respect to dissolution profile. It is seen in the above graph that the drug concentration reaches the therapeutic window within an hour of administration and then the drug release continues for the next 12hrs. This gives a sustained effect. (Figure 5, 6)
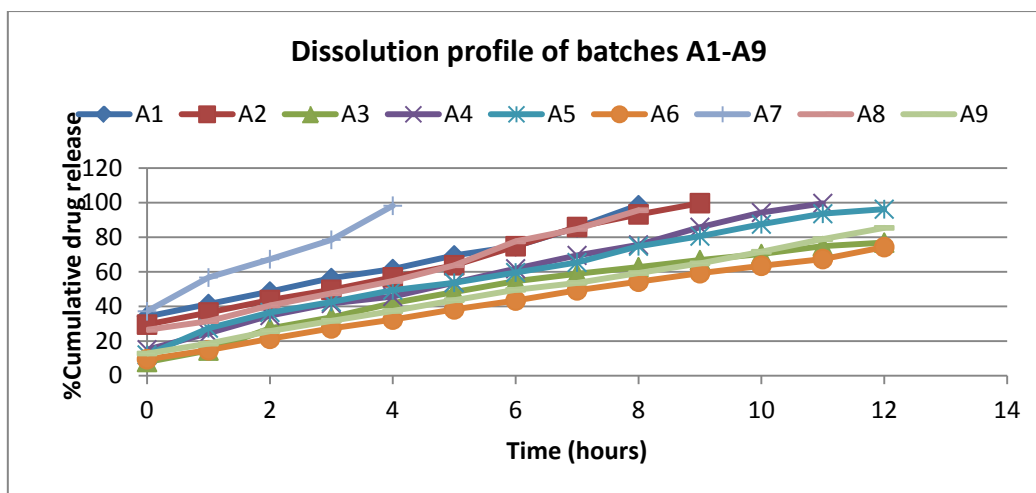
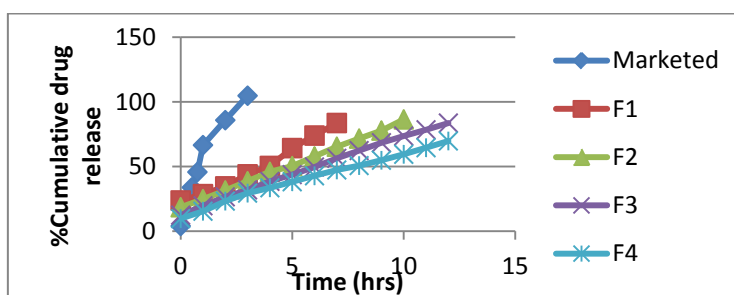Figure.5: Dissolution profile of batches A1to A9

Figure. 6: Dissolution profile of optimized batch with marketed preparation

Data Analysis and Development of Polynomial Equation by Factorial design:

The optimization study of the formulation was carried out using Design Expert software.

Statistical second order model interaction and polynomial terms were generated for the response variable. The 3D response curve and 2D contour plot were also generated.

The equation derived for the time required for 80% drug release of the factorial formulations is:

Response = 10.75 + 1.25A + 2.25B -0.25AB

Where; Response – time for 80% of drug release.

       A- Concentration of HPMC.

       B- Concentration of Xanthan gum.

The + sign of both the factors indicate that they are directly proportional to the response.

That is as the concentration of HPMC and Xanthan Gum increases the time for the drug release also increases correspondingly. (Figure 7)
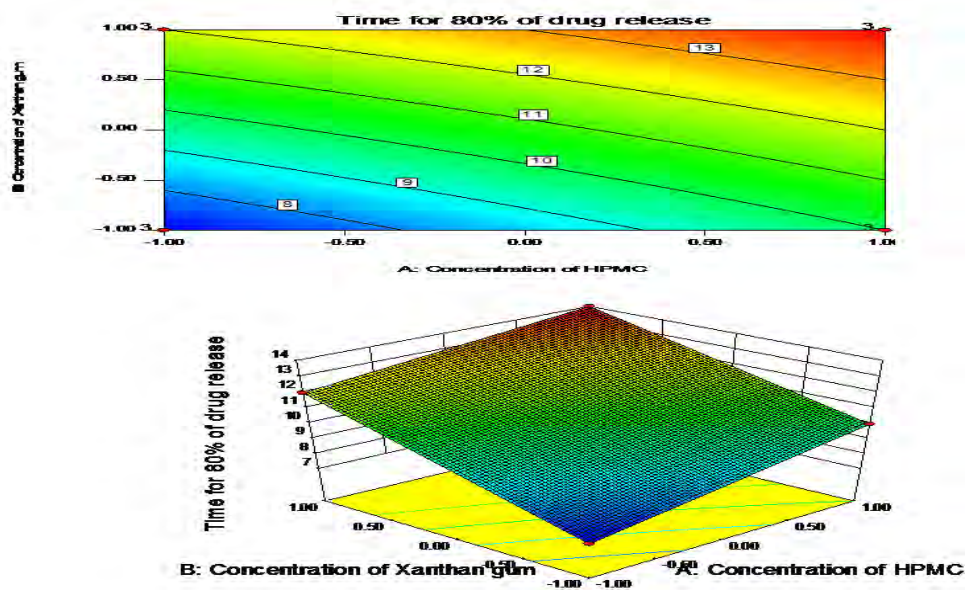
Figure 7: Contour plot and Response surface plot showing effect of factorial variables:

Conclusion:

The system consist of drug containing core gastro retentive floating tablet which is coated with upper layer of drug containing fast dissolving tablet. The outer coat dissolves in the first 10 mins, thus bringing the plasma drug concentration in the therapeutic window. Then the core tablet eventually floating in the GIT over a period of 12 hours slowly releases the drug to maintain the plasma drug concentration in the therapeutic window over the period.

A 2^2 full factorial design was studied that revealed that the concentration of HPMC and Xanthan gum significantly affects the dependent variable.

ACKNOWLEDGMENT:

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