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FORMULATION AND EVALUATION OF COLON TARGETED CHRONOMODULATED DRUG DELIVERY OF DOXOFYLLINE FOR THE TREATMENT OF NOCTURNAL ASTHMA

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ABSTRACT

The main purpose of present investigation was to formulate and evaluate a colon targeted chronomodulated drug delivery system of drug to achieve it's time specific release. Colon targeted drug delivery delivers the drug at specific site where in both local and systemic drug delivery can take place. Various novel approaches for colon targeted drug delivery include prodrug, pH & time dependent systems, and microbially triggered system. Chronomodulated drug delivery system are of interest as they deliver the drug at right site of action at the right time and in the right amount which provides more benefits than conventional dosage forms and increasing patient compliance. This system based on the circadian rhythms of the body and the release of the drug as a pulse after lag time has to be developed in such a way that a complete and rapid drug release follows the lag time. Core tablet was prepared by using xanthan gum, sodium starch glycolate, magnesium stearate and talc by direct compression. Tablets were further coated with pH sensitive polymer like HPMC K4M by compression coating technique and enteric coated tablet was prepared by Eudragit L100. Finally the tablet was coated with the organic solvent ethanol, acetone by using dip coating technique. Tablets were evaluated for hardness, friability, weight variation, drug content and in vitro drug release. The hardness of tablet was found to be 5.2±0.83 to 4.0±0.55, friability 0.45±0.07 to 0.29±0.04 and weight variation 450±0.46 to 282±0.29. The lag time (t10) and percentage drug release at 7.9 hour and time required for release 87.9 of drug were selected.

Keywords: Chronomodulated delivery, Colon targeting, circadian rhythms, Eudragit L 100

1. INTRODUCTION

Over recent years, controlled and targeted drug delivery has been dominating over the conventional dosage forms. Such system has been concentrated on constant, variable and sustained drug delivery system to target the specific site. However certain disease conditions occur during specific time of day or night so the conventional dosage form does not release in a suitable pattern. These conditions demand release of drug as a "pulse "after a predetermined lag time which has to be developed in such a way that a complete and rapid drug release follows the lag time. Such system is known as Chronomodulated drug delivery system. It is also known as chronomodulated drug delivery system or pulsatile drug delivery system [1].

Chronomodulated drug delivery system is based on circadian rhythm of the human body. Circadian rhythm regulates many functions in human body like metabolism, sleep pattern, behavior and hormone production. Disease requiring by chronomodulated deliver system are asthma, arthritis, cardiovasculardisease, diabetes mellitus, hypercholesterolemia and peptic ulcer. Such disease have predictable cyclic rhythms of the body is play an important role, pharmacokinetics and or pharmacodynamics of the drug is not constant within 24 hrs [2].

Colon targeted drug delivery has been important to deliver a variety of therapeutic agents for both local and systemic administration. The release of drug in colon is useful in the treatment of nocturnal asthma, angina, and arthritis, in the local treatment of colonic disease like ulcerative colitis, colorectal cancer and croh's disease. These conditions worsen at night with acute exacerbation being most common. A lag time of 5 hours is sufficient since gastrointestinal transit time is 3-4 hours. Various approaches are developed to increase the stability of release of drug from the colon are pH dependent delivery, pressure dependent delivery, Bacteria dependent delivery and Time dependent delivery [3].

Nocturnal asthma is two-thirds of asthmatic diseases which suffer from night time exacerbation of the symptoms like wheezing, chest tightness, increased airways responsiveness and worsening of lung function. These symptoms occur between midnight and 8:00 am, especially around 4:00 am. So it is inconvenient to take medicine at midnight because the patient is sleeping. The maintenance of constant drug level is not always required for optimal therapy. A drug should be delivered only in the minimum required dose needed [4].

Thus present study was developed for chronomodulated drug delivery system of doxofylline. Doxofylline is a new methyl xanthine derivative for the treatment of nocturnal asthma. It contained a dioxalone ring in place 7 which differ it from theophylline. It inhibits phosphodiesterase IV activities which are responsible for Broncho dilating effect. It has comparatively better safety profile over theophylline for the treatment of asthma and chronic obstructive pulmonary ailment due to reduced affinities approaching adenosine A1 and A2 receptor. It belongs to class 3 according to BCS classification. It was aimed to have lag time of 6 hours *i.e.* the system is to take medicine at bedtime and the release of drug after a period of 6 hours *i.e.* at 4:00 am occurs, when the nocturnal asthma is more prevalent [5].

The current study was development of a press coated pulsatile tablet of doxofylline for the treatment of nocturnal asthma. The proposed system consists of the core tablet with two layer tablet. Firstly core tablet is prepared by direct compression further the second layer is prepared by press coated technique. The direct compression coated tablet to prevent drug release in the stomach, had an additional lag phase to retard the drug release in the intestine, and to deliver drug specifically in the colon. Enzyme and pH controlled delivery system is used for the formulation development. Enzyme dependent polymer like Xanthan gum which mainly occur from carbohydrates source and they show some solubility in the aqueous medium and show a premature release before colon hence this is avoided by using pH dependent polymer like Eudragit S-100. Finally the coated tablets were evaluated for *in-vitro drug* release profile.

2. MATERIALS AND METHODS

Doxofylline IP was gifted by windlass Pvt, Ltd, Dehradun, India. Xanthan Gum, Sodium starch glycolate, Magnesium sterate, Talc, HPMC K4 M and Eudragit L100 were obtained from Central Drug House Pvt, Ltd, India.

2.1. Identification of drug

Identification of Doxofylline was carried out by Infra-Red Absorption Spectroscopy (FT-IR) and compared with standard IR Spectrum of Doxofylline.

2.2. Preformulation Studies

2.2.1. Determination of λmax of doxofylline

From the standard stock solution 10µg/ml was scanned under spectrum mode for 200-400nm wavelength range and a sharp peak was obtained at 276nm.

2.2.2. Preparation of standard curve in different solvents

2.2.2.1. Preparation of standard stock solution

Calibration curve of the drug was prepared into different solvents such as water, acetone and phosphate buffer (pH 6.8). Ten (10) mg of drug was weighed and dissolved in 100 ml of solvent. This solution was marked as the stock solution. From stock solution dilutions having concentration 5µg/ml, 10µg/ml, and 15µg/ml, 20µg/ml, 25µg/ml, 30µg/ml (Beer's Range 5-30µg/ml) were prepared. These dilutions were observed in UV-Spectrophotometer and absorbance was measured.

2.2.2.2. Preparation of standard curve

From the standard stock solution fresh aliquots were pipetted out and suitably diluted with purified water, phosphate buffer (pH 6.8) separately to get final concentration in the range of 5-30µg/ml. The solutions were scanned under spectrum mode for 200-400nm wavelength range and sharp peak was obtained at 276nm. A calibration curve was plotted taking an absorbance on y-axis against concentration of standard solution on x-axis.

2.3. Formulation

2.3.1. Formulation of core tablet

The inner core tablets were prepared by using direct compression method. Powder mixture of doxofylline was weighed and mixed with xanthan gum, microcrystalline cellulose, sodium starch glycoate for 15 min, followed by addition of magnesium stearate and talc as lubricant. The mixture was further blended for 10 min, 150 mg of resultant powder blend was compressed using hydraulic pressure, with 6 mm punch and die to obtain the core tablet. The formulations were named as A1, A2, A3, A4, and A5.

Table 1: Composition of core tablet of doxofylline

		Formulation code				
S.NO	**Ingredients**	**A1**	**A2**	**A3**	**A4**	**A5**
1.	Doxofylline	100	100	100	100	100
2.	Xanthan gum	80	70	60	50	40
3.	Sodium Starch glycolate	10	20	30	40	50
4.	Magnesium Stearate	6	6	6	6	6
5.	Talc	4	4	4	4	4
6.	Total (mg)	200	200	200	200	200

2.3.2. Formulation of Press Coated Pulsatile Tablet

The core tablet was compression coated with different quantities of coating material containing different ratio of HPMC K4M. Powder blend for press-coated tablet was prepared by press coating technique.

Polymers were weighed and dry blended at about 10 min and used as press-coating material to prepare press-coated pulsatile tablets, A1, A2, A3, A4, and A5 respectively. Half of the quantity of the coating polymer was placed in the die cavity, the core tablet was carefully placed in the center of the die cavity and filled with the other half quantity of coating polymer. The coating material was compressed using 12 mm flat punch by using 12 station rotary tablet compression machine.

Table 2: Composition of Press coating Tablet

Ingredients	**Core tablet**	**A1**	**A2**	**A3**	**A4**	**A5**
Core tablet	200	200	200	200	200	200
HPMC K4M	-	50	75	100	150	100
Total(mg)	200	250	275	300	350	400

2.3.3. Formulation of Pulsatile Tablet

Above formulation were enteric coated with Eudragit L-100 by dip coating method.

2.3.4. Preparation of coating solution

Coating solution was prepared by different ratios of materials like Eudragit L100. Weighed accurate quantity of polymer were dissolved in mixture of solvents and stirred on magnetic stirrer to get homogenous coating solution. Cellulose acetate phthalate was added in the solution as a plasticizer (1%w/v). After getting homogenous coating solution final coating of tablet was done.

2.3.5. Coating with Eudragit L100

Coating was done using Eudragit L100. Five formulations were formulated by varying the weight gain on tablet upon coating. The coated tablets were evaluated for *in-vitro* drug release profile as shown in table no. 3.

Table 3: Composition of coating dispersion

Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**
Eudragit L100(mg)	20	20	20	20	20
Di-butyl phthalate(mg)	3	3	3	3	3
Acetone(ml)	200	200	200	200	200

2.4. Evaluation Parameters of Press coated Pulsatile Tablet

Core and compress coated tablets were evaluated for post compression parameters such as weight variation, hardness, thickness, friability test, in vitro drug release study.

2.4.1. Weight variation test

USP weight variation test is done by weighing 10 tablets individually, calculating the average weight comparing the individual weights to the average. The tablets met the specification that not more than 2 tablets were outside the percentage limits and no tablet differed by more than 2 times the percentage limit. The official limits of percentage deviation of tablet are presented in the table 4.

Table 4: Weight variation limits

Average weight of tablet (mg)	**Maximum % difference allowed**
80 mg or less	10
More than 80 mg	7.5
250 mg or more	5

2.4.2. Hardness test

The hardness of each tablet was done by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. Three (03) tablets were chosen randomly and tested for hardness. The average hardness of 03 tablets was noted. As per I.P, the hardness must be lies within specified limits i.e±5 kg/cm^2.

2.4.3. Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was done by checking the thickness of ten tablets of each formulation.

2.4.4. Friability

Twenty (20) tablets were weighed and placed in the Roche friabilator apparatus rotated at 25 rpm for 5 minutes. After the revolutions, tablets were dedusted and weighed again. The % friability was less than 1 % in all the formulation ensuring that the tablets were mechanically stable.

The percentage friability was calculated using the formula,

%Friability= Initial weight-Final weight/Initial weight x 100

2.4.5. Disintegration time

Disintegration test was carried out as described under procedure for plain coated tablets in USP. One tablet was placed in each six tubes of the basket of the assembly was positioned in a 1 litre beaker containing pH 1.2 buffer solution at 37°C±1°C such the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablet was noted.

2.4.6. In vitro drug release study

Dissolution testing of pulsatile delivery system was done by USP dissolution test apparatus type II. The 900 ml of pH 1.2 was used as dissolution medium for 2 hrs. (because gastric emptying time is 2 hrs) and the dissolution medium was replaced at pH6.8 (because intestinal emptying time is 3 hrs) and the dissolution medium was replaced at pH7.4 for the remaining time for drug release at 37±0.5°C. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5ml of sample was pipette out at predetermined time interval and the 5ml of the fresh medium was added to maintain the sink condition. The sample was analyzed spectrophotometrically at 273nm against suitable blank using UV-visible spectrophotometer.

2.4.7. In vitro kinetic study

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q0-Q) v/s t], and Hixson Crowell plot (1-Q) $^{1/}{}_{3}$v/s t) Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

In short, the results obtained from *in vitro* release studies were plotted in four Kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time **(zero order rate kinetics)**
- Log cumulative percentage drug retained Vs. Time **(first order rate kinetics)**
- Cube root of percentage drug remainingVs time **(Hixson Crowell plot**)
- Log of cumulative percentage drug release Vs. log Time **(Peppas exponential equation)**

3. RESULTS AND DISCUSSION

The current study was development of compression coating of Doxofylline formulation for colon targeting by using microbially triggered drug delivery to colon approach using for Xanthan gum, HPMC K4 M and enteric coating polymer like Eudragit L100. All the formulations were evaluated for the physicochemical properties and *in-vitro* drug release studies.

3.1. Preformulation studies

3.1.1. Identification of drug

FTIR was performed by Diamond ATR (model no. 630). Solids are generally best analyzed on the single reflection ATR accessories; diamond being the preferred choice for most applications because of its robustness and durability.

3.1.2. Preparation of standard curve

Graph of Doxofylline was taken in phosphate buffer pH 1.2, pH 6.8, and pH7.4.

From the above results of post compression parameter of core tablet, weight deviation is less than 5%. So it indicates there was no significant weight variation in the core tablet. Hence, all the tablet formulations were passed the weight variation test. The hardness test of all the formulations indicated good mechanical strength. Friability of all the formulations were less than 1% indicates the tablet had good mechanical resistance. Drug content of all the formulations was found to be uniform.

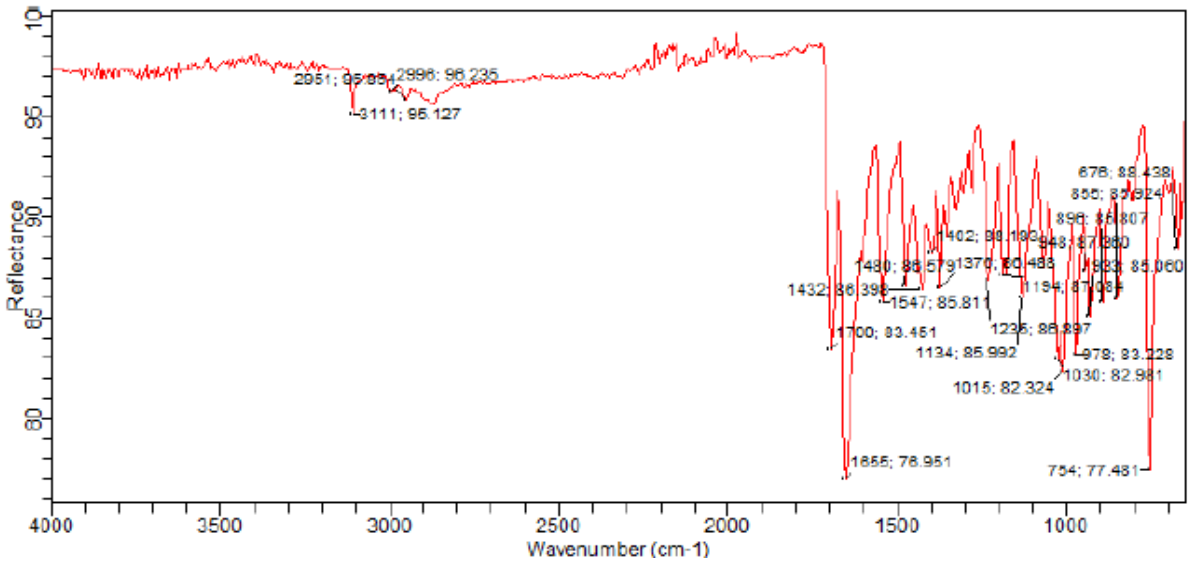

Fig. 1: IR Spectra of doxofylline

Table 5: Standard curve of doxofylline in different pH

Concentration(µg/ml)	Absorbance in pH 1.2	Absorbance in pH 6.8	Absorbance in pH 7.4
0	0	0	0
5	0.128	0.131	0.131
10	0.283	0.254	0.252
15	0.430	0.420	0.379
20	0.578	0.584	0.535
25	0.712	0.740	0.740
30	0.854	0.892	0.897

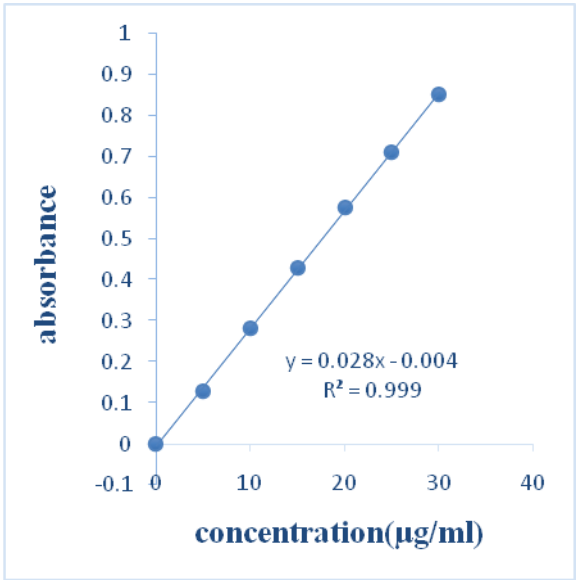

Fig. 2: Standard curve of doxofylline in pH 1.2inpH 6.8

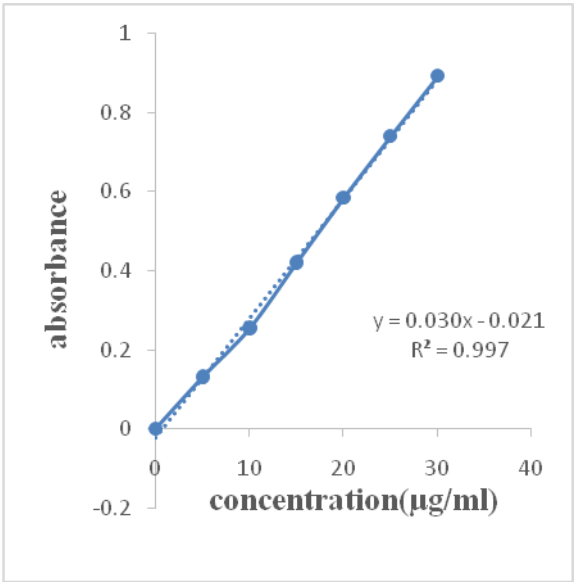

Fig. 3: Standard curve of doxofylline

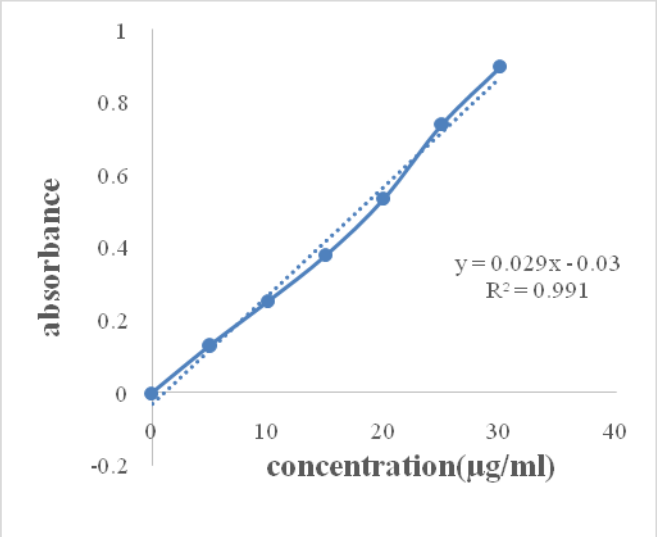

Fig. 4: Standard curve of doxofylline in pH7.4

The results of *in-vitro* disintegration time of core tablet was found that as the percentage of super disintegrating increase (2 to 6%) the disintegration time is 19 sec was observed with formulation A1 containing 10% sodium starch glycolate. Formulation A1 containing 10% sodium starch glycolate was selected and optimized core tablet was used for the preparation of compress coated tablet.

From the above results of post compression parameters of core tablet, weight deviation was less than 5% which indicates there was no significant weight variation in the core tablet. Hence, all the tablet formulations were passed the weight variation test. The hardness test of all the formulations indicates good mechanical strength. Friability of all the formulations was less than 1%, indicates the tablet had good mechanical resistance. The tablet thickness of all the formulations was found to be 4.6±0.72 to 3.9±0.63.

Table No 6: Post compression parameter of core tablet

Formulation code	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Drug content (%)	Disintegration time (sec)
A1	256±0.28	3.8±0.67	1.6±0.05	0.26±0.06	98.2±0.18	25±0.19
A2	254±0.21	3.6±0.42	1.4±0.08	0.24±0.02	97.5±0.11	22±0.18
A3	253±0.13	3.4±0.68	1.0±0.09	0.28±0.05	96.3±0.17	24±0.20
A4	252±0.19	3.2±0.55	1.2±0.03	0.29±0.04	95.2±0.12	23±0.27
A5	251±0.09	3.5±0.59	1.1±0.01	0.25±0.03	92.3±0.19	20±0.16

Table 7: *In-vitro* quality control parameter for compression coated tablet

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)
A1	450±0.46	4.6±0.72	5.2±0.83	0.45±0.07
A2	359±0.32	4.2±0.76	4.9±0.73	0.39±0.05
A3	350±0.39	4.3±0.73	4.6±0.79	0.35±0.08
A4	300±0.30	4.0±0.70	4.3±0.34	0.32±0.05
A5	282±0.29	3.9±0.63	4.0±0.55	0.29±0.04

Table 8: *In-vitro* drug release profile for coated formulation

	Formulation code				
Time (hr)	A1	A2	A3	A4	A5
0	0	0	0	0	0
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	21.2	19.8	12.4	9.35	15.3

	Formulation code				
Time (hr)	A1	A2	A3	A4	A5
7	32.1	23.5	20.1	17.2	29.6
7.1	45.6	36.4	29.8	29.3	36.2
7.2	55.6	42.5	36.2	36.9	46.3
7.3	65.2	51.2	45.1	42.1	52.4
7.4	69.2	59.6	56.2	49.6	59.8
7.5	74.5	62.3	62.2	52.2	63.3
7.6	79.2	69.1	69.6	59.6	69.9
7.7	82.5	72.3	74.3	60.2	76.2
7.8	84.5	79.1	80.2	69.3	80.3
7.9	87.9	86.5	83.2	80.2	85.2

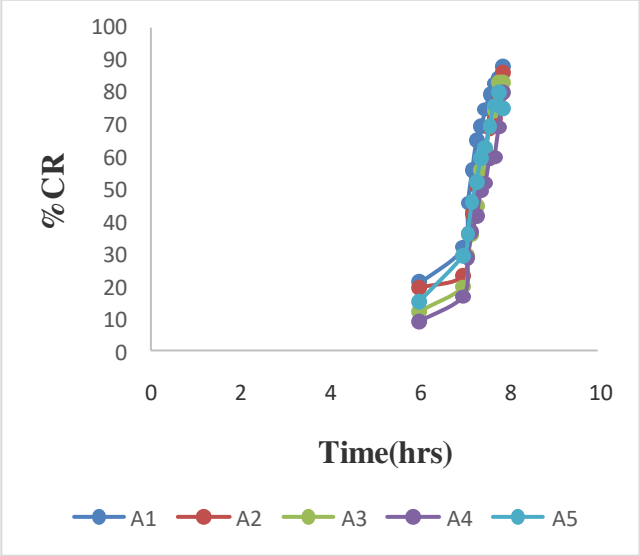

Fig. 5: Zero order kinetics (A1-A5)

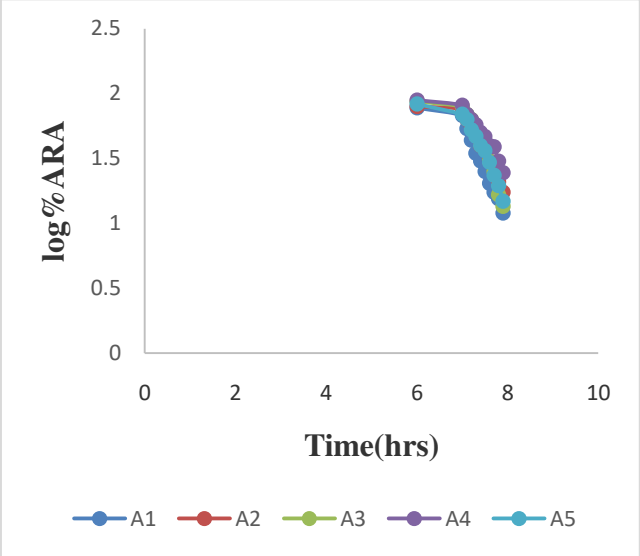

Fig. 6: First Order kinetics (A1-A5)

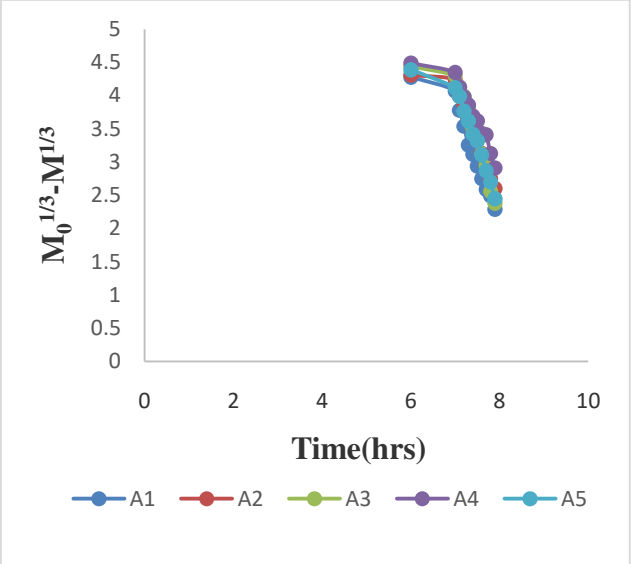

Fig. 7: Hixson Crowell Model (A1-A5)

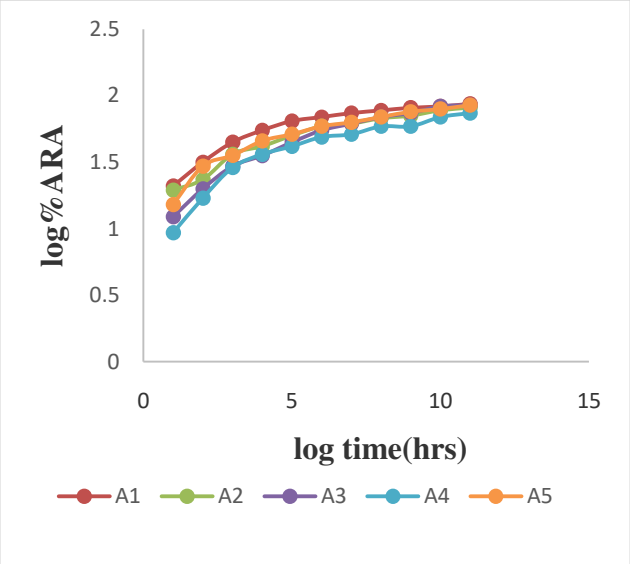

Fig. No 8:Korsmeyer Peppas kinetic (A1-A5)

Table 9: Kinetic Value of Doxofylline from Press coated Pulsatile tablet

Formulation	R^2			Peppas kinetic N-value	Best fit Model
	Zero order	First order	Hixson Crowell		
A1	0.6374	0.4398	0.5062	5.6347	Zero order
A2	0.5712	0.4001	0.4564	5.8606	Zero order
A3	0.4768	0.3170	0.3695	7.8586	Zero order
A4	0.5079	0.3851	0.4267	8.1211	Zero order
A5	0.5783	0.3919	0.4542	6.6881	Zero order

It was found that formulation A1 which is containing HPMC (50mg) and Eudragit L 100 (20mg) shows 87.9 % release in 7.9 hrs. So it was concluded that A1 shows maximum release of drug because lowering level of polymer weight in coating layer. From release profile of all the formulations it was observed that drug release from tablet was inversely proportional to coat weight. Hence the drug release was highly retarded in formulation A5 which higher level of coat weight (200 mg). Batch A1 formulation has better rate of drug relase as compared to other formulations.

4. CONCLUSION

In the present research work the formulation of Doxofylline targeted to colon by various polymers developed. Pulsatile tablets were prepared in two steps. Initially, the core tablet was prepared by using natural polymer i.e. Xanthan Gum and then tablet was coated by using different pH dependent polymers like HPMC K4M, and enteric coating polymer like Eudragit L 100. On the basis of hardness, thickness, disintegration time, friability, *in-vitro* release studies and kinetic data of the core tablet A1 was selected to optimize for the formulation of pulsatile press coated tablet. Further the pulsatile press coated tablets of doxofylline were developed which satisfactory complies all the evaluation parameters. The tablets passed all the tests. During *In vitro* release profile among all the formulations A1 showed maximum release of drug i.e. 87.9 % in 7.9 hrs because of lowering level of polymer weight in coating layer. The release of doxofylline drug from the pulsatile press coated tablet follows Zero order kinetics. It means the drug be immediately release and won't follow diffusion.

5. ACKNOWLEDGEMENT

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