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DESIGN AND EVALUATION OF COMPRESSION COATED COLON TARGETED TABLETS OF KETOROLAC TROMETHAMINE BY USING NATURAL POLYMERS AND THEIR COMBINATION WITH HPMC K100M

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ABSTRACT

The objective of the present research study is to develop compression coated tablets of Ketorolac Tromethamine (KTM) with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to achieve maximum drug release in the physiological environment of colon by applying Natural polymers like Xanthan Gum, Guar Gum, Karaya Gum and Combination of Xanthan Gum/ Guar Gum with Hpmc K100M as a compression coat over the KTM core tablets. The prepared tablets were evaluated for their pre and post compression parameters. In vitro drug release studies were conducted in pH1.2 buffer, phosphate buffer (pH7.4) and in enzyme free simulated intestinal fluid (pH6.8) and also in pH6.8 PBS containing 2%, 4% w/v of rat caecal contents. A significant difference was observed in the amount of KTM released at the end of 24hr of the dissolution study with rat caecal content medium when compared to the dissolution study without rat caecal contents.

KEYWORDS

Ketorolac Tromethamine, Simulated intestinal fluid, Phosphate buffer saline and Rat caecal contents.

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INTRODUCTION[1-6]

Pharmaceutical industry, now a days is confronting several issues and challenges owing to global competition and increasing demand for better products. The existing trend in pharmaceutical industry is to develop marked formulations of old active molecules with the support of latest formulation technologies on account of high expenses and longer duration of requirement in the new drug development. Substantial attention is

being laid to expand the advanced systems in delivery of active pharmaceutical ingredients (API). In spite of extraordinary advancements in drug delivery, the oral systems are believed as the suitable and better to administrate the therapeutic agents. This is due to the low cost involved and also the aspect of easiness involved in administration that leads to superior degree of conformity to the patient.

During the last twenty years, the Pharmaceutical scientists extensively probed in the area of colonic region for targeted drug delivery system. An ideal drug delivery system specifically to the colon avoids the drug release in stomach and small intestine, but begins delivery at the beginning of the large bowel where conditions are most favourable for drug dispersion and absorption.

However nowadays, colon is largely acknowledged as one of the sites for drug delivery because of the following preferential benefits:

1. Colon contains only fewer amounts of digestive enzymes and diminishes the possibility of drug degradation and considered as safe when compared to small intestine.
2. Colon targeting gives the efficient treatment of the disease at lesser dose with minimum side effects.

Ketorolac tromethamine (KTM) is a class of non steroidal anti inflammatory drug and non selective COX inhibitor. It has more pronounced analgesic activity and also used for the treatment of local disorders like IBD and also has short half life. If KTM releases in the upper GI tract it leads to gastric and duodenal toxic effects.

The objective of the present research study is to develop compression coated tablets of KTM with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to achieve maximum drug release in the physiological environment of colon by applying Natural polymers like Xanthan Gum, Guar Gum, Karaya Gum and combination of Xanthan Gum/ Guar Gum with Hpmc K100M as a compression coat over the ketorolac tromethamine core tablets.

MATERIAL AND METHODS

MATERIAL

Ketorolac Tromethamine was obtained as a gift sample from Drugs control office Hyderabad, Telangana and all the remaining Excipients were procured from SD Fine Chemicals Mumbai. Healthy male albino rats were obtained from Mahaveer enterprises Hyderabad.

METHOD

Direct Compression Method.

Preparation of Compression Coated KTM Tablets

Preparation of KTM Core Tablets

Ketorolac Tromethamine core tablets (70 mg) were prepared by direct compression method. The drug and remaining excipients were passed through a sieve before their use in the formulation. All the ingredients were added according to the formulae given in Table No.1, thoroughly mixed and then directly compressed into tablets using 6mm round, flat and plain punches on a 12 station tablet machine (Cadmach, Ahmedabad).

Compression Coating of KTM Core Tablets

The core tablets were compression coated with different quantities of coating materials as shown in Table No.2. Half the quantity of the coating material was placed in the die cavity, the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed using 9 mm round, flat and plain punches on a 12 station tablet machine (Cadmach, Ahmedabad).

Evaluation of Micromeritic properties of granules (pre compression parameters)

Angle of Repose

The angle of repose was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured.

The angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h / r)$$

Where 'h' and 'r' are the height and radius respectively of the granule cone.

Bulk Density (BD)

An accurately weighed granules from each formula was slightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the granules was measured which gave bulk volume. The loose bulk density (BD) of granules was determined using the following formula.

Bulk density = Total weight of granules / Total volume of granules

Tapped bulk density (TBD)

An accurately weighed granules from each formula was slightly shaken to break any agglomerates formed and it was then introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula.

Tapped bulk density = Total weight of granules / Total volume of tapped granules

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density

$$H = D_t / D_b$$

Where H is the Hausner's ratio, Dt is the tapped density of the granules and D_b is the bulk density of the granules.

Carr's Compressibility Index

It is a simple index that can be determined on small quantities of granules. The compressibility indices of the formulation blends were determined using following Carr's compressibility index formula.

Carr's Compressibility Index (%) = Tapped bulk density – Bulk density/ Tapped bulk density× 100

Determination of Physicochemical Parameters of Tablets[7-17]

(Post Compression Parameters)

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. Then each batch passes the weight variation test if not more than two of the individual tablet deviate from the average weight by more than the percentage shown in Table No.3.

Thickness

Ten tablets were selected randomly from each batch and thickness was measured by using screw guage.

Hardness

Hardness was measured by using Monsanto apparatus. For each batch ten tablets were tested. The force is measured in kilograms/cm^2.

Friability

The Lab India FT1020 friability test apparatus was used to determine the friability of the Tablets. Ten pre-weighed Tablets were placed in the apparatus and were rotated at 25 rpm for 4 minutes and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.

% friability was calculated as follows:

$$\% \text{ Friability} = (W_1 – W_2) \times 100/W_1$$

Where W_1 = Initial weight of the 10 tablets.

W_2 = Final weight of the10 tablets after friability.

Friability values below 1.0% are generally acceptable.

Drug content (assay)

Ten tablets were taken and powdered. Powder equivalent to one tablet was taken and dissolved in 50 ml of pH 6.8 phosphate buffer. The mixture was allowed to stand for 5 hr with intermittent sonication to ensure complete hydration of polymer and subsequent solubility of the drug. Then the volume was made up to 100ml. The mixture was filtered and 1ml of the filtrate was suitably diluted. The absorbance of solution was measured by using UV - Visible spectrophotometer (Elico, India) at 320 nm. Each measurement was carried out in triplicate and the average drug content in the tablet was calculated.

***In vitro* Dissolution studies**

The *In vitro* dissolution study was conducted using USP basket type apparatus at a rotation speed of 100rpm and a temperature of 37 ± 0.5^0 C. For tablets,

simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus drug release studies were carried out in the dissolution medium consisting of 900 ml of acid buffer (pH1.2) for first two hours as the average gastric emptying time is about 2hr, phosphate buffer (pH7.4) for next three hours as the average small intestinal transit time is 3hr and finally in enzyme free simulated intestinal fluid (pH6.8) and continued for 24hr to mimic colonic pH conditions. 5ml samples were withdrawn at predetermined time intervals (1 to 24hrs) and the same volume was replaced with fresh medium. The samples were filtered through Whattman filter paper and analyzed by UV spectrophotometer at 320 nm. The percentage drug release was calculated using the calibration curve of the drug in (pH1.2) acid buffer, (pH7.4) phosphate buffer and enzyme free simulated intestinal fluid (pH6.8).

***In vitro* Dissolution studies in the presence of rat caecal contents**

A. Preparation of rat caecal contents

The susceptibility of Xanthan gum coats to the enzymatic action of colonic bacteria was assessed by continuing the release studies in 100ml of 6.8pH phosphate buffer saline (PBS) containing 2%w/v and 4% w/v of rat caecal contents. The caecal contents were obtained from male albino rats after pre treatment for 7 days with Xanthan gum dispersion.

Thirty minutes before the commencement of drug release studies rats were killed by spinal traction, the abdomen was opened, the ceaci were isolated, ligated at both ends, dissected and immediately transferred into 6.8pH PBS, previously bubbled with Co2. The caecal bags were opened and their contents were individually weighed, pooled and then suspended in 6.8pH PBS to give a final caecal dilution of 2% w/v and 4% w/v.

B. Dissolution study procedure

The *In vitro* dissolution study was conducted using USP basket type apparatus at a rotation speed of 100rpm and a temperature of 37 ± 0.5^0C containing 900 ml of acid buffer (pH1.2) for first two hours, phosphate buffer (pH7.4) for next three hours. Then the drug release studies were carried out with slight modification i.e., a beaker (capacity 250ml) containing 100 ml of PBS was immersed in a vessel containing 1000ml of water which was inturn in the water bath of the dissolution apparatus . The tablets were placed in the basket and immersed in the dissolution medium containing rat caecal contents.

The experiment was carried out with the continuous supply of co_2 and the drug release studies were continued for 24hr and 1ml samples were taken at different time intervals and replaced with 1ml of fresh SIF pH6.8 bubbled with Co_2. To the samples 1ml of methanol was added to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes. The volume was made upto 10ml with PBS, centrifuged and the supernatant was filtered and filtrate was analyzed by UV spectrophotometer at 320 nm the above studies were also conducted without rat caecal contents in SIF pH6.8 by following the same conditions mentioned above.

Drug release kinetics

To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to Zero order, First order, Higuchi and Peppas models to ascertain the kinetic modelling of drug release (Table No.4).

RESULTS AND DISCUSSION

Standard graph of KTM was plotted in 0.1N Hcl, pH 7.4 and pH 6.8 and has shown a good linearity with an R^2 values of 0.999, 0.999 and 0.999 respectively which suggests that they follows “Beer- Lambert”s law.

The powder blend of formulations were characterized with respect to Bulk density, Tapped density, Angle of repose, Carr’s index, Hausner’s ratio and the values were shown in Table No.5. Angle of repose was less than 35^0 and Carr’s index was less than 21 for all the batches indicating good to fair flowability and compressibility. Hausner’s ratio was less than 1.25 for all the batches indicating fair flow properties.

The tablets of all formulations were subjected to various evaluation tests such as Weight variation,

Hardness, Thickness, Friability and Drug content. Results were shown in Table no.6. In weight variation test, the pharmacopoeial limit of percentage deviation for the tablets of less than 324 mg is ±7.5 %. The average percentage deviations of all the formulations were found to be within the limits. The hardness ranged from 4.25± 0.57 to 6.5 ± 0.3 kg/cm^2. The thickness of tablets ranged from 3.21± 0.36 to 4.2 ± 0.20 mm. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablets. The drug content was found to be uniform in all formulations and ranged from 95.28 ± 0.8 to 101.22 ± 0.88. Thus all the physical attributes of the prepared tablets were found to be practically within control.

Formulations(F1-F3)containing Xanthan gum were subjected to *invitro* drug release studies in acid buffer (pH1.2), phosphate buffer (pH7.4) and finally in enzyme free simulated intestinal fluid (pH6.8) respectively upto 24hr and the Results were shown in Figure No.1. At the end of 24hr of the dissolution study, all the tablets coated with coat formulations F1-F3 were found intact. From the dissolution data it was observed that all the formulations showed no release at pH1.2 and 7.4 and the release started in pH 6.8 buffer. The percent of drug released at 24hr was 71.76%, 55.53% and 43.54% respectively. As the percentage of polymer increased the drug release was decreased.

Formulations(F4-F8)containing combination of Xanthan gum with HpmcK100M, Guar gum and Karaya gum were subjected to *invitro* drug release studies in acid buffer (pH1.2) phosphate buffer (pH7.4) and finally in enzyme free simulated intestinal fluid (pH6.8) respectively upto 24hr and the Results were shown in Figure No.2. At the end of 24hr of the dissolution study, all the tablets coated with coat formulations F4-F8 were found intact. From the dissolution data it was observed that all the formulations showed no release at pH1.2 and 7.4 and the release started in pH 6.8 buffer. The percent of drug released at 24hr was 75.19%, 65.78%, 67.88%, 67.88%, 42.15% and 93.63% respectively.

Formulations (F9-F11) containing guar gum were subjected to *invitro* drug release studies in acid buffer (pH1.2), phosphate buffer (pH7.4) and finally in enzyme free simulated intestinal fluid (pH6.8) respectively upto 24hr and the results were shown in Figure No.3. At the end of 24hr of the dissolution study, all the tablets coated with coat formulations F9-F11 were found intact. From the dissolution data it was observed that all the formulations showed no release at pH1.2 and 7.4 and the release started in pH6.8 buffer. The percent of drug released at 24hr was 94.98%, 87.24% and 77.24% respectively. As the percentage of polymer increased the drug release was decreased.

Formulations (F12 and F13) containing combination of Hpmc K100M with Xanthan gum, Guar gum were subjected to *invitro* drug release studies in acid buffer (pH1.2), phosphate buffer (pH7.4) and finally in enzyme free simulated intestinal fluid (pH6.8) respectively upto 24hr and the results were shown in Figure No.4. At the end of 24hr of the dissolution study, all the tablets coated with coat formulations F12 and F13 were found intact. From the dissolution data it was observed that all the formulations showed no release at pH1.2 and 7.4 and the release started in pH 6.8 buffer. The percent of drug released at 24hr was 68.62% and 88.42% respectively.

Invitro drug release studies were also carried out in pH6.8 PBS containing 2%, 4% w/v of rat caecal contents and the Results were shown in Figure No.5-7. The percent of drug released from the formulations F3, F6 and F7 were found to be 98.12%, 98.64% in 24hr and 98.09% in 16hr in the presence of 2% rat caecal contents, where as in the presence of 4% rat caecal contents it was found to be 98.76% in 12hr, 97.91% in 16hr and 97.27% in 12hr the coat remained intact. A significant difference was observed in the amount of KTM released at the end of 24hr of the dissolution study with rat caecal content medium when compared to the dissolution study without rat caecal contents. The coat was almost degraded in the presence of rat caecal contents thereby releasing the drug into the dissolution medium.

The *in vitro* dissolution studies with 2% w/v of rat caecal contents were fitted to Zero order, First order, Higuchi and Peppas models and the Results were shown in Table No.6 The first order plots of all the formulations (F3 and F7) were found to be high as indicated by their high regression values when compared with zero order plots and the formulation F6 was best explained by zero order plots as indicated by their high regression values when compared with first order plot.

Formulations (F3, F6 and F7) showed good correlation in Higuchi Kinetics, clearly indicating that the drug release mechanism was predominantly diffusion controlled. To confirm the exact mechanism of drug release from these tablets, the data were fitted to Korsemeyer equation. The slope values suggested that the release of KTM from all the formulations followed non- fickian diffusion (n>0.50).

Table No.1: Composition of Core Tablet

S.No	Ingredients	Quantity
1	Ketorolac Tromethamine	10
2	Mcc	43
3	Sodium Starch Glycollate	8
4	Sodium Lauryl Sulphate	4
5	Talc	3
6	Magnesium Stearate	2

Total weight of core tablet is 70mg.

Table No.2: Composition of Compression Coating of KTM Tablets

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Xanthan Gum	184	195	207	138	149	161	161	161
2	HPMC K100M	------	-----	-----	46	46	46	-----	-----
3	Guar Gum	------	------	------	------	-----	-----	46	----
4	Karaya Gum	------	-------	------	------	-----	------	-----	46
5	Mcc	41	30	18	41	30	18	18	18
6	Talc	3	3	3	3	3	3	3	3
7	Magnesium Stearate	2	2	2	2	2	2	2	2

S.No	Ingredients (mg)	F9	F10	F11	F12	F13
1	HPMC K100M	-----	-----	-----	161	161
2	Xanthan Gum	-----	-----	------	46	----
3	Guar Gum	184	195	207	----	46
4	Mcc	41	30	18	18	18
5	Talc	3	3	3	3	3
6	Magnesium Stearate	2	2	2	2	2

Total weight of compression coat is 230mg. Total weight of final tablet (core+ compression coat) is 300mg.

Table No.3: Percentage deviation allowed under weight variation test

S.No	Average weight of tablet (mg)	Percent deviation (%)
1	130 (or) less	10
2	130-324	7.5
3	More than 324	5

Table No.4: Drug release kinetics

S.No	Model	Equation
1	Zero Order	$Q = K_0 t$
2	First order	$\text{Log } Q_t = \text{Log } Q_o + K_1 t / 2.303$
3	Peppas model	$Mt/M\infty = kt^n$
4	Higuichi model	$Q = K_2 t^{1/2}$

Table No.5: Results for Derived and Flow Properties

S.No	Formulation Code	Derived properties		Flow properties		
		Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
1	F1	0.21±0.01	0.25±0.01	25.49±0.72	14.74±0.42	1.17±0.01
2	F2	0.3±0.01	0.36±0.02	26.24±0.71	15.38±0.67	1.18±0.04
3	F3	0.27±0.04	0.32±0.02	29.05±0.73	14.28±0.56	1.16±0.02
4	F4	0.34±0.03	0.38±0.02	26.97±0.81	12.11±0.33	1.13±0.01
5	F5	0.32±0.02	0.37±0.05	29.25±0.11	13.82±0.28	1.16±0.11
6	F6	0.32±0.06	0.39±0.04	32.27±0.21	19.39±0.68	1.24±0.03
7	F7	0.52±0.04	0.62±0.04	33.65±0.22	17.17±0.44	1.2±0.03
8	F8	0.51±0.04	0.62±0.02	33.21±0.81	17.38±0.71	1.21±0.02
9	F9	0.42±0.02	0.5±0.01	26.56±0.17	16.6±0.37	1.19±0.1
10	F10	0.48±0.01	0.57±0.03	28.75±0.33	15.9±0.59	1.18±0.02
11	F11	0.47±0.03	0.56±0.04	27.33±0.32	16.07±0.43	1.19±0.02
12	F12	0.52±0.05	0.59±0.01	25.38±0.12	12.52±0.14	1.14±0.04
13	F13	0.41±0.01	0.48±0.01	26.43±0.16	14.69±0.28	1.17±0.01

*** all values were expressed as mean± SD.

Table No.6: Evaluation of Physical Parameters of the Tablets

S.No	Formulation code	Weight Variation(mg) (n=20)	Hardness (Kg/cm^2) (n=10)	Thickness (mm) (n=10)	Friability (%) (n=10)	Drug content (%) (n=10)
1	Core	72±1.2	2.8±0.5	3.45±0.35	0.42±0.02	99.2±1.45
2	F1	295.8±1.48	4.5±0.44	3.22±0.17	0.36±0.01	98.25±1.37
3	F2	300.4±0.54	6.5±0.31	3.37±0.25	0.39±0.01	95.28±0.8
4	F3	298.8±1.64	5.58±0.4	4.14±0.8	0.43±0.03	99.12±2.47
5	F4	306.3±0.41	4.66±0.55	4.2±0.2	0.12±0.01	101.22±0.88
6	F5	307.1±1.14	4.25±0.57	3.38±0.66	0.44±0.02	100.24±1.25
7	F6	301.2±0.83	5.1±0.3	3.33±0.25	0.48±0.03	99.53±1.87
8	F7	302.9±0.67	4.52±0.57	3.24±0.71	0.34±0.01	98.8±1.99
9	F8	305±0.43	6.41±0.6	3.32±0.89	0.37±0.02	95.35±1.14
10	F9	302.5±0.8	5.5±0.44	3.38±0.73	0.37±0.01	96.34±2.18
11	F10	296.2±0.83	5±0.31	4.1±0.68	0.42±0.01	97.29±0.98
12	F11	302.1±0.93	6.08±0.37	3.48±0.88	0.48±0.03	97.35±0.43
13	F12	301.2±0.97	5.41±0.7	3.21±0.36	0.15±0.01	98.88±0.88
14	F13	204.2±0.83	6.33±0.5	3.26±0.46	0.27±0.02	96.7±1.22

*** all values were expressed as mean± SD.

Table No.7: Kinetics Data of All Formulations

S.No	Formulation Code	Zero Order		First Order		Higuchi	Peppas	
		K_0	R^2	K_1	R^2		K_0	R^2
1	F3	5.21	0.846	0.243	0.9005	0.859	0.571	0.863
2	F6	5.01	0.949	0.192	0.9000	0.883	0.953	0.968
3	F7	5.29	0.855	0.267	0.8643	0.856	0.544	0.709

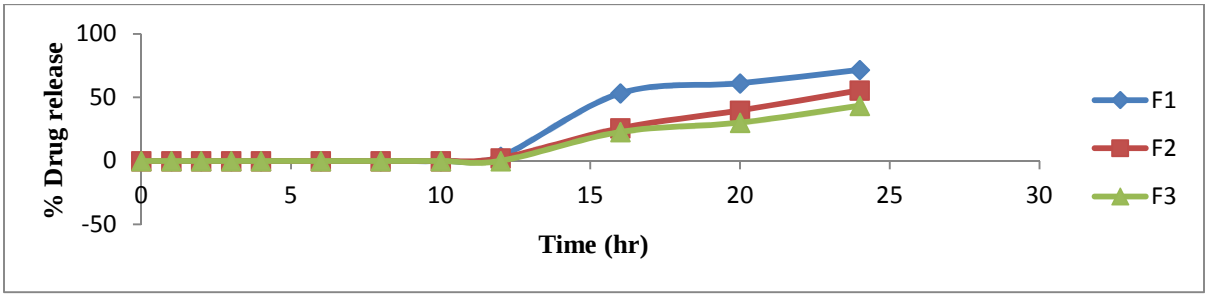

Figure No.1: Comparison of release profiles of F1-F3

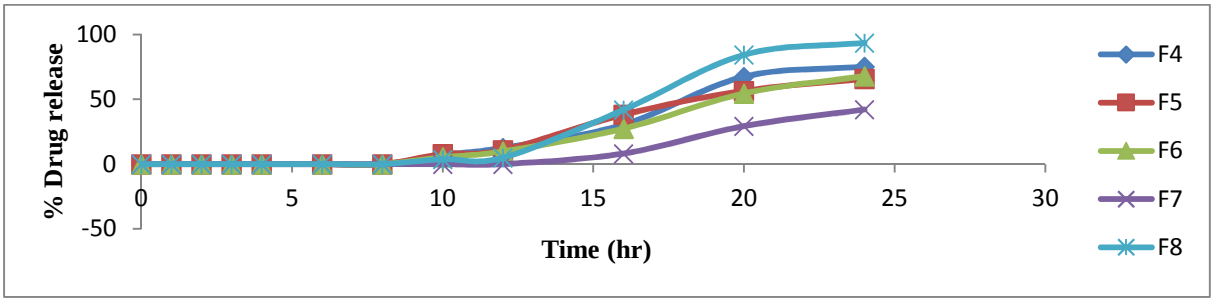

Figure No.2: Comparison of release profiles of F4-F8

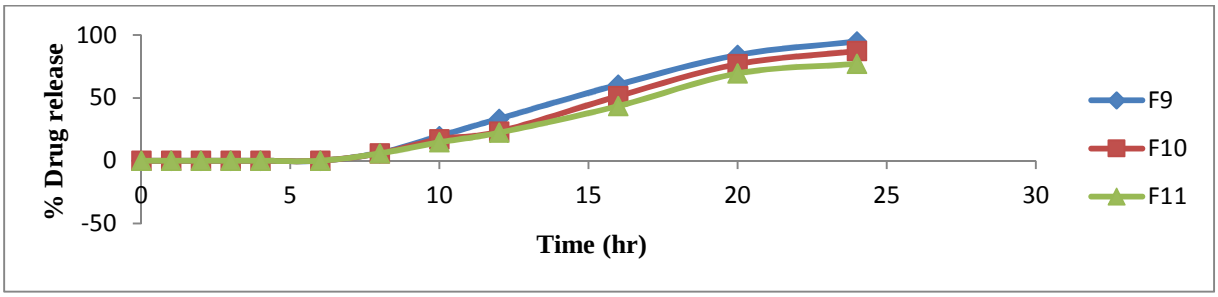

Figure No.3: Comparison of release profiles of F9-F11

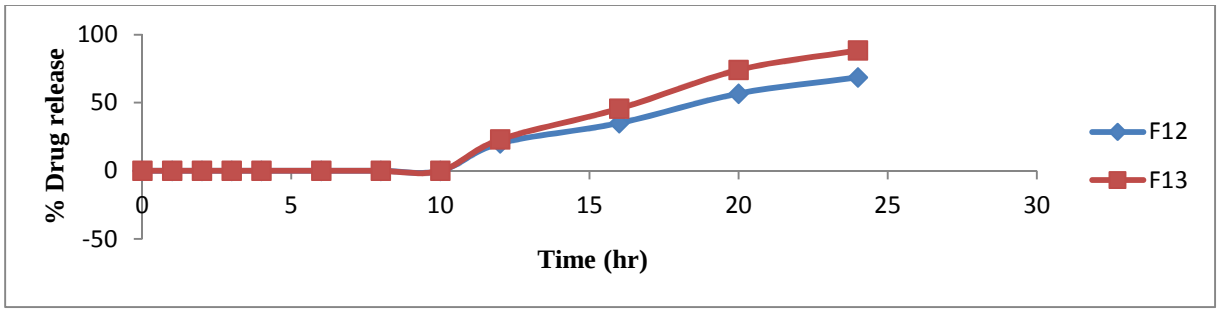

Figure No.4: Comparison of release profiles of F12-F13

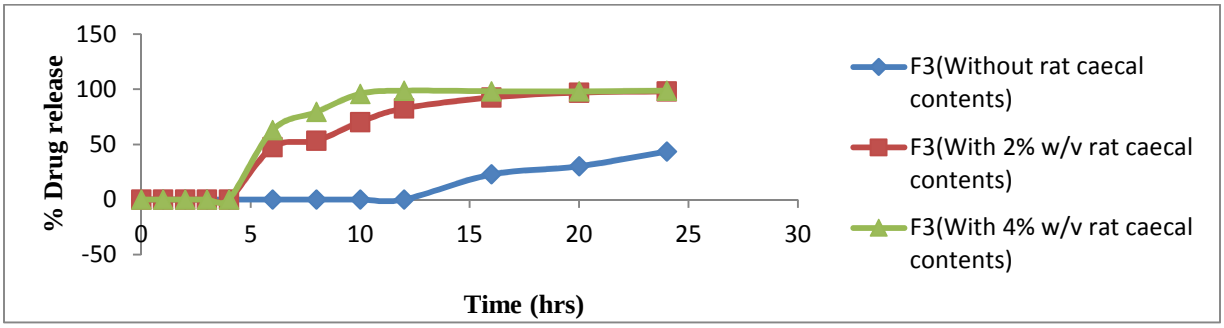

Figure No.5: Comparison of release profiles of F3 with rat caecal contents and without rat caecal contents

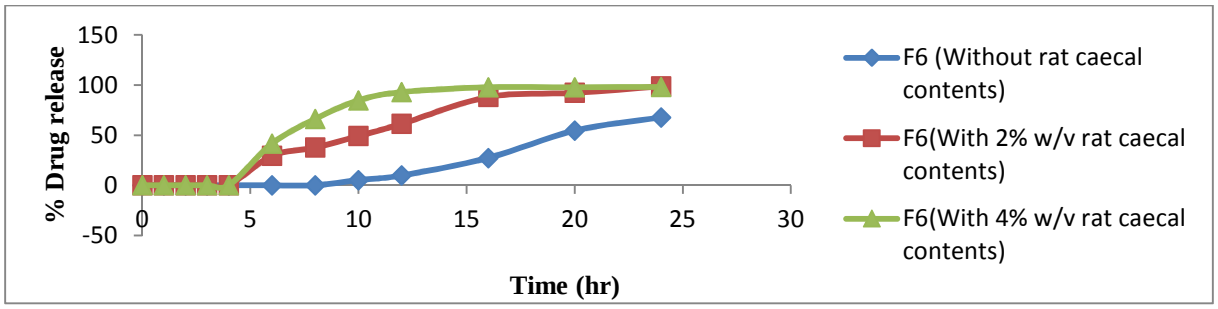

Figure No.6: Comparison of release profiles of F6 with rat caecal contents and without rat caecal contents

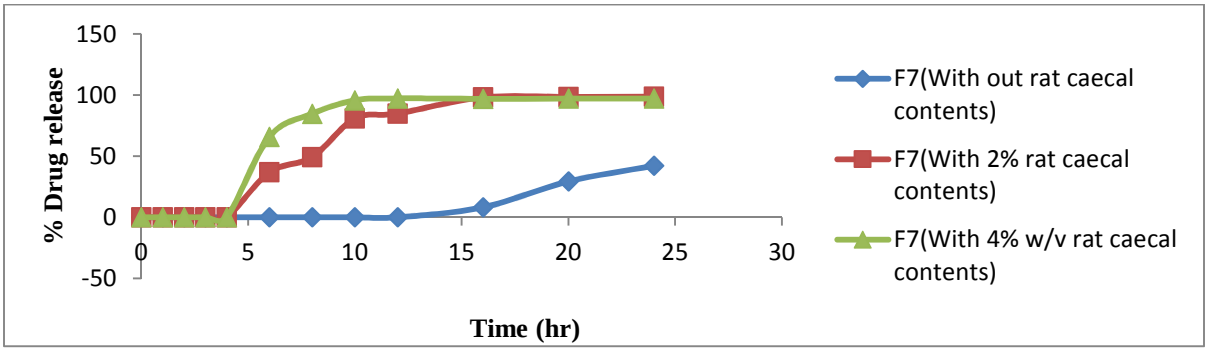

Figure No.7: Comparison of release profiles of F7 with rat caecal contents and without rat caecal contents

CONCLUSION

The present study was carried out to develop Colon targeted drug delivery systems of KTM for an effective and safe therapy of IBD. The results of the study indicate that tablets compression coated with Xanthan Gum, combination of Xanthan Gum with Hpmc K100M / Guar Gum would be potential in delivering the drug to the colon.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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