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Formulation and Evaluation of Microbially triggered compression coated tablets of Ketorolac Tromethamine

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ABSTRACT

Present study was designed to minimize the drug release in upper gastro intestinal tract and target to colon by using the principles of compression coat. Compression coated tablets are prepared by direct compression method using guar gum alone (or) combination of guar gum/metalose 90 SH polymers. Tablets are evaluated for their physicochemical properties and in vitro drug release studies. All the properties of core and coat formulations are within house specifications. In vitro drug release studies are performed without rat caecal contents (as a control) and with rat caecal contents. In the rat caecal contents formulations shows enhanced drug release due to degradation of guar gum coat by colonic galactomannanase enzyme. Coat thickness and amount of guar gum/metalose 90 SH parameters controls the release rate. Compared to individual guar gum combination of guar gum with metalose 90 SH (F9) provides minimize the drug release in upper GIT and maximizing the release of drug in colon. All the formulations are best fitted with zero order kinetics and mechanism of drug release was non-Fickian (super case -II). FTIR studies reveals there is no drug-excipient interaction. Optimized F9 formulation was a promising system targeting to colon for treatment of various colonic diseases like Inflammatory Bowel disease (IBD).

Keywords: Ketorolac tromethamine, Colon target, Microbial degradation, Metalose 90SH.

INTRODUCTION

Various drug delivery approaches are used for targeting the drugs to the target site in the human body. Now a day's colon target drug delivery is playing a crucial role due to its advantages, local and systemic actions. Targeting drugs to colon is effective and safe for the treatment of various colonic diseases like inflammatory bowel disease (IBD) including ulcerative colitis, crohn's disease, colorectal cancer, amoebiasis, constipation and irritable bowel syndrome [1].

Various strategies have been proposed for targeting the drugs to colon. These are prodrug approach [2], pH dependent [3] and time dependent systems [4], microbially triggered systems [5-7]. Prodrug and polysaccharide approaches depend on the enzymatic degradation by colonic microflora.

In all the targeting systems microbially triggered delivery system is most convenient and highly site specific for targeting to colon. Drug releases when the polysaccharides are degraded by the bacteria of colonic microflora. Several polysaccharides have been reported for colon targeting as carriers. Most commonly used polysaccharides are amylase [8], cross linked guar gum [9], chondroitin sulphate [10] chitosan [11], pectin and its salts. Guar gum used as a matrix for olden days but now it is used as compression coat [12-15].

In compression coated tablets active pharmaceutical ingredient present as inner core, surrounded by outer layer which contain polymer and other excipients. Degradation of coat occurs only in the colonic region by bacterial enzymes and subsequent drug releases in colon.

Ketorolac tromethamine (KTM) is a class of non steroidal anti-inflammatory drug (NSAID) and non-selective COX inhibitor. It has more pronounced analgesic activity and also used for the treatment of local disorders of colon like IBD and also has short biological half life [16]. If KTM releases in upper GI tract leads to gastric and duodenal toxic effects. So in the present study minimization of drug release in the upper GI tract and maximum drug release in the colonic region by applying combination of guar gum/metalose 90SH as a compression coat over the core tablets of KTM. Colonic galactomannanase enzymes are responsible for colonic degradation of guar gum to short chain fatty acids. Metalose 90SH 1, 00,000 SR (Hypromellose) is high viscosity water soluble polymer (HPMC) used in hydrophilic matrices to control the release of active pharmaceutical ingredient.

MATERIALS AND METHODS

Materials

KTM was obtained from Dr.Reddy's Laboratories (Hyderabad, India). Guar gum was a generous gift from Accord labs (Hyderabad, India).Metalose 90 SH was a gift from Dow chemical company (USA). Sodium starch glycolate (SSG) was obtained from Arabindo Pharma Ltd (Hyderabad, India). Microcrystalline cellulose, sodium lauryl sulphate (SLS), magnesium stearate, and talc were obtained from S.D.Fine chemicals Pvt. (Mumbai, India).

Preparation of Optimized core tablets of KTM

In the preliminary studies various concentrations and different types of diluents, super disintegrates are used for preparation of core tablets.. From the results optimized core tablet was formulated. Each optimized core tablet (average weight 70 mg) contains KTM (10 mg), sodium starch glycolate (SSG, 8 mg), sodium lauryl sulphate (SLS, 4 mg), microcrystalline cellulose (43 mg), magnesium stearate (2mg) and talc (3mg). For fast disintegration (disintegration time < 45 sec) SLS, SSG were incorporated in core tablets. Core tablets are prepared by direct compression method. All the materials accurately weighed, mixed manually in polybags and passed through the sieve no # 40 for uniform mixing. Finally the blend was lubricated with magnesium stearate for 3-5 min and talc was added as gliding agent. The mixed blend was

compressed into tablets using 6mm round concave punches on a 16 station rotary tablet machine (Cadmach, Ahmedabad, India).

Compression coating of core tablets

The core tablets were compression coated with different quantities (Table 1) of coating material (guar gum (or) guar gum/metalsoe 90SH) and coat weights differently (either 160 or 180 mg). Coating with guar gum alone gave soft coats, for enough hardness microcrystalline cellulose was

Table 1: Composition of compression coated tablets (CCT) of Ketorolac Tromethamine

Form-ulation	Core (mg)	Guar Gum (mg)	Metalose 90SH (mg)	MCC (mg)	Talc	Magnesium stearate(mg)	Total (mg)
F1	70	140	-	35	3	2	180
F2	70	130	-	45	3	2	180
F3	70	120	-	55	3	2	180
F4	70	110	-	45	3	2	160
F5	70	100	-	55	3	2	160
F6	70	95	5	65	3	2	160
F7	70	90	10	45	3	2	160
F8	70	85	15	45	3	2	160
F9	70	80	20	45	3	2	160
F10	70	75	25	45	3	2	160

included in the formulation. In the 9 mm die cavity half the quantity of coating material was placed; in the centre of the die cavity core material was carefully placed and the remaining half of the quantity filled in to the die cavity. In the present study combination of guar gum with high molecular weight metalose 90 SH gives enough resistance to the tablet during its passage through the GI tract.

Characterization of KTM core and compression coated tablets

Physicochemical characterization [17]

Tablet quality control tests such as hardness, weight variation, thickness, friability and *in vitro* dissolution in different media were performed on the prepared core and compression coated tablets. Hardness of the core and coated tablets (6 tablets) was measured by Monsanto hardness tester. Thickness of core and coated tablets were determined using a micrometer (Digimatic micrometer Series 293, Mitutoyo Corp, Japan). The coat thickness was taken as half of the difference between the core and coated tablet thickness. Friability was performed on core and coated tablets (20 tablets) using Roche Friabilator (Electrolab, Mumbai, India). Weight variation was done by digital balance (Shimadzu, japan) using 20 tablets.

Determination of drug content

For determination of drug content in the core and coated tablets, 10 tablets were weighed and finely powdered; quantity of powder equivalent to 100mg of KTM was transferred to 100 mL volumetric flask containing 6.8 phosphate buffer and allowed for sonication for 5 h for complete solubility of the drug. The mixture was made up to the volume with 6.8 pH phosphate buffer. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer (Elico, 161, Hyderabad. India) at 320 nm. The drug concentration was determined from the standard graph.

***In vitro* drug release studies**

With different dissolution mediums simulation of gastrointestinal transit conditions are maintained for *in vitro* drug release studies for compression coated tablets, which mimic mouth-to-colon transit. The core tablets containing 10 mg of KTM were tested in simulated gastric fluid (SGF) pH 1.2, simulated intestinal fluid (SIF) pH 6.8 and (SIF) pH 7.4. Dissolution studies were carried on USP dissolution test apparatus type 1 (Electro lab TDT-08L, USA), maintaining 37 ± 0.5 °C and rotation speed of 100 rpm.

Tablets first placed in 900 mL of simulated gastric fluid without pepsin for 2 h (gastric emptying time is 2h), replaced by 900 mL SIF which has pH of 7.4 for 3 h (average intestinal transit time is 3 h) and finally replaced by 900 mL of (SIF) pH 6.8 for remaining 19 h. Samples were withdrawn at specified intervals and the buffers were replaced with fresh dissolution mediums of respective buffer and analyzed at 320 nm using double beam UV-Visible spectrophotometer to find out amount of KTM released from compression coated tablets.

Determination of susceptibility of formulated KTM tablets to the enzymatic action of colonic bacteria, drug release studies were conducted in phosphate buffer pH 6.8 in the absence (control) and presence of rat caecal contents.

Drug release studies in presence of rat caecal contents

The susceptibility of compression coats to the enzymatic action of colonic bacteria determined by performing the release studies in pH 6.8 phosphate buffered saline (PBS) containing 4% rat caecal contents.

According to institutional guidelines albino rat's care was taken. The caecal contents were obtained from male albino rats which are maintained on normal diet. 1ml of 2% guar gum dispersion was given prior 6-7 days to rats for inducing bacterial enzymes postulated to the caecum. 30 min before the commencement of drug release studies rats are killed by spinal traction, and caecum was ligated at both ends. Caecal contents were weighed and diluted with phosphate buffer saline (pH 6.8) to obtain 4 % w/v rat caecal content which is used for further studies. PBS is previously bubbled with CO₂ gas because caecum is naturally anaerobic and all the operations are conducted under anaerobic conditions.

The drug release studies are conducted on same USP dissolution test apparatus type 1 (37 ± 5 °C and 100 rpm) with slight modifications [18]. 100 ml rat caecal content medium (4 % w/v) containing 250ml glass beaker was immersed in the 1000 mL flask of the dissolution test apparatus. After completion of the 2 h of the dissolution study in SGF (pH 1.2) and 3 h in pH 7.4 buffer, the swollen formulations were placed in basket of the dissolution test apparatus which is immersed in the rat caecal content medium and release study was conducted for up to 24 h (usual colonic transit time is 20-30 h). 2 ml of aliquot samples are withdrawn at predetermined time intervals and replaced with fresh PBS which is bubbled with CO₂ gas. The sample volume was made up to 10 mL with SIF (pH 6.8), filtered through bacteria proof filters and assayed spectrophotometrically for KTM at 320 nm. The above study was conducted for different coat compositions of KTM and also without rat caecal contents (control study) in SIF (pH 6.8).

Evaluation of Release rate kinetics

The dissolution data of various compression coated tablets of KTM was fitted into various kinetic models such as zero order [19] (cumulative percentage of drug released Vs time), first order [19] (log cumulative percentage of drug remaining Vs time), and Higuchi's [20] (cumulative percentage of drug released Vs square root of time) models. For determination of mechanism of drug release data was fitted into Korsmeyer-Peppas [21] equation.

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is fraction of drug released at time 't', 'K' represents a constant. The exponent 'n' is calculated through the slope of the straight line which indicates mechanism of drug release.

Table 2: Different mechanisms of drug release

'n' value	Type of Mechanism
less than (<) 0.5	Fickian diffusion
greater than (>) 1	Supecase II transport
between 0.5 to 1	Non- Fickian diffusion

Stability studies

A study was carried according to ICH guidelines for determination of stability of optimized KTM compression coated formulation[22]. Generally the rate of degradation at normal temperatures take prolonged time so accelerated stability principles were adopted. In this the optimized formulation (F9) was sealed in aluminum packaging laminated with polyethylene and stored at 40 °C and 75 % RH for 3 months. Samples were evaluate d for 10th, 30th, 60th and 90th days for various parameters such as physical appearance hardness, weight variation, drug content and dissolution.

Drug-excipient compatibility study by FTIR studies

For checking the compatibility between drug and used excepients FTIR study was performed. In this infrared spectrums were taken for pure drug and optimized formulation at wavelengths between 400 cm⁻¹ to 4000 cm⁻¹ using FTIR spectrophotometer (FTIR 8400 Shimadzu). Potassium bromide disc method used for obtaining the IR spectrums.

RESULTS AND DISCUSSION**Characterization of KTM core tablets**

Direct compression method is used for compression of core tablets. The results of hardness, weight variation, % friability and drug content are shown in Table 3. The hardness of the core tablets were in the range of 3.1± 0.5 kg/cm², percentage of drug content was 98.5±1.9, the mean thickness was 1.9±0.005 and the friability was less than 1%, indicates all the physicochemical properties are with in house specification for core tablets. More over the disintegration time of core tablets was less than 1 minute due to combined action of microcrystalline cellulose and SSG (super disintegrate). Dissolution studies were performed for core tablets of KTM in different buffers like pH 1.2 (SGF), pH 7.4 and 6.8 (SIF).The results of dissolution studies were shown in Figure 1, it indicates drug release was slow from SGF (pH 1.2) buffer compared to pH 6.8 and 7.4 buffers. The core tablets dissolved in 60 min from pH 6.8 buffer and 75 min from pH 7.4

buffer indicates complete drug release occurred from the core tablets. From pH 1.2 buffer complete drug release occurs in 3 h.

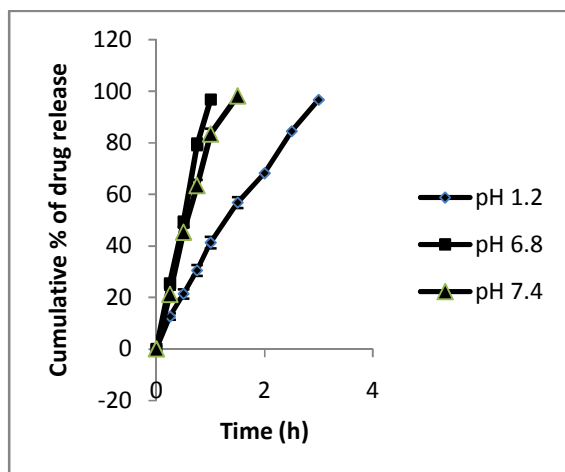


Figure 1: *In vitro* drug release of KTM core tablets in different dissolution mediums
Characterization of compression coated tablets

Table 3. Post compression parameters of core and compression coated tablets

Form-ulation	Hardness (kg/cm ²)	Weight variation (mg)	Friability (%)	Drug content (%)
Core	2.8±0.5	72±1.2	0.42	99.2
F1	5.1±0.8	251±2.1	0.63	94.8
F2	4.8±0.2	248±2.3	0.37	98.2
F3	5.3±0.7	253±1.3	0.29	103.5
F4	4.9±0.4	230±2.4	0.34	97.8
F5	5.0±0.5	232±4.5	0.56	96.9
F6	5.2±0.6	228±4.5	0.44	98.4
F7	5.3±0.4	234±0.5	0.45	99.7
F8	6.2±0.7	236±4.3	0.53	99.3
F9	6.1±0.7	232±1.2	0.67	100.1
F10	6.2±0.3	233±1.5	0.56	100.2

The coat formulations containing various proportions of guar gum and combination of guar gum/metalose 90 SH are compressed by highest compression force. Physicochemical properties of compression coated formulations were shown in Table 3. The mean thickness of compression coated formulations (uniform coating over core tablets) containing 180 and 160 mg was found to be 4.85 ± 0.005 and 4.65 ± 0.009 mm respectively. So the coat thickness for compression coated tablets of 180 and 160 mg are 1.27 ± 0.007 and 1.08 ± 0.004 mm respectively. The hardness of the compression coated tablets containing only guar gum was in the range of 4.5 ± 0.5 to 6.2 ± 0.8 kg/cm² and combination of guar gum/metalose 90 SH in the range of 5.1 ± 0.6 to 6.4 ± 0.4 kg/cm². From these results we conclude that metalose 90 SH provides mechanical strength to the tablets and crushing strength was increased when combination of polymers used. The content uniformity of the tablets was found to be 98.6 ± 0.6 and the friability of all the formulations below 1% indicates the compression coated tablets are compiled with pharmaceutical quality control standards.

***In vitro* drug release studies of compression coated tablets**

Cumulative percentage of drug released from compression coated with guar gum coat weight 180 mg (from F1 to F3) and coat weight 160 mg (F4, F5) are shown in Figures 2a & 2b. Depending upon the varying amounts of guar gum (F1 to F5) the drug release was found to be vary from 9.1 ± 1.2 to 17.5 ± 2.3 after 5 h of testing in pH 1.2 and 7.4 buffers. Figure 2c shows the cumulative amount of drug released from the combination of guar gum with metalose 90 SH. After 5 h of dissolution F8, F9 and F10 releases 10.4 %, 9.8% and 7.5% of KTM respectively. Thus in the coat either guar gum alone or combination with metalose 90 SH is able to prevent the drug release from upper gastro intestinal tract (stomach and intestine). F6 and F7 release 30.8% and 26.9% of drug respectively after 5 h.

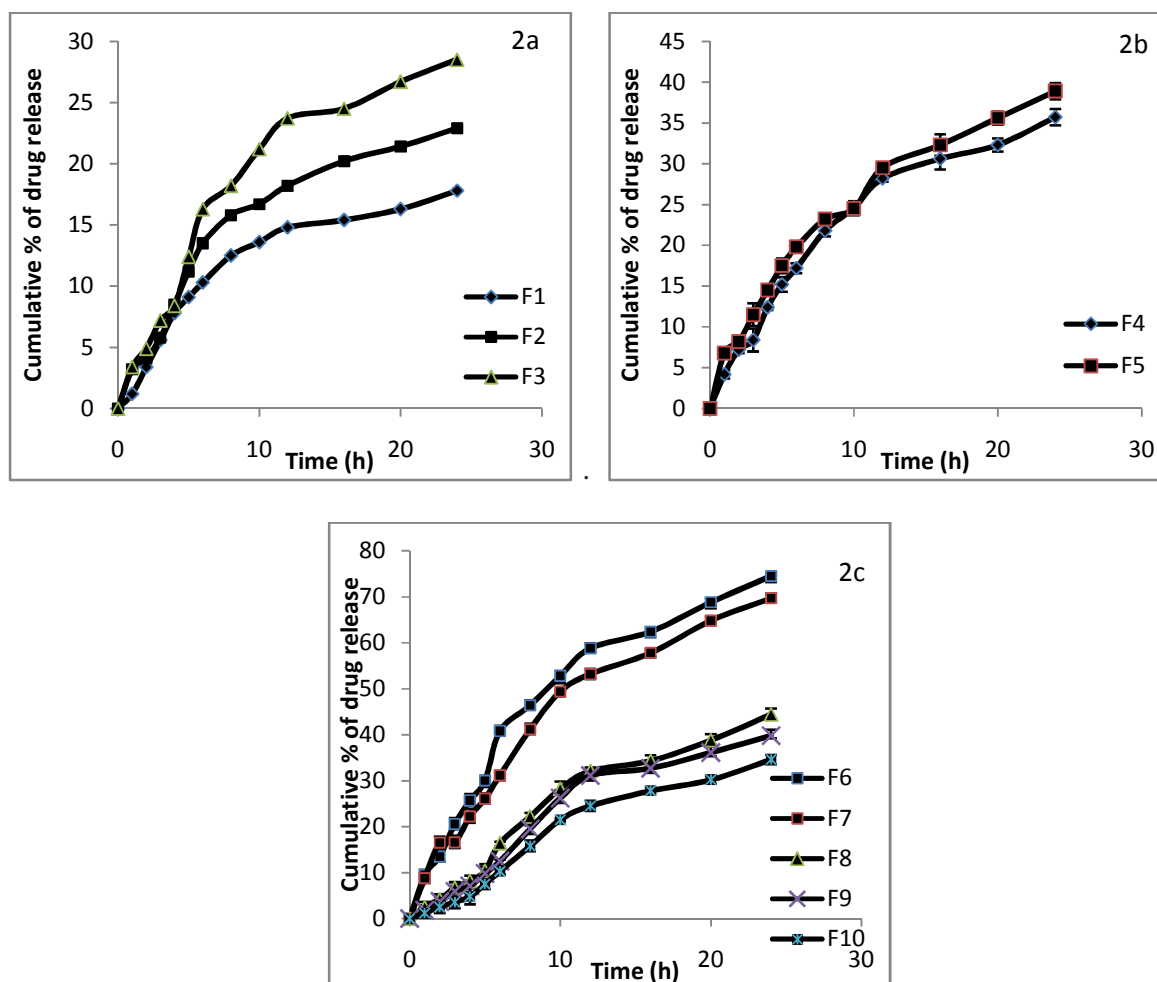


Figure 2: *In vitro* dissolution studies of core tablets (mean \pm S.D, n=3) with a) Guar gum (coat weight 180 mg) b) Guar gum (coat weight 160 mg) c) combination of guar gum with Metalose 90 SH (160 mg coat weight)

For determination of integrity of the coats, the drug release studies were continued up to 24 h in simulated intestinal fluid (pH 6.8). At the end of 24 h F1, F2 and F3 releases 17.5%, 22.7% and 28.5% of KTM respectively and the tablets were intact. The results indicate that until the coat was broken it will not release the drug from core. Percentage of drug released from F4 and F5

was found 35.8% and 38.9% respectively. F6 and F7 releases 74.5%, 69.7% of drug respectively after 24 h. 44.4%, 39.8% and 34.6% of drug released from F8, F9 and F10 respectively after 24 h.

On contact with dissolution medium guar gum swells up and the drug released by diffusion and mechanical erosion of the swollen gum layer occurs. But when the swollen gum was not eroded further hydration and swelling was not taken place and drug was not released. That's why the higher amount of guar gum and combination of polymers prevents erosion, retards drug release and remains as intact. The lesser gum content was unable to remain as intact and not prevents the drug from being released.

After 24 h of study very less amount of drug was released from F1, F2, F3 and high amount of drug was released from F6. So these four formulations were not studied further in rat caecal contents. But for determination of effect of coat thickness F3 was studied in rat caecal content.

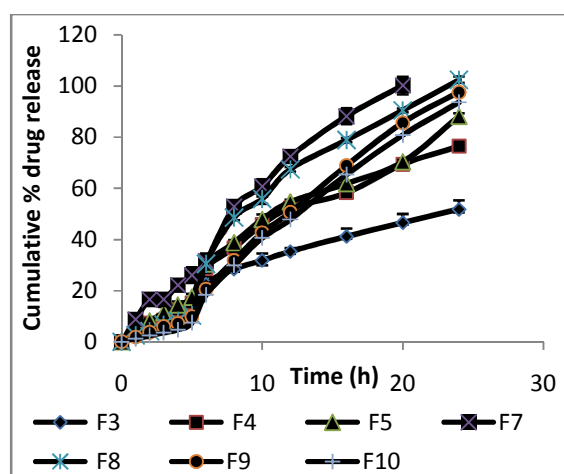


Figure 3: In vitro drug release studies of KTM compression coated tablets in 2 h in pH 1, 3 h in SIF (pH 7.4) and 19 h in SIF (pH 6.8 containing 4% rat caecal contents)

Drug release studies in rat caecal contents

Compression coated tablets of KTM targeting to colon not only protecting the release of drug in upper gastro intestinal tract but also it should release the drug in colon after enzymatic degradation by colonic bacteria. In vitro drug release studies were performed for F3, F4, F5, F7, F8, F9 and F10 formulations in pH 6.8 (SIF) buffer containing 4% w/v rat caecal contents shown in Figure 3.

After 24 h of testing (2 h in SGF pH 1.2, 3 h in SIF pH 7.4 and remaining 19 h in PBS containing pH 6.8) 51.2% KTM was released from F3. This is due to presence of higher amount of guar gum (180mg) in coat leads to thicker coat and the coat will not be disintegrated with in 24 h. F3 is only protecting being release from upper GI tract but it doesn't release the drug in the colon. 76.5% and 88.2 % of drug was released from F4 and F5 respectively and release was increased after 12 h indicating the breaking of coat was started. In F4, F5 more amount of drug was released due to fewer amounts of guar gum leads to thinner. F7, F8 releases 102.5%, 100.4% of KTM respectively after 20 and 24 h of dissolution. In both formulations the percent of drug

released increased after 8 h indicating the coat was degraded by colonic bacteria and drug releases in the dissolution medium.

When guar gum alone is used in low concentration burst release was observed. This is due to rapid swelling and erosion of polymer. When large amount is used release rate was retarded due to increase in porosity, tortuosity and the drug was not released from the intact coat. Prevention of bursting release and improvement of mechanical strength guar gum was mixed with HPMC grade polymer Metalose 90 SH. Bursting release was observed when metalose used in (F6) low concentration. After 24 h of dissolution testing in rat caecal contents, formulations F9 and F10 releases 97.5 and 93.6% of drug respectively. Most efficient targeting to colon was observed with combination of guar gum (70 mg) and metalose 90 SH (20 mg) in F9. From these results we can conclude that single hydrophilic polymer retards the drug release but addition of another polymer controls its release rate.

The results showed variation of drug release in presence and absence of rat caecal contents due to degradation of guar gum coats in the colon by galactomannanase enzyme.

Table 4: In vitro release kinetics of KTM compression coated tablets

Formulation	R ²			n
	First- order	Zero-order	Higuchi	
F3	0.971	0.938	0.942	1.01
F4	0.989	0.954	0.935	1.08
F5	0.941	0.969	0.939	1.02
F7	0.829	0.979	0.926	1.12
F8	0.748	0.952	0.900	1.33
F9	0.969	0.984	0.886	1.36
F10	0.962	0.966	0.877	1.52

Kinetic analysis of dissolution data

The results of various kinetic models and mechanism of drug release from piroxicam compression coated tablets are shown in Table 4. The results showed that all formulations best fitted with zero order kinetics, as they contain highest regression coefficient values (0.938 to 0.984). To determine mechanism of drug release the *in vitro* results are fitted into Korsmeyer-Peppas equation and the formulations showed highest linearity and the 'n' values are above 1 (1.01 to 1.52) indicating that drug release mechanism was non-Fickian super case II transport. The release of drug depends upon swelling, relaxation and polymer erosion.

Stability studies

The optimized batch (F9) was studied for stability study for 3 months. At regular time intervals the tablets were tested for physicochemical properties and in vitro dissolution studies. The result shows the average drug content was 97.6% of labeled claim and no significant change in the in vitro dissolution studies.

FTIR studies

The IR spectrums of pure drug (4a) and optimized formulation (4b) major peaks were shown in Table 5 and Figure 4. The spectrum peak points of the drug and optimized formulation are same. So there is no drug-polymer interaction was observed.

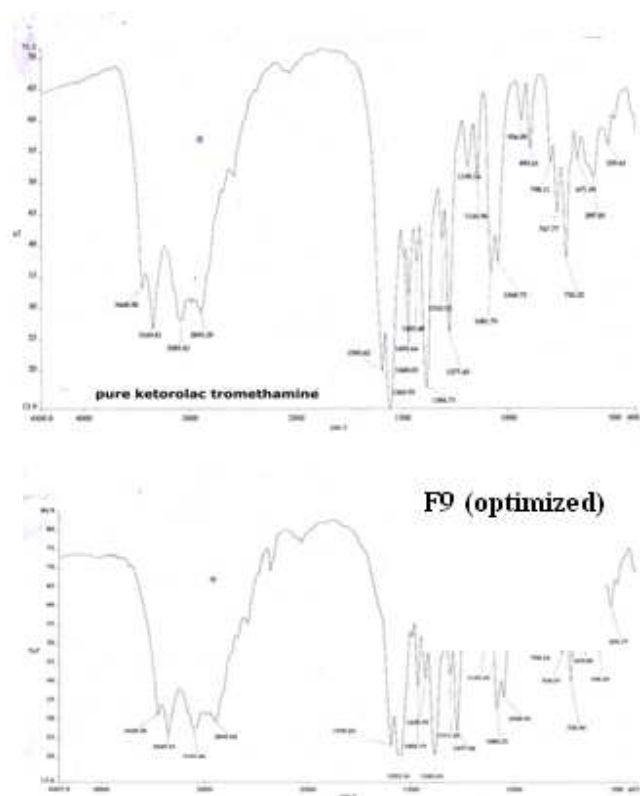


Figure 4. FTIR spectrums of Pure drug KTM & Optimized Formulation (F9)

Table 5: FTIR spectrum major peak points in KTM and optimized formulation

Group	Pure KTM (cm ⁻¹)	F9 (cm ⁻¹)
NH-stretch	3449.58	3449.31
C=O –stretch (acid)	1595.62	1596.21
O-H stretch (alcohol)	3349.81	3349.31
C=O –stretch (diaryl ketone)	1190.14	1190.93
C=C stretch (Ketone)	1277.40	1278.4
O-H bend (Carboxylic acid)	1430.48	1431.2
O-H bend (Carboxylic acid)	2895.29	2896.3

CONCLUSION

The delivery of KTM to the colon via oral route is useful for the treatment of various colonic diseases. Combination of guar gum and Metalose 90 SH, in the form of compression coated tablets is capable of preventing drug release from upper gastrointestinal tract and successfully targeting to colon. The release mechanism was non- Fickian anomalous diffusion mechanism.

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