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Ketorolac Tromethiamine Tablets Targeting to Colon through Microbial Degradation and Ph Dependence Development and Roentogenographic Studies

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Abstract

The present experiment was designed to develop colon specific drug delivery system of ketorolac tromethiamine (KT) for treatment of various colonic disorders. Matrix tablets were prepared by direct compression technique utilizing combination of guar gum with various types of biodegradable/pH dependent/hydrophilic retarders. Tablets evaluated for quality control tests and in-vitro liberation studies (24h). In vivo roentogenographic studies and stability studies performed for optimized formulation. KT containing combination of guar gum with HPMCP (Hypromellose Phthalate) 55S released negligible amount in 1.2 pH and 7.4 phosphate buffers and 70

Index terms— colon target; hpmcp 55s; ketorolac tromethiamine; roentogenographic studies.

1 Introduction

n last 3 to 4 decades, scientific and technological advancements had focused on research of site specific (or) targeting delivery of drugs to colonic region through oral route **??**Pandit JK et al.2012). From normal oral route uttermost drug liberation occurs in the upper GI tract (stomach and intestine) but in colon targeted systems, negligible quantity in upper GI tract and maximum amount of drug releases in colonic region. Targeting drugs to colon is mainly used for those drugs which have poor absorption from GI tract, drugs unstable in the stomach, intestine and high hepatic first pass effect. Colonic target also used for drugs which are used in treatment of colonic cancer and local diseases **??**Chan RP et al.1983; **??**inget R et al.1998; Watts PJ 1997) It is a non-specific prostaglandin-endoperoxide synthase (PTGS) inhibitor derived from pyrrolo-pyrrole (heterocyclic) acetic acid group and exhibits analgesic, anti-inflammatory and antipyretic activity. KT produces the anti-inflammatory effect through obstruction of prostaglandin (PGE2) biosynthesis by competitive blockade of PTGS1 and PTGS2 enzymes. As the result, there is a sharp drop-off in the production of precursors for prostaglandins and thromboxanes from arachidonic acid.

It has more pronounced analgesic activity than most NSAIDs, used to treat local disorders like inflammatory bowel disease (IBD) including ulcerative colitis, crohn's disease etc. Primary goal in treatment of IBD is to reduce inflammation that requires frequent intake of anti-inflammatory drugs in high doses. KT is a skilful drug for colonic target due to its short biological half life and its gastritis adverse effect (Goodman 2001).

Targeting drugs to colon through oral route achieved by various ways such as (1) coating with pH sensitive polymer (Tromm A et al. 1999; **??**ninsky CA et al.1991),(2) time-controlled formulation and device (MacNeil 1990), (3) coating with polymer which can be degraded by intestinal micro flora **??**Brondsted H et al.1992), (4) pressure controlled devices **??**Saffran et al.1986; **??**u Z et al.1999) and (**??**) polymeric pro drug approaches (Muraoka M et al. 1998). Considering all those points research developments utilized natural polysaccharides (like amylase, chitosan, dextrin, guar gum pectin and its salts) for colon target because these are come under the category of GRAS (Generally regarded as safe) because of their non toxic nature and degradation by of colonic micro flora bacteria.

Guar gum is a potential carrier for targeting to colon. Guar gum is a galactomann polysaccharide derived from the seeds of Cyamposis tetragonolobus. It contains linear chains of 1, 4 ? -D-mannopyranosyl units with ? -D-galactopyranosyl units attached by 1, 6 linkages (Goldstein et al. 1993

2 b) Preparation of Matrix Tablets

Direct compression technique utilized for manufacturing matrix tablets. All formulation ingredients such as10 mg KT, 30 mg guar gum,70 mg polymer (either biodegradable, hydrophilic or pH dependent as specified in Table.1),40 mg of avicel (MCC) and 5 mg of aerosil were accurately weighed and sifted through mesh no.40 (size 420 µm) sieve. After sifting, mixture was transferred to a polyethylene bag and shook for 10 minutes for uniform blending. This prelubricated blend was lubricated with blend of magnesium stearate, talc and compressed on a 16 station rotary tablet punching machine (Cadmach, Ahmedabad) using 8mm round faced concaved punches.

3 c) Physicochemical Characterization of Tablets

All batches of formulated KT matrix tablets were evaluated for their physicochemical properties. To perform mass variation, 20 tablets from each formulation were weighed using an electronic digital balance (Shimadzu, AW 120, Japan) and test done according to the official method. The crushing strength of 6 tablets with known weight and thickness measured by Monsanto hardness testing apparatus (Swastik scientific company, Mumbai, India) and values recorded in kg/cm 2 . Thickness of 6 tablets from each batch measured by Digital Vernier calipers (Mitutoyo corp, Kawasaki, Japan) and the results reported in mm. (Indian pharmacoiea 1985; USP-24) Drug content in each formulation was determined by triturating 10 tablets and quantity of powder equivalent to one tablet was transferred into 100 ml of 0.1N HCl, followed by agitation for 45 minutes. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 320 nm using 0.1 N hydrochloric acid as blank.

By using all these individual values average values and standard deviations were calculated and reported.

4 d) In vitro dissolution studies

In vitro dissolution studies carried in USP TypeII (basket) dissolution test apparatus (Electro lab, TDT-08L) with agitation speed 100 rpm at 37±0.5 o C. First 2 hrs tablets placed in 0.1N HCl, next 3 hrs in pH 7.4 phosphate buffer and remaining 19 hrs in pH 6.8 phosphate buffer. These three dissolution mediums mimics the gastrointestinal transit conditions. 5mL aliquot samples were withdrawn at specified time intervals and the buffers were replaced with fresh dissolution fluid to maintain sink conditions. The sample was filtered and analyzed at 320 nm using double beam UV-Visible spectrophotometer to find out amount of KT release. All dissolution runs were performed in triplicate.

e) Drug release studies in the presence of rat caecal contents i. Preparation of rat caecal contents

The susceptibility of natural gums (like guar gum, sodium alginate, xanthan gum used in the formulation) with the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100mL of simulated intestinal fluid (6.8) containing 4% w/v of rat caecal contents. The caecal contents were obtained from male albino rats after pretreatment for 7 days with guar gum (2% w/v polymer) dispersion.

Rats killed by spinal traction, caecal contents were isolated 30 min before drug release studies and immediately transferred into SIF (pH 6.8) which was previously bubbled with CO 2 because the caecum was naturally anaerobic and all operations conducted under anaerobic conditions.

ii.

5 Dissolution study procedure

Drug release studies were carried on same USP dissolution test apparatus I (100 rpm and 37±0.5 0 C) with slight modifications.

After completion of 2 hrs dissolution study in 1.2 pH (0.1N HCl) and 3 hrs in 7.4 phosphate buffer, the swollen formulations were placed in the 250 mL of glass beaker containing 100 mL of (4% w/v) rat caecal content which was immersed in the 1000 mL flask of dissolution test apparatus and study was continued up to 19 hrs because usual colonic transit time was 20-30 hrs. The experiment was carried out with continuous CO 2 supply into the beaker to simulate anaerobic environment of the caecum. 2 mL of aliquot samples were withdrawn at predetermined time periods and replaced with fresh phosphate buffer 6.8 pH. Sample was filtered and filtrate was analyzed for KT at 320 nm with UV-Visible spectrophotometer. The above study was carried on F2, F3, F8, F9 and F10 formulations. Later on in vitro dissolution studies of all optimized stability samples statistical analysis performed. With the assistance of ANOVA stability samples were analyzed g) Drug excipient compatibility Study DSC performed on pure KT and optimized formulation to determine the compatibility between drug and used excipients. In DSC accurately weighed 5-6 mg sample was placed in aluminum pan which was hermetically sealed and measurements were performed over 50-200 0 C under nitrogen flow of of 25 mL min -1 . Indium/zinc standards were used to calibrate the temperature and enthalpy scale in DSC.

6 h) In vivo Roentogenographic studies

In the Roentogenographic studies inclusion of radio opaque material (barium sulphate) in the formulation enables the movement location and integrity of dosage form. Institutional Human Ethical Committee of KLR Pharmacy College (New Paloncha, India) approves the roentogenographic study in consultation with radiologist and protocol no is KLRPC/IHEC/2009-2010/005. 3 healthy male human volunteers with an age of 25 ± 5 years and 50-70 kg body weight, who were non-alcoholic and non-smokers were participated in the study. A written consent was taken and purpose of the study was fully explained before the study. Optimized formulation was (F10) modified by adding 20 mg of Xray grade barium sulphate (replaced by drug 10 mg and Avicel 10mg). The volunteers were required to fast over night and each subject ingested test tablet orally with 200mL of water. After ingestion of 2 nd , 4 th hr volunteers served with breakfast and lunch respectively. Abdominal radiographs were taken after 30 min, 3, 6, 8 and 24 hrs in all subjects.

7 i) Stability Studies

From the designed matrix tablets F10 formulation was hermetically sealed in an aluminum foil which was laminated with polyethylene and stored at 40ºC± 2 ºC at 75 % ± 4% RH for 3 months according to the standard guidelines. Samples were evaluated at initial, 30, 60 and 90 days for various physicochemical parameters, drug content, drug release and statistical analysis.

8 III.

9 Results

10 a) Post compression parameters of matrix tablets

Uniform conditions were maintained to prevent batch to batch variations. Average weight variation of tablets was 164 ± 5 mg, mean thickness was 3.1 ± 0.4 mm, mean crushing strength was 3.5 ± 0.8 kg cm -2 and friability ranged from 0.6 to 0.8 % (m/m) (0.8 ± 0.1%).The content uniformity of the tablet was 98.8 ± 4.5 %.

11 b) In vitro drug release studies

The results of dissolution studies of formulations containing F1-F3 composed of combination of guar gum (20%) with biodegradable polymers (40%) such as xanthan gum, sodium alginate (SG) LFR 5/60 and LF 10/60 are shown in the Figure 1. After 2 h of dissolution in 0.1 N HCl, % of drug released from the formulations F1-F3 was 15.4%, 13.8% and 11.2% respectively. 49.4%, 34.1% and 28.8% of KT released after dissolution study in 7.4 pH buffer. With in 10 h total amount of drug released from F1(combination of Xanthan and guar gum) , whereas F2 F3 releases 92.4%, 85.6% of drug respectively in SIF containing 6.8 pH phosphate buffer. So combinations of guar gum with xanthan gum was not suitable for colon specific delivery.

The results of release studies of formulations F4-F9 composed of combination of guar gum (20%) with hydrophilic polymers (40%) such as HPC EF, HPC LF, HEC, HPMC K4M, K15 M and K100M respectively were shown in Figure 2. Matrix tablets of KT from F4-F6 releases about 32.5%, 28.2%, 26.1% after 2 h and 68.8%, 58.4% and 45.2% after 5 h respectively. The UV analysis results showed 100% drug release occurs after 8 th , 10 th and 12 th h respectively from F4-F6. Comparative dissolution profiles of F7-F9 containing combination of 20% of guar gum with 40% of different grades of hydrophilic HPMC K4M, K15M and K100M polymers are shown in Figure 2. After 2 h 20.1%, 15.4%, 6.2%, after 5 h 35.8%, 19.4%, 11.2% of KT released respectively from F7-F9. Total amount of drug released from F7 at 24 th h where as 75.8%, 60.4% released from F8, F9 respectively. F10, F11 composed of combination of guar gum (20%) with pH dependent polymers (40%) hypromellose phthalate (HPMCP) 55 and HPMCP 55S respectively (Figure **??**). These 2 formulations release about 5.8%, 2.5% after 2 h, 11.2% and 5.9% after 5 h respectively. At the end of 24 h , F10 released 56.8% where as F11 released 45.8% of KT. The results showed that pH dependent polymers prevent maximum drug release in GIT and high amounts released in colonic region.

Further study of enzymatic action of colonic bacteria on natural polysaccharides, dissolution studies were performed for F2, F3, F8, F9, F10 and F11 in rat caecal contents. From F2, F3 total amount of drug was released in rat caecal contents with in 14 and 16 h and not sustains the drug release up to 24 h. 98.5%, 99.5% of KT released with in 20 and 24 h respectively from F8, F9respectively. After 24 h 95.8% drug released from F10 where as 85.8% drug released from F11 (Figure **??**). From these results F10 containing combination of guar with pH dependent HPMCP 55 polymer was successfully targeting to the colon.

The results of various kinetic models and mechanism of drug release were showed in Table 2. The results showed that all formulations best fitted with zero order kinetics (Hadjiioannou et al. 1993), as they contain highest regression coefficient values (0.975 to 0.989). To determine mechanism of drug release the in vitro results are fitted into Korsmeyer-Peppas (Korsmeyer RW et al. 1983) equation and the formulations showed highest linearity and the 'n' values are (0.83 to 0.95) indicating that drug release mechanism was non-Fickian. The release of drug depends upon swelling, relaxation and polymer erosion. c) Drug-excipient compatibility studies DSC curves of pure drug KT and optimized formulation (F10) were done. Thermo gram of pure KT shows sharp

endothermic peak at 160.91°C and similar endothermic peak was observed for optimized formulation (combination of guar gum with HPMCP 55) at 158.56°C.

12 d) Stability Studies

Assay and drug liberation values of accelerated temperature samples at initial, 30 th , 60 th and 90 days of matrix tablet of F10 displayed acceptable results and point outs the unalterable nature of the drug in the formulations. In vitro liberation data procured from earlier and later on stability studies at 40 ± 2ºC/75 ± 4% RH and individually analyzed by ANOVA. The ANOVA tables showed that in all the stability samples table F value (0.563) was greater than calculated F value (0.003). Hence F10 revealed that there was no significant deviation in the earlier and later on in vitro liberation of drug in stability situations.

13 e) In vivo Roentogenographic studies

Roentogenographic studies of optimized formulation (F10) in all subjects showed that disintegration doesn't occur in the upper region of the GIT until reach the colon. After 5-7 h the tablets entered into the colonic region and slowly degraded by the resident anaerobic micro flora present in the colon of human volunteers. Roentogenographic results clearly revealed that location of the tablet at 30 mins, 3 h and 8 h is in stomach, caecum and ascending colon respectively. After 24 h tablet was not observed, this gives that evidence of degradation of the tablet in the colon. From these results we can confirm that combination of guar gum (20%) with pH dependent polymer HPMCP 55 (40%) was potential carrier for targeting KT to colon.

IV.

14 Discussions and Conclusions

In the preparation of matrix tablets directly compressible grade microcrystalline cellulose (Avicel) was used due to poor compressibility and flow nature of guar gum.

In caparisoning of F1-F3 formulations depicts that retardation was more in combination of guar gum with SG LF 10/60(F3) compared to SG LFR 5/60 (F2) due to high molecular weight and viscous nature (SG LFR 5/60 contains average guluronic, mannronic acid content 65-75%, 25-35% respectively, where as SG LF 10/60 average guluronic, mannronic acid content was 40-45% and 55-60%).

In the F4 to F6 formulations entire drug liberated below 10 hours. This clearly indicates combination of guar gum with hydroxyl ethyl and propyl celluloses were insufficient to retard the drug release or not suitable for target to the colonic region. Faster drug release may be due to faster dissolution of the water soluble drug from matrix tablets.

In the formulations F7 to F9, tablet integrity was poor in combination with K4M matrix tablets (F7). Figure 2 showed as the viscosity increased from 4000 cps (K4M) to 1,00,000 cps(K100M) release rate was retarded due to high polymer entanglement and more gel strength in high viscosity grade polymer. Viscosity of the polymer directs % of swelling and erosion. In K100M % swelling is more and % erosion is less compared to K15M and K4M.

The results of in vitro dissolution study and in vivo roentogenographic studies revealed that combination of guar gum with HPMCP 55S (pH dependent polymer) was most likely provide targeting KT to colonic region. The release mechanism was non-Fickian anomalous diffusion mechanism.

V. - - - - - - - HPC EF - - - 60 - - - - - - HPC LF - - - - 60 - - - - - - HEC - - - - - 60 – - - - - HPMC K4M - - - - - 60 - - - - HPMC K15M - - - - - - 60 - - - HPMC K100M - - - - - - - -**60** [1] [2] [3]

[1]( )

[2]Ketorolac Tromethiamine Tablets Targeting to Colon through Microbial Degradation and Ph Dependence: Development and Roentogenographic Studies

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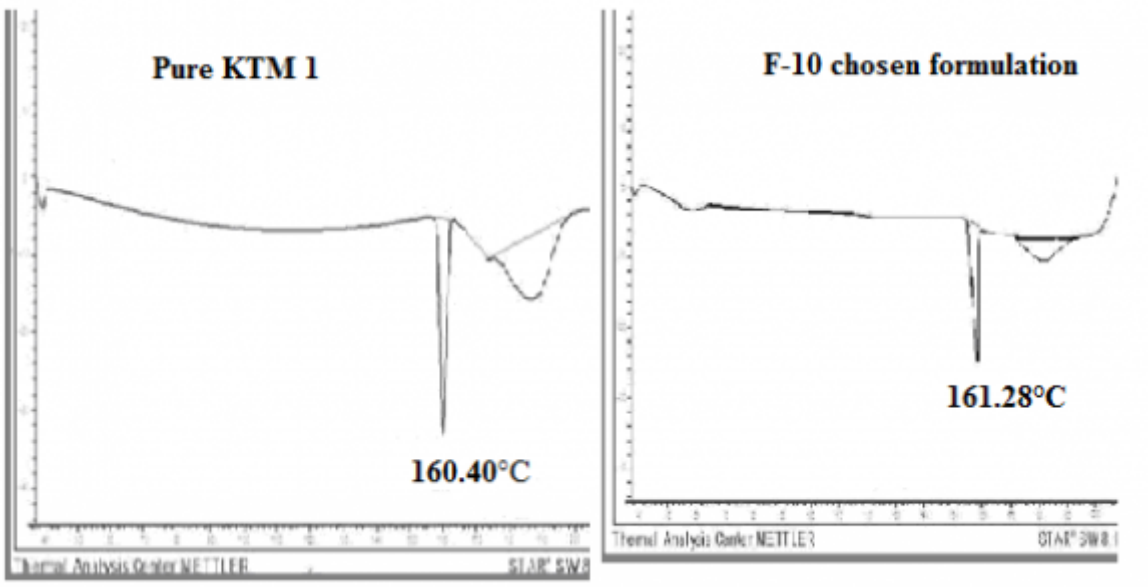
Figure 1:



1

Figure 2: Figure 1 :

2

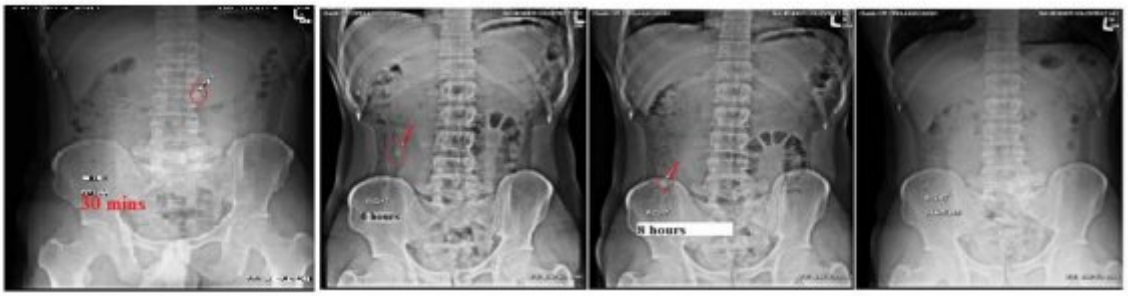


Figure 3: Figure 2 :

1

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
KT	10	10	10	10	10	10	10	10	10	10	10
Guar gum	30	30	30	30	30	30	30	30	30	30	30
Xanthan gum	60	-	-	-	-	-	-	-	-	-	-
Sodium alginate 5/60	-	60	-	-	-	-	-	-	-	-	-
Sodium alginate 10/60	-	-	60	-							

Figure 4: Table 1 :

2

Figure 5: Table 2 :

3

ANOVA table at Room temperature at 1 month Source of Variation Sum of squares Degrees of Freedom T.S.S 23581.1 15 S.S.F 0.03375 1 S.S.T 23572.88 8 E.S.S 8.18625 8 ANOVA table at Room temperature at 3 months T.S.S 23688.45 15 S.S.F 0.020417 1 S.S.T 23681.78 8 E.S.S 6.644583 8 n Zero-order First-order F2 0.985 0.943 F3 0.989 0.958 F8 0.982 0.971 F9 0.988 0.976 F10 0.985 0.973 T.S.Formulatio F11 0.977 0.968	Mean sum of squares 1572.265 0.03375 2946.989 1.016205 1579.933 0.020517 2960.89 0.83057 R 2 Higuchi 0.974 0.969 0.959 0.920 0.910 0.906	F cal 0.00344 2917.57 0.02471 3566.074 Korsmeyer- Peppas 0.980 0.984 0.974 0.951 0.948 0.951	F table 0.563133 0.380666 0.563133 0.380666 ’n’ 0.83 0.87 0.73 0.97 0.98 0.95

Figure 6: Table 3 :

.1 Acknowledgements

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