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Research Article

DESIGN AND CHARACTERIZATION OF COLON SPECIFIC TABLETS OF KETOROLAC TROMETHAMINE

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ABSTRACT

Main objective of the present study was to formulate and evaluate colon specific tablets of Ketorolac tromethamine using natural gums in view to develop delayed release dosage form which can stay in colon for prolonged period of time for continuous release of drug, maximize bioavailability of Ketorolac tromethamine and increase patient compliance. For the present study, natural polymers like chitosan, guar gum, karaya gum and xanthan gum(20%,30%,40%). Matrix tablets of Ketorolac tromethamine with natural gums were prepared by wet granulation method and then coated with combination of pH sensitive polymers (Eudragit L100 and Eudragit S100) in 1:1 proportion. IR spectra of drug, excipients and dosage forms reveals that there was no interaction and found to be compatible with each other. Prepared uncoated and coated tablets were characterized for physical parameters, drug content and *in vitro* drug release studies. *In vitro* drug release studies was carried out in 0.1 N HCl (2 hrs) then in pH 7.4 phosphate buffer (3 hrs) and then continued in pH 6.8 phosphate buffer up to 24 hr. The best formulation (F11) containing karaya gum (30%) showed 95.80% drug release up to 24 hr. The dissolution of Ketorolac tromethamine tablets followed first order kinetics. The tablets showed no significant change either in physical appearance or in dissolution pattern after storing at 40^0 C / 75% RH for three months.

Keywords: Colon specific drug delivery system, Ketorolac tromethamine, Natural polysaccharides, Eudragit L-100, Eudragit S-100.

INTRODUCTION

When people have inflammation it often hurts, they feel pain, stiffness, discomfort, distress and perhaps agony, depending on the severity of it. Pain can be constant and steady, in which case it is often referred to as an ache. Pain can be of a throbbing type, a pulsating pain, or it can be a stabbing or pinching pain. Pain is a very individual experience and the only person who can describe it properly is the one who is feeling it. Pain can be acute or chronic. Inflammation primarily causes pain because the swelling pushes against the sensitive nerve endings, which send pain signals to the brain. Inflammation is part of the healing process, it can be reduced by several treatments available now a days[1,2]**.** NSAIDs (non-steroidal anti-inflammatory drugs) are taken to alleviate pain caused by inflammation. They counteract the COX (cyclooxygenase) enzyme, which synthesizes prostaglandins which create inflammation. If prostaglandin synthesis can be blocked, pain is either eliminated or reduced. Examples of NSAIDs include naproxen, ibuprofen and aspirin, Ketorolac, indomethacin etc. Synthetic glucocorticoids are prescribed for inflammation of the joints (arthritis), dermatitis, inflammatory bowel disease, systemic lupus, hepatitis, asthma, allergic reactions, and sarcoidosis. Creams and ointments (topical formulations) may be prescribed for inflammation of the skin, eyes, lungs, bowels and nose[3]. Oral delivery systems are designed to deliver the active directly via the oral cavity with the mouth becoming the site of administration, application and absorption. In this way the drug has direct access to the systemic circulation bypassing the hepatic portal system. When drug enters into stomach there will be a possibility of chemical degradation of drug due to the gastric environment. To prevent the first pass metabolism and protect from gastric environment, now a days many advanced drug delivery systems are heading out. Colon drug delivery system is one of advanced oral controlled drug delivery system[4]. Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e., colon). Drug targeting to colon is useful when a delay in drug absorption is desired from therapeutic point of view. Drugs that are degraded and or poorly absorbed in upper gut may be preferentially absorbed from the colon because of the lower level of luminal and mucosal digestive enzymes, as compared to the small intestine. Lower doses may be adequate and so side effects may be reduced. This colon drug delivery system, by means of combination of one or more controlled release drug in the upper part of GIT, but rapidly release drug in the colon following oral administration[5]. Ketorolac

tromethamine a non-steroidal anti-inflammatory agent was chosen as model drug, which is formulated as colon specific tablet, where maximum drug get released in colon area, in sustaining manner. It is having half life of 2 to 2.5 hrs, and highly soluble in water and methanol[6,7].

MATERIALS AND METHODS

MATERIALS

Ketorolac tromethamine is a gift sample from Symed labs, Hyderabad, India. Guar gum and xanthan gum are gift samples from yarrow chemicals pvt ltd. Mumbai, India. Other ingredients used were of laboratory grade.

METHODS

Formulation

Matrix tablets of Ketorolac tromethamine were prepared by wet granulation method. Lactose was used as diluents and a mixture of talc- magnesium stearate (2:1) was used as lubricant. Karaya gums, guar gum, xanthan gum and chitosan, are natural polysaccharides were included in the formulations in various proportions. The composition of different formulation used in the study containing 20 mg of in each case. In all the formulations, karaya gum, guar gum, xanthan gum and chitosan were mixed with Ketorolac tromethamine and Lactose[8].

Table 1: Composition of colon targeted tablets of Ketorolac tromethamine with different natural gums

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketorolac tromethamine	20	20	20	20	20	20	20	20	20	20	20	20
Guar gum	20	30	40	---	---	---	---	---	---	---	---	---
Xanthan gum	---	---	---	20	30	40	---	---	---	---	---	---
Chitosan	---	---	---	---	---	---	20	30	40	---	---	---
Karaya gum	---	---	---	---	---	----	---	----	----	20	30	40
Lactose	114	104	94	114	104	94	114	104	94	114	104	94
PVP K-30	20	20	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Total	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**

*** Quantity in mg for one tablet**

Preparation of matrix tablets

The powders were blended and granulated with polyvinylpyrollidone K-30 (10% w/w in isopropyl alcohol). The wet mass was forced through 16 mesh sieve and the granules so obtained were kept in dark room for overnight drying. The dried granules were passed through 20 which is super imposed on sieve no.40. The granules which are retained on sieve no.20. and required quantity of fines was added. These granules were lubricated with mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed in tablet compression machine using 8mm round concave punches (Proton press)[9].

Preparation of coated tablets

Coating solution was made using pH sensitive polymers i.e. Eudragit L100, Eudragit S100 in 1:1 proportion. Polymeric content in the coating solution was kept constant as 10%w/v. The required quantity of polymers were dissolved in mixture of solvents (acetone & isopropyl alcohol) and stirred on magnetic stirrer to get homogeneous coating solution. Dibutyl phthalate was added in above solution as plasticizer (2% as polymer based) and titanium dioxide (5% as polymer based) was added as an opacifying agent. After getting homogeneous coating solution coating was done on tablets by dip coating method. The tablets were subjected to coat about 10%w/w of initial weight of tablet[10,11].

Evaluation of tablets

Compatibility studies

Compatibility studies of pure drug Ketorolac tromethamine with polymers and other excipients were carried out prior to the formulation of tablets. IR spectra of pure drug, polymers, other ingredients were obtained, which are depicted in Figure 1to5. All the characteristic peaks of Ketorolac tromethamine were present in spectra at respective wavelengths. Thus, indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

Physical appearance

Tablets were white in color, having concave surface with circular shape.

Uniformity in weight

The uniformity in weight for uncoated and coated formulations was carried out. All the tablets passed the uniformity in weight test, i.e., average % weight variation was found within the pharmacopoeial limits of ±7.5%.

Friability test

Friability values for batches from F_1 to F_{12} were found to be in the range 0.44 to 0.59%. The results were found to be well below the standard range (<1%) for all the prepared formulations. The data indicated tablets possess good mechanical strength.

Hardness test

Hardness of uncoated tablets for all the formulations was found to be in the range 4.1 to 4.9 kg/cm^2 and for coated tablets it was found to be in the range 5.0 to 5.7 kg/cm^2 .The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness.

Uniformity of thickness

The mean thickness of tablets (n=3) of batches from F_1 to F_{12} were found to be in the range 3.27 to 4.26 mm. The standard deviation values indicated that all the formulations were within the range and show uniform thickness.

Drug content

The average value and standard deviations were calculated. The drug content of tablets for batches from F_1 to F_{12} was found to be in the range 89.18 to 94.75%. The results were within the limit (90% to 110%) specified in pharmacopoeia.

***In- vitro* dissolution studies**

The prepared formulations of Ketorolac tromethamine were subjected for *in vitro* dissolution studies using USP – Type I dissolution apparatus (Electrolab, India) with a basket speed of 50 rpm. The dissolution study was carried out in 900 ml of three different dissolution media i.e. first 2 hrs in pH 1.2 followed by next 3 hrs in 7.4 pH and remaining in 6.8 pH buffer upto 24 hrs, maintained at 37±0.5 ^{o}C. At suitable time interval, 5 ml samples were withdrawn and replaced with equivalent amount of fresh medium to maintain sink conditions. Samples withdrawn were filtered and analyzed at 322 nm using a UV spectrophotometer. Formulation tablets containing, Guar gum (F_1, F_2 F_3), has shown 80.53%, 73.54% and 64.77% drug release in 12 hrs. Formulations Xanthan gum (F_4, F_5, F_6), have shown drug release of 55.26%, 54.08% and 57.14% in 12 hrs. Chitosan (F7-F9), based formulations have shown of 88.10%, 89.18% and 83.58% drug release after 7 to 8 hrs. The formulation with gum Karaya (F_{10}, F_{11}, F12), shown up to 79.38%, 87.42% and 80.98% drug release within 8hrs. From the dissolution data one formulation from each class selected for further studies. The selection was done on the basis of maximum drug release in lesser time. These formulations are F_1, F_8 and F_{11}. Further the selected formulations coated with Eudragit S-100 and Eudragit L-100 in combination with different coating concentration, 5% and 10%. Formulations with 5% coating have shown maximum drug release up to12 hrs. F_1C_5 had shown 86.29% drug release, F_8C_5 had shown 91.66% and $F_{11}C_5$ had shown 92.99%. When the concentration of coating was increased up to 10%, the release rate was decreased with increasing sustaining effect up to 24 hrs. F_1C_{10} had shown 92.6% drug release, F_8C_{10} had shown 90.94% and $F_{11}C_{10}$ had shown up to 95.80% drug release.

Table 2: Post-compression evaluation of the prepared tablets

Formulation code	Hardness of Uncoated Tablet (kg/cm^2) (n=3)	Hardness of Coated Tablet (kg/cm^2) (n=3)	Friability (%)	% Drug Content (n=3)
F1	4.3±0.17	5.5±0.1	0.28	93.81±3.19
F2	4.33±0.20	5.36±0.25	0.56	88.39±2.82
F3	4.5±0.26	5.46±0.25	0.41	93.15±4.63
F4	4.46±0.25	5.4±0.26	0.53	93.64±0.47
F5	4.8±0.17	5.33±0.23	0.41	94.7±0.35
F6	4.3±0.26	5.2±0.1	0.56	92.79±0.47
F7	4.43±0.40	5.3±0.26	0.41	90.87±0.70
F8	4.36±0.23	5.43±0.25	0.41	93.12±2.48
F9	4.53±0.15	5.4±0.2	0.41	94.44±2.63
F10	4.33±0.32	5.4±0.26	0.27	90.61±1.45
F11	4.46±0.25	5.23±0.15	0.42	93.06±0.95
F12	4.23±0.15	5.33±0.28	0.28	89.18±1.10

Table 3: Post-compression evaluation of the prepared tablets

Dissolution medium	Time (Hrs)	% Cumulative drug release		
		F_1C_5	F_8C_5	$F_{11}C_5$
0.1 N HCl	0.0	0.0	0.0	0.0
	0.5	9.55±0.55	11.25±0.32	16.40±1.58
	1	12.33±0.63	13.53±0.74	21.67±2.20
	1.5	14.82±0.73	17.67±0.33	27.55±1.89
	2	17.52±0.74	20.55±0.28	31.84±0.28
7.4 pH buffer	3	31.75±1.37	39.91±0.84	61.45±3.38
	4	37.67±1.03	47.95±1.38	67.79±1.85
	5	40.57±0.82	56.74±2.14	72.00±2.32
6.8 pH buffer	6	50.95±1.73	65.45±1.47	77.01±2.47
	7	59.10±1.56	69.61±0.92	79.87±4.01
	8	62.13±5.24	71.97±1.43	82.19±3.24
	9	76.07±2.35	74.34±0.87	84.84±3.16
	10	80.85±1.39	82.80±2.94	86.74±3.01
	11	85.35±1.20	88.40±0.71	88.59±2.94
	12	86.29±1.54	91.96±2.75	92.99±1.31

Table 4: *In vitro* drug release study of coated matrix tablets F_1C_5, F_8C_5, $F_{11}C_5$ with Eudragit L-100 and Eudragit S-100 (5% concentration)

Formulation code	Uniformity of thickness (mm) (n=3)	Weight variation of uncoated tablet (mg)	Weight variation of coated tablet (mg)
F1	3.83±0.49	179.66±2.30	207±1.0
F2	4.05±0.095	178.66±0.57	207.33±1.52
F3	4.03±0.020	182±2.0	201.33±3.21
F4	4.04±0.062	182±2.64	204.66±3.51
F5	4.016±0.0057	181.66±1.52	205.33±5.03
F6	4.11±0.04	181.33±0.57	203.33±2.08
F7	4.1±0.055	181±2.0	205.33±2.30
F8	4.22±0.030	181.66±0.57	205±2.64
F9	4.11±0.078	181±1.73	209.33±1.15
F10	4.14±0.098	179.33±1.52	206±1.73
F11	4.08±0.12	180±1.0	204±3.46
F12	4.11±0.10	180.66±1.52	204.66±2.51

Table 5: *In- vitro* drug release study of coated matrix tablets F_1C_{10}, F_8C_{10}, $F_{11}C_{10}$ with Eudragit L-100 and Eudragit S-100 (10% concentration)

Dissolution medium	Time (Hrs)	% Cumulative drug release		
		F_1C_{10}	F_8C_{10}	$F_{11}C_{10}$
0.1 N HCl	0.0	0.0	0.0	0.0
	0.5	0.775±0.18	0.705±0.0057	0.165±0.005
	1	0.785±0.20	0.706±0.096	0.221±0.096
	1.5	0.785±.20	0.761±0.096	0.221±0.096
	2	0.999±0.16	2.01±0.094	0.387±0.094
7.4 pH buffer	3	5.285±1.19	5.8±0.58	6.80±0.58
	4	12.70±0.16	9.65±1.66	9.98±1.66
	5	20.45±0.43	11.14±1.32	13.93±1.32
6.8 pH buffer	6	32.19±1.04	18.28±1.59	21.54±1.59
	7	43.63±3.30	25.85±1.00	28.29±1.00
	8	53.56±1.57	34.14±5.63	35.34±5.63
	9	63.37±0.31	44.79±0.75	47.88±0.75
	10	70.68±0.93	56.39±1.00	58.89±1.00
	11	79.44±4.05	70.67±2.21	66.88±2.21
	12	85.74±2.18	80.06±3.33	78.99±3.33
	18	90.61±1.46	87.99±0.73	92.80±0.73
	24	92.6±2.34	90.94±1.40	95.80±1.40

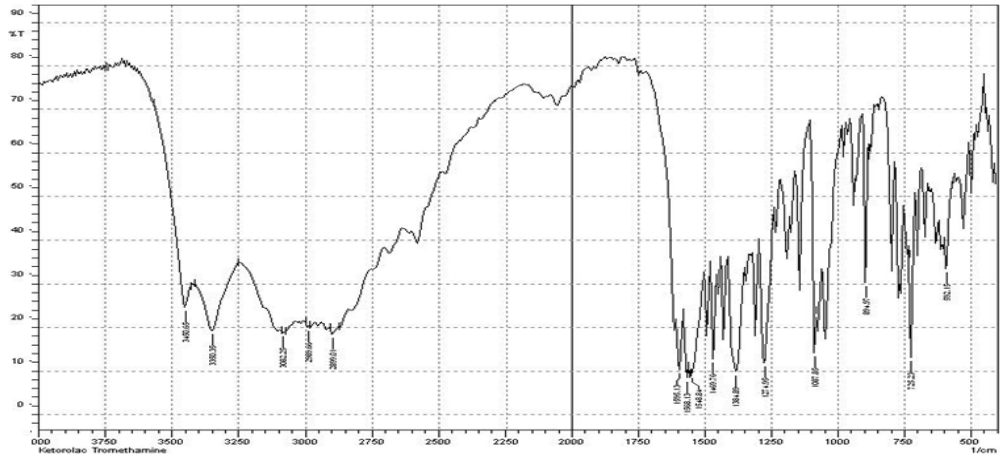

Figure 1: FT-IR Spectra of Ketorolac tromethamine (pure)

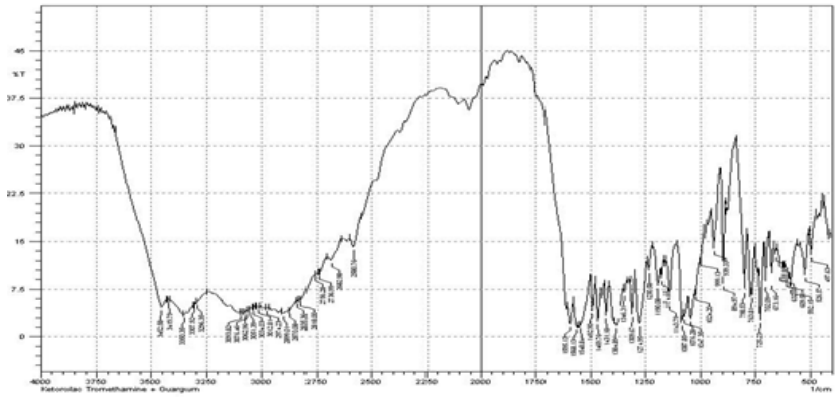

Figure 2: FT-IR spectra of Ketorolac tromethamine and Guargum

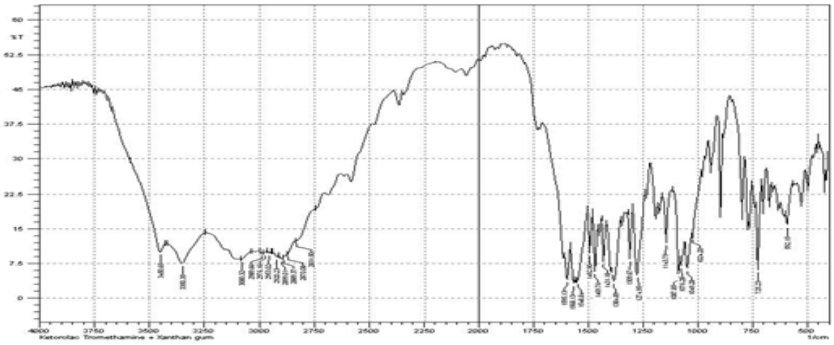

Figure 3: FT-IR spectra of Ketorolac tromethamine and Xanthan gum

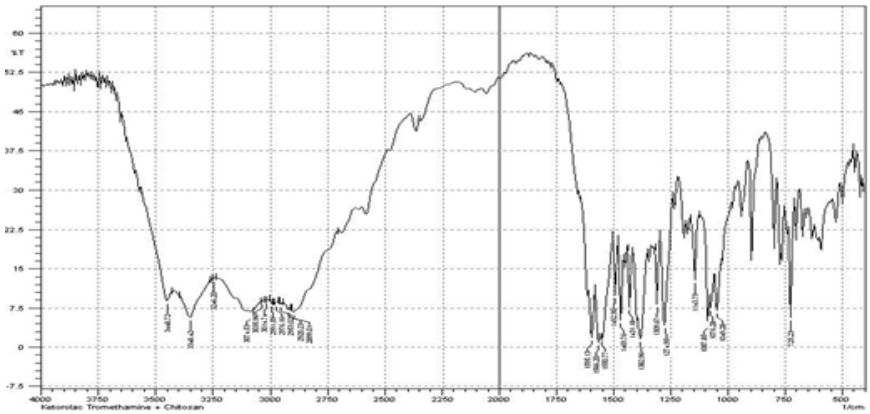

Figure 4: FT-IR spectra of Ketorolac tromethamin and Chitosan

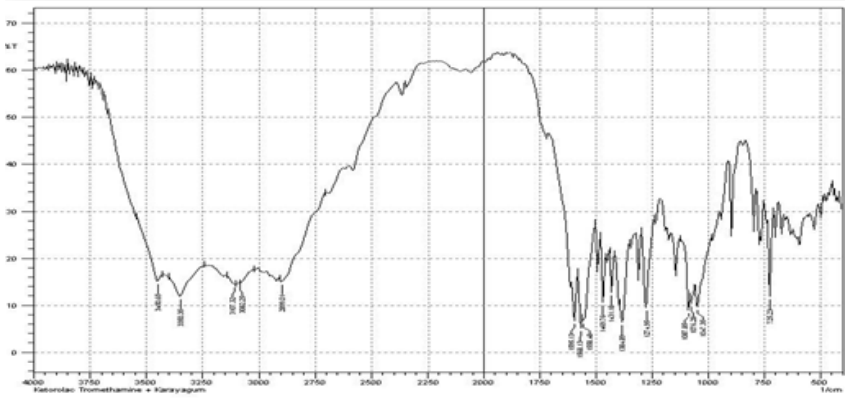

Figure 5: FT-IR spectra of Ketorolac tromethamine and Karayagum

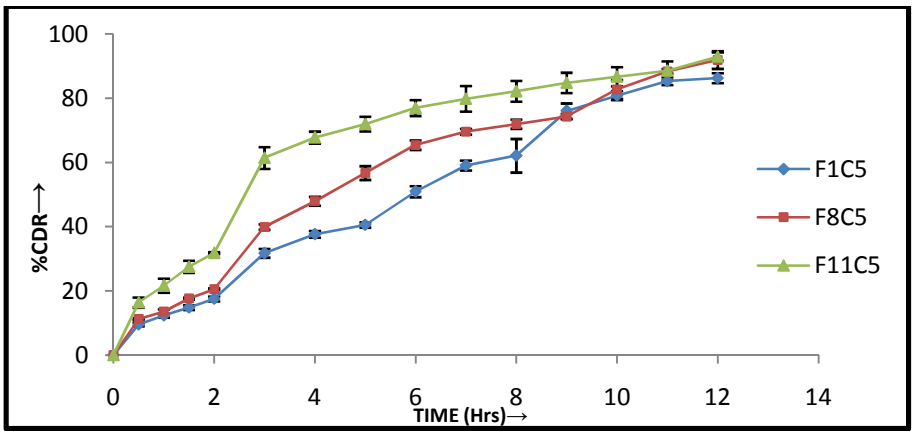

Figure 6: % Cumulative drug release Vs Time for best formulations F_1C_5, F_8C_5, $F_{11}C_5$ with 5% coating concentration

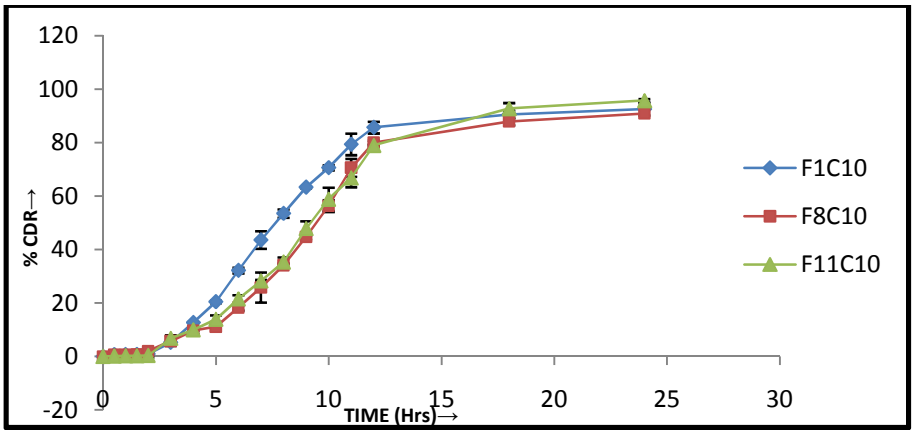

Figure 7:% Cumulative drug release Vs Time for best formulations F_1C_{10}, F_8C_{10}, $F_{11}C_{10}$ with 10% coating concentration

RESULTS AND DISCUSSION

In present study, utilization of the metabolic activity and the colonic environment in the lower gastrointestinal tract has attained immense value in the design of colon specific drug delivery systems by the utilization of natural biodegradable polymers. Colon-specifc drug delivery holds promise for direct, more effective delivery of therapeutic agents to the colon for patients being treated for illnesses, such as amoebiasis irritable bowel syndrome (IBS), colonic cancer, ulcerative colitis, Crohn's disease, etc. These delayed release mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are needed the most, and also minimize the potential side effects and drug instability issues that are frequently associated with premature release of drug in the upper parts of the GIT, namely the stomach and small intestine.This study attempts to design and characterize colon specific drug delivery system of Ketorolac tromethamine, for the treatment of acute to chronic pain, arthritis, ulcerative colitis. As Ketorolac tromethamine is Non-steroidal anti-inflammatory agent, It has relatively poor pharmacokinetic profile undergoing extensive 1st pass metabolism with half life 2.7 to 5.5 hours.Prior to formulation, preformulation studies were carried out in order to establish compatibility between drug and polymers by IR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of the drug. The matrix tablet containing Ketorolac tromethamine, (20 mg) as a active ingredient, was prepared by wet granulation method using 4 different natural polysaccharides , guar gum,xanthan gum,karaya gum and chitosan) in different proportion (20%, 30% and 40%). The tablets were coated with combination of pH sensitive polymers, Eudragit L100 and Eudragit S100 by dip coating method to reduce the drug release in acidic environment of stomach. The coated and uncoated tablets were developed to a satisfactory level, in terms of their physical parameters weight variation, thickness, hardness, friability, drug content. Coated tablets were subjected for *in vitro* dissolution studies and stability studies. From the *in vitro* release studies of tablets, it was observed that with all formulations, there was drug release up to 24 hrs in a controlled manner. Formulation containing 30% karaya gum was considered as best formulation as it has shown 95.80% drug release up to 24 hrs in controlled manner. From stability studies, it was observed that there was no significant change in the drug content and percentage drug release, therefore the formulation was quite stable.

CONCLUSION

Colon specific tablets of Ketorolac tromethamine were prepared by using natural polymers and coated with Eudragit S & L-100.Coated tablets were evaluated for in-vitro release study. From *in- vitro* drug release profiles for all the twelve

formulations with different concentration of natural polysaccharides indicated that dissolution rate is inversely proportional to the polymer concentration present in tablet. Coated matrix tablets were help retard or delayed the release of drug up to 24 hrs. Release profile of all optimum formulations followed First order kinetics. Formulation containing 30% karaya gum shown maximum drug release up to 24 hrs. which is considered as best formulation. Stability studies for formulation containing 30% karaya gum proved that the formulation was quite stable.

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