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Research Article

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Design and development of guar gum and borax crosslinked guar gum matrix tablets of theophylline for colon specific drug

P. J. Subrahmanyam

Dr. Reddy's laboratories limited, Hyderabad

ABSTARCT

The present study was carried out to develop an oral colon targeted drug delivery system, which consists of Theophylline matrix tablets prepared using guar gum and borax cross linked guar gum as rate controlling polymers in different concentrations. These tablets were evaluated for weight variation, friability, hardness uniformity of content and in vitro drug release under specified conditions. The dissolution data revealed that the tablets containing guar gum and borax cross linked guar gum in higher concentrations each (120mg) showed 87.567±0.42% and 76.186±0.17% of drug release respe ctively. And selected tablets of borax cross linked guar gum were subjected to in vitro drug release study in presence of rat caecal content medium. Results clearly indicate that there is an increase in the release of the drug to 98.930±0.38%.

Key words: Theophylline, Guar gum, Borax cross linked guar gum.

INTRODUCTION

Targetting of drugs to specific sites gaining more attention today as we can increase the efficacy, reduce the undesirable effects of drugs with the site specificity. Now a days Colon specific drug delivery is not only used for the delivery of peptides and proteins which are susceptible to degradation in the upper parts of the gastro intestinal tract but also for the delivery of drugs which are used to treat the diseases associated with the colon , large intestine such as ulcerative colitis, diarrhea and colon cancer. Colon drug delivery is usually employed to achieve one of the four objectives, the desired outcomes can be (a) sustained delivery to reduce dosing frequency; (b) to delay delivery to the colon to achieve high local concentrations in the treatment of diseases of the distal gut (c) to delay delivery to a time appropriate to treat acute phases of diseases (chronotherapy) (d) to deliver to a region that is less hostile metabolically e.g. to facilitate absorption of acid and enzymatically labile materials, especially peptides[1]. Approaches used in the colon delivery of drugs include use of prodrugs[2], pH sensitivce polymer coating, time dependent formulations, bacterial degradable coatings[3], and intestinal luminal pressure controlled colon delivery capsules[4].

Guar gum is a natural polysaccharide obtained from the endosperm of the Cyamopsis tetragonoloba belongs to the family Leguminosae

EXPERIMENTAL SECTION

2.1 Materials

Theophylline and guar gum were obtained as a gift sample from Natco-Pharma Pvt. Ltd, Hyderabad, India. Ethanol and Disodium tetra borate (borax) were procured from S.D. Fine Chemicals Mumbai, India. All other reagents used in the study were of analytical grade.

2.2 Methods

2.2.1 Preparation of borax guar gum

4gms of guar gum was dispersed for 1 hr at room temperature in 400 ml of distilled water with the help of mechanical stirrer. The dispersion was kept aside for 2 hrs for swelling. 80 ml of 1%w/v aqueous solution of borax (disodium tetra borate) was added to the guar gum dispersion and stirred for 30 min with the help of mechanical stirrer then kept aside for another 4 hrs without stirring. The formed hydrogel was rinsed with distilled water to remove untreated borax and then the hydrogel was dried at room temperature for 3 days. The dried Borax cross linked guar gum was triturated in a mortar for size reduction and passed through sieve no 100.

2.2.2 Estimation of free borax and cross linked borax by titration with 0.05N HCl[5]:

200 mg of guar gum was taken in conical flasks and dispersed in 30 ml of distilled water to make uniform dispersion. To the dispersion, methyl red was added and titrated against 0.05M HCl solution. The guar gum dispersion titrate value was taken as blank value.200 mg of borax cross linked guar gum was taken in conical flasks and dispersed in 30 ml of distilled water to make uniform dispersion. To the dispersion methyl red was added and titrated against 0.05 M HCl solution. Titrate value was taken as free borax value. In the same way again 200 mg of borax cross linked guar gum was taken and dispersed in 30 ml of distilled water to make uniform dispersion. The dispersion was heated at 70^0C to break the cross linked bonds of borax with guar gum and then to the dispersion methyl red was added and titrated against 0.05 M HCl solution and the results are shown in **table1.**

It is direct titration of strong alkaline borax with strong acid HCl. One mole of borax reacts with 2 moles of HCl. Methyl red is used as an indicator because it is not affected by weak acid (Boric acid) end point is colour change from yellow to pink[6].

$$Na_2B_4O_7 \longrightarrow 2Na^+ + B_4O_7^{-2}$$
$$B_4O_7^{-2} + 7H_2O \longrightarrow 4H_3BO_3 + 2OH^-$$
$$2HCl + 2OH^- \longrightarrow 2H_2O + 2Cl^-$$
$$Na_2B_4O_710H_2O + 2HCl \longrightarrow 2NaCl + 4H_3BO_3 + 5H_2O$$

2.2.3 Preparation of Theophylline matrix tablets

Theophylline matrix Tablets were prepared by wet granulation technique using PVPK30 as binder in IPA. All the ingredients as mentioned in **Table2** were passed through sieve No. # 40 mesh except magnesium stearate and talc (#80 mesh), powder was thoroughly mixed and granulated until dough mass formed. Granules were prepared by passing through sieve no 16 and were lubricated with talc and magnesium stearate then compressed in to tablets on a 16-station rotary tablet punching machine (M/S. Cadmach Machinery Co. Pvt. Ltd., India) fitted with 9 mm round, standard concave punches with hardness at a range of 5-7 Kg/cm^2.

2.2.4 Rheological studies of Guar gum and Borax cross linked Guar gum

Viscosity of 1%w/v dispersion of Guar gum and Borax cross linked Guar gum in water, 0.1N HCl, pH 7.4 and pH 6.8 Phosphate Buffers was measured by using Brookfield viscometer and results are shown in **table 3.**

2.2.5 Swelling studies of Guar gum and Borax cross linked Guar gum[7]

Swelling capacity of both Guar gum and Borax cross linked Guar gum was studied in distilled water, 0.1N HCl, pH 7.4 and pH 6.8 phosphate buffers

1gm of gum was taken in a measuring cylinder to this 10 ml of distilled water was added and shaken vigorously for 10min and allowed to stand for 24hrs. Swelling capacity can be determined by,

$$\text{Swelling Capacity (\%v/v)} = [X_v / X_i] \text{ X100}$$

Where X_v denotes the final volume occupied by swollen material after 24hrs and X_i denotes the initial volume of the powder in graduated measuring cylinder.

Same procedure was repeated to study the swelling capacity of both gums in 0.1N HCl, pH 6.8 and pH 7.4 phosphate buffers and results are shown in **table 4**.

2.2.6 Evaluation of tablets

Formulated tablets were evaluated for the following physicochemical characteristics like weight variation, hardness, friability, uniformity of drug content and all the tablets followed the official compendial standards as per the I.P. specifications, results are shown in **table 5.**

2.2.7 In vitro dissolution studies[8]:

Dissolution studies were carried out using USPXXII, type I apparatus (Model: DISSO 2000, M/s. Lab India) at 100 rpm. The tablets were placed in 900 ml of simulated gastric fluid (pH 1.2) for 2 hr, simulated intestinal fluid (pH 7.4) for 3 hr and simulated colonic fluid (pH 6.8) for 19 hr. sampling was done at regular time intervals and the same were estimated for drug content after suitable dilution by using double beam UV-visible spectrophotometer and drug release profiles are shown in fig1.

2.2.7.1 Preparation of rat caecal medium[9]:

In vitro drug release studies were performed in the presence of rat caecal content after 5 hrs of dissolution (first 2 hrs in 0.1 N HCl and another 3 hrs in pH 7.4 Phosphate buffer). The albino rats weighing between 150-200 gm were selected and 1 ml of 1% w/v solution of borax cross linked guar gum was administered with the help of teflon tubing directly into the esophagus region via oral cavity. The treatment was continued for 6 days to induce enzyme responsible Borax guar gum degradation, animals were sacrificed before 30 min of dissolution studies and the caecum was exteriorized for content collection. The caecal content (anaerobic) was immediately transferred into buffer saline solution of pH 6.8 and 2%w/v concentration of solution was prepared by diluting with pH 6.8 phosphate buffer which was bubbled with CO_2 to maintain the anaerobic environment .Dissolution studies were carried out using USPXXII type I (basket) dissolution test apparatus. As the caecum is anaerobic in nature, the experiment was carried out with continuous CO_2 supply into the dissolution apparatus.5 ml of the samples were with drawn at regular time intervals for about 19 hrs and the volume was replaced with fresh medium.

2.2.8 Drug release kinetics

Drug release from the tablets can be explained by two different methods, Model dependent and model independent methods.

In model-dependent approach, the dissolution data can be fitted in to five popular release models such as zero-order, first-order, higuchi diffusion, hixson-crowell erosion and Korsmeyer-Peppas equations[10].

Mathematical models for comparison of the dissolution profiles

Model	Equation
Zero-order	$Q_t = Q_0 + k_0 t$
First-order	$\ln Q_t = \ln Q_0 - k_1 t$
Higuchi	$Q_t = k_H \sqrt{t}$
Hixon-Crowell	$Q_o^{1/3} - Q_t^{1/3} = k_s t$
Korsmeyer-Peppas	$Q_t / Q_\infty = k_k t^n$

Q_t: amount of drug released in time t, Q_0: initial amount of drug in the Tablet, Q_t/Q_∞: fraction of drug released at time t, k_0; k_1; k_H; k_k; k_s: release rate constants, n: the release exponent indicative of the mechanism of drug release.

The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using higuchi or erosion equation. The n value is obtained as a slope for different batches of matrix tablets by plotting log percent drug dissolved against log time. If the value of n = 0.45 indicates Fickian (case I) release; 0.45 < n < 0.89 for non-Fickian (anomalous) release;

n=0.89 case II and > 0.89 indicates super case II transport. Case II generally refers to the erosion of the polymeric chain and non-Fickian diffusion refers to a combination of both diffusion and erosion mechanism from the controlled drug release tablets[11].

Infrared Spectroscopy Studies:
The IR spectra of pure drug and the optimized formulation (pure drug with Borax cross linked guar gum) were recorded using KBr pellet technique (1:100) at resolution rate of $4cm^{-1}$. Spectrum was integrated in transmittance mode at the wave number range $400\text{-}4000cm^{-1}$

RESULTS AND DISCUSSION

3 Tabletting parameters
All the prepared tablets comply with the compendial standards for uniformity of weight and drug content uniformity as per the I.P. specifications. Hardness and friability values were found to be in the range of 5-7 kg/cm^2 and the results are shown in **Table 5.**

3.1 Drug release profiles
Drug release profiles of guar gum and borax cross linked guar gum are presented in fig 1,2and 3 from the results it was observed that the as the concentration of guar gum increased from 60 to 140 mg there was decrease in drug release rate which was due to high viscosity of guar gum. When the guar gum was replaced by borax cross linked guar gum of same concentration drug release was further controlled which was due to the increase in viscosity and less swelling Index of the borax cross linked guar gum compared with guar gum. Increase in viscosity allows the drug to travel along the longer diffusional path. When the dissolution of the formulation F10 was carried in presence of caecal content maximum amount of drug was released compared to dissolution of formulation F10 in medium with out caecal content indicating the enzyme dependent degradation of borax guar gum.

3.2 kinetic analysis of the dissolution data
All the prepared formulations were fit in to popular models like zero order, first order,higuchi,erosion and peppas equations and the results are shown in **table 6** results of drug release kinetics showed that all the formulations followed zero order release from the higuchi and equations it was found that F1,F2,F3formulations followed non fickian diffusion mechanism while the remaining followed erosion mechanism.

3.3 IR spectra analysis
From the IR spectra it was concluded that the drug was compatible with the all excipients used in the formulation.

Table no 1:- Titration of 200 mg of Guar Gum, Borax Cross linked Guar Gum and Borax Cross linked Guar Gum While Heating

S. No	Contents in Conical Flask	Burette reading		Titer Value ml	Amount of Borax Present in mg
		V1 ml	V2 ml		
1	200 mg of Guar Gum + 30 ml Water	50	49.8	0.2	----------
2	200 mg of Borax Cross linked Guar Gum + 30 ml Water	49.8	49.4	0.4	0.766 mg/200 mg of polymer(Unreacted $B_4O_7^{-2}$)
3	200 mg of Borax Cross linked Guar Gum + 30 ml Water While heating	49.4	46	3.4	11.5 mg/200 mg of polymer (Crosslinked $B_4O_7^{-2}$)

Unreacted $B_4O_7^{-2}$ present in 200 mg of Borax crosslinked Guar Gum is 0.766 mg
Unreacted $B_4O_7^{-2}$ present in 1g of Borax crosslinked Guar Gum is 3.83 mg.
Crosslinked $B_4O_7^{-2}$ present in 200 mg of Borax crosslinked Guar Gum is 11.5

Table 2: Formulation of Theophylline tablets with guar gum and borax cross linked guar gum

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Theophylline	200	200	200	200	200	200	200	200	200	200
Guar Gum	60	80	100	120	140	----	----	----	----	----
Borax Guar Gum	----	----	----	----	----	60	80	100	120	140
PVP K 30 (3%)	8	8.5	9	9.5	10	8	8.5	9	9.5	10
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3
Total weight	274	294.5	315	335.5	356	274	294.5	315	335.5	356

Table 3: Viscosity studies of 1%w/v Dispersions of Guar gum and Borax cross linked guar gum

1%w/v Dispersion of Polymer	Viscosity in Water(cps)	Viscosity in 0.1 N HCl(cps)	Viscosity in pH 6.8 Phosphate Buffer(cps)	Viscosity in pH 7.4 Phosphate Buffer(cps)
Guar gum	114.7	110.3	113.1	117.4
Borax guar gum	181.2	177.9	179.7	184.6

Table 4: Swelling index studies of guar gum and borax treated guar gum

Polymer	Swelling Index in Water	Swelling Index in 0.1 N HCl	Swelling Index in pH 6.8Phosphate Buffer	Swelling Index in pH 7.4Phosphate Buffer
Guar gum	8.5	9.1	8.7	8.4
Borax guargum	5.1	5.6	5.3	4.9

Table 5: Physical properties of the Theophylline tablets formulated with various polymers.

Formulation	Theoretical weight	Average weight	% Drug content	Hardness kg/cm^2	% Friability
F_1	274	274.6	101.2±0.98	6.8	0.46
F_2	294.5	294.1	98.45±1.01	5.5	0.32
F_3	315	314.2	100.89±0.81	5.9	0.37
F_4	335.5	334.8	99.43±0.53	6.4	0.46
F_5	356	356.7	98.88±0.79	6.6	0.32
F_6	274	275.1	101.26±0.21	7.2	0.38
F_7	294.5	295.2	98.24±o.43	6.9	0.48
F_8	315	315.7	99.32±0.27	5.8	0.41
F_9	335.5	334.3	98.86±0.29	6.1	0.38
F_{10}	356	355.2	100.58±0.23	6.5	0.43

Fig 1: Comparative Dissolution Profiles of Theophylline matrix Tablets Formulated with Guar gum (F1 to F5):

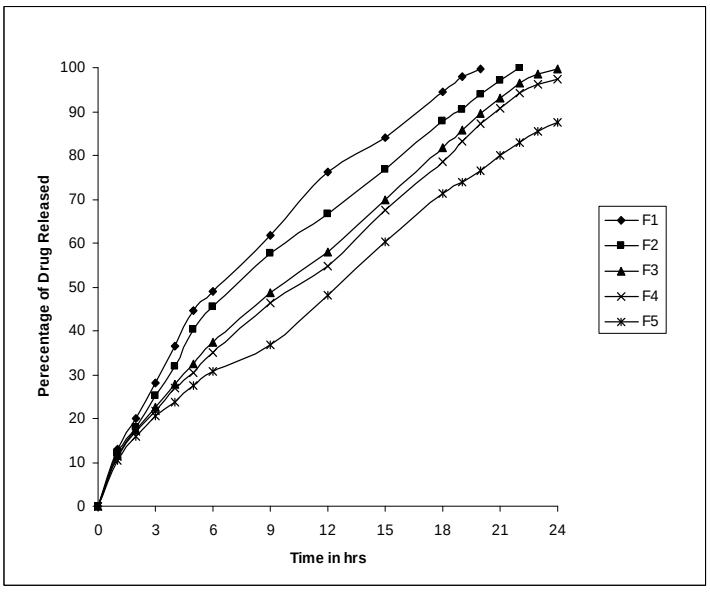

Fig 2: Comparative Dissolution Profiles of Theophylline Tablets Formulated with Borax cross linked guar gum (F6 to F10)

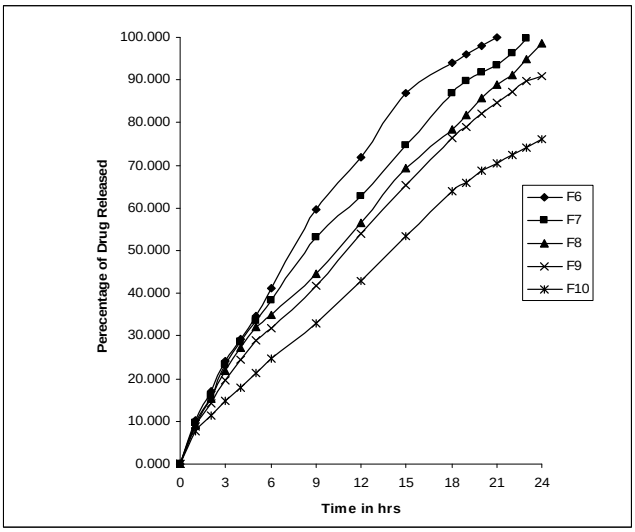

Fig 3: Comparative Dissolution Profiles of Theophylline Formulations F5 (best formulation with Guar gum) and F10 (best formulation with Borax Cross linked Guar gum) Without Caecal Content and With Caecal Content

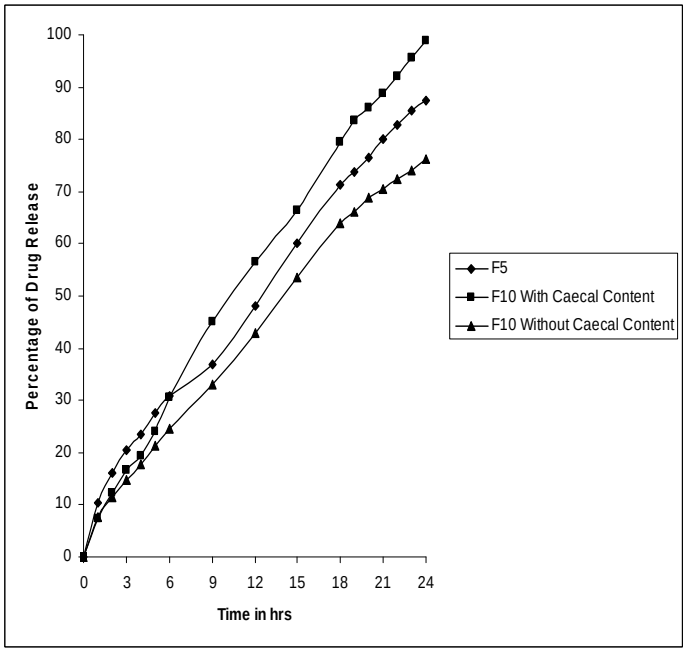

Fig 4: IR Spectrum of formulation

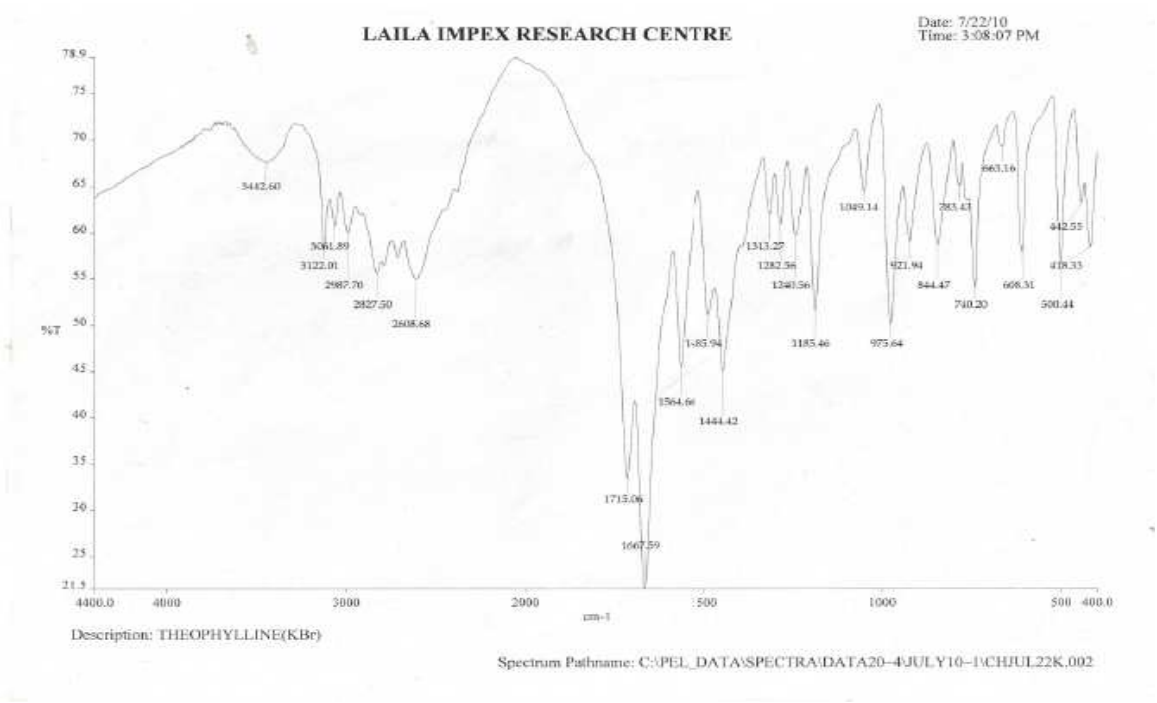

Fig 5: IR Spectrum of formulation

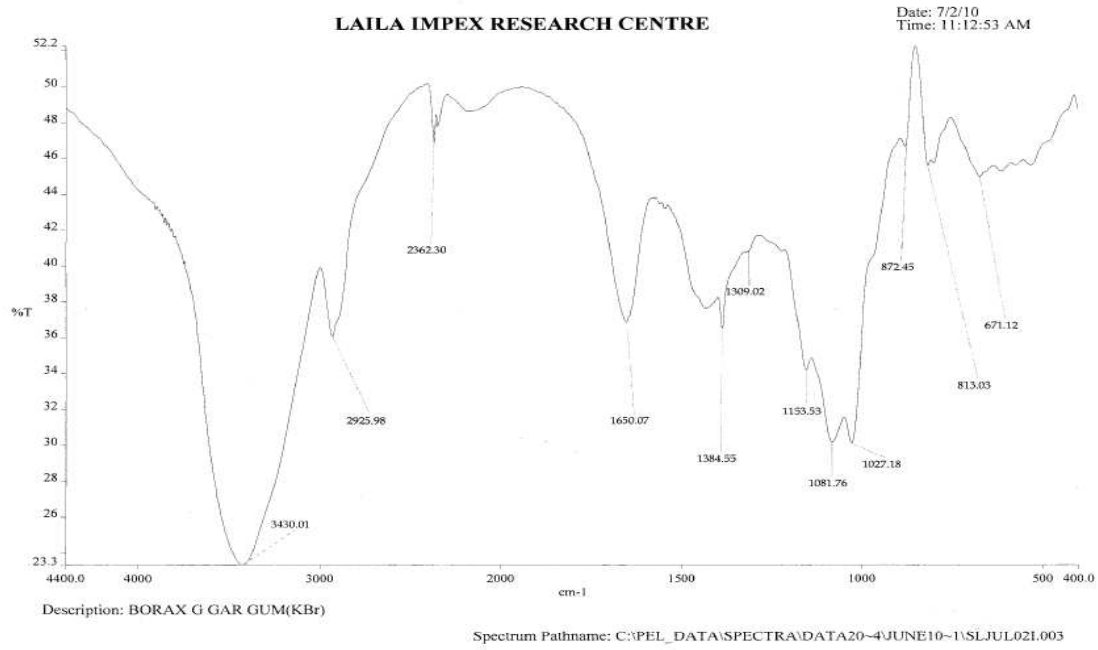

Table 6: in vitro drug release kinetics of Theophylline tablets

Formulation	correlation coefficient					
	Zero order	First order	Hixson crowell	Higuchi	Peppas	Exponential coefficient (n)
F_1	0.9449	0.8645	0.9774	0.9841	0.9977	0.6987
F_2	0.9524	0.8070	0.9665	0.9823	0.9981	0.6989
F_3	0.9747	0.8243	0.9561	0.9715	0.9990	0.6871
F_4	0.9784	0.9171	0.9735	0.9675	0.9985	0.6906
F_5	0.9802	0.9708	0.9889	0.9621	0.9947	0.6670
F_6	0.9722	0.8688	0.9812	0.9672	0.9986	0.7697
F_7	0.9714	0.8612	0.9754	0.9732	0.9992	0.7529
F_8	0.9795	0.9051	0.9749	0.9679	0.9990	0.7386
F_9	0.9832	0.9719	0.9933	0.9642	0.9995	0.7500
F_{10}	0.9907	0.9899	0.9969	0.9528	0.9969	0.7559
F_{10}+Caecal Content	0.9932	0.8866	0.9685	0.9490	0.9976	0.8301

DISCUSSION

Guar gum a naturally occurring polymer can be used for the colon targeting of the drugs in the present research guar gum was crosslinked with the borax to enhance the viscosity of the gum there by increasing its efficiency as controlled release polymer. Amount of free borate in the formulation was estimated by titrimetry. Viscosity and swelling studies were conducted for guar gum as well as crosslinked guar gum form the results it was observed that crosslinking with borax enhanced the viscosity and reduced the swelling of the polymer. Formulations were prepard as per Table 1 by wet granulation technique and the granules were compressed using 16 station rotary compression. Prepared tablets were evaluated for quality control parameters and results are shown in Table 5.Dissolution studies were performed for all the formulations in 0.1N HCl (pH 1.2) for first two hours, simulated intestinal fluid (pH 7.4) for 3 hr and simulated colonic fluid (pH 6.8) for 19 hr. Comparative dissolution profiles of Theophylline matrix tablets formulated with guar gum are shown in figures 1-3. Dissolution data was fitted in to popular kinetic models like Higuchi, Hixon-Crowell cube root model,Peppas and values are given in table 6 from the kinetic analysis of the data it was shown that optimized formulation F10 followed zero order release with non-fickian diffusion mechanism in the absence of caecal content and it followed erosion mechanism in the presence of caecal content indicating the degradation of polymer in the presence of colonic microflora . The IR spectra of the pure drug and best formulation indicated that no chemical interaction occurred between the drug, Theophylline and the carriers used.

CONCLUSION

In this study the influence of cross linking agent borax on drug release characteristics was studied. The cross linking of borax on guar gum can increase the viscosity and reduce the swelling index of the polymer so the cross linking can retard the drug release efficiently when compared to normal guar gum. Cross linked guar gum was estimated for the determination of any free borate ions by titrimetry. Dissolution profiles of formulations formulated with the guar gum and borax cross linked guar gum were compared and results showed that cross linked guar gum controlled the drug release efficiently than the untreated guar gum; this was further conformed by the swelling studies of the formulations. Maximum amount of the drug was released in the presence of caecal content it can be correlated with the drug release in the colon due to microbial degradation. From this study it was concluded that borax cross linked guar gum a novel polymer can be used as controlled release polymer.

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