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Research Article

DESIGN AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY OF NAPROXEN SODIUM USING GUAR GUM AND CROSSLINKED GUAR GUM

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ABSTRACT

The purpose of this research was to develop and evaluate a matrix system for Chronotherapeutic delivery of NSAID (Naproxen Sodium) containing Guar gum and chemically modified guar gum in the treatment of Rheumatoid Arthritis. Matrix tablets of Naproxen Sodium- Guar gum were prepared by using wet granulation method and evaluated by different in vitro tests and release profiles. The release profile of Naproxen Sodium from the matrix tablets is dependent upon the gelling property of Guar gum and degradation of Guar gum by colonic bacteria. In Stomach, the release rate was much slower; however, the drug was released quickly in the lower part of GIT after 4 hours. The dissolution data revealed that the tablets containing guar gum and cross linked guar gum in higher concentrations each showed 84.956±0.42% and 78.286±0.17% of drug release respectively with in 24hrs study period. And selected tablets of 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% due presence of ceacal content. The results were subjected to study the release kinetics. The values of correlation coefficient indicated that the drug release followed Zero order drug release kinetics with Peppas drug release mechanism.

Keywords: Colon specific drug delivery, Nocturnal Rheumatoid Arthritis, Naproxen Sodium, Guar gum, Carboxy methylated guar gum (CMG).

INTRODUCTION

The site specificity of drugs to the colonic part is advantageous for the localized and systemic treatments of various diseases conditions. Colon targeting was attained a significant role in treatment of local pathologies and Chronotherapy of various disorders includes Asthma, Rheumatoid arthritis and Hypertension. Colon drug delivery system is valuable design, when a delay in absorption is therapeutically vital in the treatment of chronic medical conditions like nocturnal rheumatoid arthritis.The aim of this study was to explore the feasibility of the guar gum dependent Chronotherapeutic drug delivery system (CDDS), NSAID being selected as a model drug. Naproxen Sodium (widely used NSAID) was frequently used for treating rheumatoid arthritis, which had apparent circadian rhythms and peak symptoms in the early morning[1]. When orally administering Naproxen Sodium conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patients' incompliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation. However, colon specific Naproxen Sodium delivery is not only effective, but also more convenient for administration than the conventional formulation to get the drug release after desired time period because of the few physiological facts like

- Transit time to colon
- Colonic bacteria triggered degradation
- pH triggered effect

Naproxen sodium possesses good oral bioavailability and adequate colon absorption. Hence it was selected as an ideal candidate for the colon drug delivery system. This system when administered in night was aimed to achieve an elevated Naproxen sodium levels overnight where the risk of Rheumatoid arthritis was found to be maximum.

The present study focused on development of Colonic bacterial enzyme degradable polymer matrix formulation to treat the nocturnal symptoms of Rheumatoid arthritis. The use of natural gums in their putative form requires in large quantities for achieving colon delivery of drugs due to high solubility of non-cross linked molecules in the acidic pH. Therefore, the recent emphasis is on the use of biodegradable polymer combinations that are cross linked with each other or with ions in order to render them insoluble in acidic pH[2].

The natural polysaccharide, Guar gum, was used as a carrier for drug delivery along with three different polymeric binders to optimize the proper formulation for Chronotherapeutic drug delivery. Tablets of Naproxen sodium were proposed to be developed by employing Guar Gum and Ammonium Crosslinked CMG as rate controlled polymer. Ammonium Crosslinked CMG forms hydrogel, it has high viscosity and low swelling index, so drug release can be retarded in simulated fluids when compared to the Guar Gum.

MATERIALS AND METHODS

Materials

Naproxen Sodium & Guar gum were obtained as gift samples from Granules India Ltd & Natco Pharma Pvt. Ltd, Hyderabad, India. Talc and magnesium stearate used for the preparation of tablets were of Pharmacopeial grade.

Preparation of Crosslinked Guar gum[3]

100g of guar gum was added in a mixture of 630 ml of ethanol and 554 ml of toluene. To this 44.8% w/v NaOH was added gradually and mixed thoroughly. This mixture was kept at room temperature for 30 min. Monochloro-acetic acid (120g) was gradually added with agitation to this mixture and kept overnight. The excess alkali was neutralized with glacial acetic acid using phenolphthalein indicator. The product was filtered, washed with ethanol and dried. A dispersion of Carboxy methylated guar gum was prepared by use of distilled water a concentration of 10% w/v, with the help of mechanical stirrer. The dispersion was kept aside for 2 hrs for swelling. This polymeric solution was dropped into an Ionic cross linker i.e., Ammonium hydroxide (4% w/v) and stirred well for about one hour with the help of mechanical stirrer, then kept aside for 2 hours without stirring. The formed hydrogel was washed with distilled water to remove the

unreacted ammonium. Finally the hydrogel was dried at room temperature for about 3 days. After drying the formed polymer was allowed to grinding by using of mortar and pestle and passed through a sieve no 100.

Preparation of Naproxen Sodium matrix tablets[4]

Naproxen Sodium, polymer and PVP K 30 were triturated well and moistened with Isopropyl alcohol and water mixture in the ratio of 1:1 to form a damp mass. The damp mass was passed through sieve no 12 to obtain granules. The granules thus obtained were dried at 50 ^{0}C. The dried granules were sieved through sieve no 16 and lubricated with talc and magnesium stearate. The granules were compressed by employing 9 mm round shaped die with Cadmach CMS 25 tabletting machine to get tablets. The compositions of various formulations were shown in Table 1.

Studies on Viscosities of polymers[4]

Viscosities of 1%w/v dispersion of Guar Gum, Carboxy methylated guar gum and Ammonium cross linked Carboxy methylated Guar Gum in water, 0.1N HCl, P^{H} 7.4 and P^{H} 6.8 Phosphate Buffers were measured by using Brookfield viscometer. The results were tabulated in Table No2.

Determination of Swelling indexes of Polymer [4]

Swelling capacity of Guar Gum, Carboxy methylated guar gum and Ammonium Crosslinked Carboxy methylated Guar Gum was studied in distilled water.

1gm of gum was added to 10 ml of distilled water. The measuring cylinder was shaken vigorously for 10min and allowed to stand for 24hrs. Swelling capacity was expressed as

Swelling Capacity (%v/v) = [X_v /X_i] X 100

Where X_v is 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, P^{H} 6.8 and P^{H} 7.4 phosphate buffers. The results were tabulated in Table No 3.

In-Process Quality Control Parameters of Tablets[6, 7]

The Formulated Tablets were evaluated for different IPQC parameters like Drug content, Weight Variation, Hardness, Thickness, Diameter, and Friability. The results were tabulated in Table No 4.

Preparation of rat caecal content medium[1 &4]

Before Commencement of the experimentation on animals, the experimental protocol was subjected to the scrutiny of the Institutional Animal Ethical Committee (IAEC/iii/17/BCOP/2011), and was approved by the same in time.

The albino rats weighing between 150-200 g were kept on normal diet and administered with 1 ml of 1% w/v solution of Ammonium cross linked CMG in water 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 Ammonium Crosslinked Carboxy methylated Guar Gum degradation, animals were sacrificed before 30 min of commencing drug release studies and the caecum was exteriorized for content collection. The caecal content (anaerobic) were immediately transferred into buffer saline solution P^{H} 6.8 to obtain an appropriate 4%w/v concentration solution which was bubbled with carbon dioxide gas to maintain anaerobic environment.

***In vitro* drug release studies**

The Susceptibility of the matrix tablets of Naproxen Sodium to remain intact and the release of the active ingredient in the physiological environment of stomach, small intestine and colon was assessed by conducting in vitro drug release studies under conditions mimicking mouth to colon. This study was carried out using USP dissolution test apparatus- II at 50rpm and 37±0.5^{0}c. The tablets were tested for drug release in 0.1N HCl (900ml) for first 2h as average gastric emptying time was estimated as 2h. A sample of 5ml of the dissolution medium was withdrawn after 2hr to determine the drug release. The amount of drug release was analyzed by UV spectrophotometer at 270nm. The dissolution media was replaced with 7.4 pH Sorensen's phosphate buffer (900ml) for 3h as the average small intestine transit time is about 3h. The amount of drug release was analyzed by UV spectrophotometer at maximum wavelength of 270nm[5].

The susceptibility of polysaccharides in matrix tablets to enzymatic action of colonic bacteria were assessed by continuing the drug release studies in 100ml of pH 6.8 phosphate buffer containing 4%w/v rat caecal content after 5hr. The study was continued from 6hr to 24hr and samples were withdrawn at regular intervals for analysis and each time replaced with fresh PBS media containing rat caecal material bubbled with CO_2. The withdrawn samples were diluted with PBS and centrifuged. The supernatant was filtered through a bacteria proof filter and filtrate was analyzed for Naproxen Sodium content at 270nm using Shimadzu UV-150 Double beam UV spectrophotometer. The above study was also carried out without rat caecal content in 6.8 pH phosphate buffer as a control. The results were shown in fig 1& 2.

RESULTS AND DISCUSSION[6]

Viscosity and Swelling Indexes of Guar gum and Crosslinked guar gum were measured in 0.1 N HCl, P^{H} 7.4 phosphate buffer, P^{H} 6.8 phosphate buffer. Viscosities of Ammonium cross linked guar gum were found to be high when compared to guar gum and highest viscosities were found in 7.4 phosphate buffer (Table 2). This result clearly indicated that cross linking of polymer with Ammonium enhances the viscosity.

Swelling Index of Ammonium cross linked guar gum and guar gum were measured by using same buffers. Swelling Index of Ammonium cross linked guar gum was found to be low when compared to guar gum and lowest swelling index was found in P^{H} 7.4 phosphate buffer (Table No 3).

Tablets were prepared using wet granulation technique because the drug has poor flow properties. Tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per Pharmacopeial specification. The hardness of all tablets was found to be in between 5-7.5 kg/cm^2. The friability and drug content were measured and the tablets satisfied all the official requirements (Table No 4).

The formulations were subjected to drug release studies in varied dissolution mediums namely 0.1 N HCl for 2 hrs, then P^{H} 7.4 phosphate buffer for 3 hrs, then P^{H} 6.8 phosphate buffer till the end. Comparative dissolution profile of Naproxen sodium matrix tablets formulated with these two polymers were shown in fig no. 1&2. In the dissolution study influence of cross linking agent Ammonium on drug release characteristics was studied. Among all formulations F10 formulation exhibited low amount of drug release in the simulate gastric conditions (0.1 N HCl) that was 11.4 %, in the simulated intestinal conditions (P^{H} 7.4 phosphate buffer) the cumulative amount of drug released was 21.4 % and in the simulated colonic conditions (without caecal content) the cumulative amount of drug released was 76.1% and in the presence of 4%w/v rat caecal content in the simulated colonic fluid P^{H} 6.8 phosphate buffer was found to be 98.93%.

From these results it was clearly evident that the cross linking polymer reduces the drug release by enhancing the viscosity and reducing the swelling index.

In all the formulations developed the results were subjected to study the release kinetics. The values of correlation coefficient indicated that the drug release followed Zero order drug release kinetics with Peppas drug release mechanism. The values of $t_{50\%}$ and $t_{90\%}$ were found to be increased with increasing the proportion of polymers (Table no 5, 6, &7).

Table 1: Composition of Naproxen Sodium Matrix Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Naproxen sodium	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5	412.5
Guar gum (GG)	123.75	165	206.25	247.5	288.75	--	--	--	--	--	--	--	--
Carboxymethylated guar gum (CMG)	--	--	--	--	--	206.25	247.5	288.75	--	--	--	--	--
Ammonium cross linked CMG	--	--	--	--	--	--	--	--	123.75	165	206.25	247.5	288.75
PVP- K 30 (3%)	16	17.3	18.5	19.8	21	18.5	19.8	21	16	17.3	18.5	19.8	21
Mg stearate	5.5	6	6.5	7	7.5	6.5	7	7.5	5.5	6	6.5	7	7.5
Talc	5.5	6	6.5	7	7.5	6.5	7	7.5	5.5	6	6.5	7	7.5
Total weight	563.25	606.8	650.25	693.8	737.75	650.25	693.8	737.75	563.25	606.8	650.25	693.8	737.75

Table 2: Viscosities of different polymeric dispersions (1%w/v)

Polymer Dispersion (1%)	Viscosity in Water (cps)	Viscosity in 0.1 N HCl (cps)	Viscosity in P^H 7.4 Phosphate Buffer (cps)	Viscosity in P^H 6.8 Phosphate Buffer (cps)
Guar Gum	117.9	109.6	122.1	116.5
Carboxy methylated Guar Gum(CMG)	116.2	104.8	118.4	115.6
Ammonium Crosslinked CMG	192.4	182.4	189.7	183.6

Table 3: Swelling Index of Guar gum and chemically modified Guar gum

Polymer	Swelling Index in Water	Swelling Index in 0.1 N HCl	Swelling Index in P^H 7.4 Phosphate Buffer	Swelling Index in P^H 6.8 Phosphate Buffer
Guar Gum	8.1	8.9	8.4	8.3
Carboxymethylated Guar gum(CMG)	9.1	8.6	8.3	8.9
Ammonium Crosslinked CMG	4.9	5.8	5.2	4.5

Table 4: IPQC Parameters of Naproxen Sodium Matrix Tablets

Formulation	Theoretical weight (mg)	Average weight	%DrugContent	Hardness (kg/cm)	% Friability
F_1	563.25	563.6	99.23±0.18	5.5	0.39
F_2	606.8	606.7	99.85±0.1	6.2	0.31
F_3	650.25	650.33	101.39±0.21	5.2	0.35
F_4	693.8	693.4	99.93±0.23	6.5	0.41
F_5	737.75	737.55	101.88±0.39	6.4	0.29
F_6	650.25	650.15	100.16±0.51	6.3	0.32
F_7	693.8	693.8	99.64±0.63	6.6	0.38
F_8	737.75	737.35	101.24±0.17	5.2	0.45
F_9	563.25	563.24	101.16±0.39	5.9	0.38
F_{10}	606.8	606.5	100.58±0.23	6.1	0.40
F11	650.25	650.26	98.34±0.27	5.7	0.33
F12	693.8	693.4	99.86±0.39	6.3	0.35
F13	737.75	737.71	101.8±0.33	6.7	0.37

Table 5: *In Vitro* release kinetics of Naproxen sodium matrix tablets prepared with Guar Gum

Formulation	Correlation coefficient					Release rate Constants				
	Zero order	First order	Hixson crown well	Higguchi	Peppas	K_0 (mg/hr)	k_1 (hr^{-1})	T_{50} Hr	T_{90} Hr	Exponential coefficient (n)
F_1	0.9547	0.8745	0.9577	0.9728	0.9967	4.0943	-0.1534	8.9	19.3	0.6895
F_2	0.9619	0..8347	0.9674	0.9834	0.9914	3.9681	-0.1423	10.4	19.5	0.6899
F_3	0.9524	0.9124	0.9734	0.9756	0.9954	3.3998	-0.1387	11.3	22.4	0.6788
F_4	0.9505	0.8736	0.9577	0.9689	0.9955	3.2066	-0.1289	12.1	25.1	0.6902
F_5	0.9623	0.9215	0.9766	0.9855	0.9971	3.1994	-0.1123	13..7	26.3	0.6670

Table 6: In vitro release kinetics of Naproxen sodium matrix tablets prepared with Carboxy methylated Guar gum (F6-F8)

Formulation	Correlation coefficient					Release rate constants				
	Zero order	First order	Hixson crown well	Higguchi	Peppas	K_0(mg/hr)	k_1(hr^{-1})	T_{50}Hr	T_{90}Hr	Exponential coefficient (n)
F_6	0.9411	0.8345	0.9565	0.9676	0.9963	3.86457	-0.060	10.4	19.1	0.7723
F_7	0.9554	0.8643	0.9678	0.9711	0.992	3.7308	-0.054	11.5	20.3	0.7883
F_8	0.9725	0.8611	0.9729	0.9834	0.9916	3.73575	-0.047	13.4	22.4	0.7903

Table 7: In vitro release kinetics of Naproxen sodium matrix tablets prepared with Ammonium Cross linked Guar Gum (F9-F13)

Formulation	Correlation coefficient					Release rate constants				
	Zero order	First order	Hixson crown well	Higguchi	Peppas	K_0(mg/hr)	k_1(hr^{-1})	T_{50}Hr	T_{90}Hr	Exponential coefficient (n)
F_9	0.9714	0.9212	0.9563	0.9875	0.9938	4.0698	-0.1124	10.1	18.9	0.7699
F_{10}	0.9770	0.9440	09544	0.9562	0.9956	3.92434	-0.0843	11.6	19.4	0.7735
F_{11}	0.9665	0.9271	0.9476	0.9845	0.9977	3.4818	-0.064	12.4	20.1	0.7983
F_{12}	0.9397	0.8732	0.9375	0.9796	0.9985	3.02133	-0.054	13.2	22.3	0.7847
F_{13}	0.9709	0.8877	0.9447	0.9822	0.9969	3.0307	-0.048	14.5	25.5	0.7996
F13 with caecal content	0.9537	0.9503	0.9564	0.9876	0.9992	3.5807	-0.076	11.5	20.3	0.8204

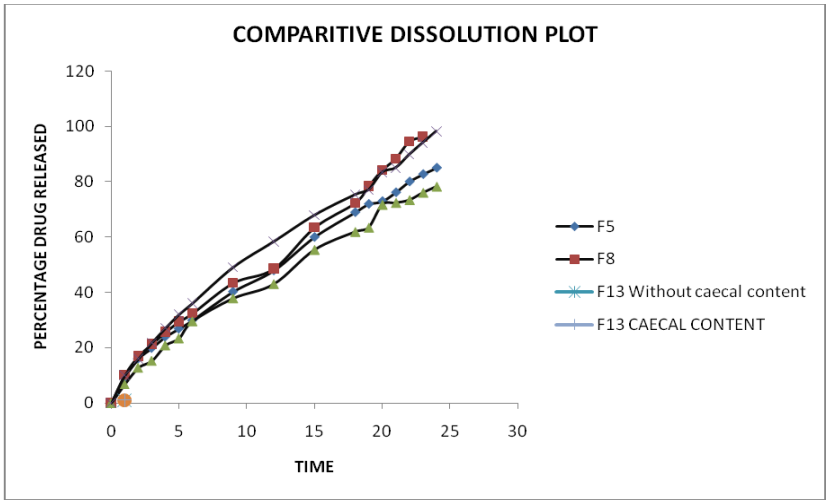

Fig. 1: Comparative Dissolution Profile of Naproxen sodium Matrix Tablets formulated with GG, CMG & AmCMG {F5, F8, F13&F13 (caecal content)}

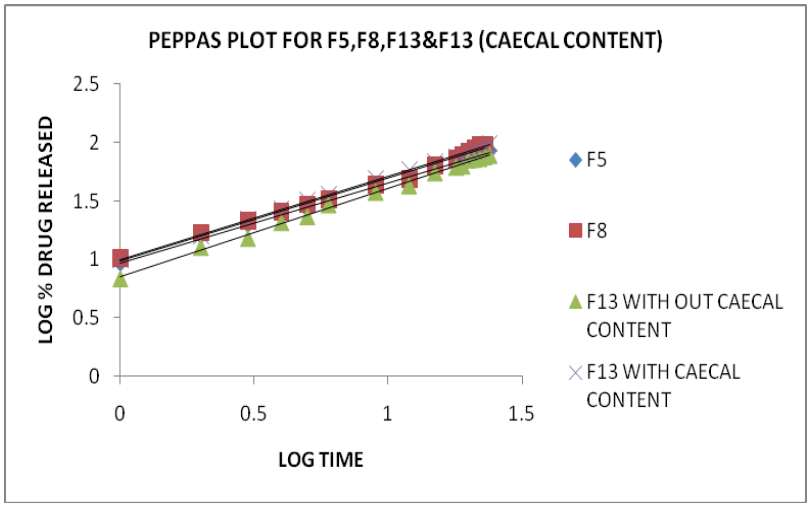

Fig. 2: Peppas comparative profiles for Naproxen Sodium Matrix Tablets formulated with GG, CMG & AmCMG {F5, F8, F13&F13 (caecal content)}

CONCLUSION

A comparison study was done by using guar gum and Ammonium Crosslinked guar gum matrix tablets of Naproxen sodium and matrix tablets were prepared by using both polymers at same concentrations. Naproxen sodium matrix tablets prepared with Ammonium Crosslinked guar gum had slow drug release when compared with guar gum matrix tablets. The study shows that the release of Naproxen sodium in the physiological environment of colon is due to the microbial degradation of Ammonium cross linked guar gum in the presence of rat caecal content. The drug release was more in the presence of caecal content than without caecal content. From this study it could be concluded that presence of Ammonium as cross linking agent enhanced the viscosity of polymer. So the study revealed that cross linking of polymer was more beneficial than the use of natural polymer alone. The matrix tablets of Naproxen sodium by employing Ammonium guar gum could be used for Chronotherapy of RA to treat nocturnal symptoms.

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