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RESEARCH ARTICLE

Formulation and Evaluation of Compressed Coat Tablets of Naproxen for Colon Targeting

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ABSTRACT

The present endeavor was directed towards fabrication of the novel drug delivery system of naproxen. The fast disintegrating core tablets of Naproxen were prepared by direct compression technique. These tablets were coated with Guar gum& Xanthan gum (Polysaccharide polymer). . The tablets were evaluated for hardness, friability, weight variation, swelling index, drug content, *in vitro* release studies. In vitro drug release studies were carried out in presence and absence of rat cecal contents and revealed that Guar gum & Xanthan gum, when used as compression coating, protected the drug from being released in the upper parts of the gastro intestinal tract (GIT). Completely protected the drug from being released in the upper parts of the GIT, and released the drug only in the colon by bacterial degradation of gums. It was found that the polysaccharide polymer Guar gum & Xanthan gum completely protect the drug release in the upper digestive tract and exhibited different release profiles in presence and absence of rat cecal contents. Hence, Guar gum & Xanthan gum can be used for targeting the drug to the colon for controlling the release of drugs.

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Keywords: Naproxen, Colon, Compress coat, Guar gum, Xanthun gum.

1. INTRODUCTION

Oral controlled release formulations for small intestine and colon have received considerable attention in the past 20-25 years for variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release formulation . [1] The large intestine, though difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon. [2] Colon is a site where both local and systemic delivery can take place. Local drug delivery could allow topical treatment of inflammatory Bowel Diseases like Crohn's disease or Ulcerative colitis. A number of other serious diseases of the colon like colorectal cancer might also be capable of being treated more effectively if drugs are targeted to the colon. Colonic drug delivery is also useful for systemic absorption of drugs, especially peptides and proteins, because of less hostile environment prevailing in the colon compared to stomach and small intestine. [3] The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through thestomach and about 6 meters of the small intestine. [4] Due to the distal location of the colon in the gastrointestinal tract, a colon specific drug delivery should prevent drug release in the stomach and small intestine and produce an abrupt onset of drug release upon entry into the colon. It was also reported that Guar gum & Xanthan gum is capable of protecting the drug from being released in the acidic environment prevailing in the stomach and small intestine. They are degraded by the colonic bacterial enzymes, thereby releasing the drug in the colon where there is local action and improved absorption. [5] Polysaccharide based drug delivery systems attracting a lot of attention for drug targeting the colon particularly in terms of site-specificity and safety since these polymers of monosaccharide's are found in abundance, have wide availability are inexpensive and are available in a variety of structures with varied properties.

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They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides. Therefore, they fall into the category of "generally regarded as safe" (GRAS). [6]

2.MATERIAL AND METHOD:

Materials: The drug Naproxen was obtained as a gift sample from RPG life science, Mumbai. Guar Gum, Xanthan Gum was obtained as gift sample from Remidix Pharmaceutical, Banglore.

Methods:

Preparation of Fast disintegrating core tablets of Naproxen Direct compression technique:

The core tablets of Naproxen prepared by direct compression method. All the weights are in milligram. All the ingredients from 1 to 5 were firstly weighed and mixed in the geometric fashion. Then mixture equivalent to 150 mg of Naproxen (175mg) was weighed and then compressed by Cadmac tablet punching machine using 8 mm flat punches, optimizing the hardness and die cavity of the machine, so that the tablets will be of uniform hardness and with minimal weight variation. [7, 8]

PREPARATION OF COMPRESSION COATING OF NAPROXEN TABLETS

Preparation of Coating Material:

Compression coating material was prepared by Wet Granulation Method. Guar gum, Xanthan gum Lactose were passed through mesh no.250 and the powders were mixed and granulated with 8% starch mucilage and wet mass were passed through a mesh no.12, then granules were dried at 50° C .The dried granules were pass through a mesh no.22 and these granules were lubricated with the mixture of talc, magnesium stearate (2:1), Finally granules were Compressed in the following manner.

Compression of core tablet:

The 40% weight of Coating mixture was kept in die cavity first and then core tablet was placed on it in centered position and then remaining 60% of coating mixture was added to cavity and compressed in to tablets, using 11.5 mm flat punch using Cadmac tablet punching machine optimizing the hardness and die cavity of the machine. So that the tablets will be of uniform hardness with minimal weight variation. [9]

EVALUATION OF TABLET PROPERTIES [10]

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with and without cecal content media.

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Pfizer hardness tester. The hardness was measured in terms of kg/cm^2

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 RPM dropping the tablets through distance of six inches with each revolution. After 4 min the apparatus was stopped tablets were removed and weighed, the percentage loss in weight was determined.

Tablet thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier Caliper. It was determined by checking ten tablets from each formulation.

Weight variation

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if no more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table 1.

Sl. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324 or more	5

Table 1: Weight variation limits

Content Uniformity

The Naproxen tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 150 mg was weighed accurately and mixed in 100ml of phosphate buffer pH 7.4. The mixture was shaken properly. The undissolved matter

was removed by filtration through Whatman No.41 filter paper. Than the serial dilution were carried out. The absorbance of the solution was measured at 332 nm. The concentration of the drug was computed from the standard curve of the Naproxen in phosphate buffer pH 7.4.

***INVITRO* DRUG RELEASE STUDIES** [11, 12, 13]

Immediate Release Naproxen core Tablets:

Drug release studies were carried out using Electro lab TDL-08L (USP) dissolution rate test apparatus (at 50 rpm, 37°C) in the 900 ml of the dissolution medium 7.4 pH phosphate buffer.

Compression coated tablets:

The ability of guar gum and xanthan gum compression coat based Naproxen CT1; CT2 and CT3 tablets were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. Drug release studies were carried out using a Electro lab TDL-08L(USP) dissolution rate test apparatus (apparatus 1, 50 rpm, 37°C)in 0.1 N HCl (900 ml) for 2h as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with 900ml pH 7.4-phosphate buffer and the dissolution was continued up to 24 hours and the 5ml sample were withdrawn at a specific time period (0.5, 1, 2, 4, 5, 6, 8-24h) & diluted to 10 ml and analyzed for Naproxen at 332 nm using a double beam UV/VIS Spectrophotometer (Systronic, Mumbai, India) and the fresh 5 ml dissolution medium was added.

Compression Coated Tablet (CT_3)

Compression Coated Tablet (CT_3**)** with a Gum Ratio of 2:1 GG:XG of Naproxen which shows the retardation of drug in the upper gastrointestinal tract and the tablet remain almost intact after 5 hours and release the more drug at the end of 24 hours in 1.2, 7.4pH phosphate buffer compared to CT_1 ,CT_2 . So it was considered as best formulation and was evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. Drug release studies were carried out using a Electro lab TDL-08L(USP) dissolution rate test apparatus (apparatus 1, 50 rpm, 37°C)in 0.1 N HCl (900 ml) for 2h as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4-phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3 h. under conditions mimicking mouth to colon transit. Further dissolution was continued in order to check the susceptibility of guar gum coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 900 ml of pH 7.4 phosphate buffer containing 4%w/v of rat caecal contents. The caecal contents were obtained from male albino rats.

3. RESULTS AND DISCUSSION:

The present investigation was carried out to develop colon targeted drug delivery for naproxen for an effective and safe therapy of arthritis **.**Compression core coated tablet was able to retard the drug in upper gastrointestinal tract which is highly desirable to reduce adverse effects in the GIT and further the sustained release of the drug in the colon was achieved by modifying the coat GG: XG ratio with 2:1. Hence such a design can be used for colon targeted delivery of naproxen for the treatment of Arthritis. Increase the amount of xanthum gum with guar gum polymeric ratio (CT1,CT2) was not suitable for colonic delivery of drug. *In vitro* drug release of compression coated colon drug delivery showed release of drug 99% with rat caecal content. On the basis of *invitro* drug release studies, CT3 was selected as an optimized formulation for designing coated tablet for colonic drug delivery. Therefore the study proves that naproxen can be successfully colon targeted by design of compression coated tablet as chronopharmaceutical formulation. Colon drug delivery over a period, consistent with the requirement for chronopharmaceutical drug delivery was achieved, in which core tablet of naproxen was coated by compression coating technique for preparing colon specific drug delivery system and hence in chronotherapeutic management of Arthritis. During *in vitro* dissolution study 4%w/v rat caecal content weighed and immediately transferred into pH 7.4 Phosphate buffer, previously bubbled with Co_2. As the caecum is naturally anaerobic, all these operations were carried out under CO_2. The drug release studies were carried out in Eelctro lab TDL-08L (USP) dissolution test apparatus (apparatus 1, 50 rpm, 37°C) containing 900ml of phosphate buffer 7.4 with 4%w/v rat caecum content for 24h. The tablets were placed in the baskets of the apparatus and immersed in the dissolution added to ensure solubility offinely suspended drug particles released due to break down of the coat by the caecal enzymes. The 5 ml of sample were withdrawn and the volume was made up to 10 ml with Phosphate buffer, centrifuged and the supernatant was filtered through a bacteria-proof filter and the filtrate was analyzed for Naproxen content 332 nm as described above. The above study was carried out on Naproxen tablets compression coated with 2:1 GG: XG Coat formulation (CT3).

Sl. no	Ingredients	F1	F2
1	Naproxen	150	150
2	Microcrystalline Cellulose	21	20
3	Sodium starch glycolate	2	3
4	Magnesium stearate	0.5	0.5
5	Talc	1.5	1.5
	Total weight	**175**	**175**

Table 2: The core tablet formulation

Sl. no	Ingredients	XG1	XG2	XG3
1	Guar Gum	200	200	200
2	Xanthan Gum	150	125	100
3	Lactose	130.5	155.5	180.5
4	Starch	31.5	31.5	31.5
5	Magnesium stearate	5	5	5
6	Talc	8	8	8
7	Total weight	525	525	525

Table 3 Composition of Compression Coat Formulation

Formulation code	Hardness	Persentage weight variation	Percentage friability
CT1	6.5	701.5	0.071
CT2	6.2	700.5	0.050
CT3	6.4	701.5	0.064

*All values are expressed as mean ± S.D, n = 3.

Table 4 Physicochemical properties of tablets

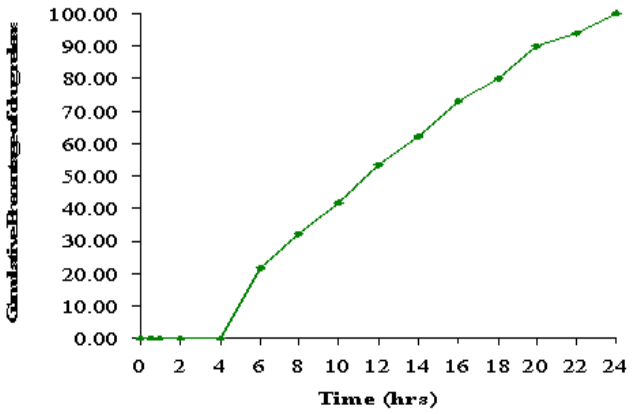

Fig 1 Percentage of drug release

Time (hrs)	Cumulative Percentage of drug release		
	CT1	CT2	CT3
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.5	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
6	7.70 ± 0.26	10.64 ± 0.54	15.10± 0.36
8	16.81 ± 0.48	18.55 ± 0.48	22.60± 0.56
10	23.61 ± 0.47	27.21 ± 0.31	30.01± 0.31
12	29.63 ± 0.39	33.11 ± 0.39	36.00± 0.41
14	37.30 ± 0.40	40.74 ± 0.58	43.30± 0.58
16	43.45 ± 0.38	46.48 ± 0.38	49.23± 0.42
18	50.17 ± 0.17	53.66 ± 0.36	56.57± 0.46
20	57.70 ± 0.41	59.91 ± 0.27	62.11± 0.37
22	64.10 ± 0.16	67.17 ± 0.37	69.40± 0.41
24	70.90 ± 0.57	73.03 ± 0.32	76.39± 0.35

Table 5 percentage drug release

Sl.No	Time (hrs)	Cumulative Percentage of Drug Release in caecal Medium
1	0	0.00 ± 0.00
2	0.5	0.00 ± 0.00
3	1	0.00 ± 0.00
4	2	0.00 ± 0.00
5	4	0.00 ± 0.00
6	6	21.74 ± 1.02
7	8	32.18 ± 0.98
8	10	41.59 ± 0.89
9	12	53.44 ± 1.11
10	14	62.18 ± 1.15
11	16	73.12 ± 0.95
12	18	80.01 ± 0.86
13	20	89.94 ± 0.92
14	22	93.90 ± 1.08
15	24	99.80 ± 0.95

*All values are expressed as mean ± S.D, n = 3.

Table 6: Dissolution profile for CT3 tablets of naproxen in caecal content media

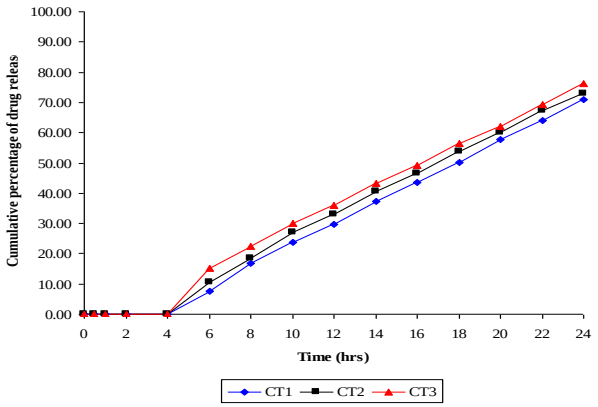

Fig 2 : Cumulative percentage drug release.

4. CONCLUSION:

Based on the results obtained, the CT3 was considered as the optimum formulation to design colon drug delivery system. Polymers employed in study are suitable for colon targeting. By *invitro* dissolution study, the cumulative percentage of drug release in phosphate buffer 7.4 with rat caecal medium was 99.80%.

Compression core coated tablet was able to retard the drug in upper gastrointestinal tract which is highly desirable to reduce adverse effects in the GIT and further the sustained release of the drug in the colon was achieved by modifying the coat GG: XG ratio with 2:1. Hence such a design can be used for colon targeted delivery of naproxen for the treatment of Arthritis.

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Conflict of Interest: None Declared

