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POLYSACCHARIDE MATRIX TABLET FOR COLON SPECIFIC DRUG DELIVERY

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ABSTRACT

The objective of the present study was to prepare a matrix tablet for colon targeting. Natural gaums (guar gum and xanthan gum) were used for the preparation of colon targeted drug delivery system. Different concentrations of guar gum and xanthan gum and their combinations were tried for the purpose. The prepared tablets were evaluated for in-process parameters as well as colon targeting characteristics. The colon targeting properties were evaluated by analysing the formulations for drug release in physiological pH medium of colon. All the formulations were found to be suitable in in-process quality control parameters. The guar gum and xanthan gum were used from 10% to 30% concentration in the formula. The third series of formulations contained guar gum and xanthan gum combinations in ratios of 10% and 20%, 20% and 10% and 15% and 15% respectively. The drug release was found to be 82% to 100% for guar gum formulations, 85% to 99% for xanthan gum formulations and 87% to 100% for the combination of xanthan gum and guar gum. The dissolution study shows that both the natural gums are suitable for use to develop colon targeted drug delivery system.

INTRODUCTION: In recent years colon-targeted delivery systems have gained increased importance and interest since the colon is now considered as a suitable site not only for the local treatment of a variety of bowel diseases, but also for improving systemic absorption of drugs with problems of poor stability or irregular absorption in the upper gastrointestinal tract [1].

Several methods have been developed for confining drug release to the colon. One of the oldest and the most commonly employed method uses enteric polymers as coating materials over tablets, granules, or pellets. These rely upon the difference in pH values in the gastrointestinal tract (GIT) [2]. Others include time-controlled release systems [3], pressure controlled release systems [4], prodrugs [5], polysaccharide-based delivery systems [6, 7] and osmotically controlled release systems [8]. Among the various systems developed for colon-specific drug delivery, prodrugs and polysaccharide-based delivery systems rely upon the enzymatic degradation of the carrier in the colon, thereby resulting in drug release. The inherent bacterial flora present in the colon carries out this enzymatic degradation.

The enzyme-trigger mechanism in such delivery systems makes them highly site specific. Prodrugs, however, can only be formed with a limited number of drug moieties due to a chemical linkage required in their formation. Further, as new chemical entities, prodrugs require a detailed toxicological study to be performed before being used as drug carriers.

Natural polysaccharides, including chitosan, guar gum, pectin, dextran, cyclodextrin, inulin etc. remain undigested in the stomach and small intestine and are degraded by the vast anaerobic microflora of the colon, e.g. bacteroides, bifidobacteria, eubacteria, clostridia to smaller monosaccharides, which are then used as energy source by the bacteria.

The present investigation is aimed at using the inexpensive, naturally occurring, and abundantly available polysaccharides for colon-targeted drug delivery. An attempt has been made to formulate a dosage that;

1) Retards drug release in the tracts of the upper GIT,
2) Consists of biodegradable polysaccharides as the main constituent,
3) Is degradable by a wider range of microbial species,
4) Shows rapid drug release in the tracts of the colon due to the presence of a high concentration of degradable polysaccharides in the tablet, and additionally
5) Could be formulated using the usual tableting techniques [9].

Working on this rationale, matrices were proposed for the above purpose. A drug release-retarding ingredient belonging to polysaccharides, i.e., xanthan gum, was selected for the study [10, 11].

Guar gum, another polysaccharide being widely used for colon targeting, was selected as the other ingredient. Guar gum (GG) alone has earlier been used in colon-specific drug delivery as matrix forming material and as a compression coat [12-14]. Xanthan gum (XG) is known to have a greater drug release-retarding property and synergistically enhanced gel properties in presence of galactomannan gums such as guar [15].

So, a combination of these gums was proposed for achieving the above objective. A mixture of these gums was evaluated for its drug release-retarding properties under simulated gastrointestinal tract (GIT) conditions. This mixture was proposed to retard drug release more significantly in conditions of the upper GIT (as compared to guar alone) but still retained biodegradability due to the presence of guar gum. Xanthan gum is a high molecular weight polysaccharide gum produced by pure-culture aerobic fermentation with gram negative bacterium, Xanthomonas campestris. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid. It is used in oral and topical pharmaceutical formulations as a suspending, stabilizing, thickening, and emulsifying Agent [10].

Guar gum is a natural nonionic polysaccharide derived from the seeds of Cyamopsis tetragonolobus (Family: Leguminosae). It consists of linear chains of (1–4)-beta-D-mannopyranosyl units with alpha-D-galactopyranosyl units attached by (1–6) linkages. It is used in pharmaceutical preparations in the form of binders and disintegrating, suspending, thickening, and stabilizing agents. Starch, usually a filler in the tablet dosage form, was used in the formulation to take advantage of its biodegradation in the colon by the resident bacteria [16].

MATERIALS AND METHODS: 5-Amino salicylic Acid (5 ASA), Guar gum and xanthan gum were obtained as gift sample from Alembic Research Centre, Vadodara, Gujarat, India. Starch, Dibasic calcium phosphate and talc used for the preparation of tablets were of pharmacopoeial grade.

Preparation of Tablets: Matrix tablets containing 200 mg of 5-ASA, xanthan gum (XG) and guar gum (GG) in varying ratios and their combinations (as per **Table 1**) were prepared by wet granulation using 10% starch paste as the binder. The wet mass was passed through an 8 mesh sieve and the prepared granules were dried at 45°C for 6 h. The dried granules were passed through a 16-mesh sieve and were lubricated with talc. The lubricated granules were compressed into tablets using 10 mm, circular, biconcave punches.

The in-process parameters like thickness, weight variation, friability etc. were optimised during compression for optimal performance of compression. The compressed matrix tablets were tested for hardness, drug content and drug release characteristics.

TABLE 1: FORMULATION DETAILS OF MATRIX TABLETS CONTAINING DIFFERENT CONCENTRATIONS OF XANTHAN GUM AND GUAR GUM

Sr. no	Ingredients	G1	G3	G5	X1	X2	X3	XG1	XG2	XG3
1	5-Amino salicylic acid	200	200	200	200	200	200	200	200	200
2	Guar gum	50	100	150	-	-	-	50	100	75
3	Xanthan gum	-	-	-	50	100	150	100	50	75
4	Starch (as 10% paste)	50	50	50	50	50	50	50	50	50
5	Microcrystalline cellulose (Avicel PH 101)	175	125	75	175	125	75	75	75	75
6	Talc	25	25	25	25	25	25	25	25	25
7	Total weight	500	500	500	500	500	500	500	500	500

In-process characterization of Compressed Tablets: The hardness of all the formulations kept at a constant value. All other in-process parameters like weight variation, tablet thickness, friability etc. were kept uniform in all formulations for better evaluation of effect of change of polymer.

Content uniformity: Samples were analyzed for uniformity of drug content in the formulations. Samples from all formulations were analyzed for drug content to check uniformity of drug content.

Dissolution: The dissolution study of the developed drug delivery system was planned on the basis of mimicking the body physiological condition. The media for dissolution is as follows: 1) 0.1M HCl for 2 hrs (mimicking gastric condition), 2) pH 6.8 phosphate buffer for 3 hrs (mimicking upper intestinal condition) and 3) pH 6.8 phosphate buffer with 2% fresh rat caecal contents for 8 hrs (mimicking colonic condition). Fresh rat caecal contents of rat were used after feeding guar gum and xanthan gum to them. The volume of media was kept 900 ml to maintain sink condition. The apparatus for dissolution used was rotating basket at 100 rpm. Aliquots were withdrawn at 1 hr interval from a zone midway between the surface of dissolution medium and top of the rotating paddle not less than 1 cm apart from the suitable replacements with fresh medium was also made. Each sample solution was filtered through Whatman no. 41 filter paper. The absorbance was measured after proper dilution with dissolution media at 302 nm for buffer pH 1.2 and 330 nm for buffer pH 6.8 and pH 6.8 with rat caecal content media using spectrophotometer.

RESULT AND DISCUSSION:

In-process characterization of Compressed Tablets: Tablets of all the formulations were found to be of uniform hardness and in the range of 60-100N. All other in-process parameters were also found to be uniform and with in the accepted range.

Content uniformity: The result of content of uniformity showed that all the formulations were uniform for drug content. The drug contents in all the formulations were found to be in the range of 95-105%. This limit is found to be uniform and acceptable as per general chapters of British pharmacopoeia and USP.

Dissolution: The result of the drug release study of all the formulations are given below in **Table 2**.

TABLE 2: DISSOLUTION STUDY RESULT OF THE MATRIX TABLETS

Media	Time (hr)	Cumulative % Drug released								
		G1	G2	G3	X1	X2	X3	XG1	XG2	XG3
0.1M HCl	**1**	6.5	0.4	0.2	10.1	6.8	2.1	2.5	1.4	0.1
	2	12.8	1.4	0.4	14.7	8.5	7.5	6.5	3.8	0.3
pH 6.8 Ph. buffer	**3**	28.5	4.6	3.9	31.4	17.8	13.2	12.5	11.2	0.8
	4	43.7	6.8	6.4	44.6	26.2	19.2	21.6	16.8	3.8
	5	51.5	9.1	8.2	49.6	30.7	23.8	29.6	23.5	8.0
pH 6.8 Ph. Buffer with 2% rat caecal content	**6**	57.6	20.1	18.1	58.7	34.6	28.6	38.9	28.7	17.4
	7	68.2	29.2	28.4	69.8	43.7	33.7	49.8	38.2	28.7
	8	78.3	41.6	39.6	78.6	52.8	41.4	59.1	50.1	42.3
	9	85.4	51.4	46.7	88.3	61.7	50.8	66.9	59.0	50.2
	10	91.7	65.6	54.5	92.6	68.9	61.9	76.8	64.5	58.6
	11	96.7	78.5	63.8	97.8	78.5	70.6	87.2	74.3	66.7
	12	98.4	86.8	76.7	98.6	86.4	78.4	95.3	82.4	76.9
	13	99.7	97.2	81.9	98.8	94.6	84.8	100.1	92.6	86.8

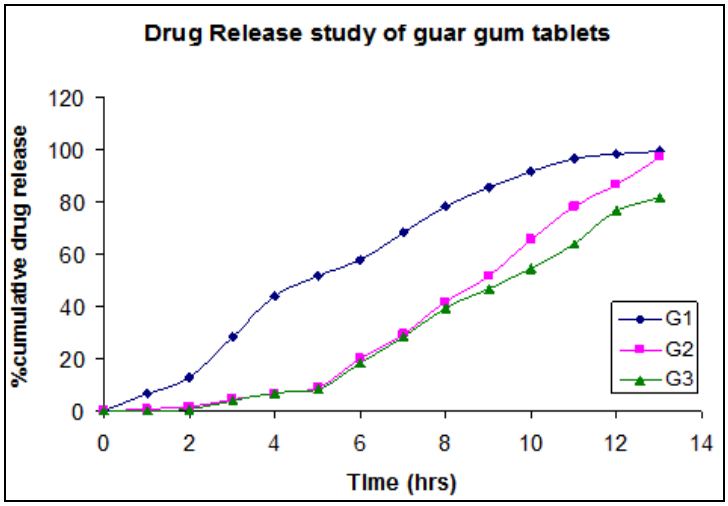

FIG. 1: DRUG RELEASE STUDY OF GUAR GUM TABLETS

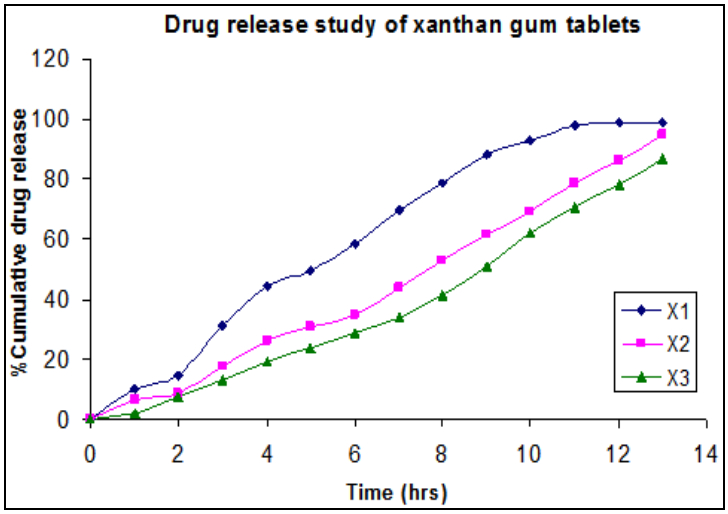

FIG. 2: DRUG RELEASE STUDY OF XANTHAN GUM TABLETS

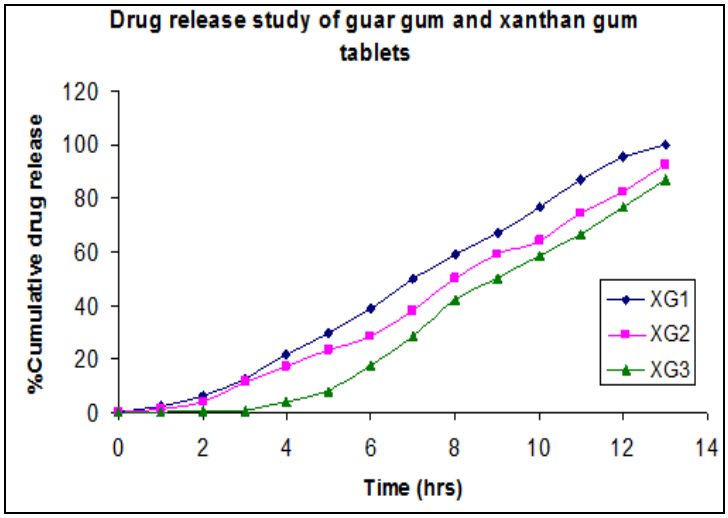

FIG. 3: DRUG RELEASE STUDY OF GUAR GUM AND XANTHAN GUM TABLETS

For the formulation of a delivery system for colon targeting, it is a prerequisite that the drug release should be minimal until the dosage form reaches the colon.

The result shows that the G1 formulations are faster in drug release and there is no change in pattern of drug release when transited from pH 6.8 phosphate buffer media to pH 6.8 phosphate buffer with caecal contents. More than 50% of the drug is released before reaching the colonic media. Also there is no effect of 2% rat caecal matter on the release of drug from the formulation. Hence, we can conclude that this formulation is not suitable for colon targeted drug delivery. The formulation G2 shows a retarded drug release when compared to G1 formulation during the initial phase.

Only 1.4% of drug is released in 2 hrs at the gastric pH. After 5 hrs less than 10% of drug is released from the formulation in pH 1.2 and pH 6.8 media. When the formulation is transited to pH 6.8 phosphate buffer with 2% rat caecal content media, there is a increase in drug release rate. This indicates that there is an effect of rat caecal content on drug release property of formulation G2. The drug release result of G3 formulation shows that, the drug release is slowest among all the guar gum formulations. Nearly 8% of drug is released in 5 hrs till it reaches the colonic media, i.e. pH 6.8 phosphate buffer with 2% rat caecal contents.

Also we can see the positive effect of rat caecal content on the drug release property of the formulation. But the formulation releases only approximately 80% of the drug after 13 hrs. This may be due to gelling characteristics of higher concentration of guar gum in the formulation which may hindered drug release from the formulation.

The formulation X1 shows a faster release of the drug, which is independent of rat caecal matter. Approximately 50% of the drug is released in 5 hrs. The release pattern is similar to G1 formulation except X1 is little faster than G1. The drug release from X2 formulation is slower than X1, but still 30% of drug is released before it reaches the colonic media. 23% of drug is released from X3 formulation in 5 hrs. The X3 formulation shows an incomplete release of drug after 13 hrs. It shows a release of 84%, which may be due to the gelling of higher concentration of xanthan gum. Though it is slower than X2 and slowest among all the xanthan gum formulations, it is not satisfactory for a colon targeted drug delivery system.

Also the result shows that the rat caecal matter has little effect on drug release property of xanthan gum tablets.

The formulation XG1, XG2 and XG3 show retarded drug release than the xanthan gum tablets, but they lack the rat caecal content effect on their drug release. The % of drug released in pH 6.8 phosphate buffer media is more than the guar gum microspheres. Also the XG3 formulation shows an incomplete drug release after 13 hrs which may be due to gelling property of the higher concentration of xanthan gum and guar gum.

SUMMARY AND CONCLUSION: The colon contains some microbial organisms, which help in degradation of the natural gums. Basing upon this principle, natural gums are widely used for developing colon targeted drug delivery systems. Here we observed the suitability of guar gum 20% in a matrix tablet as a suitable colon targeted drug delivery system.

Also there is a scope for other natural gums and their combinations which can be used suitably in different concentrations and in suitable dosage forms for developing colon targeted drug delivery systems.

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