Research Article Arch Pharm Sci & Res Vol 1 No 1 48-53 July 2009

DEVELOPMENT AND *IN-VITRO* EVALUATION OF COLON-SPECIFIC FORMULATIONS FOR ORALLY ADMINISTERED DICLOFENAC SODIUM.

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The aim of the present study is to develop colon targeted drug delivery system i.e. matrix tablet of Diclofenac sodium by using gaur gum as a carrier and sodium-CMC, sucrose 70% and ethyl cellulose as a binder. Matrix tablets containing various proportions of gaur gum as a carrier and sodium-CMC, Sucrose 70% and ethyl cellulose as a binder were prepared by wet granulation technique. The prepared matrix tablets were evaluated by different In-Process Quality Control tests like content uniformity and drug release study. Drug release profile was evaluated in simulated gastric fluid, intestinal fluid and simulated colonic fluid. The matrix tablets (F-9)containing gaur gum as a carrier and ethyl cellulose as a binder was found to be suitable for targeting diclofenac sodium for local action in the colon as compared to other matrix tablets containing different binders because of amount of drug release (13-33%) in simulated gastric fluid and intestinal fluid. Matrix tablets containing gaur gum and ethyl cellulose released 94-100 % of diclofenac sodium in simulated colonic fluid. *In vitro* release studies indicated that matrix tablets F1-F6 failed to control the drug release in the physiological environment of stomach and small intestine. On the other hand, formulations F7-F9 were able to protect the tablet cores from premature drug release in stomach and small intestine, but released 94-100 % of diclofenac sodium in simulated colonic fluid. **S**elective delivery of Diclofenac sodium to the colon could be achieved using a gaur gum and ethyl cellulose mixture in the form of carrier and binder for preparation of colon targeted drug delivery system i.e. matrix tablets.

Keywords: Diclofenac sodium, Gaur-gum, Colon targeted drug delivery system, Matrix Tablet.

INTRODUCTION

Due to the lack of digestive enzymes and the long transit time, colon is considered as suitable site for the absorption of various drugs. Colon drug delivery system is useful in administering drugs that are irritant to the upper gastrointestinal tract such as non-steroidal anti-inflammatory agents, or drugs such as peptides that are degraded by gastric juice or an enzyme present in the upper gastrointestinal tract. Drugs for the treatment of colonic disease (e.g. diarrhea, constipation, IBD, Colon carcinoma) and hronotherapeutic drugs for rheumatoid arthritis, asthma, and hypertension will also benefit from incorporation into colon targeting systems[1].

Colon-specific drug delivery has gained increased importance in the delivery of drugs for the treatment of local diseases associated with the colon, such as Crohn's disease, ulcerative colitis, colorectal cancer and amoebiasis.Control Drug Delivery System (CDDS) has been developing as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. The necessity and advantage of CDDS have been well recognized and reviewed recently[2]. In view of CDDS specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases.

CDDS would be advantageous when a delay in absorption is desirable from a therapeutic point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthama, angina and rheumatoid arthritis[3].

Various approaches have been proposed for targeted colon drug delivery, namely pH- and time-dependent systems, pressure-controlled release systems, osmotic systems, prodrugs and polysaccharide-based delivery systems[4]. The pH approach has been shown to lack site-specificity because of inter/intra subject variation and the similarity of the pH between the small intestine and the colon. Timed-release systems depend on the relative consistency of the small intestinal transit times, but the high variability in gastric retention times makes prediction of the accurate location of drug release difficult[5]. Prodrugs and

polysaccharide-based delivery systems depend on the enzymatic degradation carried out by the inherent bacterial flora present in the colon, thereby resulting in drug release. The enzyme trigger mechanism in such delivery systems makes them highly site-specific. Prodrugs, however, are considered as new chemical entities from a regulatory perspective which requires a detailed toxicological study to be performed, before being used as drug carriers. Natural polysaccharides, however, fall under the category of "GRAS" (Generally regarded as safe), thus resolving the general problems associated with safety. Natural polysaccharides, including chitosan, pectin, guar gum, xanthan gum, dextran and inulin remain undigested in the stomach and small intestine and are degraded by the huge numbers of anaerobic microflora in the colon.[6] The potential of pectins as carriers for colonic drug delivery has been demonstrated previously .Pectins are heterogeneous polysaccharides composed mainly of galacturonic acid and its methyl ester. They are refractory to host gastric and intestinal enzymes, but are almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligogalacturonates. Depending on the plant source and preparation, they contain varying degrees of methyl ester substituents.The degree of methoxylation determines many of their properties, especially solubility and requirements for gelation. High methoxy pectins (HM) are poorly soluble and require a minimum amount of soluble solids[7] .The potential of pectins as carriers for colonic drug.

The aim of present study was to explore the comparative utility of the different polymers and polysaccharides like gaur gum as a carrier for preparation of colon specific diclofenac sodium matrix tablet containing various excipients by application of the usual simple tabletting techniques.

Colonic Properties Of Guar Gum[8]

Guar gum is being used to deliver drug to colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine. The anaerobic bacteria that are responsible for the degradation of guar gum in the colon are *Bacteroides species (B. fragilis, B. ovatus, B. Variabilis, B. uniformis, B. distasonis and B. thetaiotaomicron*). The gelling property retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment. Homogenized and diluted feces from human source were incubated with the guar gum to investigate the degradation of polysaccharide by intestinal microflora. It produced a rapid decrease in viscosity and fall in pH while no such results were observed when it was incubated with autoclaved fecal homogenates.

It is to be noted that the utility of guar gum as a colon-specific drug delivery carrier is based on its degradation by colonic bacteria. The colon is rich in anaerobic bacteria. It implies that guar gum in the form of either a matrix tablet or as a compression coat over the drug core might have been degraded to a larger extent by the action of anaerobic microbial population of large intestine.

MATERIALS AND METHODS

Materials

All the following materials were used as received:

Diclofenac sodium (Free gifted sample by A-KLASS Drugs and Pharmaceutical Pvt.Ltd. Khamgaon. (M.S.) and all other remaining chemicals like Guar Gum, Microcrystalline cellulose, Sodium carboxy methyl cellulose, sucrose, ethyl cellulose, talc and magnesium stearate were of reagent grade.

Preparation of granules and matrix tablets[9]

Matrix tablets, each containing 50 mg diclofenac sodium and weighing with average wt. 500 mg were prepared by wet granulation and direct compression techniques using other excipients as per (Table 1). Tablet formulations (F1–F3) prepare by passing item no.1-4 from sieve no.80 after that wet mass formed by adding binder solution i.e. isopropyl alcohol in sufficient quantity to form dough wet mass. The wet mass formed passed from sieve No.# 8 .Formed wet uniform granules were dried at temp.60 c in oven for 30 minutes. After that the dried granules passed through sieve no. #18 and lubricated with magnesium stearate and talc (1:2) and compressed on a 10 station single hopper tablet

Table No.1: Composition of different matrix tablets of Diclofenac Sodium[10]

Sr. no.	Name of ingredients	Quantity per Tablet in mg								
		Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Diclofenac Sodium	50	50	50	50	50	50	50	50	50
2	Gaur-Gum	50	75	100	50	75	100	50	75	100
3	MCC	380	350	320	380	350	320	380	350	320
4	Sodium CMC 10% aq. solution)	005	010	015	-	-	-	-	-	-
5	Sucrose 70%	-	-	-	005	010	015	-	-	-
6	Ethyl Cellulose	-	-	-	-	-	-	005	010	015
7	Magnesium Stearate	005	005	005	005	005	005	005	005	005
8	Talc	10	10	10	10	10	10	10	10	10
9	Purified Water	-	-	-	Q.S.	Q.S.	Q.S.	-	-	-
10	Isopropyl Alcohol	Q.S.	Q.S.	Q.S.	-	-	-	Q.S.	Q.S.	Q.S.
	Total weight of Tablet	500	500	500	500	500	500	500	500	500

Study of In-Process Quality Control (IPQC) Parameters[11]

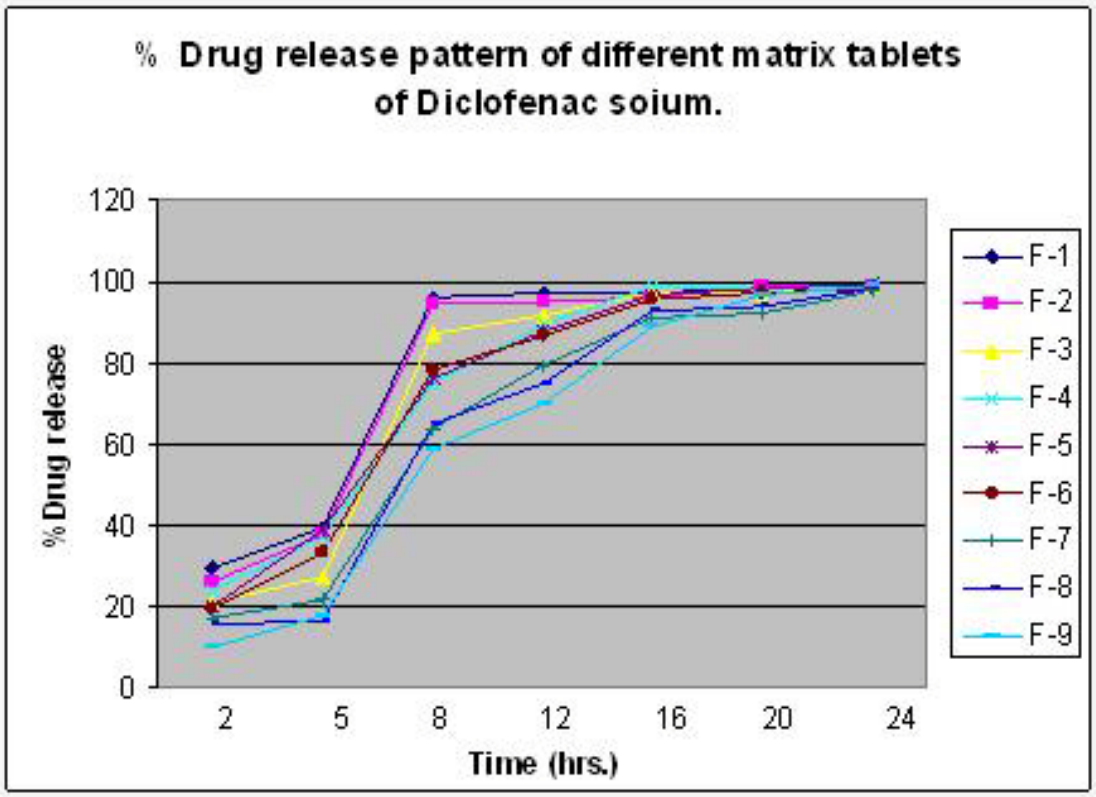
Table No.2: In-Process Quality Control (IPQC) Parameters of different matrix tablets of Diclofenac sodium.

Formulations	% Weight variation	Thickness(mm)	Hardness (kg/cm2)	% Friability
F-1	2.02+-1.05	3.53+-0.012	3.50	0.16+-0.05
F-2	1.81+-0.95	3.44+-0.022	3.70	0.47+-0.02
F-3	1.80+-0.8	3.65+-0.072	4.00	0.11+-0.02
F-4	1.74+-0.82	3.34+-0.028	3.20	0.17+-0.04
F-5	1.65+-0.8	3.34+-0.03	4.5	0.16+-0.01
F-6	2.0+-1.05	3.50 +-0.010	4.2	0.18 +-0.05
F-7	1.8+-0.8	3.3 +-0.021	5.5	0.37 +-0.02
F-8	1.74+-0.82	3.63 +-0.070	5.8	0.11+-0.02
F-9	1.6+-0.8	3.25 +-0.028	5.8	0.10 +-0.04

Table No.3: Dissolution behavior of different matrix tablets of Diclofenac Sodium.

Dissolution Media	Time (Hrs.)	Cumulative % Drug Release								
		Formulation Codes								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Simulated Gastric fluid	02	29.50	26.30	21.24	23.89	20.20	19.60	17.30	15.69	9.90
	05	39.50	37.82	27.14	37.24	38.67	33.19	21.59	16.54	17.87
Simulated intestinal fluid	08	96.25	94.42	87.34	74.83	75.89	78.43	63.85	64.98	59.10
	12	97.10	94.78	91.63	89.60	88.00	86.65	79.54	75.20	70
Simulated Colonic fluid	18	97.25	96.10	97.41	98.81	96.84	95.63	91.13	92.89	88.63
	20	98.4	98.94	97.23	98.40	98.50	97.10	92.10	94.15	96.51
	24	98.7	98.98	99.08	99.12	99.54	98.57	97.62	98.55	98.87

Figure No.1-Graph showing % Drug Release of different matrix tablets of Diclofenac Sodium.



compression machine, using 10 mm round flat punches. Tablet formulations (F4-F6) were prepare by passing item no.1-3 from sieve no.80 after that wet mass formed by adding aqueous solution of sucrose 70% in sufficient quantity to form dough wet mass. The wet mass formed passed from sieve no. # 8 .Formed wet uniform granules were dried at temp.60 c in oven for 30 minutes. After that the dried granules passed through sieve no. #18 and lubricated with magnesium stearate and talc (1:2) and compressed on a 10 station single hopper tablet compression machine, using 10 mm round flat punches. Tablet formulations (F7-F9) prepare by passing item no.1-3 from sieve no.80 after that wet mass formed by adding solution of ethyl cellulose in isopropyl alcohol in sufficient quantity to form dough wet mass. The wet mass formed passed from sieve no. # 8. Formed wet uniform granules were dried at temp.60 c in oven for 30 minutes. After that the dried granules passed through sieve no. #18 and lubricated with magnesium stearate and talc (1:2) and compressed on a 10 station single hopper tablet compression machine, using 10 mm round flat punches.

Tablets were evaluated during compression for different IPQC parameter like weight, hardness, thickness diameter and friability. Thickness and diameter were measured using vernier caliper scale. Hardness was evaluated manually by using Monsanto hardness tester. Friability test was performed at speed of 25 rpm with tablet dropping at the height of 6 inches wit beach revolution Electro lab make, model no. EF -1w, voltage 220 vAC. After the test, the tablets were dedusted and reweighed. Results are shown in table2.

Content Uniformity Test

Tablets were analyzed as per Indian Pharmacopoeia method and result showed that tablet conform to I.P. specifications.

Preparation of Dissolution Media[12]

Simulate Gastric Fluid: Dissolve 2 gm of sodium chloride and 3.2 gm purified pepsin i.e. derived from porcine stomach mucosa with an activity of 800 to 2500 unit/mg of protein in 7ml of hydrochloric acid and sufficient quantity of water to make 1000ml.This test solution has a pH of about 1.2.

Simulated Intestinal Fluid: Dissolve 6.8 gm of monobasic potassium phosphate in 250 ml of distilled water, mix and add 77 ml of 0.2N sodium hydroxide and 500 ml of distilled water .Add 10 gm of pancreatin and mix and adjust resulting solution with either 0.2 N sodium hydroxide or 0.2N hydrochloric acid to a pH of 6.8 +_ and dilute it with distilled water to 1000ml.

Simulated Colonic Fluid: Dissolve 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in sufficient quantity of distilled water.

In-vitro release study[13]

Drug release studies were conducted under conditions mimicking mouth-to-colon transit [19, 20]. The dissolution medium consisted of 900 ml 0.1 mol/l HCl for 2 h, replaced by 900 ml phosphate buffer pH 7.4 for 3 h kept at 37 ± 0.5°C and for remaining hours in simulated colonic fluid stirred at 50 rpm, using USP dissolution apparatus II (paddle). Samples were withdrawn at the end of the specified periods (2, 5, 8,12,16,20 and 24 hours), filtered and diluted up to 50ml with respective dissolution medium and assayed spectrophotometrically for Diclofenac Sodium, at 273 nm in 0.1 mol/l HCl , 276 nm in pH 7.4 buffer and at 276 nm in 6.8 pH.

RESULTS AND DISCUSSION:

In vitro release studies indicated that matrix tablets F1-F6 failed to control the drug release in the physiological environment of stomach and small intestine. On the other hand, formulations F7-F9 were able to protect the tablet cores from premature drug release in stomach and small intestine, but released 94-100 % of diclofenac sodium in simulated colonic fluid.

CONCLUSION:

This study showed that it is possible to control the release rate of diclofenac sodium over a wide time scale using gaur gum as a carrier and ethyl

cellulose as a binder. It was also observed that the release of diclofenac is slower in pH 1.2 and pH 6.8 and much higher in pH 7.4. This finding showed that the release system is effective as a controlled release system for colon specific drug delivery. It is also concluded that selective delivery of Diclofenac sodium to the colon could be achieved using a gaur gum and ethyl cellulose mixture in the form of carrier and binder for preparation of colon targeted drug delivery system i.e. matrix tablets.

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