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COLON TARGETED MATRIX TABLET OF BIODEGRADABLE SWELLABLE POLYMERS

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ABSTRACT

The colon targeted drug delivery has a number of important implications in the field of pharmacotherapy. Oral colon targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration. Targeting of drugs to the colon via oral administration protect the drug from degradation or release in the stomach and small intestine. It also ensures abrupt or controlled release of the drug in the proximal colon. Various drug delivery systems have been designed that deliver the drug quantitatively to the colon and then trigger the release of drug. This review will cover different types of polymers which can be used in formulation of colon targeted drug delivery systems.

INTRODUCTION: The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug. Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs [1].

Various bacteria present in the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-D- glucosidase, dextranase, α-D-xylosidase [2]. These polymers are inexpensive and are available in a variety of structures.

Linear polysaccharides remains intact in stomach and small intestine but the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems [3].

Guar gum is derived from the seeds of the *cyomopsis tetragonolobus* (Fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches [**Figure 1**] [4].

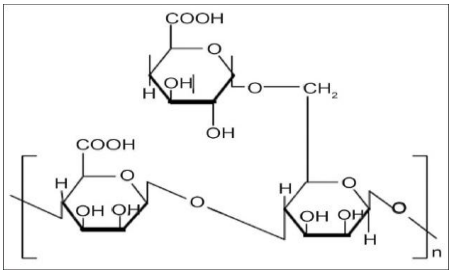


FIGURE A: STRUCTURE OF GUAR GUM

Pectin is a linear, heterogeneous polysaccharide which is mainly composed of galacturonic acid and its methyl ester. These are predominantly linear polymers of mainly (1→4) linked D-galacturonic acid residue interrupted by 1, 2-linked L-rhamnose residue with a few hundred to about one thousand building blocks per molecule [**Figure 2**] [5].

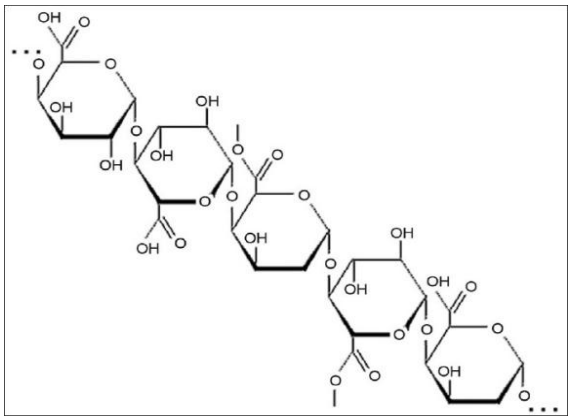


FIGURE 2: STRUCTURE OF PECTIN

Mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process [6].

Coating with polymers: The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.

1. **Coating with pH-sensitive polymers:** The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. In the present investigation, cellulose acetate phthalate (pH-5) was used as the pH sensitive polymer [7].

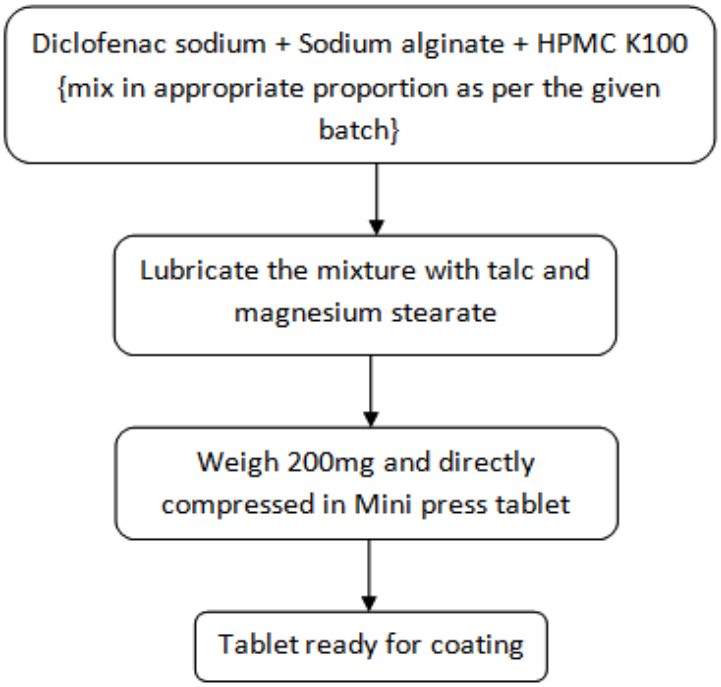
2. **Embedding in biodegradable matrices:** The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for liberation of entrapped drug. Polysaccharides, the polymer of monosaccharides retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes [8].

MATERIALS AND METHOD:

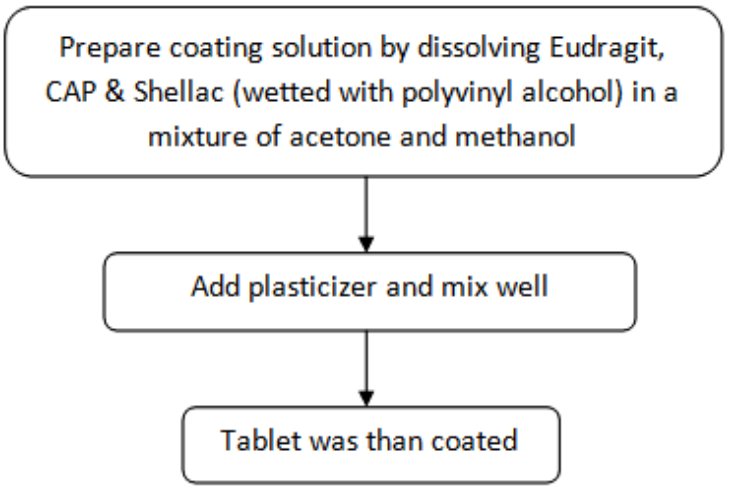
Material: Diclofenac Sodium, Sodium Alginate and Talc were generous taken from Shree Krishna Institute of Pharmacy, Shankhalpur. HPMC K 100 was purchased from panacea Biotech (India). Magnesium stearate was taken from Signet Chem. Mumbai, India.

Coating Ingredients: Cellulose Acetate phthalate and Dibutyl phthalate were purchased from Signet Chem., Mumbai, India. Methanol and Acetone were taken from Ronak Laboratory, India.

Method: (Graphical Method was described in Graph: 1 and Graph: 2) [5]



GRAPH 1: PREPARATION OF DICLOFENAC SODIUM TABLET



GRAPH 2: PREPARATION OF DICLOFENAC SODIUM TABLET COATING SOLUTION:

Evaluation Parameters [9]:

Quality control:

- In process quality control (IPQC)
- Finished product quality control
    - **In process quality control**
        - Appearance of the tablet:
        - Weight variation
        - Thickness
        - Hardness
        - Friability

Finished Product Quality Control [10]:

Content Uniformity Study: Powdered 20 tablets and take 100mg equivalent weight of Diclofenac sodium. Dissolve it in a 100ml of methanol. Take 10ml from it and dilute up to 100ml with methanol. Then take 0.5ml and dilute up to 10ml with methanol, measure absorbance of final solution at 276 nm.

***In-Vitro* Dissolution Studies:** The USP 24 (8) method for enteric-coated tablets (basket method, 75 rpm, 37 _ 0.5°C) using a USP dissolution test apparatus was used for all experiments. For the initial 2 h, the study was conducted in 750 ml of 0.1 mol L–1 HCl, followed by dissolution at a pH of 6.8 (adjusted by addition of 250 mL of 0.2 M trisodium phosphate) (8–11). Aliquots were collected manually at predetermined time intervals and analyzed for indomethacin using a UV-visible spectrophotometer at a _max of 276 nm (Shimadzu 1601, Japan).

RESULTS AND DISCUSSION: All the enteric-coated systems showed no drug release in the first 2 h in the simulated gastric environment. Ethyl cellulose-coated tablets also showed negligible drug re- lease in the initial 2 h of dissolution. Afterwards, a different drug release profile was evident for each polymer.

Eudragit S-100 coating: Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the thickness of the coat applied (**Fig. 1a)**. A significant difference ($p < 0.001$) was observed in the percentage of drug released for different coating concentrations, from 4 h, to 12 h during the dissolution study. Drug release was found to be of zero-order ($n > 0.9$) at all three coat concentrations. At a coat concentration of 1% (*m/m*), the percent drug release in the first 3 h of dissolution at pH 6.8 (small intestinal environment and transit time) was 39%. Increasing the coat thickness to 1.5% and 3% reduced the drug release to 28% and 18%, respectively. All the coated tablets showed a nearly complete drug release in the next 20 h.

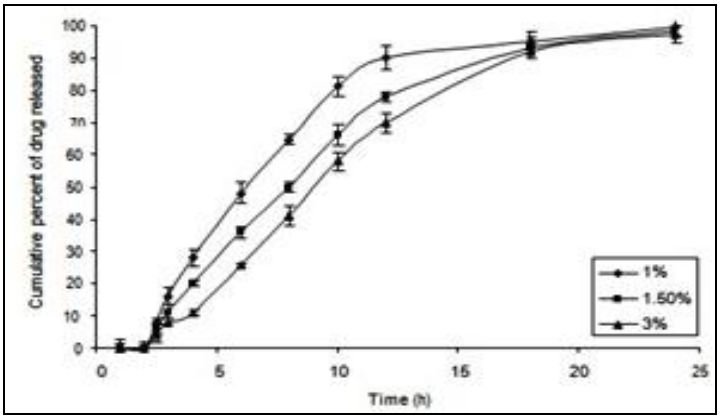


FIG. 1A: CUMULATIVE PERCENTAGE OF DRUG RELEASED (mean ± SD), n= 6 VERSUS TIME PROFILE FOR TABLETS COATED WITH EUDRAGIT S-100

Cellulose Acetate Phthalate Coating: Similarly, varying the coat thickness of CAP varied the percent drug release from the tablet significantly at the end of 3 h, up to 18 h ($p < 0.001$) (**Fig. 1b**). Drug release kinetics was found to follow non-fickian kinetics at a coat concentration of 1.5 % (*m/m*) ($n = 0.802$) whereas it was zero-order at the other two coat concentrations (3% and 5%) ($n > 0.9$). The formulation with a 5% coat showed as low as 25% drug release in the first 3 h of dissolution at pH a 6.8.

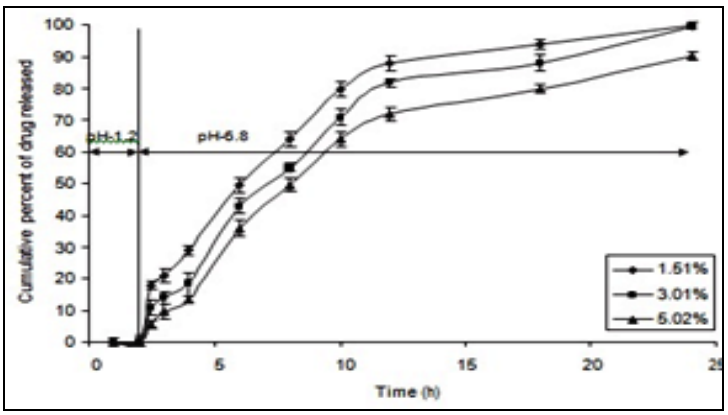


FIG. 1A: CUMULATIVE PERCENTAGE OF DRUG RELEASED (mean ± SD), n= 6 VERSUS TIME PROFILE FOR TABLETS COATED WITH CAP

A total of 90% drug was released in the next 20 h. The results for CAP are also in agreement with the studies con- ducted by Levine *et al.* [15], since they also found the usefulness of this polymer for de livery of beclomethasone dipropionate to the colon. This may be attributed to the fact that the dissolution medium (pH 6.8) which is well above the pH of CAP solubilization.

Shellac: Shellac, however, showed a different drug release profile (**Fig. 1c**) with a high *n* value (1.4–1.27), which is beyond the range of fickian, non-fickian or zero-order release. A significant difference ($p < 0.001$) was observed in the percent drug released from the tablets with different coating concentrations from the second hours up to 9 hours of the dissolution study. A coat concentration of 1.5% retarded drug release for the first 2 h and percent drug release during this time was almost with after 6 h it was 42.2 2.2% and around 100% drug was released in 12 h of dissolution (1c). Increasing the coat concentration to 3% almost resisted drug release for the initial 4 h of dissolution at pH 6.8 where after, a rapid drug release was observed, which became 100% in the tenth hour. The ability of shellac to resist drug release for 3–4 h, followed by a rather rapid drug release, can be exploited for delivery of various drug molecules to the colon.

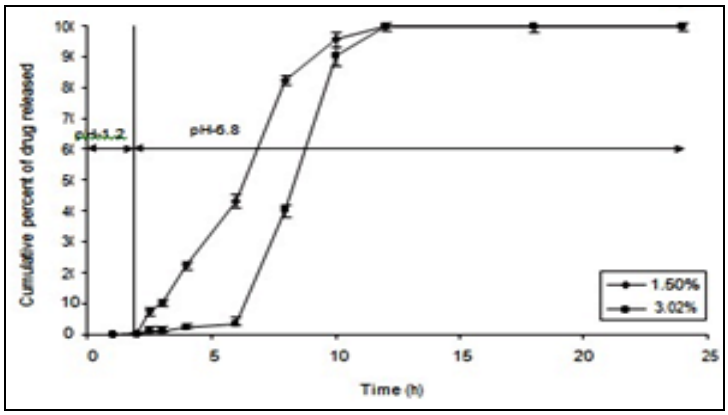


FIG. 1A: CUMULATIVE PERCENTAGE OF DRUG RELEASED (mean ± SD), n= 6 VERSUS TIME PROFILE FOR TABLETS COATED WITH SHELLAC

Ethyl Cellulose Coating: The drug release from the EC coated tablets was zero-order ($n = 1.0$) at the lowest coat concentration and increasing the coat concentration changed the drug release kinetics to non-fickian ($n = 0.671$), and further to fickian diffusion ($n = 0.328$). These tablets also showed a decrease in drug release upon increasing the coat mass (Fig. 1d). Percent drug release varied significantly from the end of the third hour up to 24 h ($P < 0.001$) at different coat concentrations. The amount of drug released (at pH 6.8) decreased upon increasing the coat concentration. Different behavior observed in the case of shellac compared to other polymers can be explained by the fact that, unlike other polymers such as Eudragit and CAP, shellac solubilizes rather slowly.

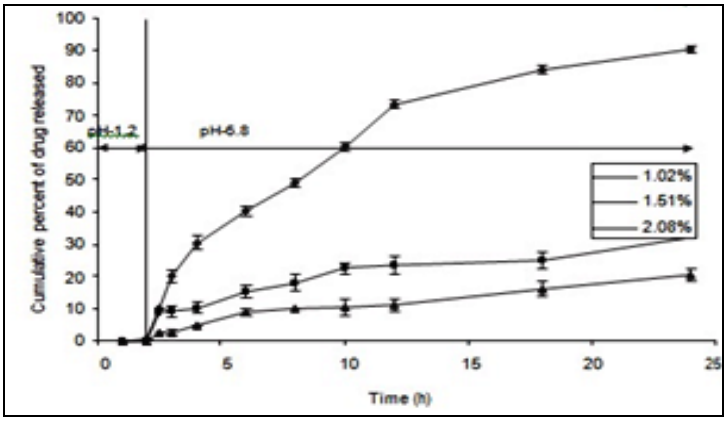


FIG. 1A: CUMULATIVE PERCENTAGE OF DRUG RELEASED (mean ± SD), n= 6 VERSUS TIME PROFILE FOR TABLETS COATED WITH ETHYL CELLULOSE

Evaluation parameter of IPQC: Tablet appearance were measured and described in **Table 3**. In that, all formulation give some appearance like round and concave shape, its color was white. The diameter of tablet by all formulation was measured and it is 8 mm and its thickness was 3 mm. these was also in the range what we want. The weight variation of tablets was measured and its range was nearer to 200-210 mg so its percentage deference was 7.5 % and so those all formulation give result comply.

The hardness of tablet was measured by the Monsanto hardness tester and it gives all formulation in range 5-6 kg/cm^3. We also measured the friability of tablets by Roche friability machine its result was comply.

TABLE 1: COMPOSITION OF TABLET

Ingredients	F1	F2	F3	F4
Diclofenac sodium	100mg	100mg	100mg	100mg
Sodium alginate	-	50mg	70mg	30mg
HPMC K100	40mg	60mg	80mg	100mg
Talc	1%	1%	1%	1%
Magnesium stearate	1%	1%	1%	1%

TABLE 2: COMPOSITION OF COATING SOLUTION

Ingredients	F1	F2	F3	F4
Eudragit- S100	12.5%	-	-	-
Cellulose Acetate Phthalate (CAP)	-	15 %	-	-
Shellac	-	-	30%	-
Ethyl cellulose	-	-	-	20%
PEG-400	1.25%	-	-	-
Dibutyl phthalate	-	25%	-	-
Propylene Glycol	-	-	10 %	-
Acetone	75 ml	75 ml	75 ml	75 ml
Methanol	25 ml	25 ml	25 ml	25 ml

TABLE 3: EVALUATION PARAMETER OF IPQC

Sr. no.	IPQC parameters	F1	F2	F3	F4
1.	**Appearance**	Round, concave, dull white	Round, concave, dull white	Round, concave, dull white	Round, concave, dull white
2.	**Dimensions**				
	• Diameter	8 mm	8 mm	8 mm	8 mm
	• Thickness	3 mm	3 mm	3 mm	3 mm
3.	**Weight variation**				
	• Ave. wt.	205.5mg	202.3mg	204mg	208.4mg
	• % difference	7.5%	7.5%	7.5%	7.5%
	• Result	Comply	Comply	Comply	Comply
4.	**Hardness**	6.0kg/cm^2	5.5kg/cm^2	5.5kg/cm^2	5.5kg/cm^2
5.	**Friability**	0.6%	0.8%	0.8%	0.85

CONCLUSION: At a coat concentration of 3%, shellac provided the most appropriate polymer coat for colon specific drug delivery in the present study, which may be useful for local colonic pathologies and for systemic drug delivery. Shellac is a natural polymer that is also abundantly available and cost effective. Moreover, the study shows that it provides a site-specific drug delivery. Variation in shellac coat thickness can facilitate drug delivery to terminal ileum, distal or proximal colon.

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