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Formulation and Evaluation of Colon Targeted Drug Delivery System of Budesonide Using Xylan as a Carrier

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ABSTRACT

Budesonide has been identified as a potential candidate to treat cancer particularly colorectal cancer. High dose is required in order to make sufficient quantity available at the desired site to elicit therapeutic response. Budesonide gets absorbed in upper part of intestine making its availability in the colon extremely low. Colon targeting approach with xylan matrix tablet of Budesonide hold tremendous potential for treatment of colon cancer. In the present research work, to prepared colon targeted matrix tablet investigate the release profile of budesonide from xylan based matrix tablets and attempts were also made to explore the feasibility of xanthan gum, guar gum and pectin as colon specific carrier for budesonide. The matix tablet was prepared four different formulations with different percentage of xylan. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl pH 1.2 for 2 hrs, the dissolution medium was replaced with pH 7.4 for 3 hrs and then replaced with phosphate buffer pH 6.8 next 19 hrs. the in-vitro dissolution studies it was found to be that formulation F1 with 10% Xylan, F2 with 20% Xylan, F3 with 30% Xylan and F4 with 40 % Xylan all retard drug release in the stomach and small intestine effectively. F1 Xylan (10%) & F3 Xylan (30%) emerged to be best because it exhibits the best overall general appearance, hardness of 6.2 ± 0.498Kg/cm^2, friability of 0.19802%, percentage drug released 53.51 ± 0.850 & hardness of 5.9 ± 0.124Kg/cm^2, friability of 0.2004%, percentage drug released 42.75 ± 0.106 without rat caecal content at the end of 24 h *in-vitro* dissolution studies respectively. the matrix formulation containing **10% Xylan** and **30% xylan is** most like to target budesonide to colon without being release significantly in stomach & small intestine.

K**eywords:** Colon Targeted drug delivery system, Budesonide, Xylan.

INTRODUCTION

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease [1,2]. Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs, which are destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained

colonic release of drugs can be useful in the treatment of nocturnal asthma, angina pectoris and arthritis. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of vermicides and colonic diagnostic agents require smaller doses [3]. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability [4].

The bacterial enzymes of the colon degrade the carrier polymer in a well-defined way and release the content for localized colonic delivery or systemic absorption through colon. Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a polysaccharide based delivery system for colon is the presence of large amount of bacteria in the human colon as the colon is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D-glucosidase, β -D-galactosidase, amylase, pectinase, xylanase, β -D-xylosidase, dextranase, etc. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylase, xylan and locust bean gum. Natural polysaccharides remain undigested in the stomach and small intestine and are degraded by the enzymes released by bacteria present in the colon.

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect. It binds to the glucocorticoid receptor with a higher binding affinity than cortisol and prednisolone. When budesonide is systemically administered, suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function has been observed. Furthermore, a decrease in airway reactivity to histamine and other entities has been observed with the inhaled formulation [5-7]. Colon targeting approach with xylan matrix tablet of Budesonide hold tremendous potential for treatment of colon cancer.

Keeping the above in view attempts have been made to investigate the release profile of Budesonide from xylan based matrix tablets. Attempts were also made to explore the feasibility of xanthan gum, guar gum and pectin as colon specific carrier for Budesonide.

MATERIALS AND METHODS

Material

Budesonide was a gift sample from Avik Pharma Pvt. Ltd., Vapi, Gujarat. (India). Xylen was purchased from Himedia laboratory, Mumbai, Microcrystallin cellulose (MCC), Talc and Magnessium stearate was purchased from loba chemical for this study. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

Method

Formulation of Colon Targeted Matrix Tablet:

Budesonide was chosen as model drug which is poorly soluble in water. Matrix tablet of Budesonide were prepared by the direct compression technique. MCC was used as diluent and the mixture of talc & magnesium stearate at 2:1 ratio was used as lubricant. The composition of different matrix formulation used in the study containing 75 mg of Budesonide given in table 1.

Table 1. Composition of colon targeted matrix tablet of Budesonide

Sr No.	Ingredients	Qty. taken
1	Budesonide	15%
2	Xylan	10-40%
3	Mcc	qs 100%
4	Talc	2%
5	Magnesium stearate	1%

Four different formulation having different quantities of xylan (10 to 40 % of total weight) were prepared by direct compression method. The tablets were prepared as described above. The composition of different formulations is shown in Table 2.

Table 2. Formulation of colon targeted matrix tablet of Budesonide

S. No.	Tablet Ingredients (mg/tab)	Formulation code			
		F1	F2	F3	F4
		10%	20%	30%	40%
1	Budesonide	9	9	9	9
2	xylan	50	100	150	200
3	Mcc	360	310	260	210
4	Talc	10	10	10	10
5	Magnesium stearate	5	5	5	5

Evaluation of Colon Targeted Matrix Tablet of Budesonide

General Appearance and Physical Parameters

Thickness of tablets

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zetasizer.

Vesicle morphology

The diameter of vesicle in a transferosome can be determined by dynamic light scattering method. The samples are passed through 0.2mm diameter of membrane filter. Before the samples are prepared by distilled water. Filtered sample is diluted with saline which is also filtered. Then size measurement is done by dynamic scattering method. Although the vesicle of transferosome can be visualized by TEM. Stability of the vesicle determined by size and structure of the vesicle. Mean size of the vesicles is performed by DLS method. System by Malvern Zetasizer.

Weight variation test:

The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit [7,8].

***In-vitro* Drug Release study:**

Budesonide matrix tablet release from was performed by dissolution test apparatus USB type I (paddle method). The test was performed using 900ml of 0.1N HCL at $37^0 \pm 0.5^0$C and 100 rpm for first 2 hrs. Then replaced with 7.4 pH phosphate buffer and continued for 24 hrs. A liquot volume of 5ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. The sample was analysed for the drug content by measuring absorbance by 272 nm in double beam spectrophotometer [11-15].

. RESULTS AND DISCUSSION:

The prepared matrix tablets were subjected to post compression parameter i.e. thickness, weight variation, hardness, friability, content uniformity. All the matrix tablet formulation complies for all the physical parameter and drug content uniformity. The results are as follows.

Table 5. Characteristics of xylan based colon targeted matrix tablet of Budesonide

Formulation code	Thickness (mm)	Weight (mg)	Hardness (kg/cm2)	Friability (%)	Content uniformity (%)
F1	4.1 ± 0.0816	509.05 ± 0.639	5.7 ± 0.498	0 .153± 0.18	89.59 ± 0.44
F2	3.8 ± 0.1247	504.7 ± 0.997	5.8 ± 0.286	0.168± 0.29	89.96 ± 1.60
F3	4.4 ± 0.3741	507.1 ± 0.719	5.9 ± 0.124	0.208± 0.27	94.15 ± 0.67
F4	4.2± 0.4784	502.3 ± 0.714	5.7 ± 0.329	0.183± 0.19	93.99 ± 2.09

Table 6. Result of in-vitro drug release study of colon targeted matrix tablet formulation of Budesonide

Time(hrs)	Cumulative % drug release			
	F1	**F2**	**F3**	**F4**
2	2.25 ± 0.091	1.255 ±0.154	0.790 ±0.004	0.533 ±0.094
5	4.03 ± 0.544	3.66 ± 0.590	2.72 ± 0.078	3.47 ± 0.340
7	7.53 ± 0.624	11.38 ± 0.86	6.54 ± 0.018	7.43 ± 0.463
9	9.46 ±0.661	12.87 ±0.50	10.74 ±0.023	11.93 ±0.735
12	13.29 ± 0.92	18.83 ±0.162	15.33 ±0.056	16.98 ±0.700
15	23.26 ±0.665	25.76 ±0.994	21.48 ±0.004	22.38 ±0.912
18	39.49 ±0.654	30.75 ±0.515	27.92 ±0.011	28.51 ±0.354
21	48.25 ±0.628	39.20 ±0.932	35.04 ±0.023	35.05 ±0.929
24	53.51 ±0.850	44.21 ±0.330	42.75 ±0.106	42.67 ±0.599

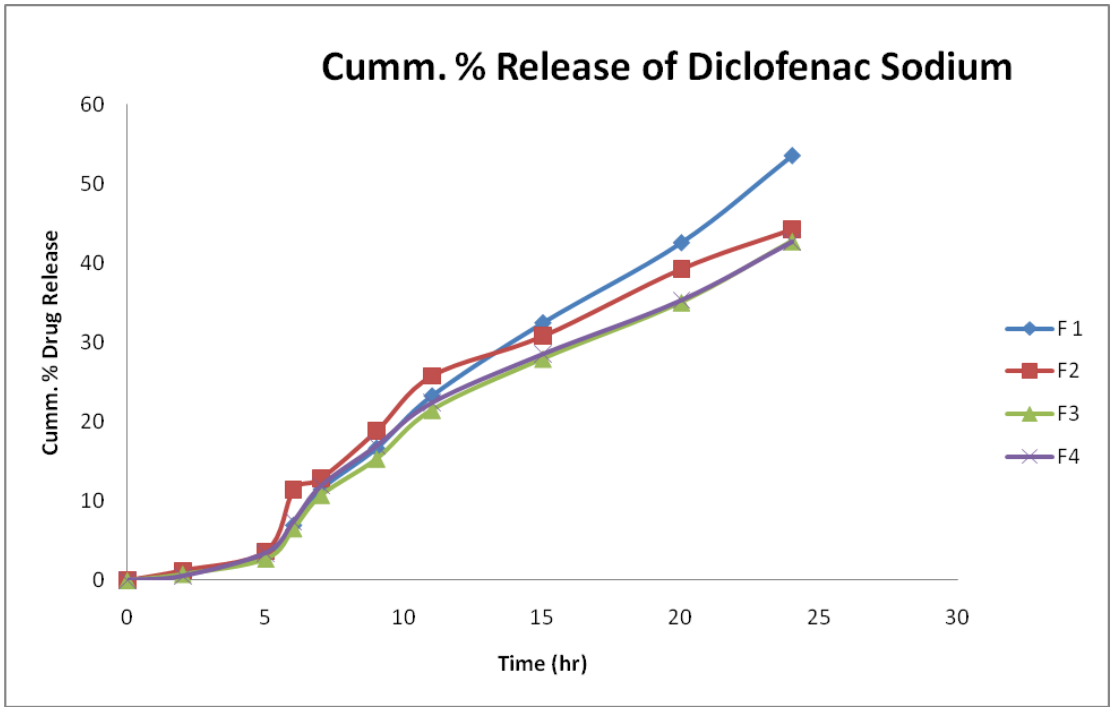

Fig. 1. Cumulative percent of Budesonide released from colon targeted matrix tablet containing varying proportion of xylan in absence of rat caecal content.

The *in-vitro* dissolution studies it was found to be that formulation **F1** with **10% Xylan, F2 with 20% Xylan, F3 with 30% Xylan** and **F4 with 40 % Xylan** all retard drug release in the stomach and small intestine effectively. From that it can be concluded that the formulations containing **10%, 20%, 30%** and **40** % of **Xylan** all target the colon in the form of colon targeted matrix tablet.

CONCLUSION

The colon targeted matrix tablet formulations of Budesonide were prepared by direct compression technique using various proportion of xylan as polymer. Four batches were prepared with various percentage of xylan to retard the drug release in to the stomach & small intestine.

Budesonide, a widely used non-steroidal anti-inflammatory drug has recently been found having high potential in colon cancer treatment. However, this suffers from one disadvantage i.e. on oral administration it gets absorbed in upper part of the intestine making its availability in the colon extremely low.

All the colon targeted matrix formulations prepared were evaluated for physicochemical parameters such as appearance, physical properties, drug content and *in-vitro* dissolution studies. All the physical characteristics of the formulations like thickness, hardness, friability, drug content, and *in vitro* dissolution study were found to be well within the limits and official standards. From the *in-vitro* dissolution studies it was found to be that formulation **F1** with **10% Xylan, F2 with**

20% Xylan, F3 with 30% Xylan and **F4 with 40 % Xylan** all retard drug release in the stomach and small intestine effectively. From that it can be concluded that the formulations containing **10%, 20%, 30%** and **40** % of **Xylan** all target the colon in the form of colon targeted matrix tablet.

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CONCLUSION:

From this study, it was concluded that the transferosomal formulations of curcumin, with high EE % and small particle size. Also, the preparation of curcumin as transfersomal gel has the ability to overcome the barrier properties of the skin and increase the drug release.

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