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Original Article

DESIGN AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY OF BUDENOSIDE

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ABSTRACT

Objective: The objective of this research is to design and evaluate a colon specific drug delivery of budenoside using guar gum as enzyme dependent polymer.

Methods: Matrix tablets of Budenoside were prepared by using wet granulation technique with different proportions of guar gum and evaluated for different evaluation tests and release profiles.

Results: The formulations were studied for post compression parameters like hardness, friability, weight variation and drug content are in acceptable range of pharmacopoeial specifications. *In vitro* swelling and Invitro release studies was carried out at different pH ranges (1.2, 6.8 and 7.4). The release profile of budenoside from the matrix tablets is dependent upon the gelling property of guar gum and degradation of guar gum polysaccharide by colonic bacteria. High concentration of guar gum showed less drug release in the stomach as an enzyme dependent polymer. *In vitro* release data revealed that the presence of rat caecal content in dissolution medium showed the significant increase in drug release (97.12%), when compared to drug release study in absence of caecal content (76.86).

Conclusion: The results were subjected to study the release kinetics. The values of correlation coefficient indicated that the drug release followed Zero order drug release kinetics with Peppas drug release mechanism. *In vitro* drug release studies shows that guar gum with high concentration (25%) has optimum release in a controlled manner for 24 hours.

Keywords: Colon specific drug delivery, Budenoside, Asthma & Chronotherapy.

INTRODUCTION

Colon targeting is acquired a lot of importance in the treatment of various diseases of colon like Inflammatory bowel disease, Crohn's disease, colon cancer & various local infections of the colon. The technique is also used for chronotherapeutic delivery of drugs E. g. Treatment of nocturnal asthma etc. The current study focused on development of timed controlled formulation to treat the nocturnal symptoms of asthma. If the formulation is administered in the night, symptoms that are occurring in an early morning hours could be avoided. Different approaches are used for colon targeted drug delivery, which include pH sensitive polymer coated drug delivery to the colon, delayed (time controlled release system) release drug delivery to colon, microbial triggered drug delivery to colon and newly developed approaches are pressure controlled drug-delivery systems, novel colon targeted delivery system, osmotic controlled drug delivery system[1].

There is a steep gradient of enzyme activity derived from gut micro flora along the gastrointestinal tract. In humans, the stomach and small intestine contain roughly 103–104 colony forming units/ mL. However, the concentration of microflora rises drastically from the terminal ileum to the ascending colon where the numbers reach 1,011–1,012 CFU/mL. These bacteria survive by fermenting a wide variety of substrates (e. g. polysaccharides, oligosaccharides, mucopolysaccharides) left undigested in the small intestine. Hence, enzymatically controlled delivery system is considered convenient approach for site-specific drug delivery to the colon where no drug release can occur unless the system arrives to the colon [2].

Budesonide (BUD), a second generation glucocorticoid exhibits high affinity to the corticosteroid receptors with a high ratio of topical to systemic anti-inflammatory activity by decreasing the production of cytokines and interleukins. Budesonide have half life of 2-4 h with an oral bioavailability of 10%. Budesonide is used in the treatment nocturnal asthma [3]. BUD is approximately twice as active as beclomethasone dipropionate and it is over 1,000 times more active than either prednisolone or hydrocortisone in inducing intra cutaneous vasoconstriction (as a marker of anti-inflammatory activity). BUD is commercially available in the market in the form of enteric-coated preparations mainly for the treatment of small intestine active Crohn's disease. However, these products, similar to other available site specific dosage forms, are not sufficiently selective to treat colonic inflammatory bowel disease [4].

MATERIALS AND METHODS

Materials

Budenoside & Guar gum were obtained as gift samples from Granules India Ltd & Natco Pharma Pvt. Ltd, Hyderabad, India. Talc and magnesium stearate used for the preparation of tablets were of Pharmacopeias grade.

Studies on viscosities of polymers [5]

Viscosities of 1%w/v dispersion of guar gum in 0.1N HCl, P^H 7.4 and P^H 6.8 Phosphate buffers were measured by using Brookfield viscometer. The results were tabulated in table No.1.

Determination of swelling indexes of polymer [5]

1 gm of guar gum was added to 10 ml of distilled water. The measuring cylinder was shaken vigorously for 10 min and allowed to stand for 24 hrs. Swelling capacity was expressed as.

Swelling capacity (%v/v) = $[X_v / X_i]$ X100

Where X_v is the final volume occupied by swollen material after 24 hrs and X_i denotes the initial volume of the powder in the graduated measuring cylinder. Same procedure was repeated to study the swelling capacity of both gums in 0.1N HCl, P^H 6.8 and P^H 7.4 phosphate buffers. The results were tabulated in table No 1.

Preparation of Budenoside matrix tablets [5]

The formulation containing 50mg of Budenoside and different proportions of guar gum (5-25% of total weight). Lactose was used as diluent and a mixture of talc–magnesium stearate (1:1) was used

as the lubricant. Matrix tablets of Budenoside were prepared by wet granulation method. Guar gum was included in the formulations in various proportions. The granules obtained were dried at 50 ^{0}C and were sieved through # 16 and lubricated with talc and magnesium stearate. The granules were compressed by employing 9 mm round shaped die with Cadmach CMS 25 tableting machine to get tablets. The composition of various formulations is shown in Table 2.

In-process quality control parameters of tablets [6, 7]

The formulated tablets were evaluated for different IPQC parameters like Drug content, Weight Variation, Hardness, Thickness, Diameter, and friability. The results were tabulated in table No 3.

Preparation of rat caecal content medium [7]

The albino rats weighing between 150-200 g were kept on the normal diet and administered with 1 ml of 1% w/v solution of guar gum in the water with the help of Teflon tubing directly into the esophagus region via an oral cavity. The treatment was continued for 6 days to induce enzyme responsible guar gum degradation, animals were sacrificed before 30 min of commencing drug release studies and the caecum was exteriorized for caecal content collection. The caecal content (anaerobic) was immediately transferred into buffer solution P^{H}6.8 to obtain an appropriate 4%w/v concentration solution which was bubbled with carbon dioxide gas to maintain an anaerobic environment.

***In vitro* drug release studies [7-9]**

The susceptibility of the matrix tablets of Budenoside to remain intact and the release of the active ingredient in the physiological environment of stomach, small intestine and colon was assessed by conducting *In vitro* drug release studies under conditions mimicking mouth to colon. This study was carried out using USP dissolution test apparatus- II at 50rpm and 37±0.5^{0}C. The tablets were tested for drug release in 0.1N HCl (900 ml) for first 2h as average gastric emptying time was estimated as 2h. A sample of 5 ml of the dissolution medium was withdrawn after 2hr to determine the drug release. The amount of drug release was analyzed by UV spectrophotometer at 247 nm. The dissolution media was replaced with fresh buffer (900 ml) for 3h as the average small intestine transit time is about 3h. The amount of drug release was analyzed by UV spectrophotometer at the maximum wavelength of 247 nm.

The susceptibility of polysaccharides in matrix tablets to enzymatic action of colonic bacteria were assessed by continuing the drug release studies in 900 ml of pH 6.8 phosphate buffer containing 4%w/v rat caecal content after 5 hours. The study was continued from 6 hours to 24hours and samples were withdrawn at regular intervals for analysis and each time replaced with fresh PBS media containing rat caecal material bubbled with CO_2.

The withdrawn samples were diluted with PBS and centrifuged. The supernatant was filtered through a bacteria proof filter and filtrate was analyzed for drug content at 247 nm using Shimadzu UV-150 double beam UV spectrophotometer. The above study was also carried out without rat caecal content in 6.8 pH phosphate buffers as a control. The results were tabulated in table No.4.

RESULTS AND DISCUSSION

Viscosities & Swelling index of Guar gum was measured in 0.1 N HCl, P^H 7.4 phosphate buffer, P^H 6.8 phosphate buffer. From this, it was observed increased viscosity shown decrease in swelling index, where decreased swelling index showed decreased drug release.

Table 1: Viscosities and swelling index of different polymeric dispersions (1%w/v)

1%w/v Guar gum dispersion	Water	0.1 N HCl	pH 6.8 Phosphate buffer	pH 7.4 Phosphate buffer
Viscosity (cps)	104.3	110.6	113.1	117.4
Swelling index	5.1	5.6	5.3	4.9

Table 2: Composition of Budenoside Matrix tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Budenoside	50	50	50	50	50
Guar Gum	15	30	45	60	75
Lactose	193	178	163	148	133
Starch	36	36	36	36	36
Talc	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3
Total	300	300	300	300	300

Table 3: IPQC Parameters of Budenoside Matrix Tablets

Formulation	Average weight (mg)	% Drug content	Hardness kg/cm	% Friability
F_1	300	101.2	6.8	0.46
F_2	301	98.45	5.5	0.32
F_3	299	100.89	5.9	0.37
F_4	302	99.43	6.4	0.46
F_5	303	98.88	6.6	0.32

From the study of drug and polymer properties, it was found that both drug and polymers have poor flow and compaction properties. Hence in formulation wet granulation method was employed to prepare matrix tablets. All the granules were found to have improved flow properties when compared to drug and polymers. All the formulations were prepared according to the composition showed in Table 1.

The formulations were developed by employing the different proportion of guar gum in order to study their influence on drug release properties. The hardness of all tablets was found to be in between 5.5-6.8 kg/cm^2. The friability and drug content was measured and the tablets satisfied all the official requirements.

The formulations were subjected to *In vitro* drug release studies in varied dissolution mediums namely 0.1 N HCl for 2 hrs, then P^H 7.4 phosphate buffer for 3 hrs, then P^H 6.8 phosphate buffer till the end. In all the formulations developed the results were subjected to study the release kinetics. The values of correlation coefficient indicated that the drug release followed Zero order drug release kinetics with Peppas drug release mechanism. The values of $t_{50\%}$ and $t_{90\%}$ increase with increasing the proportion of polymers table no 4.

Table 4: *In vitro* release kinetics of Budenoside Matrix tablets

Formulation	Correlation coefficient					Release rate			
	Zero order	First order	Hixson crown well	Higguchi	Peppas	K_0 (mg/hr)	k_1 (hr^{-1})	T_{50} Hr	T_{90} Hr	Exponential coefficient (n)
F_1	0.9802	0.9708	0.9889	0.9621	0.9947	3.9255	-0.0715	12.7	22.9	0.6670
F_2	0.9722	0.8688	0.9812	0.9672	0.9986	5.5377	-0.1643	9.0	16.3	0.7697
F_3	0.9714	0.8612	0.9754	0.9732	0.9992	4.8798	-0.1295	10.2	18.4	0.7529
F_4	0.9795	0.9051	0.9749	0.9679	0.9990	4.4261	-0.1020	11.3	20.3	0.7386
F_5	0.9832	0.9719	0.9933	0.9642	0.9995	4.2046	-0.0831	11.9	21.4	0.7500
F_5+Caecal Content	0.9932	0.8866	0.9685	0.9490	0.9976	4.3853	-0.1042	11.4	20.5	0.8301

CONCLUSION

From the observations, it was found to be that the physical characteristics of the formulations like thickness, hardness, weight variation, friability and *In vitro* dissolution study were found to be within the normal limits of official standards. From the dissolution studies it was found to be that formulation F1 with 5% guar gum failed to retard the drug release, it might be due to the rele/ase of the majority of drug within 5 hr in the region of stomach & small intestine. Formulation F5 with 25% guar gum emerged to be the best one, because it exhibits the best overall general appearance, hardness of 6.6±0.01 Kg/cm^3, friability and a maximum percentage drug release of 97.12% with rat caecal content at the end of 18 hr in in-vitro dissolution studies. The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by performing the drug release studies in medium containing rat caecal material (4%). In the present study, the matrix formulation containing 25% guar gum is most likely to target drug to colon without being released significantly in the stomach and small intestine.

CONFLICT OF INTERESTS

Declared None

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