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Formulation and evaluation of Prednisolone tablet for colon targeted drug delivery system

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ABSTRACT

The purpose of this study was to prepare prednisolone pH-dependent release tablets and evaluate their advantages as a colon targeted drug delivery system. prednisolone insoluble in water and unstable in gastric environment was formulated into pH-dependent tablets coated with combinations of two methacrylic acid copolymers Eudragit L100 and Eudragit S100. The influence of core tablet compositions, polymer combination ratios and coating levels on the in vitro release rate of prednisolone from coated tablets was investigated. The results showed that less than 10% drug was released in 0.1 N HCl within 2 hr, and about 90% of the drug was released in the pH 7.2 phosphate buffer within 6 hr. Colon drug delivery is advantageous in the treatment of colonic disease and oral delivery of drugs unstable or susceptible to enzymatic degradation in upper GI tract. In this study coated tablets that is resistant to gastric and small intestinal pH conditions but can be easily dissolved in colonic pH. The results of the present study have demonstrated that the pH-dependent tablet system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of prednisolone for the treatment of ulcerative colitis.

Key words: Prednisolone; colon targeted drug delivery; enteric coating; in vitro dissolution; pH-Dependent delivery system.

INTRODUCTION

In recent years, colon targeted delivery systems have been the focus point of formulation laboratories because the colon is considered as a suitable site for delivery of both conventional and labile molecules, and it is also a site for some specific diseases, such as, ulcerative colitis, Crohn's disease, bowel cancer, some infections, and constipation, which require local delivery of

the drug. Various approaches have been used for oral delivery of drug to the colon which includes time-dependent delivery, pH-dependent systems and bacteria-dependent delivery [1, 2, 4]. Attempts have also been made to develop delivery system that utilize multiple principles such as pH-dependent system and enzymes produced by bacteria residing at the colon. But so far, the pH-dependent systems have found Practical application.

Oral ingestion has long been the most convenient and commonly employed route of drug delivery [3]. Despite widespread use of pH-dependent systems for colon-targeted delivery of drugs, there has always been controversy about their usefulness for the intended purpose mainly because of (*a*) high GI pH variability among individuals and (*b*) lack of proper coating material that would dissolve at the desired pH of the colon, thus bypassing the effect of the stomach and the small intestine on the dosage form. Although methacrylic acid copolymers such as Eudragit L100, and Eudragit S100 have commonly been used as pH-dependent polymers for coating solid dosage forms (because of their solubility at pH 6.0 or higher, and 7.0 or higher, respectively), none of them is suitable for use alone for coating of dosage forms that would start releasing the drug specifically at pH 6.5, which is generally considered as the suitable pH for colon-targeted delivery.

Prednisolone is an anti inflammatory drug, for oral administration in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption [8,9,10]. The absolute oral bioavailability is 75-98 %. It has a half life of 2-4 hr. [14, 15]

EXPERIMENTAL SECTION

Materials

prednisolone IP, microcrystalline cellulose ,cross carmellose sodium, sodium starch glycollate, aerosil, isopropyl alcohol, talc, magnesium stearate, Eudragit L100, Eudragit S 100, DEP, TIO_2. All the material was provided by Lincoln Pharmaceutical Ltd. Equipments used included: Rotary tablet machine, Roche friabilator, Bulk Density measuring apparatus (Electro lab B.D/T.D. measuring apparatus), Monsanto Hardness Tester.

Table-1 Tablet formulation

** All the ingredients are in mg*

S.NO	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
1	Drug	20	20	20	20	20	20	20	20
2	Microcrystalline cellulose	62	65	65	68	63	63	64	64
3	Sodium Starch Glycollate	8	4	6	2	6	7	6	7
4	Cross Carmellose Sodium	4	5	3	4	5	4	4	3
5	Aerosil	2	2	2	2	2	2	2	2
6	Talc	2	2	2	2	2	2	2	2
7	Magnesium Stearate	2	2	2	2	2	2	2	2

Method

Preparation of core tablets

The core tablet of prednisolone 100 mg were prepared by direct compression method of manufacture using MCC (AVICEL) as the main constituent. Prednisolone, MCC, SSG, Cross carmellose sodium were passed through sieve no #40 and thoroughly mixed in a polythene bag (approx. 10 min). Loss on Drying (LOD) was measured by halogen moisture balance (Mettler Toledo). Above mixer was lubricated granules were lubricated with talc ,aerosil and Magnesium

stearate which were already passed through sieve no # 60 and compressed in to tablets on a 35 station single rotary machine using 8/32 inch Standard concave, Plain/Plain punch. The compression pressure level was kept constant for all the batches by adjusting the pressure control knobs to the same setting.

Table – 2 Composition of coating solution

S. No	Ingridents	SF1 (5%)	SF2 (5%)	SF3 (7%)	SF4 (7%)	SF5 (7%)	SF6 (10%)	SF7 (10%)	SF8 (10%)
1	Eudragit L100	30	15	30	25	20	30	25	20
2	Eudragit S100	20	35	20	25	30	20	25	30
3	DEP	2.5	2.5	3	3	4	4	4	4
4	TIO_2	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
5	Acetone	150	150	150	150	150	150	150	150
6	IPA	350	350	350	350	350	350	350	350

Coating of the tablets

It was done by using the standard coating pan, where fixed numbers of tablets were coated each time by atomizing the polymeric coating solution through the means of spray gun. The scale-up variables including pan loading, pan speed, number of spray guns, spray rate, and inlet airflow etc. were considered. About 500 tablets of prednisolone tablet were taken and allow to coatings in pan coater at 30 rpm and 50^{o}C temperature. Coating was carried out with praying method and dried with same.

Evaluation of tablets

The prepared tablets were evaluated for the following parameters Hardness, measured by tablet hardness tester; schleuniger in kp (Kilo Pascal), Weight variation (Average weight of ten tablets by electronic weighing balance), Thickness which was measured by Vernier Caliper in millimeter (mm), Friability was checked by USP apparatus (Roche friabilator) for 100 rpm.

Table–3 Evaluation of uncoated tablet

Formulation	Hardness (Kg/sq.cm^2±SD)	Friability (%)	Thickness (mm)	Weight variation (Mg)	Average Weight (Mg)
SF1	7.5± 0.15	0.3±0.023	2.72±.01	0.2±0.06	95-105
SF2	*9.4 ±0.15*	0.6±0.012	2.86±.01	0.4±0.10	95-105
SF3	9.2± 0.15	0.4±0.056	2.79±.01	0.3±0.24	95-105
SF4	11.6 ± 0.15	0.7±0.034	2.8±.03	0.2±0.07	95-105
SF5	8.7±0.14	0.3± 0.12	2.76±.01	0.4± 0.17	95-105
SF6	9.3±0.18	0.5±O.21	2.92±.02	0.3±0.20	95-105
SF7	8.3±0.16	0.2±0.19	2.9±.01	0.6±0.16	95-105
SF8	9.7±0.14	0.4±0.13	2.84±.01	0.5±0.19	95-105

In-vitro drug release studies

The *in-vitro* dissolution studies were carried out using USP dissolution apparatus type II in different medium.

Acid stage: Two hours in 900 ML 0.1N HCL at 75 rpm.

Buffer stage: Three hour in 900 ML pH 4.5 phosphate buffers at 75 rpm, 1 hour in 900 ML pH 7.2 simulated colonic fluid at 75 rpm. Dissolution test was carried out for a total period of 6 hours. Analysis for prednisolone was done by UV detected at 247 nm. Table no**.** 4 shows the results of in vitro drug release studies.

Table 4: Cumulative percentage drug release of prednisolone P^H dependent Tablets

Time(hr)	1	2	3	4	5	6
pH	1.2		4.5			7.2
SF1	5.48	9.82	10.9	15.04	19.1	102.4
SF2	3.84	4.73	8.09	12.1	16.2	97.13
SF3	2.76	9.34	11.56	15.79	18.96	101.4
SF4	1.6	2.7	5.2	6.36	11.56	91.86
SF5	2.1	3.2	5.4	7.5	12.1	94.8
SF6	2.1	2.7	5.7	9.2	10.4	95.4
SF7	1.08	2.2	3.3	4.5	6.7	98.2
SF8	1.08	2.1	3.4	4.6	5.6	99.11

RESULTS AND DISCUSSION

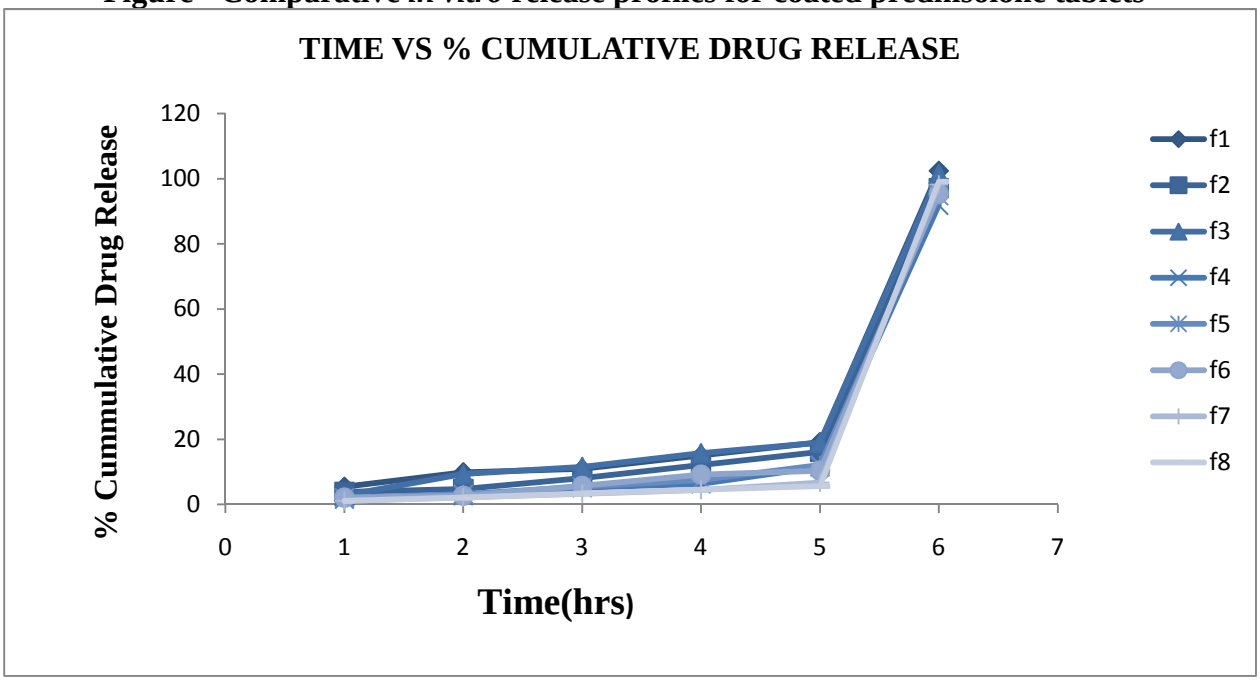
The expected *in vitro* release pattern selected for the colon targeting was not more than 10% of drug release up to the end of 5hrs.Eudragit L-100 and Eudragit S-100 were used in different concentration; 5%, 7% and 10% coating level. The batch SF1 and SF2 with 5% coating showed a release of more than 10% in less than five hours i.e. 19.1 % & 16.2 % respectively, which is not acceptable. Hence these formulations were excluded from further studies. However the SF7 and SF8 formulation showed a release of less than 10% in the first five hour of dissolution study.

The drug release was directly related to the concentration of polymer in solution and the % coating level. Percent of drug release vs. time plot shows that the dissolution rate was inversely proportional to the coating level applied. A significant difference was observed in the percentage of drug released for different coating level. All the coated tablets with variable coating level showed a nearly complete drug release in the 6 hr.

In the formulation SF3 ,SF4 and SF5 where 7% polymer coating was applied in the ratio 3:2,1:1,2:3. The % drug release after 5hr was 18.96 %, 11.56 %, 12.1 % respectively. The solubility of the films from various combinations of Eudragit L100–Eudragit S100, and the release rate of drug from the coated tablets in various pH media could be controlled by varying the ratios of the two polymers.

For formulation SF6, SF7 and SF8 where, 10% coating in the ratio 3:2, 1:1, 2:3; was applied. The drug release at 5^{th} hr and 6^{th} hour 10.4% 95.4% respectively in the formulation SF5 observed. In the SF7 & SF8 polymer was able to control the drug release after 5^{th} hr the drug release was well within the desired limits of less than 10% i.e. 6.7% and 5.6%. The drug released from these formulations at the end of dissolution run was 98.2% & 99.1%. It was observed that the drug release was controlled by increase the coating level. Based on the above studies, the optimum formulation, formulation SF8 coated with Eudragit L100–Eudragi S100 at a combination ratio of 2:3 and at the coating level of 10%, was chosen for studying the effect of pH of the buffer media on the release profiles, as shown in Figure. As anticipated, the release profiles were obviously faster in pH 7.2 than in pH 4.5 buffer media.

Figure - Comparative *in vitro* release profiles for coated prednisolone tablets



CONCLUSION

The present study was carried out to investigate the ability of methacrylate co-polymers for targeting the drug release in colon. From results obtained in the present study, it was concluded that the resulted optimum formulation was the one coated with 10% coating level of Eudragit L100 and Eudragit S100. The in vitro studies showed that this formulation successfully deliver the maximum amount of drug in intact form to the colon. The combined action of the super disintegrant; cross carmellose sodium and sodium starch glycollate have been contributed to such a fast disintegration property. It prevents the drug release in the stomach and intestine so we can solve the problem of side effect of anti inflammatory drug in this area & also prevents ulcerative colitis.

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