Formulation and Evaluation of Mucoadhesive Colon Targeted Drug Delivery System for Prednisolone

Santhi priya Jupalli*, Sirisha Davuluri[1], Charishma Amathi[2], Jyothi Behra[3] ,Sahani Satheendhar[4], Sk Aakhil[5]
Department of pharmaceutics
Vishwa Bharathi College of Pharmaceutical Sceinces,Perecherla,Guntur,Andhra Pradesh,India.
Corresponding Author:Santhi Priya Jupalli

ABSTRACT:

The purpose of this study was to prepare prednisolone colon targeted drug delivery tablets and evaluate their advantages as a colon targeted drug delivery system. prednisolone insoluble in water and unstable in gastric environment was formulated intocolon targetedrug delivery 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.

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 ofthe drug. Various approaches have been used for oral delivery of drug to the colon which includes time-dependent delivery(.O.Munjeri *et al*), 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(K. Purushothama Rao *et al*), 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(Salunkhe KS, Kulakarni MV *et al*), 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 (V.Ravi *etal)(*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.

MATERIALS:

prednisoloneip,pectin,poly vinyl pyrolidine,carbopol,methnol,sodium dihydrogen phosphate,lactose,magnesium stearate all materials was provided by ,drugs india,hyderabad and s.pchemicals mumbai, tablet press(9station,single rotatory)chamunda pharma,fribilator singhalascientific,ambala, dissolution apparatus(usp type2)eloctrolab,mumbai, monsanto hardness tester,singhalascientific,ambala,u.v.visible spectrophotometer,shimadju,mumbai,digital vernier caliperse,digimate,hyd,ph meter,systronic,hyd,stability study chamber,eloctrolab,mumbai.

TABLE:1TABLET FORMULATON

S.No.	Ingredient	Category	Formulations Code (Weights in 'mg')							
			F1	F2	F3	F4	F5	F6	F7	F8
1	**Prednisolone**	API	30	30	30	30	30	30	30	30
2	**PVP**	Rate Controlling Polymer	20	40	60	80	100	120	140	-
3	**Pectin**	Rate Controlling Polymer	120	100	80	60	40	20	-	140
4	**Lactose**	Filler	76	76	76	76	76	76	76	76
5	**Talk Powder**	Glidant	1	1	1	1	1	1	1	1
6	**Starch Mucilage**	Binder	2	2	2	2	2	2	2	2
7	**Mg. Sterate**	Lubricant	1	1	1	1	1	1	1	1
8	**Carbopol**	Mucoadhesion	50	50	50	50	50	50	50	50
		Total =	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

METHOD:

1.Preparation of Mucoadhesive Bilayer Tablets

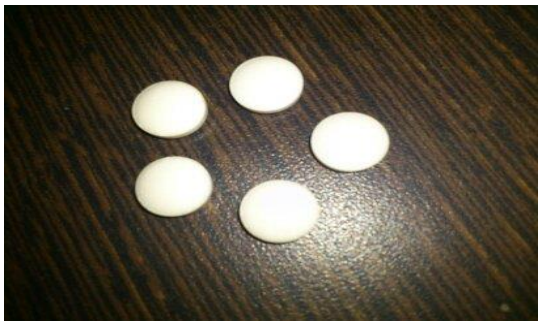
Accurately weighed 250mg dried granules were compressed using an 8 mm diameter die in a 9 station rotary punching machine (Chamunda Pharma, Ahmadabad, India). The upper punch was raised and exactly weighed 50mg of carbapol was placed and spreaded evenly above the compressed tablet. The carbopol is used as a mucoadhesive layer. Compression machine was rotated again to make a bilayer tablet. Total weight of each tablet is 300 mg which includes Prednisolone layer and mucoadhesive layer.

Photograph of Uncoated Tablets

2.Coating of Tablets:

The prepared bilayer tablet which gave longer release of Prednisolone is coated with Eudragit polymer. This coating was used to avoid the release of drug in the stomach. Five ml of Eudragit L-100 polymer was dissolved in 50 ml of Ethanol. This Eudragit solution was used to coat the bilayer tablet. Coating was performed by dip coating method. Each tablet was dipped in Eudragit polymer solution carefully with the help of forcipes. The tablet was removed from beaker and it was dried by using hair dryer. This process was repeated twice to ensure the proper uniformity of coated layer. The tablet weight was taken before and after the coating.

Photograph of Coated Tablets



EVALUATION OF TABLET:

The prepared tablets were evaluated for the following parameters hardness,measured by tablets hardness tester,schleunigerin kp ,weight variation,thickness (O.Munjeri *et al*) which was measuredby vernier calipersein millimeter(Kiran S *etal*),friability was checked by USP apparatus for 100 rpm

Evaluation of Tablets:

Table no:2

Formulation Code	Thickness (mm)	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (mg)
F1	3.12 ±0.03	299±1.55	4.2±0.15	0.43±0.025	29.57±0.41
F2	3.19±0.02	297±0.94	4.1±0.25	0.54±0.03	29.85±0.19
F3	3.11±0.03	300±0.81	4.3±0.31	0.60±0.042	29.32±0.48
F4	3.15±0.05	298±0.72	3.9±0.21	0.48±0.036	29.26±0.41
F5	3.18±0.03	300±0.19	4.3±0.2	0.48±0.01	29.45±0.15
F6	3.19±0.04	297±0.84	4.2±0.26	0.51±0.02	30.19±0.01
F7	3.13±0.07	299±0.38	4.2±0.31	0.61±0.038	29.21±0.03
F8	3.16±0.02	298±0.52	4.5±0.25	0.54±0.025	29.15±0.65

***i.In-vitro* drug release study:** The dissolution test was performed for all the prepared formulations(Nirav V *et al*). The slightly modified USP type II rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 900 ml of phosphate buffer having pH 7.4. The release study was performed at 37 ± 0.5˚C, with a rotation speed of 50 rpm. Then samples were collected at regular intervals of time and absorbance was measured at 250 nm. The backing layer of the muco adhesive Tablet (Irit Gliko-Kabir et al) was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were diluted with phosphate buffer pH 7.4 and were analyzed spectrophotometrically at 250 nm. The release rates of Prednisolone from all the prepared formulations were calculated.

In-vitro Drug Release Study From Tablets

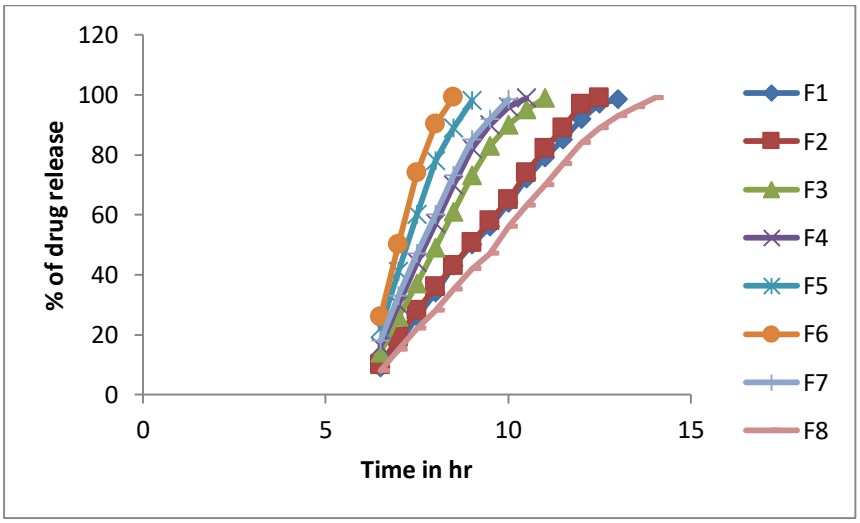
Dissolution Medium	Time (hr)	Formulation Code (%CDR)							
		F1	F2	F3	F4	F5	F6	F7	F8
Gastric pH	**1-2**	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
Intestinal Ph	**3-6**	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
Colon pH	**6.5**	09.00	10.00	14.00	16.00	22.00	26.00	18.00	08.00
	7.0	17.00	19.00	26.00	30.00	41.00	50.00	33.00	15.00
	7.5	26.00	28.00	37.00	44.00	60.00	74.00	47.00	22.00
	8.0	34.00	36.00	49.00	57.00	78.00	90.20	60.00	28.00
	8.5	43.00	43.00	61.00	70.00	89.00	99.10	73.00	35.00
	9.0	50.10	50.70	73.00	82.00	98.00	99.10	85.00	42.00
	9.5	56.00	58.00	83.00	90.00	98.00	99.10	92.00	47.00
	10.0	64.00	65.00	90.00	96.00	98.00	99.10	98.60	56.00
	10.5	72.00	74.00	95.00	99.00	98.00	99.10	98.60	63.00
	11.0	79.00	82.00	99.00	99.00	98.00	99.10	98.60	70.00
	11.5	85.00	89.00	99.00	99.00	98.00	99.10	98.60	77.00
	12.0	92.00	96.80	99.00	99.00	98.00	99.10	98.60	84.00
	12.5	97.00	99.00	99.00	99.00	98.00	99.10	98.60	89.00
	13.0	98.60	99.00	99.00	99.00	98.00	99.10	98.60	93.00
	13.5	98.60	99.00	99.00	99.00	98.00	99.10	98.60	96.00
	14.0	98.60	99.00	99.00	99.00	98.00	99.10	98.60	99.00

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.

For formulation SF6, SF7 and SF8 where, 10% coating in the ratio 3:2, 1:1, 2:3; was applied. The drug release at 5th hr and 6th hour 10.4% 95.4% respectively in the formulation SF5 observed. In the SF7 & SF8 polymer was able to control the drug release after 5th 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.

In-vitro drug release data for all the formulation F1 – F8



CONCLUSION:

The aim of present work is to deliver the Prednisolon at colon for longer periods as possible. The objective of this study is to develop a colon targeted mucoadhesive bi layer controlled release tablet for Prednisolon. The various Prednisolone sustained release bilayer tablets (Forrmulation F1 to F8) were prepared by wet granulation method using different rate controlling polymers such as Pectin, PVP and Carbopol as a mucoadhesive layer. Drug-polymer compatibility studies by FTIR indicates there is no possible interactions between the drug and polymer and prepared tablets were characterized for their physico-chemical characteristics pH resistant, mucoadhesive strength, *in-vitro* drug release shows reproducible results. Among all, formulations F8 found as best formulation, as it passes all the evaluation tests (weight variation, hardness, thickness, friability) and various physiochemical parameters.

ACKNOWLEDGEMENT:

The Authors are greatful to management of Vishwa Bhartahi college of pharmaceutical sciences,perecherla,Guntur, Andhra Pradesh,India.for support and providing the facilities of present study.

REFERENCES:

1.O.Munjeri, J.H.Collett and J.T.Fell, "Hydrogel beads based on amidated pectins for colon specific drug delivery: the role of chitosan in modifying drug release", *Journal of Controlled Release*, 46 (1997) 273-278.

2.Sayeh F. Ahrabia, Jyrki Heina ma kib, Sverre A. Sandea and Christina Graffnerc, "Influence of neutron activation factors on matrix tablets for site specific delivery to the colon", *European Journal of Pharmaceutical Sciences*, 10 (2000) 225–235.

3.K. Purushothama Rao and CC Patil, "Development of colon specific drug delivery system of Naproxen", *The Indian pharmacist*, March 2005, 70-72.

4.Salunkhe KS, Kulakarni MV, *Journal Of Pharmaceutical Research*., oct 2007, vol 6, No 4, Pg No:248-250.

5.V.Ravi, T.M. Pramod Kumar and siddaramaiah**,** *Indian Journal Of Pharmaceutical Sciences.*, 2008, 70(1), Pg No:111-113.

6.Nirav V. Patel et al. Design, development and in vitro evaluation of Mesalamine Tablets containing Pectin and Chitosan for colon-specific drug delivery Int. *J. ResPharm. Sci.* Vol-1, Issue-2, 94-102, 2010

7.Nath, B. S., Venkatesh and Hiremath, D, "Formulation and evaluation of Sustained Release Dosage form of Theophylline Using combined Hydrophobic and Hydrophilic Matrix", *Ind. J. Pharma. Sci.* , 62 (1), 33, 2000.

8.V.S.Mastiholimath, P.M.Dandagi, S.Samata Jain, A.P.Gadad and A.R. Kulakarni, "Time and P^H dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma", *International Journal of Pharmaceutics*, 328 (2007) 49-56.

9.F. J Ahmed and R. K Khar, "Development of colon specific drug delivery system of 5- Amino salicylicacid", *Indian Journal of Pharmaceutical Sciences*, 2000, 527.

10.Kiran S. 'Effect of Oppositely Charged Polymer and Dissolution Medium on Swelling,Erosion, and Drug Release From Chitosan Matrices" *AAPS pharm sci tech* 2007; 8 (2) Article 44.

11.S. Bozdağ†, **"**in *vitro* evaluation and intra-articular administration ofBiodegradable microspheres containing naproxen sodium" journal *of microencapsulation* 2001, vol. 18, no. 4, 443-456.

12.Y.S.R Krishnaiah, K. Latha, L. Nageswararao and V. Satyanarayana, "Development of colon targeted oral guar gum matrix tablets of Albendazole for treatment of helmenthiasis", *Indian j. Pharm. Sci.* , 2003, 65(4), 378-385.

13.Aswar P.B. "Development and in-vitro evaluation of colon-specific formulations for orally administered diclofenac sodium" Arch Pharm Sci & Res Vol 1 No 1 48-53 July 2009.

14.Irit Gliko-Kabir, Boris Yagen, Adel Penhasi and Abraham Rubinstein, "Low swelling, Cross linked Guar and Its Potential Use as Colon-Specific Drug Carrier", *Pharmaceutical research*, Vol. 15, No. 7, 1998.

15.Vikas Kumar1 A.K.Tiwary "Investigations on chitosan-carboxymethyl guar gum complexes interpolymer complexes for colon delivery of fluticasone" *International Journal of Drug Delivery vol 2* (2010) 242-250.

16.Klaus Florey, *Analytical Profiles of Drug Substances*, volume 4, page no. 471-475, New York: Elsevier Publishers, 2005.

17.Sonali Sheorey and Meera Honrao, *Pharmaceutical analysis –I (Practical)*, Pg No. 13-14, Career Publications.

18.Girish K Jain and Dhiren P shah " Gums and mucillages : versatile excipients for pharmaceutical formulations" *Gums and mucillages\ Asian journal Pharmaceutical Sciences* 2009,4(5): 309-323

19.Vikas Kumar1 A.K.Tiwary "Investigations on chitosan-carboxymethyl guar gum complexes interpolymer complexes for colon delivery of fluticasone" *International Journal of Drug Delivery* vol 2 (2010) 242-250.

20.N.K.Jain, *Advances In Controlled and Novel Drug Delivery*., First Edition, Pg. No: 89-112, New Delhi: CBS publishers& distributors.

21.Lachman, L, Lieberman, H. A., Kanig, J. L., The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Bombay, 297, 1987.

22.Klaus Florey, *Analytical Profiles of Drug Substances*, volume 4, page no. 469-470, Elsevier Publishers.

23.Indian Pharmacopoeia 1996, Ministry of Health & Family Welfare, The Controller of Publications, New Delhi, 2, 750, 1996.

24.Indian Pharmacopoeia 1996, Ministry of Health & Family Welfare, The Controller of Publications, New Delhi, 2, 750, 1996.

25.Glibert S Banker (ed.), Modern Pharmaceutics (4th edn), Marcel Dekker, New York, 2002, 527-584.