CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

DESIGN AND *IN-VITRO* EVALUATION OF PREDNISOLONE MUCOADHESIVE TABLETS FOR COLON TARGETED DRUG DELIVERY SYSTEM

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Abstract:

The study was designed to develop mucoadhesive tablets of using PVP and Pectin inter polymer complexes and to systematically evaluate their in-vitro and ex-vivo performances. Prednisolone is a synthetic glucocorticoid, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune conditions. Colon targeted drug delivery is an active area of research for local diseases affecting the colon, as it improves the efficacy of therapeutics and enables localized treatment, which reduces systemic toxicity. Targeted delivery of therapeutics to the colon is particularly advantageous for the treatment of inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease. Mucoadhesive tables were prepared by direct compression method. The physicochemical interaction between PVP and Pectin was investigated by FTIR studies. Tablets were evaluated their compatibility studies by using FT-IR, micrometrics properties, post formulation characters such as hardness, thickness, friability, content uniformity, Ex vivo mucoadhesive strength and in-vitro dissolution studies.

Key Words: *Prednisolone, Mucoadhesive, PVP, Pectin, Ex-vivo, In-vitro.*

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Please cite this article in press as ***V.Jayasankar Reddyand G.Sindhu, Design and In-Vitro Evaluation of Prednisolone Mucoadhesive Tablets for Colon Targeted Drug Delivery System****, Indo Am. J. P. Sci, 2016; 3(6).*

INTRODUCTION:

Colon is being extensively investigated as a drug delivery site. Colon targeted drug delivery system (CTDDS) has been developed by means of one or more controlled released mechanisms. It is convenient for treating localized colonic diseases, i.e. Ulcerative colitis, Crohn's diseases and constipation etc.

Its potential applications include Chronotherapy, Prophylaxis of colon cancer and treatment of Nicotine addiction. The treatment of Inflammatory Bowel Disease (IBD) with anti-inflammatory drugs is particularly improved by local delivery to bowel by using CTDDS. For successful colon specific drug delivery, many physiological barriers must be overcome; the major one is being absorption or degradation of the active drug in the upper part of the GIT. The minor is disease state, which can potentially alter the delivery and absorption characteristics of drugs from the colon.

The CTDDS should protect the drug from the absorption and degradation in the stomach and small intestine, the drug should be absorbed only at the colonic site. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery[4]. The colon is a suitable absorption site for peptides and protein drugs .

isms.

1. Diffusion
2. Polymer erosion
3. Microbial degradation
4. Enzymatic degradation (mammalian and/or bacterial)

In addition, drug solubility and formulation of polymer mixes play important roles in determining the extent of drug delivery and release in the colon.

Two broad categories of biopolymers have been employed for formulating colonic systems: Biodegradable and Non-biodegradable polymers.

Considerations for designing of Colon Targeting formulations:

To achieve a desired therapeutic action of dosage form, it is necessary to design a suitable formulation with suitable qualities. In general, delayed release dosage forms are designed to provide a burst release or a sustained/ prolonged release once they reach colon. Various factors includes are

- Pathology and pattern of diseases, especially the affected parts of lower GIT or, Physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.
- Physicochemical properties and biopharmaceutical properties of the drug such as solubility , stability and permeability at the intended site of delivery, and
- The desired release profile of the active ingredient.

Prednisolone is a glucocorticoid that prevents or suppresses inflammation and immune responses when administered at pharmacological doses. At a molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately protein synthesis to achieve the steroid's intended action.

Such actions may include: inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humeral immune responses. In many tissues, the overall effect is catabolic, i.e. some of the net effects include reduction in edema or scar tissue, as well as a general suppression in immune response.

MATERIALS AND METHOD:

Prednisolone (Bufna Pharmaceutical Ltd. Chennai), Pectin, Chitosan (SD fine chemicals, Boisar), Potassium hydrogen phosphate (SD fine chemicals, Boisar), Sodium dihydrogen phosphate (SD fine chemicals, Boisar), Magnesium stearate (SD fine chemicals, Boisar), Lactose (SD fine chemicals, Boisar).

Drug – polymer compatibility studies by FTIR:

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy) [60]. FTIR absorption spectra of drug and all the polymers pectin, eudragit, PVP, Carbopol were taken individually and in the combinations. Two mg of sample mixed with 200mg of IR grade KBR in a silicon mortar and this mixture pressed into a disk. Disk was carefully kept in a position of FTIR. Infrared (IR) spectra were obtained in the scanning range of 400 to 4000 cm^{-1}.

Preparation of mucoadhesive bilayer tablets:

Accurately weighed 250mg dried granules were compressed using an 8 mm diameter die in a 8 station rotary punching machine (KAMBET). 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.

Table1: Formulations of Fabricated Prednisolone Mucoadhesive Tablets

S.No.	Ingredient	Formulations Code (Weights in 'mg')							
		F1	F2	F3	F4	F5	F6	F7	F8
1	**Prednisolone**	20	20	20	20	20	20	20	20
2	**PVP**	15	25	35	45	55	65	75	-
3	**Pectin**	85	75	65	55	45	35	25	100
4	**Lactose**	80	80	80	80	80	80	80	80
5	**Talk Powder**	2	2	2	2	2	2	2	2
6	**Starch Mucilage**	2	2	2	2	2	2	2	2
7	**Mg. Stearate**	1	1	1	1	1	1	1	1
8	**Carbopol**	50	50	50	50	50	50	50	50

Pre formulation studies:

Determination of bulk density and tap density:

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho b = M/Vb$$

The measuring cylinder containing a known mass of powder or granules was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula

$$\rho t = M/Vt$$

Compressibility index:

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as

$$I = (\rho t - \rho o / \rho t) \times 100$$

Where,

ρt = Tapped density ρo = Initial bulk density

The value below 15 % indicates a powder which usually give rise to good flow characteristics whereas above 25 % indicate poor flow ability.

Angle of repose:

The frictional forces in a loose powder can be measured by the angle of repose (θ). It was determined using funnel method. The powder or granules were poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated as $\theta = Tan^{-1} (h/r)$.

Evaluation of prepared bilayer tablets:

The prepared bilayer tablets were evaluated for following physicochemical properties.

Thickness:

The thickness of the each tablet was measured by using vernier caliper and the average thickness was calculated.

Weight variation:

Formulated tablets were tested for weight uniformity. Twenty tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\%\ \text{Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X 100$$

Hardness:

The hardness of Tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability:

The Roche friability test apparatus was used to determine the friability of the Tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\%\ \text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X 100$$

Drug Content:

Drug content uniformity was determined as triplicate by dissolving the tablets in DMSO (Dimethyl sulfoxide) and filtering with Whatman filter paper (0.45 µm, Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 240 nm using a UV spectrophotometer.

***Ex vivo* mucoadhesive strength:**

A modified physical balance method was used for determining the *ex vivo* mucoadhesive strength. Fresh sheep colon mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and

then with phosphate buffer. The two sides of the balance were made equal before the study, by keeping a buffer solution at 37^{o}C. The Sheep colon mucosa was cut into pieces and washed with phosphate buffer. A piece of colon mucosa was tied to the glass vial, which was filled with phosphate buffer.

The glass vial was tightly fitted into a glass beaker so that it just touched the mucosal surface. The mucoadhesive Tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive and adds weight on the right-hand pan. A weight of 5 g was removed from the right hand pan. This lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min). To the right-hand pan until the Tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of then Mucoadhesive Tablet in grams.

Force of adhesion (N) = (Mucoadhesive strength (g) ×9.8)/1000

Bond strength (N m–2) = Force of adhesion / surface area.

***In-vitro* drug release study:**

The dissolution test was performed for all the prepared formulations. 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 mucoadhesive Tablet 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.

RESULTS & DISCUSSION:

Drug –polymer compatibility studies by FTIR

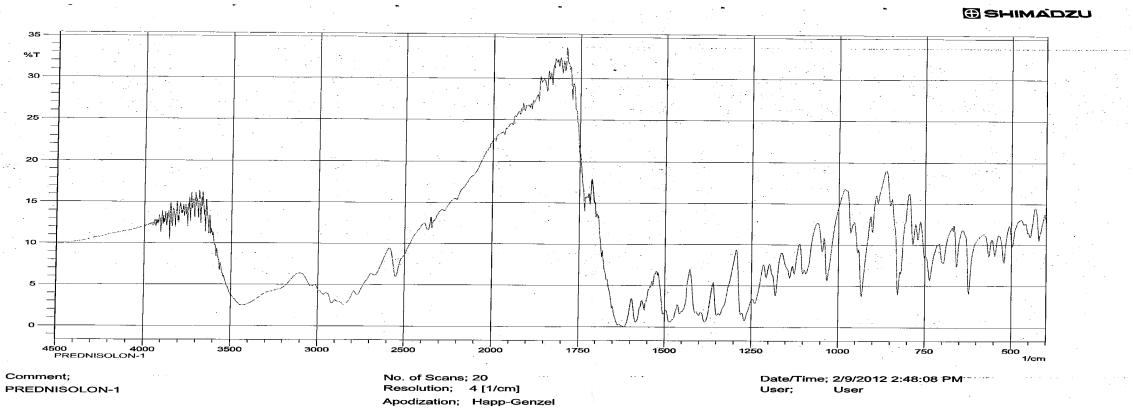

Fig1: FTIR spectra of Prednisolone

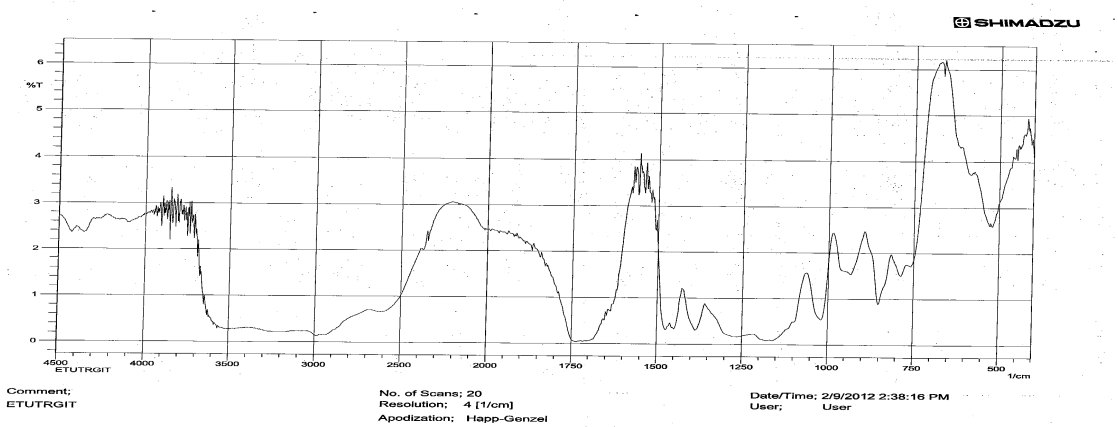

Fig 2: FTIR spectra of Eudragit

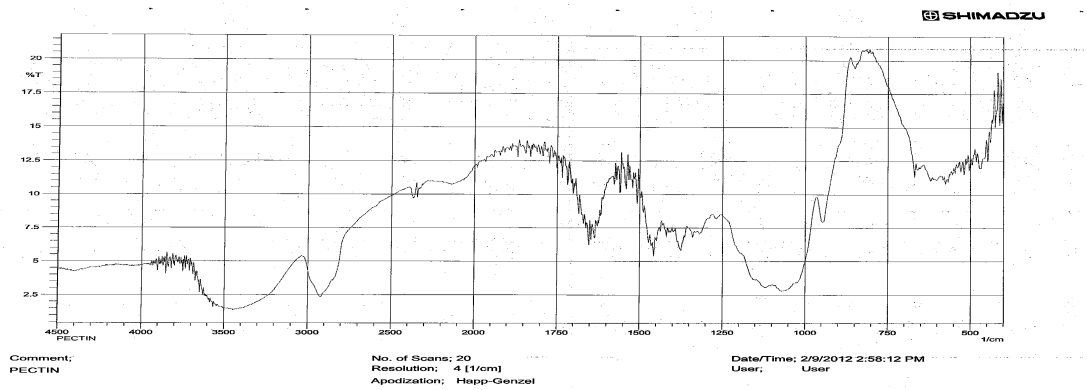

Fig 3: FTIR spectra of Pectin

Evaluation of granules:

Table 2: Results for Derived and Flow properties

Formulation Code	Derived properties (mean±SD)		Flow properties (mean±SD)		
	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.327±0.01	0.373±0.015	24.45±0.30	11.44±1.97	1.116±0.02
F2	0.337±0.015	0.413±0.02	25.21±0.39	10.22±1.96	1.115±0.03
F3	0.383±0.015	0.416±0.01	21.97±0.68	10.84±3.97	1.135±0.05
F4	0.336±0.015	0.426±0.015	20.21±0.96	9.48±1.81	1.125±0.02
F5	0.323±0.02	0.496±0.03	22.94±0.73	10.65±2.25	1.117±0.03
F6	0.332±0.01	0.343±0.006	21.25±0.36	10.22±3.16	1.113±0.04
F7	0.323±0.025	0.416±0.025	23.21±0.29	12.54±1.19	1.112±0.02
F8	0.325±0.01	0.410±0.017	22.87±0.40	13.69±3.61	1.114±0.05

***Ex vivo* mucoadhesive strength:**

Table 3: Measurement of Mucoadhesive

Formulation code	Mucoadhesive Strength in g
F1	31.1
F2	23.3
F3	20.2
F4	17.4
F5	14.4
F6	12.2
F7	14.5
F8	30.4

Evaluation of tablets:

Table 4: Physico chemical evaluation of bilayer Mucoadhesive Tablets of Prednisolone

Formulation Code	Thickness (mm)	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (mg)
F1	2.92 ±0.01	279±1.45	5.2±0.14	0.43±0.01	27.57±0.21
F2	2.93±0.03	267±0.84	4.2±0.22	0.52±0.02	27.85±0.29
F3	2.92±0.01	299±0.82	4.6±0.33	0.50±0.04	27.32±0.38
F4	2.92±0.02	295±0.62	4.9±0.11	0.46±0.03	27.26±0.21
F5	2.92±0.01	293±0.21	4.5±0.12	0.43±0.01	27.45±0.25
F6	2.93±0.02	287±0.92	4.3±0.16	0.49±0.02	28.19±0.01
F7	2.92±0.01	293±0.28	4.4±0.11	0.41±0.03	27.21±0.03
F8	2.92±0.01	292±0.42	4.3±0.23	0.44±0.02	28.15±0.45

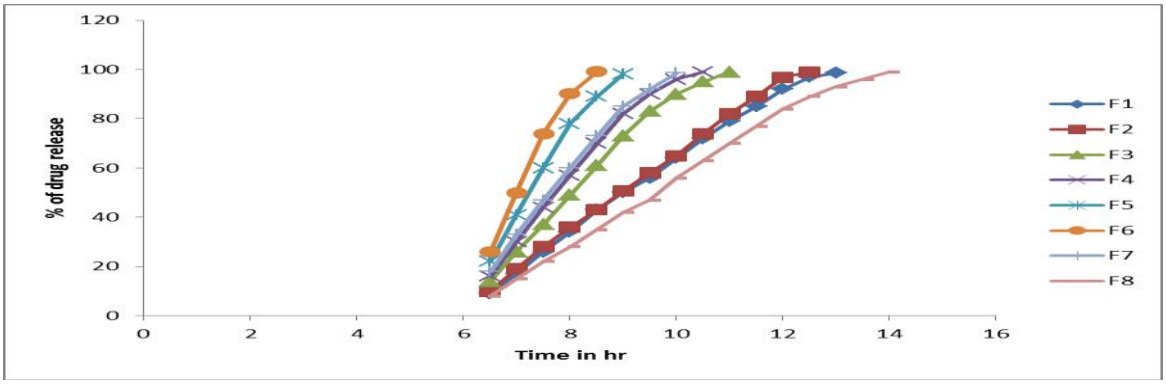

Fig 4: In-vitro drug release data for all the formulation F1 – F8

CONCLUSION:

The prednisolone sustained release bilayer tablets were prepared by wet granulation method using different mucoadhesive polymers such as Pectin, PVP along with Carbopol 934P 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 consists of prednisolone (15 mg), pectin (100mg), lactose (80mg), Carbopol (50mg) was selected as best formulation. Various physiochemical parameters tested for this formulation showed good results. Formulation F8 was stable and non-significant from P value obtained by one way ANOVA.

Hence prednisolone sustained release mucoadhesive tablets could be maintain and treat such local infections to develop a mucoadhesive bilayer tablet which adhere at the colon to release the Prednisolone for a longer time, minimize the dosing intervals.

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