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FORMULATION AND EVALUATION OF PREDNISOLONE MATRIX TABLETS FOR COLON TARGETED DRUG DELIVERY SYSTEM

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Abstract:

The aim of this work is to formulate Prednisolone matrix tablets for colon targeting drug delivery system by using pectin and chitosan polymers. Prednisolone is synthetic Glucocorticoids, 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. Prednisolone matrix tablets were prepared by wet granulation technique by using different polymers such as chitosan and pectin are sustained release polymers. Starch mucilage is a granulating agent .The matrix tablets were evaluated their compatibility studies by using FT-IR, micromeritics properties, post formulation characters, stability and in vitro dissolution studies.

Key words: Matrix tablets, Prednisolone, Pectin, Chitosan, IBD.

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INTRODUCTION:

Colon specific drug delivery has gained increasing importance for the delivery of drugs in the treatment associated with the colon and also acts as the potential site for the systemic delivery of the therapeutic peptides and proteins [1]. Colonic delivery refers to targeted delivery of drugs into the lower GI tract which occurs primarily in the large intestine [2, 3]. Colon specific delivery systems prevent the release of the drug in the upper part of the GIT and require a triggering mechanism to release the drug on reaching the colon [1]. Due to the lack of digestive enzymes and the long transit time colon is considered as suitable site for the absorption of various drugs [5]. Colon specific drug delivery mainly shows topical action in case of inflammatory bowel disease by using drugs like hydrocortisone, budenoside, mesalazine. They exert local action in treatment of chronic pancreatitis. They also show systemic action for oral delivery of peptides and vaccines using the drugs like 5 fluorouracil, NSAIDS [4].

The primary approaches to obtain colon specific delivery are based mainly on prodrug and polymer [5].

1. Polymer based approaches

- Biodegradable matrix and hydrogel systems
- pH sensitive polymer system
- Biodegradable polymer system
- Bio adhesive polymer systems
- Redox sensitive polymeric system

2. Prodrug based approaches

- Polymer based azo bond prodrugs
- Glycoside conjugated polymer drug
- Dextran conjugated prodrugs
- Polypeptides conjugated prodrugs

Prednisolone is a glucocorticoid. Soluble in ethanol (95 %) and in methanol , sparingly soluble in acetone , slightly soluble in $CHCl_3$,very slightly soluble in water. It is a synthetic adrenocortical steroid drug with predominantly gluco-corticoid properties. Some of these properties reproduce the physiological actions of endogenous gluco corticoids [6-9].

Prednisolone mainly promotes gluconeogenesis, increased deposition of glycogen in liver, inhibition of utilization of glucose, anti insulin activity, increased catabolism of protein [10-12]. Prednisolone is mainly used for topical treatment of Inflammatory Bowel Disease like Ulcerative colitis, Crohn's disease. It can also be used as an immunosuppressive drug for organ transplants and in cases of adrenal insufficiency, Asthma, Uveitis, Rheumatoid arthritis, Ulcerative colitis, temporal arthritis [13].

Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1,4-a-glucosides, with a molecular weight of 30 000–100 000. Pectin has been used as an adsorbent and bulk-forming agent, and is present in multi-ingredient preparations for the management of diarrhea, constipation, and obesity; it has also been used as an emulsion stabilizer. Experimentally, pectin has been used in gel formulations for the oral sustained delivery of ambroxol. Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract [14, 15].

It has also been used in a colon-biodegradable pectin matrix with a pH-sensitive polymeric coating, which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract

The objective of the study is to design and evaluate matrix tablets of Prednisolone using polymers such as Chitosan and Pectin. And to carry out the Pre and post compressional parameters for the powder blend of matrix tablets as well as final finished dosage form.

MATERIALS AND METHODS:

Table 1 shows the chemical/reagent and drugs and their source. And table 2 shows the source of instruments used for this study.

Table 1: Source of chemicals and ingredients

S. No.	Ingredients/chemicals/solvents	Manufacturer /supplier
1	Pectin, Chitosan	SD fine chemicals, Boisar
2	Methanol	SD fine chemicals, Boisar
3	Potassium dihydrogen phosphate	SD fine chemicals, Boisar
4	Lactose	. SD fine chemicals, Boisar
5	Magnesium stearate	SD fine chemicals, Boisar
6	Starch	SD fine chemicals, Boisar
7	Talc	SD fine chemicals, Boisar

All the chemical were of AR grade

Table 2: Manufacturers of Instruments/Apparatus

S. No.	Instrument/Apparatus	Manufacturer/ Supplier
1	Tablet Press (8Station, Single Rotary)	Kambert Pharma, Ahmadabad.
2	Friabilator	Singhala Scientific, Ambala.
3	Dissolution Apparatus (USP Type II)	Electrolab, Mumbai.
4	Monsanto Hardness Tester	Singhala Scientific, Ambala.
5	U.V.Visible Spectrophotometer	Shimadju, Mumbai.
6	Digital VernierCaliperse	Digimate, Hyd.
7	pH meter	Systronic, Hyd.
8	Stability study chamber	Electrolab, Mumbai.

Formulation of Matrix Tablets:

Wet Granulation Technique:

Granules containing prednisolone were prepared by using wet granulation technique. The polymer, lactose, and the active ingredient were mixed homogeneously. Starch mucilage (5%W/V) was used as a granulating agent. The granules were prepared and dried in a conventional hot air oven. The dried granules were sieved through 40/60 meshes. Magnesium stearate and talc was added as a lubricant and the granules were compressed into tablets using Kambert rotary tablet punching machine.

Table 3 Formulation of Fabricated Matrix Tablets

S.No.	Ingredients	Category	Batch Code					
			F-I	F-II	F-III	F-IV	F-V	F-VI
1	Prednisolone	Active ingredient	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
2	Pectin	Polymer	78 mg	99 mg	198 mg	--	--	--
3	Chitosan	Polymer	--	--	--	78 mg	99 mg	198 mg
4	Starch mucilage	Granulating agent	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
5	Lactose	Diluent	144.5 mg	123.5 mg	104.5 mg	144.5 mg	123.5 mg	104.5 mg
6	Magnesium stearate	Lubricant	1%	1%	1%	1%	1%	1%
7	Purified talc	Lubricant	2%	2%	2%	2%	2%	2%

Pre Formulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage form.

Determination of Bulk Density and Tapped 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 flowability.

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 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.

***In-Vitro* Drug Release Studies:**

In vitro drug release studies of prednisolone were studied using dissolution apparatus USP type II paddle method with a stirring speed of 50rpm at 37°C±0.5°C in 900ml of pH-6.8 phosphate buffer for 12hrs. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution media. The collected samples were diluted and the absorbance was measured spectrophotometrically at 250nm. The percentage of Prednisolone released at various time intervals were calculated from the standard graph.

In vitro dissolution studies were carried out in pH-6.8 phosphate buffer for 12hrs. In order to find out the order of release and mechanism, which was predominantly influences the drug release from the tablet, *in vitro* dissolution data was subjected to 3 different modes of graphical treatment. They are

1. Percentage cumulative drug release Vs time.
2. Percentage cumulative drug release Vs square root of time.
3. Log percentage drug release Vs time.

The slope value and the degree of linearity of the above graphical treatments were considered as important statistical parameters to interpret the *in vitro* profile of all formulations.

pH Resistant: The matrix tablet was kept for a dissolution study at the pH 1.2. No drug should be released at this pH. Release of 0% of drug at this pH indicates the proper polymer and thus the drug will not be released in the stomach. In the same passion, the dissolution was performed at the pH 6.8, to check the release of drug in the small intestine. Release of 90% of drug ensures the proper rate release of polymer.

RESULTS AND DISCUSSION

Drug –Polymer Compatibility Studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). FTIR absorption spectra of drug and all the polymers pectin, chitosan were taken individually and in the combinations. Two mg of sample mixed with 200mg of IR grade KBR in a silicon mortor 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 4000 to 400cm^{-1}

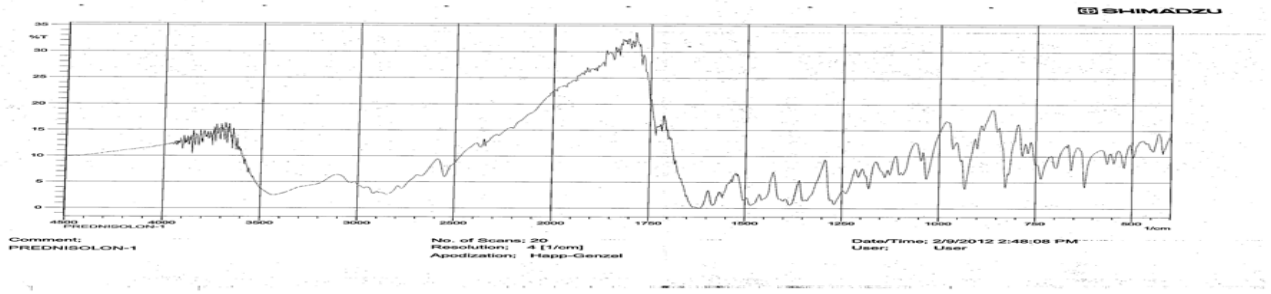

Fig 1: FTIR Spectra of Prednisolone

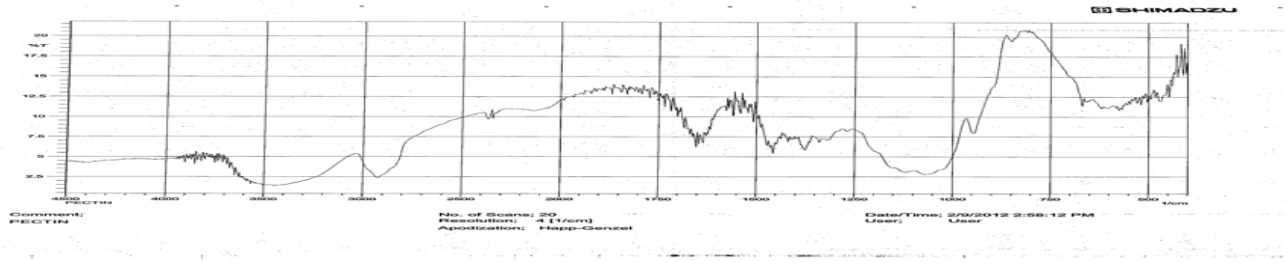

Fig 2: FTIR Spectra of Pectin

Table 4: Evaluation of Granules

Formulation Code	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Compressibility Index(%)	Angle of Repose
F-I	0.458±0.029	0.35±0.018	14.46±3.12	26º63”±0.20
F-II	0.444±0.005	0.529±0.008	16.02±2.39	27º50’’±2.46
F-III	0.42±0.008	0.471±0.01	10.74±0.588	27º63’’±2.46
F-IV	0.268±0.005	0.316±0.005	15.24±1.68	28º37’’±2.62
F-V	0.244±0.008	0.283±0.01	13.90±3.12	29º37’’±0.81
F-VI	0.217±0.02	0.244±0.04	10.88±2.29	30º28’’±1.65

Table 5: Evaluation of Tablets

S.No.	Parameters	F-I	F-II	F-III	F-IV	F-V	F-VI
1.	Average hardness (kg/cm^2)	4.33± 0.57	4.45± 0.57	4.87± 0	4.46± 0.02	4.74± 0.0	4.85± 0.14
2.	Average thickness (mm)	0.5± 0.0	0.5± 0.0	0.5± 0	0.5± 0.0	0.5± 0.0	0.5± 0.0
3.	Average diameter in (mm)	1±0	1±0	1±0	1±0	1±0	1±0
4.	Average friability (%)	0.88	0.78	0.74	0.93	0.78	0.82
5.	Average weight variation (mg)	255± 0.92	254± 0.42	255± 0.85	257± 0.78	256± 0.53	255± 0.39
6.	Average content uniformity (%)	98.6	99.3	98.9	99.4	98.6	99.2

The oral bio availability of prednisolone has been reported to be significant. It is well absorbed from colon when administered orally. Colon targeted drug delivery ensures specific release of prednisolone which affects time delay between administration and onset of action. Colon targeted delivery is one approach where transit time is prolonged in order to promote good absorption.

Pectin and chitosan are used as polymers because of less susceptibility to degradation in upper part of GIT by human digestive enzymes. Moreover, these polymers had gained increasing importance in achieving site-specific delivery to colon. Lactose is used as diluent. Talc and magnesium stearate are used as lubricants.

In the present study the formulations were prepared by using different proportions of polymer. The prepared formulations were evaluated for different physicochemical characteristics such as thickness and diameter, drug content, weight variation, hardness and friability. The release characteristics of formulation were studied *in vitro* condition.

a) Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Hardness of the tablet was found to increase with increasing polymer concentration.

b) Thickness and diameter

The thickness and diameter of tablets were found to be 0.5cm, 1.0cm respectively.

c) Weight Variation Test

All tablets were found to pass the weight variation test. The percentage deviation of the individual tablet weights from the average tablet weight was found to be within the USP limits ± 7.5%.

d) Drug Content Uniformity

The drug content uniformity was examined as per USP specifications. All the batches of tablets were found to comply with uniformity of content test.

***In Vitro* Dissolution Study**

Dissolution apparatus USP XXI type II was used to carry out *in vitro* drug release studies on the prepared batches of matrix tablets with a paddle speed of 50rpm at 37°C ± 0.5°C in 900ml of pH 6.8 phosphate buffer for 12 hours.

Analysis of Samples

1ml of sample was drawn at periodic intervals 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 6^{th},7^{th}, 8^{th},9^{th}, 10^{th}, 11^{th}, 12^{th} hour and it was made up to 10ml with pH 6.8 phosphate buffer which is colon pH. 1ml of fresh dissolution medium was replaced after each time the sample was drawn. At the end of first hour, study of dissolution rate indicated that the drug is unable to release in the stomach. Now dilution is performed with a buffer of pH-6 for the next 3 hours and dissolution is carried out. The result showed that there is no release of drug in this case. Finally, a buffer of pH-6.8 was used and the rate of dissolution was increased gradually. The sample was analyzed spectrophotometrically at 250nm for the drug content against the blank. The mean percentage of prednisolone released at various time intervals was calculated and plotted against time.

Formulations P-I, P-II, P-III, P-IV, P-V and P-VI were released 88.23%,96.79%, 92.74%, 86.42%, 91.83% and 94.99%drug respectively at the end of 12 hours.

From the results obtained it was observed that the significant enhancement of the dissolution rate that occurred may be attributed to improved absorption of the drug in to dissolution medium.

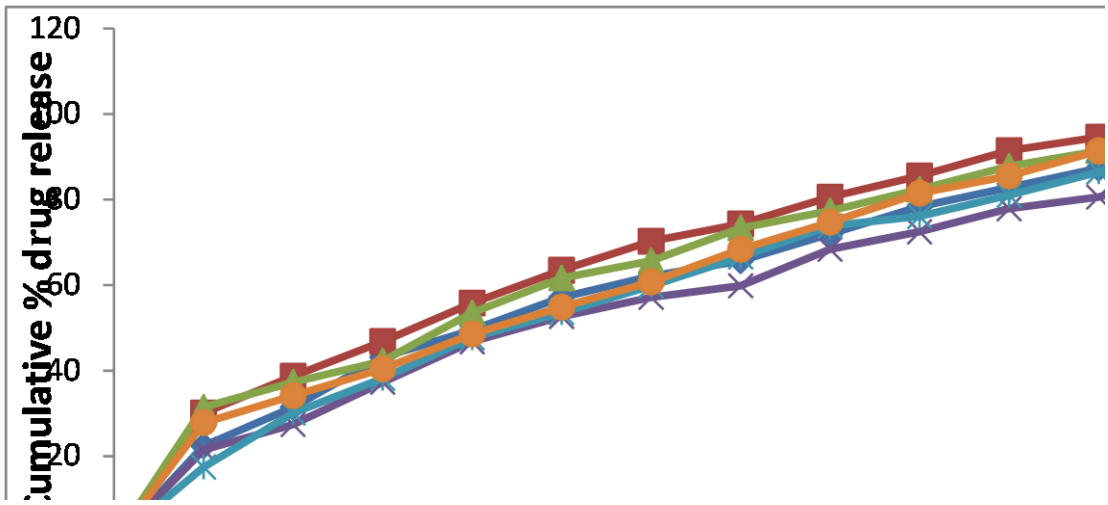

Fig 3: Comparative *in vitro* Release Profiles for Prednisolone Matrix Tablets F1-F6

CONCLUSION:

The approach of the present study was to develop matrix tablets of Prednisolone for colon targeted drug delivery system and henceforth evaluate the release profiles of these formulations. Formulation F-II containing 20mg of prednisolone and 99mg of pectin was found to release a maximum of 96.79% at the 12th hour. The drug release from F-II was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release. Comparison of all formulation of prednisolone revealed the fact that developed formulation F-II showed comparable release characteristics, thus it may have fair clinical efficacy. Hence, the formulation F-II has met the objectives of the present study.

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