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Research Article

DEVELOPMENT OF COLON TARGETED SUSTAINED RELEASE MATRIX TABLETS OF PREDNISOLONE

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ABSTARCT

In the present research work sustained release matrix formulation of prednisolone targeted to colon by using various polymers developed. Various eudragit polymers were employed as polymers. Prednisolone dose was fixed as 20 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 30, 60 and 90 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e., 98.78 % in 10 hours. It contains the eudragit polymer Prednisolone as sustained release material. It followed zero order release kinetics mechanism.

KEYWORDS: *Prednisolone, Colon targeted drug delivery system, Ethyl cellulose, Eudragit L100, Eudragit S 100.*

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and gets absorbed from these regions of the gastrointestinal tract (GIT) depending upon the physicochemical properties of the drug [1-3].

The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon [4, 5].

Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GIT. Due to the lack of digestive enzymes, colon is considered as suitable site for the absorption of various +-drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery [6].

Seriousness from constipation and diarrhea to the debilitating inflammatory bowel diseases (Ulcerative colitis and Crohn's disease) through to colon carcinoma which is two third cause of cancer in both man and women. Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy. Colon having the lower level of luminal and mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. E.g.to facilitate absorption of acid and enzymatically labile materials especially proteins and peptides. Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma and arthritis Targeted delivery ensures the direct treatment at the disease site, lower dosing, and reduction in side effects. Colonic drug delivery is also found useful for improving systemic absorption of drugs like nitr-endipine (calcium channel blocker), metoprolol (anti-hypertensive), iso-sorbide mononitrate (anti-anginal). The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon. Retardation of drug release in the diverse and hostile conditions of the stomach and small intestine is not easily achieved, since the dosage form will be subjected to a physical and chemical assault that is designed to break down ingested materials. While in the colon, the low fluid environment and viscous nature of luminal contents may hinder the dissolution and release of the drug from the formulation. Moreover, the resident colonic microflora may impact on the stability of the released drug via metabolic degradation. In spite of these potential difficulties, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure, bacteria and prodrug approach [7-10].

The aim of the present research work was to develop sustained release matrix formulations of prednisolone targeted to colon by using various polymers and in-vitro drug release study.

Prednisolone- A glucocorticoid with the general properties of the corticosteroids. It is the drug of choice for all conditions in which routine systemic corticosteroid therapy is indicated, except adrenal deficiency states.

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Prednisolone is a synthetic glucocorticoid used as antiinflammatory or immunosuppressive agent. Prednisolone is indicated in the treatment of various conditions, including congenital adrenal hyperplasia, psoriatic arthritis, systemic lupus erythematosus, bullous dermatitis herpetiformis, seasonal or perennial allergic rhinitis, allergic corneal marginal ulcers, symptomatic sarcoidosis, idiopathic thrombocytopenic purpura in adults, leukemias and lymphomas in adults, and ulcerative colitis. Glucocorticoids are adrenocortical steroids and cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli [11, 12].

Materials used:

Prednisolone, Ethyl Cellulose, Eudragit L-100, Eudragit S-100, PVPK30, Magnesium stearate, Micro crystalline cellulose, Talc. Etc. Received as gift samples from Karthikeya drugs and pharmaceuticals pvt Ltd. As gift samples.

METHODOLOGY

Analytical method development:

a) Determination of absorption maxima:

A solution of containing the concentration 10 µg/ml was prepared in 0.1N HCl, 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Drug – Excipient compatibility studies:

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Differential Scanning Calorimetry (DSC):

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with a monitor and printer. The instrument was calibrated with indium. Accurately weighed 5 mg of sample were placed in an open, flat bottom, aluminium sample pans. Thermograms were obtained by heating the sample at a constant rate 10 minute. A dry purge of nitrogen gas (20ml/min) was used for all runs sample heated from 35°C to 400°C.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation of core tablet:

The core tablets are formulated by using 05 mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in below table.

Table No. 1: Composition of core tablet

Ingredient Name	Quantity (mg)
Prednisolone	5
Sodium starch glycollate	50
Talc	2
Magnesium stearate	2
MCC pH102	Qs
Total weight	140

Total weight of core tablet was fixed as 140 mg. The tablets are prepared by using 7mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. the composition of coating layer is given in below table.

Table No. 2: Composition of coating layer

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	50	100	150						
Eudragit S100 (mg)				50	100	150			
Eudragit L100 (mg)							50	100	150
PVP K30	40	40	40	40	40	40	40	40	40
Magnesium stearate (mg)	4	4	4	4	4	4	4	4	4
Talc (mg)	4	4	4	4	4	4	4	4	4
MCC pH 102 (mg)	q.s	qs	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	400	400	400	400	400	400	400	400	400

Compression coating layer was divided into two equal portions i.e., 200mg of each quantity .Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 12 mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm^2.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

Evaluation of post compression parameters for prepared Tablets:

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Application of Release Rate Kinetics To Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

The present study was aimed to developing Sustained release tablets of Prednisolone using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method:

Graphs of Prednisolone was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 263 nm and 265 nm respectively.

FTIR spectrum of optimized formulation:

By observing the above spectrums it was observed that there was no considerable change in the occurrence of the pure drug functional

groups in the optimized formulation hence considered there was no incompatibility between the drug and the materials selected

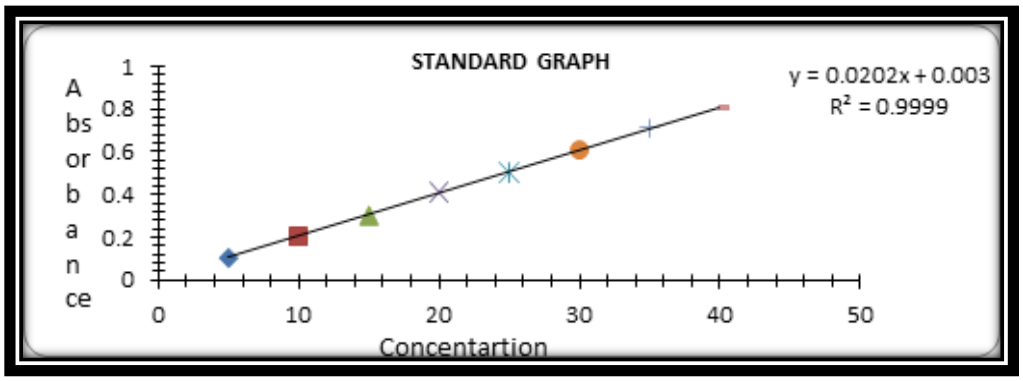

Fig. 1: Standard graph of Prednisolone in 0.1N HCl

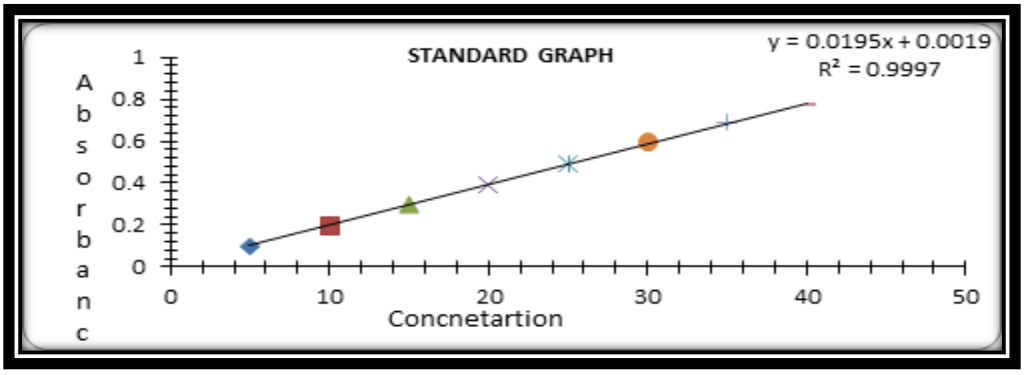

Fig. 2: Standard graph of Prednisolone pH 6.8 phosphate buffer (265nm)

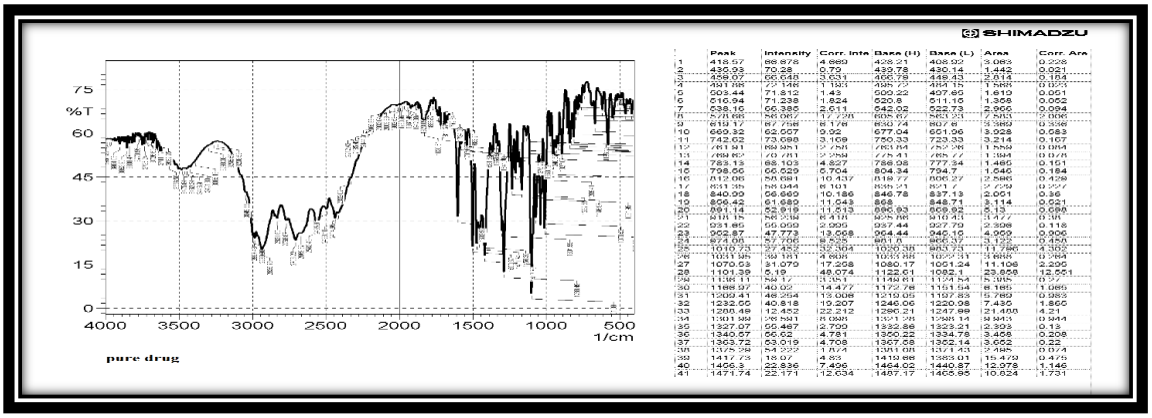

Fig. 3: Drug and excipient compatability studies

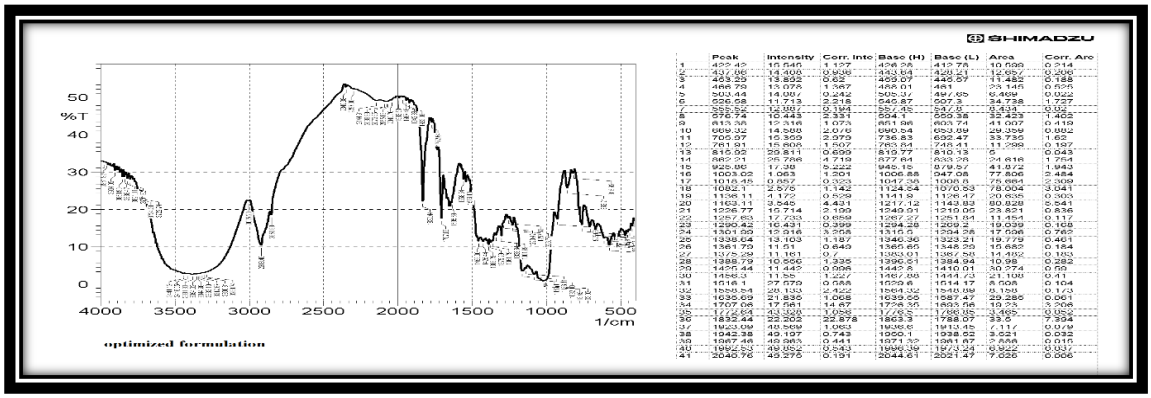

Fig. 5: FTIR spectrum of pure drug

Preformulation parameters of powder blend:

Table No. 3: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 6 to 8 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Invitro quality control parameters for tablets:

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table No. 4: Quality control parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	300.5	4.5	0.50	3.8	99.76
F2	305.4	4.5	0.51	3.9	99.45
F3	308.6	4.4	0.51	3.9	99.34
F4	300.6	4.5	0.55	3.9	99.87
F5	309.4	4.4	0.56	3.7	99.14
F6	300.7	4.5	0.45	3.7	98.56
F7	302.3	4.1	0.51	3.4	98.42
F8	301.2	4.3	0.49	3.7	99.65
F9	298.3	4.5	0.55	3.6	99.12

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

Table No. 5: Dissolution Data of Prednisolone Tablets Prepared With Eudragit RSPO in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.5	25.5	20.1	16.4	17.25	16.42	14.62	10.4	9.4	8.5
1	46.7	39.4	26.7	38.26	25.73	19.86	16.5	15.6	14.5
2	76.5	55.3	34.6	54.16	36.63	22.35	28.6	21.4	18.4
3	98.4	75.3	42.54	72.01	45.04	31.45	39.5	36.7	23.4
4		87.3	50.46	88.26	58.25	39.80	48.5	42.4	28.2
5		99.4	52.77	97.10	65.33	45.25	59.4	49.6	34.8
6			85.73		76.41	58.24	69.2	55.3	40.2
7			91.57		84.84	66.73	74.5	60.3	44.8
8			97.32		97.80	71.34	82.3	72.8	50.4
9						75.52	87.78	83.52	63.34
						82.17	98.78	88.65	69.27

From the dissolution data it was evident that the formulations prepared with Eudragit RSPO as polymer were unable to retard the drug release up to desired time period i.e., 10 hours.

Whereas the formulations prepared with Eudragit S 100 retarded the drug release in the concentration of 30 mg (F7 Formulation) showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 98.78 % in 10 hours with good retardation.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

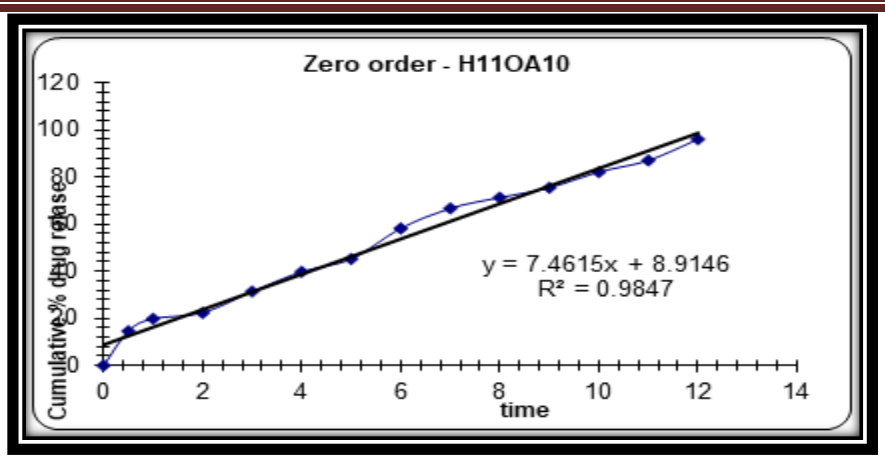

Fig 7.6 : Zero order release kinetics graph

(From the above graphs it was evident that the formulation F7 was followed Zero order release kinetics.)

CONCLUSION

In the present study we developed sustained release formulation of Prednisolone to maintain constant therapeutic levels of the drug for over 10 hrs. Various eudragit polymers were employed as polymers. Prednisolone dose was fixed as 20 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 30, 60 and 90 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e., 98.78 % in 10 hours. It contains the eudragit polymer Prednisolone as sustained release material. It followed zero order release kinetics mechanism.

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