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FORMULATION, DEVELOPMENT AND EVALUATION OF ENTERIC COATED TABLET AS A COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT :

The physicochemical qualities of the medication determine whether or not oral administration of standard dosage forms dissolves in the stomach or intestinal fluid and absorbs from these areas of the GIT. There are several benefits to dosage forms that enter the colon as opposed to the upper gastrointestinal tract. Using the wet granulation process, hydroxypropyl methylcellulose was used to generate the sustained release formulation for prednisolone (core tablets). The drug release was conducted in a pH 7.2 phosphate buffer, ideally for eight batches. The cumulative percentage release of T1 to T8 batches 57.7%, 69.89%, 80.46%, 89.06%, 91.14%, 96.32%, 97.42%, 109% respectively and the release profile of T6 batch is match with theoretical release profile. Eudragit S100 used as an enteric coating polymer to retard the drug release in upper part of the GI tract and to release drug at the site of action which can provide improved therapeutic effect for treatment of inflammatory bowel disorders. The results showed that Eudragit S100 gives protection to drug in physiological changes of environment of stomach.

Keywords: Enteric coated tablet, In-vitro dissolution technique, Prednisolone and Wet granulation technique.

1. Introduction :

The use of enteric coatings on solid substrates has been the most widespread use of a formulation method for colonic administration. This is a logical progression of traditional coating technologies to evade gastrointestinal release, hence avoiding issues like deterioration or adverse pharmacological effects like nausea and stomach irritation. Using polymers that can tolerate the lower pH levels of the stomach yet dissolve and release the medication when the pH in the small intestine rises has been the fundamental idea behind this strategy.

1.1 Factors Affecting during Design of Colon Specific Targeted Drug Delivery System

The distal end of the ileum to the anus is where the large intestine stops. The big intestine of a human is around 1.5 meters long. The colon is mostly located in the belly and is the upper five feet of the large intestine[3,4,5]. The colon is a cylinder with a lumen, or passageway, that is between two and three inches in diameter. The mucosa, or soft pink lining, that lines the colon is moist. There can be differences in pH across and among subjects in the gastrointestinal system. The pH of the gastrointestinal fluid is influenced by food consumption, illness status, and diet. One method of targeted colon medication administration has been the change in pH along the gastrointestinal system.

1.2 Introduction to Inflammatory Bowel Disease

Both ulcerative colitis and Crohn's disease are long-term inflammatory gastrointestinal disorders that alternate between periods of remission and recurrence over many years. Despite having extremely different pathologies, they are frequently treated similarly, even when it comes to medication therapy.

Diffuse colonic mucosal inflammation is a hallmark of ulcerative colitis. Distal and more extensive diseases can be used to classify illness extent. Proctitis, or colitis limited to the rectum, and proctosigmoiditis, or rectum and sigmoid colon, are examples of distal illness. Pancolitis, which affects the whole colon, extensive colitis up to the hepatic flexure, and left-sided colitis up to the splenic flexure are examples of more severe disease[11,12].

Material and Methods :

Apparatus and chemicals: Prednisolon by M/s Lincoln Pharmaceuticals Ltd., PVP K30 by Dr. Reddy's Laboratories, Hyderabad, HPMC K 4M, HPMC, K 100M, Isopropyl Alcohol by Ranchem Ltd.., India, Hydroxy Propyl Cellulose by Loba Chemie, Mumbai.

Methods: The most popular technique for producing ODFs is solvent casting, which involves dissolving medication, polymers, and water-soluble excipients in de-ionized water. High shear pressures produced by a shear processor are then used to produce a uniform mixture. To produce high-quality films, the prepared solution is then placed onto a petri plate, and the solvent is allowed to dry by being exposed to a high temperature. Using various grades of Lycoat and HPMC, an orodispersible film of tianeptine sodium was effectively created by the solvent casting approach. Film-forming polymer is typically steeped in the proper solvent for a whole night when using the solvent casting process.

Table 1: Formulation of Preliminary Trials

	Batch Name (All the ingredients are in mg.)							
INGREDIENTS	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**
Prednisolone	20	20	20	20	20	20	20	20
MCC	30	30	30	40	35	30	30	20
Lactose	30	30	30	40	35	30	25	20
Mannitol	-	-	-	-	10	20	25	40
HPMC K 4M	10	20	30	10	10	10	10	10
HPMC K 100M	30	20	10	10	10	10	10	10
PVP K 30	5	5	5	5	5	5	5	5
Mg Stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Total Wt.	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**

Experimental work

3.1 Preformulation Studies

The study of a medical ingredient's physical and chemical properties, both alone and in conjunction with excipients, is known as preformulation. Preformulation studies aim to identify the physicochemical properties and excipients that may affect the manufacturing process, formulation design, and pharmacokinetic-biopharmaceutical aspects of the final product.

3.2 Determination of Solubility

Solubility checked in various medias like ethanol, methanol, dehydrated alcohol, acetone, chloroform, ether, water, 10%v/v HCl and 10% w/v NaOH.

3.3 Determination of Bulk density and Tapped density

Density may be calculated by dividing the powder's weight by its volume. It is expressed in g/cm[3]. A graduated cylinder's bulk volume and weight of dry powder are used to calculate bulk density (ρB). The total of the tapped and vacant volumes makes up the bulk volume of powder[4].

3.4 Angle of Repose

Density may be calculated by dividing the powder's weight by its volume. It is expressed in g/cm[3]. A graduated cylinder's bulk volume and weight of dry powder are used to calculate bulk density (ρB). The total of the tapped and vacant volumes makes up the bulk volume of powder[4].

$$\tan \theta = H/R$$

3.5 Selection and Jusification of Excipients[13]

1.Diluents: In view of the low drug dose it is essential to add bulking agents or diluents to increase the weight of the tablet starch was selected as the main diluent.

2.Binder: PVP K 30 was used as a tablet binder in the concentration of 5-10 %.

Formulators skilled in art can determine the binder level for the formulations, but binder usage level of 2-20 % in tablet formulations is common. Granulations using a water system granulate well, compress extremely well. It is used widely because of economicity.

3.Matrix-forming Polymers: HPMC is most widely used matrix-forming polymer because of its compatibility, multifunctionality and low cost. It is available in different grades depending upon its viscosity. In present study, two grades of HPMC are used: HPMC K 4M and HPMC K 100M.

4.Lubricants: Magnesium Stearate and talcum powder are widely used as Tablet and Capsule lubricants. Magnesium Stearate is generally used in the concentrations between 0.5 – 2.0%. Talc is generally used in the concentrations between 1.0 – 2.0 %.

Result and discussion

4.1 Preformulation Study

4.1.1 Description

White or almost white, crystalline powder; hygroscopic.

4.1.2 Result of Solubility

Soluble in ethanol (95%) and in methanol; sparingly soluble in acetone; slightly soluble in chloroform; very slightly soluble in water. Soluble in 10%v/v HCl and in 10%w/v NaOH.

4.1.3 Result of Density and Flow Properties

Density and Flow Properties were shown in Table no.2.

S.N.	Density (g/ml)		Flow properties	
	Bulk	Tapped	Carr's index	Hausner Ratio
1.	0.410	0.523	21.60%	1.275

The above observation indicates that the Prednisolone has fair to passable flow properties.

4.2 Result of Melting Point

The melting point of Prednisolone was found to be 230°C.

4.2.1 Drug - Excipients Compatibility Study

FT-IR Study

FT-IR studies were carried out for pure drug alone and along with excipients. The results are summarized as follows. The FT-IR spectrum of pure prednisolone is shown in the Figure 1 and peaks are listed in the Table 3. Similarly FT-IR spectra of prednisolone in combination with excipients and in optimized formulation are shown in Figures 1 to 4. The peaks given in the Table 3 can be considered as characteristic peaks of prednisolone. These peaks were not affected and prominently observed in FT-IR spectra. This indicates that there is no interaction between prednisolone and excipients and the drug was compatible with the formulation components.

Drug only

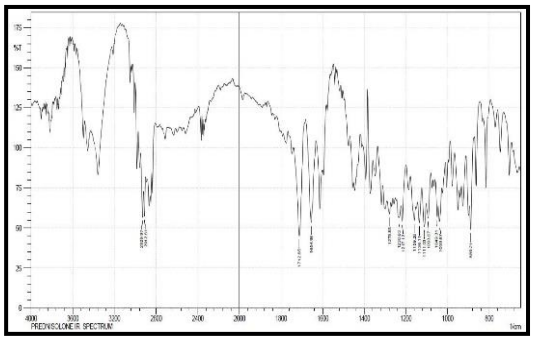


Figure 1 FT-IR Spectra of Prednisolone

Drug + Lactose

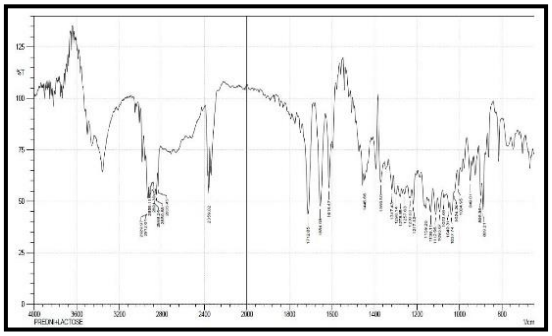


Figure 2 FT-IR Spectra of Prednisolone + Lactos

Drug + HPMC K 4M

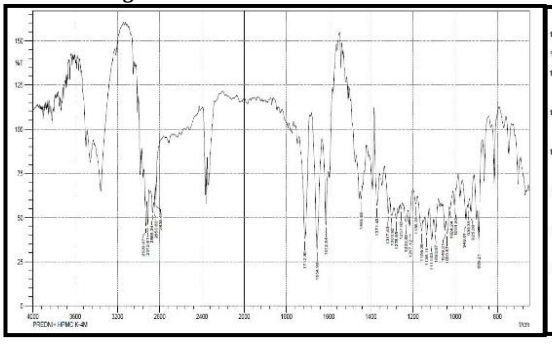


Figure 3 FT-IR Spectra of Prednisolone + HPMC K 4M

Drug+HPMC K 100M

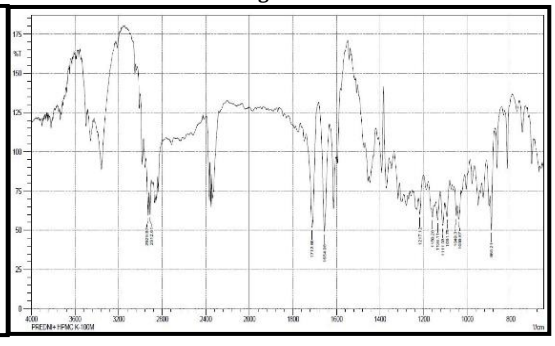


Figure 4 FT-IR Spectra of Prednisolone + HPMC K 100M

Table 3: Infrared Spectrophotometer Studies for Sustained Release Matrix Tablet of Prednisolone

Vibrations	Range (cm^{-1})	Pure drug Figure (cm^{-1})	Eudragit S 100	HPMC K 4M	Mannitol	Lactose	Mixture
Oxygen susbsti-yuted steroidal moiety	1600-1630 Doublet	1614.47	-	-	-		1614.47
O-H	3400-3600	-	3415.87	3456.87	3668.24	3668.24	3668.24
-C=O (stretching)	1700-1730	1712.85	-	-	-	1712.85	1712.85
-C-H (out of plane)	Below 900	889.21	-	-	-	-	889.21
Ar=O (out of plane)	1650-1675	1654.98	-	-	-		1654.98
=C-O	1150-1050	1136.11	1057.03	1057.03	-		1136.11
C=C	1650-1500	-	-	-			1647.18

Evaluation of Tablets

In present investigation attempt was made to prepare SR Matrix Tablet formulation of Prednisolone using HPMC K 100M & HPMC K 4M by wet granulation method using Rotary Tablet Machine-32 Station.

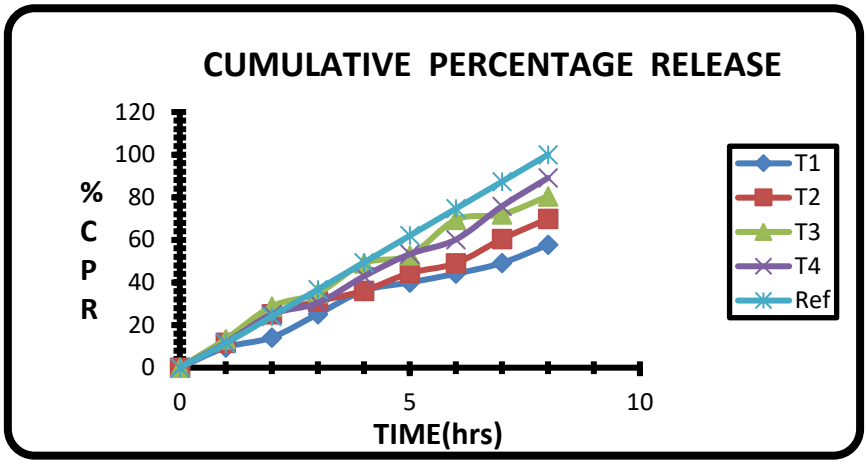
Table 4: Evaluation Parameters of Prednisolone SR Matrix Tablets

Batch code	Hardness (n=5) kg/cm^2	Thickness (n=5) mm	%Friability (n=10)	Weight Variations (n=20)
T1	6.2	2.8	0.10	100±2.50
T2	6.9	2.9	0.21	100±2.00
T3	7.4	2.9	0.19	100±2.74
T4	6.8	2.7	0.23	100±2.15
T5	8.1	2.9	0.30	100±2.54
T6	8.1	2.7	0.13	100±2.15
T7	6.7	2.7	0.19	100±2.54
T8	9.0	2.8	0.22	100±2.00

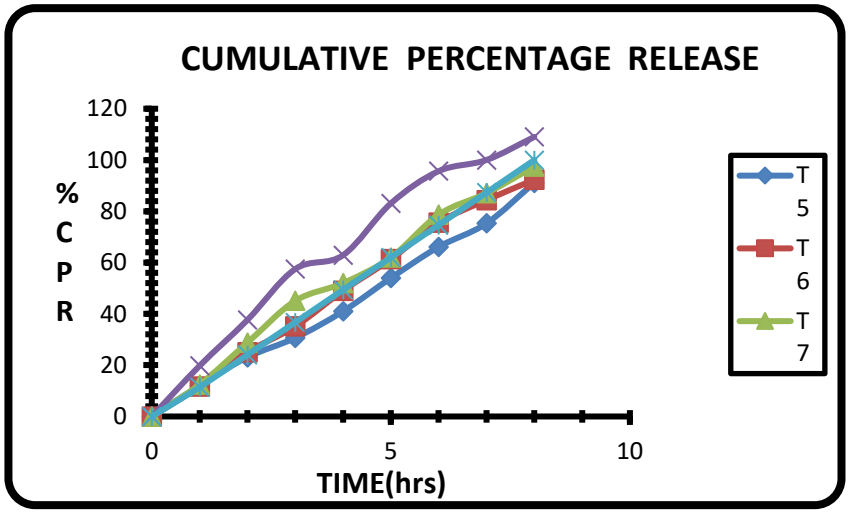
***In-Vitro* Dissolution Profile of Prepared Prednisolone Sustained Release Matrix Tablet**

Table 5: Cumulative Percentage Release of Batches T1 to T8 of Prednisolone SR Matrix Tablets

Time(hr)	T1	T2	T3	T4	T5	T6	T7	T8	Ref.
0	0	0	0	0	0	0	0	0	0
1	9.52	11.76	13.46	11.68	12.05	11.7	12.46	19.75	11.4
2	14.21	25.06	28.76	25.01	23.11	25.09	28.76	37.63	24.05
3	25.15	31.11	35	30.43	30.65	35.11	45.08	57.48	36.7
4	36.12	36.15	49.06	42.87	41	49.05	52	62.88	49.35
5	40.02	44.42	52.77	53.32	53.98	61.33	61.96	83.07	62
6	44.13	49.03	69.42	60.16	66.13	75.61	78.69	95.66	74.65
7	49.16	60.38	71.98	75.76	75.29	84.39	87.07	100	87.3
8	57.7	69.89	80.46	89.06	91.14	96.32	97.42	109	100.0



(Figure 5: Comparison Dissolution Profiles of T1, T2, T3, T4 with Reference)



(Figure 6: Comparison Dissolution Profiles of T5, T6, T7, T8 with Reference)

The prepared prednisolone sustained release matrix tablets were evaluated for various physical properties. All the batches were prepared under similar condition to avoid processing variables. These were evaluated for various physical parameters such as weight variation, thickness, hardness, friability and drug content. A FT-IR study were carried out for pure drug alone and along with excipients to check the interaction between prednisolone and excipients and the drug was compatible with the excipients and mixtures. As shown in Table 4 eight different formula (T1toT8 Batches) were prepared for prednisolone sustained release matrix tablets with different concentration of synthetic polymers like HPMC K 4M and HPMC K 100M. As shown in table 6.4 the cumulative percentage release of T1 to T4 batches were 57.7%, 69.89%, 80.46%, 89.06% respectively but the release profile was not match with reference. So further trials were carried out to get good release profile which matched with Theoretical release profile. So, further batches were formulated with the same concentration ratio of HPMC K 4M: HPMC K 100M (26:26) in combination with different concentration of mannitol like 13%, 26%, 32.5%, 52% .The cumulative percentage release of T5 to T8 batches were 91.14%, 96.32%, 97.42%, 109% respectively and the release profile of T6 batch was matched with Theoretical release profile. Dissolution profile of T6 batch matched with theoretical release profile. So it is consider to be the best batch in all and applied the similarity factor which shown in Table 6.6 and the f2 value of T6 batch is 87.55% so T6 batch optimized formula of prednisolone sustained release tablet. Coating was applied by using Eudragit S 100 about 13.75% on optimized formula T6 batch and the in vitro dissolution study of prednisolone enteric coated tablet was carried out which is shown in Table 5. Accelerated Stability was performed at 40 °C with 75% RH revealed that there was no significant change in appearance and drug release profile (shown in Table no 5).

The preformulation studies have been carried out for the development of formulation. FT-IR Study Shows no interaction between drug and Excipients. Prednisolone(core tablet) sustained release formulation was developed using Hydroxypropyl methylcellulose by wet granulation method and the drug release was carried out in,pH 7.2 phosphate buffer preferably for eight batches.. The cumulative percentage release of T1 to T8 batches 57.7%, 69.89%, 80.46%, 89.06%, 91.14%, 96.32%, 97.42%, 109% respectively and the release profile of T6 batch is match with theoretical release profile. The batch optimized by comparative dissolution profile with theoretical release profile. And it is further confirmed by using similarity factor (f2 value) so T6 batch is optimized.

Eudragit S100 used as an enteric coating polymer to retard the drug release in upper part of the GI tract and to release drug at the site of action which can provide improved therapeutic effect for treatment of inflammatory bowel disorders.

Conclusion :

When administering medication to patients, the oral route is seen to be the most practical. The physicochemical qualities of the medication determine whether or not oral administration of standard dosage forms dissolves in the stomach or intestinal fluid and absorbs from these areas of the GIT. It is a significant disadvantage when a medicine needs to be shielded from the harsh environment of the upper gastrointestinal tract or when targeted drug delivery in the colon is necessary. There are several benefits to dosage forms that enter the colon as opposed to the upper gastrointestinal tract. Prodrug, pH-sensitive polymers, bacterial degradable polymers, hydrogel, matrices, and multicoating time-dependent delivery systems are a few pharmaceutical techniques that may be used to create colon-targeted drug delivery systems. Since the majority of a standard oral sustained release formulation is released in the colon, the medication should have an absorption window that extends across the gastrointestinal system or the colon.

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