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CHARACTERIZATION AND EVALUATION OF PREDNISOLONE TABLETS AS A COLON TARGETED DELIVERY SYSTEM

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ABSTRACT

Prednisolone is a corticosteroid drug that is used to treat many diseases. The present investigation was concerned with the formulation of prednisolone as an oral modified release tablet for colonic targeting. Many trials were performed to prepare a satisfactory formula using the wet granulation method with various additives and coatings. We found that lactose as a diluent provided the most reasonable release for prednisolone among other diluents. In addition, the formula containing 1% Eudragit RS PM was the best with regard to 100% release of drug in comparison with other concentrations and other retardant types. Avicel was used as a canalizing agent, and the results showed that the formula containing 30% Avicel PH 302 demonstrated faster release. Eudragit S 100 provided the best release of drug in phosphate buffer, pH 7.4. The effect of the percent of binding agent polyvinylpyrrolidone (PVP) (5%, 10%, and 15%) was studied, and the best results were obtained with a concentration of 10%. The trials in this study successfully formulated prednisolone-modified release tablets (coated matrix) using a wet granulation method as a potential colon delivery system.

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Key Words

Prednisolone; Colon Delivery
System; Eudragit

INTRODUCTION

The oral route is considered the most suitable for administration of drugs to patients. The orally administered dose normally dissolves in the stomach fluid and/or in intestinal fluid, and it absorbs

from these regions of the gastrointestinal tract (GIT) depending on the physicochemical properties of the active constituent 1. In the colon, both local and systemic drug delivery can take place 2. As a result, oral drug delivery systems have considerable advantages that could be targeted to the colon; for example, such a delivery system would permit topical treatment of inflammatory bowel disease, e.g., ulcerative colitis or Crohn's disease 3. Target-specific means of drug delivery could allow oral administration of peptide and protein drugs, which normally become inactive in the upper parts of the gastrointestinal tract 4, 5. When diurnal rhythm is evident, colon-specific systems could be used, e.g., for asthma, rheumatic disease, ulcer disease, and ischemic heart disease 6. The colon forms the lower region of the GIT and extends from the ileocaecal junction to the anus 7. Many drugs are absorbed from the colon by passive diffusion via the paracellular route. The surface area of the colon for absorption is smaller than that of the small intestine, and this is compensated by the slow transit time 8. An oral colonic delivery system should delay the release of drug in the stomach and small intestine but permit complete release in the colon. Many approaches and systems have been used to manufacture such colonic targeting systems. The major approaches used for targeting mechanisms are as follows 9, 10:

1. pH-dependent delivery: The pH-dependent systems take advantage of the pH changes in the human GIT, which gradually increase from the stomach (pH 1-2, which increases to 4 during digestion) 11, 12 to the small intestine (pH 6-7) at the site of digestion, and finally to pH 7-8 in the distal ileum 13. The polymers used for colon targeting should be able to resist the lower pH values of the stomach and proximal portion of the small intestine; moreover, the polymers should be able to disintegrate or dissolve at the neutral or slightly alkaline pH of the terminal ileum, preferably at the ileocaecal junction 14, 15.

2. Time-dependent delivery: The principle of designing timed-released systems is used to counteract the low pH of the stomach and establish a lag time of a predetermined time span, after which the release and absorption of drug take place. The lag time in this situation is the time needed to transit from the mouth to colon 16.

3. Pressure-dependent delivery: As a consequence of peristalsis, higher pressures are found in the colon than in the small intestine; to take advantage of this increased pressure, Takaya and co-workers developed pressure-dependent colonic delivery capsules prepared from ethyl cellulose, which is insoluble in water 17. In these systems, drug release occurs after disintegration of a water-insoluble polymer capsule due to pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is a crucial factor for disintegration of the formulation 18.

4. Bacteria-dependent delivery: These systems clearly appear in the prodrug sulphasalazine, which is composed of two separate moieties, sulphapyridine and 5-aminosalicylic acid, linked by an azobond. This system remains intact across the upper portion of the gut; once in the colon, the azo-bond is cleaved by the bacteria present in the colon, resulting in liberation of the carrier molecule sulphapyridine and the pharmacologically active agent 5-aminosalicylic acid 19. This idea has led to the development of other novel azo-bond-based polymers (azopolymers) for this purpose; such potential materials include inulin 20 and dextran 21. Prednisolone is also known as 1, 2- Dehydrohydrocortisone, Deltahydrocortisone, metacortandralone, and 11, 17, 21-Trihydroxy pregna-1, 4- diene-3, 20-dione; its chemical formula is $C_{21}H_{28}O_5$, and its molecular weight is 360.4 KD 22. Prednisolone is completely absorbed from the gastrointestinal tract. When administered orally, around 80% of the prednisolone is absorbed. The bioavailability of prednisolone depends on the dissolution rate of the dosage form. Peak plasma concentrations are obtained 1 or 2 hours after oral administration, and it has a typical plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food 23.

MATERIAL AND METHODS

Chemicals and reagents

The following materials of the highest available purity were used in this study: Acetone, Ethanol 99% (BDH chemicals, India Ltd), Eudragit L 100, S100, RSPM, RL-copolymers of methacrylic acid and methyl acrylate (Gift From Themis Chemicals Ltd), Glucose, Mannitol, Starch (Merck, India), Lactose, Hydrochloric acid, Ethyl cellulose, Methanol (BDH chemicals India, Ltd), Microcrystalline cellulose-Avicel -PH 101, PH 102, PH 302, Polyvinylpyrrolidone (PVP K 30) (Themis Chemicals, Ltd, India), Potassium dihydrogen phosphate (Pharma Impex, Calcutta), Sodium hydroxide, Zinc stearate and Prednisolone (gift from Pharma Impex, Calcutta).

Method Formulation of prednisolone tablets

Different formulas (Table 1) were prepared using the wet granulation method. After appropriate dry blending of the previously sieved ingredient, the powder was granulated by adding an appropriate amount of binding solution. It was subsequently kneaded to the proper consistency. The wet mass was passed through a 1-mm sieve (18 mesh) and dried in a pre-warmed tray dryer.

The dry granules were then reduced in size by passing them through a 0.8-mm sieve (20 mesh). A known weight of granules was mixed with a specified amount of disintegrant in a closed container; the samples were then mixed with zinc stearate (previously sieved and dried) for 1 minute and compressed into tablets using 6-mm biconcave punches at 6 ton/inch². Three coating formulas were used: Eudragit S 100, Eudragit L 100, and cellulose acetate phthalate (CAP). Calibration curves of the drug in phosphate buffer at pH 6.8 and 7.4 and in 0.1 N HCl were constructed by preparing various concentrations of the drug (5, 10, 15, 20 µg/ml); the samples were analysed spectrophotometrically at a λ_{max} of 248 nm²⁴, and the absorbance was then recorded and plotted versus the concentration.

RESULTS AND DISCUSSION

Different formulas were prepared as shown in Table 1; an acceptable formula could resist the 0.1 N HCl, not release the active ingredient in phosphate buffer at pH 6.8, and release the active ingredient at pH 7.4 within an acceptable period of time.

Table - 1 Constituents of Different Formulas of Prednisolone-Modified Release Tablets.

Formula No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Prednisolone	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28	14.28
PVP K 30	10	5	15	10	10	10	10	10	10	10	10	10	
Eudragit RS PM		1	1	1			1	1	1	1	1		2
3													
Eudragit RL				1									
EC					1								
Mannitol						44.22							
Glucose								44.22					
<u>α-Lactose</u>	44.22	49.22	39.22	44.22	44.22				44.22	44.22	45.22	43.22	42.22
Starch								44.22					
Avicel 302	30	30	30	30	30	30	30	30			30	30	30
Avicel 102									30				
Avicel 101										30			
Zinc Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Mechanism of prednisolone release from different matrices

In order to characterise the mechanism of drug release from the matrices, the data were fit to the following mathematical model 26:

$$F = \frac{Mt}{M\infty} = K t^n$$

where, $Mt/M\infty$ is the fraction of drug released up to time t (F), K is the rate constant, and n is the release exponent indicative of the release mechanism. The results (Table 2) showed high n values (> 0.5), which indicate a coupling of diffusion and erosion mechanisms, a so-called anomalous diffusion due to the presence of swelling polymers within the matrix structure during dissolution. Similar results have been observed by other investigators 27. Tablets containing 1% ethyl cellulose (formula 5) remained intact during the release studies; therefore, erosion can not consider as one of the release mechanisms. The n value obtained was 0.5, indicating that the mechanism was Fikian diffusion.

CONCLUSION

Prednisolone is a corticosteroid drug that is used to treat many diseases, such as ulcerative colitis or Crohn's disease. The trials investigated in this study resulted in successful formulation of prednisolonemodified release tablets (coated matrix) using the wet granulation method. Based on the results obtained, the following may be concluded: Lactose can be selected as a diluent due to its reasonable dissolution release profile compared to other diluents. Eudragit RS PM at a concentration of 1% w/w of the total tablet weight was utilised for prepared tablets, and the formula provided acceptable retardation of drug release with a dissolution time of about 6.5 hrs. Avicel PH 302 was the best type of Avicel for use, as it provided a reasonable dissolution rate compared to other types. Eudragit S 100 is more suitable for colonic targeting in comparison to other types of coating formulas (Eudragit L100 and cellulose acetate phthalate). Polyvinylpyrrolidone (PVP) at a concentration of 10% was an excellent binder. Further investigations will be carried out (*in vivo* evaluation) to evaluate the efficiency of prednisolonemodified release tablets for the treatment of ulcerative colitis or Crohn's disease.

Table - 2 Values of The Kinetic Parameters For the Release Mechanism of Prednisolone From Different Prepared Formulas.

Formulation Variable	Formula no.	n value	Type of release
Effect of Eudragit RS PM concentration	1	1.4	anomalous
	12	1.3	anomalous
	13	1.2	anomalous
Effect of changing the grade of Avicel	1	1.4	anomalous
	9	1.17	anomalous
	10	1.12	anomalous
Effect of changing the type of polymer matrix tablet	1	1.4	anomalous
	4	0.66	anomalous
	5	0.5	Fikian diffusion
Effect of changing the concentration of binder	1	1.4	anomalous
	2	0.86	anomalous
	3	1.28	anomalous

REFERENCES

1. Sarasija S, Hota A. Colon-specific drug delivery systems. *Ind. J. Pharm. Sci.* 2000; 62: 1-8.
2. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* 2001; 18: 433-458.
3. Boot C, Rudolph MW. In vivo evaluation of a novel pH-and time- based multiunit colonic drug delivery system. *Alimentary pharmacology and therapeutics* 2004; 3: 347-353.
4. Yang L, Chu J, Fix J. Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. *Int. J. Pharm.* 2002; 235: 1-15.
5. Mackay M, Phillips J, Hastewell J. Peptide drug delivery: colonic and rectal absorption. *Adv. drug Del. Rev.* 1997; 28(2): 253-273.
6. Shareef MA, Khar RK, Ahuja A, Ahmad FJ, Raghav S. Colonic drug delivery: An update Review. *AAPS PharmSciTech* 2003; 5(2): E 17.
7. Watts PJ, Illum, L. Colonic drug delivery. *Drug Dev Ind Pharm* 1997; 23: 893-913
8. Edwards CA. Anatomical and physiological basis. In *Physiological factors influencing drug absorption. Colonic drug absorption and metabolism.* Bieck PR (ed). Marcel Dekker Inc., New York, 1993; pp. 1-28.
9. Ibekwe VC, Kendall RA, Basit AW. Drug delivery to the colon. *The Drug Delivery Companies Report* (Spring/ Summer), PharmaVentures Ltd, Oxford, UK 2004: 27-30.
10. AL-Taani BM, Tashtoush BM. Effect of microenvironment pH of swellable and erodible buffered matrices on the release characteristics of diclofenac sodium. *AAPS PharmSci Tech.* 2003; 4(3) : Article :43
11. Rubinstein A.: Approaches and opportunities in colon-specific drug delivery. *Crit. Rev Ther. Drug Carrier Syst* 1995; 12: 101-149.
12. Wilson CG, Washington N. The stomach: Its role in oral drug delivery. In *Physiological Pharmaceutics: Biological Barriers to Drug Absorption*, Rubinstein MH(ed). Chichester, UK: Ellis Horwood Limited, , 1989; 47-70.
13. Evans DF, Pye G, Bramley R, Clark AG, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 1988; 29: 1035-1041.
14. Dew MJ, Hughes PJ, Lee MG, Evans BK, Rhodes J. An oral preparation to release drugs in the human colon. *Br. J. Clin. Pharmacol.* 1982; 14: 405-408.
15. Tuleu C, Andrieux C, Cherbuy C, Darcy- Vrillon B, Duee PH, Chaumeil JC: Colonic delivery of sodium butyrate via oral route: Acrylic coating design of pellets and in vivo evaluation in rats. *Methods Find Exp Clin. Pharmacol* 2001; 23(5): 245.
16. Li J, Yang L, Ferguson SM, Hudson TJ, Watanabe S, Katsuma M, Fix JA. In vitro evaluation of dissolution behavior for a colon-specific drug delivery system (CODES™) in multi-pH media using United States Pharmacopeia Apparatus II and III. *AAPS PharmSciTech.* 2002; 3(4): article 33.
17. Takaya T, Ikeda C, Imagawa N, Niwa K, Takada K.: Development of a colon delivery capsule and the pharmacological activity of recombinant human granulocyte colony-stimulating factor in beagle dogs. *J. Pharm. Pharmacol.*, 1995; 47(6): 474-478.
18. Lieberman HA, Lachman L. Tablets. In *Pharmaceutical dosage forms*, Marcel Dekker, Inc. New York and Basel, 1980; Vol. 1: pp. 214.
19. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. *J. Pharmacol. Exp. Ther* 1972; 181(3): 555–562.
20. Fish NW, Bloor JR. Drug delivery to the colon. *Expert Opinion on Ther Patents* 1999; 9: 1515-1521.
21. Pang N-Y, Zhang Y, Zhang, Z-R. Synthesis of an enzyme-dependent prodrug and evaluation of its potential colon targeting. *World J Gastroenterol* 2002; 8(5): 913-917.
22. The pharmaceutical Codex (12th ed). *Principle and practice of pharmaceuticals*, Walter Lund (ed). The Pharmaceutical Press, London, 1994; pp. 1048.
23. Mycek MJ, Harvey RA, Champe PC. Androgens. In: *Lippincotts Illustrated Reviews: Pharmacology* (3rd ed.). Alwolters Kluwer Company 2004: 271- 277.
24. Konishi H, Kanemoto K, Ikuno Y, Minouchi T, Inoue T, Hodohara K, Fujiyama Y, Yamaji A. Fluctuation in Therapeutic Control Associated with Interchange of Prednisolone Tablet Formulations: Assessment of Bioequivalence by Dissolution Test. *Yakugaku Zasshi* 2002; 122(10): 813-817.

25. Martin A. Physical pharmacy (4thed). Lea and Febiger, Philadelphia, 1993: 497, 515-517,595.

26. Masuda K, Ashraful SM et al. Controlled release of naproxen sodium from Eudragit RS 100 transdermal film. Dhaka University J Pharm Scie 2002; 59(3): 193-198.

27. Anjali M, Steven H. Wet granulation fine particle ethylcellulose tablets; AAPS Pharm. Sci. . 2003; 5(2), article 13
