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Matrix Tablets Of 5-Aminosalicylic Acid For Possible Treatment Of Inflammatory Bowel Diseases Affecting The Small And Large Intestines

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Abstract: The three most common sites of intestinal involvement in Chron's disease are ileal, ileocolic and colonic. Therefore for effective therapy, dosage forms should be targeted to the ileum and colon simultaneously. The objectives of the present study are to develop and evaluate matrix tablets of 5-Aminosalicylic acid for targeted delivery to the ileum and colon, which would be capable of releasing drug over a period of 12-18 hours of time. Matrix tablets are formulated in two steps. The core tablets containing the drug are developed with different polymers like Pectin, Hydroxypropylmethylcellulose (HPMC) K4M, HPMC K15M and HPMC K100M, by wet granulation. Thereafter, the core tablets were compression coated with four different polymers namely, Eudragit S100, Shellac, HPMC E15 LV and HPMC K4M. The coated and uncoated tablets were evaluated by physical parameter testing and in-vitro dissolution studies. All the tablets passed the physical parameter testing. The in-vitro dissolution studies revealed that three formulations F4C4, F2C4 and F4C3 were well able to satisfy the objectives of the study.
Keywords: Chron's disease, Matrix tablets, Ileum, Colon, Compression coating.

INTRODUCTION:

Colon targeted drug delivery systems are often targeted to release drug selectively in the colon, avoiding the stomach and the small intestine. The different types of delivery systems utilized for colon targeting include matrix tablets[1,2,3,4], multiparticulate systems[5,6], microparticles[7,8], nanoparticles[9], osmotic delivery systems[10], pressure controlled systems[11], etc.

However, the inflammatory bowel diseases including chron's disease and ulcerative colitis can affect both the large and small intestines [12]. Chron's disease can in fact occur anywhere in the digestive tract, however the three most common sites of intestinal involvement in chron's disease are ileal, ileocolic and colonic[13]. Therefore, for effective therapy, both the colon and the small intestine (especially the ileum) may be targeted for drug release.

Furthermore, the duration of drug release from the delivery system is a very important factor to be considered. Most oral dosage forms are removed from the gastrointestinal tract after a day or so, therefore they are often designed to release all drug within 12-18 hours in the gastrointestinal tract [14]. For targeted drug release in the ileum and the colon, the transit times through the gastrointestinal tract should be taken into account, which is

elaborated in Table 1. The transit time from mouth to cecum (first part of large intestine) ranges from 3-7 hours. Colonic transit time may vary from 10-20 hours[14]. Therefore, it can be concluded that the drug release should start after 3 hours to achieve targeted drug release in the ileum.

Therefore the objectives of the present study are:

1. To develop formulations to target the ileum and the colon for drug release.
2. To develop formulations which would release all drug within 12-18 hours of dissolution.
3. To achieve targeted drug release after 3 hours of dissolution studies.

Table 1: Transit time at different segments of the Human G.I. tract[14]

Anatomical site	Fasting state Transit time (H)	Fed state Transit time (H)
Stomach	0.25	1
Duodenum	0.26	0.26
Jejunum	1.7	1.7
Ileum	1.3	1.3
Cecum	4.5	4.5
Colon	13.5	13.5

MATERIALS:

5-Aminosalicylic acid (Spectrochem Pvt. Ltd., Mumbai), Hydroxypropylmethylcellulose (HPMC) K4M, K15M, K100M (Yarrow Chem products, Mumbai), Pectin (Loba Chemie, Mumbai), Eudragit S100 (Yarrow Chem products, Mumbai), Shellac (Yarrow Chem products, Mumbai), HPMC E15LV Premium (Loba Chemie, Mumbai), Polyvinylpyrrolidone (PVP K-30)(CDH Pvt. Ltd., New Delhi), Microcrystalline cellulose (CDH Pvt. Ltd., New Delhi), Magnesium stearate (Loba Chemie, Mumbai), Talc (New Bengal Drug House, Kolkata), Propylene glycol (CDH Pvt. Ltd., New Delhi).

METHODS:

Preparation of core and compression coated tablets:

Core tablets were prepared by wet granulation method using the polymers Pectin, HPMC K4M, HPMC K15M and HPMC K100M and using purified water as the granulating fluid. Table 2 represents the various formulations. PVP K30 was used as binder for Pectin core tablets. However, in HPMC core tablets, no extra binder was added as HPMC can itself act as a binder.

Compression coated tablets were prepared with several polymers like Eudragit S100, Shellac, HPMC K4M and HPMC E15LV. The polymers for coating were granulated with a solution consisting of 2.5%w/v PVP K30 and propylene glycol in isopropanol. PVP K30 was used as binder and Propylene glycol as plasticizer to increase the cohesiveness of the coating mix. The binder concentration was kept low to achieve targeted drug release in the ileum, that is, after 3 hours of dissolution. Table 3 elaborates the compositions of the compression coats used and Figure 1 represents the transverse section of a compression coated tablet.

Table 2: Formulation of the core tablets

Materials	Percentage of materials used in Formulations (%w/w)			
	F1	F2	F3	F4
5-Aminosalicylic acid	25.8	25.8	25.8	25.8
Pectin	**56.8**	-	-	-
PVP K30	15.4	-	-	-
HPMC K4M	-	**61.9**	-	-
HPMC K15M	-	-	**20.62**	-
HPMC K100M	-	-	-	**5.2**
Microcrystalline cellulose	-	10.3	51.6	67.0
Magnesium stearate	1	1	1	1
Talc	1	1	1	1

Table 3: Formulation of the compression coated tablets

Materials	Percentage of materials used in Formulations (%w/w)			
	C1	C2	C3	C4
Eudragit S100	84.8	-	-	-
Shellac	-	84.8	-	-
HPMC E15 LV Pr.	-	-	84.8	-
HPMC K4M	-	-	-	84.8
Microcrystalline cellulose	12.7	12.7	12.7	12.7
Propylene glycol	1	1	1	1
PVP K30	0.5	0.5	0.5	0.5
Magnesium stearate	1	1	1	1

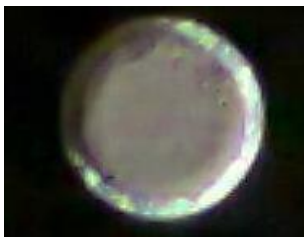

Fig. 1: Transverse section of compression coated tablet

Evaluation of Tablets:

Physical parameters:

The coated and core tablets were evaluated by several tests including weight, hardness, friability and content uniformity.

In-vitro drug release studies:

In-vitro drug release studies for core tablets:

Four batches of formulations were developed with Pectin, HPMC K4M, HPMC K15M and HPMC K100M and optimized to achieve drug release over a period of 12 hours. The dissolution studies were carried out in 900 ml of phosphate buffer pH 6.4 at 37±0.5°C for 12 hours at 100 rpm stirring speed in USP Dissolution apparatus 2.

In-vitro drug release studies for compression coated tablets for determination of lag times:

The four core tablets were compression coated with four different coating polymers and the lag times of drug release were tested in pH 1.2 HCl buffer for 2 hours and simultaneously in phosphate buffer pH 6.4 for 3 hours in USP Dissolution apparatus 2 at 100 rpm.

Table 4: Drug release of the core tablets

Time (HR.)	Formulations % Drug Release			
	F1	F2	F3	F4
0.25	4.187	2.917	4.163	4.514
0.5	7.328	3.943	6.925	4.972
1	17.149	7.346	12.77	7.521
2	36.598	14.628	23.589	12.476
3	57.738	26.161	33.063	17.498
4	72.743	36.166	41.125	21.223
5	83.552	51.576	50.116	24.68
6	93.257	61.319	55.267	33.991
7	90.343	72.281	62.236	40.677
9	85.167	82.954	69.552	55.598
10	85.814	82.521	72.406	58.594
11	85.493	83.19	77.605	68.672
12	82.898	81.902	78.752	77.564

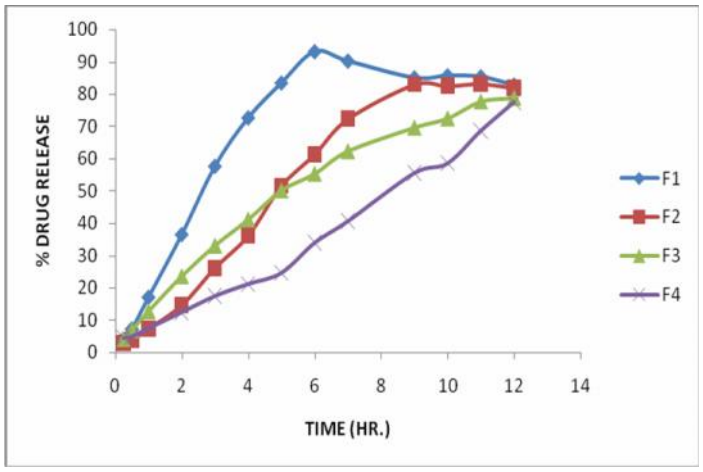

Fig. 2: Drug release profile of core tablets

RESULTS AND DISCUSSION:

The formulations of the core tablets were optimized to obtain sustained release of the drug over 12-18 hours. The formulations prepared with HPMC released about 75-80% of the drug in 12 hours, whereas the Pectin formulation released about 95% drug within 7 hours of dissolution. 60% w/w of HPMC K4M, 20% w/w HPMC K15M and 5% w/w of HPMC K100M gave equivalent drug release profiles and released about 75-80% drug in 12 hours. Table 4 and Figure 2 represent the drug release profile of the core tablets.

From the release studies of the compression coated tablets, the following observations were made.

- Eudragit S100 coated tablets: These tablets were not able to restrict drug release in the first 3 hours of dissolution. This may be due to the rapid erosion of the coatings due to low percentage of binder used. Of the four batches, the HPMC tablets performed better releasing about 6% drug in 2 hours and 25% drug in 3 hours.
- Shellac coated tablets: The tablets gave better drug release profiles than Eudragit S100 coated tablets. Shellac coated HPMC core tablets gave better release profiles of them, the best formulation being F2C2 releasing about 12.2 % drug in 3 hours.
- HPMC E15LV: The tablets gave better performance than the previous two batches of coated tablets. The best formulation among the four batches was F4C3, followed by F2C3, releasing 5.9% and 10.6% drug in 3 hours respectively.
- HPMC K4M coated tablets: HPMC K4M has higher viscosity (4000mPas)[15]than HPMC E15LV(15mPa s)[15] and therefore, these batches of formulations gave better release profile than HPMC E15LV coated tablets and the best release profile compared to all other formulation batches of coated tablets. The best formulation among the four batches was F4C4, followed by F2C4, followed by F3C4 and F1C4 releasing 2.8%, 3.1%, 9% and 11.8% drug in 3 hours of dissolution.

Observing the various batches of the coated formulations, it can be stated that the HPMC coated tablets performed better and the higher viscosity HPMC, that is, HPMC K4M gave the best release profiles. Of the two enteric polymers used for coating, shellac coated tablets gave better release profiles, having better compressibility than Eudragit S100.

The three best formulations which were able to fulfill the objectives of the study were F4C4, F2C4 and F4C3 cumulatively releasing 2.8%, 3.1% and 5.9% drug in first three hours of dissolution. The formulations were able to release 20% drug within 5 hours, after avoiding drug release in the first 3 hours of dissolution (no significant drug release in first three hours), indicating that the tablets would be able to resist drug release in the stomach, and upper parts of the small intestine and would selectively start releasing drug in the ileum. It further indicates that the compression coating has given way to the core tablet, which can now give sustained release for more than 12 hours. Therefore, the effective duration of drug release would range from 12-18 hours. Table 5 compares the release of the compression coated tablets and Table 6 elaborates the cumulative drug release after 2 and 3 hours of dissolution study of the coated tablets. Figures 3,4,5,and 6 represent the drug release profiles of the compression coated tablets.

Table 5: Drug release of compression coated tablets

TIME (HR.)	PERCENTAGE RELEASE OF FORMULATIONS (%)															
	F1C1	F2C1	F3C1	F4C1	F1C2	F2C2	F3C2	F4C2	F1C3	F2C3	F3C3	F4C3	F1C4	F2C4	F3C4	F4C4
0.5	3.8	1.7	1.3	1.2	1.8	0.9	1.4	0.87	0.76	0.2	0.6	0.43	0.4	0.3	0.5	0.3
1	4.1	1.5	2.2	1.4	2.9	1.3	2.1	1.3	2.05	1.4	0.42	0.15	0.3	0.2	0.4	0.2
2	7.6	2.6	3.4	2.2	4.8	2.1	3.2	2.5	21.4	1.9	7.7	1.6	2.5	0.4	2.6	0.4
3	28.3	25.2	13.1	18.7	35.4	7.9	16.5	19.5	38.2	7.1	16.3	3.8	8.6	2.2	5.8	1.9
4	41.7	39.9	17.8	20.5	39.0	10.8	17.1	18.9	53.9	18.1	25.2	10.2	22.5	11.4	12.8	9.0
5	51.1	48.4	20.3	21.3	42.6	11.8	22.2	17.5	57.7	30.0	36.1	16.9	33.5	20.2	18.1	18.1

Table 6: Cumulative drug release of compression coated tablets

TIME (HR.)	CUMULATIVE PERCENTAGE RELEASE OF FORMULATIONS (%)															
	F1C1	F2C1	F3C1	F4C1	F1C2	F2C2	F3C2	F4C2	F1C3	F2C3	F3C3	F4C3	F1C4	F2C4	F3C4	F4C4
AFTER 2 HR	15.5	5.8	6.9	4.8	9.5	4.3	6.7	4.67	24.21	3.5	8.72	2.15	3.2	0.9	3.5	0.9
AFTER 3 HR	43.8	31	20	23.5	44.9	12.2	23.2	24.17	62.41	10.6	25.02	5.95	11.8	3.1	9.1	2.8

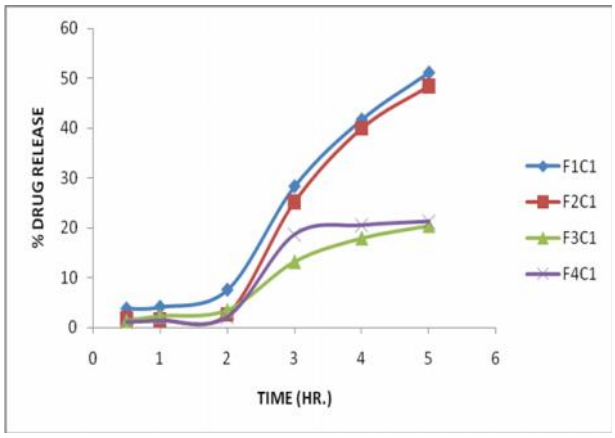

Fig. 3: Drug release profile of Eudragit S100 coated tablets

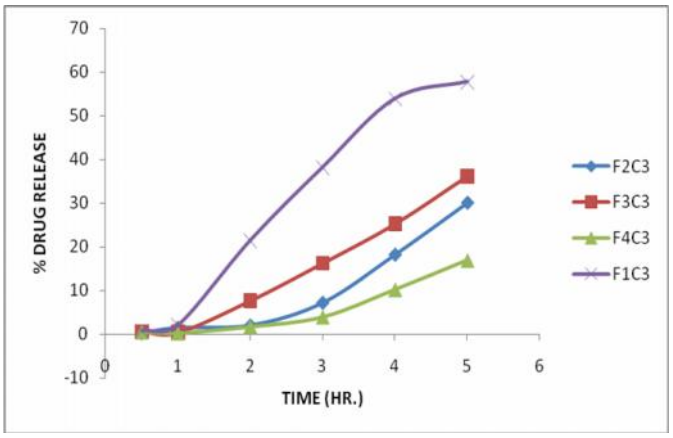

Fig. 5: Drug release profile of HPMC E15LV coated tablets

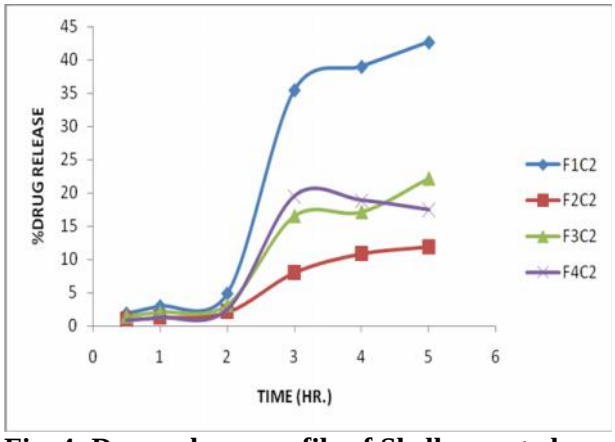

Fig. 4: Drug release profile of Shellac coated tablets

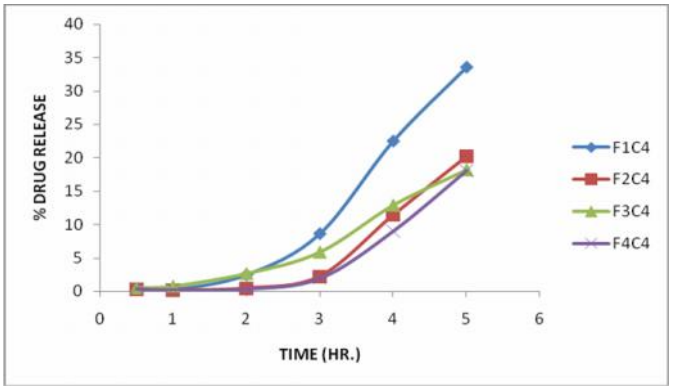

Fig. 6: Drug release profile of HPMC K4M coated tablets

CONCLUSION:

Among the developed formulations in the present study, three formulations were well able to satisfy the above-mentioned objectives, F4C4, F2C4 and F4C3, cumulatively releasing 2.8%, 3.1% and 5.9% drug in the first 3 hours and about 20% drug in the first 5 hours, and thereafter can sustain drug release for more than 12 hours. Therefore, they can be used to target the inflammatory bowel diseases affecting both the small and large intestines together.

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REFERENCES:

1. Gupta S., Bedi P.M.S. and Bedi N., Development and *in vitro* evaluation of eudragit RS100 and inulin coated pectin matrix tablets of 5-fluorouracil for colon targeting, Int. J. Appl. Pharma., 2010, 2(1), 1-6.
2. Krishnaiah Y.S.R., Satyanarayana V., Kumar B.D. and Karthikeyan R.S., *In vitro* drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil, Eur. J. Pharm. Sci., 2002, 16, 185-192.
3. Ravi V., Kumar T.M, Siddaramaiah, Novel Colon Targeted Drug Delivery System using natural Polymers, Indian J. Pharm. Sci. 2008, 70(1), 111-113.
4. Ravi V., Kumar T.M.P., Influence of natural polymer coating on novel colon targeted system, J. Mater. Sci.- Mater. Med., 2008, 19(5), 2131-2136.
5. Rhodes J., Evans B.K., Delayed release oral dosage forms for treatment of intestinal disorders, United States Patent, USS 5401512, 1995.
6. Siepmann J. et al., Novel polymeric film coatings for colon targeting: Drug release from coated pellets, Eur. J. Pharm. Sci. 2009, 37, 427-33.
7. Shivani N., Hetal P., Rajesh K., Murthy R.R., Colon delivery of 5-Fluorouracil using cross-linked chitosan microspheres coated with eudragit S 100, Int. J. Drug Del., 2011, 3, 260-268.
8. Lorenzo-Lamosa M.L, Remunan-Lopez C., Vila-Jato J.L, Alonso M.J., Design of microencapsulated chitosan microspheres for colonic drug delivery, J. Control. Release 1998, 52, 109-118.
9. Laroui H., Dalmasso G., Nguyen H.T, Yan Y., Sitaraman S.V, Merlin D., Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a mouse model, Gastroenterology, 2010, 138(3), 843-853.
10. Verma R.K, Krishna D.M, Garg S., Formulation aspects in the development of osmotically controlled oral drug delivery systems, J. Control. Release, 2002, 79, 7-27.
11. Shibata N. et al. Application of pressure-controlled colon delivery capsule to oral administration of glycyrrhizin in dogs. J. Pharm. Pharmacol. 2001, 53, 441-444.
12. Ehrlich A. B. and Schroeder C. L., Medical Terminology for Health Professions 5/e, Cengage Learning, Delmar, USA, 2004, 230.
13. Baumgart D. C. and Sandborn W. J., Chron's disease, The Lancet, 380 (9853), 1590-1605.
14. Wen H. and Park K., Introduction and overview of oral controlled release formulation design in: Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, John Wiley & Sons Inc., New Jersey, 2010, 3.
15. Rowe R.C., Sheskey P.J. and Quinn M.E., Handbook of Pharmaceutical Excipients, 6th ed., Pharmaceutical Press, London, U.K. and The American Pharmacists Association, Washington, USA, 2009, 328.

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