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Design and development of enteric and compression coated colonic tablets: an *in vitro* evaluation

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Abstract

Colon targeted delivery of metronidazole, which immediately releases the drug as soon as the drug delivery system reaches the colon was formulated for treatment of Crohn's Disease. To prepare colonic tablets the core tablets of metronidazole were first compression coated with time dependent polymer, PEO/ HPMC, and then with pH dependent polymer, Eudragit® S100. Swelling study concluded that PEO showed higher swelling capacity compared to HPMC. Metronidazole core tablets compression coated with 250 mg PEO (Polyox® 1105) and enteric coated with 6% w/w of Eudragit® S100 showed 100% drug release within 1 h after the delivery system reaches the colon.

Keywords: Crohn's disease, PEO, HPMC, swelling study

Introduction

During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. The colon is a site where both local and systemic drug delivery can take place (Bussemer et al. 2001). A local means of drug delivery could allow topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Treatment might be more effective if the drug substances are targeted directly to the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon (Yang et al. 2002).

Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity, much greater response to absorption enhancers, and the presence of large amounts of enzymes (e.g., b-D-glucosidase, b-D-galactosidase, amylase, pectinase, xylase, dextranase, etc.) for polysaccharides, which are secreted by a large number and variety of colonic bacteria (Sinha and Kumria 2001). Various systems have been developed for colon-specific drug delivery. These include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time dependent release systems, and enzymatically controlled delivery systems (Patel et al. 2007). Enteric coated systems are the most commonly used for

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colonic drug delivery, but the disadvantage of this system is that the pH difference between small intestine and colon is not being very definite. Thus, these delivery systems do not allow reproducible drug release. The limitation of time dependent release system is that it is not able to sense any variation in the upper gastro-intestinal tract transit time, any variation in gastric emptying time may lead to drug release in small intestine before arrival to colon. The microflora of the colon can split polymers. However, such enzymatic degradation is usually excessively slow. The bioavailabilities of drugs from such formulations can be low. In addition, little is known about the safety of the polymers and few have been accepted for use in relation to medicines. Apparently, the most convenient approach for site-specific drug delivery to colon is combining time and pH dependent system.

Compression-coating methodology has been used by some researchers for directing drugs to the colon (Sinha et al. 2004, Nunthanid et al. 2008). Compression-coated core tablet formulations are simple formulations to manufacture, and were used in this study.

The primary objective of the present study was to design Enteric and compression coated colonic tablets (ECCCT) consisting of both time and pH release system for oral colonic targeting. The ECCCT system used in this study composed of three components; a drug-containing core tablet (rapid release function), the compression-coated layer (timed-release function) and an enteric coating layer (acid resistance function). The ECCCT system was fabricated in such a fashion that it provides maximum drug release in colon as soon as the system reaches colon. Timed release function in ECCCT was imparted by using hydrophilic polymers like hydroxypropyl methylcellusose (HPMC) or polyethylene oxide (PEO) of different viscosity and molecular weight. Acid resistance function was provided by Eudragit® S 100. The pictorial representation of the ECCCT system is shown in Fig. 1.

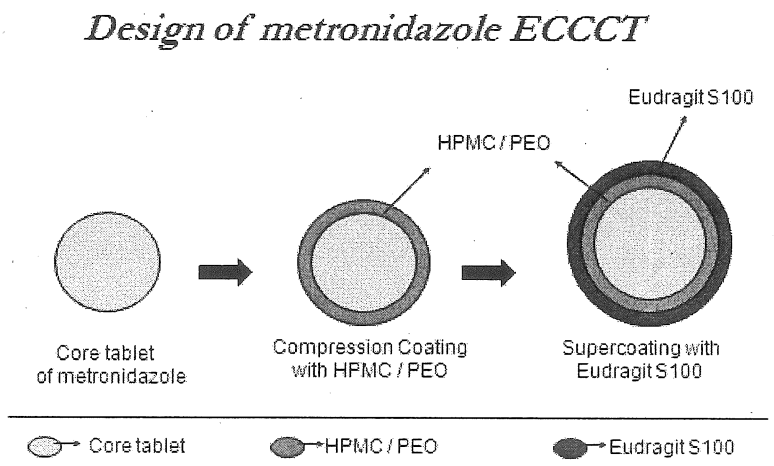

Figure 1. Design of metronidazole ECCCT

Hydrophilic polymers such as PEO and HPMC are dominant matrix excipients for most modified release tablet preparations (Kim 1998, Razaghi and Schwartz 2002, Choi et al. 2003). Once in contact with a liquid, these polymers would hydrate and swell, forming a hydrogel layer that regulates further penetration of the liquid into tablet and dissolution of the drug from within (Colombo et al. 2000). As contact time of a polymer with the liquid increases, it would take

more time for drug to diffuse out of the core, since the diffusion path is lengthened by polymer swelling.

In matrix systems either swelling or dissolution can be the predominant factor for a specific type of polymer (Sujja-areevath et al. 1998), in most cases drug release kinetics is a result of a combination of these two mechanisms (Efentakis and Buckton 2002). But in case of compression-coated systems consisting of hydrophilic polymer we expected polymer swelling and erosion can be the main mechanism for drug release. The second objective of the study was to compare the erosion and swelling behavior of two different hydrophilic polymers hydroxypropyl methylcellusose (HPMC) and polyethylene oxide (PEO) of different viscosity and molecular weight.

The ECCCT does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves, and the intestinal fluid begins to slowly swell the compression-coated hydrophilic polymer layer, and when the erosion front reaches the core tablet, rapid drug release occurs. The duration of lag phase can be controlled either by the weight or composition of the hydrophilic polymer layer. Therefore, the intestinal transit time of dosage forms after gastric emptying is rather constant, such systems can deliver drugs to the desired site in the colon. Lag time of the system to reach colon is basically controlled by swelling and erosion property of compression-coated hydrophilic polymer layer. In the present study, lag time to reach small intestine was taken as 2 h and lag time to reach colon was taken as 5 h.

Materials and Methods

Materials

Metronidazole was obtained as a gift sample from J. B. Chemicals, India. Eudragit® S100 was generously gifted by Rohm Pharma, Germany. Polyvinyl Pyrollidone K90 (PVP K90) was gifted from Anshul Agencies, India. Methocel® (HPMC) and Polyox® (PEO) were kindly gifted by Colorcon, India. Crosscarmellose Sodium was obtained as a gift sample from Gujarat Microwax Pvt. Ltd., India. Polyvinyl pyrrollidone K30 (PVP K30) and lactose were purchased from S.D. Fine-Chem Ltd., India and CDH, India, respectively. Double distilled water was used throughout the study and all other chemicals used were of analytical reagent grade.

Preparation of core tablets of metronidazole

Weighed quantity of metronidazole (200 mg/tablet), lactose (diluent) and Cross-carmellose sodium (5%) were passed through 30# sieve. Both the ingredients were mixed for 15 min in bin blender (Tapasya Engineering, India). Binder solution consisting of equal quantities of PVP K30 and PVP K90 (5%) in isopropyl alcohol (IPA) was prepared on a magnetic stirrer. Binding solution was added to the above blend to prepare a dough mass. The dough mass was forced though 16# sieve and the granules so obtained were dried at 40 ± 5°C in a tray dryer (USICO, India) till LOD reaches between 3 to 4. The dried granules were passed through 24# sieve. Talc (2%) and magnesium stearate (1%) were sifted through 40# sieve. The dried granules were lubricated with talc and magnesium stearate for 5 min. The lubricated granules were compressed into tablets weighing 400 mg using rotary tablet machine (Rimek, Karnavati Engineering Pvt. Ltd., India) using 11 mm concave punch. The core tablets were tested for hardness, thickness, content uniformity, friability, and disintegration.

Preparation of compression-coated tablets

After confirming compliance with the above mentioned tests, the core tablets were compression coated with different coat powders of HPMC and PEO. Exactly 50% of the coat powder was first placed in the die cavity of the compression machine. Then, the core tablet was carefully positioned at the center of the die cavity, which was filled with the remainder of the coat powder. It was then compressed around the core tablets by using 13-mm concave punches. Two different grades of HPMC (Methocel® E15, Methocel® K4M) were tried individually and in combination (Table 1) for compression coating.

Table 1. HPMC used as a compression coat

Batch No.	HPMC K4M (mg)	HPMC E15 (mg)
K1	150	-
K2	200	-
K3	250	-
E1	-	200
E2	-	300
HE1	100	100
HE2	75	125
HE3	50	150
HE4	25	175
HE5	12	187.5

Five different grades of PEO (Polyox® WSR N-80, WSR N-750, WSR 1105, WSR 301, WSR 303) of different molecular weights were tried at different weights as shown in Table 2. The compression-coated metronidazole tablets were then evaluated for drug content, hardness, friability, thickness, and drug release.

Table 2. Different types of Polyox® (PEO) used as a compression coat

Sr. No.	Polyox® Grade	Molecular Weight (Daltons)	Batch No.	Compression coat weight (mg)
1	WSR N-80	2,00,000	PN1	200
			PN2	250
			PN3	300
2	WSR N-750	3,00,000	PN4	200
			PN5	250
3	WSR 1105	9,00,000	PN6	200
			PN7	225
			PN8	250
4	WSR 301	40,00,000	PN9	200
5	WSR 303	70,00,000	PN10	200

Preparation of coating solution and coating of core tablets

The coating solution was prepared by dissolving Eudragit® S100 (10%w/v) in acetone:isopropyl alcohol (IPA) using a magnetic stirrer at 50 rpm. After complete solubilization of polymer, 4% w/v of dibutyl phthalate (plasticizer) was added to the coating solution. The solution was stirred for 15 min. Talc (25% w/w of polymer content) was added to the coating process. Coating was carried out in pan coater (Neocota Minimax, India). The tablets were loaded in the pan and warmed to achieve product temperature of 38°C. 20 tablets were sampled and their average weight was taken. Coating process was set with inlet temperature of 45°C, Exhaust at 35°C, Spray rate at 9 g/min and pan rpm of 20. Spraying was continued till desired weight gain was obtained. Weight gain was calculated on dry average tablet weight basis.

Preparation of enteric coated time dependent compression-coated tablets

Enteric coated time dependent compression-coated tablets (ECCCT) were prepared by first applying compression-coating on core tablets with either HPMC or PEO. Above this coat an enteric coat of Eudragit® S coating was applied. Eudragit® S was tried at different coating levels. Coating level was calculated in terms of % weight gain on core tablet weight basis.

Table 3. ECCCT batches

Batch No.	Compression coat Batch	Enteric Coat (% w/w)
KE6	HE5	5.0
KE7	HE5	7.5
KE8	HE5	10.0
KE9	HE5	12.5
KE10	HE5	15.0
KE11	HE4	5.0
PS1	PN6	10.0
PS2	PN7	10.0
PS3	PN8	6.0
PS4	PN8	7.5

In vitro drug release studies

In vitro drug release studies were carried out using USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm/min, 37 ± 0.5°C). The time dependent compression-coated tablets were evaluated by exposing them to 900 mL pH 7.4 phosphate buffer solution (simulated intestinal fluid, SIF) for 3 h, which was later replaced by 900 mL pH 6.8 phosphate buffer solution (simulated colonic fluid, SCF), and tested for release for the rest of the dissolution run.

ECCCT were evaluated by keeping them in 900 mL 0.1 N HCl (simulated gastric fluid, SGF) for 2 h, which was then replaced with 900 mL SIF wherein it was kept for 3 h and lastly SIF was replaced with 900 mL SCF for the rest of the dissolution run. The drug release at different time intervals was analyzed by UV double beam spectrophotometer (Shimadzu UV 1601, Japan) at 276.5 nm in SGF, 319.4 nm in SIF and 320.4 nm in SCF. Each test was performed in triplicate.

Swelling study

Swelling studies were performed using a modification of a previously described method (Ebube et al. 1997). Briefly, initial diameter and height of individual matrices were measured and were placed in a dissolution medium (phosphate buffer pH 6.8) at 37 ± 0.5°C in the manner similar to *in vitro* drug release study. Swollen/hydrated tablets were withdrawn from the medium at the end of the dissolution run, extra buffer present on the matrix surface was gently wiped with the soft tissue, and individual diameter and height were measured at the end of the study. Percent of the radial (diameter) and axial (height) swelling of tablet was calculated according to the following formula:

$$\text{Radial swelling (\%)} = \frac{\text{swollen diameter} - \text{original diameter}}{\text{original diameter}} \times 100$$

$$\text{Axial swelling (\%)} = \frac{\text{swollen thickness} - \text{original thickness}}{\text{original thickness}} \times 100$$

Swollen thickness and diameter in this work reflects the entirely free axial and radial swelling of the matrix without any constraint imposed on the swelling. This approach is entirely novel and different to the visually observed swelling reported by some authors where thin discs of pure polymers are sandwiched between two Plexiglas plates and radial expansion of the constrained discs are investigated (Colombo et al. 1999, Bettini et al. 2001).

Stability Study

Optimized formulations of metronidazole were packed in 75 mL HDPE bottles. The packed formulations were placed in a controlled temperature cabinet maintained at 40 ± 2°C and 75 ± 5 %RH for 3 months in order to perform the accelerated stability test. The samples were withdrawn at the end of each month and evaluated for changes in physical appearance, drug content, hardness and *in vitro* drug release studies.

Results and Discussion

Core tablets

The aim of the present investigation was to release the drug as soon as it reaches colon. Thus, core tablets of metronidazole were prepared with the aim of having disintegration time (D.T.) lower than 5 min. The optimized batch containing 5% cross carmellose sodium showed D.T. of 4 min with 100% drug being released in 12 min. The tablets hardness was found between 4.2 to 6.4 kp, and the friability of these tablets was 0.12%. The assay was found between 97.2 to 103.7%.

Compression-coated tablets

Compression coating was performed using two different polymers HPMC and PEO. Two different viscosity grades of HPMC were tried, HPMC K4M having higher viscosity (4000 cp) and HPMC E15 having lower viscosity (15 cp). HPMC K4M even when used at lower compression coat weight of 150 mg (Batch K1) showed only 12.94% release after 480 min, whereas HPMC E15 even when used at compression coat weight as high as of 300 mg (Batch E2), showed 100% drug release within 180 min (Fig. 2).

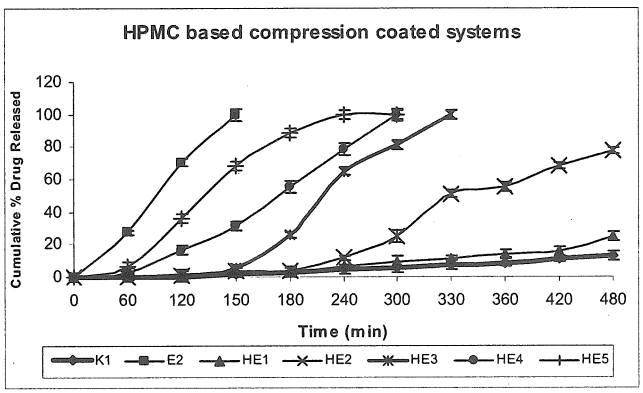

Figure 2. HPMC based compression coated systems (data shown as mean ± SD, n=3)

Thus, combination of HPMC K4M and E15 was tried in order to achieve desired lag time and drug release profile. Different combinations of HPMC K4M:E15 tried at 200 mg compression coat weight are given in Table 1. Of the different combinations, only Batch HE1 and HE2 consisting of HPMC K4M:E15 in the ratio of 100:100 mg and 75:125 mg respectively, cannot be used for further studies since only about 25 and 77% drug released at the end of 480 min. From the Fig. 2, it can be concluded that in the combination of two HPMC, as the proportion of HPMC K4M decreases drug releases faster. For HPMC based system Batch HE4 and HE5 were used for preparation of ECCCT.

In order to increase the sustainability of the compression coated tablet other hydrophilic polymer PEO was tried. Different grades of Polyox® (PEO) having different molecular weights were tried at different compression coating weight (Table 2). From the preliminary trials it was found that as the compression coat weight increases drug release delayed. Polyox® WSR 301 and 303 at compression coat weights of 150 mg exhibited extensive drug delay, where less than 5% drug released even after 18 h. Moreover, the tablets adhered to the dissolution vessel and thus it was not used for further studies. Batch PN3 and PN5 in which core tablets were compression coated with Polyox® N-80 and N-750 at 300 and 250 mg respectively, showed premature drug release. Fig. 3 compares the release profile of different grades of Polyox® (WSR N-80, WSR N-750, WSR 1105).

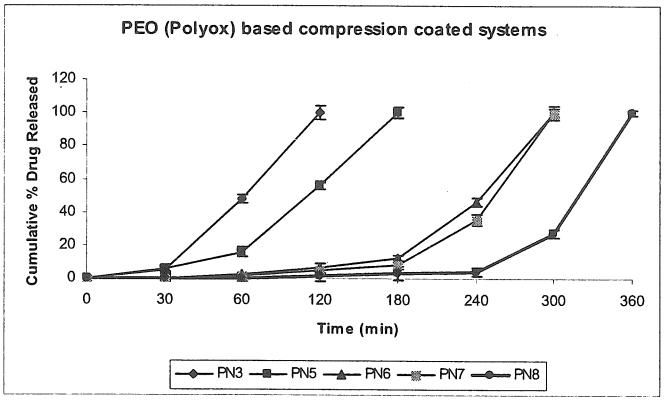

Figure 3. PEO (Polyox®) based compression coated systems (data shown as mean ± SD, n=3)

As expected, it was found that as the molecular weight of Polyox® increases drug release delay increases (refer Fig. 3). Of the different grades tried, for surprise it was found that Polyox® 1105 gave burst release after specific lag times. For batch PN8 it was found that only 27.37% drug released till 300 min and at 360 min 100% drug released. It was found that till 300 min gel was intact whereas after 360 min gel completely ruptured after swelling. This indicates that as the molecular weight of Polyox® (PEO) increases, its swelling capacity increases which finally results in erosion of the layer and complete release of the drug. For PEO based system Batch PN6, PN7 and PN8 were considered for further preparation of ECCCT.

In general it can be said that the lag time imparted to the compression coat system is dependent on both polymer viscosity and compression coat weight.

Colonic tablets

In order to direct drug to the colon there was a need to provide some additional coat on compression coated tablets since compression coated tablets alone were unable to meet the desired criteria of preventing drug release till 5 h, which is lag time to reach colon, and provide 100% drug release as the system reaches the colon. Additional coat of Eudragit® S100 was provided on compression tablets prepared using HPMC and Polyox®.

From the earlier results it was concluded that HPMC K4M and HPMC E15 cannot be used alone since HPMC K4M delays the release excessively, whereas HPMC E15 causes premature release of the drug. In addition, combination of HPMC K4M and E15 favorable ratios are HPMC

K4M:E15, 25:175 mg (HE4) and 12.5:187.5 mg (HE5). Eudragit® S 100 was coated at different coating levels varying from 5 to 15% w/w. Initial trials indicated that even 5% coating level on batch HE4 delayed drug release to more than 8 h and thus did not fit our criteria, since our aim was to have immediate release of drug as soon as the system reaches the colon. Batch KE6 containing HPMC K4M:E15 in the ratio of 12.5:187.5 mg (Batch HE5) as a compression coat and supercoated with Eudragit® at 5% coating level exhibited 100% drug release within 5 h, thus showed premature release. From the different batches shown in Figure 4, Batch KE8 compression coated using HPMC K4M:E15::12.5:187.5 mg and supercoated at 10% Eudragit® S coating level met the criteria of delaying drug release till the drug reaches colon (8.2% at the end of 300 min) and releasing almost 100% drug within 1 h after it reaches the colon. Thus, Batch KE8 can be considered as best batch prepared using HPMC and Eudragit® S100.

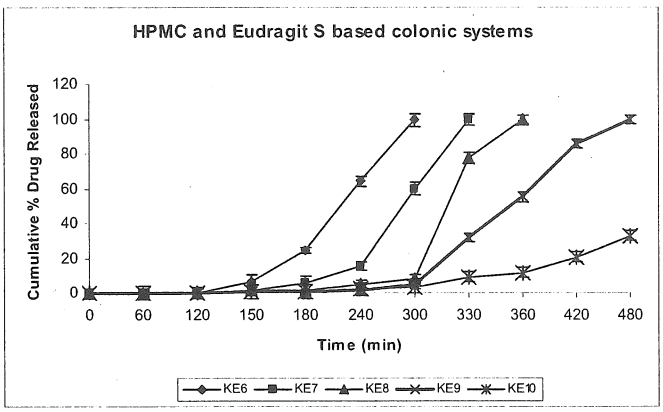

Figure 4. HPMC and Eudragit® S based colonic systems (data shown as mean ± SD, n=3)

From the compression coating study using Polyox® it was found that only Polyox® WSR 1105 was found to be suitable for providing time dependent release. Different combinations were tried with Polyox® 1105 as inner compression coat and Eudragit® S 100 as outer enteric coat. Batch PS1 and PS2 containing batch PN6 (200 mg) and PN7 (225 mg) as compression coated tablet, when coated at 10% coating level of Eudragit® S show delayed release after the system reaches colon. For both PS1 and PS2, after 300 min when the system enters colon it takes another 3 h to achieve 100% release, whereas batch PS3 containing 250 mg Polyox® 1105 and 6% Eudragit® S showed only 5.57% release till 300 min and 100% release in 360 min, indicating 100% drug release in colon within 1 h after system reaches colon (Fig. 5). Thus, Batch PS3 meets the desired criteria.

It can be concluded that Eudragit® S is responsible for delayed release of drug since higher coating levels of Eudragit® will require more time to dissolve and rupture in intestine. Also at higher coating levels of Eudragit® S, amount of fluid penetrating the compression coated system will be less in initial phase after the system reaches the intestine.

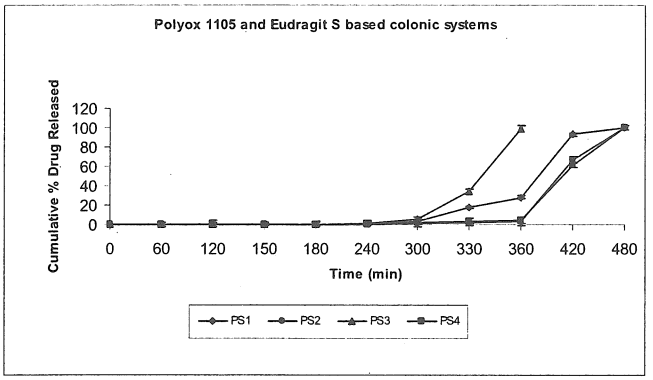

Figure 5. Polyox® 1105 and Eudragit® S based colonic systems (data shown as mean ± SD, n=3)

Swelling study

Swelling study was performed for both, only compression coated tablets and ECCCT. Measurement of swelling/hydration rates of different tablets were carried out to gain insight into the observed phenomena of drug release from the tablets. Results of axial and radial expansion for batch K1, E2 and HE5 and PN8 are enumerated in Table 4 and the photographs at different time intervals are presented in Fig. 6(A).

Table 4. % axial and radial swelling

Batch Code	% Axial Swelling	% Radial Swelling
K1	29.26	50.00
E2	23.07	23.84
HE5	26.66	46.15
PN8	37.50	61.50
PS3	31.70	56.06

From Table 4 it is clear that % axial and radial swelling of Polyox® (PN8) was higher, 37.5 and 61.5% respectively, compared to HPMC (HE5), 26.66 and 46.15% respectively, which reflects faster erosion property of Polyox®. Swelling study results characteristically complement *in vitro* release study data. On comparing Batch K3 and PN5 both of which are having nearly similar viscosities and compression coated at similar coating levels of 250 mg each, it was observed that Batch PN5 showed 100% drug release within 3 h whereas Batch K3 showed only 8% drug release after 8 h. Thus, it was concluded that PEO swell and erode faster whereas HPMC have a slower swelling property. In general, it can be said that PEO has a lower gel strength compared to HPMC. PEO does not retain the gel structure formed after swelling, for a longer time, as long as HPMC does.

Compared to batch E2, batch K1 showed higher swelling since batch K1 contains HPMC K4M having higher viscosity compared to HPMC E15 having lower viscosity. Thus, it can be concluded that as the viscosity of the polymer increases gel strength increases and thus erosion is prolonged.

In the swelling study, it was found that terminal radial/axial swelling was less steep because the diffusion path length and distance to be traveled for dissolution media to reach the dry core increases with time. Fig. 6(B) depicts photographs at different time interval for PS3. From the

Fig. 6(B) it can be concluded that after the system reaches intestine the outer coat of Eudragit® S starts dissolving. The compression coat system made from hydrophilic polymer swells and forms a hydrogel layer when they are placed in an aqueous medium. With the diffusion of medium into the polymer a hydrogel layer forms. As soon as the compression coat comes in contact with the dissolution fluid, the system starts swelling and the drug is released from the system after it completely ruptures. Thus, it can be concluded that swelling and erosion are dominant release mechanism compared to diffusion.

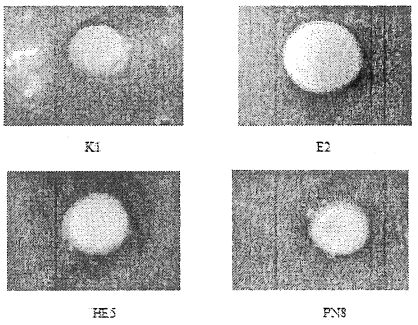

Figure 6(A). Swelling study using HPMC and PEO

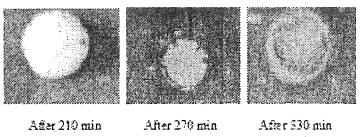

Figure 6(B). Swelling study for Batch PS3

Stability Study

Physical appearance of the all the stability Batches of PS3 was similar to the fresh batch. Hardness of the batch varied from 13.65 to 17.8 kp. Drug content varied from 97.9 to 102.3%.

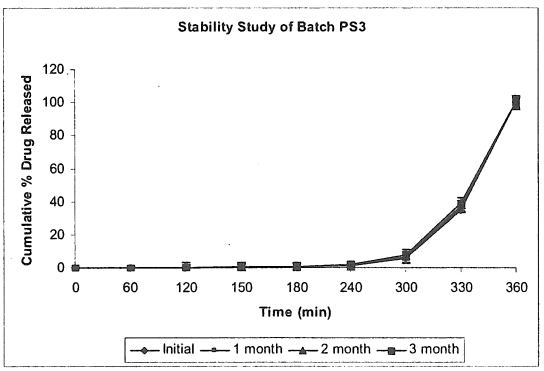

Figure 7. Stability study of batch PS3 (data shown as mean ± SD, n=3)

There was no substantial change in *in vitro* drug release profile between all the stability batches (Fig. 7). Thus, Batch PS3 was considered as the best batch prepared by ECCCT.

Conclusion

Colonic drug delivery systems prepared using ECCCT technique can be successfully used to deliver drug to the colon. Both HPMC and PEO can be used as a compression coat. However, for HPMC based system, selection of appropriate viscosity grade will play an important role

since in present study combination of two different viscosity grades, HPMC K4M (4000cp) and E15 (15cp) was used to fabricate ECCCT. From the formulation aspect at larger scale it will be preferable to have a single polymer having desired viscosity.

Whereas, PEO showed efficient release profile using Polyox® WSR 1105. Erosion behavior is faster for Polyox®, compared to HPMC. Thus, colonic tablets prepared using PEO show faster release after the system reaches colon. Thus, ECCCT prepared using PEO as a compression coat and Eudragit® S100 as an enteric coat can be used in acute treatment of Crohn's disease.

References

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A. and Colombo, P. (2001). Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. *J. Control. Release* 70: 383–391.

Bussemer, T., Otto, I. and Bodmeier, R. (2001). Pulsatile drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* 18: 433– 458.

Choi, S.U., Lee and J., Choi, Y.W. (2003). Development of a directly compressible poly (ethylene oxide) matrix for the sustained-release of dihydrocodeine bitartrate. *Drug Dev. Ind. Pharm.* 29: 1045–1052.

Colombo, P., Bettini, R. and Peppas, N.A. (1999). Observation of swelling process and diffusion front position during swelling in hydroxypropylmethylcellulose (HPMC) matrices containing a soluble drug. *J. Control. Release* 61: 83–91.

Colombo, P., Bettini, R., Santi, P. and Peppas, N.A. (2000). Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. *Pharm. Sci. Technol. Today.* 3: 198–204.

Ebube, N.K., Hikal, A.H., Wyandt, C.M., Beer, D.C., Miller, L.G. and Jones, A.B. (1997). Sustained release of acetaminophen from heterogeneous matrix tablets: influence of polymer ratio, polymer loading, and co-active on drug release. *Pharm. Dev. Technol.* 2: 161–170.

Efentakis, M. and Buckton, G. (2002). The effect of erosion and swelling on the dissolution of theophylline from low and high viscosity sodium alginate matrices. *Pharm. Dev. Technol.* 7: 69–77.

Kim, C.J. (1998). Effects of drug solubility, drug loading, and polymer molecular weight on drug release from Polyox® tablets. *Drug Dev. Ind. Pharm.* 24: 645–651.

Nunthanid, J., Huanbutta, K., Luangtana-anan, M., Sriamornsak, P. Limmatvapirat, S., Puttipipatkhachorn, S. (2008). Development of time-, pH-, and enzyme-controlled colonic drug delivery using spray-dried chitosan acetate and hydroxypropyl methylcellulose. *Eur. J. Pharm. Biopharm.* 68: 253–259.

Patel, M., Shah, T. and Amin, A. (2007). Therapeutic opportunities in colon-specific drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* 24: 147–202.

Razaghi, A.M. and Schwartz, J.B. (2002). Investigation of cyclobenzaprine hydrochloride release from oral osmotic delivery systems containing a water swellable polymer. *Drug Dev. Ind. Pharm.* 28: 631–639.

Sinha, V.R. and Kumria, R. (2001). Polysaccharides in colon-specific drug delivery. *Int. J. Pharm.* 224: 19–38.

Sinha, V.R., Mittal, B.R., Bhutani, K.K., Kumria, R. (2004). Colonic drug delivery of 5-fluorouracil: an *in vitro* evaluation. *Int. J. Pharm.* 269: 101–108.

Sujja-areevath, J., Munday, D.L., Cox, P.J. and Khan, K.A. (1998). Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. *Eur. J. Pharm. Sci.* 6: 207– 217.

Yang, L., Chu, J.S. and Fix J.A. (2002). Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. *Int. J. Pharm.* 235:1–15.

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