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Research paper

Microporous bilayer osmotic tablet for colon-specific delivery

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ABSTRACT

Microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium was developed using a new oral drug delivery system for colon targeting. The tablets were coated with microporous semipermeable membrane and enteric polymer using conventional pan-coating process. The developed microporous bilayer osmotic pump tablet (OPT) did not require laser drilling to form the drug delivery orifice. The colon-specific biodegradation of pectin could form in situ delivery pores for drug release. The effect of formulation variables like inclusion of osmogen, amount of HPMC and NaCMC in core, amount of pore former in semipermeable membrane was studied. Scanning electron microscopic photographs showed formation of in situ delivery pores after predetermined time of coming in contact with dissolution medium. The number of pores was dependent on the amount of the pore former in the semipermeable membrane. *In vitro* dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h. The developed tablets could be effectively used for colon-specific drug delivery to treat IBS.

1. Introduction

The colonic region of the gastrointestinal tract is one area that would benefit from the development and use of modified release technologies. The colon is vulnerable to a number of disorders including ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS) and carcinomas. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower dosing rate and reduce systemic side effects [1]. IBS is a mild intestinal chronic disorder highly associated with abdominal pain, altered bowel motility resulting in either diarrhea or obstipation, and an increase in visceral hypersensitivity and visceral pain [2]. Although IBS is not a life-threatening illness [3], the subjective nature of IBS diagnosis presents special challenges for both clinicians and researchers [4]. With regard to specific IBS symptoms, women with IBS are more likely to report problems with constipation, while men more commonly report diarrhea. Epidemiological studies have demonstrated that women with IBS are at higher risk of abdominal surgery including hysterectomy [5].

There is currently no universally effective therapy for IBS. Standard therapy generally involves a symptom-directed approach: anti-diarrheal agent for bowel frequency, soluble fiber or laxative for constipation, and smooth muscle relaxants and anti-spasmodic for pain [6]. Anti-spasmodic drugs have traditionally formed the basis of treating IBS. Dicyclomine hydrochloride, an anti-cholinergic drug, has direct smooth muscle relaxant action, in addition being weak anti-cholinergic, and exerts anti-spasmodic action [7].

The bilayer-core osmotic pump tablet had several advantages, including (a) suitability for delivering water-insoluble drugs; (b) release profile much closer to zero order, higher cumulative release [8]. In addition, tablets such as bilayered tablets and even triple-layered tablets have been developed to achieve controlled drug delivery with predefined release profile for different active ingredients [9].

The bilayer system is a unique drug delivery device, which overcomes the major disadvantage of non-linear release associated with most diffusion-controlled matrix devices. This system also has the advantage of being compatible with conventional manufacturing methods [10].

Drug delivery systems for treating the colonic disorders such as IBS are failing as the drugs do not reach the site of action in appropriate concentration. Thus, there is a need to develop effective and safe therapy for the treatment of these colonic disorders, using site-specific drug delivery approach. However, development of such system is a challenging task to the pharmaceutical technologists.

The available conventional dosage forms are not very effective in the treatment of these colonic diseases as dosing frequency is quite high which leads to many adverse effects.

The aim of this work was to design and characterize a microporous bilayer-core osmotic tablet for colon-specific delivery, which can reach intact to the site of action and could deliver drug at

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constant rate for 24 h. Such system was expected to be helpful in reducing the dosing frequency and side effects, thus increasing the patient compliance.

2. Materials and methods

2.1. Materials

Dicyclomine hydrochloride and diclofenac potassium were purchased from Jackson laboratories Pvt. Ltd. (Amritsar, India). Microcrystalline cellulose, (MCC) mannitol, PVP K-30 and magnesium stearate were purchased from Central drug house (P) Ltd. (New Delhi, India). Cellulose acetate (CA) (acetic acid content 53.5–56%) was purchased from Qualikems fine chemicals Pvt. Ltd. (New Delhi, India). Triethyl citrate (bp 235 °C/150 mm Hg; d 1.14), hydroxy propyl methyl cellulose (HPMC) (100,000 cps, viscosity 2 wt% in water) and carboxy methyl cellulose sodium (NaCMC—medium viscosity 400–800 cps) were purchased from Sigma–Aldrich (USA). Pectin from citrus fruits and pectinase from Aspergillus aculeatus were procured from Sigma–Aldrich (Denmark). Eudragit l-100 was a gift sample from Degussa (Germany). Sunset yellow lake (colour) was obtained as gift sample from Cadila Pharmaceutical Ltd. (Jammu, India). Solvents of reagent grade and bidistilled water were used in all experiments.

2.2. Methods

2.2.1. Drug analysis

Colorimetric assay method for dicyclomine hydrochloride using bromocresol green [11] and spectrophotometric method for determination of diclofenac potassium [12] were used. The calibration curve of dicyclomine hydrochloride ($y = 0.0123x$) was linear between 10 μg/ml and 80 μg/ml ($r^2 = 0.9991$). The calibration curve of diclofenac potassium ($y = 0.0309x$) was linear between 1 μg/ml and 30 μg/ml ($r^2 = 0.9993$). The drug content of the formulation and the amount of the drug released in dissolution fluids were determined (with appropriate dilution) by using calibration curves.

2.2.2. Granulation and tablet compression

The granules were prepared by wet granulation method. The granules were prepared separately for both the layers. The ingredients (Table 1) were passed through sieve #40 and mixed. PVP K-30 (10% w/v) in isopropyl alcohol was used as binder. The wet mass was passed through sieve #20. The resultant granules were dried at 45 °C for 4 h. Dry granules were lubricated with magnesium stearate (1% w/w). Bilayered tablets were prepared by double compression method. First, the die cavity was adjusted to required weight of lower layer followed by its compression. This compressed lower layer was again placed into the die cavity, adjusted for required weight of upper layer and compressed to produce two-layered tablet [13]. The average hardness of compressed tablets was found to be 6.5 ± 0.70 kg/cm^2, while the average thickness was found 2.912 ± 0.396 mm.

2.2.3. Coating

Three coating solutions of cellulose acetate in acetone containing different levels of pore-forming agent i.e., pectin (10% w/v, 20% w/v and 30% w/v) were prepared for semipermeable membrane coating [14]. The compositions of coating solutions are given in Table 2. Triethyl citrate (2% w/w of total weight of coating materials) was added as plasticizer. Different levels of enteric coating materials Eudragit L-100-55 (8% w/v, 6% w/v and 4% w/v) in isopropyl alcohol and acetone were prepared. Triethyl citrate (1.5% w/w of total coating materials) was added as plasticizer [15]. The compositions of coating solutions are given in Table 3. The coating was carried out by pan coater (Macro Scientific works (R), New Delhi, India), having diameter of 50 cm. The rotating speed was kept at 30 rpm. The coating solution was sprayed with the help of air-less spray gun (Manik Radiators Pvt. Ltd., Mumbai) at a fixed rate of 3 ml/min. The coated tablets were dried at 50 °C for 4 h. The average thickness and average weight gain of the tablet after microporous semipermeable membrane coating (Fig. 1) were found to be 3.135 ± 0.0372 mm and 7.11 ± 0.0488%, respectively. The average thickness and average weight gain of the tablet after enteric coating were found to be 3.382 ± 0.0567 mm and 13.89 ± 0.0532%, respectively.

2.2.4. In vitro dissolution

Dissolution studies were carried out using USP XXV (basket method) dissolution test apparatus (Electro lab TDT-08L). The rotation speed of basket was kept at 100 rpm, and the temperature was maintained at 37.5 ± 0.5 °C. Four-step dissolution test was carried out to simulate the physiological condition of GIT and to obtain colon-specific delivery. The dissolution media consisted of simulated

Table 2
Compositions of coating solutions used for different formulations.

Coating composition	Coating code (s)		
	O1	O2	O3
Cellulose acetate (gm)	1.8	2.2	2.6
Pectin (gm)	1.2	0.8	0.4
Triethyl citrate (ml)	2	2	2
Acetone (ml) q.s.	100	100	100

Table 3
Compositions of different enteric coating solutions.

Coating composition	Coating code		
	E1	E2	E3
Eudragit L-100 (gm)	15.5	11.5	7.5
Titanium dioxide (gm)	2.0	2.0	2.0
Colour (gm)	0.50	0.50	0.50
IPA (ml)	104	104	104
Acetone (ml)	75	80	84
Triethyl citrate (ml)	3	3	3

Table 1
Content of core formulation.

Ingredients	Formulation									
	Dicyclomine hydrochloride					Diclofenac potassium				
	FDH 1 (mg)	FDH 2 (mg)	FDH 3 (mg)	FDH 4 (mg)	FDH 5 (mg)	FDP 1 (mg)	FDP 2 (mg)	FDP 3 (mg)	FDP 4 (mg)	FDP 5 (mg)
Drug	50	50	50	50	50	100	100	100	100	100
MCC	–	75	88	95	80	–	152	178	192	160
Mannitol	96	22	5	–	14	194	44	10	–	30
HPMC + NaCMC	1	-	5	3	4	2	–	10	6	8
Sunset yellow lake	1	1	1	1	1	–	–	–	–	–
Magnesium stearate	2	2	1	1	1	4	4	2	2	2

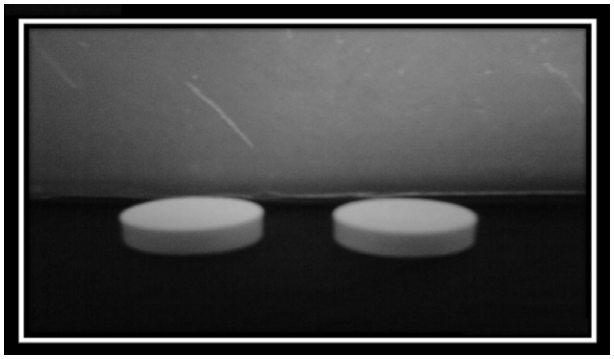

Fig. 1. Bilayer tablet after coating of microporous semipermeable membrane.

gastric fluid of pH 1.2 for 1st hour, mixture of simulated gastric and intestinal fluid of pH 4.5 for 2nd and 3rd hours, simulated intestinal fluid of pH 6.8 for 4th and 5th hours, and simulated intestinal fluid of pH 7.5 for subsequent hours. Aliquots of dissolution fluid were removed at every hour and assayed for dicyclomine hydrochloride and diclofenac potassium by UV–visible spectrophotometer (Shimadzu 1700) λmax of 420 nm and 285 nm, respectively [16].

2.2.5. Scanning electron microscopy

Coated tablets (with varying pectin concentration) obtained before and after complete dissolution were examined for their surface morphology by scanning electron microscopy (Leo Electron microscopy Ltd.). The tablets were dried at 50 °C for 6 h and stored between sheets of wax paper in dessicator. The samples were coated with gold palladium for 120 s and examined under scanning electron microscopy [13].

2.2.6. Release models and kinetics

Generally, the release of drug from oral osmotic systems is controlled by various factors such as osmotic pressure, aperture diameter, coating thickness, permeability of membrane, solubility of drug pore-forming agent, etc. The *in vitro* release from system F2O2 (which did not contain any polymer) showed comparatively fast release of drug ($t_{80\%}$ in 8 h) then the formulations containing polymer. Release kinetics of drugs for the formulations (F5O2E1, F5O2E2 and F5O2E3) were determined utilizing various mathematical equations [17].

2.2.7. Stability studies

To assess stability of the drug and formulation, studies were performed according to ICH and WHO guidelines. Optimized formulation (F5O2E2) sealed in aluminum foil coated inside with polyethylene was kept in the stability chamber (REMI, India) maintained at 40 C ± 2 and 75% RH ± 5 for 3 months. The samples were analyzed for the drug content, *in vitro* dissolution, physicochemical parameters and FTIR spectroscopy at three time intervals i.e. 1, 2 and 3 months [18,19].

3. Results and discussion

3.1. Formulation aspects of core tablets

3.1.1. Effect of HPMC and NaCMC

HPMC and NaCMC are hydrophilic materials. Change in the concentration of HPMC and NaCMC in the formulation leads to change in drug release. The $t_{80\%}$ values (Table 4 and Fig. 2) calculated from percent cumulative drug release versus time plots and release rate diagrams confirmed the effect of HPMC and NaCMC on the release rate of dicyclomine hydrochloride and diclofenac potassium. Formulation F5O2 showed slower release ($t_{80\%}$ in 17 h) compared to formulation F3O2 ($t_{80\%}$ in 12 h), and both the formulations gave relatively slower release rate than formulation F2O2 ($t_{80\%}$ in 8 h) which contains no hydrophilic polymers (HPMC + NaCMC). This may be due to the fact that in the dissolution medium, hydration of HPMC and NaCMC results into swelling of matrix, creating a gel barrier layer through which the drugs have to diffuse out. The results suggest that appropriate addition of release retardants especially hydrophilic polymers (HPMC + NaCMC) can control the release of highly water-soluble drug from the osmotic pumps.

Table 4
Average release rate, $t_{80\%}$ values.

Formulations	Dicyclomine hydrochloride release		Diclofenac potassium release	
	Average release rate (%/h)	$t_{80\%}$ (h)	Average release rate (%/h)	$t_{80\%}$ (h)
F2O2	9.49 ± 5.00	8	9.02 ± 1.38	9
F3O2	6.66 ± 3.50	12	6.66 ± 1.78	13
F4O2	2.01 ± 0.930		1.90 ± 0.568	
F5O2	5.126 ± 1.285	17	5.226 ± 1.419	18
F5O1	3.029 ± 1.369		2.8 ± 0.723	
F5O2	5.126 ± 1.285	17	5.226 ± 1.419	18
F5O3	8.933 ± 5.102	8	9.027 ± 1.397	9

3.1.2. Effect of osmogen

The release profile of formulations F5O2, F4O2, F3O2 and F2O2 was used to assess the influence of osmogen (Fig. 3). It was noted that release rate increased as the amount of mannitol increased. The formulation F5O2 showed lesser average release (5.126 ± 1.285 and 5.226 ± 1.419%) compared to formulation F3O2 (6.66 ± 3.50 and 6.66 ± 1.78%) and formulation F2O2 (9.49 ± 5.00 and 9.02 ± 1.38%). The formulation F4O2 showed very low average release (2.01 ± 0.930 and 1.90 ± 0.568%). The formulation F4O2 which contained no osmogen (mannitol) showed only 40% of drug release in 24 h, indicating that no osmotic pressure developed in the core tablet.

3.2. Evaluation of membrane variables

3.2.1. Effect of concentration of pore-forming agent

Formulation F5O2 released more than 80% of drug within 16 h and formulation F5O3 released more than 80% of drug within 9 h, while formulation F5O1 released only 65% of drug up to 24 h (Table 4 and Fig. 4). Formulation F5O3 showed very fast release possibly due to high concentration of pore-forming agent, and this result suggested that higher concentration of pore-forming agent results in higher drug release. Formulation F5O1 showed very low release due to low concentration of pore-forming agent. By slightly reducing the concentration of pore-forming agent, release can be extended for longer period of time, as formulation F5O2 showed $t_{80\%}$ within 16 h. The results suggested that slightly higher concentration of pore-forming agent may be useful to affect optimum release of both the drugs.

3.2.2. Effect of concentration of enteric polymer

Formulations coated with different concentrations of Eudragit L-100 (4, 6 and 8% w/w) did not release drug in buffer of pH 1.2, 4.5 and 6.8. All the formulations exhibited drug release in buffer pH 7.4 with the addition of pectinase. Formulation (F5O2E1) with higher concentration of enteric polymer (8% w/w) showed much delayed drug release compared to other formulations (F5O2E2 and F5O2E3) having lower concentration (6% and 4% w/w) of enteric polymer (Fig. 5). As concentration of Eudragit L-100 was

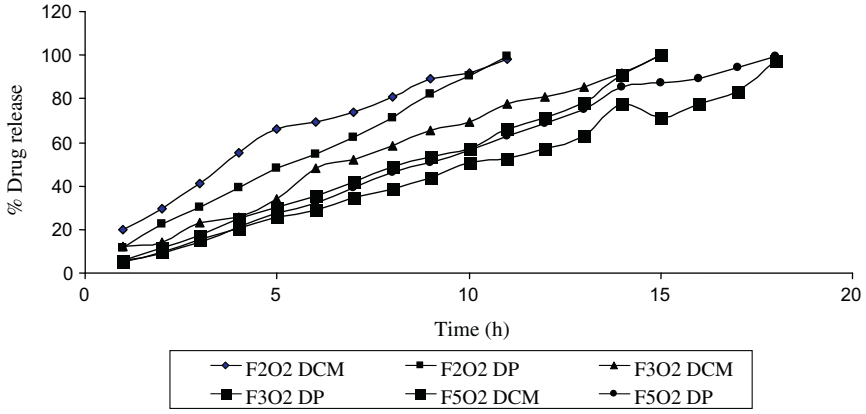

Fig. 2. Effect of concentration of hydrophilic polymers on release rate of the drug (s). (DCM – Dicyclomine hydrochloride, DP – Diclofenac potassium.)

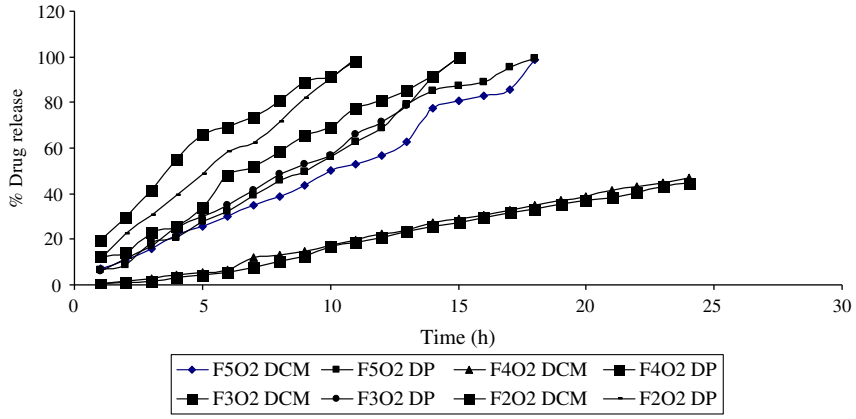

Fig. 3. Effect of concentration of osmogen on release rate of the drug (s). (DCM – Dicyclomine hydrochloride, DP – Diclofenac potassium.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

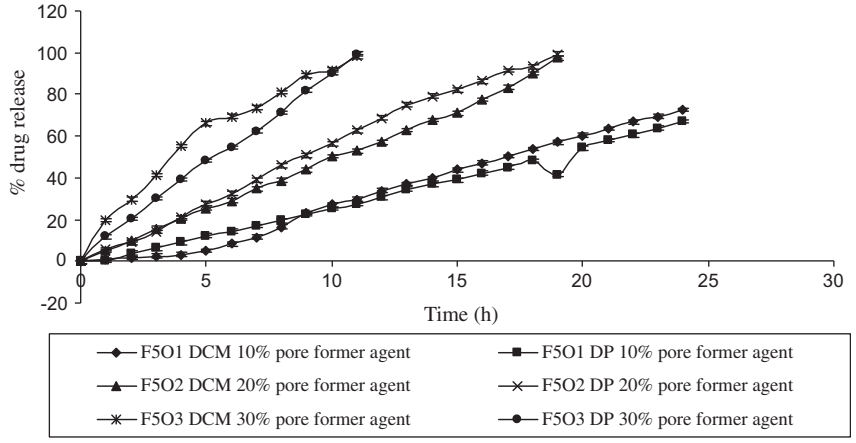

Fig. 4. Effect of concentration of pore former on release rate. (DCM – Dicyclomine hydrochloride, DP – Diclofenac potassium.)

increased, no significant difference was found in release profiles ($P < 0.05$). This result probably suggested that enteric polymer (Eudragit L-100) dissolved too quickly in simulated intestinal fluid (SIF) and changed the release profiles significantly.

3.2.3. Scanning electron microscopy (SEM)

Formulations F5O1E2, F5O2E2 and F5O3E2 containing pore-forming agent (pectin) in concentration 10%, 20% and 30% w/w, respectively, obtained before and after complete dissolution, were subjected to SEM studies. Formulations showed non-porous region before dissolution (Fig. 6a). After dissolution, formulation showed microporous region (Fig. 6b–d). The pore size was found to be between 8 μm and 30 μm. After dissolution, membrane containing 10% of pore-forming agent (formulation F5O1E2) showed pore size between 8 μm and 10 μm (Fig. 6b), membrane containing 20% of pore-forming agent (formulation F5O2E2) showed pore size between 15 μm and 20 μm (Fig. 6c), while membrane containing 30% of pore-forming agent (formulation F5O3E2) showed larger

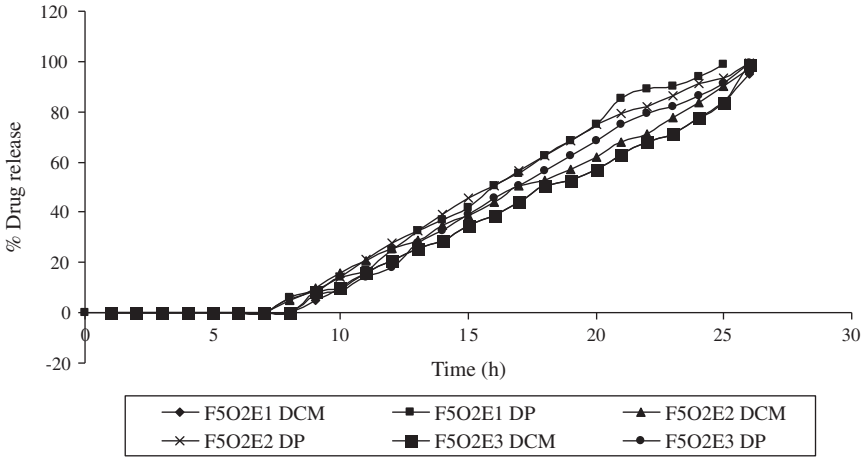

Fig. 5. Effect of concentration of enteric polymer. (DCM – Dicyclomine hydrochloride, DP – Diclofenac potassium.)

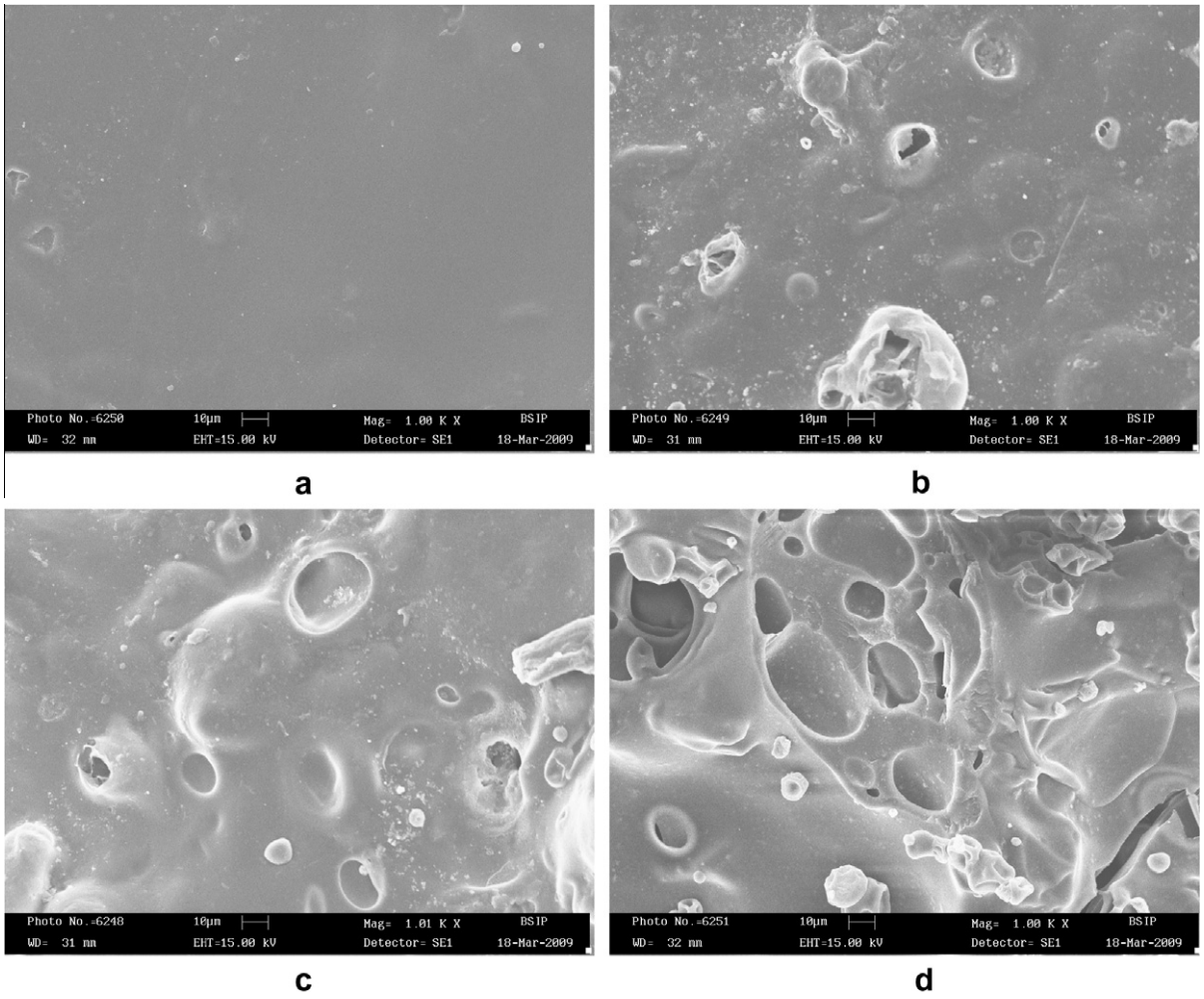

Fig. 6. Scanning electron microphotograph of the tablet after dissolution (a) obtained before dissolution, (b) porous region of membrane containing 10% w/w pectin, (c) porous region of membrane containing 20% w/w pectin, (d) porous region of membrane containing 30% w/w pectine.

pore up to 30 µm (Fig. 6d). Formulation containing 20% of pore-forming agent ruptured, showing that more than 30% (w/w) of pectin would cause rupturing of membrane during dissolution. The SEM study suggested that 20% (w/w) of pectin can be considered as an optimum concentration to obtain maximum release rate without rupturing of the membrane.

3.3. Drug release kinetics

The linear nature of the plots between percent cumulative drug release and time suggests that none of the formulations follow first-order kinetics, which is further confirmed by the higher sum of square residuals and comparatively less volumes of correlation

coefficient. The linear nature of the curves obtained for zero order, Higuchi model and Hixson–Crowell model suggests that the release from the formulations may follow any one of these models. While considering the higher correlation coefficient values and less sum of squared residual (SSR) values, the release data seem to better fit with zero-order model. Hixson–Crowell and Higuchi models moreover showed higher SSR values and comparatively small correlation coefficient volumes. Based on Korsenmayer–Peppas power model, drug release data were further analyzed for curve fitting and the results confirmed that the formulations showed non-Fickian diffusion kinetics ($n > 0.5$) (Table 5).

Table 5
Statistical analysis and correlation coefficient values for dissolution data of different formulation based on various kinetic models.

Kinetics models	Parameters	Formulations					
		F5O2E1		F5O2E2		F5O2E3	
		DCM	DP	DCM	DP	DCM	DP
Zero order	R	0.9972	0.9966	0.9984	0.9967	0.9951	0.9975
	SSR	55.988	87.890	26.335	32.345	57.716	54.841
	k_0	5.877	4.920	5.397	4.909	5.423	4.887
First order	R	0.8941	0.9061	0.8750	0.8776	0.8059	0.8516
	SSR	279.84	296.65	289.94	284.74	279.87	299.67
	K_1	0.0532	0.0857	0.0604	0.0819	0.0675	0.0867
Higuchi model	R	0.9924	0.9939	0.9929	0.9978	0.9904	0.9972
	SSR	163.65	176.87	195.74	189.93	185.43	202.54
	K_H	19.358	46.346	18.901	41.728	18.78	42.03
Hixson–Crowell	R	0.9747	0.9770	0.9747	0.9652	0.9844	0.9680
	SSR	142.53	134.76	146.94	138.85	152.43	149.92
	K_{HC}	0.115	0.162	0.111	0.147	0.108	0.148

Table 6
Physicochemical properties of optimized formulation during 3-month stability studies.

Formulation code	Average hardness (kg/cm^2 ± SD)			Drug content (% ± SD)					
	After 1 month	After 2 months	After 3 months	After 1 month		After 2 months		After 3 months	
				DCM	DP	DCM	DP	DCM	DP
F5O2E2	8.0 ± 0.0	8.0 ± 0.0	8.0 ± 0.0	98.77 ± 0.613	98.92 ± 0.462	98.34 ± 0.491	98.32 ± 0.753	97.45 ± 0.821	97.72 ± 0.693

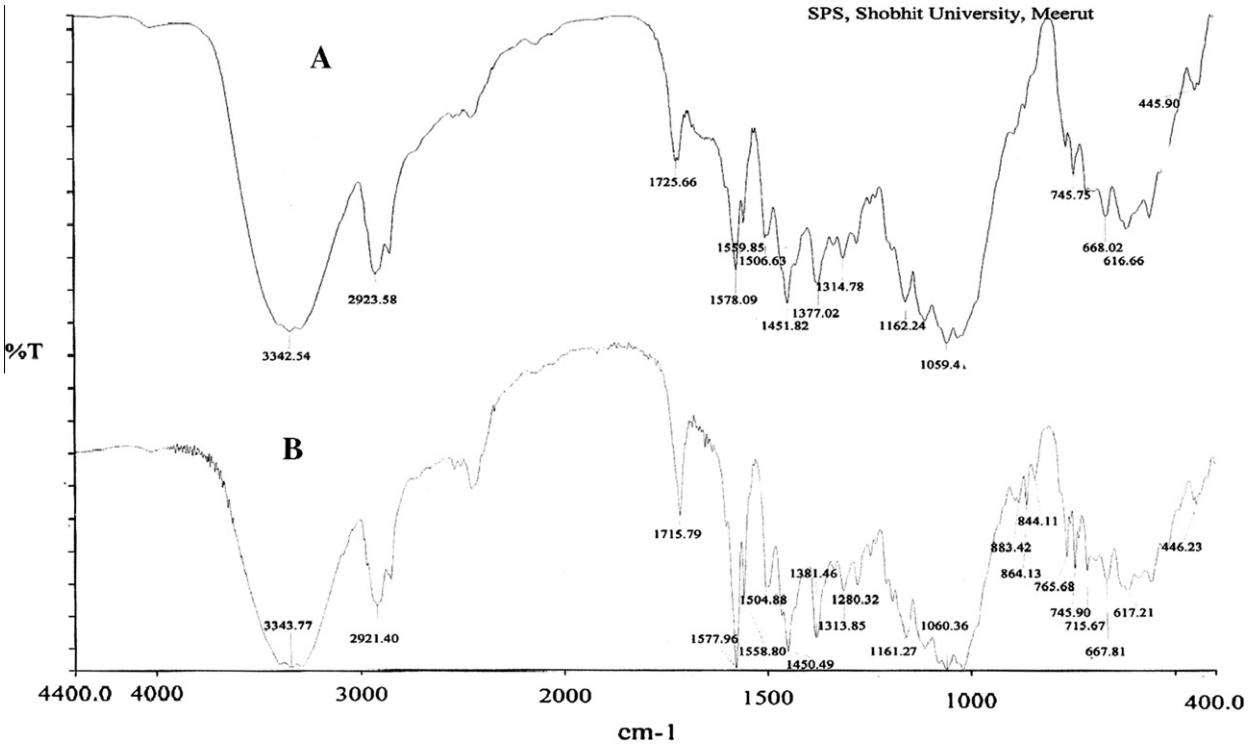

Fig. 7. FTIR spectra of optimized formulation (A) initial (B) after 3 months of exposure at 40 °C and 75% relative humidity.

3.4. Stability studies

During 3 months of stability studies, formulation was characterized for *in vitro* drug release, drug content, hardness and FTIR spectroscopy. The results indicated no significant difference in drug release ($P < 0.05$). The drug contents were 97.45 ± 0.821 and 97.72 ± 0.693 for both the drugs, and hardness was also within the limits (8.0 kg/cm^2). The Fourier transform infrared spectroscopy (FTIR) indicated no interaction between drugs, and formulation was found to be stable (Table 6 and Fig. 7).

4. Conclusions

The present study was carried out in order to develop microporous bilayer osmotic tablet for colon-specific delivery for the treatment of irritable bowel syndrome. The preparation of microporous bilayer osmotic tablet was simplified by coating the core tablet with an indentation, and the cost was reduced with the elimination of laser drilling. It may be concluded from *in vitro* study that colon-targeted coated tablets successfully maintained their integrity till the time they reach the colonic fluids. Drug release started when formulation reached the colonic fluids. Drug release from the systems followed zero-order kinetics, and statistical analysis of release rate data proved that system could provide required controlled release rate of both the drugs up to 24 h. The method seams promising for the preparation of microporous bilayer osmotic tablets to treat the irritable bowel syndrome (IBS).

References

[1] B.K. Mishra, Colon targeted drug delivery systems – an overview, Curr. Drug Deliv. 5 (2008) 186–198.
[2] A.D. Kraneveld, A. Rijinierse, F.P. Nijkamp, J. Garssen, Neuro-immune interaction in inflammatory bowel disease and irritable bowel syndrome: future therapeutic targets, Eur. J. Pharmacol. 585 (2008) 361–374.
[3] Y. Cong, N. Dai, H. Yuan, Prevalence of irritable bowel syndrome among undergraduates in southeast China, Dig. Liver Dis. 40 (2008) 418–424.
[4] J.H. Gurwitz, S.E. Andrade, S.L. Goff, K. Dodd, Administrative data used to identify with irritable bowel syndrome, J. Clin. Epidemiol. 61 (2008) 617–621.
[5] M. Heitkemper, M. Jarrett, Irritable bowel syndrome: does gender matter, J. Psychosom. Res. 64 (2008) 583–587.
[6] M.J.G. Farthing, Treatment option in irritable bowel syndrome, Best Prac. Res. Clin. Gastroenterol. 18 (2004) 773–786.
[7] KD. Tripathi, Essential of Medical Pharmacology, Jaypee Brother Medical Publishers (P) LTD, New Delhi, 2004.
[8] L. Liu, X. Xu, Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet, Int. J. Pharm. 352 (2008) 225–230.
[9] C.Y. Wu, J.P.K. Seville, A comparative study of compaction properties of binary and bilayer tablets, Powder Technol. (2008) 1–10.
[10] S.S. Poddar, S. Abdul, A flexible technology for modified release of drugs: multi layered tablets, J. Control. Release. 97 (2004) 393–405.
[11] M.A. Raggi, V. Cavrini, P.A.M. Di, A calorimetric assay method for dicyclomine hydrochloride using bromocresol green, J. Pharm. Biomed. Anal. 3 (1985) 287–291.
[12] M. Tubino, R.L. Desouza, Spectrophotometric determination of diclofenac in pharmaceutical preparations, J. Braz. Chem. Soc. 16 (2005) 1068–1073.
[13] S.P. Vyas, D. Prabhakaran, P. Sing, P. Kanaujia, K.S. Jaganathan, A. Rawat, Modified push–pull osmotic system for simultaneous delivery of theophyllin and salbutamol: developed and in vitro characterization, Int. J. Pharm. 284 (2004) 95–108.
[14] T.M. Rafiee, A. Ghaffari, K. Navaee, M. Oskoui, K. Bayati, Preparation and characterization of free mixed-film of pectin/chitosan/Eudragit RS intended for sigmoidal drug delivery, Eur. J. Pharm. Biopharm. 67 (2007) 175–186.
[15] W.S. Pan, X.G. Yang, S.F. Nie, L.L. Wei, H. Liu, Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: screening of formulation variables and in vitro investigation, Int. J. Pharm. 332 (2007) 115–124.
[16] M.K. Chourasia, S.K. Jain, Design and development of multiparticulate system for targeted drug delivery to colon, Drug Deliv. 11 (2004) 201–207.
[17] S.P. Vyas, D. Prabakaran, P. Singh, P. Kanaujia, Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps, Int. J. Pharm. 259 (2003) 173–179.
[18] Z. Rahman, M. Ali, R.K. Khar, Design and evaluation of bilayer floating tablets of captopril, Acta Pharma. 56 (2006) 49–57.
[19] L. Edward, Preformulation studies, in: S. Ahuja (Ed.), Handbook of Modern Pharmaceutical Analysis, vol. III, Elsevier, California, 2005, pp. 445–483.