Design and Evaluation of Microporous Membrane Coated Matrix Tablets for a Highly Water Soluble Drug

Madhusmita MISHRA and Brahmeshwar MISHRA*

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University; Varanasi–221 005, India.
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Microporous coated matrix tablet consists of a microporous membrane which is produced directly from a nonporous polymer coating during transit in the gastro-intestinal tract. In the present study, efforts have been made to develop and evaluate the *in-vitro* performance of a matrix embedded microporous controlled release system to deliver a drug with high aqueous solubility (≥3 g/ml), high pK_a (≥9.0) and low molecular weight (<500 Da). The matrix embedded core tablets were prepared and coated using film former (2% w/w) and different pore formers (1—20% w/w of film former) such as plasticizer (PEG 4000), surfactant (Tween 80) and polysaccharide (Dextran) in a conventional coating pan. The tablets were evaluated for various physical parameters, coat tensile strength and *in-vitro* drug release characteristics. The ethyl cellulose films suppressed the initial burst effect in drug release more than cellulose acetate and polymethacrylates films. PEG 4000 was found to be most effective plasticizer and pore former in controlling drug release, followed by Tween 80 and dextran. The prepared formulations provided prolonged and zero-order drug release.

Key words microporous membrane; controlled release; film former; pore former

The development of oral controlled release delivery systems for highly water soluble drugs possesses a significant challenge to the formulation scientists. The most commonly used method of modulating drug release is to include it in a matrix system.[1] There is considerable slowing of drug release rate with respect to time for these systems. Salt addition results in the suppression of the solubility of a highly soluble salt form of a drug due to the common-ion effect. But, salt addition causes additional effects like increase in osmotic pressure at higher effective concentrations. Some researchers have also reported that salts of highly hydrophilic nature[2] are effective as release retardants by competing with the drug for solvent molecules, resulting in lower drug dissolution. Release rate of basic drugs can also be decreased by ionic interaction with alginates,[3] λ-carrageenan,[4] dextran salts or by addition of osmogens.[5] The failure of these delivery systems are usually associated with burst release, dose dumping and thus, are likely to produce toxic concentration of the drug on oral administration.

Many controlled-release systems in pharmaceutical industry rely on membrane technology in which a drug containing core is surrounded by a membrane, and the release rate of the drug is controlled by its diffusion through the membrane. Microporous membrane coated tablets[6,7] consists of microporous membranes which are produced directly from a nonporous polymer coating during transit in the gastro-intestinal tract (Fig. 1). In the present study, efforts have been made to develop and evaluate the *in-vitro* performance of a microporous membrane coated system to deliver a model drug, Tramadol Hydrochloride (TH) with high aqueous solubility (≥3 g/ml), high pK_a (≥9.0) and low molecular weight (<500 Da). TH is a synthetic opioid analgesic agent with a half-life of about 5.5 h. It is expected to reduce the frequency of drug administration and to improve patient compliance. This approach does not require the addition of osmogens.

Experimental

Materials TH was a gift sample from Win Medicare Ltd. (India). Eudragit RLPO and Eudragit RSPO were obtained from Degussa India Pvt. Ltd. (India). Cellulose acetate, Ethyl cellulose, Polyethylene glycol 4000 and Dextran were purchased from Central Drug House (India). All other ingredients and solvents used were from Qualigens Fine Chemicals (India).

Determination of Coat Tensile Strength The cellulose acetate (CA) films were prepared by solvent evaporation technique in a glass mold.[8,9] Briefly, 2% w/v polymeric solution in acetone–isopropyl alcohol mixture containing 0—50% w/w (of CA) PEG 4000 was cast on the glass mold followed by drying overnight at 40 °C. The polymeric film (5 cm×1 cm) was cut into the specified shape (Fig. 2) and clamped on the tensile testing machine (Instron Ltd., U.S.A.) using flat-faced metal grips with surfaces laminated with sand paper for better hold. The initial gauge length was set at 50 mm with extension speed of 5 mm/min. The tests were carried out at ambient conditions of 22±2 °C and 55±2% RH. The tensile strength and elongation percentage were computed from the stress–strain profiles.[10]

Preparation of Microporous Coated Matrix Tablet. Preparation of Core Matrix Tablets The core tablets (300 mg) of TH were prepared using microcrystalline cellulose (MCC) and dibasic calcium phosphate (DCP) or hydroxypropyl methyl cellulose K100M (HPMC) on a single station punching machine (Manesty E2, U.K.) equipped with 8 mm concave

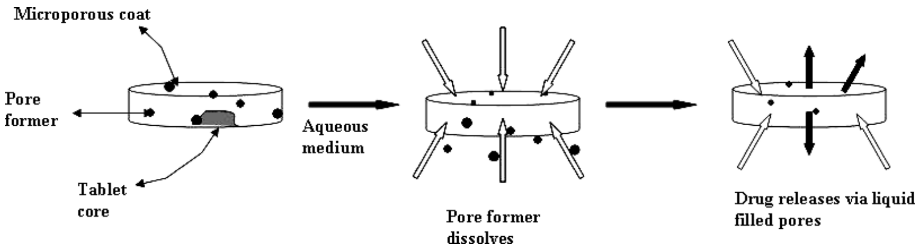

Fig. 1. Diffusion of Drug through the Microporous Membrane after Leaching of the Pore Formers (White Arrow Indicates Entry of Aqueous Medium and Black Arrow Indicates Drug Release *via* Liquid Filled Pores)

* To whom correspondence should be addressed. e-mail: bmishrabhu@rediffmail.com

punches. In case of core I, accurately weighed quantities of all the ingredients (Table 1) were passed through 85 mesh (180 μm) and compressed directly. For core II and III, all the ingredients (Table 1) except talc was granulated using 2% w/v methanolic solution of ethylcellulose. The sieve 18 (850 μm) fraction of the wet mass was dried in an oven at 60 °C for 6 h, followed by addition of talc. Accurately, weighed lubricated granules were then compressed on a single station punching machine. The compression force was adjusted to obtain a hardness of 4.5 to 5.5 kg/cm^2 in all the batches.

Coating of Core Matrix Tablets Coating solution (Table 2) comprising 2 and 5% w/v of film formers like cellulose acetate (CA), ethyl cellulose (EC) and polymethacrylates (MA *i.e.* Eudragit RSPO : Eudragit RLPO= 1 : 2) and 1—20% w/w (of film former) of different pore former (PEG 4000, Tween 80 and Dextran) in acetone–isopropyl alcohol mixture was prepared under mechanical stirring for 30—60 min before coating. Each batch of 100 convex shaped core tablets were coated in a conventional standard coating pan (Scientific Instruments, India). The coating conditions were as follows: inlet air temperature, 40 °C; air flow rate, 1.2 kg/cm^2; coating spray rate, 4—5 ml/min and pan speed, 25 rpm. Coating process was repeated until desired coat weight was obtained on the core tablets.[11]

Physical Characterization The tablets were evaluated for appearance and the coated tablets were visually inspected for film smoothness, uniformity of coating, edge coverage, luster and tablet to tablet variation. The core tablet weight variation, hardness, crown thickness and friability were measured as per I.P 1996. Depleted coated tablets were carefully peeled and washed to remove any insoluble solid contents and dried. Average coat thickness was measured by weighing 10 such tablets in a batch using a standard screw gauge (Campbell Electronics, Mumbai, India). For determination of content uniformity, accurately weighed tablets (n=20) were extracted in distilled water and analyzed after suitable dilutions on UV Spectrophotometer at 271 nm (Jasco-7800, Japan).

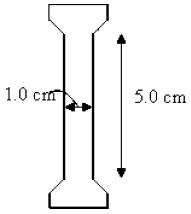

Fig. 2. Sample Specimen for Tensile Testing

***In-Vitro* Drug Release Characteristics** *In vitro* drug release from the prepared tablets were studied in 900 ml of distilled water for 8 h stirred at 50 rpm and maintained at 37±0.5 °C using USP XXIV type II dissolution apparatus (Campbell Electronics, India). Aliquot samples were withdrawn at regular intervals, filtered and analyzed spectrophotometrically as described earlier. The dissolution data were fitted to various models like Korsmeyer and Peppas, Higuchi, first order and zero order models to determine the mechanism of drug release.[12]

The influence of the concentration of different film former, pore former, coat thickness and agitation intensity were investigated on drug release performance of prepared tablets. The dissolution medium pH change method (initial 2 h in pH 1.2, next 2 h in pH 4.5, 2 h in pH 6.8 and finally for 2 h in pH 7.4) was also used to study the effect of pH on drug release.

Morphology of Microporous Films The polymeric films of CA (2% w/v) with different pore formers (15% w/w of CA) such as PEG 4000 (batch IIIC2P15), Tween 80 (batch IIIC2T15) and dextran (batch IIIC2D15) were cast on glass molds as described earlier. These unleached films were then separately kept in a beaker of distilled water for 24 h and later dried in an oven for 72 h to obtain microporous (leached) films. Morphology of the films were examined by scanning electron microscopy (SEM) (QUANTA 200 FEI) after sputter coating with gold for 5 to 10 min. Samples were imaged using a 5 kV accelerating voltage, 10 mm working distance and emis-

Table 1. Composition of the Uncoated Core Tablet in Different Batches

Batch code	TH (mg)	MCC (mg)	DCP (mg)	HPMC K100 (mg)	TALC (mg)	Total weight (mg)
Core I	90.0	47.0	150.0	0	3.0	300.0
Core II	90.0	47.0	120.0	30.0	3.0	300.0
Core III	90.0	47.0	135.0	15.0	3.0	300.0

Table 2. Compositions of Coating Solutions for Core Tablets

Batch code		Film former (% w/v)			Pore former (% w/w of film former)			IPA (% v/v)	Acetone (% v/v)
		CA	EC	MA	PEG 4000	Tween 80	Dextran		
Core I	IC2P5[a]	2	—	—	5	—	—	10	90
	IC2P2[a]	2	—	—	2	—	—	10	90
	IC2P1	2	—	—	1	—	—	10	90
	IC5P1	5	—	—	1	—	—	10	90
Core II	IIC2P10	2	—	—	10	—	—	10	90
	IIC2P15	2	—	—	15	—	—	10	90
	IIC2P20	2	—	—	20	—	—	10	90
Core III	IIIC2P10	2	—	—	10	—	—	10	90
	IIIC2P15	2	—	—	15	—	—	10	90
	IIIE2P10	—	2	—	10	—	—	10	90
	IIIE2P15	—	2	—	15	—	—	10	90
	IIIE2P20	—	2	—	20	—	—	10	90
	IIIM2P10	—	—	2	10	—	—	10	90
	IIIM2P15	—	—	2	15	—	—	10	90
	IIIM2P20	—	—	2	20	—	—	10	90
	IIIC2T10	2	—	—	—	10	—	10	90
	IIIC2T15	2	—	—	—	15	—	10	90
	IIIC2T20	2	—	—	—	20	—	10	90
	IIIC2D10	2	—	—	—	—	10	10	90
	IIIC2D15	2	—	—	—	—	15	10	90
	IIIC2T20	2	—	—	—	—	20	10	90

a) Indicates lower coat thickness of 60 μm rather than the normal 120 μm thickness of coat in all other batches; '—' indicates no ingredient; MA indicates polymethacrylates (Eudragit RSPO : Eudragit RLPO in 1 : 2 ratio).

sion current of 348 μA.

Statistical Analysis The cumulative amount release from all formulations (core I, core II and core III coated tablets) was statistically compared using similarity factor (f_2 and S_d). The results were also evaluated using dissolution efficiency (DE) and mean dissolution time (MDT) and $T_{50\%}$. The data analysis was performed using the SigmaStat® statistical software package (Jandel Corporation, San Rafael, CA, U.S.A.).

Results and Discussion

Mechanical Properties An ideal film coat should be hard and tough without being brittle. The mechanical properties of CA polymeric films are shown in Table 3. It was found that with the increase of PEG loading, the tensile strength of membrane decreases but the elongation at rupture increases. However, phase separation occurs in films with 40% and 50% PEG and their mechanical properties deteriorate significantly. This is evidenced by a tremendous decrease in elongation at rupture and tensile strength. Thus, from the above observations PEG concentration was preferably restricted between 10 to 30% for CA containing films.

Physical Characterization The various physical parameters evaluated for core tablets were found to be within official limits. The crown thickness was found to be between 3.50 to 3.55 mm. The drug content uniformity for core tablets I, II and III were found to be 98%, 101.01% and 100.12%, respectively. The increase in weight of tablets following single coating and double coating with various composition of film former and pore former in isopropyl alcohol (IPA)–acetone mixture were in the range of 5.05±0.02% and 15.05±0.29%, respectively.

***In-Vitro* Drug Release Characteristics. Drug Release from Core Tablets** The core I tablets containing MCC and DCP only, exhibited more than 80% drug release in less than 2 h (Fig. 3). HPMC K-100M a hydrophilic matrixing agent was used in combination with a hydrophobic polymer EC (granulating agent) in the preparation of core II and core III tablets. It was observed that these matrix embedded tablets (core II and III) initially at 1 h gave high (35—37%) drug release but provided slower drug release thereafter till 8 h. MDT and DE was also used to determine the drug release retarding efficiency of polymer. MDT was shown to increase from 5.34 h (Core I) to 7.20 h (Core II) and 6.82 h (Core III) which indicates that EC incorporation in the hydrophilic matrix resulted in slower drug release. This may be attributed to decreased penetration of the solvent molecules in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix. However, on comparing core II (10% w/w of HPMC) with core III (5% w/w of HPMC) drug release was not significantly different as is evident from S_d (0.044) and $t_{50\%}$ (>2.5 h) values. Drug release data of core II and III tablets fitted well into the Higuchi equation (r^2=0.982 and 0.9796, respectively).

Table 3. The Mechanical Properties of Cellulose Acetate (2% w/v) Films Containing Varying Concentrations of PEG 4000

PEG 4000 (%)	Tensile strength	% Elongation
0	35	6.5
10	16	7.5
20	13	20
30	8	40
40	5	20
50	1	5

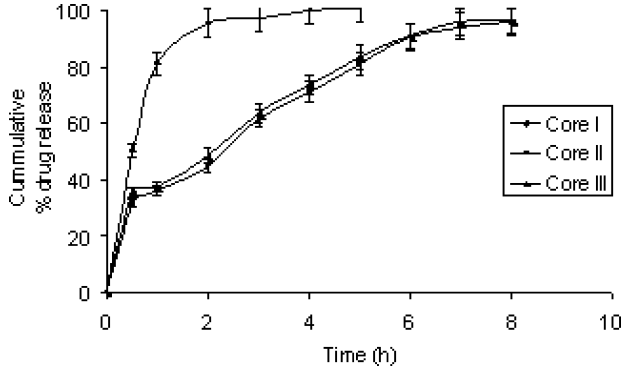

Fig. 3. *In-Vitro* Release Profiles of TH from Uncoated Core I, Core II and Core III Tablets

Vertical bars represent S.D.

Drug Release from Core II Coated Tablets The profile of drug release from core II coated tablets are shown in Fig. 4b. The time taken to release 30% of TH was considerably increased from 1 h in case of coated core I tablets to more than 8 h for coated core II tablets thereby, reducing the chances of dose dumping associated with membrane coated systems. It was also observed that at high HPMC concentration (10%), pore former (10%) and a coat thickness of 120 μm, there was only 20% drug release from the coated core II tablets (IIC2P10) in 8 h study. The high polymer concentration provided a considerable dense barrier thus inhibiting drug release considerably. The DE of core II coated tablets in 8 h was found to be in the order of batch IIC2P10<batch IIC2P15<batch IIC2P20. Batches IIC2P10 and IIC2P15 showed high linearity with zero order correlation values 0.9056 and 0.9852, respectively. As considerable swelling of the core II tablets in the dissolution medium was observed, further studies were conducted using 5% of HPMC as in core III.

Drug Release from Core III Coated Tablets The cumulative percentage drug release from core III tablets coated with CA and PEG 4000 as a pore former are shown in Fig. 4c. When the PEG content was increased from 10 to 15% there was 1.55 fold increase in the extent of drug release and nearly 1.43 fold increase was seen on further increasing its concentration from 15 to 20%. This may be due to the fact that at higher PEG content, the film coats had more pores (higher porosity) after exposure to dissolution medium. Nearly, two fold increase in DE was seen from batch IIIC2P15 in comparision to batch IIC2P15 tablets both coated with 2% w/v CA and 15% PEG 4000. Further, the burst effect seen in case of core I coated tablets was also suppressed when composition was changed to core III coated tablets. Batch IIIC2P15 exhibited zero-order release kinetics (r^2=0.9911) and prolonged the drug release optimally thus, providing promising results for further study.

Effect of Type and Quantity of Film Former The film polymers were chosen based upon their permeability characteristics namely, EC (Impermeable), CA (Semi-permeable) and MA (Permeable). To compare the effect of concentration of film formers on the *in-vitro* release profiles of TH the core I tablets were coated with 2 and 5% w/v CA and 1% w/w (of CA) PEG 4000. The MDT of batch IC2P1 and IC5P1 de-

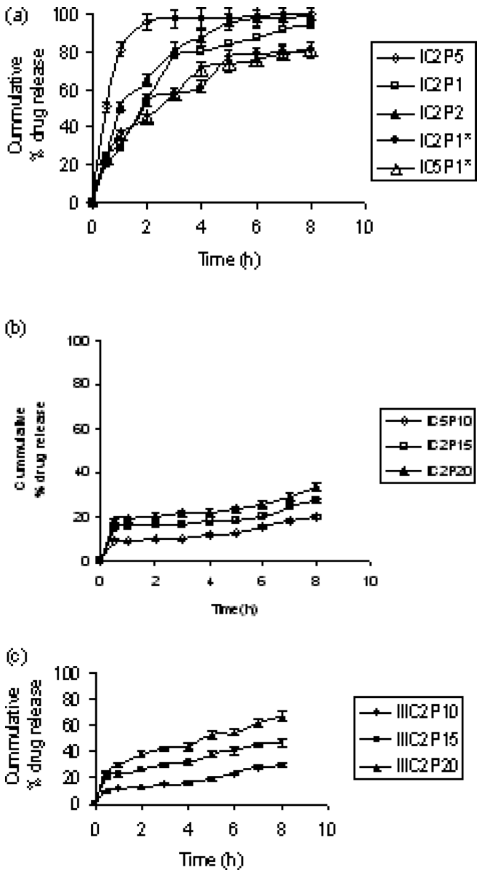

Fig. 4. *In-Vitro* Release Profiles of TH from (a) Coated Core I, (b) Coated Core II and (c) Coated Core III Tablets

Vertical bars represent S.D.

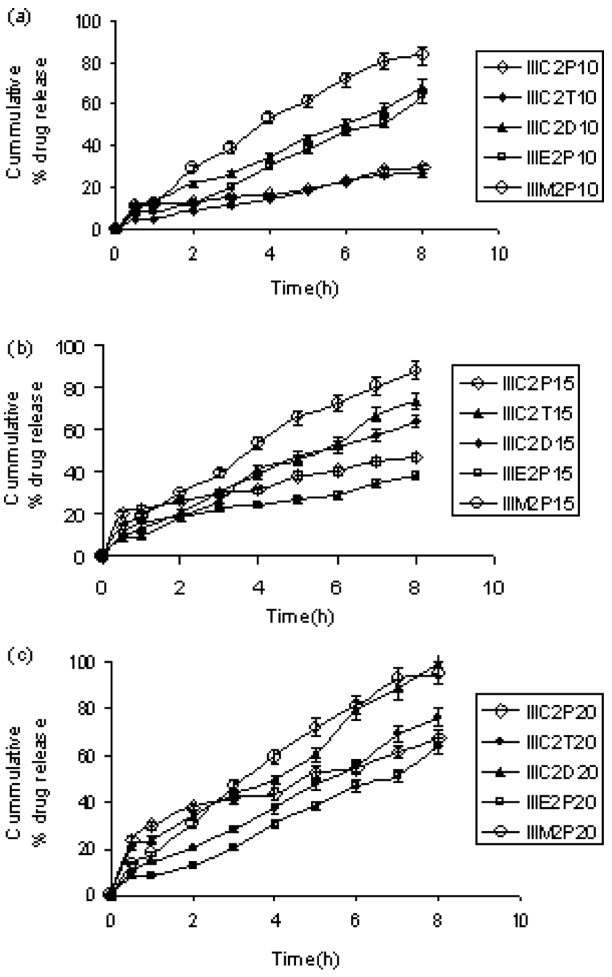

Fig. 5. *In-Vitro* Release Profiles of TH from Coated Core III Tablets with Different 2% w/v Film Formers (Cellulose Acetate, Ethyl Cellulose and Polymethacrylates) and Pore Former (PEG 4000, Tween 80 and Dextran) at (a) 10%, (b) 15% and (C) 20% w/w of Film Former

Vertical bars represent S.D.

creases while DE in 8 h was found to be similar. In both the cases, burst effect was observed (Fig. 4a). At higher polymer concentration, there was chances of clogging the sprayer and so difficult to coat. Therefore, an optimum concentration of CA was chosen as 2% w/v for further study.

Application of EC coating drastically impaired the initial burst release (Figs. 5a—c). The initial decrease in the drug release after coating could be due to prevention of penetration of water into the hydrophobic matrix system. The results of the dissolution studies of batch IIIE2P10 (Fig. 5a), IIIE2P15 (Fig. 5b) and IIIE2P20 (Fig. 5c) indicated that incorporation of water-soluble excipients in the film former, even at 20% PEG 4000 aided in the suppression of initial burst release. The $t_{50\%}$ of IIIE2P20 was observed to be 5.9 h.

In the present study a combination of Eudragit RSPO (water permeable) and Eudragit RLPO (water impermeable) was used in 1 : 2 ratio. From the drug dissolution study, it was found that the Eudragit films containing 10% (Fig. 5a) and 15% (Fig. 5b) PEG gave similar release profile. MDT was greater than 8 h for the batches IIIM2P10, IIIM2P15 and IIIM2P20 indicating higher drug release from these formulations. The above results clearly indicate that the drug release rate is significantly influenced by the film former property (Table 4).

Effect of Type and Concentration of Pore Former The pore formers chosen were water soluble polymers with different physico-chemical properties namely, PEG 4000 (Plasticizer), Tween 80 (Surfactant) and Dextran (Polysacharide).

Table 4. Comparision of *in-Vitro* Release Data of Core III Coated Tablets

Batch code	MDT (h)	DE (%)	$t_{50\%}$ (h)[a]
IIIC2P15	2.4	21.53	12.42
IIIC2T15	3.9	21.2	5.55
IIIC2D15	3.4	22.04	5.9
IIIE2D15	2.9	15.48	19.27
IIIM2D15	3.4	30.64	3.67

a) Calculated according to Peppas model.

The batch IIIC2T10 tablets coated with 10% w/w (of CA) Tween 80 exhibited much slower rate and extent of drug release (Fig. 5a) as compared to tablets coated with 15% w/w (IIIC2T15) and 20% w/w Tween 80 (IIIC2T20) as shown in Figs. 5b and c, respectively. However, batches IIIC2P15 and IIIC2T20 exhibited almost similar drug release profiles (S_d=0.041) indicating that 15% and 20% concentration of Tween 80 could not exhibit any difference in drug release rate.

There was no significant increase in drug release rate on increasing the dextran (pore former) concentration from 10 to 20% probably because of the relatively large size of the dextran molecule (Figs. 5a—c). Owing to the large size of

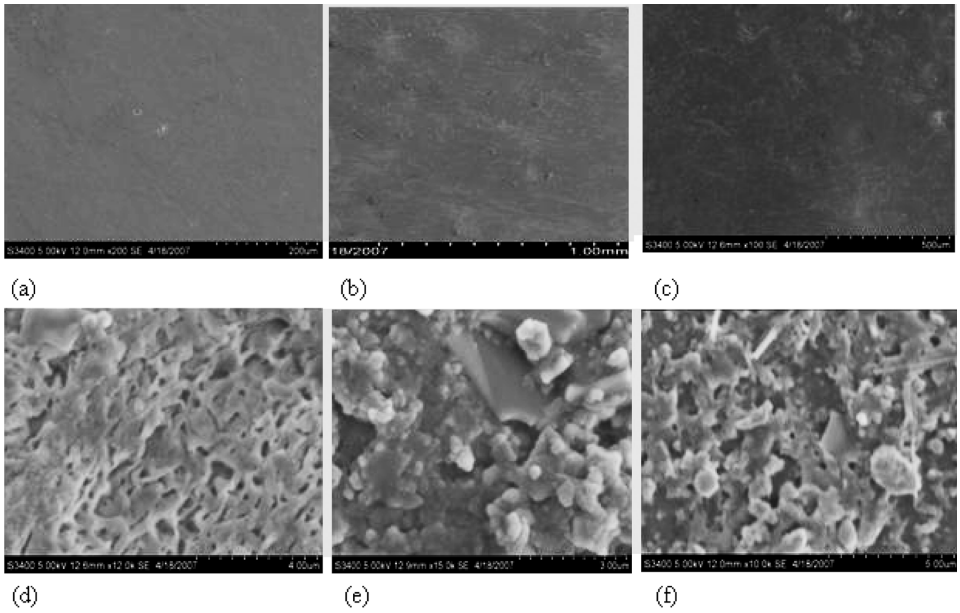

Fig. 6. SEM Micrograph of the Coating Membrane of (a) and (d) Batch IIIC2P15, (b) and (e) Batch IIIC2T15 and (c) and (f) Batch IIIC2D15 before and after Dissolution, Respectively

the molecule, dextran did not dissolve in the dissolution medium completely and hence did not provide pores for enhanced drug diffusion at 10% and 15% concentration from batches IIIC2P10 (Fig. 5a) and IIIC2P15 (Fig. 5b). An increase in the release rate at 20% PEG (batch IIIC2P20) was observed (Fig. 5c). The release profiles of batch IIIC2D10 and batch IIIC2D15 were observed to be similar (f_2=29.21).

Effect of Gastrointestinal pH The possible alteration in the drug release profile of a formulation in dissolution media of different pH can be attributed to two factors. One is pH dependent solubility of drug molecule and the other is variation in polymer characteristics in different media. To study the effect of above mentioned variable, release profile of batch IIIC2P15 (core III tablets coated with 2% w/v CA and 15% w/v PEG 4000) was determined in sequential gastrointestinal fluid (pH 1.2, 4.5, 6.8, 7.4) and in distilled water. No significant difference was observed in the drug release in both the dissolution media based on the MDT ($p<0.05$) and f_2 (>80) values obtained. This could be explained on the basis of pK_a value of TH (≥9.0). This basic drug remains predominantly in non ionic state in the pH range studied and solubility[13] does not change significantly at pH values of 1.2—7.4. Apart from above, the polymers like HPMC and EC, embedded in the matrix core, being cellulose derivatives, exert resistance to changes in pH or ionic content of the medium.[14] Therefore, effect of alteration in pH of the media is not significant on drug release profile.

Effect of Agitational Intensity of Dissolution Medium The release profiles (results not shown) obtained under varying rotational speeds was found to be similar. The f_2 values were found to be 96.67 (between 25 rpm and 50 rpm), 93.25 (between 50 rpm and 100 rpm) and 91.89 (between 100 rpm and 150 rpm), respectively. The tablet coats remained intact throughout the 8 h of dissolution study. The results were in agreement with earlier reports.[1]

Morphology of Porous Films SEM was utilized to visualize a possible *in-situ* formation of micropores in films after leaching of the pore formers from the films in aqueous medium. Micrographs clearly revealed the formation of a significant number of pores on all investigated films (Figs. 6d—f) after dissolution as compared to before dissolution (Figs. 6a—c). The pore size was larger in case of PEG 4000 (Fig. 6d) as compared to Tween 80 (Fig. 6e). More inter-connected channels were distributed in case of PEG as shown in Fig. 6d. The micrographs of dextran containing films (Fig. 6f) showed solid deposition on the films while mosaic like fissured films were obtained in case of Tween 80 (Fig. 6e).

Conclusion

It was observed that the polymer based matrix tablets coated with microporous controlled release membrane exhibited promising extended and controlled drug release for a period of 12 h as compared to only MCC/DCP based microporous controlled release tablets. The ethyl cellulose films suppressed the initial burst effect in drug release more than cellulose acetate and polymethacrylates films. PEG 4000 containing films exhibited promising controlled and extended drug release characteristics than Tween 80 and Dextran. The dissolution results were consistent with the SEM micrographs. Mathematical analysis of the release data indicates that microporous controlled release tablets of TH exhibited zero-order release pattern. Thus, microporous membrane coated matrix delivery systems can be utilized to develop formulation for providing prolonged and controlled release of highly water soluble drugs.

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