Psychosis, an abnormal condition of the mind, is a generic psychiatric term for a mental state which may occur throughout the day or may precipitate at any time (1). Treatment of psychosis may require continuous supply of drug to the brain. Conventional formulations may require high dosing frequency to maintain the drug within therapeutic plasma level for prolonged duration. Increased dosing frequency for psychotic may cause poor patient compliance, which remains a challenge to the pharmaceutical scientists. One useful approach to improve compliance is to dispense the drugs in controlled delivery systems like osmotic pump that releases the drugs in a controlled manner within therapeutic concentrations over a prolonged period of time and may also minimize the risk of emergence of potential toxicity (2).

Microporous osmotic pump tablet (MOPT) works on the principle of osmosis, where the drug moiety moves from its higher concentration to lower concentration area until equilibrium at both sides (3, 4). The MOPT generally consists of a compartment containing drug and osmotic agents (osmogen) covered with a microporous membrane (MPM) embedded with in situ micropores former. Water leachable polymers are present in MPM which get dissolved when it comes in contact with release media, creating in situ micropore formation generating osmotic pressure within MOPT to release the drug in controlled manner (5). The advantages of MOPT, that holds a prominent place among controlled release systems, are pH independent drug release, reduced adverse reactions, improved safety profile, enhancement of activity duration for drugs exhibiting short half-life and good in vitro-in vivo correlation without need of mechanical drilling contrary to EOPT since the micro pores are formed in situ (6, 7).

Quetiapine fumarate (QTF), a BCS class II drug, was chosen as a model drug. The dose of QTF was 25–50 mg twice to thrice in a day, then the dose was gradually increased up to 400 mg per day owing to its shorter plasma half life (6–8 h) (8). QTF shows pH dependent solubility – it is highly soluble in acidic environment, moderately soluble in water and in basic environment (9). For osmotic system, the solubility of drug should be within 50–300 mg/mL to attain zero order release rate (5). Thus, core needs to have sufficient osmotic pressure to deliver the drug outside. The moderate aqueous solubility of QTF is insufficient to generate very high osmotic

Abstract: The present work investigates the feasibility of the design of an enteric coated microporous osmotic pump tablet (ECMOPT) to prolong the drug release of an antipsychotic drug, quetiapine fumarate (QTF). The ECMOPT consisted of an osmotic core coated with a microporous membrane (MPM) made up of cellulose acetate and PEG 4000 as in situ micropore former. The effect of formulation variables such as concentration of sodium chloride, types of pore former (PEG 400, PEG 4000 and PEG 6000), coat thickness (100 and 200 µm) of MPM were evaluated for drug release characteristics. The FTIR, DSC and XRD analyses were carried out to characterize physico-chemical changes of powder blend and final formulation. SEM images have confirmed in situ micropores formation in MPM. A zero order release was obtained for QTF. The formulations were found to be stable up to 3 months when tested for stability at 40°C/75% RH.

Keywords: enteric coating, microporous membrane, osmotic pump tablet, polyethylene glycol, quetiapine fumarate

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pressure within the core compartment of tablet to deliver the drug by osmosis. Our system consists of a core tablet containing the drug, diluents, pH modulator, osmotic agent further coated with cellulose acetate (CA) containing in situ micropore former and a final enteric coat. Citric acid has been chosen as pH modulator expecting to increase the solubility by decreasing the pH and exerting osmotic pressure within the core compartment (10). Further, to increase the release of QTF from MOPT, sodium chloride was chosen as osmotic agent, because it could generate high osmotic pressure gradient to deliver poorly or moderately soluble drugs (5). The core tablet is coated with microporous membrane (MPM; 2% w/v cellulose acetate in acetone containing PEG 4000 as pore former) to form MOPT. To design and fabrication of ECMOPT, a MOPT may further be coated with enteric coating polymer (HPMCP 5.5) (Fig. 1).

QTF is gastric irritant in nature. Among various approaches, enteric coating of formulation with pH dependent solubility is most commonly employed approach to check the release of drug in the stomach. Phthalate derivatives (HPMCP 5.5) are most commonly used coating materials which get dissolved at pH 5.5 and thus drug is exposed to duodenal pH (> 5.5) (11). The present study was aimed towards the development of ECMOPT of QTF and to deliver a constant, predetermined amount of drug in solution form, over fixed span of time in the intestine and independent of the external environmental conditions. On extensive literature survey, no report has been found in the area of ECMOPT based oral drug delivery systems for QTF. The excipients used for the manufacturing of ECMOPT are GRAS (generally regarded as safe) within their IIG limits (acceptable safety limits from FDA).

MATERIALS AND METHODS

Materials

QTF was kindly procured from Jubilant Life Sciences (New Delhi, India) as a gift sample. HPMCP 5.5 was obtained from Ranbaxy (New Delhi, India) as a gift sample. The following chemicals and excipients were purchased from commercial sources and used as received: cellulose acetate (39.8% acetylation), polyvinyl pyrrolidone (PVP), mannitol, microcrystalline cellulose (MCC; Avicel PH101) and talc from Central Drug House (New Delhi, India). Acetone (AR grade) was purchased from Qualigens Chemicals (Mumbai, India). Dibutyl phthalate and PEG 400, 4000 and 6000 were purchased from S.D. Fine Chemicals (Mumbai, India).

Drug – excipient compatibility studies

Fouier Transform Infrared (FT-IR) spectroscopy

Infrared spectra were recorded on FT-IR instrument (Shimadzu, Japan) equipped with temperature controlled high sensitivity DLTGS detector. Samples were prepared and compressed with KBr on Minipress (Jasco, Japan) to form discs. The compressed discs were scanned over 400 to 4000 cm⁻¹ and characteristic peaks were recorded and evaluated (12).

X-ray diffraction (X-RD)

Powder X-ray diffraction (PXRD) patterns of QTF and physical mixture were collected in transmission using an X-ray diffractometer (Rigaku, Japan) with Cu-rotating anode (radiation; λ = 1.54 nm) generated at 18 kW. Powder diffractometer operating on Bragg-Brentano geometry was fitted with a curved crystal graphite monochromator in the diffraction beam from the range of 20–40° (2θ). The powder was packed into the rotating sample holder (13).

Differential scanning calorimetry (DSC)

The physical state of drug in the optimized formulation was determined by measuring the thermograms by differential scanning calorimetry (Shimadzu DSC-50, Japan). The instrument was calibrated with 5 mg of indium at a heating rate of 10°C/min. The thermal behavior was studied by

Figure 1. Schematic diagram describing stepwise mechanism of pore formation and drug release from ECMOPT composed of MOPT, surrounded by enteric coating layer. Diagram also describing the release of enteric coating after it comes in contact to release media (pH > 5.5) followed by in situ micropores formation in MPM layer.
heating 4–8 mg of the QTF and physical mixture of QTF and excipients at a rate of 10°C/min from 50 to 220°C in a hermetically sealed pan with a pinhole in the lid under a nitrogen purge of 20 mL/min with an empty pan as a reference (14).

Preparation of core tablets

Core tablets of QTF were prepared by wet granulation method. Different compositions (Table 1) of drug and excipients (except talc) were passed through no. 60 sieves and mixed together for 10 min in a glass bottle. The blend was granulated using 5% w/v solution of PVP in acetone and wet mass was passed through no. 36 mesh sieve. Granules were dried in oven at 50°C for 2 h. Dried granules were lubricated with talc (passed through no. 60 mesh sieve). Lubricated blend was compressed with average weight of 300 mg on a single station tablet punching machine (Cadmach, Ahmedabad, India) fitted with 8 mm round standard concave punch (12).

Fabrication of microporous osmotic pump tablet (MOPT)

MOPT tablets were prepared by coating core tablets with a mixture of cellulose acetate (2% w/v), PEG 4000 (30% w/w of cellulose acetate) and acetone to form MPM. Conventional laboratory coating pan (Scientific Instruments, New Delhi, India) fitted with three baffles placed at angle of 120° having outer diameter of 10 cm was used. Coating process was optimized (50 tablets/batch) with the following conditions: preheating temperature, 50°C; preheating time, 30 min; inlet temperature, 48–50°C; outlet temperature, 38–40°C; atomizing air pressure, 1.1 bar; spray rate, 6–10 mL/min. The layered tablets were further dried in the coating chamber for additional 30 min at 50°C to evaporate the residual moisture. The coated tablets were withdrawn from coating pan, when desired coating weight was achieved (15).

Fabrication of enteric coated microporous osmotic pump tablet (ECMOPT)

MOPT was coated with a solution of HPMCP 5.5 (2% w/v) in dichloromethane (enteric coating solution) using dibutyl phthalate (10% w/w of HPMCP 5.5) as plasticizer. The coating was performed in conventional laboratory coating pan as described above and dried additional 30 min at 50°C to evaporate the residual moisture. Coating was continued until desired weight of enteric coated layer was layered on tablet. The tablets were dried in the coating pan for additional 30 min (16).

Powder characterization

Angle of repose

Angle of repose (θ) of granules was determined by funnel method. Funnel slope of 32° to the vertical axis and 3.2 cm orifice opening was used. The granules were allowed to flow through funnel freely onto the clean surface. Funnel was placed in such a height that bottom tip of funnel should not touched apex of heap of granules (17). Height and radius of cone were measured through scale and values were placed in equation:

\[ θ = \tan^{-1} \frac{h}{r} \]

where, \( θ \) = angle of repose; \( h \) = height of cone; \( r \) = radius of cone base.

Bulk and tapped density

Bulk and tapped density of granules were determined using tap density tester USP method-II (ETD-1020, Electrolab, India) (18). Carr’s compressibility index and Hausner ratio were represented by Eq. 2 and 3:

\[ \text{Carr’s compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \]

\[ \text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Evaluation of tablets

Thickness

The thickness of six tablets was measured using digital vernier calipers (Absolute Digimatic, Mitutoyo Corp., Japan). The thickness of each tablet was deviation from ± 5% of mean value.

Hardness

Hardness of tablets was determined using digital hardness tester (Campbell Electronics, Mumbai, India). The instrument was calibrated using standard weight of 5 kg.

Weight variation test

Twenty tablets were selected at random and average weight was determined. Individual tablet was weighed and compared with the average weight. Percentage deviation and weight variation were calculated for all the batches (18).

Content uniformity test

Ten tablets were weighed and powdered. The powder weight equivalent to 300 mg of QTF was dissolved in a 100 mL volumetric flask filled with distilled water using magnetic stirrer (Eltek MS 203, India) for 24 h. Solution was filtered through Whatman filter paper No. 1, diluted suitably and analyzed spectrophotometrically at 289 nm (Shimadzu-1700, Japan) (19).
Effect of pH

It is important to maintain the physical integrity of coating layers of ECMOPT. ECMOPT was evaluated for physical integrity of coating in USP XXIV release apparatus type II in SGF (pH 1.2) for the first 2 h, phosphate buffer pH 4.5 for next 2 h and pH 6.8 for remaining hours, and volume being 900 mL. The temperature was maintained at 37 ± 0.5°C and rotation speed was 50 rpm (18). The dimensional stability of ECMOPT was observed visually. The measurement was carried out for each series of tablet (n = 3).

Measurement of coat weight and coat thickness

Ten ECMOPT were weighed and average weight was determined. Average weight of coat was calculated by deducting average weight of precoated tablets from average weight of coated tablet and the thickness was measured by digital vernier calipers.

In vitro drug release

In vitro release study of ECMOPT was determined using USP XXIV release apparatus type II (Campbell Electronics, Mumbai, India) at 50 rpm in 900 mL of simulated intestinal fluid (SIF; pH 6.8), maintained at temperature of 37 ± 0.5°C. At predetermined time intervals, 1 mL aliquots were withdrawn, filtered and analyzed spectrophotometrically at 289 nm (10). Three replicates were performed (n = 3).

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations, release studies of the optimized formulations were conducted according to pH change method. The release media were: simulated gastric fluid (SGF; pH 1.2) for first 2 h, phosphate buffer (pH 4.5) for next 2 h, followed by phosphate buffer (pH 6.8) for remaining periods of 20 h (18).

Effect of agitation intensity

To study the effect of agitation intensity of the release media at various rotational speed 50, 100 and 150 rpm, stirred and stagnant conditions were induced in a dissolution apparatus of USP XXIV, type-II. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically at 289 nm (19).

Scanning electron microscopy (SEM) study

Surface morphology and effect of release media on MPM was studied by SEM (JEOL, JSM-6100, Japan). Before and after 24 h of release in SIF (pH 6.8) the microporous membrane was air dried and placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape. The mounted samples were sputter coated for 5 min with gold using fine coat ion sputter (JEOL, JFC-1100, Japan) and examined under 100× SEM (5).

Accelerated stability studies

Accelerated stability studies of optimized tablets of ECMOPT were carried out at 40°C/75% RH for 3 months according to ICH guidelines. The tablets were packed in high density polyethylene (HDPE) container and placed in stability chamber (Narang Scientific Works, New Delhi, India). The samples were withdrawn after 3 months and evaluated in terms of drug content, hardness, compatibility and drug release (20).

Statistical data analysis

Results of in vitro drug release profile were expressed as the mean ± standard deviation (SD). Release profiles of various batches were compared using model independent pairwise approach, which includes calculation of difference factor ($f_1$) and similarity factor ($f_2$).

$$f_1 = \frac{\sum |R_j - T_j|}{\sum R_j} \times 100 \quad \text{Eq. 4}$$

$$f_2 = 50 \times \log \left[ \frac{1 + (1/n) \sum R_j - T_j}{\sum \left( R_j - T_j \right)^2 \times 100} \right] \quad \text{Eq. 5}$$

where, $n$ is sampling number, $R_j$ and $T_j$ are percent dissolved of the reference and test products at each time point $j$. The two release profiles are considered to be similar, if $f_1$ value is lower than 15 (between 0 to 15) and $f_2$ value is more than 50 (between 50 to 100) (21).

Mathematical modeling of in vitro release kinetics

Various pharmacokinetic models were assessed by fitting in vitro release data into different mathematical models to analyze the release of pharmaceutical dosage from and the best fitting release mechanism were ascertained. These models were zero-order kinetics, first order kinetics, Higuchi and Korsmeyer-Peppas employing the following set of equations:

Zero order; \[ C_0 - C_t = Kt \quad \text{Eq.6} \]

First order; \[ \log C_t/C_0 = Kt \]

or \[ \log C_t - \log C_0 = Kt \quad \text{Eq. 7} \]
Higuchi:  \[ \frac{Q}{Q_0} = Kt^{1/2} \]  
Eq. 8

Korsmeyer-Peppas:  \[ \frac{Q}{Q_0} = Kt^n \]  
Eq. 9

where \( C_0 \) is the initial concentration of drug in tablet (concentration that is to be released outside), \( C_t \) is concentration at time \( t \) present in the solution (concentration that is released outside tablet), \( K \) is the rate constant, \( t \) is time, \( Q/Q_0 \) is the fraction of drug released and \( n \) is release exponent in Korsmeyer-Peppas model. The value of \( n \) is used to indicate different release mechanisms. Value of \( n = 0.5 \) indicates Fickian (case I) release, \( > 0.5 \) but \( < 0.89 \) for non-Fickian (anomalous) release, \( n = 1 \) indicates case-II transport (zero-order release) and \( > 1 \) indicates super case II type of release (22).

RESULTS AND DISCUSSION

Spectroscopic studies

Figure 2 shows characteristic peaks of excipients, pure drug and physical mixture of both and after 3 months storage the spectra revealed no incompatibility between drug and excipients.

Diffractograms of excipients, pure drug, and physical mixture of both and after 3 month storage are shown in Figure 3. The major peaks for QTF was seen at 12, 15, 18, 22 and 25° at angle of diffraction (2θ) and remained the same in physical mixture. There was no sign of formation of any new peak or
absence/shift in original characteristic peak of QTF. The XRD data revealed crystalline nature of drug, physical compatibility between drug and excipients and stability of ECMOPT even after 3 months of storage.

The physical state of drug in the optimized formulation was determined by differential scanning calorimetry (DSC). Interactions in the samples were ascertained from DSC by changes in the thermal events, such as elimination of an endothermic or exothermic peak, or appearance of any new peak. It is to be noted that some broadening and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction. Figure 4 shows a DSC thermograph of pure QTF (before storage) with a sharp endothermic peak corresponding to melting point of QTF at 173°C. Thermographs of QTF with excipients did not show any significant shift in endothermic peak of QTF even after 3 month storage under ICH guidelines (40°C and 75% RH for 3 months) (13).

**Formulation aspects of core tablet**

In our preliminary studies, the core drug tablet without any osmotic agent was coated with MPM composed of 2% cellulose acetate in acetone. It is evident from Figure 5 that the drug release from the batches without an osmotic agent is very low. This could be due to low osmotic pressure inside the tablet core due to moderate solubility of QTF. Assuming a tablet core of pure drug, the fraction of drug released with zero-order kinetics is given by:

$$F(z) = 1 - \frac{S}{\rho}$$  \hspace{1cm} \text{Eq. 10}

where $F(z)$ is the fraction released by zero-order kinetics, $S$ is the drug's solubility (g/cm³), and $\rho$ the density (g/cm³) of the core tablet. Drugs with a solubility of $< 50$ mg/mL would be released with $> 95\%$ zero-order kinetics according to Eq 10. However, the zero order release rate would be slow according to Eq 11, due to the small osmotic pressure gradient.

$$\frac{dm}{dt} = \frac{A}{h} \Delta L \left( \Delta \pi - P \right)$$  \hspace{1cm} \text{Eq. 11}

where; $\frac{dm}{dt}$ is the drug delivery rate; $A$ and $h$ are the membrane area and thickness, respectively; $C$ is the concentration (or the solubility, when excess of drug is present in the core) of drug in the dispensed fluid, $\Delta \pi$ is the osmotic pressure difference across

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**Table 1. Formula for different ingredients used in development of ECMOPT**

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</th>
<th>Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>QTF</td>
<td>173</td>
</tr>
<tr>
<td>Mannitol</td>
<td>–</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>–</td>
</tr>
<tr>
<td>Citric acid</td>
<td>–</td>
</tr>
<tr>
<td>MCC</td>
<td>117</td>
</tr>
<tr>
<td>PVP-K30</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Pore former (mg/tablet)</td>
<td>PEG 4000</td>
</tr>
<tr>
<td></td>
<td>PEG 400</td>
</tr>
<tr>
<td></td>
<td>PEG 6000</td>
</tr>
<tr>
<td>Thickness of MPM (µm)</td>
<td>100</td>
</tr>
</tbody>
</table>

QTF = quetiapine fumarate, MCC = microcrystalline cellulose, CA = cellulose acetate, MPM = microporous membrane.
the film, $\delta L_p$ is the hydraulic permeability of the membrane and $P$ is the hydrostatic pressure within the core compartment (23). By combination of above two equations Eq. 10 and Eq. 11, another equation can be derived as Eq. 12 which is given by:

$$\frac{dm}{dt} = P_m A_m S_d \left( \pi_i - \pi_o \right) / h_m$$  

Eq. 12

where $dm/dt$ is the rate of drug release per unit time, $P_m$ is the permeability of membrane, $S_d$ is the solubility of solute (drug), $A_m$ is the area of membrane, $\delta$ is the osmotic pressure inside the OPT, $\pi_i$ is the osmotic pressure outside the tablet and $h_m$ is the membrane thickness (23).

The rate of drug release from an osmotic system is directly proportional to aqueous solubility of drug and osmotic pressure developed inside the tablet. Thus, low solubility drug requires osmotic agents and solubility enhancers (wicking agents). The above equations give an idea of rate of drug release per unit time but not the exact value. Thus, hypothesis about effect of solubility of drug can be interpreted.

The in vitro release profile of preliminary batches showed less than 5% drug release within 24 h (Fig. 5, batch I). The incorporation of osmotic agents (mannitol, sodium chloride) increased the release significantly (batch II). The desired aqueous solubility of a drug to formulate as osmotic pump tablet is 50–300 mg/mL (4). QTF is weakly basic drug having pKa value 6.8 thus exhibiting higher aqueous solubility in acidic pH (9). Addition of pH modulating agents (citric acid) in batch III is expected to increase the drug release by creating acidic environment inside the core of ECMOPT (Fig. 5).

**Effect of osmotic agents**

QTF is moderately soluble drug exerting low osmotic pressure, thus, to increase its release, core needed to have sufficient osmotic pressure to deliver the drug outside the tablet. Stronger osmotic agents would be expected to produce greater osmotic pressure in core. In order to study the effect of different types of osmotic agent, batch IV containing mannitol and batch V containing sodium chloride (strong osmotic agents) were compressed and coated with MPM. The in vitro release profile of batch IV and batch V is shown in Figures 5 and 6, respectively. It is clearly evident that the release of batch IV is lower than batch V. This is so because release of drug is dependent upon the osmotic pressure inside (Fig. 6). The higher the osmotic pressure inside the better will be the release of drug from MOPT. The osmotic pressure of sodium chloride is almost 10 times higher (356 atm) than that of mannitol (38 atm) (4, 24). Thus, sodium chloride best suits as an osmotic agent for moderately or poorly soluble drug for the formulation of OPT. On increasing the concentration of sodium chloride from batch V to batch VIII drug release increases (Fig. 6).

**Effect of pH modulating agent**

The performance of pH modulating agent was studied by comparing in vitro release profile of batch
III and batch IV (containing citric acid) with batch I and II without citric acid in SIF (pH 6.8) at previously described conditions. Solubility of QTF is increased significantly in acidic environment and below pH 5.5, QTF is freely soluble (9). The in vitro release profile of batch III and IV is higher than batch I and II (Fig. 5). The increase in drug release could be due to two facts; first, citric acid maintains the acidic micro environment inside the tablet core. Thus, increases the solubility of drug thereby increases the osmotic pressure inside. Secondly, citric acid itself acts as an osmotic agent that synergizes the release of drug (4, 24). However, it is seen in Figure 5 that on increasing the concentration of citric acid (batch IV), there is initial burst release followed by gradual decrease in release onward. The pH inside the core could be due to the fact that higher concentration of citric acid initially decreases the pH significantly thus giving initial burst release. This pH then may gradually be increased due to
buffering capacity of release media (SIF pH 6.8) thereby decreasing the solubility of QTF and release subsequently. Thus citric acid cannot be used beyond a certain threshold limit.

Formulation aspects of coating systems

**Microporous membrane**

Pore formers were added in coating agent solution to form *in situ* micropores in MPM. The polymers used as pore former should be hydrophilic in nature so that after coming in contact with release media they get dissolved and pores are formed *in situ*. Polyethylene glycol (PEG) derivatives (PEG 400/600/1500/4000/6000) are most commonly used pore formers. In order to compare the effect of different grade of pore formers on *in vitro* release profile, batch VII containing PEG 4000, batch VIII containing PEG 400 and batch IX containing PEG 6000 were considered. The order of *in vitro* release profile of different batches were found as VII > IX > VIII in Figure 6. It is clearly evident that an increase in grade of pore former (PEG from 400 to 6000) significantly increases the release of QTF. Thus, grade of polymer has direct effect on the drug release. The release of drug is purely dependent upon the size and number of micropores formed *in situ* and the size of pore formation depends upon the molecular size of polymers. High grade polymer has high molecular size and weight and vice versa. On increasing the grade of polymer, the size of pore is increased (i.e., pore size PEG 400 < 4000 < 6000). In case of batch VIII, PEG 400 is of low grade thus pore size is very small (Fig. 7B) which is gradually increasing on increasing the grade from 4000 (Fig 7C) to 6000 in which PEG 6000 possesses the widest micropore compared to other. Thus, batch IX has the highest drug release profile (25).

To study the effect of coat thickness on *in vitro* release profile of QTF, batch VII having coat thickness 100 µm was compared with batch X having coat thickness 200 µm. It was evident from the release profile (Fig. 6) that increasing the coat thickness increases the lag time and vice versa. Further increase in coat thickness decreases the drug release but was not very significant. This may be so because coating thickness increase the time for solvent to penetrate the SPM, which increases the lag time but once the solvent dwelled inside, osmotic pressure will rise and releases the drug but slowly compared to batch VII of lower thickness (5).

Scanning electron microscopy studies (SEM)

In order to study the changes in the membrane structure of cellulose acetate (CA) of optimized formulation (batch VII) throughout the release procedure and the mechanism of drug release from MOPT, the membranes of coated tablets obtained after release studies, were investigated at magnification of 100x. The leaching of PEG from the membrane leads to the *in situ* micropores formation and thus the release of drug takes place. Figure 7A shows the smooth surface of MPM containing PEG 4000 before release. Figures 7B and 7C represent the membrane obtained after release studies in SIF. Figure 7B (batch VIII) and 7C (batch VII) show SEM micrographs of membrane compositions of different grade of water leachable polymer (PEG) (Fig. 7B and 7C containing 30% PEG 400 and PEG 4000 w/w of CA, respectively, with the weight gains of 5% w/w of core tablet weight). Prior to dissolution (Fig. 7A), no porous structure in MPM was observed with the presence of PEG 4000 as pore former. The surfaces of coated tablets were yellowish, glossy and the membrane appeared to be integral and smooth with no visible imperfections. During dissolution, the enteric membrane gets dissolved but micropores formation was still not significant in the MPM containing PEG 400 (batch VIII). This is because of low molecular size of the PEG which impedes the drug (Fig. 7B), whereas significant numbers of micro channels were observed under SEM micrograph of MPM containing PEG 4000 which possibly acted as an exit for the drug release (Fig. 7C).

When comparison was made in terms of *in vitro* release, between the membranes of Figures 7B and 7C containing 30% PEG 400 and PEG 4000 w/w of CA, respectively, it was found that the latter became more porous and leachable to drug after release studies. The size of micropores in Figure 7B containing PEG 400 was in the range of 2–8 µm, whereas microporous channels were observed in Figure 7C containing PEG 4000 (batch VII). The SEM study indicated that *in situ* micropores formation was dependent upon molecular size of pore former (hydrophilic polymers). The numbers of pores were directly proportional to the initial level of pore former present in the membrane. From the above study it can be concluded that for a moderately soluble drug, higher molecular grade of micropore former is preferred to lower molecular grade for optimum release of drug within controlled manner.

QTF is gastric irritant thus to avoid the release of drug in the stomach it is necessary to coat the system, either incorporating a pore former in CA coating solution which get dissolved or acted by colonic bacteria (like guar gum which get dissolved in colon by the action of colonic bacteria) and releases the
The whole system could be coated with such a polymer which must be insoluble in acidic environment like phthalate derivatives (e.g., HPMCP 5.5, CAP, Eudragit L 100, Eudragit S 100, Eastacryl 30D etc.). These insoluble polymers will prevent the drug release in the stomach. Our formulation consists of an enteric coating of HPMCP 5.5, which would get dissolved at pH 5.5.

### Effect of pH

The effect of pH on release profile was studied on optimized batch VII under three different pH conditions, pH 1.2 (SGF) for first 2 h, pH 4.5 for next 2 h and pH 6.8 for remaining 20 h. From batch VII less than 0.5% drug was released at pH 1.2, whereas almost 10% and 85% of drug was released after 4 and 24 h at pH 4.5 and pH 6.8, respectively. It is seen in Figure 8 that drug release at pH 4.5 is a little higher than at pH 6.8, but drug release rate at pH 4.5 was not much more significant than at pH 6.8. This could be due to the fact that below pH 5.5, QTF is freely soluble as compared to pH 6.8. Linear pattern of drug release under two different pH conditions shows that the drug release from ECMOPT was found to be independent to the pH of surrounding environment. Thus, ECMOPT system follows zero order release kinetic at all pH conditions (4).

Less than 0.5% drug release within 2 h in pH 1.2 clearly represents the robustness of enteric coat.

### Effect of agitation intensity

To assess the effect of agitation intensity on release profile, three different agitation intensities (50, 100, and 150 rpm) were selected for batch VII. The difference ($f_1$) and similarity ($f_2$) factor for ECMOPT at three different rotation speeds are presented in Table 2. The difference factor ($f_1$) and similarity factor ($f_2$) values were found to be 6.146 and...
78.942 (50 rpm), 12.648 and 65.314 (100 rpm), and 21.094 and 54.059 (150 rpm). Release profile of QTF from ECMOPT at different agitation intensities are shown in Figure 9. It has been found that different rotation speeds could not significantly affect drug release. Thus, it can be expected that a large extent of drug release from ECMOPT is dependent upon osmotic pressure built inside the ECMOPT and independent of the hydrodynamic conditions of the absorption site (4).

Evaluation of optimal formulation

It is necessary to evaluate all the pharmacopoeial or non-pharmacopoeial process parameters of tablet manufacturing (bulk density, tapped density, angle of repose, compressibility index, hardness, friability and content uniformity), to obtain reproducible and robust ECMOPT tablets. Batch VII was subjected to various pharmacopoeial and non-pharmacopoeial tests, results of which are listed in Table 3. The lubricated granules had shown excellent free flowing characteristic as demonstrated by angle of repose (< 30). Compressibility parameters like Carr’s index and Hausner ratio were 27.2% and 1.4, respectively, and also showed passable limit on the scale of flowability. Hardness (7 ± 0.5 kg/cm²) and friability (0.3%) of the tablet were found to be good and within the limits. An ideal zero order release profile gives linear equation between C<sub>t</sub> vs. t, and may be considered as reference. The regression coefficient (R²) value for reference should be 1. The release profiles of all the developed batches were compared to reference and difference factor (f<sub>1</sub>) and similarity factor (f<sub>2</sub>) were calculated and presented in Table 2.

It was found that optimized batch VII of ECMOPT showed desired and more controlled release compared to other batches (Fig. 6). The release from batch VII was found to be 13.6%, 29.21%, 56%, 84% and 98% in 3rd, 6th, 12th, 18th and 24th h. There were no visible cracks in the coating and it remained intact in all the batches after 24 h of release study.

Accelerated stability study

Stability study provides the evidence on the quality of drug product. ECMOPT (batch VII) formulation was studied for 3 months according to ICH guidelines. Samples withdrawn after 3 months showed no significant difference in the characteristic peaks of FTIR, XRD, and also in terms of physical properties, drug content and hardness. The in vitro release before and after 3 months storage was found to be similar.

Mathematical modeling of in vitro release kinetics

In vitro release data of different batches were fitted to various mathematical models in order to ascertain the kinetics of drug release. Based on Korsmeyer-Peppas power model, drug release data were analyzed for curve fitting and drug release exponents (n). Results confirmed that batches I, II, VI and X showed super case II type of release, batches III, IV and V showed non-Fickian diffusion kinetics, whereas batches VII, VIII and IX showed zero order kinetics. The linear nature of plots
between percent cumulative drug release and time suggests that batch VII followed very close zero-order kinetics, which was further confirmed by the higher sum of correlation coefficient ($R^2 = 0.9964$, $n = 0.9351$, almost equivalent to 1) among all batches (Table 4) (22).

CONCLUSION

From the present study an optimized ECMOPT for QTF, a gastric irritant and a moderately water soluble drug, was successfully prepared with the aim of improving therapeutic performance for longer duration. Developed ECMOPT showed excellent zero order drug release up to 24 h. The data of physical parameters provided an insight for selection of excipients for the development of ECMOPT. Drug release from ECMOPT system was found to be independent on pH and hydrodynamic conditions of the release medium. However, there was no release of drug from ECMOPT in acidic environment (pH 1.2). Mathematical modeling of drug release data suggested that ECMOPT could follow zero order kinetics and provide required controlled release up to 24 h. Accelerated stability data confirmed that the developed ECMOPT were stable and complied with reproducible release performance. In view of overall results reported in the present study, it may be proposed that ECMOPT can be an excellent osmotic drug delivery platform for controlled delivery of moderately water soluble class of drugs with the aid of strong osmotic agents. ECMOPT also suits for industrial point of view since they need not be drilled mechanically, an important hurdle in pharmaceutical industry.

REFERENCES


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