Original article

DELIVERY OF POORLY WATER SOLUBLE DRUG FROM SWELLABLE ELEMENTARY OSMOTIC PUMP AND EFFECT OF FORMULATION VARIABLES

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Abstract

An elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble drugs was designed and studied effect of composition factors. The designed system, called swellable elementary osmotic pump (SEOP). . Effect of composition factors on the release of drug from the SEOP tablets containing a poorly water-soluble drug, etodolac, have been studied. The release behaviour of drug from different formulations of this dosage form was studied at pH 6.8 for a period of 24 h. The formulations were compared based on four comparative parameters, namely, D_{24h} (total release after 24 h), t_L (lag time), RSQ_{zero} (R square of zero order equation) and $D_{\%zero}$ (percentage deviation from zero order kinetics). The drug release profile from osmotic devices showed that the type of polymer in the core formulation can markedly affect the drug release. Results showed that SEOP could be a novel way for the oral administration of poorly water soluble drug like etodolac.

Key words: Controlled drug delivery, Etodolac, SEOP, Zero order release, Lag time.

Suda Az Çözünür İlacın Şişebilen Basit Osmotik Pompa ile Taşınımı ve Formülasyon Değişkenlerinin Etkisi

Suda az çözünen ilaçların etkin taşınımı için basit bir osmotik pompa tablet (EOP) tasarlandı ve bileşen faktörlerinin etkisi çalışıldı. Tasarlanan sistem şişebilen basit osmotik pompa (SEOP) olarak adlandırıldı. Formülasyon parametrelerinin suda az çözünen bir ilaç olan etodolak içeren SEOP tabletlerinden ilaç salımı üzerine olan etkileri incelendi. Bu dozaj formunun farklı formülasyonlardan ilacın salımı pH 6.8'de ve 24 saat boyunca değerlendirildi. Formülasyonlar D_{24h} (24 saat sonundaki toplam ilaç salımı), t_L (gecikme süresi), $RSQ_{sıfır}$ (sıfırıncı derece eşitlik için r^2) ve $D_{\%sıfır}$ (sıfırıncı derece kinetikten yüzde sapma). Osmotik cihazlardan ilaç salım profile çekirdek formülasyondaki polimer tipinin ilaç salımı üzerine önemli ölçüde etki ettiğini göstermiştir. Sonuçlar, SEOP'nın etodolak gibi suda az çözünen ilaçların oral uygulaması için yeni bir yol olabilceğini göstermiştir.

Anahtar kelimeler: Kontrollü ilaç salımı, Etodolak, SEOP, Sıfırıncı derece salım, Gecikme süresi.

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INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). Among various NDDS available in the market, per oral controlled release (CR) systems hold the major market share because of their advantages over others (1). Majority of per oral CR systems fall in the category of matrices, reservoirs and osmotic devices. Osmotic systems for controlled drug-delivery applications are well established, both in human pharmaceuticals and in veterinary medicine. Several one compartment and two-compartment osmotic systems have been reviewed previously (2-5). Osmotic drug delivery systems utilize osmotic pressure as energy source and driving force for delivery of drugs. pH, presence of food and other physiological factors may affect drug release from conventional CR systems (matrices and reservoirs), whereas drug release from per oral osmotic systems is independent of these factors to a large extent (6,7). Many different systems have been developed based on principles of osmotic pressure such as elementary osmotic pump, EOP (5, 8), sandwiched osmotic tablet system, push–pull systems (6,9) controlled porosity osmotic pumps(10-12), asymmetric membrane osmotic pumps (2,13-15), single composition osmotic tablet, SCOT (1) and osmotic systems made by swellable core technology (2). In 1974 Theuwes invented elementary osmotic pump (16). This system represents the definitive simplification of the original Rose–Nelson pump (8). EOP was fabricated as tablet containing an osmotic agent having suitable osmotic pressure coated with semi-permeable membrane. This membrane contains an orifice of critical size through which agent is delivered (16, 17). In operation the drug or osmotic core acts by imbibing water from the surrounding medium via semi permeable membrane, dissolving the drug and osmogen and delivering the drug with constant rate under the effect of constant osmotic pressure generated inside the core (18). EOPs are generally applied for delivering of high to moderate water-soluble drugs (19). Because of the simple structure and high efficiency, EOPs are the most commercially important osmotic devices. Procardia XL and Adalat CR (nifedipine), Acutrium (phenylpropanolamine), Minipress XL (prazocine) and Volmax_ (salbutamol) are examples of EOPs available in the market (1).

Etodolac is non-steroidal anti-inflammatory drug (NSAID) acting by a preferential inhibition of cyclo-oxygenase- 2 (COX-2) enzymes. It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, osteoarthritis, and for the treatment of acute pain. It has an elimination half-life of 7 h, and the recommended oral dose, 200 to 400 mg, is given every 6 to 8 h to a maximum of 1.2 g daily (20). To provide the desired drug concentration at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency, controlled-release preparations for once-daily use are desirable.

In this study, a swellable elementary osmotic pump (SEOP) for delivery of an insoluble drug with constant release rate (zero order release) was developed. In the core of this device, a significant amount of water-swellable and gel forming polymer(s) as well as wetting agent is employed. In these systems, the hydrostatic force were produced by osmotic agents and polymer swelling force employed concurrently for driving the drug out of the system through the orifice. After exposure of this system to water, imbibed water through the system was absorbed by a gelling agent and a uniform gel containing drug particles formed inside the device. Wetting agent which was used in formulations helps in uniform dispersion of the drug and prevents agglomeration of drug particles by enhancing the wettability of the particles. Further water imbibitions through the SPM increase the gel volume and push the drug and gelling agent out of the device through the small orifice. In order to optimize release rate (a uniform and constant drug release from SEOP devices) from the osmotic devices the effects of type and amount of gelling agent, type and percent of osmotically active agents and wetting agent, amount of plasticizers, membrane thickness and orifice diameter were studied.

EXPERIMENTAL

Materials

Etodolac powder (a poorly water-soluble drug) was gifted by Jai Radhe Sales, (Gujrat, India). Cellulose acetate, Carbopols 940 cps and NaCMCs 200 cps, were purchased from Sigma Aldrich (India). HPMCs K100M and E5LV, and PVP K30 were supplied by SD Fine (India). NaCl, KCl, CaCl$_2$, fructose and other chemicals such as Sodium lauryl sulphate (SLS), caster oil, potassium dihydrogen phosphate, acetone, ethanol and glycerin were procured from (Merck, Germany).

Method

Determination of partition coefficient

The partition coefficient was determined in n-octanol and isotonic phosphate buffer pH 7.4 system. Both the phases and quilibrium concentration of etodolac was measured by UV spectroscopy. The partition coefficient was calculated by formula 1.

$$P = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

Drug-polymers compatibility study

The physicochemical compatibility between drug and polymers used in the formulations was studied by using differential scanning calorimetry (DSC, Perkin-Elmer-Pyris 6 DSC, USA) and fourier transform infrared (FTIR, Perkin Elmer, Spectrum BX, USA) spectroscopy. In DSC analysis, the samples were weighed (5 mg), sealed in flat bottom aluminum pans, and heated over a temperature range of 50-250°C at scanning rate 10°C/min. in an atmosphere of nitrogen. The thermograms obtained for drug, polymers and physical mixture of drug with polymers were compared.

The Infrared (IR) spectra were recorded by KBr pellet method and spectra were recorded in wavelength region 14000 to 400 cm^{-1}. The spectra obtained for drug, polymers and physical mixture of drug with polymers was compared.

Preparation of core tablets

The drug (etodolac), osmogent (fructose, mannitol, potassium chloride, or sodium chloride), a filler (Avicel® PH101) and SLS (as suspending and wetting agents) were separately passed through sieve no. 20. The sieved powders were mixed for 10 min using a pestle and mortar. Finally, the lubricants (magnesium stearate and talc) were added and gently mixed for another 3 min. with the previously blended powders. The core tablet formulae (F1–F12), each containing 200 mg etodolac and accurate weights of 400 mg of each mixture were pressed in the tablet press machine to produce the desired core tablets. The core tablets were prepared by direct compression using a single punch tablet press machine (Royal artist, Bombay, India) equipped with concave punches (10.0 mm). The composition of different core formulations (F1–F12) is listed in Table 1. All devices made from these formulations contained 1% caster oil, 2% glycerin (as plasticizers) and the thickness of coating layer (cellulose acetate) around the devices was 0.13 mm with an orifice of 600 µm.

Table 1. The compositions (milligrams) of core formulation for formulations F1–F12.

Formu-lations Code	drug	SLS	PVP K-30	HPMCs		Osmogenetic agents				Talc	MgSt	Avicel (PH101)
				E5LV	(K100M)	KCl	NaCl	Mann -itol	Fruct -ose			
F1	200	60	-	-	30	50	-	-	-	5	5	50
F2	200	60	-	-	30	-	50	-	-	5	5	50
F3	200	60	-	-	30	-	-	50	-	5	5	50
F4	200	60	-	-	30	-	-	-	50	5	5	50
F5	200	60	-	-	45	50	-	-	-	5	5	35
F6	200	60	-	-	60	50	-	-	-	5	5	20
F7	200	60	-	30	-	50	-	-	-	5	5	50
F8	200	60	-	45	-	50	-	-	-	5	5	35
F9	200	60	-	60	-	50	-	-	-	5	5	20
F10	200	60	30	-	-	50	-	-	-	5	5	50
F11	200	60	45	-	-	50	-	-	-	5	5	35
F12	200	60	60	-	-	50	-	-	-	5	5	20

Coating and drilling

The best achieved core tablets (formula F1) were coated with cellulose acetate. Cellulose acetate (5 g) and a plasticizer (caster oil or PEGs with different concentrations) were dissolved in 100 ml acetone–ethanol mixture (40:60 v/v). The cores were coated by spray coating pan (Karishma Pharma Machines, Mumbai, India). The membrane thickness of the basic formulations was regulated in the range of 130 ± 10 μm. For coated tablets, a small orifice was drilled through the one side of each coated tablet by standard mechanical micro-drills with various diameters (ranging from 355 to 900 μm). The semi- permeable membrane (SPM) compositions for different formulations are listed in Table 2.

Table 2. The compositions of membrane formulation for formulations F10–F22.

Formulation code	SLS(mg)	SPM thickness (mm)	SPM plasticizers (%w/w)		Orifice diameter (μm)
			Caster Oil	Glycerin	
F-13	60	0.13	1	2	355
F-14	60	0.13	1	2	450
F-15	60	0.13	1	2	555
F-16	60	0.13	1	2	755
F-17	60	0.13	1	2	900
F-18	60	0.13	0.5	2	600
F-19	60	0.13	1.5	2	600
F-20	60	0.13	2	2	600
F-21	60	0.13	1	-	600
F-22	60	0.08	1	2	600
F-23	60	0.20	1	2	600

In vitro release test

The drug release studies were performed in a USP Dissolution Tester Apparatus, type-I (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ, USA) at 37±0.5°C. The dissolution medium was phosphate buffer (pH 7.4, 900 ml) throughout the study period(11). The investigated formulae were placed within the baskets that rotated at a speed of 100 rpm(11). At definite time intervals, aliquot samples (5 ml) from the dissolution medium were withdrawn and filtered through a cellulose acetate membrane (0.45 μm). Replacement with an equal volume of fresh medium was done at each time of withdrawal. The time required for 50% drug release ($t_{50\%}$) from each formula was calculated. The results are expressed as mean values (± S.D.) of three determinations. The data were statistically analyzed (SPSS 14.0, Chicago, USA) applying one-way ANOVA at P value <0.05. Post hoc multiple comparisons between formulae were performed using the least square difference test.

Mathematical treatments

Release data obtained for various formulations were analyzed by different mathematical and statistical parameters. An ideal osmotic system should be able to release a high percentage of drug content with a constant release rate (zero order kinetics) during 24 h. Various parameters, mainly, Q_{24h} (percent of the drug released within 24 h), t_L (lag time of the drug release from device), RSQ_{zero} (R square of release data fitted to zero order equation) and $D_{\%zero}$ (mean percentage deviation of the release data from zero order release), were used to compare different formulations. Formulations with acceptable Q_{24h} (i.e., Q > 75%) were adopted for further evaluations. Among selected formulations, those with t_L > 4 h were rejected and other formulations were compared in terms of the RSQ_{zero} and $D_{\%zero}$. t_L is the time required to reach steady state release of drugs from osmotic devices, in fact, t is the time required for imbibitions of water through the movement of the formed gel containing drug particles through the small drug delivery orifice. It has been shown that since active material in the tablets does not induce

an osmotic effect due to its poor solubility in water, an initial lag-time of 1 h is necessary to moisten the device and the penetration of water into the core(21). The time, during which it is necessary to moisten the tablets, may be reduced by the addition of a surface-active agent to the coating material[21]. $D_{\% \ zero}$ was calculated according to Eq. (1)

$$D_{\%zero} = \frac{100}{N} \times \sum \frac{(Q_{cal} - Q_{obs})}{Q_{obs}} \tag{1}$$

Where, Q_{obs} is amount of the drug released measured in each sampling time, Q_{calc} is amount of the drug released which calculated using zero order equation for the same time and N is the number of sampling times.

Polymer suitability

This test was designed for initial analysis of swelling characteristics of different polymers for primary selection of suitable polymers for core formulation. In this test, different core formulations were made using NaCMCs (200 cps), Carbopols (940 cps), HPMCs (K100M and E5LV) and PVP K30 with different percentages (1%, 5%, 10%, 15%, 20%, 30% 40% and 50% w/w) as gelling agents. The prepared core formulations were coated with cellulose acetate by spray pan coating technique (with 130 ± 10 lm thickness) and tablets were drilled in various diameter on one side of the tablet. These systems were exposed to dissolution medium for 24 h. After this time, the SPMs of devices were examined optically and microscopically to determine which tablet maintain the integrity of membrane during 24 h dissolution test.

RESULTS

Etodolac showed partition coefficients (log octanol/buffer: 3.39±0.86). FTIR studies reveal that there is no appearance of new peaks and disappearance of existing peaks, which indicated that there is no interaction between the drug and polymer used. The characteristic ketone (C=O) stretching vibration at 1743 cm^{-1}, C-H bending at 1411 cm^{-1}, C-O stretching at 1265.0720 cm^{-1}, C-N vibration at 1313.29 cm^{-1} and aromatic C-H stretching at 744.38 cm^{-1} were identified in all the spectrums. The DSC analysis of drug alone showed a sharp endothermic peak at 146.1 °C corresponding to its melting point. The DSC analysis of physical mixture of drug and polymers demonstrated negligible change in the melting point of drug in the presence of any polymer mixture studied as shown in Fig. 1.
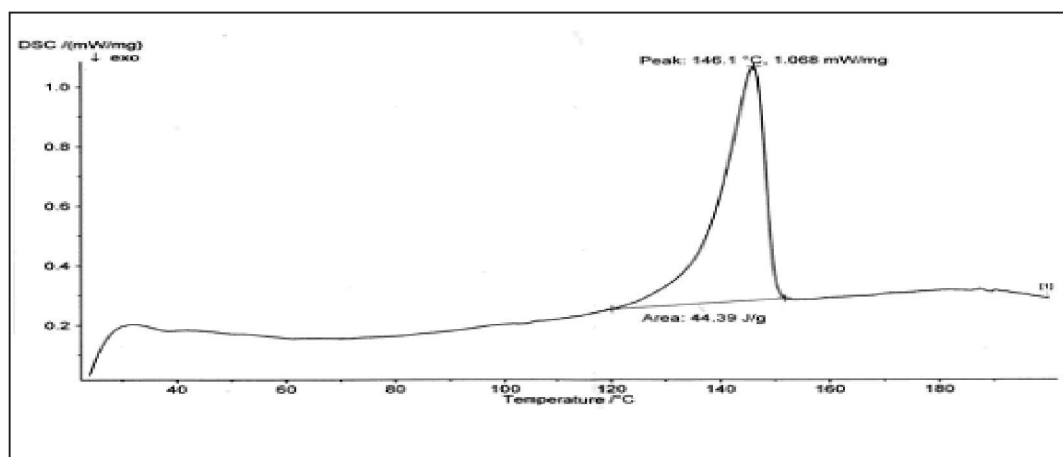

Figure 1. Thermogram of Etodolac with polymers.

Selection of suitable polymers for the formulation of osmotic device

Various polymers were incorporated in the core formulation to select suitable polymer(s) for the formulation of osmotic devices. The results showed that the osmotic devices containing Carbopols (940 cps) and NaCMCs (200 cps), disintegrated after a few hours of exposure to the dissolution medium. The osmotic devices containing HPMC K100M and PVP K30 concentration up to 30% w/w, remained intact after 24 h exposure to the dissolution medium. The results of this test are shown in Table 3. According to Table 3 the suitable polymers were selected and further formulations were prepared and their compositions are listed in Table 1.

Table 3. The results of polymer swellability test (+ indicate disintegrated devices and - indicates intact devices after 24 h exposure to dissolution medium).

Polymer (%w/w)	PVP-K30	HPMCs		NaCMCs	Carbopols
		(K 100M)	(E5LV)	(200cps)	(940 cps)
1	-	-	-	-	+
5	-	-	-	+	+
10	-	-	-	+	+
15	-	-	+	+	+
20	-	-	+	+	+
30	-	-	+	+	+
40	-	+	+	+	+
50	-	+	+	+	+

The effect of type and polymer concentration on the release rate from osmotic devices

Fig. 2 shows the drug release profiles of formulations containing constant amounts (30 mg) of different polymers (F1, F7 and F10 contained HPMC K100M, HPMC E5LV and PVP K30, respectively). As shown in this figure, the type of polymer in the core formulation can markedly affect the drug release from the osmotic devices. D_{24h} were 89.58%, 28.50% and 85.81% for the core formulations containing HPMC K100M (F1), HPMC E5LV (F7) and PVP K30 (F10) respectively. The shortest t_L (2.25 h) and the highest RSQ_{zero} (0.9967) belonged to formulation F1. Formulation F10 containing PVP K30 as gelling agent did not show suitable drug release profile (the high lag time, 6.01 h, high $D_{\%zero}$, 498.57, and low RSQ_{zero}, 0.8952).
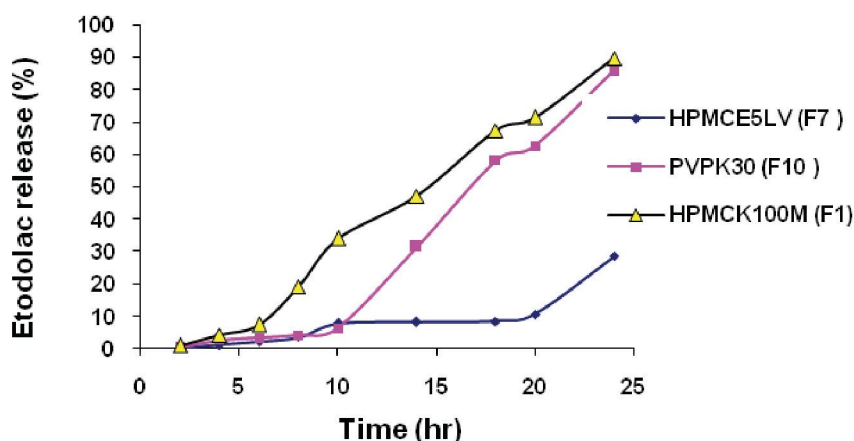
Figure 2. Release profile of etodolac from formulations containing HPMC K100M, HPMC E5LV and PVP K 30.

In order to investigate the effect of amount of HPMC K100M on release rate of etodolac, various concentrations of HPMC K100M were incorporated in the core osmotic device and the results of release studies for these SEOP systems are shown in Fig. 3. The release profiles of drug from SEOPs containing 30 mg (F1), 45 mg (F5) and 60 mg (F6) HPMC K100M are shown in Fig. 3. The results showed that there was no linear relationship between the percent drug released and amount of the polymer in the formulation.

The highest release rate was obtained for formulation F5 in the initial sampling times but the drug release data from this formulation did not follow zero-order kinetics in comparison with formulation F1 (RSQ_{zero} was 0.9967 and 0.8254 for F1 and F5, respectively). An increase in amount of polymer from 45 to 60 mg resulted in a decrease in the drug release from device in the first 10 h. According to this fig. 2, the optimum amount of HPMC K100M in this osmotic system is 30 mg. This amount of HPMC K100M has a capability to create suitable release pattern (Table 4).
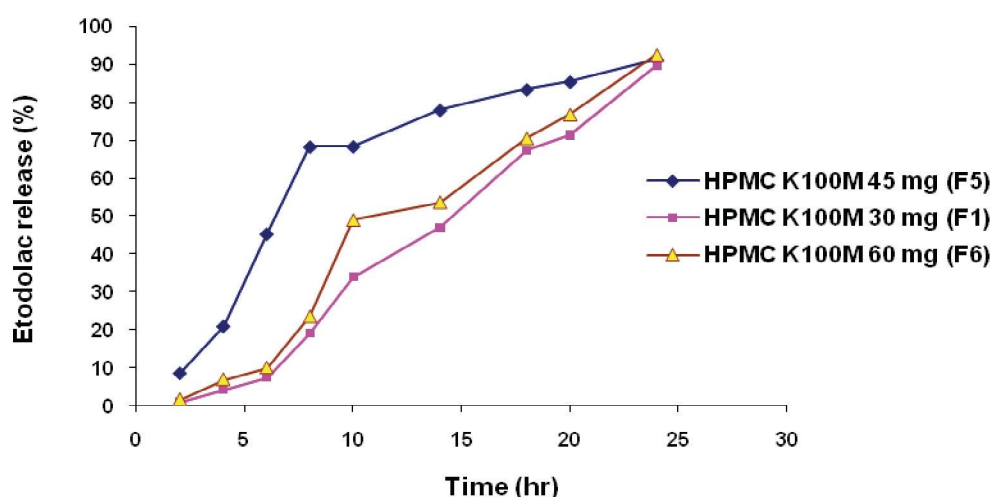

Figure 3. Release profile of etodolac from formulation containing different concentration of HPMC K100M.

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Type and amounts of osmotically active agents

Release profiles of formulations containing 50 mg KCl (F1), NaCl (F2), mannitol (F3) and fructose (F4) as osmotically active agents are shown in Fig 3.
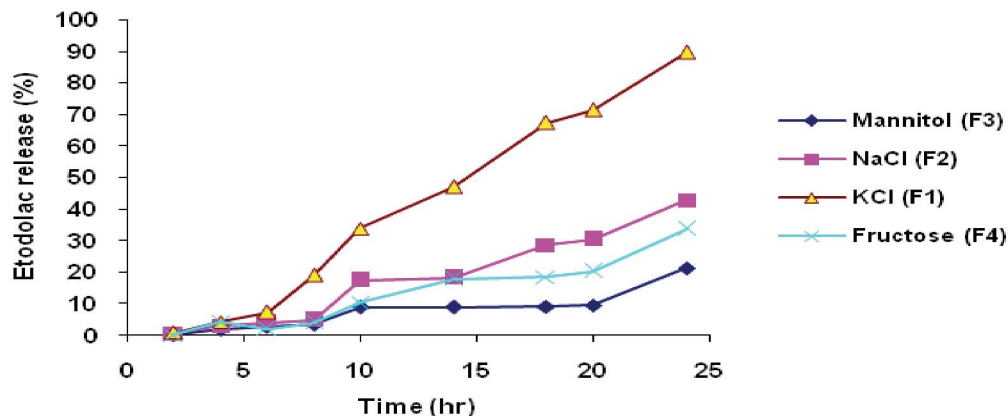

Figure 4. Release profile of etodolac from formulation containing Mannitol, NaCl, KCl, Fructose as osmotic agent in the core formulations.

As shown in this figure, the type of osmotically active agent in the core formulation dramatically affected the drug release from osmotic devices. The effects of osmotic agents on the release behaviour of drugs from osmotic devices have been studied(6,7,21). It is clear from the figure the highest release rate was observed for the devices containing KCl. D_{24h} for F3, F4 and F5 were 85.07, 31.44 and 15.25%, respectively. Comparing RSQ_{zero} values of release data from osmotic devices containing fructose, NaCl or KCl showed the highest RSQ_{zero} for the device containing KCl. The value of RSQ_{zero} was 0.9967, 0.9134, 0.9286, and 0.9381 for F1 (KCl), F2 (NaCl) F3 (mannitol) and F4 (fructose), respectively. In other words, osmotic pumps containing KCl as the osmotic agent followed zero order release pattern. The results also showed that the presence of KCl markedly diminished t_L of the drug release from osmotic system (2.25 h for F1 versus 4.67, 4.22 and 4.19 h for F2, F3 and F4 respectively). The lowest D_{24h} (21.32%) and long t_L (4.22h) were related to F3 formulation which contained mannitol as osmotic agent.

Wetting agents also play an important role in the SEOP systems. SLS will modify the solubility of the drug inside the system. Based the above results, F1 was adopted as a suitable formulation and further investigations were carried out on this formulation to examine the effect of coating parameters, mainly the orifice size, thickness of coating and the concentration of plasticizers.

Table 4. The main comparative parameters of osmotic systems including D_{24h}, D_{10h}, RSQ_{zero}, t_L and $D_{\%zero}$.

Formulation code	$D_{\%zero}$	RSQ_{zero}	t_L (h)	D_{10h}	D_{24h}
F1	182.32	0.9967	2.25	33.95	89.58
F2	28.11	0.9134	4.67	17.54	42.81
F3	126.65	0.9286	4.22	8.91	21.32
F4	128.34	0.9381	4.19	10.45	33.65
F5	55.67	0.8254	2.99	68.31	91.21
F6	1543.89	0.9678	2.91	48.93	92.48
F7	520.34	0.8845	7.83	7.68	28.50
F8	132.73	0.9432	6.23	4.29	26.71
F9	142.20	0.9639	5.12	3.56	20.26
F10	498.57	0.8952	6.01	6.25	85.81
F11	511.67	0.8625	6.84	4.96	87.18
F12	698.16	0.8462	7.16	5.78	82.50
F13	578.67	0.9156	3.01	28.93	74.20
F14	411.37	0.9210	2.47	26.38	74.23
F15	383.79	0.9352	2.99	28.31	79.55
F16	498.57	0.8625	2.71	31.93	89.21
F17	41.69	0.9120	1.57	34.49	92.56
F18	-	-	-	-	-
F19	578.67	0.9478	2.89	39.19	87.62
F20	611.37	0.9045	5.36	29.41	84.46
F21	2563.78	0.8456	8.87	2.08	64.29
F22	-	-	-	-	-
F23	7682.91	0.8934	2.45	21.45	72.12

* Indicates broken systems.

Type and amounts of plasticizers

Once the tablet formulation was decided, the membrane will be a key aspect in relation to release profile of the monolithic osmotic tablet system. Plasticizers are added to modify the physical properties and improve film-forming characteristics of polymers. As plasticizers will also affect the permeability of polymers films, thus, it is important to investigate the effect of plasticizer on the release rate of drug from osmotic devices. Fig. 5 shows the release profiles of formulations containing different types and different amounts of plasticizers. As mentioned earlier, caster oil and glycerin were used as lipophilic and hydrophilic plasticizers in the

formulation of SPM, respectively. The SPM of formulations F18, F17, F19 and F20 contains 0.5, 1, 1.5 and 2% w/w caster oil, respectively (concentration of glycerin was 2% w/w in all of these formulations). It was observed that the SPM of F18 containing 0.5% caster oil did not maintain its integrity and was cracked after a few hours exposure to the dissolution medium. The results showed that caster oil decreased the release rate, whereas the presence of glycerin increased the release rate, when they were incorporated into the membrane (compare release profile of F1 and F21 in Fig. 5). Fig. 5 also shows that the increase of caster oil concentration lead to a reduction of drug release rate. It is clear from this figure and also from the results listed in Table 4, the lag time values of the formulations were also affected by the percentage of caster oil in SPM composition. Increasing caster oil percentage from 1% to 2% increased the lag time from 2.25 h (F1) to 5.36 h (F20).
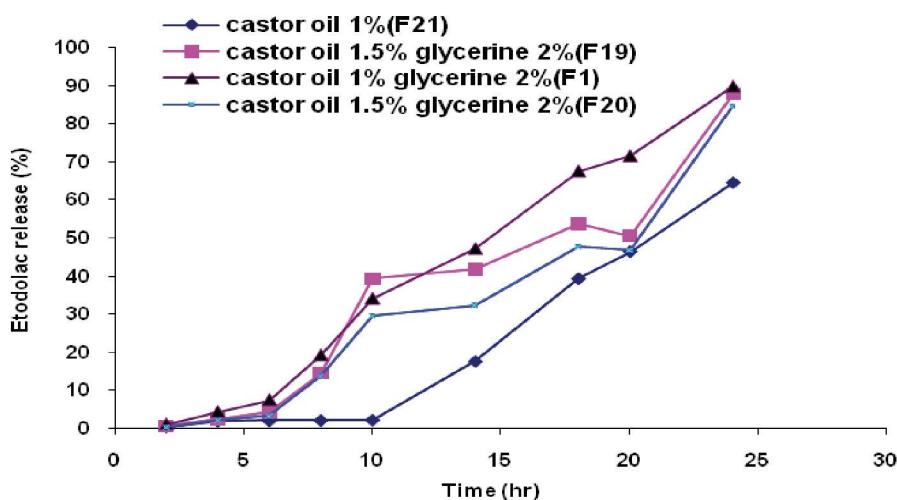

Figure 5. Release profile of etodolac from formulation containing different percentage of glycerin and castor oil in the SPM formulation.

Similar results were reported about the relationship between water imbibitions rate and hydrophilicity of SPM(5,21,22). Increasing the hydrophobic plasticizer concentration in SPM did not increase D_{24h} significantly (89.58%, 87.62% and 84.46% for F1, F19 and F20, respectively). The absence of glycerin from SPM prolonged the lag time from 2.25 h (F1) to 8.87 h (F21). D_{24h} also decreased from 89.58 in F3 to 64.29 % in F21 formulation (without glycerin). The change in SPM also decreased RSQzero from 0.9912 to 0.8469 and increased $D_{\%zero}$ from 155.7 to 2334.6 for F1 and F21, respectively. Comparing the results in Table 4, it can be concluded that membranes containing 1% w/w caster oil and 2% w/w glycerin (F1) are optimum percentages in SPM formulation to obtain zero order release device.

Aperture diameter

Aperture diameter is one of the critical parameters that greatly influences release rate, lag time and release kinetics of the osmotic drug delivery devices. Thus, the size of delivery orifice must be optimized in order to control the drug release from osmotic systems(19,21,22) Majority of the previous studies emphasize on optimization of aperture diameter for achieving zero order release from osmotic systems. Fig. 6 shows the release profiles of the drug from formulations with different aperture diameters. The orifice sizes of F13, F14, F15, F1, F16 and F17 osmotic devices were 355, 450, 555,600, 755 and 900 μm, respectively. No systematic trends were observed between release rate of drug and the orifice diameter between 355 and 555 μm. In other words, no significant difference (p > 0.05) existed in the release profiles for orifice

diameters ranging from 355 μm to 555 μm. our results showed significant changes in some of the release parameters due to the change in orifice size of F13, F14 and F15. More specifically, t_L, RSQ_{zero} and specially $D_{\%zero}$ were remarkably improved by increasing the aperture diameter from 355 to 555 μm (Table 4). However, the release was somewhat rapid with an orifice diameter of 600 or 900 μm. This may be due to the result of diffusion from the bigger orifice. As shown in Table 4, D_{24h} was increased and lag times of the systems were decreased significantly as increasing the orifice diameter. D_{24h} was increased from 74.20 % in F13 with 355 μm to 92.56% in F17 with 900 μm orifice size. Lag time was decreased from 3.01 and 1.57 h as the orifice size was increased from 355 μm (F13) to 900 lm (F17), respectively. These results indicate the importance of orifice diameter to control the drug release from the osmotic devices. Among these formulations, F17 had highest D_{24h} and shortest lag time.

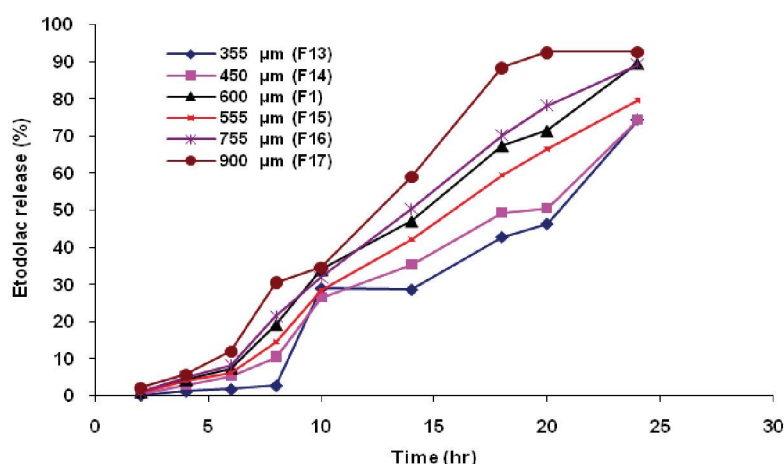**Figure 6.** Release profile of etodolac from osmotic devices with different aperture size.

SPM thickness

Proper selection and optimization of the SPM thickness is one of the best ways to achieve a constant release rate of drugs from osmotic systems(2). Fig. 7 represents the release profiles of osmotic devices formulated with different SPM thicknesses. The optimal tablets were coated to thickness of 0.08 (F22), 0.13 (F1) and 0.20 mm (F23), respectively (the concentrations of caster oil and glycerin were constant; Table 2). It was observed that the SPM of F22 was cracked and disintegrated after the exposure of the tablet to the dissolution medium. Fig. 7 shows that increasing the membrane thickness results in the enhanced resistance of the membrane to dissolution medium diffusion followed by a reduction in the liquefaction rate of the tablet core which, ultimately, leads to the reduced drug release rate from osmotic devices. Table 4 shows that increasing SPM diameter from 0.13 to 0.20 mm increased lag time and decreased D_{24h} significantly ($p < 0.05$). It has been reported that increasing the SPM thickness can increase the time required for moistening of membrane and hence, increase t(2,21)
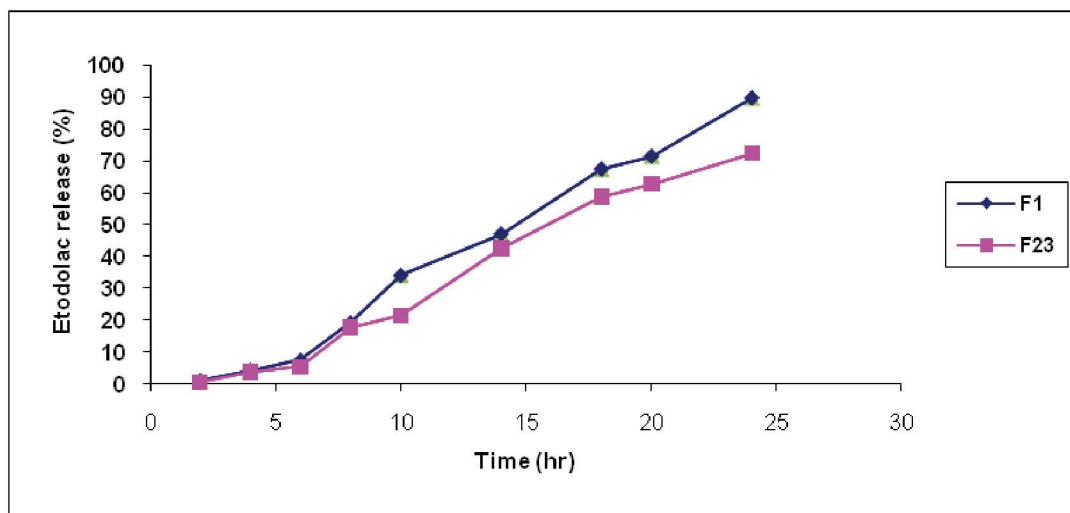
Figure 7. Release profile of etodolac from osmotic devices with different SPM thicknesses.

Thickening the SPM can decrease the rate of water penetration through the membrane resulting in the increased t and decreased release rate of the drug. It can be seen that from given Eq. (2) that release rate from osmotic system is inversely proportional to membrane thickness.

$$\frac{dM}{dt} = \frac{A}{h} K\pi C \qquad (2)$$

where dM/dt is drug delivery rate, A and h are the membrane area and thickness, respectively. C is the concentration of compound in the dispersed fluid (soluble fraction of the drug), p is the osmotic pressure of the system and K is the equation constant.

Evaluation of the parameters related to release kinetics in Table 4 revealed that the drug release from formulation with 0.13 mm SPM thickness, F1, followed zero order kinetics in comparison with F23. RSQ_{zero} was 0.9967 and 0.8934 and $D_{\%zero}$ was 182.32 and 7682.91 for formulations F1
and F23, respectively. These results demonstrated that SPM thickness should be optimized in order to make sure the pressure produced during swelling does not lead to rupture of the system and also moisten the tablet in acceptable time ranging. Optimization of SPM thickness makes the osmotic system suitable in the case of release rate, release kinetics, lag time and other basic features.

DISCUSSION

In the study of selection of suitable polymers for the formulation of osmotic device the results showed that carbopol and NaCMC both were not suitable polymers for delivery system. The effect probably aroused from the high swelling power of carbopol and NaCMC polymers. In other words, disintegration occurred probably as a result of greater rate of polymer swelling (volume expansion) than the rate of the swelled polymer departure through the orifice; this could increase the pressure within the device resulting in disintegration of the device after a few hours of exposure to dissolution medium. Furthermore, these polymers also can produce a highly viscous solution after the exposure to dissolution medium which may block the orifice of the device and consequently increase the internal pressure of the system and possible rapture of the semipermeable membrane coating.

In the study of the effect of type and polymer concentration on the release rate from osmotic devices it was shown that D_{24h} for F7 formulation was considerably lower than the acceptable range (28.5%). Low D_{24h} of F7 is probably due to the lower swelling ability of HPMC E5LV compared to other polymers. This indicates that apart from osmotic pressure, the swelling of polymers is very important in controlling the amount of drug release from osmotic devices. Thus, it can be concluded that the mechanism of release of drug from these devices is not a simple osmotic mechanism and swelling of polymer is another driving force for the release of drug. The slow swelling rate of PVP K30 in comparison with other polymers made it inappropriate as swelling agent for these systems. These results demonstrated that HPMC K100M is the first choice for Etodolac SEOP system to obtain zero order release and reasonable amount of drug release for a period of 24 h. On increasing in amount of polymer from 45 to 60 mg resulted in a decrease in the drug release from device in the first 10 h, these effect probably can be attributed to the high viscosity of HPMC K100M (viscosity of 2% of HPMC K100M solution at 20 °C is 100,000 cps). High viscosity of the gel produced inside the system made it difficult to depart from the system through the small orifice of the semi permeable coating.

In the study of effects of type and amounts of osmotically active agents, the lowest release rate for the devices containing mannitol could be due to a low osmotic activity of mannitol as a result of having nonionic nature. The superiority of KCl as osmotic agent in osmotic devices also was confirmed by previous studies(6,7,21).

Wetting agents play an important role in the SEOP systems. These materials, as noted earlier, help in the uniform dispersion of the drug particles throughout the gel which formed after penetration of water into the device. These chemicals also facilitate surface wetting of the drug particles and prevent the drug particle agglomeration. Wetting agents also can enhance water solubility of drugs and increase the soluble fraction of the drug in the device. In other words, SLS will modify the solubility of the drug inside the system. Enhancing the soluble fraction of drugs can increase release rate (especially in the initial times) and decrease lag time[1,19]. Because of ionic nature of SLS, the substance can also act as osmotic agent and increase the driving force to push the drug out of the device through the orifice(21,22).

In the study of effect of type and amounts of plasticizers it was shown that caster oil decreased the release rate, whereas the presence of glycerin increased the release rate, when they were incorporated into the membrane. This may be explained by the difference in hydrophilicity and hydrophobicity of the two plasticizers. As glycerin is a hydrophilic plasticizer, it could be leached easily and leave behind an entirely porous structure, which increases membrane permeability and drug release rate. In contrast, as caster oil is insoluble in water, it is difficult to leach. Because of its hydrophobic character, the residual caster oil would resist water diffusion and, as a consequence, the drug release was decreased. Fig. 4 also shows that the increase of caster oil concentration led to a reduction of drug release rate. The more caster oil incorporated into the membrane, the more difficult it was to leach, and in turn, the lower permeability of the membrane, the lower the drug release rate obtained.

It is clear from this figure and also from the results listed in Table 4, the lag time values of the formulations were also affected by the percentage of caster oil in SPM composition. The SPM of F18 containing 0.5% caster oil, was cracked after a few hours exposure to the dissolution medium which probably aroused from a very high internal hydrostatic pressure. Caster oil, which was added to the coating formulation as lipophilic plasticizer, can increase the hydrophobicity of SPM and decrease the rate of water penetration across the membrane and thus, increase lag time of osmotic systems. Since glycerin is a hydrophilic plasticizer, the more glycerin incorporated into the membrane, the more void space formed after leaching and, as a result, the higher the permeability of membrane the higher the drug release rate. It can be concluded that a good hydrophilic/lipophilic balance in SPM structure is required to achieve desirable release profile with zero order kinetics.

Aperture diameter is one of the critical parameters that greatly influences release rate, lag time and release kinetics of the osmotic drug delivery devices. These results demonstrated that

optimum aperture size in SEOP systems is considerably larger than ordinary EOP systems which are used for delivering high to moderately water-soluble drugs. This difference probably originates from different mechanisms of drug release between these systems. EOPs generally released their drug content in soluble form whereas SEOPs release their drug in soluble form and in suspended solid particles concurrently. It has previously shown that the optimum aperture size of the osmotic devices containing moderately soluble drugs is significantly smaller than those containing poor soluble or practically insoluble drugs(6,21,22).

It was observed that the SPM of F22 was cracked and disintegrated after the exposure of the tablet to the dissolution medium. This was probably due to the lack of the resistance of a very thin layer of SPM around the tablet which was unable to tolerate the internal pressure of the system as a result of hydrostatic pressure and pressure induced from polymer swelling.

CONCLUSION

In conclusion, the results obtained suggest the feasibility of designing successful and effective SEOP systems for Etodolac. The results showed by prepared SEOP proved that this is an effective device for the delivery of poorly water-soluble drugs with zero order patterns. These devices can release their drug contents in a form of soluble or solid suspended particles out of the system by constant release rate. The main system characteristics including D_{24h}, t_L, RSQ_{zero} and $D_{\%zero}$ can be improved by optimizing the formulation parameters. The optimized system in this study was able to release etodolac at zero order kinetics for 24 h when tested at pH 6.8 medium.

REFERENCES

1. Javad S, Ahmadi P, Rashidi P, Shahsavari M, Ali RS, Ali N, Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs, Eur J Pharma Biopharm 68, 289–297, 2008.
2. Thombrea AG, Appelb LE, Chidlawb MB, Daugheritya PD, Dumonta F, Evansa LAF, Sutton SC, Osmotic drug delivery using swellable-core technology, J Contr Release 94, 75– 89, 2004.
3. Rao BS, Kumar NR, Madhuri K, Narayan PS, Murthy KVR, Osmotic drug delivery systems, Eastern Pharmacist 44(521), 21– 28, 2001.
4. Verma RK, Mishra B, Garg S, Osmotically controlled oral drug delivery, Drug Dev Ind Pharm 26 (7), 695– 708, 2000.
5. Verma RK, Krishna DM, Garg S, Formulation aspects in the development of osmotically controlled oral drug delivery system, J Contr Release 79, 7–27, 2002.
6. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB, Nifedipine controlled delivery by sandwiched osmotic tablet system, J Contr Release 68, 145–156, 2000.
7. Makhija SN, Vavia PR, Controlled porosity osmotic pump-based controlled release system of pseudoephedrine J Contr Release 89, 5–18, 2003.
8. Santus G, Baker RW, Osmotic drug delivery: a review of the patent literature, J Contr Release 35, 1–21, 1995.
9. Wong PSL, Barclay BL, Deters JC, Theeuwes F, Osmotic device for administering certain drugs, US Patent No. 4765, 989, 1988.
10. Zentner GM, Rork GS, Himmelstein KJ, Osmotic flow through controlled porosity films: an approach to delivery of water soluble compounds, J Contr Release 2, 217– 229, 1985.
11. Zentner GM, McClelland GA, Sutton SC, Controlled porosity solubility and resim-modulated drug delivery systems for release of diltiazem hydrochloride, J Contr Release 16, 237– 244, 1991.

12. Thombre AG, Zentner GM, Himmelstein KJ, Mechanism of water transport in controlled porosity osmotic devices, J Membrane Sci 40, 279–310, 1989.
13. Thombre AG, Cardinal JR, DeNoto AR, Herbig SM, Smith KL, Asymmetric membrane capsules for osmotic drug delivery: II. In vitro and in vivo drug release performance, J Contr Release 57, 65– 73, 1999.
14. Ende MT, Herbig SM, Korsmeyer RW, Chidlaw MB, Osmotic drug delivery from asymmetric membrane film coated dosage forms, In: D. L. Wise (Ed.), Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, New York, NY, 751–785, 2000.
15. Thombre AG, Cardinal JR, DeNoto AR, Herbig SM, Smith KL, Asymmetric membrane capsules for osmotic drug delivery: I. Development of a manufacturing process, J Contr Release 57, 55–64, 1999.
16. Theeuwes F, In: Rate Controlled in Drug Therapy, Presscott LF and Nimmo WS (Ed.), Churchill Livingstone, Edinburgh, 116, 1985.
17. Parmar NS, Vyas SK, (Ed) Jain NK, In: Advanced in controlled and novel drug delivery, CBS Publisher, 28-29, 2003.
18. Kumar P, Mishra B, Studies on elementary osmotic pump tablets of naproxen sodium, Acta Pharm Turcica 46, 35-41, 2004.
19. Verma RK, Kaushal AM, Garg S, Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology, Int J Pharm 263, 9–24, 2003.
20. Ahmed AE, Tadros MI, Ahmed AAE, Development and in vitro/in vivo evaluation of etodolac controlled porosity osmotic pump tablets, AAPS Pharm Sci Tech 12(2), 2011.
21. Liu L, Khang G, Rhee JM, Lee HB, Monolithic osmotic tablet system for nifedipine delivery, J Contr Release 67, 309–322, 2000.
22. Ozdemir N, Sahin J, Design of a controlled release osmotic pump system of ibuprofen, Int J Pharm 158, 91–97, 1997.