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Research paper

Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs

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Abstract

A new type of elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs has been designed. Drug release from the system, called swellable elementary osmotic pump (SEOP), is through a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption. SEOP tablets were prepared by compressing the mixture of micronized drug and excipients into convex tablets. Factors affecting the release of drug from the SEOP tablets containing a poorly water-soluble drug, indomethacin, have been explored. The release behaviour of indomethacin 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. The results showed that concentration of *wetting* agent in the core formulation was a very important parameter in D_{24h} and release pattern of indomethacin from SEOP system. Increasing the amount of *wetting* agent to an optimum level (60 mg) significantly increased D_{24h} and improved zero order release pattern of indomethacin. Increasing concentration of caster oil (hydrophobic) in the semipermeable membrane of the device or hydrophilic plasticizer (glycerin) in coating formulation markedly increased t_L and decreased D_{24h}. The results also demonstrated that aperture size is a critical parameter and should be optimized for each SEOP system. Optimum aperture diameter for the formulations studied here was determined to be 650 μm for zero order release pattern. t_L and $D\%_{zero}$ were dramatically decreased whereas D_{24h} and RSQ_{zero} increased with increasing the aperture size to optimum level. This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics.

Keywords: Controlled drug delivery; Indomethacin; SEOP; Zero order release; Lag time

1. 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 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 [2–4]. Many different systems have been developed based on principles of osmotic pressure such as

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elementary osmotic pump, EOP, [3,5–7], sandwiched osmotic tablet system, SOTS [3], push–pull systems [3,6,8–10], controlled porosity osmotic pumps [4,6,11–13], asymmetric membrane osmotic pumps [14–17], single composition osmotic tablet, SCOT [1] and osmotic systems made by swellable core technology [18]. An EOP device basically consists of an osmotically active core surrounded by a semipermeable membrane (SPM) usually of cellulose acetate and a small orifice drilled through the coating using LASER or mechanical drills [5,7]. In fact, an EOP system is really a coated tablet with an aperture and represents the ultimate simplification of the original Rose–Nelson pump [5]. EOPs are generally applied for delivering of high to moderate water-soluble drugs [5–7]. When these systems exposed to an aqueous environment, the osmotic pressure difference between inside of the device and environment draws water through the semipermeable membrane [5]. Imbibitions of water through the system increase the inner hydrostatic pressure and leading the saturated drug solution to flow through the small orifice. Because of the simple structure and high efficiency, EOPs are the most commercially important osmotic devices and more than 240 patents have been devoted [5]. Procardia XL® and Adalat CR (nifedipine), Acutrium® (phenylpropanolamine), Minipress XL® (prazocine) and Volmax® (salbutamol) are examples of EOPs available in the market. In this study, an attempt was made to design a new EOP like osmotic system for delivery of an insoluble drug with constant release rate (zero order release). This device is called swellable elementary osmotic pump (SEOP) that is structurally similar to EOP but with different core formulation. 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.

2. Materials and methods

2.1. Materials

Indomethacin powder (a poorly water-soluble drug) as the model drug was purchased from Zahravi Pharmaceuticals (Tabriz, Iran). Cellulose acetate with 40% acetyl groups (Fluka, Switzerland) was used as a SPM. HPMCs (K100M, E50LV, E15LV and E5LV) (Colorcon, England), Carbopols 940 and 934 (B.F. Goodrich, USA), NaCMCs 200 and 1500 cps (Clariant, Switzerland) and PVP K30 (BASF, Germany) were used as water-swellable and gelling agent. NaCl, KCl, $CaCl_2$ and fructose (Merck, Germany) were applied as osmotically active agents. Other chemicals such as Sodium lauryl sulphate (SLS), caster oil, PEG 300, 600 and 20000, potassium dihydrogen phosphate, acetone, ethanol and glycerin were obtained from Merck, Germany.

2.2. Preparation of core tablets

Indomethacin powder was micronized by jet mill (Fritsch FE 80N, Germany) before tabletting process. Particle size of the drug was measured by centrifugal particle size analyzer (Shimadzu SA-CP3, Japan). The micronized drug powder and other core ingredients were mixed and compressed into convex tablets with 9 mm (diameter) concave punches using a single punch tabletting machine (Korsch, Germany). In order to keep the volume and surface area of tablets relatively constant, the final weight of each tablet was maintained at 360 mg. All of the core formulations contained 75 mg indomethacin and different amounts of various polymers, osmotically active agents and SLS (as suspending and wetting agents). The composition of different core formulations (F1–F19) 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 650 μm.

2.3. Coating and drilling

The tablets 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 dip coating technique. Coating process was carried out in the same condition for all tablets and thickness of the coats was periodically controlled using digital micrometer (Mitotoyo, Japan). 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 250 to 800 μm). After drilling, the orifice size was controlled and measured microscopically (BAUSH & LOMB, Balplan microscope, USA) to make sure the right orifice size was used for dissolution studies. Any deviation in orifice size by more than 10 μm from the target orifice size was rejected and not used in dissolution studies. Fig. 1 shows a schematic diagram of the monolithic osmotic tablet system. The SPM compositions for different formulations are listed in Table 2.

Table 1
The compositions of core formulation for formulations F1–F19[a]

	SLS	PVPK30	HPMCs				Osmotic agents		
			E5LV	E15LV	E50LV	K100M	KCl	NaCl	Fructose
F1	–	–	–	–	–	30	150	–	–
F2	30	–	–	–	–	30	150	–	–
F3	60	–	–	–	–	30	150	–	–
F4	60	–	–	–	–	30	–	150	–
F5	60	–	–	–	–	30	–	–	150
F6	60	–	–	–	–	45	150	–	–
F7	60	–	–	–	–	60	150	–	–
F8	60	–	–	–	30	–	150	–	–
F9	60	–	–	–	45	–	150	–	–
F10	60	–	–	–	60	–	150	–	–
F11	60	–	–	30	–	–	150	–	–
F12	60	–	–	45	–	–	150	–	–
F13	60	–	–	60	–	–	150	–	–
F14	60	–	15	–	–	–	150	–	–
F15	60	–	30	–	–	–	150	–	–
F16	60	–	45	–	–	–	150	–	–
F17	60	30	–	–	–	–	150	–	–
F18	60	45	–	–	–	–	150	–	–
F19	60	60	–	–	–	–	150	–	–

[a] All these formations contained 1% caster oil, 2% glycerin, cellulose acetate with a thickness of 0.13 mm and the orifice diameter of 650 μm.

2.4. In vitro release test

All drug release experiments were carried out using a dissolution apparatus (Erweka DT-6R, Germany), paddle method, rotating at 100 rpm at 37 °C in 900 ml phosphate buffer solution (pH 6.8). Samples of 5 ml (which were replaced with fresh medium) were taken at distinct time intervals (1, 2, 4, 6, 8, 10, 12, 14, 18 and 24 h) and the drug concentration in samples was determined spectroscopically (UV spectrophotometer, Shimadzu Mini 1240, Japan) at a wavelength of 318 nm. The release test was performed at least for three tablets and mean and standard deviations were obtained.

2.5. 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_L is the time required for imbibitions of water through the semiperme-

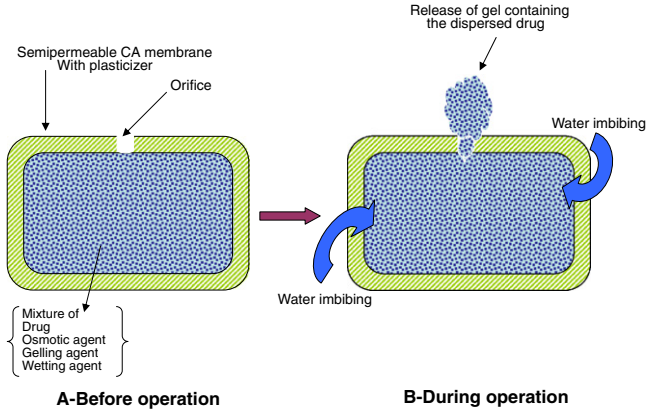

Fig. 1. Schematic diagram of the monolithic osmotic tablet system composed of a monolithic tablet surrounded by a cellulose acetate (CA) membrane drilled with an orifice.

Table 2
The compositions of membrane formulation for formulations F20–F33

	SLS (mg)	SPM thickness (mm)	SPM plasticizers (%w/w)		Orifice diameter (μm)
			Caster oil	Glycerin	
F20	60	0.13	1	2	350
F21	60	0.13	1	2	450
F22	60	0.13	1	2	550
F23	60	0.13	1	2	800
F24	60	0.13	0.5	2	650
F25	60	0.13	1.5	2	650
F26	60	0.13	2	2	650
F27	60	0.13	1	–	650
F28	60	0.07	1	2	650
F29	60	0.19	1	2	650
F30	15	0.13	1	2	650
F31	30	0.13	1	2	650
F32	45	0.13	1	2	650
F33	75	0.13	1	2	650

able coating, gel forming process, volume enhancement of the gel and 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 [20]. 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 [20].

$D\%_{zero}$ was calculated according to Eq. (1)

$$D\%_{zero} = \frac{100}{N} \times \sum \left(\frac{Q_{calc} - Q_{obs}}{Q_{obs}} \right) \quad (1)$$

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.

2.6. 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 and 1500 cps), Carbopol®s (934 and 940), HPMCs (K100M, E50LV, E15LV and E5LV) and PVP K30 with different percentages (1%, 2%, 5%, 10%, 15%, 20%, 30% and 40% w/w) as gelling agents. The prepared core formulations were coated with cellulose acetate by dip coating technique (with 130 ± 10 μm thickness) and an orifice with 500 μm diameter was drilled 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.

3. Results and discussion

3.1. Selection of suitable polymers for the formulation of osmotic device

In order to select suitable polymer(s) for the formulation of osmotic devices, various polymers were incorporated in the core formulation. The results showed that the osmotic devices containing Carbopol®s (934 and 940) and NaCMCs (200 and 1500 cps) disintegrated after a few hours of exposure to the dissolution medium with an exception of the devices containing 1% NaCMC200. This 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. The osmotic devices containing HPMC K100M, HPMC E50LV, HPMC E5LV or PVP K30 with lower than 20% w/w, and HPMC E5LV with lower than 10% 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.

3.2. 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 (F3, F8, F11, F15 and F17 contained HPMC K100M, HPMC E50LV, HPMC E15LV, 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 85.07%, 74.29%, 99.59%, 18.35% and 86.19% for the core formulations containing HPMC K100M (F3), HPMC E50LV (F8), HPMC E15LV (F11), HPMC E5LV (F15) and PVP K30 (F17), respectively. D_{24h} for F15 formulation was considerably lower than the acceptable range (18.35%). Low D_{24h} of F15 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

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	
		K100M	E50LV	E15LV	E5LV	200 cps	1500 cps	934	940
1	−	−	−	−	−	−	+	+	+
2.5	−	−	−	−	−	+	+	+	+
5	−	−	−	−	−	+	+	+	+
10	−	−	−	−	−	+	+	+	+
15	−	−	−	−	+	+	+	+	+
20	−	+	+	+	+	+	+	+	+
30	−	+	+	+	+	+	+	+	+
40	−	+	+	+	+	+	+	+	+

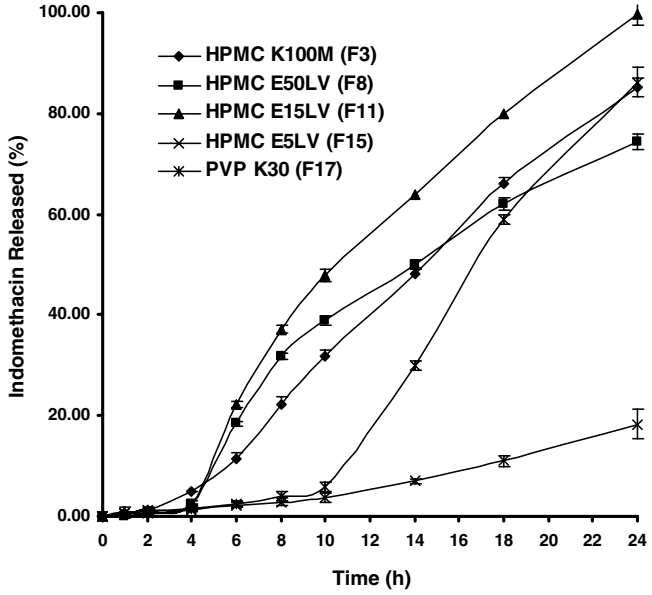

Fig. 2. Release profiles of indomethacin from formulations containing HPMC K100M, HPMC E50LV, HPMC E15LV, HPMC E5LV and PVP K100M (amount of polymer is 30 mg polymer in all formulations).

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 shortest t_L (2.47 h) and the highest RSQ_{zero} (0.9958) belonged to formulation F3. Formulation F17 containing PVP K30 as gelling agent did not show suitable drug release profile (the high lag time, 6.9 h, high $D\%_{zero}$, 552.98, and low RSQ_{zero}, 0.8718). 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 indomethacin SEOP system to obtain zero order release and reasonable amount of drug release for a period of 24 h. In order to investigate the effect of amount of HPMC K100M on release rate of indomethacin, 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 indomethacin from SEOPs containing 30 mg (F3), 45 mg (F6) and 60 mg (F7) 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 F6 (D_{8h} was 22.14, 61.61 and 31.98 for F3, F6 and F7, respectively) in the initial sampling times but the drug release data from this formulation did not follow zero-order kinetics in comparison with formulation F3 (RSQ_{zero} was 0.9958 and 0.803 for F3 and F6, 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. This 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 semipermeable coating. According to this figure, 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).

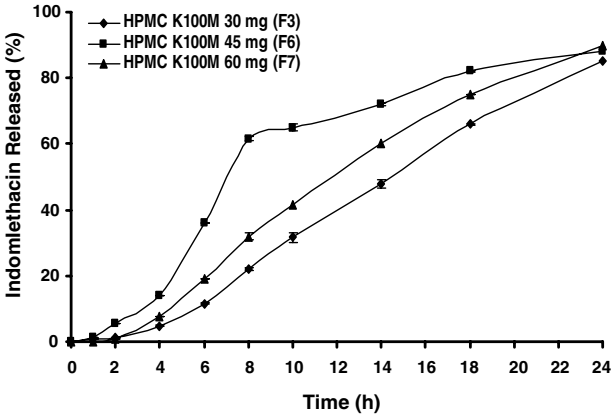

Fig. 3. Release profiles of indomethacin from formulations containing different concentration of HPMC K100M (30, 45 and 60 mg).

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

	$D\%_{zero}$	RSQ_{zero}	t_L (h)	D_{10h}	D_{24h}
F1	51.72	0.8868	7.74	3.22	17.24
F2	255.31	0.9027	7.08	5.22	54.5
F3	185.81	0.9912	2.47	31.68	85.07
F4	26.81	0.9776	4.60	14.98	31.44
F5	127.65	0.9896	4.80	4.57	15.25
F6	59.73	0.803	1.92	64.98	88.21
F7	1875.3	0.9865	2.63	41.64	89.89
F8	250.15	0.9508	3.18	38.94	74.29
F9	396.54	0.9732	3.46	37.37	74.97
F10	494.16	0.9657	4.66	22.7	85.58
F11	250.47	0.9711	3.37	47.75	99.59
F12	135.04	0.9732	3.43	42.87	89.23
F13	539.73	0.9653	4.48	22.72	78.33
F14	547.55	0.8885	7.90	6.24	64.08
F15	119.55	0.9412	5.82	3.71	18.35
F16	139.23	0.9561	4.95	3.74	15.63
F17	456.32	0.8852	5.89	5.83	84.26
F18	552.98	0.8718	6.90	3.22	86.19
F19	700.7	0.8594	7.20	3.77	81.37
F20	512.48	0.9533	3.09	20.47	62.17
F21	482.02	0.9578	2.94	21.28	62.74
F22	298.44	0.9716	2.67	23.42	69.69
F23	26.47	0.9876	0.79	34.61	89.52
F24[a]	–	–	–	–	–
F25	686.39	0.9735	2.33	35.14	84.73
F26	858.19	0.9622	4.44	29.05	83.96
F27	2334.6	0.8469	9.86	1.538	68.46
F28[a]	–	–	–	–	–
F29	2786.02	0.9739	2.83	23.31	77.96
F30	2971.29	0.963	3.15	22.32	80.58
F31	1448.54	0.9737	2.96	22.62	81.706
F32	1682.55	0.9827	2.63	25.33	81.14
F33	5389	0.9615	3.25	19.19	80.58

[a] Indicates broken systems.

3.3. Type and amounts of osmotically active agents

Fig. 4 shows release profiles of formulations containing 150 mg KCl (F3), NaCl (F4) and fructose (F5) as osmotically active agents. 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 [3,4,20,21]. 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 (RSQ_{zero} was 0.9912, 0.9776 and 0.9896 for F3 (KCl), F4 (NaCl) and F5 (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 (2.67 h for F3 versus 4.6 and 4.8 h for F4 and F5, respectively). The lowest D_{24h} (15.25%) and longest t_L (4.8h) were related to F5 formulation which contained fructose as osmotic agent. The lowest release rate for the devices containing fructose could be due to a low osmotic activity of fructose as a result of having nonionic nature. The superiority of KCl as osmotic agent in osmotic devices also was confirmed by previous studies [3,4,21].

3.4. Concentration of wetting and solubilizing agent

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 [2,7,19]. SLS was used with various percentages as *wetting* agent in osmotic pump devices. 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 [20–22]. Release profiles of the drug from devices with different amounts of SLS (0, 15, 30, 45, 60 and 75 mg) are shown in Fig. 5. As shown in this figure, the presence of SLS in the core formulation obviously increased the percentage and the release rate of the drug from the devices. Incorporation of 15 mg SLS to the core formulation increased D_{10h} and D_{24h} from 3.22 (F1) to 22.32% (F30) and from 17.23% to 80.58%, respectively. SLS also decreased t_L from 7.74 h in F1 to 2.95 h in F3 formulation. Formulation containing SLS showed higher RSQ_{zero} compared to the formulation without SLS (RSQ_{zero} for F1 and F3 was 0.886 and 0.973, respectively). The results also showed that concentration of SLS has remarkable effects on lag times. For instance, lag times were 7.74, 3.14, 2.95, 2.62 and 2.1 h for formulations containing 0 (F1), 15 (F30), 30 (F31), 45 (F32) and 60 mg (F3) SLS, respectively. Kinetics related parameters including RSQ_{zero} and $D\%_{zero}$ were also improved by increasing the SLS to optimum level (Table 4). An increase in SLS concentration from 60 mg (F3) to 75 mg (F33) increased t_L (3.25 h) significantly. The increased lag time in the presence of higher amounts of SLS (>60 mg) in the core formulation probably aroused from high viscosities of system as a result of high SLS concentrations in the devices.

Based the above results, F3 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.

3.5. Type and amounts of plasticizers

Once the tablet formulation was decided, the membrane will be a key factor in relation to release profile of the

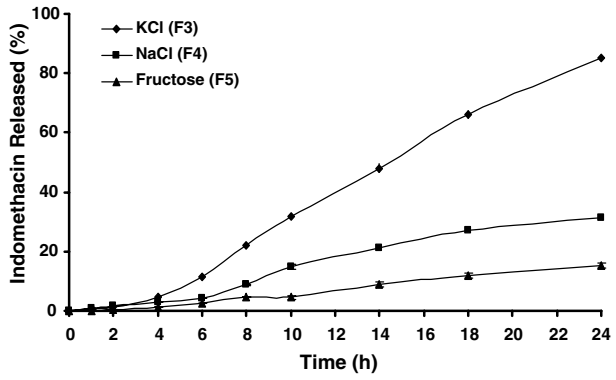

Fig. 4. Release profiles of indomethacin from formulations containing KCl, NaCl and Fructose (F5) as osmotic agent in the core formulations.

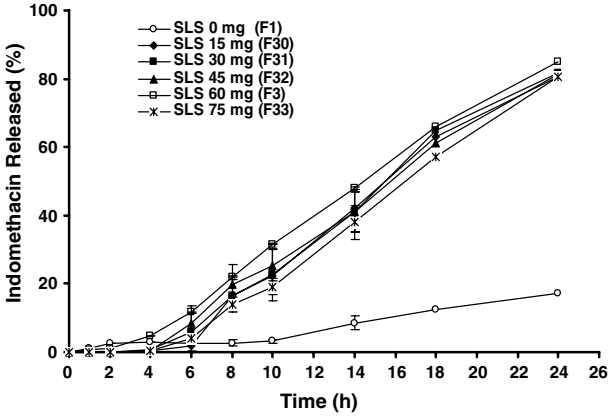

Fig. 5. Release profiles of indomethacin from formulations containing different concentrations of SLS (0, 15, 30, 45, 60 and 75 mg) in core formulation.

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. 6 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 F24, F23, F25 and F26 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 F24 containing 0.5% caster oil did not maintain its integrity and was cracked after a few hours exposure to the dissolution medium which probably aroused from a very high internal hydrostatic pressure. 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 F3 and F27 in Fig. 6). 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. 6 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. 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. Increasing caster oil percentage from 1% to 2% increased the lag time from 2.47 h (F3) to 4.44 h (F26). Similar results were reported about the relationship between water imbibitions' rate and hydrophilicity of SPM [6,21,22]. Increasing the hydrophobic plasticizer concentration in SPM did not increase D_{24h} significantly (85.7%, 84.73% and 83.96% for F3, F25 and F26, respectively). The absence of glycerin from SPM prolonged the lag time from 2.47 h (F23) to 4.44 h (F27). D_{24h} also decreased from 85.07 in F3 to 68.46% in F27 formulation (without glycerin). 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. This change in SPM also decreased RSQ_{zero} from 0.9912 to 0.84.69 and increased $D\%_{zero}$ from 155.7 to 2334.6 for F3 and F27, respectively. It can be concluded that a good hydrophilic/lipophilic balance in SPM structure is required to achieve desirable release profile with zero order kinetics. Comparing the results in Table 4, it can be concluded that membranes containing 1% w/w caster oil and 2% w/w glycerin (F3) are optimum percentages in SPM formulation to obtain zero order release device.

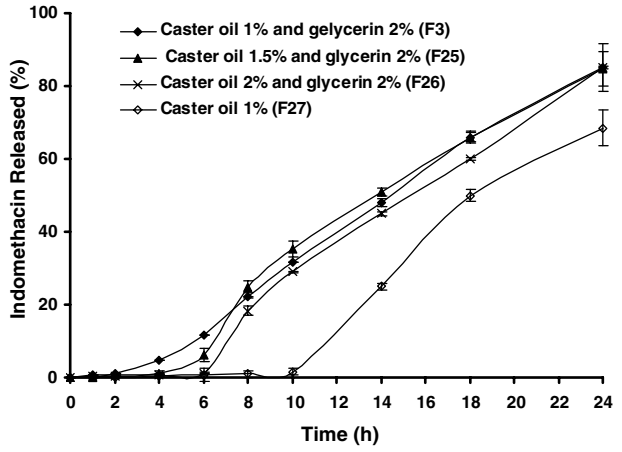

Fig. 6. Release profiles of indomethacin from formulations containing different percents of glycerin (0% and 2%) and caster oil (0.5%, 1%, 1.5% and 2%) in the SPM formulation (F24 containing 0.5% caster oil was cracked and broken during dissolution process).

3.6. 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 [2,20–22]. Majority of the previous studies emphasize on optimization of aperture diameter for achieving zero order release from osmotic systems. Fig. 7 shows the release profiles of the drug from formulations with different aperture diameters. The orifice sizes of F20, F21, F22, F3 and F23 osmotic devices were 350, 450, 550, 650 and 800 μm, respectively. No systematic trends were observed between release rate of drug and the orifice diameter between 350 and 550 μm. In other words, no significant difference ($p > 0.05$) existed in the release profiles for orifice diameters ranging from 350 μm to 550 μm. Similar results were reported on osmotic devices of naproxen [22] and nifedipine [3] where there was no significant difference in release rate of drugs from their osmotic devices having the orifice size from 0.25 to 1.41 and 1 to 1.5 mm, respectively. However, our results showed significant changes in some of the release parameters due to the change in orifice size of F20, F21 and F22. More specifically, t_L, RSQ_{zero} and specially $D_{\%zero}$ were remarkably improved by increasing the aperture diameter from 350 to 550 μm (Table 4).

However, the release was somewhat rapid with an orifice diameter of 650 or 800 μm. This may be due to the result of diffusion from the bigger orifice. As shown in Table 4, D_{24h}

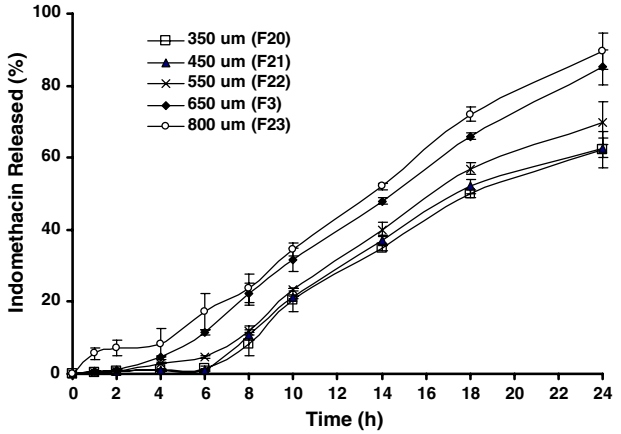

Fig. 7. Release profiles of indomethacin from osmotic devices with different orifice size (aperture diameters were 350, 450, 550, 650 and 800 μm).

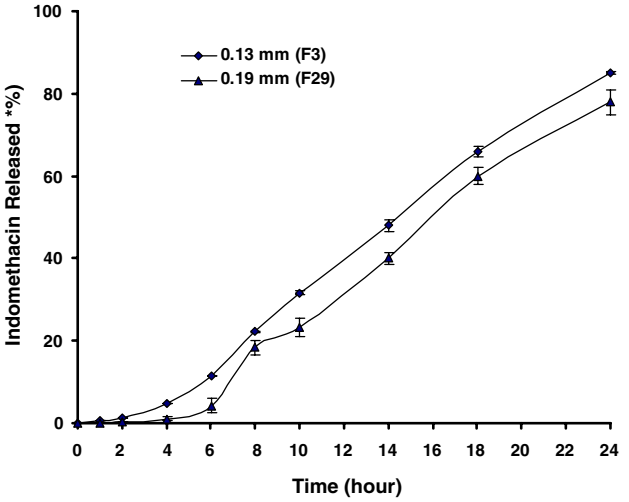

Fig. 8. Release profiles of indomethacin from osmotic devices with different SPM thicknesses (0.070, 0.130 and 0.19 mm) [F28 with a SPM thickness of 0.07 mm was cracked and broken during dissolution process].

was increased and lag times of the systems were decreased significantly as increasing the orifice diameter. D_{24h} was increased from 62.17% in F20 with 350 μm to 89.52% in F23 with 800 μm orifice size. Lag time was decreased from 3.09 and 0.79 h as the orifice size was increased from 350 μm (F20) to 800 μm (F23), respectively. These results indicate the importance of orifice diameter to control the drug release from the osmotic devices. Among these formulations, F23 had highest D_{24h} and shortest lag time. 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 [3,21,22].

3.7. 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. 8 represents the release profiles of osmotic devices formulated with different SPM thicknesses. The optimal tablets were coated to thickness of 0.07 (F28), 0.13 (F3) and 0.19 mm (F29), respectively (the concentrations of caster oil and glycerin were constant; Table 2). It was observed that the SPM of F28 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. Fig. 8 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 0.19 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_L[18,19,21]. Thickening the SPM can decrease the rate of water penetration through the membrane resulting in the increased t_L and decreased release rate of the drug. It can be seen that from Eq. (2) that release rate from osmotic system is inversely proportional to membrane thickness.

$$\frac{dM}{dt} = \frac{A}{h} K \pi C \tag{2}$$

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), π is the osmotic pressure of the system and K is the equation constant. On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release. In a study by Herbig et al. [14], release rates were found to be virtually unaffected by the overall membrane thickness in the range of 0.095–0.15 mm. The possible reason for this may be the unique structure of the asymmetric membrane coating in which the porous substrate consists of open pores (void volume between 60% and 90%).

Evaluation of the parameters related to release kinetics in Table 4 revealed that the drug release from formulation with 0.13 mm SPM thickness, F3, followed zero order kinetics in comparison with F29. RSQ_{zero} was 0.9912 and 0.9739 and $D\%_{zero}$ was 185.81 and 2786.02 for formula-

tions F3 and F29, 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.

4. Conclusion

The SEOP was simple to prepare, because there was no need for a push compartment. The results showed that the SEOP can be a very effective device for the delivery of poorly water-soluble drug with zero order pattern. 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 indomethacin at a zero order kinetics for 24 h when tested at pH 6.8 medium.

References

[1] M. Speers, C. Bonnano, Economic aspects of controlled drug delivery, in: E. Mathiowitz (Ed.), Encyclopedia of Controlled Drug Delivery, Wiley, New York, 1999, pp. 341–347.
[2] R.K. Verma, A.M. Kaushal, S. Garg, Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology, Int. J. Pharm. 263 (2003) 9–24.
[3] L. Liu, J. Ku, G. Khang, B. Lee, J.M. Rhee, H.B. Lee, Nifedipine controlled delivery by sandwiched osmotic tablet system, J. Control. Release 68 (2000) 145–156.
[4] S.N. Makhija, P.R. Vavia, Controlled porosity osmotic pump-based controlled release system of pseudoephedrine, J. Control. Release 89 (2003) 5–18.
[5] G. Santus, R.W. Baker, Osmotic drug delivery: a review of the patent literature, J. Control. Release 35 (1995) 1–21.
[6] R.K. Verma, D.M. Krishna, S. Garg, Formulation aspects in the development of osmotically controlled oral drug delivery systems, J. Control. Release 79 (2002) 7–27.
[7] D. Prabakaran, P. Singh, P. Kanaujia, S.P. Vyas, Effects of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps, Int. J. Pharm. 259 (2003) 173–179.
[8] F. Theeuwes, Osmotic system for delivering selected beneficial agents having varying degrees of solubility, US Patent No. 4111, (1978) 201.
[9] R. Cortese, F. Theeuwes, Osmotic device with hydrogel driving member, US Patent No. 4327, (1982) 725.
[10] P.S.L. Wong, B.L. Barclay, J.C. Deters, F. Theeuwes, Osmotic device for administering certain drugs, US Patent No. 4765, (1988) 989.
[11] G.M. Zentner, G.S. Rork, K.J. Himmelstein, Osmotic flow through controlled porosity films: an approach to delivery of water soluble compounds, J. Control. Release 2 (1985) 217–229.
[12] G.M. Zentner, G.A. McClelland, S.C. Sutton, Controlled porosity solubility- and resin-modulated drug delivery systems for release of diltiazem hydrochloride, J. Control. Release 16 (1991) 237–244.
[13] A.G. Thombre, G.M. Zentner, K.I. Himmelstein, Mechanism of water transport in controlled porosity osmotic devices, J. Membr. Sci. 40 (1989) 279–310.
[14] S.M. Herbig, J.R. Cardinal, R.W. Kosrsmeyer, K.L. Smith, Asymmetric-membrane tablet coating for osmotic drug delivery, J. Control. Release 35 (1995) 127–136.
[15] A.G. Thombre, J.R. Cardinal, A.R. DeNoto, S.M. Herbig, K.L. Smith, Asymmetric membrane capsules for osmotic drug delivery: I. Development of a manufacturing process, J. Control. Release 57 (1999) 55–64.
[16] A.G. Thombre, J.R. Cardinal, A.R. DeNoto, S.M. Herbig, K.L. Smith, Asymmetric membrane capsules for osmotic drug delivery: II. In vitro and in vivo drug release performance, J. Control. Release 57 (1999) 65–73.
[17] A.G. Thombre, A.R. DeNoto, D.C. Gibbes, Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients, J. Control. Release 60 (1999) 333–341.
[18] A.G. Thombre, L.E. Appel, M.B. Chidlaw, P.D. Daugherity, F. Dumont, L.A.F. LEvans, S.C. Sutton, Osmotic drug delivery using swellable-core technology, J. Control. Release 94 (2004) 75–89.
[19] R.K. Verma, S. Garg, Development and evaluation of osmotic controlled oral drug delivery system of glipzide, J. Control. Release 57 (2004) 513–525.
[20] N. Ozdemir, J. Sahin, Design of a controlled release osmotic pump system of ibuprofen, Int. J. Pharm. 158 (1997) 91–97.
[21] L. Liu, G. Khang, J.M. Rhee, H.B. Lee, Monolithic osmotic tablet system for nifedipine delivery, J. Control. Release 67 (2000) 309–322.
[22] E.-X. Lu, Z.-Q. Jiang, Q.-Z. Zhang, X.-G. Jiang, A water-insoluble drug monolithic osmotic tablet system utilizing gum Arabic as an osmotic, suspending and expanding agent, J. Control. Release 92 (2003) 375–382.