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Investigations on the drug releasing mechanism from an asymmetric membrane-coated capsule with an in situ formed delivery orifice

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Abstract

Asymmetric membrane-coated capsules with in situ formation of a delivery orifice were examined for their improved osmotic effects. The release mechanisms were investigated for drugs with both moderate to high water solubility and those with poor water solubility. The capsule wall membrane was produced by a phase-inversion process, in which an asymmetric membrane was formed on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymeric material followed by dipping into a quenching solution. In situ formation of a delivery orifice in the thin membrane was proven by visualization of a jet stream of chlorophyll being released from the capsule. The release mechanism for drugs with moderate to high water solubility was mainly controlled by the osmotic effect, which is a function of the drug's solubility. Permeability across the asymmetric membrane of the capsule was determined to be 4.28×10^{-6} cm^2/h-atm at 37 °C for drugs with water solubilities in a moderate to high range. Accordingly, the poorly water-soluble drug, nifedipine, was unable to create enough of an osmotic effect to activate drug release. Solubilization either by the addition of the solubility enhancer, SLS, or by a solid dispersion with HPMC could increase the solubility of nifedipine to a sufficient extent to activate drug release. It was found that the suspending ability induced by the viscous nature of HPMC further interacted with SLS to synergistically increase the maximal percent release and the release rate of nifedipine. The osmotic effect of this suspension ability was proposed as the underlying mechanism responsible for the release of poorly water-soluble drugs, i.e. nifedipine, from this system.
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Keywords: Asymmetric membrane; Osmotic pressure; Cellulose acetate; Nifedipine; In situ formation

1. Introduction

It is known that pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure. There has been increasing interest in the development of osmotic devices over the past two decades. Designs of various types of osmotic pumps have been reported [1–3] and reviewed [4,5]. Osmotic tablets with an asymmetric membrane coating, which can achieve high water fluxes, have been described [6]. The asymmetric membrane capsule described [7,8] is also an example of a single-core osmotic delivery system consisting

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of a drug-containing core surrounded by an asymmetric membrane. One of the advantages of the asymmetric membrane capsule is the higher rate of water influx, allowing the release of drugs with lower osmotic pressures or lower solubilities. In spite of this advantage, there are many instances where the solubility of a drug is too low to provide a reasonable driving force for water ingress. In such situations, various methods have been reported to enhance this driving force either by improving drug solubility, including the use of crystal habit modifiers [9], assisting with lyotropic crystals [10,11], adding pH-regulating excipients [12,13], complexing with inclusion compounds [14], or by enhancing the contact surface area of the drug by utilizing wicking agents [15].

In a majority of cases, osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. Pre-formation and in situ formation are two possible ways of creating delivery orifices in membranes. Laser drilling is one of the most commonly used techniques to create preformed delivery orifices in osmotic tablets [16]. The use of modified punches for producing a preformed delivery orifice in osmotic dosage forms is also possible [17]. Controlled-porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in in situ formation of a microporous membrane [18–20]. The resulting membrane is substantially permeable to both water and dissolved solutes. Because of that, the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion to a minor extent. Systems with passageways formed in situ are also described in US patent no. 5,736,159 [21]. A small opening is formed at the edge of the tablet caused by the expansion of expandable material in the core.

The size of the delivery orifice must be optimized in order to control the amount and rate of drug released from osmotic systems. Preformed delivery orifices would be advantageous for the design of delivery orifices and hence the ability to control drug release. However, a complicated continuous process such as laser drilling, or specially designed machinery such as modified punches would be required for commercial production scale. Therefore, in situ formation of delivery orifices in the semipermeable membrane of osmotic systems would be less burdensome for commercial production. Although it is known that delivery orifices can be created in situ in semipermeable membranes, it is still necessary to utilize expanding material in the core of or added pore formers in the membrane. Since asymmetric membranes in osmotic membranes consist of a very thin, dense skin structure supported by a thicker, porous structural layer, in situ formation of delivery orifices on this thin layer is potentially possible with no assistance. In this study, we explored whether delivery orifices could be formed in situ on asymmetrically coated membranes. Compliance with an osmotic control mechanism of drug release and the influential factors were investigated.

2. Experimental section

2.1. Materials

Cellulose acetate (CA 398-10) was supplied by Eastman Chemicals Co. (Kingsport, USA). Nifedipine (NF) and felodipine (FL) were provided by Merck (Darmstadt, Germany) and the Sigma Chemical Co. (St Louis, MO, USA), respectively. As nifedipine was light sensitive, all samples were kept in an amber-colored container, wrapped in aluminum foil, or covered by a blanket during the whole experimental process. Chlorpheniramine maleate, pyridoxine, theophylline, chlorophyllin, glycerin, Tween 80, sodium lauryl sulfate (SLS) were from the Sigma Chemical Co. (St Louis, MO, USA). Triethyl citrate (TEC), acetonitrile, methanol were from Merck (Germany). Hydroxypropylmethylcellulose (HPMC, 5 cps, 15 cps and 50 cps) was purchased from the Shin-Etsu Chemical Co. (Japan).

2.2. Methods

2.2.1. Capsule preparation

Capsules with asymmetric membranes were produced using a dip-coating process. The stainless steel mold pins were dipped into polymer solutions consisting of 15% w/v cellulose acetate (CA 398-10, Eastman Fine Chemical) dissolved in a mixture of acetone/alcohol/glycerin (62 ml/34.5 ml/10 g), followed by quenching in an aqueous solution (10%

w/v glycerin). After quenching, the pins were withdrawn and allowed to air-dry. Then, the capsules were stripped off the pins, trimmed to size, and kept in desiccators until use.

2.2.2. Osmotic pump capsule preparation

Asymmetric membrane capsules were fabricated and filled with the desired amount of drug or drug–excipient mixture by hand. Physical mixtures of nifedipine were prepared simply by mixing nifedipine and sodium lauryl sulfate with hand shaking in a plastic bag for at least 15 min. A solvent method was employed to prepare solid dispersion systems for nifedipine. HPMC were selected as the water-soluble polymers. After dissolving nifedipine and HPMC in a suitable volume of an acetone/water mixture, the solvent mixture was completely evaporated in a forced-air convention oven at a temperature of 50–60 °C. Dried residues were ground with a coffee mill, and granules passing an 80-mesh sieve were collected. These solid dispersion samples were then stored in desiccators protected from light until use. After the filling operation, the capsules were capped and sealed with a sealing solution, which contains 16% cellulose acetate in a mixture of acetone/alcohol (62 ml/34.5 ml).

2.2.3. Solubility tests

Excess drugs were suspended in deionized water and maintained at 37 °C for at least 72 h with intermittent shaking. Immediately after filtration from the syringe, filtrate in the middle portion was sampled and properly diluted. The drug concentration was assayed with a validated method to determine the solubility in deionized water at 37 °C.

2.2.4. Release test

An in vitro dissolution test was performed using USP dissolution methodology (Apparatus 2, 50 rpm, 37 °C, 500–1000 ml of medium with sinker) (JASCO, Model DT-610). In all cases, an appropriate volume of sample was withdrawn at predetermined time intervals and assayed by either a validated UV absorbance measurement or by an HPLC/UV method (Helios, Unicam and Dynamax, Rainin Instrument).

2.2.5. HPLC analysis

The HPLC system consisted of a Rainin solvent delivery pump (Dynamax, model SD-200), a UV detector (Dynamax, model UV-1), an automatic sample injector (Dynamax, model AI-3), and an SISC for data analysis. The UV detector wavelength was set at 350 nm for nifedipine. Separation was achieved using an Inertsil column (C_{18}, 5×250 mm). The mobile phase consisted of water and acetonitrile in a ratio of 3:7 (v/v). A flow-rate of 0.8 ml/min was used.

2.3. Theoretical considerations

For drug delivery systems that release a drug by osmotic pressure, the volumetric flux of water from the surrounding aqueous medium into the device core is given by:

$$\frac{dV}{dt} = \frac{A}{h} L_p \sigma \Delta\pi \tag{1}$$

where dV/dt is the volumetric influx rate of water into the device core, A is the surface area of the capsule, h is the wall thickness, L_p is the filtration coefficient, σ is the reflection coefficient, and $\Delta\pi$ is the osmotic pressure difference across the wall. The zero-order release rate during the initial portion of the release profile is given by:

$$\frac{dM}{dt} = \frac{dV}{dt} S \tag{2}$$

where dM/dt is the release rate, dV/dt is given by Eq. (1), and S is the concentration of the component in the fluid being pumped. If the capsule contains only one component, the osmotic pressure difference is caused by a saturated solution of the component on one side of the capsule wall and sink conditions (assumed) outside the capsule walls. Also, assuming ideality, the expression for $\Delta\pi$ can be written as:

$$\Delta\pi = MRT = \frac{S}{M.W.} RT \tag{3}$$

where R is the universal gas constant, T is the temperature, $M.W.$ is molecular weight, and S is the saturation solubility of the single component (drug). Substituting for $\Delta\pi$ into Eq. (1) and substituting the resultant expression for dV/dt into Eq. (2), the following relation is obtained:

$$\frac{dM}{dt} = \left(\frac{A}{h} L_p \sigma RT\right) \frac{S^2}{M.W.} \quad (4)$$

Eq. (4) indicates that a plot of the release rate versus ($S^2/M.W.$) should be linear with a slope given by the expression in parentheses. Based on Eq. (4), the water permeability (L_p) of the asymmetric membrane capsule wall was calculated.

3. Results and discussion

The asymmetric membrane-coated capsules prepared appeared to be white, opaque, and glossy with no visible imperfections. Weight variations in the asymmetric membrane capsules and their dimensions were demonstrated to be consistent with little variation. This confirms that the process of producing these capsules is reproducible. Scanning electron micrographs (SEMs) of the capsule walls show that the membrane was asymmetric with a relatively thin dense region on a porous substrate with longer micropores (Fig. 1). No pore structures were shown in the dense region (Fig. 1A). The porous region at both ×100 (Fig. 1B) and ×200 magnification (Fig. 1C) reveals numerous pore structures.

In situ formation of a delivery orifice for releasing drug was proven with photographs as shown in Fig. 2 in which a deeply colored jet stream of chlorophyll from an open hole can be observed when an asymmetric membrane-coated capsule encapsulated with chlorophyll was suspended in the water medium. This delivery process continued for another 30 min as demonstrated by Fig. 2B. However, when this capsule was suspended in a 5% NaCl solution, the osmotic effect was inactivated, and no release of chlorophyll (Fig. 2C) was observed. This indicates that in situ formation of a delivery orifice is possible in the thin structure of the asymmetric membrane. The osmotic pressure created might play an important role in the switching on or off of this mechanism.

The osmotically controlled drug release mechanism from asymmetric membrane-coated capsules was further characterized based on Eq. (4) using drugs of varying solubilities. The core formulation consisted of drug alone but with varying solubilities

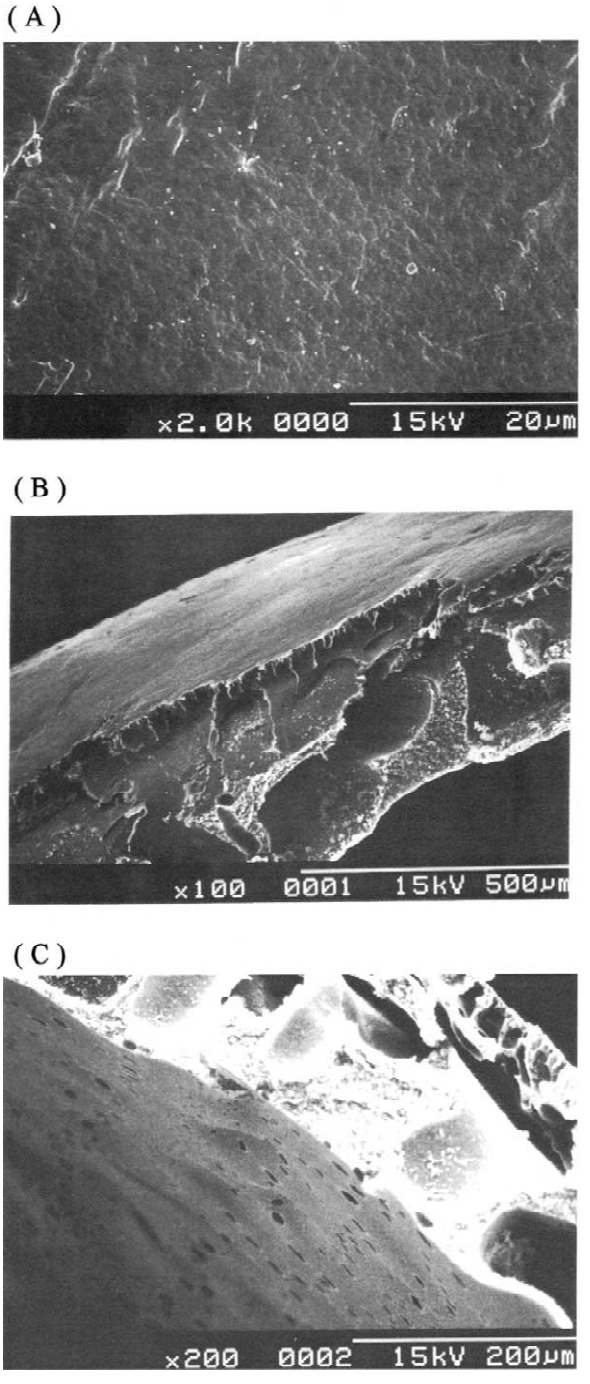

Fig. 1. Scanning electron micrographs of asymmetric membrane capsule wall at formulation A (A) dense region (outer layer) at ×2000 magnification, (B) cross-section at ×100 magnification, (C) porous region (inner layer) at ×200 magnification.

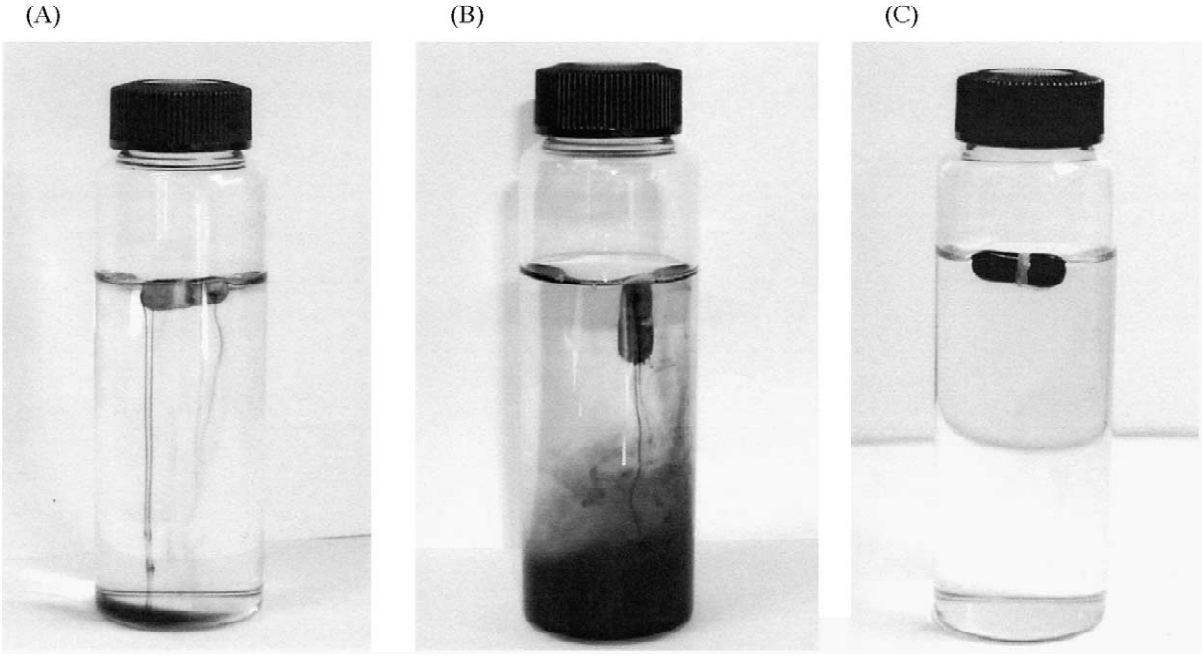

Fig. 2. Photograph of asymmetric membrane capsule with chlorophyllin in water. (A) After 30 min, (B) After 90 min, (C) In NaCl 5% solution.

in water (chlorpheniramine maleate, pyridoxine, theophylline, felodipine, and nifedipine); these were individually loaded into the asymmetric membrane capsule. The in vitro drug release profiles from asymmetric membrane capsules are shown in Fig. 3. The initial portion of the drugs release profiles were

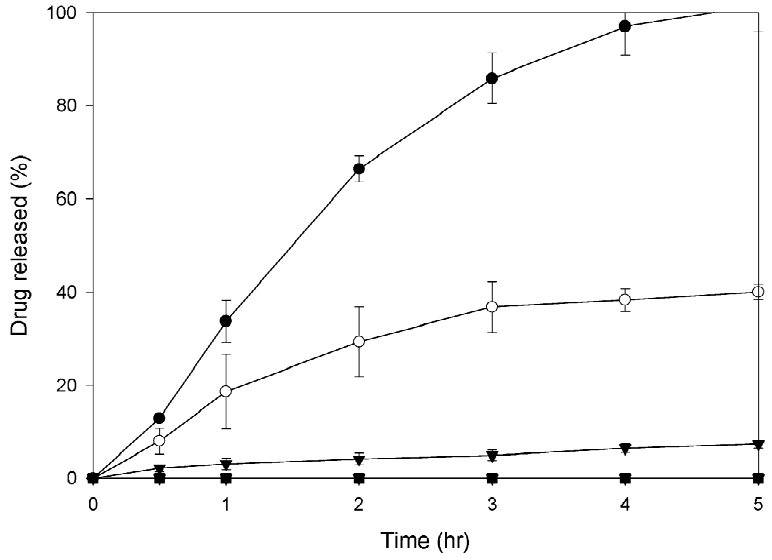

Fig. 3. Release profiles of drugs from asymmetric membrane capsule (formulation A) in water (50 rpm, $n=3$). Key: (●) Chlorpheniramine maleate 50 mg; (○) pyridoxine 50 mg; (▼) theophylline 50 mg; (▽) felodipine 50 mg; (■) nifedipine 50 mg.

Table 1
The solubility of drugs in water at 37 °C ($n=3$)

Drug	*M.W.*	*S* (mg/ml)	$S^2/M.W.$	Release rate (%/h)	Release rate (mg/h)
Chlorpheniramine maleate	390	576.72±16.24	852.84	33.90	16.95
Pyridoxine	205	224.47±0.96	245.79	12.58	6.29
Theophylline	180	7.18±0.03	0.29	1.30	0.65
Felodipine	384	<1	~0	~0	~0
Nifedipine	346	<1	~0	~0	~0

used to calculate the initial drug release rate. The results in Fig. 3 reveal that both the amount released and the release rate were a function of drug solubility. In comparison with the drug solubilities listed in Table 1, the amount released was larger and the drug release rate was faster as drug solubility increased.

The graph displayed in Fig. 4 plots the release rate (dM/dt) versus the ratio of the square of drug solubility to molecular weight ($S^2/M.W.$) based on Eq. (4). A linear correlation between the initial drug release rate (calculated from the slope of the drug release profile) and $S^2/M.W.$ was observed. The slope of linear portion is 0.0185 cm h^{-1} M^{-1}. By keeping all other factors constant, the drug release rate in the initial portion of the profiles increased linearly with respect to the square of the drug solubility divided by the molecular weight of the corresponding drug as predicted by Eq. (4). A statistically significant correlation of $r^2=0.9936$ was demonstrated. This complies with the drug released by an osmotic pumping mechanism. Assuming ideality, where R is the Universal Gas Constant and T is the absolute temperature, L_p (at 37 °C) is calculated to be 4.28×10^{-6} cm^2/h-atm based on Eq. (4) with known values of $h=0.02$ cm and $A=3.4$ cm^2. This value is comparable to that from a similar membrane design reported in the literature [8].

As concluded for asymmetric membrane-coated capsules with an in situ formed delivery system, the

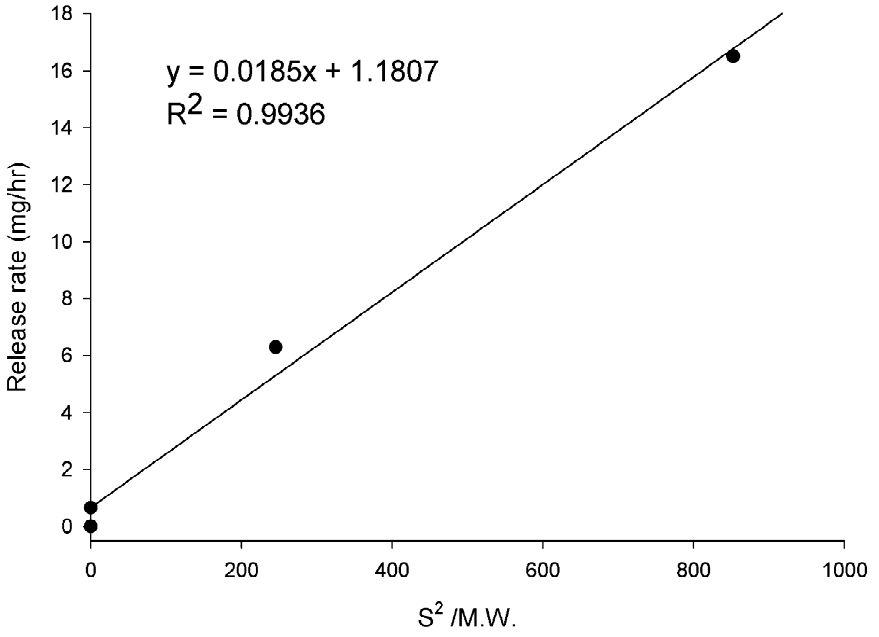

Fig. 4. Linear relationship between the release rate and the square of solubility divided by molecular weight of the drug.

osmotic effect is the main activation force for drug release. Similarly, drug solubility is expected to be the determining factor for the success of engineering asymmetric membrane-coated capsules with an in situ formed delivery orifice with a desirable release rate. It is likely that a drug with low solubility would not create enough osmotic pressure to activate drug release. Because of this, the drug release mechanism from an asymmetric membrane-coated capsule with in situ formation of a delivery orifice was further studied by examining the influence of core formulation variables including the added amount and viscosity of hydroxypropylmethylcellulose (HPMC) and the amount of sodium lauryl sulfate (SLS). Nifedipine was selected as a model drug because it has poor water solubility. All subsequent release studies were done in water medium with the addition of 1% Tween 80 as the solubilizing agent.

Fig. 5 shows that the amount of SLS in the core formulation had a marked influence on nifedipine release. When the added amount of SLS was at a 1:1 ratio to the nifedipine amount, only 2% of the nifedipine was released, whereas the release amount of nifedipine increased to 40% by adding SLS at a 20:1 ratio to the nifedipine amount. The release rate apparently increased with the increased amount of added SLS. Possibly, the greater the amount of SLS is which is incorporated into the capsule, the larger the osmotic effects will be which can be activated to cause a greater amount of nifedipine to be dissolved and released. The osmotic effects of SLS on the release rate and the released amount of nifedipine could be attributed to two factors. One is the solubilization effect of SLS (Table 2) in enhancing the dissolved amount of nifedipine in the core medium for increasing the osmotic effect, and the other is that the dissolved SLS acts as an osmotic agent to increase the osmotic effect. Since SLS was

Table 2
The solubility of nifedipine in SLS solution at 37 °C ($n=3$)

SLS concentration (w/v%)	Solubility (mg/ml)	S.D.
0.1	0.021	0.0002
0.5	0.166	0.0028
1.0	0.371	0.0063
2.5	0.799	0.0092
5.0	1.362	0.0099
10.0	2.296	0.0104
20.0	3.280	0.0425

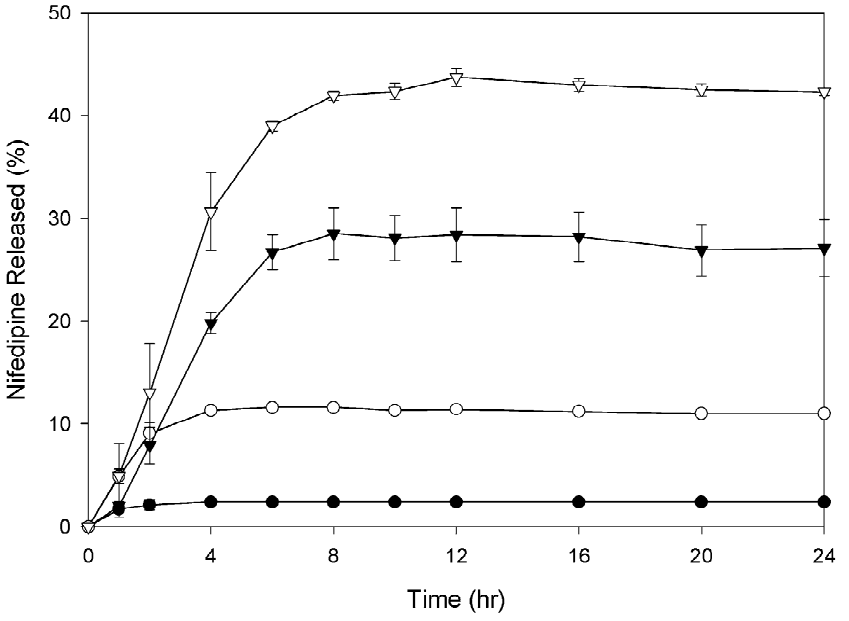

Fig. 5. Release profiles of nifedipine from asymmetric membrane capsule in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by physically mixed method with SLS (S). NF/S ratio: (●) 1/1, (○) 1/5, (▼) 1/10, (▽) 1/20.

released through the in situ formed delivery orifice, it was released in company with nifedipine. When the SLS was exhausted, both mechanisms ceased, which terminated the release of nifedipine from these capsules. This leads to the released amount of nifedipine being proportional to the added amount of SLS. This quantitative relationship is illustrated in Fig. 6 by plotting the maximal percent released versus the ratio of SLS to nifedipine. The slope (2.196) of the linear plot can be used to predict what added amount of SLS per unit amount of nifedipine would be necessary to reach a maximal 100% release of nifedipine from this capsule system. Based on this, quite a large amount (about 440 mg) of SLS was possibly needed to completely release 10 mg nifedipine from this type of capsule by extrapolation. An in vitro dissolution test of nifedipine mixed with sodium lauryl sulfate at a weight ratio of 1:44 had been performed. It was fairly confirmed that the extent of drug release from this formulation was increased to about 85%. The result shown is closely consistent with the extrapolated prediction.

Fig. 7 illustrates the effect of viscosity grades of HPMC at the same level on the release pattern of nifedipine from these osmotic capsules with an in situ formed delivery orifice. Nifedipine was incorporated with HPMC in a solid dispersion form prepared by the solvent method and then physically mixed with SLS. Compared with the core formulation which only contains nifedipine and SLS at a ratio of 1:10, the addition of HPMC of varying viscosities further increased both the release rate and the released amount of nifedipine. At the same level of HPMC, an increase in the released percentage of 60% was shown for HPMC with a viscosity of 5 cps, whereas increases to 70–80% were observed for HPMC with a viscosity of either 15 or 50 cps. The further promotion of the released amount of nifedipine by all viscosity grades of HPMC could be attributed to the enhancement of nifedipine solubility with the aid of the solid dispersion. However, this seems to indicate that the higher the viscosity of HPMC used, the larger amount of nifedipine which could be released and the faster the release rate which would result. Since the enhancement of nifedipine solubility using various grades of HPMC is comparable (Table 3), another mechanism seems to be operating to have such an influence.

Fig. 8 demonstrates the effect of different added amounts of HPMC of the same viscosity grade (50 cps) on the release pattern of nifedipine. The added amount of HPMC also had a pronounced influence on the release profile. Since an improvement in solubility of nifedipine using different ratios of

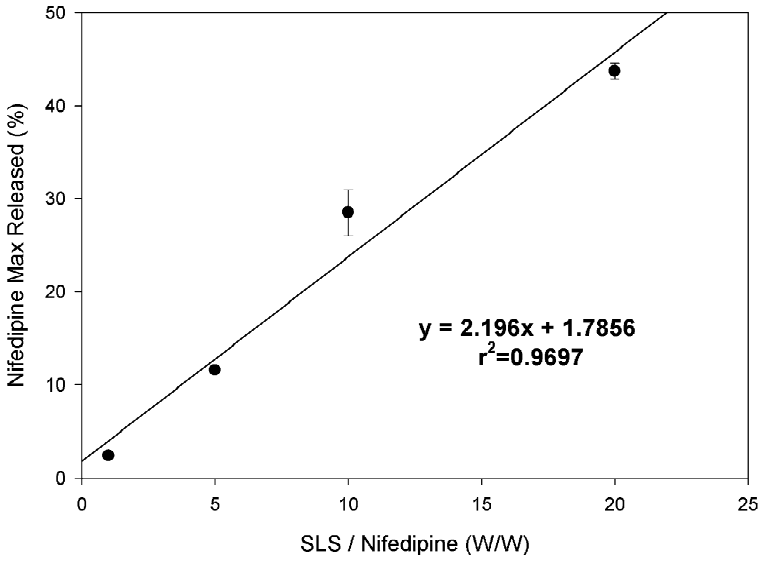

Fig. 6. Correlation of max released and SLS/nifedipine ratio.

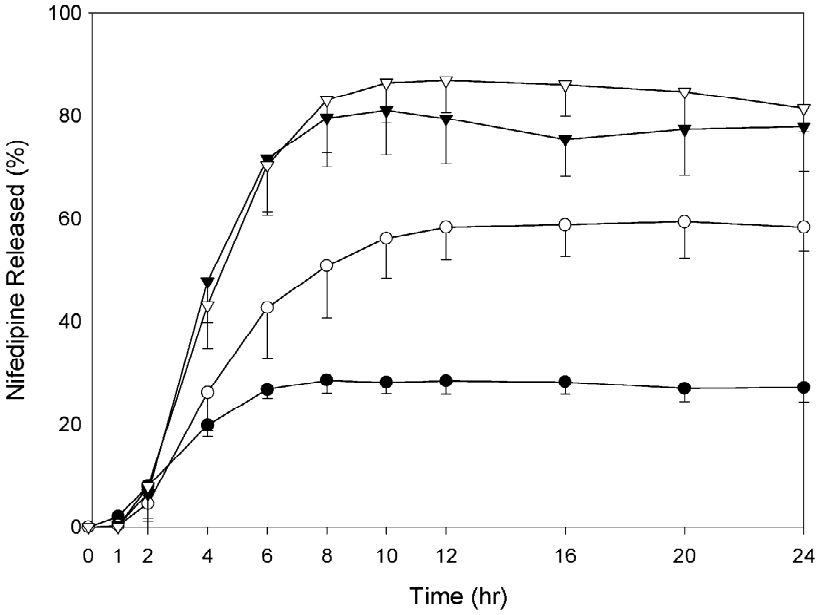

Fig. 7. Release profiles of nifedipine in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by solvent method with HPMC and physically mixed with SLS (S). Key: (●) NF/S ratio: 1/10; (○) NF/HPMC 5 cps/S ratio: 1/10/10; (▼) NF/HPMC 15 cps/S ratio: 1/10/10; (▽) NF/HPMC 50 cps/S ratio: 1/10/10.

HPMC to nifedipine was not obvious, the role HPMC plays as a thickening agent in elevating the viscosity of the core suspension and, subsequently, preventing precipitation of nifedipine particles was suspected of possibly being the expression of a larger surface for dissolution. The larger the amount of HPMC used, the higher the viscosity of the core suspension would be, leading to the efficient suspension of nifedipine particles in the capsule. As a consequence, the release rate increased when increasing the added amount of HPMC by increasing the available surface area for dissolution. This mechanism seems capable of being explained by the effect of HPMC of varying viscosity grades. That is, a higher-viscosity HPMC would promote the more-efficient suspension of nifedipine particles for dissolution, leading to an increase in the released amount with an increase in the viscosity grade of HPMC used for preparing the solid dispersion.

Table 3
The solubility of various forms of nifedipine in water at 37 °C ($n=3$)

Formulation	Ratio	Solubility (mg/ml)
Nifedipine	–	0.011[a]
Nifedipine/HPMC 5 cps	1:10	0.0422±0.0010
Nifedipine/HPMC 15 cps	1:10	0.0463±0.0021
Nifedipine/HPMC 50 cps	1:10	0.0439±0.0021
Nifedipine/mannitol	1:5	0.0132±0.0001
Nifedipine/mannitol	1:10	0.0104±0.0003

[a] From Ref. [22].

Based on the above release profiles, we concluded that this asymmetric membrane-coated capsule with an in situ formed delivery orifice was able to release a water-insoluble drug such as nifedipine in the presence of an osmotic agent with the aid of a solubilizing agent and a suspension agent. Therefore, the system was operated by an osmotic-suspension co-controlled delivery mechanism somewhat different from either the generic EOP or the push–pull osmotic tablet. This proposed mechanism was further supported by the results demonstrated in Fig. 9.

Fig. 9A shows that the release of nifedipine was activated with a 1-h delay from the time the capsules were filled with the physical mixture of nifedipine and SLS at a ratio of 1:10. Two hours later, equilibrium had been reached with a release rate of about 0.5 mg/h, after which the release rate declined

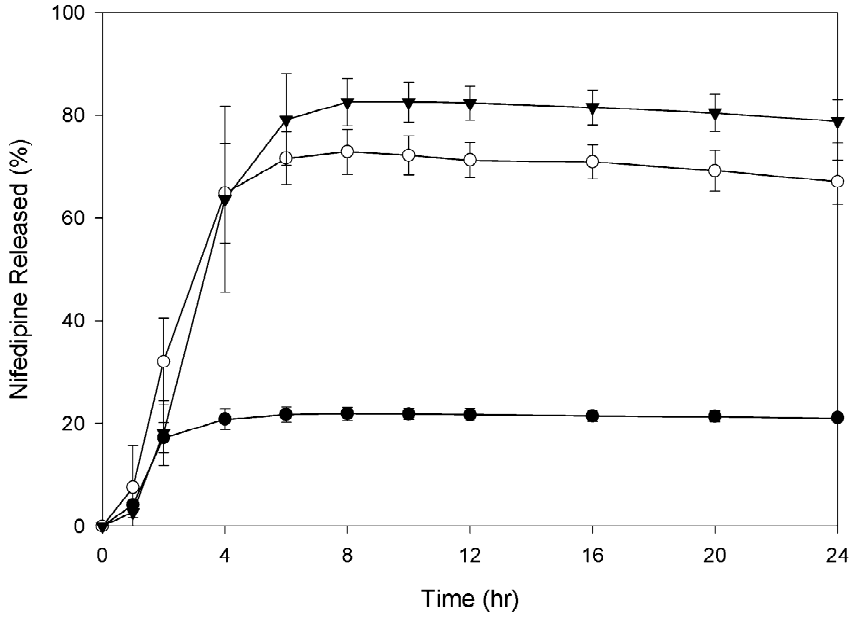

Fig. 8. Release profiles of nifedipine in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by the solvent method with HPMC 50 cps (H) and physically mixed with SLS (S). NF/H/S ratio: (●) 1/1/10, (○) 1/5/10, (▼) 1/10/10.

4 h afterward, and the release of nifedipine had almost completely ceased by 10 h. In the presence of an osmotic agent such as SLS, water imbibed by the semi-permeable membrane into the capsule was gradually saturated with SLS to further build up the osmotic pressure difference between the internal system and the external environment. Simultaneously, the dissolved SLS caused the solubilization of nifedipine which was then available for release. During this period, the in situ formed delivery orifice might be created at the weakest point in the asymmetric membrane with an increase in osmotic pressure. It is expected that there is a lag time to reach such a state, which means that the release of drug is only activated with a 1-h lag time as shown in Fig. 9A for SLS. After that time, dissolved nifedipine and SLS were delivered through the orifice which had formed in situ. However, with the release of nifedipine at the expense of SLS, the osmotic effect gradually diminished and the solubilization effect was also retarded. This led to the release rate of nifedipine gradually decreasing with time. Then the release of nifedipine came to a complete stop when all the added amount of SLS was exhausted.

Nevertheless, Fig. 9A also shows that the release of nifedipine continued for more than 24 h with nifedipine in a solid dispersion form with HPMC. The release rate gradually reached its maximum at 8 h and was maintained at a plateau until 20 h. Compared to SLS, a longer period of release time but a lower release rate of nifedipine with HPMC was demonstrated. A longer period of release occurred because it takes time for all the HPMC to completely dissolve in such quiescent conditions inside the capsule, and the longer-sustained osmotic effect of HPMC might be a result of it being too large in size to be released. A lower release rate of nifedipine with HPMC might be attributed to a lower solubilization effect of HPMC which resulted in a reduced osmotic effect. However, maintaining a maximal release rate of 0.25 mg/h with a drug solubility of 43.9 μg/ml (refer to Table 3) requires an osmotic pressure higher than 7.8×10^3 atm according to Eq. (4). The induction of osmotic pressure by the presence of HPMC was determined to be minimal (data not shown), since osmotic pressure is a colligative property that is determined by the molecular number, which would be less for such a polymer as HPMC with a high molecular weight.

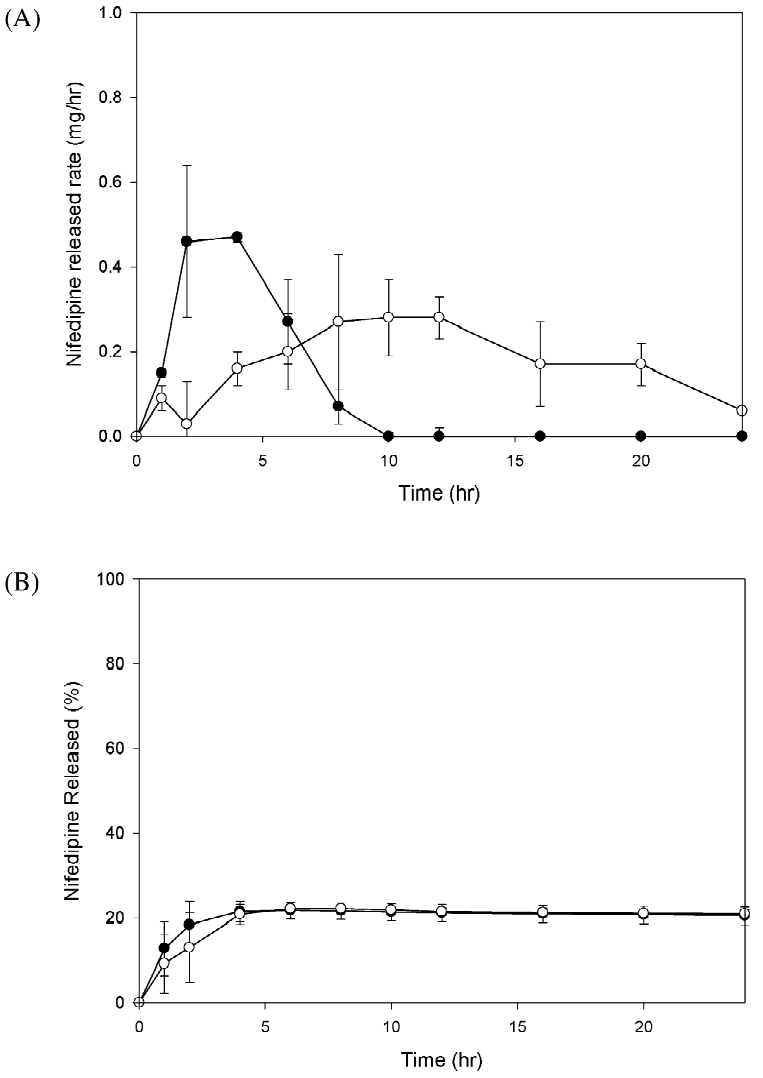

Fig. 9. Release rate of nifedipine from asymmetric membrane capsule in 1% Tween 80 solution (50 rpm, $n=3$). (A) Nifedipine (NF) was made by physically mixed with SLS (S) or solvent method with HPMC 50 cps (H). Key: (●) NF/S ratio: 1/10; (○) NF/H ratio: 1/10. (B) Nifedipine (NF) was made by the solvent method with mannitol (M) and physically mixed with SLS (S). NF/M/S ratio: (●) 1/10/10, (○) 1/5/10.

Therefore, the exact mechanism causing such a release rate with such a drug solubility was not due to the induction of a greater osmotic pressure. Because of that, with the same osmotic effect as in the case of SLS only, there must necessarily be a larger excess value in the solubility term than the real solubility to have such a large release rate and a cumulative released amount. This large excess value in the solubility term could be attributed to nifedipine being released in both its insoluble and soluble forms, the latter of which stands for the exact solubility.

Fig. 9B further shows the release pattern of nifedipine from an encapsulated mixture consisting of a solid dispersion of nifedipine with mannitol prepared by the solvent method and physically mixed with SLS. A maximal amount of 20% was released for both mixtures, but with a faster rate for a larger

amount of mannitol. Mannitol is known for being an osmotic agent which should induce osmotic pressures proportional to its amounts which will synergize with the osmotic effect of SLS. This reveals that the higher osmotic effects induced by a larger amount of mannitol with the same amount of SLS does lead to an increase in the release rate, and it is maintained as it is until both are exhausted. Nevertheless, it is the solubility that determines the cumulative released amount of nifedipine during the active period of osmotic pressure as predicted by Eq. (4). Since the increase in nifedipine solubility with a two-fold increase in the amount of mannitol was insignificant as shown in Table 1, similarity in the maximal amount released is expected for both mixtures under a reasonable assumption that the active period of the osmotic effect for both cases did not significantly differ. The effect of solubility on the cumulative amount is predictable by Eq. (4). This means that only the soluble form of nifedipine was released from this formulation, which differs from both the insoluble and soluble forms of nifedipine being released from formulations containing HPMC.

We concluded that both insoluble and soluble forms of nifedipine were released from encapsulated formulations containing HPMC through the in situ formed delivery orifice, whereas only the soluble form of nifedipine was released from that containing mannitol. It is possible that HPMC acts as a thickening agent causing nifedipine particles to be suspended. During the experiment, water was imbibed creating a viscous suspension in situ inside the capsule, which resulted from the thickening agent (HPMC) and the imbibed water. Both the insoluble and soluble forms of nifedipine in the suspension were subsequently pumped out through the in situ formed delivery orifice. This explains why only the soluble form of nifedipine was released in formulations containing mannitol, which did not sufficiently increase the viscosity of the solution inside the capsule to suspend the insoluble form of nifedipine so it could be released. Therefore, drug release operated by both osmotic and suspension mechanisms. It should be pointed out that the sustainability of drug suspension caused by the thickening effect of the polymer was equally important as that of the osmotic action.

4. Conclusions

The in situ formed delivery orifice in controlled-release polymeric capsules with an asymmetric membrane wall is mainly responsible for the delivery of both soluble and poorly soluble drugs. In vitro release studies indicate that drug delivery from this asymmetric membrane-coated system is principally controlled by osmotic pressure for those drugs with moderate to high water solubilities. The asymmetric membrane-coated capsule prepared in this study has a permeability of 4.28×10^{-6} cm^2/h-atm. This parameter can be used to predict the release rate of any drug encapsulated in this asymmetric membrane capsule. Solubilization of poorly water-soluble drugs with the incorporation of solubility enhancers is able to increase the release rate and the cumulative released amount. It was further found with solubilization in solid dispersions using a thickening agent such as HPMC, both insoluble and soluble forms of nifedipine were released as a result of the viscous solution induced by HPMC being able to suspend the insoluble form of nifedipine, rendering it available for release. This is not applicable for formulations containing an osmotic agent such as mannitol, which has no ability to induce the viscosity required to suspend nifedipine particles. Therefore, it was proposed that the mechanisms responsible for the release of nifedipine from this system were the simultaneous osmotic and suspension effects.

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