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Asymmetric membrane capsules for delivery of poorly water-soluble drugs by osmotic effects

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Abstract

A non-disintegrating polymeric capsule system, in which asymmetric membrane offers an improved osmotic effect, was used to deliver poorly water-soluble drugs in a control manner. The capsule wall membrane was made by a phase inversion process, in which 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 quench solution. This study evaluates the influence of coating formulation that was cellulose acetate (CA), ethylcellulose (EC), and plasticizer (glycerin and triethyl citrate). Results show capsule that made by CA with glycerin (formulation A), which appear in asymmetric structure and are able to release chlorpheniramine maleate (CM) in significant percentage. Two poorly water-soluble drugs of felodipine (FL) and nifedipine (NF) were selected as the model drug to demonstrate how the controlled release characteristics can be manipulated by the design of polymeric capsules with an asymmetric membrane and core formulations. Results show that sodium lauryl sulfate (SLS) is able to promote the release of FL from polymeric capsules prepared with CA with asymmetrical membrane. The addition of solubilizer, including RH40, PVP K-17, and PEG 4000 could enhance the release of FL but with an extent not being related to its solubility. Based on these results, influence of core formulation variables, including the viscosity and added amount of hydroxypropyl methylcellulose (HPMC), the added amount of SLS, and drug loading were examined on the release of NF. It was found that HPMC of 50 cps was suitable to be a thickening agent and both added amount of HPMC and SLS showed a comparable and profoundly positive effect, whereas NF loading had no influence on the drug release percent and rate. There existed a synergistic interaction between HPMC and SLS on the release percent and rate.

Keywords: Asymmetrical membrane; Osmotic effect; Poorly water-soluble drugs; Sodium lauryl sulfate

1. Introduction

There has been an increasing interest in the development of osmotic devices in the past two decades.

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Various types of osmotic pumps have been reviewed by Santus and Baker (1995). The elementary osmotic pump (EOP), which was comparably simple to manufacture and was able to release drug at an approximate zero-order rate, was firstly introduced by Theeuwes in the 1970s (Theeuwes, 1975). However, this type of the EOP is only suitable for the delivery of water-soluble drugs. To overcome the limit of EOP, a push–pull osmotic tablet was developed in the 1980s. While the push–pull osmotic tablet succeeds in delivering water-insoluble drug (Swanson et al., 1987), it has two disadvantages: (1) the tablet core is prepared by compressing two kinds of compartments together, a complex technology as compared with that of EOP; (2) after coating, a complicated laser-drilling technology should be employed to drill the orifice next to the drug compartment (Theeuwes et al., 1978). Osmotic tablets with an asymmetric membrane coating, which can achieve high water fluxes, have been described (Herbig et al., 1995). The asymmetric membrane capsule described (Thombre et al., 1999a,b,c) is also an example of a single core osmotic delivery system consisting of a drug-containing core surrounded by an asymmetric membrane. One of the advantages of asymmetric membrane is the higher rate of water influx, allowing the release of drugs with a lower osmotic pressure or lower solubility. In spite of this advantage, there are many instances where the solubility of the drug is too low to provide a reasonable driving force for water ingress. Therefore, the aims of this work were: (1) to develop asymmetric membrane capsules to deliver poorly water soluble drug such as NF; (2) to evaluate the influence of core formulation variables including viscosity and added amount of HPMC, added amount of SLS, and drug loading on the release characteristics.

2. Experimental methods

2.1. Materials

Cellulose acetate (CA 398-10) was supplied by Eastman Chemicals Co. (Kingsport, USA). Ethylcellulose (EC, 50 cps) was obtained from Wako Pure Chemicals Co. (Osaka, Japan). Nifedipine (NF) and felodipine (FL) were provided by Merck (Darmstadt, Germany) and Sigma Chemical Co. (St. Louis, MO, USA), respectively. Glycerin, Tween 80, acetonitrile, methanol, and triethyl citrate (TEC) were from Merck (Germany). Chlorpheniramine maleate (CM), sodium lauryl sulfate (SLS), and PEG 4000 were from Sigma Chemical Co. (St. Louis, MO, USA). Hydroxypropylmethylcellulose (HPMC, 5, 15, and 50 cps) was purchased from Shin-Etsu Chemical Co. (Japan). Polyvinyl pyrrolidone K-17 (PVP K-17) and Cremophor RH 40 (RH40) was supplied by BASF Wyandotte Co. (Germany).

2.2. Preparation of asymmetric membrane capsule

Capsules with asymmetric membrane were produced using a dip-coating process. The mold pins were dipped into polymer solutions consisting of polymeric solution (Table 1) dissolved in the mixture composed of acetone, alcohol, glycerin, or TEC in various ratio (detail shown in Table 1), 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 the desiccators until use (Fig. 1). Asymmetric membrane capsule so fabricated were filled with a desired amount of drug or drug–excipient mixture by hand. After filling, the capsules were capped and sealed with a sealing solution, which contains cellulose acetate 16% in the mixture of acetone/alcohol (62 ml/34.5 ml).

2.3. Preparation of core formulations for FL and NF

NF and FL were passing a 100-mesh sieve and the particle size was below 150 μm. Physical mixtures of FL were prepared simply by mixing FL and SLS at a weigh ratio of 1:5 and 1:10 with hand shaking in a plastic bag for at least 15 min. Solid dispersions of FL were prepared by fusing FL and Cremorphor RH 40 or PEG 4000 at a weigh ratio of 1:20 at temperature of 100 °C with stirring until completely dissolved, whereas FL with PVP K-17 at a weight ratio of 1:20 was heated at a temperature of 170 °C with stirring until completely dissolved. Table 2 listed the details for the core formulations of NF examined in this study. All formulations were prepared by physically mixing.

2.4. Release test

The in vitro dissolution test was performed using USP dissolution methodology of Apparatus II (500 ml

Table 1
Characterization of asymmetric membrane capsules

	Formulation				
	A	B	C	D	E
Polymeric solution					
CA 398-10 (g)	15	15	–	–	–
EC 50 cps (g)	–	–	15	15	15
Acetone (ml)	62	62	62	62	62
Alcohol (ml)	34.5	34.5	34.5	34.5	34.5
Glycerin (g)	10	–	10	5	–
TEC (g)	–	10	–	–	–
Physical characterization					
Appearance	Opaque	Transparent	Opaque	Opaque	Opaque
Capsule	++	+	–	+	+
Asymmetric	++	–	++	+	–

(++) Good; (+) moderate; (–) poor.

of 1% Tween 80 medium stirred at 50 rpm and 37 °C) (JASCO, Model DT-610) under light protection. Capsules were kept in the basket, which suspended above the paddle and inside the medium. An appropriate volume of samples were withdrawn at predetermined time intervals and assayed by a validated UV method for FL (wavelength 362 nm), CM (wavelength 244 nm), and a validated HPLC method for NF described below. The same volume of fresh medium was replaced to maintain constant volume for dissolution.

2.5. UV and HPLC analysis

UV method for assaying FL was validated with examining the accuracy and precision for interday and intraday. In a linear range of 4–24 μg/ml ($r^2 = 0.9998$),

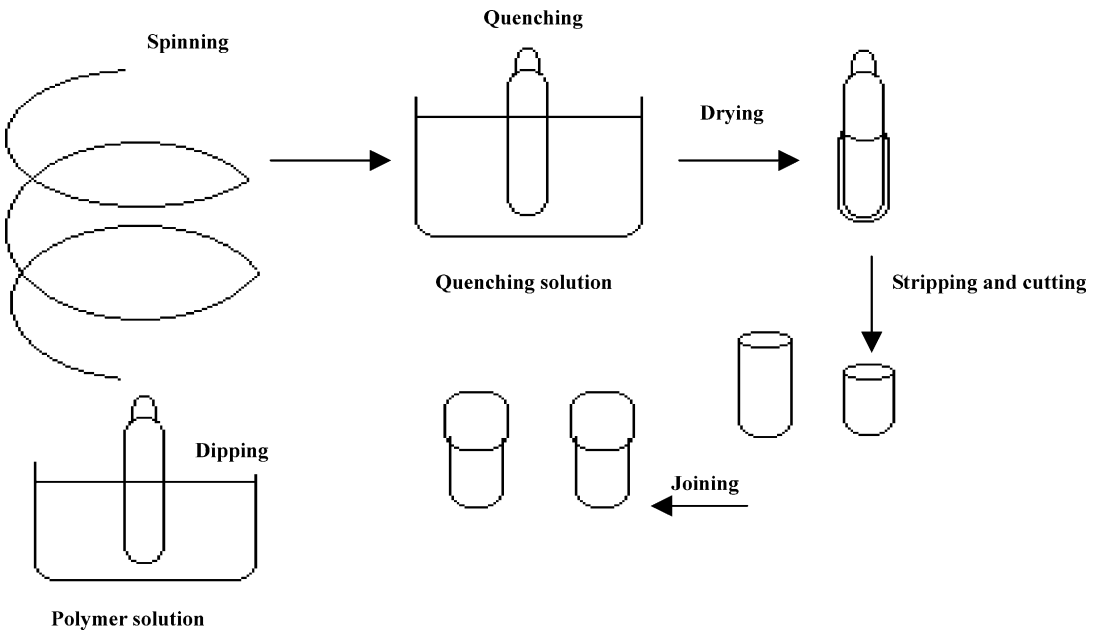

Fig. 1. Process for the preparation of asymmetric membrane capsule.

Table 2
Characteristics of asymmetric membrane capsules of formulation A

Weight variation (mg)	High	Low	Average
	43.6	34.1	38.0
Dimensions	**Body**	**Cap**	**Joined**
Length (mm)	14	9	18
Diameter (mm)	6.1	6.5	–
Membrane thickness (mm)	0.2		

the accuracy and precision for interday and intraday were 1.57–3.27% and 0.32–2.74%, respectively. UV method for assaying CM was also validated. In a linear range of 20–120 μg/ml ($r^2 = 0.9999$), the accuracy and precision for interday and intraday were 0.28–3.02% and 0.16–0.57%, respectively. The HPLC system consisted of a Rainin solvent delivery pump (Dynamax, model SD-200), an UV detector (Dynamax, model UV-1), an automatic sample injector and a SISC for data analysis. The UV detector wavelength was set at 350 nm for NF. Separation was achieved using an Inertsil column (C18, ODS, 4.6 mm × 250 mm). The mobile phase consisted of water and acetonitrile in a ratio of 3:7 in volume. A flow rate of 0.8 ml/min was used. In a linear range of 4–24 μg/ml ($r^2 = 0.9999$), the accuracy and precision for interday and intraday were 0.75–2.23% and 0.10–0.24%, respectively.

3. Theoretical considerations

For drug delivery systems that release 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 the surface area of the capsule, h the wall thickness, L_p the filtration coefficient, σ 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 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:

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

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

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

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 permeability ($L_p\sigma$) of the asymmetric membrane capsule wall is calculated.

4. Results and discussion

The easiness of preparation and physical characteristics of polymeric capsules with asymmetrical membrane to induce osmotic effects were compared by using various solvent compositions to dissolve cellulose acetate and ethylcellulose with adding different kinds of plasticizer. The physical characteristics of asymmetric membrane capsules so obtained shows in Tables 1 and 2. Formulation A appears to be the easiest in the preparation of polymeric capsules, formulations B, D, and E to be the next, and polymeric capsules prepared with formulation C were soft and easily broken. It was transparent for polymeric capsules prepared with formulation B, whereas it was opaque for all three other formulations. Fig. 2 shows scanning electron micrographs (SEM) photographs to demonstrate the asymmetry of polymeric capsule membrane. Polymeric capsule membrane appears to be asymmetrical for formulations A and C, whereas it was less obvious in the asymmetry for formulations B, D, and E.

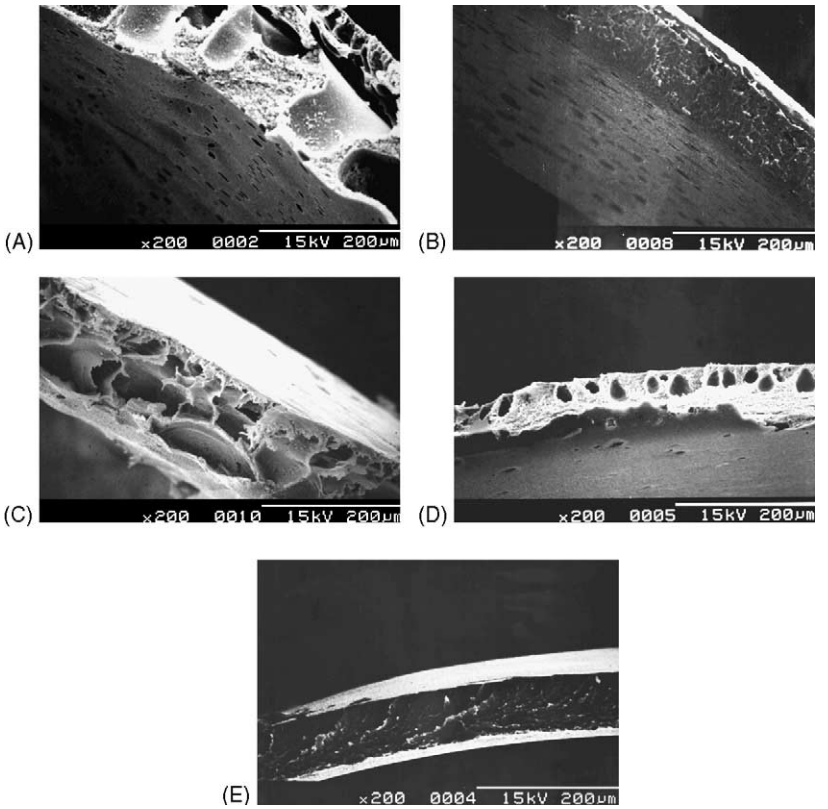

Fig. 2. Scanning electron micrographs of asymmetric membrane capsule wall at 200× magnification. (A) Formulation A, (B) formulation B, (C) formulation C, (D) formulation D, (E) formulation E.

Asymmetrical membrane is generally composed of a dense and thin outer layer without pore structure and a loose and thick inner layer with pore structure. The formation of asymmetry in polymeric capsule membrane is a result of phase inversion when coating solution is contacted with quenching solution on the outer surface. Fig. 2A and C illustrate that there has numerous larger pores in polymeric capsule membrane prepared with formulations A and C resulting in the profound asymmetry in the membrane. Both contain the same amount of glycerin but different kind of polymeric materials. However, when glycerin in formulation A was replaced by TEC in formulation B leads to the formation of polymeric capsule membrane with less pore structure. Similarly, the decreases of glycerin amount in the coating solution containing EC as polymeric material proportionally produces less pore structure in the resulting polymeric capsule membrane. It is concluded that glycerin is a determinant in the formation of asymmetrical membrane for both polymeric materials. The main influencing characteristics to consider could be its plasticizing capacity and water solubility.

According to Eq. (4), it is known that the drug permeability across asymmetric membrane wall with osmotic effects was dominantly controlled by permeant solubility and polymeric material at the same thickness of rate-determining membrane. Fig. 3 demonstrates the releasing profiles of a highly water-soluble drug of CM (solubility in water: 576.7 ± 16.2 mg/ml) from polymeric capsule membranes prepared with these four formulations. Results show that only polymeric capsule membrane prepared with CA was able to release CM in a significant percentage, whereas only a small percentage of CM was released from these membranes prepared with EC. This seems to indicate that porous structure in the polymeric membrane is not the

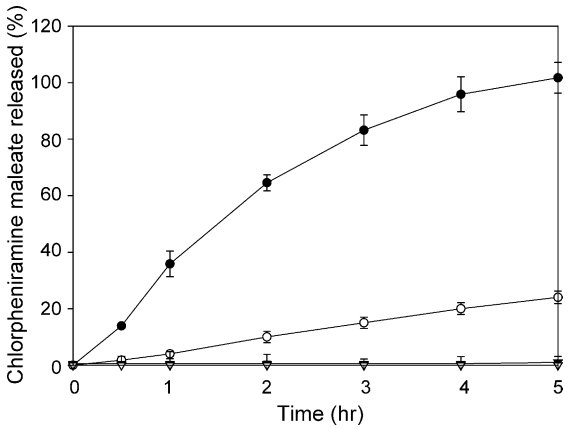

Fig. 3. Release profiles of CM from four-type asymmetric membrane capsule wall in water (50 rpm, $n = 3$). Key: (●) formulation A, (◯) formulation B, (▼) formulation D, (▽) formulation E.

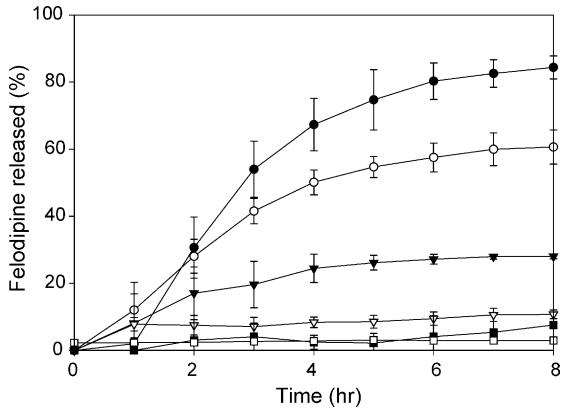

Fig. 4. Release profiles of FL from asymmetric membrane capsule in 1% Tween 80 solution (50 rpm, $n = 3$). FL was made by physically mixed method with SLS and fusion method with Cremopher RH40, PVP K-17, PEG 4000. Key: (●) FL/Cremoppher RH40: 1/20, (◯) FL/SLS: 1/10, (▼) FL/SLS: 1/5, (▽) FL/PVP K-17: 1/20, (■) FL/PEG 4000: 1/20, (□) FL alone.

only factor control the releasability of drug from this membrane. Therefore, CM was still released from the polymeric membrane with less porous structure that prepared from formulation B, and the released extent of CM did not increase with increasing glycerin amount as a pore-forming additive. This difference might be attributed to the hydrophobicity of EC making it is less permeable to water than that for CA. Even that, it was failed to use a water-soluble additive, such as HPMC, to increase its hydrophilicity and potentials of pore formation making it more permeable to water (data not shown). Since that, polymeric capsule membrane with asymmetrical structure prepared with formulation A was selected to examine the influence of core formulation on the delivery of poorly soluble drug, FL and NF.

Core formulations for FL and NF were prepared with the addition of solubility enhancer either by physical mixing or by fusion method. The core formulations consisted of FL or NF modified to have varying solubility in water was filled into asymmetric membrane capsules. The in vitro release profiles of FL from nominally one-component formulations filled into asymmetric membrane capsules are shown in Fig. 4. It indicates that FL is released only in a very small percent without any additives to enhance its water solubility. With increasing the mixing amount of SLS to 1:5 and 1:10, the release of FL is proportionally increased. Since SLS has been used as an osmotic agent and a micellar solubilizer, this should be attributed to the possible effects of SLS as osmotic agent to induce osmotic pressure and also as solubilizer to enhance drug solubility for releasing. Further, the addition of various types of solubilizers, including RH40, PEG 4000, and PVP K17, promotes the release percent of FL in different extent at a weight ratio of 1:20, in which RH40 is the most effective in promoting the release of FL, and PVP K17, and PEG 4000 enhance that in a less extent with the former little higher than the latter. This seems to indicate that the enhancement of drug solubility is not the sole prerequisite for promoting the release of poorly water-soluble drugs from polymeric capsule with asymmetrical membrane. Since the enhancement of NF solubility by incorporation of SLS, Cremophor RH40 and PVP K-17 are comparable (Table 3), another mechanism seems to operate to have such an influence. Whether or not, the incorporation of PVP K-17 to increase the viscosity and PEG 4000 to solidify particles leading to retardation dissolution of resulting particles for releasing is worthy of further exploration.

Based these results, several trials were pre-tested to select the most efficient additive in promoting the release of NF from this system. It was concluded that SLS was similarly able to enhance the release percent of NF proportional to its added amount and HPMC was the best among the polymeric solubilizers for the purpose. To study the influences of core formulation variables on the release of poorly water-soluble drugs from

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

Formulation	Ratio	Solubility (mg/ml)
NF	–	0.011
NF/PVP K17	1:5	0.0252 ± 0.0077
NF/PVP K17	1:10	0.0324 ± 0.0024
NF/PVP K17	1:20	0.0488 ± 0.0019
NF/HPMC 5 cps	1:10	0.0422 ± 0.0010
NF/HPMC 15 cps	1:10	0.0463 ± 0.0021
NF/HPMC 50 cps	1:10	0.0439 ± 0.0021

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

Partial from Ref. (Lin and Ho, 2003).

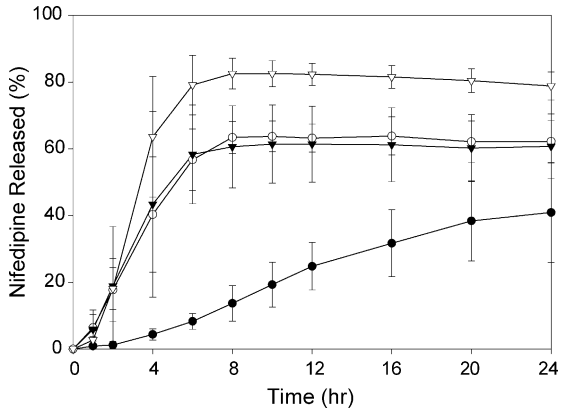

Fig. 5. Release profiles of NF in 1% Tween 80 solution (50 rpm, $n = 3$). NF was made by solvent method with HPMC 50 cps (H) and physically mixed with SLS (S). NF/H/S ratio: (●) 1/10/0, (◯) 1/10/3, (▼) 1/10/5, (▽) 1/10/10.

polymeric capsules with asymmetrical semi-permeable membrane by osmotic pressure, several core formulations based on these additives for NF were designed. The core formulation variables examined including viscosity and added amount of HPMC (50 cps), amount of SLS, and NF loading. Table 4 lists the exact experimental values for each variable in these core formulations.

Compared with the core formulation, which contains NF and SLS, the addition of HPMC of varying viscosities further increased both the release rate and the released amount of NF. At the same level of HPMC, an increase in the release percent 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 (data not shown). However, this was to indicate that the higher the viscosity of HPMC used, the larger amount of NF that could be released and the faster the release rate, which would result.

Based on a previous test, HPMC with viscosity of 50 cps was adopted in this study. The maximal release percent determined at 24 h from release profiles for each core formulation is summarized in Table 4 as well. Fig. 5 shows that the added amount of SLS has a marked enhancement on both of the release percent and release rate of NF. The larger amount of SLS incorporated into

Table 4
The experimental values of core formulation variables and maximal release percent at 24 h

Formulation no.	Independent variables (mg)			Dependent variables
	NF (X_1)	HPMC 50 cps (X_2)	SLS (X_3)	Max released (%) (Y)
1	10	0	10	2.4
2	10	0	50	11.6
3	10	0	100	28.5
4	10	0	200	43.7
5	10	100	0	40.9
6	10	50	100	72.8
7	10	100	30	63.8
8	10	100	50	61.4
9	10	100	100	86.8
10	10	10	100	21.8
11	20	100	100	82.0
12	30	100	100	82.5

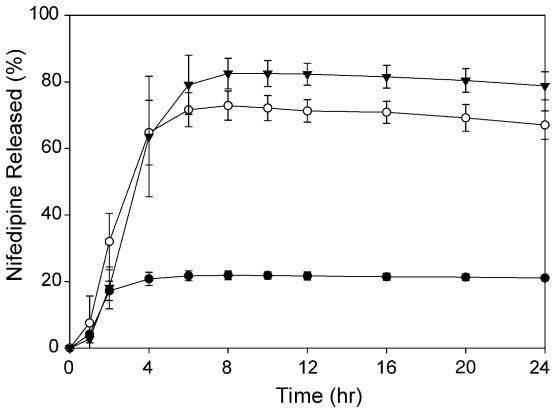

Fig. 6. Release profiles of NF in 1% Tween 80 solution (50 rpm, $n = 3$). NF was made by solvent method with HPMC 50 cps (H) and physically mixed with SLS (S). NF/H/S ratio: (●) 1/1/10, (◯) 1/5/10, (▼) 1/10/10.

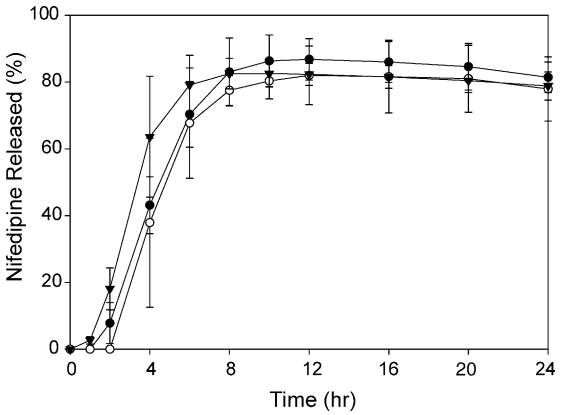

Fig. 7. Release profiles of NF in 1% Tween 80 solution (50 rpm, $n = 3$). NF was made by solvent method with HPMC 50 cps (H) and physically mixed with SLS (S). NF/H/S ratio: (●) 1/10/10, (◯) 2/10/10, (▼) 3/10/10.

the capsule, the larger amount of water is imbibed and the greater quantity of core formulation could be dissolved and, as a consequence, greater amount of NF was dissolved and released.

Fig. 6 illustrates that added amount of HPMC also had a pronounced influence on the release profile. Since the improvement of solubility of NF was not obvious, the role of HPMC playing as a thickening agent to elevate the viscosity of the core suspension, and subsequently, preventing precipitation of NF particles was expectedly possible to express larger surface for dissolution. The larger the amount of HPMC used, the higher the viscosity of the core suspension would be, leading to efficiently suspend NF particles in the capsule. As a consequence, the release rate increases with increasing the added amount of HPMC by increasing available surface area for dissolution. Fig. 7 shows the effect of NF loading on drug release. It is clear that NF loading has insignificant influence on the release profile of NF from this asymmetric membrane capsules.

To quantify the influence of formulation variables on maximal percent released at 24 h from asymmetric membrane capsule, multivariable linear regression analysis was conducted based on this experimental design. A multivariable linear function in the form $Y = f(X_i)$ was used as the fitting equation. X_i is independent variable ($i = 1, 2, 3$) representing the NF loading, the added amount of HPMC, and the added amount of SLS, respectively, and Y is the dependent variable representing the maximal percent released of NF at 24 h.

The regression equation was obtained as follows by stepwise method:

$$Y = 2.0195 + 0.4193X_2 + 0.2202X_3 + 0.0021\ X_2X_3$$

The calculated value by fitting equation and the experimental value of the maximal percent released at 24 h was fairly correlated as shown in Fig. 8 ($r = 0.9446$). From the regression results, the following conclusions could be reached: (1) a positive coefficient (X_2, X_3 and X_2X_3) for these factors means that the increase of individual factor increases the maximal percent released (Y); (2) NF loading (X_1) has no influence on the maximal release percent, whereas both the added amount

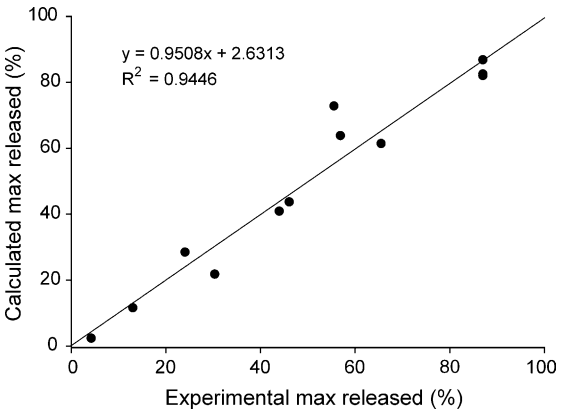

Fig. 8. Correlation of calculated and experimental values of maximal release (%) of NF at 24 h.

of HPMC (X_2) and SLS (X_3) significantly enhance the maximal release percent; (3) a synergistic interaction of the added amount of HPMC and SLS (X_2X_3) is examined to be statistically significant on the maximal release percent.

The asymmetric membrane capsule described (Thombre et al., 1999a,b,c) is also an example of delivery poorly water-soluble drug, such as glipizide, which has a pH-dependent solubility. In the case of glipizide, the authors added salts to adjust the pH value then enhance the drug solubility. In order to avoid depleting the excipient from the core before complete drug release, two tablets was encapsulated in the same capsule; one tablet coated with a rate-controlling membrane and the other was uncoated. Our study also shows asymmetric membrane capsules for delivery of poorly water-soluble drugs, such as NF, which has non-pH-dependent solubility. It is an example of a single core osmotic systems consisting of drug-containing core surround by an asymmetric membrane and then, evaluate the influence of core formulation.

5. Conclusions

Polymeric capsules with an asymmetric membrane wall are successfully developed for the delivery of poorly soluble drugs. In vitro release studies indicate that the drug delivery operated by osmotic effect using asymmetric membrane could be achieved with its solubility modified to a proper extent. On the other hand, the release percent and rate of poorly water-soluble drugs from capsules with asymmetric membrane could be enhanced with the addition of solubilizers, but not being related to enhancement extent of drug solubility. SLS plays an important role in this system as an osmotic agent and a micellar solibilizer for both FL and NF. There shows a synergistic effect of SLS with the addition of thickening agent (HPMC) to improve the release percent and release rate for NF.

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