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Osmotic Delivery of Flurbiprofen through Controlled Porosity Asymmetric Membrane Capsule

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The release of poorly water-soluble drug, flurbiprofen, through asymmetric membrane capsule of cellulose acetate containing different pore forming agents like glycerol, polyethylene glycol 400, and dibutyl phthalate, in presence of sodium lauryl sulfate was investigated. The asymmetric membrane was fabricated in the shape of capsule body and cap by phase inversion technique. The type of pore forming agent incorporated had a marked influence on the porosity of the asymmetric membrane. However flurbiprofen due to its poor solubility was unable to create enough osmotic pressure and hence less than 10% of drug was released from all the systems with out SLS. However when the study was conducted with SLS, a maximum release of 72% was observed from the capsule with 70% glycerol. The release rates were found to increase with the increase in the concentration of pore forming agent and the amount of SLS encapsulated.

Keywords cellulose acetate; glycerol; controlled porosity; osmotic pressure; flurbiprofen

INTRODUCTION

Osmotic pressure is widely utilized as a driving force for controlled delivery of drugs from the osmotic systems. The simplest design of an osmotic drug delivery system is elementary osmotic pump that consist of an osmotic core surrounded by a semipermeable membrane with one or more delivery pores. When the dosage form comes in contact with aqueous fluid, it imbibes water at rate determined by the permeability of the membrane and osmotic pressure of the core formulation. The imbibition of water results in saturated solution of drug within the core and is dispensed at a controlled rate from the system (Theeuwes, 1975). Numerous such designs of osmotic systems have been reported (Verma et al., 2002).

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The asymmetric membrane capsule for osmotic delivery of drug consists of very thin, dense skin structure supported by a thicker, porous sub-structural layer (Cardinal et al., 1997a; Cardinal et al., 1997b; Herbig et al., 1995). The asymmetric membranes have high flux due to their porous nature and hence find their use in achieving higher release rate for poorly soluble drugs (Thombre, 1999). To ensure osmotic delivery of drug from asymmetric membrane capsule, osmotically active agents called osmogents or solubilizing agents can be directly incorporated into the drug core for drugs having low osmotic pressure and solubility (McClelland & Zentner, 1990; Verma & Mishra, 1994). In case highly water-soluble drug is to be delivered in a sustained fashion, a solubility suppressant can be incorporated in the core (Zentner et al., 1991). Asymmetric membrane coated osmotic tablets have also been described to achieve high water fluxes (Makhija & Vavia, 2003). The porosity of the asymmetric membrane can be controlled by the type and amount of pore forming agent, thus controlling the lag time and duration of drug release.

Asymmetric membrane capsule consist of a cap and body, which are so manufactured that they can snugly fit into each other. The wall of asymmetric membrane capsule is made up of water insoluble polymer like cellulose acetate, ethyl cellulose, cellulose acetate butyrate, and their mixtures. The capsule shell is prepared by phase inversion technique, which involves precipitation of membrane on to the stainless steel mould pin. These molds are dipped into the polymeric solution and then immersed into a non-solvent quench bath, whereby polymer undergoes phase inversion; the shells so formed are removed from the moulds (Thombre et al., 1999). The water-soluble additives, which serve as pore former, can be directly incorporated into the polymeric solution, from which asymmetric membranes are to be prepared. The membrane when in contact with aqueous medium results in in situ pore formation due to leaching of the water-soluble additives in aqueous medium. The release of the drug takes place through these pores by osmotic pumping; the mechanism of drug release follows osmotic principle, with simple diffusion playing a minor role

(Zentner et al., 1990). Water-soluble additives, used for this purpose, are glycerol, polyethylene glycols, amino acids, etc. These capsules release the drug over a prolonged time by osmosis, depending upon the composition of the drug core.

Moreover release from this system is independent of pH and has been shown to follow zero order kinetics (Zentner et al., 1985).

In this study (Zentner et al., 1985a; Zentner et al., 1985b) the asymmetric membrane capsules of cellulose acetate were prepared, with different pore forming agents at different concentrations. The release of poorly water drug, flurbiprofen was studied as the function of porosity of asymmetric membrane and concentration of solubilizing agent SLS.

MATERIALS AND METHOD

Cellulose acetate was obtained from Glaxo lab. Ltd., India, Sodium lauryl sulfate, PEG-400 and Dibutyl phthalate were obtained from S.D. Fine Chemicals Ltd Delhi; The Drug Flurbiprofen was a gift sample from FDC Pharmaceutical, Ltd. Bombay India.

PREPARATION OF ASYMMETRIC MEMBRANE CAPSULE

Controlled porosity asymmetric membranes of cellulose acetate (CA) were prepared by dip coating process. Solution of CA (15% w/v) was prepared in acetone/water (9:1) solvent system. Weighed quantity of CA was added to solvent system, the resulting mixture was stirred in a well-closed beaker until a homogeneous solution was formed. To the resulting homogeneous solution required quantity of pore forming agent: glycerol, polyethylene Glycol-400 (PEG-400), and Dibutyl phthalate (DBT) were added separately (50, 60, and 70% w/w of CA) and stirring continued to ensure proper uniform mixing of added pore forming agent.

The stainless steel mould pins were fabricated with the dimensions so as to form a capsule body and cap. The molds were dipped in the coating solution of cellulose acetate and glycerol for 2 minutes, and then removed carefully so as to form a thin layer of solution on the mold. The pins were taken out of the coating solution and briefly air dried for 30 sec, followed by quenching in aqueous solution of glycerol (10% w/v) 3 min. This resulted in phase inversion and formation of asymmetric membrane. The resulting membrane was stripped off and trimmed to desired size and stored for future study. The thickness and total surface area of capsules was determined by using digital micrometer (Mitutoyo, Japan). The porosity and structure of the asymmetric membrane was characterized by scanning electron microscopy (Lyca electron optics—340).

FILLING AND SEALING OF ASYMMETRIC MEMBRANE CAPSULE

The fabricated asymmetric membrane capsules with different type of pore forming agent were filled with the mixture of drug and solubilizing agent. The physical mixture of drug and the SLS was prepared by mixing them thoroughly in laboratory blender for 10 min followed by screening through sieve No. 80. Each of the capsules containing 50, 60, and 70% (w/w of CA) of pore forming agent were filled with mixture of drug (100 mg) and solubilizing agent in the ratio of 1:1, 1:5, and 1:10, keeping the quantity of drug same. The mixture of drug and SLS was filled in the body of capsule and the cap was snugly fitted to the body of the capsule. The cap and body were finally sealed with the 16% cellulose acetate solution only without any pore-forming agent to ensure no drug released through the seal.

SOLUBILITY STUDY

Excess of drug was added to the phosphate buffer pH 7.2 (B.P.) and maintained at 37°C for 48 h with intermittent shaking. Immediately after filtration from the syringe, filtrate in the middle portion was sampled and properly diluted. The concentration was determined by using UV spectrophotometer at 247 nm λ_{max}, it was 0.9545 mg/mL.

RELEASE RATE STUDY

The in vitro release study of drug from each of the capsule (n=3) was studied as the function of both the amount of pore forming agent added and the amount of SLS used in each system. The filled capsules were subjected to release rate study using USP dissolution apparatus II (50 rpm, 37°C. The dissolution medium used was phosphate buffer pH 7.2 (B.P.), 900 mL. The samples were withdrawn hourly for 9 h and analyzed using UV spectrophotometer at 247 nm.

RESULT AND DISCUSSION

In situ pore formation in asymmetric membrane wall for releasing drug was proven by filling the capsule with water-soluble dye, amaranth. A stream of colored dye was observed to be diffusing from capsule wall when suspended in water medium after lag time. This indicates in situ pore formation of delivery orifice due to leaching of pore forming agent present in the asymmetric membrane. However, no release was observed when such capsule was suspended in 10% solution of sodium chloride. In such case the osmotic effect gets nullified, suggesting that the prepared system follows osmotic principle for releasing its encapsulated contents.

Average Membrane thickness and surface area (Table 1) were found to be almost same for asymmetric membrane capsule with different pore forming agnets. The SEM of asymmetric membrane incorporated with different pore forming agent indicate, increase in the porosity of asymmetric membrane as the concentration of pore forming agent is increases. The porosity of the membrane was found to alter significantly with nature of pore forming agent used as shown in Figures. 1a, 1b, and 1c. The porosity and size of the vacuoles were found to decrease in the following order of pore forming agents used: glycerol > PEG-400 > DBT.

TABLE 1
Average Physical Characteristics of Asymmetric Membrane Containing Different Pore Forming Agent

Con. of Pore Forming Agent (% w/w)	Glycerol			PEG-400			DBT		
	50%	60%	70%	50%	60%	70%	50%	60%	70%
Membrane thickness (cm)	0.0273 ± 0.003	0.0244 ± 0.002	0.0224 ± 0.004	0.0291 ± 0.002	0.0262 ± 0.002	0.0276 ± 0.001	0.0272 ± 0.001	0.0278 ± 0.002	0.0260 ± 0.0028
Surface area (cm^2)	6.39 ± 0.015	6.41 ± 0.0157	6.43 ± 0.014	6.41 ± 0.0023	6.44 ± 0.0116	6.43 ± 0.008	6.38 ± 0.0032	6.42 ± 0.0171	6.45 ± 0.008

FIGURE 1. Scanning electron micrographs of asymmetric membrane containing 70% glycerol at X 60 magnification (a), 70% PEG-400 at X 180 magnification (b) and 70% DBT at X 521 magnification (c).

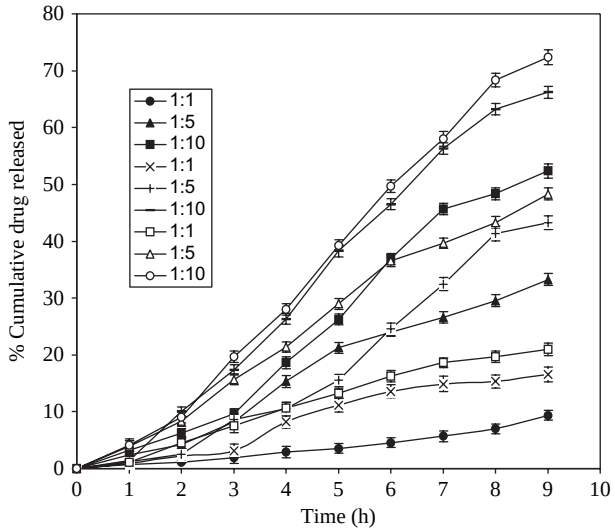

FIGURE 2. Release profile of flurbiprofen from asymmetric membrane capsule containing glycerol (50, 60, and 70%) filled with various ratios of drug: SLS. 50% glycerol-1:1 (●), 1:5 (▲), 1:10 (■), 60% glycerol—1:1 (×), 1:5 (+), 1:10 (—). 70% glycerol—1:1 (□), 1:5 (Δ), 1:10 (❍).

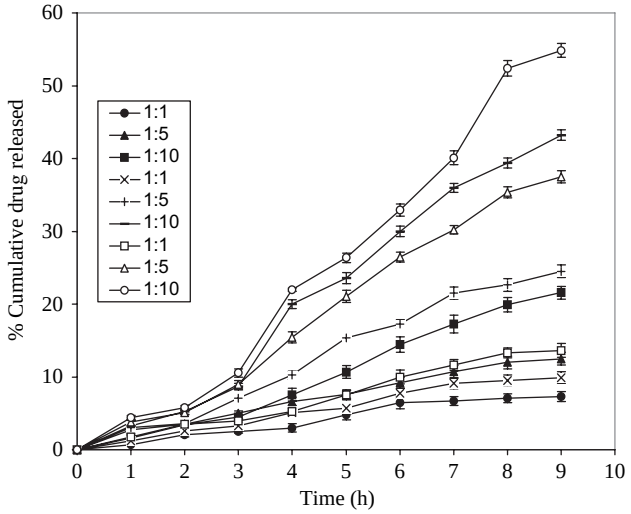

FIGURE 3. Release profile of flurbiprofen from asymmetric membrane capsule containing PEG-400 (50, 60, and 70%) filled with various ratios of drug: SLS. 50% PEG-400-1:1 (●), 1:5 (▲), 1:10 (■). 60% PEG-400 – 1:1 (×), 1:5 (+), 1:10 (—). 70% PEG-400 – 1:1 (□), 1:5 (Δ), 1:10 (❍).

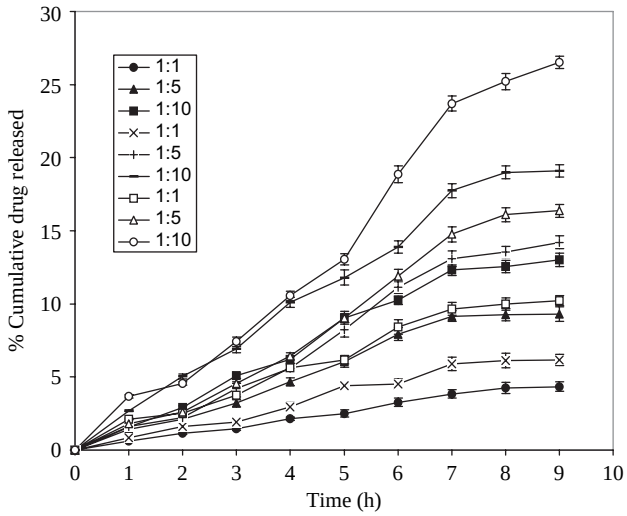

FIGURE 4. Release profile of flurbiprofen from asymmetric membrane capsule containing DBT (50, 60, and 70%) filled with various ratios of drug: SLS. 50% DBT-1:1 (●), 1:5 (▲), 1:10 (■). 60% DBT – 1:1 (×), 1:5 (+), 1:10 (—). 70% DBT – 1:1 (□), 1:5 (Δ), 1:10 (❍).

TABLE 2
Percentage of Maximum Drug Released from Different Asymmetric Membrane Capsule Filled with Pure Drug and with Different Ratios of Drug: SLS

Con. of Pore Forming Agent (% w/w)	Maximum Drug Released (%)			
	Drug	1:1	1:5	1:10
Glycerol 50%	2.85	9.37	33.26	52.36
Glycerol 60%	3.67	16.54	43.26	66.23
Glycerol 70%	5.67	21.01	48.32	72.36
PEG-400 50%	1.84	7.29	12.49	21.56
PEG-400 60%	2.14	9.93	24.52	43.21
PEG-400 70%	3.26	13.64	37.46	54.84
DBT 50%	–	4.34	9.31	13.02
DBT 60%	1.13	6.17	14.21	19.08
DBT 70%	2.07	10.21	16.37	26.51

The in vitro release rate study of flurbiprofen from capsule having different pore forming agent is shown in Figures 2, 3, and 4. The in vitro results revels that as the concentration of pore forming agent is increased the amount of drug released also increases. The type of pore forming agent used has a prominent effect on the amount of drug released as shown in Table 2. The amount of drug released with glycerol was found to be highest, followed by PEG-400 and DBT. The result is further substantiated by SEM study which shows that the porosity and size of pores decreases in the following order of pore forming agent used: glycerol > PEG-400 > DBT. The difference in the amount of drug released from each of the system can be attributed to the porosity of asymmetric membrane. The higher release rate from the capsule containing glycerol is due to its high porosity causing higher influx of dissolution medium resulting in rapid solubilization of drug in presence of SLS, hence quick build up of osmotic pressure inside the system. Similar justification can be given for the decreased amount of drug being released from the system with PEG-400 and DBT as pore forming agents.

The amount of drug released was found to increase with the increase in the amount of SLS encapsulated along with the drug in each system irrespective of the type and concentration

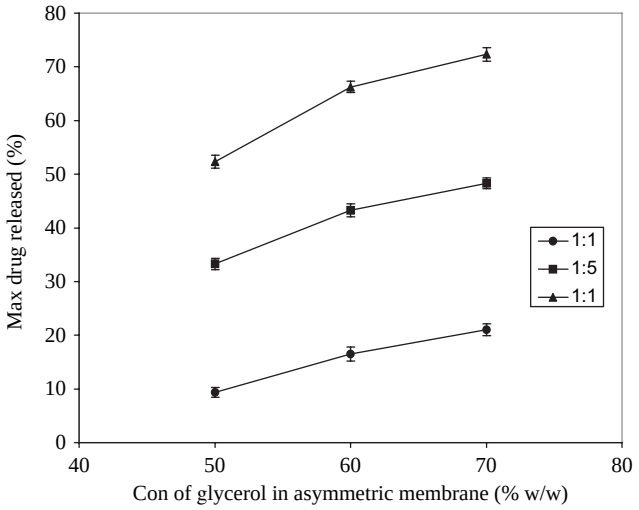

FIGURE 5. Correlation of concentration of pore forming agent (Glycerol) and maximum drug released at different ratios of drug: SLS.

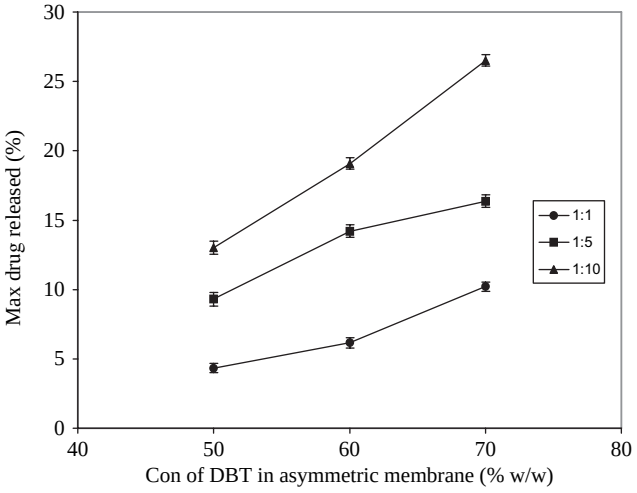

FIGURE 7. Correlation of concentration of pore forming agent (DBT) and maximum drug released at different ratios of drug: SLS.

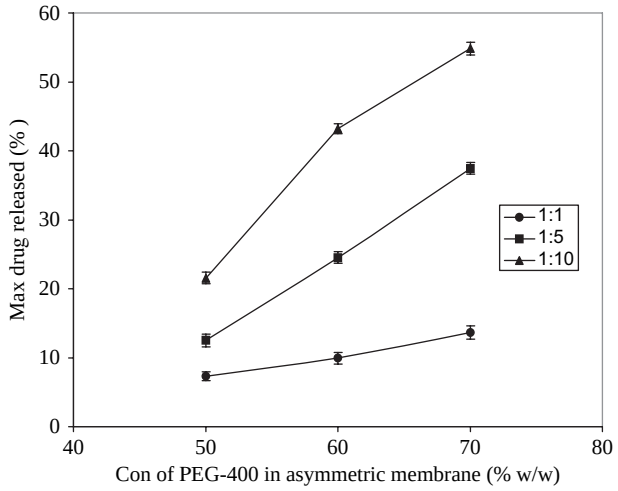

FIGURE 6. Correlation of concentration of pore forming agent (PEG-400) and maximum drug released at different ratios of drug: SLS.

of pore forming agent used. This suggests that the release of poorly water-soluble drug flurbiprofen increased with the amount of SLS added to the core of the formulation. This may be primarily due to the solubilizing effect of SLS, causing increased solubility of drug and subsequently increased osmotic pressure resulting in increased amount of drug being released from the system. It appears that SLS besides imparting solubilizing effect also acts as an osmogent in dissolved form.

The result in Figures 5, 6, and 7 shows that when the amount of each of the pore-forming agent is increased from 50 to 70% the release rate apparently increased (Table 3). The increase in the release rate with increase in the added amount of pore forming agent is further substantiated by the correlation coefficient of linear relationship as shown in Table 4. But

TABLE 3
In Vitro Kinetics of Release from Different Asymmetric Membrane Capsule

Con. of Pore Forming Agent (% w/w)	Regression Coefficient					
	1:1		1:5		1:10	
	r^2	k_0	r^2	k_0	r^2	k_0
Glycerol 50%	0.957	0.973	0.983	3.966	0.972	6.506
Glycerol 60%	0.954	2.107	0.951	5.289	0.987	8.243
Glycerol 70%	0.984	2.532	0.983	5.678	0.992	8.769
PEG-400 50%	0.962	0.891	0.989	1.371	0.983	2.571
PEG-400 60%	0.983	1.176	0.983	2.929	0.981	5.231
PEG-400 70%	0.984	1.605	0.987	4.498	0.976	6.501
DBT 50%	0.989	0.507	0.969	1.148	0.977	1.572
DBT 60%	0.972	0.746	0.976	1.751	0.986	2.255
DBT 70%	0.973	1.195	0.981	2.015	0.978	3.162

TABLE 4
Correlation Data of Different Concentration of Pore Forming Agent (50, 60, and 70%) and Maximum Drug Released at Constant Ratio of Drug: SLS

Pore Forming Agent	Regression Coefficient (r)					
	1:1		1:5		1:10	
	r^2	k	r^2	k	r^2	K
Glycerol	0.982	0.582	0.965	0.753	0.952	0.998
PEG-400	0.991	0.317	0.992	1.241	0.972	1.671
DBT	0.954	0.293	0.952	0.353	0.992	0.674

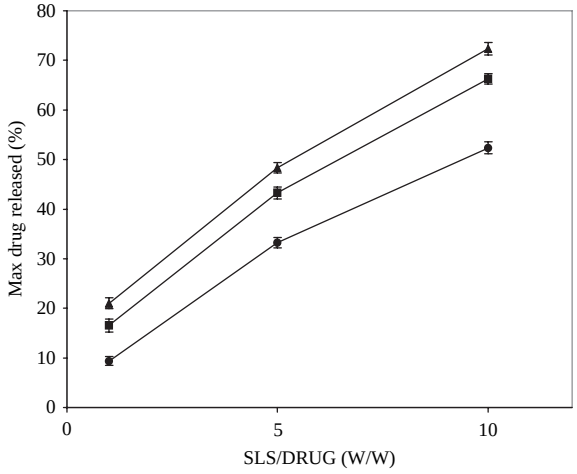

FIGURE 8. Correlation of maximum drug released and SLS: Drug ratio at different concentration of glycerol (•) 50%, (■) 60%, (▲) 70%.

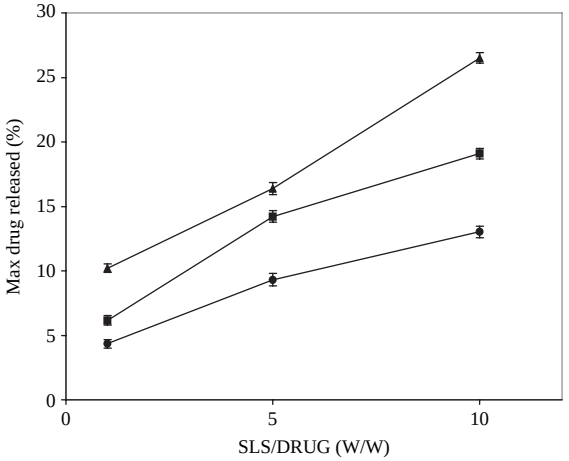

FIGURE 10. Correlation of maximum drug released and SLS: Drug ratio at different concentration of DBT (•) 50%, (■) 60%, (▲) 70%.

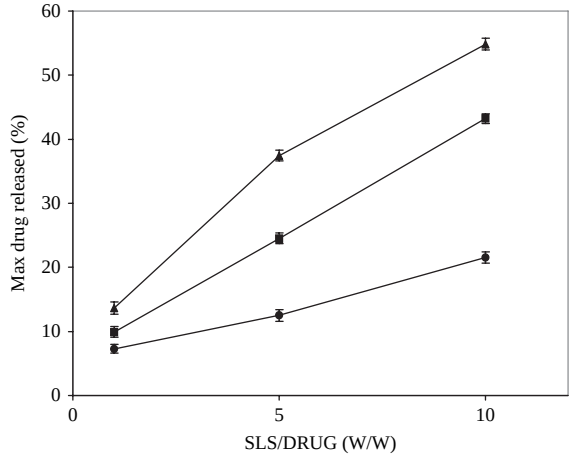

FIGURE 9. Correlation of maximum drug released and SLS: Drug ratio at different concentration of PEG-400 (•) 50%, (■) 60%, (▲) 70%.

when the same systems were filled with increased amount of SLS, higher release rates were observed (Figures 8, 9, and 10). This suggests that increase in porosity does affect the release rate, but the amount of SLS present in the core of the formulation has a marked influence in increasing the release rate as shown in Table 5. There exist a linear relationship between the maximum drug released and the amount of SLS in the core; thus the amount of SLS required for 100% release of the encapsulated drug can be predicted.

The fluid permeability (σ *Lp*) and the osmotic pressure difference ($\Delta\Pi$) across the each of the capsule wall were calculated by the mathematical relationships reported by Theeuwes, 1975. The in vitro release rate data, solubility of the drug in dissolution medium, thickness of the membrane (*h*), surface area of the capsule (A) gas constant (R), and temperature (T) were used to calculate the fluid permeability as the function of the type and level pore forming used and the osmotic pressure difference as the function of the amount of SLS encapsulated with the drug. The *Lp* σ data (Table 6) for different asymmetric membrane at constant ratio of drug: SLS revels that as the concentration of each of the pore forming agent is increase in the capsule wall the fluid permeability of the membrane also increases. The fluid permeability of the asymmetric capsule wall containing glycerol was found to be highest, followed by PEG-400 and DBT. The osmotic pressure difference ($\Delta\Pi$) across the capsule wall was found to increase with the increase in amount of the SLS encapsulated along with the drug (Table 7). This indicates that the osmotic pressure increases with the

TABLE 5
Correlation Data of Different Drug: SLS Ratios (1:1, 1:5, and 1:10) and Maximum Drug Released at Constant Concentration of Pore Forming Agent

Glycerol (% w/w)	Drug: SLS r^2	Drug: SLS *K*	PEG-400 (% w/w)	Drug: SLS r^2	Drug: SLS *K*	DBT (% w/w)	Drug: SLS r^2	Drug: SLS *K*
50%	0.983	4.738	50%	0.991	1.592	50%	0.978	0.978
60%	0.988	5.483	60%	0.999	3.701	60%	0.958	1.417
70%	0.989	5.668	70%	0.976	4.532	70%	0.994	1.820

TABLE 6
Fluid Permeability ($Lp\ \sigma$) of Different Asymmetric Membrane

Conc. of Pore Forming Agent (% w/w)	$\sigma\ Lp$ (cm^2/h-atm)		
	1:1	1:5	1:10
Glycerol 50%	0.0418	0.1572	0.2571
Glycerol 60%	0.0829	0.2081	0.3242
Glycerol 70%	0.0914	0.2251	0.3562
PEG-400 50%	0.0385	0.0643	0.1201
PEG-400 60%	0.0497	0.1242	0.2211
PEG-400 70%	0.0716	0.2001	0.2891
DBT 50%	0.0221	0.0503	0.0692
DBT 60%	0.0334	0.0785	0.1011
DBT 70%	0.0501	0.0845	0.1322

TABLE 7
Osmotic Pressure Difference ($\Delta\Pi$) Across the Asymmetric Membrane Encapsulated with Different Ratios of Drug: SLS

Conc. of Pore Forming Agent (% w/w)	$\Delta\Pi$ (atm)		
	1:1	1:5	1:10
Glycerol 50%	0.0041	0.0151	0.0256
Glycerol 60%	0.0080	0.0201	0.0313
Glycerol 70%	0.0088	0.0198	0.0306
PEG-400 50%	0.0038	0.0062	0.0116
PEG-400 60%	0.0048	0.0119	0.0213
PEG-400 70%	0.0069	0.0193	0.0281
DBT 50%	0.0021	0.0048	0.0067
DBT 60%	0.0032	0.0076	0.0097
DBT 70%	0.0048	0.0817	0.0128

increase in the amount of encapsulated SLS. Justifying that SLS besides acting as a solubilizing agent also acts as an osmogent.

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