OSMOTIC PUMP CAPSULE FOR DELIVERY OF FLURBIPROFEN

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ABSTRACT

In the present investigation, osmotic pump capsule were designed, for delivery of poorly water-soluble drug flurbiprofen. The capsule membrane was prepared by phase inversion technique involving dipping of stainless steel moulds in the solution of cellulose acetate containing castor oil as plasticizer. The drug selected for this study, flurbiprofen, has low aqueous solubility and hence would be unable to create enough osmotic pressure to cause its own release. This study was conducted with a solubility enhancer, sodium lauryl sulfate to enhance solubility of the drug and the osmotic pressure of the core. The release of flurbiprofen from the developed osmotic pump was inversely proportional to the osmotic pressure of the release medium, suggesting that the osmotic release was the major mechanism for the release of the drug.

Key words: capsule, cellulose acetate, castor oil, flurbiprofen, osmotic release.

INTRODUCTION

The utilization of osmotic pressure for controlled delivery of pharmaceutical agents was extensively studied and explained by Theeuwes [1]. Osmotically controlled drug delivery systems release the therapeutic agent at a predetermined, typically zero-order, and delivery rate based upon the principle of osmosis [2, 3]. The release rate from such system can be made independent of pH and rate of agitation by use of semipermeable membrane and osmotic excipients [4]. Osmotic drug delivery system consist of an osmotically active core surrounded by a semipermeable membrane, which is defined as a membrane that is permeable to a solvent, but impermeable to ionic compound and higher molecular weight compounds [5]. The semipermeable membrane for osmotic capsule can be prepared by phase inversion technique using hydrophobic plasticizer. The hydrophobic plasticizer would not leach out during the manufacturing process or dissolution. Hence the process of phase inversion will result into the formation of micro porous semipermeable membrane and not an asymmetric membrane [6, 7].

EOP (elementary osmotic pump) are designed to have an osmotic core surrounded by a semi-permeable membrane that allows water to move in at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core but prevents salt and drug molecules from moving out. The drug molecules exit only through a small orifice drilled in the membrane at a controlled rate due to the increase in osmotic pressure brought about by the volumetric increase inside the core [1]. Osmotic drug delivery system consists of at least one delivery orifice in the coating membrane to release the drug by virtue of increased osmotic pressure inside the system. Numerous designs of such osmotic pumps have been reported [8, 9].

Moderately aqueous solubility of drug is a prerequisite for the drug to be osmotically released from the system. Hence increasing the solubility of the poorly water-soluble drugs in the core becomes the prime concern for their osmotic delivery. This can be done by incorporating osmotically active agents called osmogents e.g. sodium chloride, mannitol [10], solubilizing agents [11] or using cyclodextrin derivatives [12].

Based upon these assumptions, OP (osmotic pump) capsules of cellulose acetate membrane were prepared by phase inversion technique for delivery of poorly water-soluble drug FLUR (flurbiprofen) by using a solubilizing agent, SLS (sodium lauryl sulfate). FLUR is a potent non-steroidal anti-inflammatory agent, having short plasma half-life of 3-3.6 hrs, though it is the safest propionic acid derivative but is associated with gastro-intestinal hazards. Hence this drug was considered for development of oral sustained/controlled release formulation. Thus an effort has been made to design and evaluate an oral OP capsule of FLUR for its controlled delivery.

MATERIALS AND METHODS

Cellulose acetate (CA) was obtained from Glaxo lab. Ltd., India, Sodium lauryl sulfate (SLS), was obtained from S.D. Fine Chemicals Ltd Delhi; the

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drug Flurbiprofen (FLUR) was a gift sample from FDC Pharmaceutical, Ltd Bombay India.

Solubility studies

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming that the capsule formulation consisted of only pure drug, the fraction of the drug that would be released with zero-order kinetics is given by equation (1)[7]

$$F_{(z)} = 1 - \frac{S}{\rho} \qquad (1)$$

Where $F_{(Z)}$ is the fraction released by zero-order kinetics, S is the drug solubility (g/cm^3) and ρ is the density of (g/cm^3) of the drug. The drugs with solubility ≤ 0.05 g/cm^3 would be released with ≥95% zero order kinetic according to equation (1). However the zero order release would be slow due to small osmotic pressure gradient. Conversely highly water-soluble drugs would demonstrate a high release rate that would be zero-order for small percentage of initial drug load. The aqueous solubility of the drug was determined by adding excess of drug to double distilled water to ensure saturation. The solution was maintained at 37^0 C for 72 hrs with intermittent shaking. The saturated solution was filtered and the concentration determined by UV Spectrophotometer (Thermospectronic, UV 1-103909, UK) at 247.00 nm.

Preparation of osmotic pump capsule of FLUR

Cellulose acetate solution (15% w/v) was prepared in acetone/water (90/10) solvent system. Accurately weighed quantity of CA was added to acetone/water solvent system and the resulting mixture was stirred in a well-closed beaker to obtain a homogeneous solution. The required quantity of plasticizer, castor oil [13] (10% w/w of CA) was added to the solution while stirring. The stainless steel moulds fabricated in the dimension so as to form capsule body and cap were dipped in the coating solution for 2 minutes and then removed carefully so as to form a thin layer of solution on the mould, followed by brief air drying for 5 minutes. The pins were then immersed in aqueous solution (10% w/v glycerol), to effect phase inversion and formation of semipermeable membrane of CA. The resulting membrane was stripped off and trimmed to desired size and stored for future use. The delivery orifice of caliber 0.3 mm was drilled manually by means of a micro driller on one side of the capsule i.e. on the cap of the capsule. The thickness *(h)* of the capsule wall and the area *(A)* of capsule were determined by digital micrometer (Mitutoyo Japan). A scanning electron microscope (SEM, Lyca electron optics-340) was used to observe the morphology of the prepared semipermeable membrane.

Table 1: Kinetics of *in-vitro* release and dissolution parameters of different OP capsule.

Drug: SLS	Zero-order		First Order		Higuchi		Lag-time (hr)	Max drug released (%)
	K_0 (%/h)	r^2	K_1 (h^{-1})	r^2	K_H (%/$h^{1/2}$)	r^2		
1:0.25	5.469	0.9857	-0.0284	0.9857	23.944	0.9832	2.04	32.14±0.95
1:0.5	7.966	0.9852	-0.0455	0.9941	35.082	0.9839	1.99	48.29±0.86
1:0.75	9.025	0.9871	-0.0551	0.9961	39.729	0.9951	1.84	54.26±0.88
1:1	10.383	0.9881	-0.0706	0.9981	45.712	0.9969	1.58	67.85±1.06

Filling of osmotic pump capsule

The osmotic pump capsules were filled with different proportions of FLUR and SLS as solubilizing agent, to study the effect of solubilizing agent on the osmotic release of drug from the capsule. The amount of the drug in the mixture was kept constant (100 mg) and the proportion of SLS were varied as; 25 mg, 50 mg, 75 mg and 100 mg respectively. The physical mixtures of FLUR and SLS were prepared by mixing them thoroughly in laboratory blender for 10 minutes and subsequently passing the mixture through sieve No. 80. Each of the mixtures was filled in the body of the capsule and the micro drilled cap was snuggly fitted to the body and finally sealed with a 16% w/v solution of CA only so as to ensure that

Table 2: Influence of external osmotic pressure on the release rate and lag-time of the selected formulation (n=3)

π_{out} (atm)	dM/dt	Lag-time (hr)
30.26	15.87	1.23±0.010
40.24	13.17	1.37±0.011
60.37	9.84	1.88±0.010
80.51	4.62	2.06±0.012
100.48	2.83	2.19±0.019

no release takes place through the seal of the capsule.

In vitro drug release test

The *in vitro* release studies were performed according to USP dissolution apparatus II (50 rpm, 37^{o} ± 5 ^{o} C); and distilled water was used as a dissolution medium. The samples were withdrawn hourly for nine hours and analyzed by using UV spectrophotometer at 247nm λmax. To investigate the effect of osmotic pressure on the drug release behavior, release of the drug was studied in aqueous solutions of different osmotic pressure. Linear regression was carried out for the linear part of the dissolution curve for each capsule. The extrapolated intersection with the time axis was lag-time and the slope of the regression line was the dissolution rate.

Theoretical consideration[14]

For the osmotic drug delivery system that releases the drug by osmotic pressure, the water influx from the surrounding aqueous medium into the core is given by:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{A}{h} L_P \sigma(\Delta\pi - \Delta\mathrm{p}) \qquad (2)$$

Where, d*V*/d*t* is the volumetric influx rate 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, Δπ and Δp are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system. The volumetric influx is proportional to the amount of the drug released per unit time thus:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{\mathrm{d}V}{\mathrm{d}t} C \qquad (3)$$

Where, d*M*/d*t* is the release rate, d*V*/d*t* is given by equation (2) and *C* is the concentration of the component in the fluid being pumped.

As the size of the delivery orifice increases, ydrostatic pressure difference is minimized and Δπ ≥ Δp. By substituting the value of d*V*/d*t* in equation (3) following equation is obtained:

$$\frac{dM}{dt} = \left(\frac{A}{h} Lp\sigma C\right)\Delta\pi \qquad (4)$$

Equation 4 indicates that a plot of release rate versus Δπ should be linear with a slope give by the expression in parenthesis.

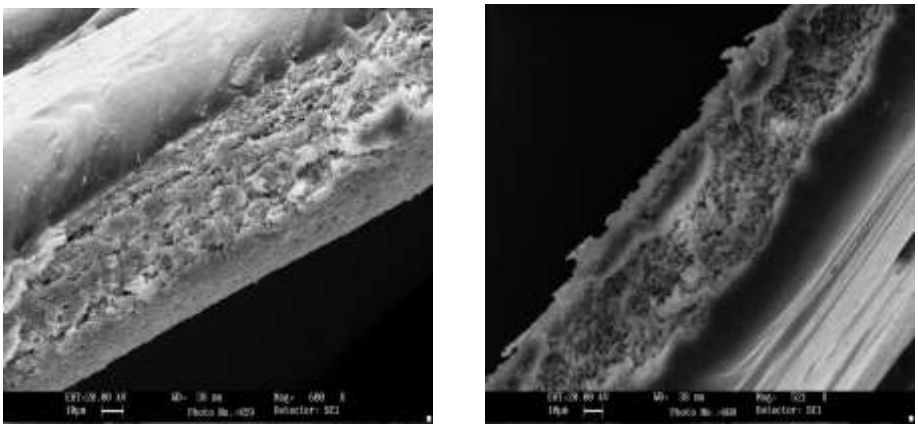
Statistical analysis:

The in-vitro dissolution studies were carried out in triplicate. The results obtained were expressed as mean±S.D.

Figure 1: Elementary osmotic pump capsule.

RESULT AND DISCUSSION

Fitting the solubility (6.51 mg/cm^3) and density (307.2 mg/cm^3) data of FLUR in equation (1) the $F_{(z)}$ for 100 mg drug was calculated to be 0.978. Hence for 100 mg drug 97.8 mg of the drug was anticipated to be released in a zero order pattern, considering that only pure drug is present inside such system. However the zero order release would be slow due to low aqueous solubility of drug causing small pressure gradient. Thus to increase the osmotic pressure gradient the drug was encapsulated with a solubility enhancing agent, SLS. The prepared OP



(a) (b)

Figure 2: Cross section of semipermeable membrane at (a) X 600 and (b) X 521

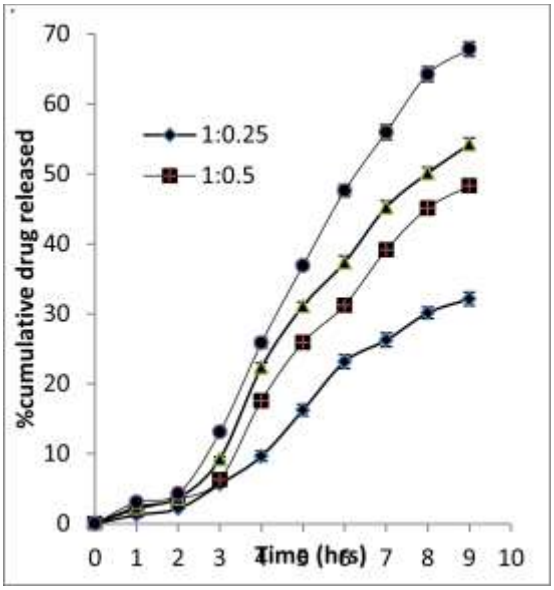


Figure 3: Release profile of flurbiprofen from OP capsule filled with different ratio of drug: SLS (●) 1:0.25, (■) 1:0.5, (▲) 1:0.75 & (×) 1:1.

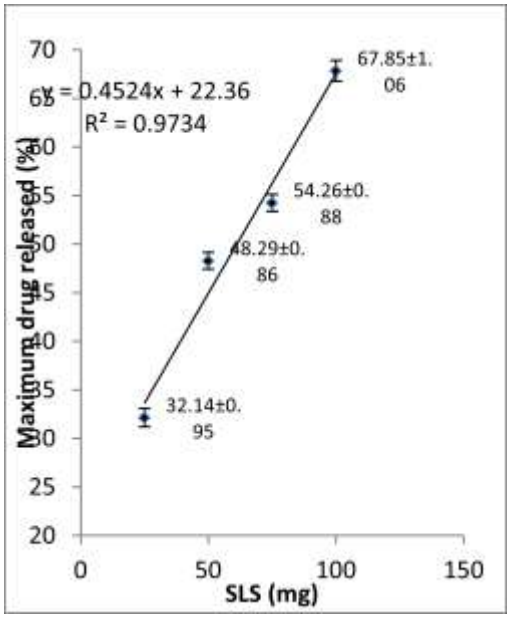


Figure 4: Linear relationship between maximum drug released (%) and the amount of SLS (mg) in the core of formulation.

capsules appeared to be white and opaque with no physical defects as shown in fig.1. The SEM micrograph (fig. 2) of the membrane clearly shows that a micro porous membrane supported on a non pours substrate has resulted from the phase inversion process.

The OP capsules were subjected to dye-test to prove that the prepared system followed osmotic principle for releasing the encapsulated content. For this purpose the capsules were filled with a water soluble dye amaranth. The dye was found to be diffusing from the micro drilled orifice when placed in distilled water after time lag of 22 minutes, where as no release of dye took place when such system was suspended in 10% sodium chloride solution, this is due to the higher osmotic pressure of release medium in later case, which nullifies the osmotic release of encapsulated material from the system. The lag time observed is due to the time required for hydration and subsequent permeation of water through the wall of OP capsule, which results in solubilization and formation of saturated solution of dye resulting in increase of hydrostatic pressure

inside the system and causing its release. No dye was found to be releasing form the wall of OP capsule and the seal, which further justifies the semi permeable nature of the wall of OP capsule. The semi-permeable membrane allows water to move in, but prevents salt and drug molecules moving out through it. The results of dye test are in close conformation with our previously published work on asymmetric membrane capsules [10, 15].

In vitro release rate study showed that as the amount of SLS was increased in the core of OP capsule the amount of drug released also increased as shown in fig.3. This may primarily be due to the solubilization effect of SLS, resulting in increased solubility of drug and subsequent increase of osmotic pressure inside the system causing increased amount of drug being released from the system. As SLS is also released along with the drug, hence its solubility effect inside the core would be terminated more promptly at when it is present at low level (25 mg) as compared to its higher proportion in the core (100 mg). This leads to the released amount of FLUR being proportional to the added amount of SLS. When the maximum drug released from the OP Capsule with different proportion of SLS was plotted against the amount of SLS in the core a linear relationship ($r^2 = 0.9734$) was obtained, fig.4. The slope (*0.4524*) of the linear plot was used to predict the amount of SLS required for 100% release of FLUR from the system. Based on this the amount of SLS required for 100% release was calculated to be 171.62 mg.

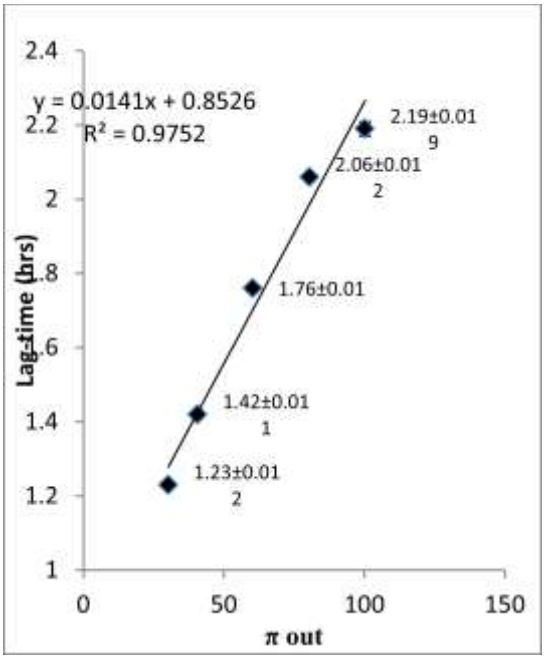


Figure 5: Influence of the external osmotic pressure (π_{out}) on the lag-time.

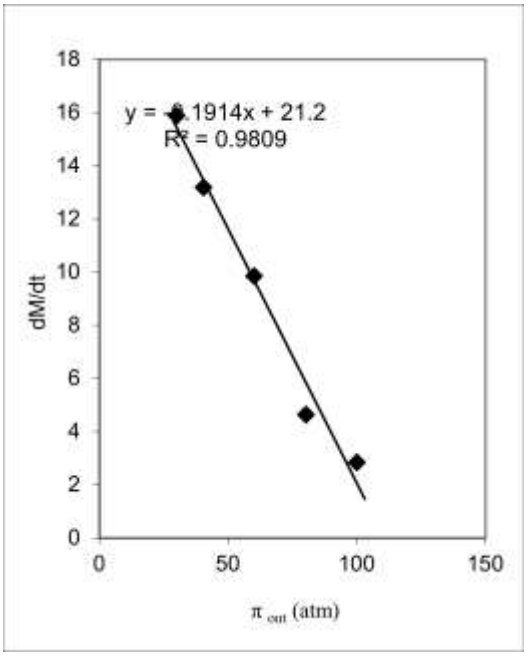


Figure 6: Correlation between the release rate *(dM/dt)* and the external osmotic pressure (π_{out}).

Dissolution data of all the formulations was fitted to various mathematical models (zero order, first order and Higuchi) to describe the kinetics of drug release Drug release from the formulation fitted well into first order model (Table 1), suggesting that the release of the drug depends upon the concentration of the components incorporated in the core of the formulation. The lag-time which was the extrapolated intersection with the time axis was found to decrease with the increase in the amount of SLS in the core (Table 1). This is because solubility is achieved more promptly at higher level of SLS inside the core of the formulation resulting in quick built up of osmotic pressure and subsequent release of the drug as compared to the lower levels of SLS. According to equation (4) the amount of drug released per unit time is directly proportional to osmotic gradient inside the system.

An in-vitro dissolution test of OP Capsule containing the mixture of the drug with calculated amount of SLS (171.62 mg) for 100% release was

carried out. The amount of drug released at the end of dissolution run was 98.39% which is in close consistence with the extrapolated result. The drug release rate from this system was also established as function of external osmotic pressure (π_{out}). With the increase in the osmotic pressure of the dissolution medium, the lag time was prolonged (Table 2). The lag time increased as a linear function of sodium chloride osmolality *(r^2=0.9752)* fig.5. The result of the release studies showed that the drug release rate is highly dependent on the osmotic pressure of the release medium (fig. 6). Drug release rate decreased with increment of the external osmotic pressure. When the dM/dt obtained at different osmotic pressure were plotted against π_{out} a well linear relationship was obtained *(r^2= 0.9809)* with a slope equal to $(A/h)L_p\sigma C$. From fig. 6, the slope of the linear fit was 0.1914 mg/h atm. $L_p\sigma$ was calculated to be 7.72×10^{-5} cm^2/h atm based on equation (4), by substituting the values of A = 6.17 cm^2, h = 0.0162 cm and C = 6.51 mg/cm^3. The value was in close correspondence with those reported previously [14, 1]. These results suggests that osmotic pressure difference across the semipermable membrane is the principal factor affecting the drug release rate and that osmotic pumping is the major mechanism governing drug release from the prepared OP capsule.

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