RESEARCH PAPER

Accepted 10 April 2005
Revised 26 October 2004
Received 18 August 2003
Indian J. Pharm. Sci., 2005, 67(2): 200-205

Nasal Delivery of Propranolol Hydrochloride From Sorbitan Monosterate Organogels: Preformulation Study

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The purpose of research was to evaluate suitability of sorbitan monosterate organogels for nasal delivery of propranolol hydrochloride. The organogels of liquid paraffin were rigid and that with cottonseed and sesame oil were weak. Sorbitan monosterate organogels in isopropyl myristate has desired stability and consistency. Water incorporates the desired polarity for gel formation while alcohol breaks the interconnected gel network. The X-ray diffraction pattern confirms incorporation of water in micellar gel network. Polysorbate cosurfactants enhance the stability of organogels by increased viscosity. The viscosity increase was proportionate to chain length of tween surfactants. The water holding capacity, and hence the electrical conductivity increases with sorbitan monosterate concentration. The release retardant effect of propranolol hydrochloride through sheep nasal mucosa was observed with the order of Tween 20<Tween 60<Tween 80. The organogels exhibit useful pharmaceutical properties. However the gels need to be further optimized for sustain transnasal drug administration.

The greater permeability of drug through nasal mucosa has potential to overcome limitations of oral route and duplicate the benefits of intravenous injection. Challenges in the development of formulation for nasal administration include low residence time and non-reproducible absorption profiles[1]. Propranolol hydrochloride has been reported to be absorbed effectively via nasal route with bioavailability comparable to i.v. administration[2]. However, its short biological half-life (2 h) is unfavorable to sustain the drug levels in the systemic circulation. An erythrocyte based bioadhesive system and proliposomes containing propranolol hydrochloride has been reported with low loading efficiency and hence higher dose size[3,4]. The discovery of a number of biocompatible substances capable of gelling various oils is emerging area of research in formulation design[5]. Florence *et al.* have revealed that organogels of diverse physicochemical properties exhibit pharmaceutically useful properties like thermoreversibilty, ability to incorporate all types of drug molecules, controlled release, increased resistance to microbial contamination and reduced risk of irritation[6]. The potential of hydrogels as drug delivery system necessitates the use of penetration enhancers and has limited stability against temperature, moisture, and microbial contamination.

Sorbitan monosterate is non-toxic biocompatible surfactant capable of gelling of organic solvents and vegetable oils. The concept of gelling organic vehicles (isopropyl myristate) with non-ionic surfactant, sorbitan monosterate, has been reported for short depot release of model antigen by Florence *et al*[5]. These authors have indicated that such a system can be exploited for mucosal drug administration. Application of organogels for nasal drug administration is not attempted. The present research work is aimed to incorporate propranolol hydrochloride in sorbitan monosterate organogels for sustained transnasal delivery. The properties of the gels are confirmed and the effects of cosurfactant on in-vitro drug release are investigated.

MATERIALS AND METHODS

Sorbitan monosterate was obtained from Loba Chemi-

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cals, Pvt. Ltd. Mumbai. Isopropyl myristate, cottonseed oil, sesame oil and liquid paraffin were gift samples from S. D. Fine Chemicals, Mumbai. The polysorbate surfactants (tween 20, tween 60 and tween 80 were purchased from Thomas Baker, Mumbai. Propranolol hydrochloride (BPH/013/2002) was a gift sample from Sigma Laboratories, Goa. All other chemicals of ultrapure grade were used.

Gel forming ability of oils:

Organogels of sorbitan monosterate (SMS, 10% w/v) were prepared with liquid paraffin, isopropyl myristate, cottonseed and sesame oil separately. The oil-surfactant mixture was heated at 60° to obtain a clear solution, which on cooling forms organogels[7]. The temperature of 2 ml of organogel at 60° in test tube sealed with aluminium foil was decreased using cryostatic bath by 1° / 2 min. Gelation is said to have occurred when the meniscus would not move immediately upon tilting through 90°. The viscosity of each sample at room temperature was measured using Brookfield's DV-II viscometer.

Phase behavior and properties of formulations:

Gels were prepared containing 5-20 % w/v of sorbitan monosterate in isopropyl myristate. The specified amount of water viz. 5-25% v/v for each SMS concentration was added, while vortexing, both phases being at 60°. These gels were observed for isotropic solution, organogel and w/o emulsion.

SMS organogels in isopropyl myristate (10% w/v) containing 2% w/v each of Tween 20, Tween 60, and Tween 80 were prepared separately. The gel samples cooled to 20° (1° / 2 min) were studied for gel forming temperature and gel lifetime. Plain SMS (7.5% w/v) organogel and gel containing 2 % w/v each of Tween 20, Tween 60, and Tween 80 in isopropyl myristate were prepared separately. Accurately measured water (5-25%v/v) in small increments was added with vortexing.

XRD analysis of plain and organogel with water were performed using D500 diffractometer equipped with a copper tube and a quartz primary-beam monochromater of λ=1.54056A. The X-ray tube was run at 45 kv and 30 ma while the samples mounted in a flat-plate surface were measured (2θ,1-35°) using scintillation detector. The conductance of various gels was measured using a modified Wayne-Kerr conductivity bridge[8]. The viscosity of the gels was measured using Brookfield's DV-II viscometer.

Calibration curve for propranolol hydrochloride:

Aqueous solutions of propranolol in the concentration range of 5–25 µg/ ml were prepared in double distilled water. The standard curve was obtained from the absorbance measured at 254 nm. The diffusion samples (0.5 ml diluted to 2 ml) were analyzed at 254 nm using the standard curve.

***In vitro* nasal diffusion cell:**

The water-jacketed nasal diffusion cell (60 ml) with a flanged top of 3 mm, a lid having 3 openings with 10 cm long donor chamber tube (id, 1.13 cm) was fabricated in glass[9]. The sheep nasal mucosa, separated from sublayer bony tissue and blood, was attached to donor chamber tube.

Effect of polysorbate on drug release from organogels:

Gels containing propranolol hydrochloride (10 % w/v) in 7.5 % w/v of SMS containing 2 % w/v each of Tween 20, Tween 60 and Tween 80 were prepared separately by dissolving the drug in water (20 %v/v) and incorporating the aqueous drug solution in oil phase. Aqueous drug solution of identical strength was also prepared. A w/o emulsion of 7.5 w/v of sorbitan monooleate, 2 % w/v of tween 20, and 20 %v/v of aqueous drug solution (10% w/v) were prepared in isopropyl myristate. The recipient chamber of nasal diffusion cell was filled with 40 ml of buffer (pH 6.8) and the donor chamber tube with 0.1 ml of gel sample on mucosa was lowered to touch the diffusion medium. The diffusion sample (0.5 ml) removed at predetermined intervals was transferred to amber colored ampoules and analyzed spectrophometrically. The percent drug release with the time of diffusion was estimated.

RESULTS AND DISCUSSION

The gel forming temperatures for isopropyl myristate and liquid paraffin was in the range of 41-43° and 51-53°, respectively (Table 1). Sorbitan monosterate forms the gel network throughout the isopropyl myristate and gels were found to be stable for 12 h. After which it shows the separation of liquid component suggesting the syneresis effect. Cottonseed oil, sesame oil failed to produce really the gel structure at 10 % w/w sorbitan monosterate throughout the temperature range (60-20°). However, slight increase in viscosity was observed below 40-43°. The significantly higher viscosity and increase in stability was shown by organogels of liquid paraffin at about 52-54° within 30 sec. Gelation is slow process and the solvent has a prime role in gelation process[10]. Cottonseed and sesame oil (less than 5 carbon chain) were unable to provide a required solubility-

TABLE 1: PROPERTIES OF ORGANOGEL COMPOSITIONS

Gelling oil	Aqueous solvent (20 % v/v)	Co-surfactant (2% w/v)	Gelation Temp(°)	Gel Life (h at 25°)
Isopropyl Myristate	—	—	41-43	12±0.2
Liquid Paraffin	—	—	52-54 Rigid Gel	168
Cottonseed oil	—	—	40-43*	4±0.15
Sesame oil	—	—	41-43*	4±0.23
Isopropyl Myristate	PEG 400	—	41-43*	48±0.4
Isopropyl Myristate	Ethanol	—	No Gel	No Gel
Isopropyl Myristate	Water		43-44	95
Isopropyl Myristate	—	Tween 20	40-41	168
Isopropyl Myristate	—	Tween 60	44-45	168
Isopropyl Myristate	—	Tween 80	49-51	168

*Viscous liquid

insolubility balance for SMS. However, long chain synthetic esters, isopropyl myristate, as well as liquid paraffin provided efficient gelation. Isopropyl myristate gels having desired consistency were processed further.

The effect of water fraction on the nature of phases in sorbitan monosterate-isopropyl myristate-water system is shown in fig.1. Sorbitan monosterate gels isopropyl myristate due to tubular aggregation as temperature decreases[6]. The concentration of sorbitan monosterate below 5 % w/v in presence of or absence of water was insufficient to cause gelation. However, 10 % w/v plain organogel without water is sufficient to form the gels, while sorbitan monosterate in proportion of more than 20% w/v could not be solubilized in isopropyl myristate at 60°. The occurrence of gel phase was sorbitan monosterate concentration dependent and observed in 5-20% w/v of system. The water enhanced holding capacity of sorbitan monosterate organogel is attributed to increased area of inverted micellar aggregates with higher sorbitan monosterate. The addition of hydrophilic tween surfactants (2 % w/v each, separately) in 10 % w/v sorbitan monosterate organogel significantly improve the gel lifetime beyond 7 day. The gelation with each tween 80, 60, and 20 was found to be achieved at 49-50°, 44-45° and 40-41°, respectively. The stability of gel to be used as drug delivery system is important to retain its structure during storage, for uniform consistency during use and for reproducible release profile. Tweens with polyoxyethylene chains participates in tubular aggregates of SMS and stabilizes gel.

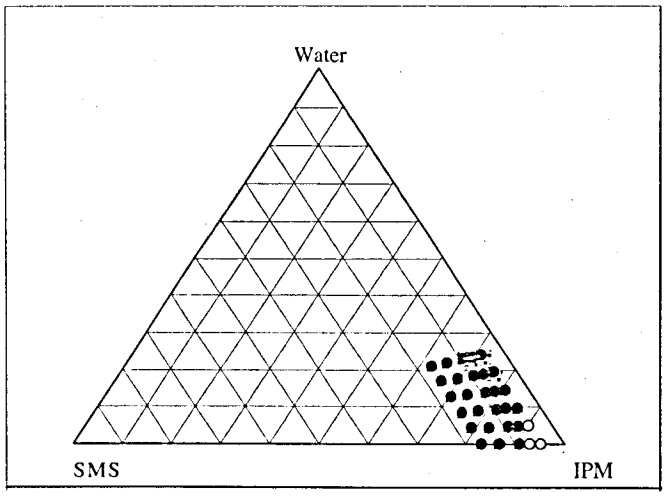

Fig. 1: Three component triangular diagram for sorbitan monosterate.

Three component triangular diagram showing existence of isotropic solution (blank circle), organogel (dark circle) and w/o emulsion (dotted circle).

Three smaller peaks at 2θ value 19.5, 19.8 and 21.6 were observed in X-ray diffraction analysis of both plain and organogel containing 20%v/v of water with identical d-spacing (fig. 2). However, the intensity of small diffraction peak was relatively low for organogels containing water as

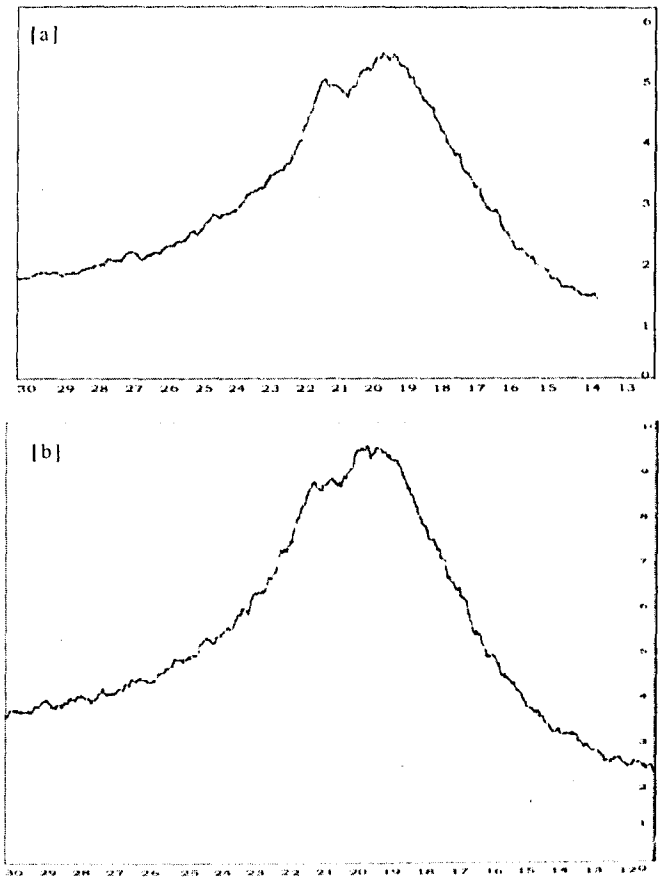

Fig. 2: X-ray diffraction patterns.

X-ray diffraction patterns of a. Plain SMS gel and b. SMS organogel containing water.

compared to plain organogels. The predominant diffraction peak growth was clearly observed at 2θ value of 21 of 4.4×10^3 intensity in organogel containing water. In case of sorbitan monosterate saturated solution a peak at 2θ value 21.6 is a short d-spacing band corresponding a repeat distance of hydrocarbon chain of sorbitan monosterate in liquid state. The invert micelle of tubular aggregates of sorbitan monosterate band is observed at 2θ value 19.8 and the long spacing band corresponding to separating distance of structure composing the mesomorphous phase is observed at 2θ value of 19.5. The same bands of equal d-spacing but with reduced intensity were observed for organogel containing 20 % v/v of water. The XRD pattern shows a weak diffraction due to presence of isopropyl myristate. It is postulated that the organogels incorporating water will show increased d-spacing at 2θ value 19.5 due to increased micellar size. However, addition of water does not increase spherical size of micelles. But water incorporation shows cylindrical branching of linear micellar aggregates (giant micellar structure)[11-13]. Hence diffraction peak corresponding to 2θ value of 21.0, with d-spacing of 2.1514 was observed. Similar effect has been observed for structural determination of solid components of low molecular weight organogelators (c-36) gels[14]. This confirmed the incorporation of water in bilayers of tubular aggregates.

The electrical conductance values of organogels are very low owing to oily nature of organogels. The electrical conductance with 7.5 %w/v of sorbitan monosterate and 2 % w/v each of tween 20, tween 60, and tween 80 at various proportion of water is shown in fig. 3. The electrical conductivity increases with increase in the number and size of micelles in tween 60 and tween 80. The increase in conductance with gradual addition of water reveals the development of increased interconnected tubular network. The excess of water may be placed as small droplets through-

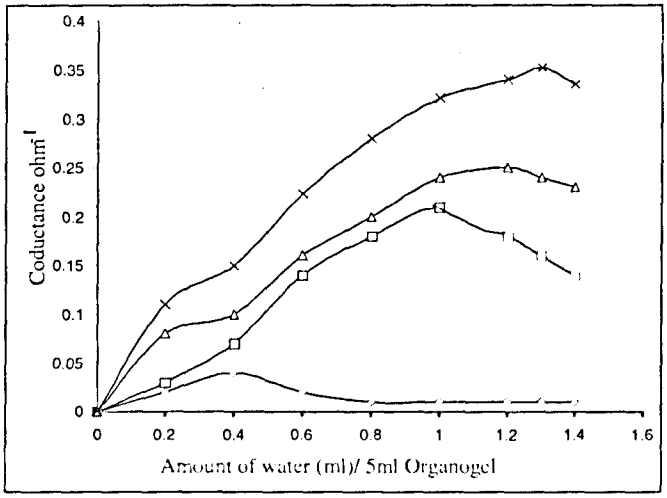

Fig. 3: Electrical conductivity of organogels

(-◊-) Plain SMS organogel, (-□-) SMS organogel with Tween 20, (-△-) SMS organogel with Tween 60 and (-×-) SMS organogel with Tween 80.

out the gel structure.

The viscosity of the organogels increases drastically

in the gelation range. The viscosity rise being maximum for Tween 80 followed by Tween 60 and Tween 20. The rheological behavior reveals the linear increase in viscosity with decrease in temperature of the gels indicating reverse thermal gelation and homogenous nature of gel (fig. 4). The effect is more pronounced for tween 80 and then tween 60. The hydrophilic polar heads of tween are made up of same number of oxyethylene chains. However the hydrophobic carbon chain increases from C-12 for tween 20 to C-18 for tween 60 and tween 80. Tween 80 with number of unsaturation has more hydrophobic character[15-16]. The increase in size of the hydrophobic groups leads to a greater decrease in free energy of invert micellization of SMS in isopropyl myristate. This promotes the micelles formation and results in decreased CMC and hence increased aggregation number. The proportion of bound water to oxyethylene groups increases and also growth of polar regions of invert micelles (SMS/IM)[17-18]. Hence viscosity of organogels increases.

The standard curve for analysis of propranolol hydrochloride is shown in fig. 5. The linearity was evident between the concentrations and absorbance at 254 nm. The equation of calibration curve was $y=0.0182+0.0013$ and $R^2=0.9998$. The gel additives in diffusion sample didn't interfere with the estimation of drug. Propranolol hydrochloride is a hydrophilic drug with low molecular weight (295.81) and hence diffuses freely through leaky nasal mucosa. The release of drug from aqueous solution was completed within

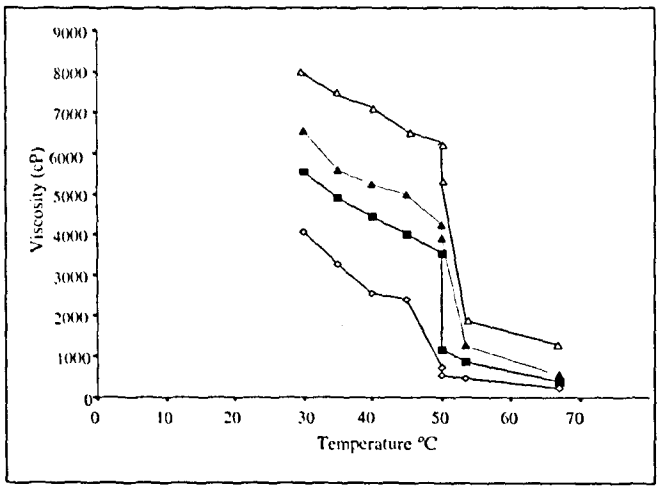

Fig. 4: Effect of cosurfactants on temperature- viscosity profile of SMS organogels

(-◊-) Plain SMS gel, (-■-) SMS gel with Tween 20, (-▲-) SMS gel with Tween 60 and (- △-) SMS gel with Tween 80.

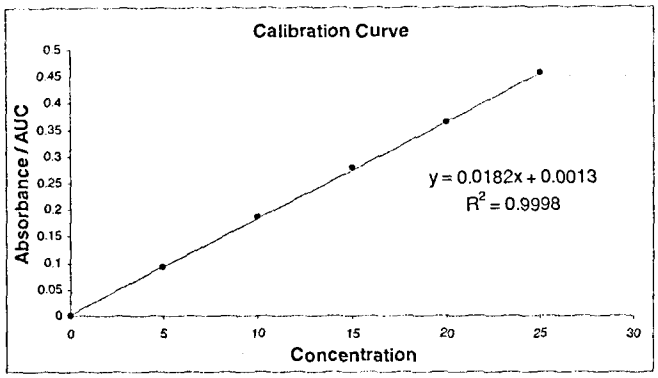

Fig. 5: Standard curve for estimation of propranolol hydrochloride

90 min and from the emulsion within 2 h. Flux of drug release was retarded with the incorporation of polysorbate cosurfactants with the order of Tween 20>Tween 60>Tween 80 (fig. 6). The changes in the microstructure of the organogel as discussed above and the increased viscosity of the corresponding gels contributes to the decreased drug release. Although the electrical conductivity of the organogels increases with Tween 20<Tween 60<Tween 80 indicating the interconnected tubular network, the increased micellar drug portioning and viscosity may be responsible for sustained effect. The peak fluxes observed along the diffusion may indicate gel fragmentation due to penetration of the water during the course of diffusion. The lower flux of diffusion after 3 h may correspond to the drug diffusion totally

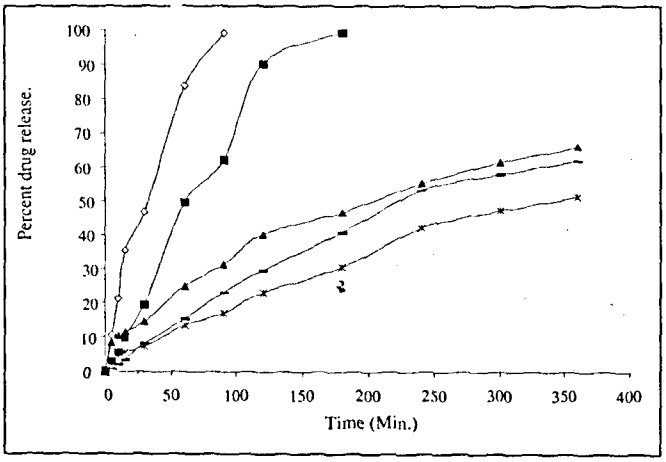

Fig. 6: Effect of cosurfactants on drug release from SMS organogels

Drug release from plain gel (-◊-),W/O emulsion (-■-),Organogel containing Tween 20 (-▲-),Tween 60(---) and Tween 80(-x-)

from miceller fraction. The study reveals that organogels are well suited for sustained nasal delivery of propranolol hydrochloride. The formulation optimization studies are in progress.

ACKNOWLEDGEMENTS

SSP gratefully acknowledge the All India Council for Technical Education (AICTE), New Delhi, for providing financial assistance for the present research project in the form of 'Career Award For Young Teachers 2002'. Authors are also thankful to Bharati Vidyapeeth Deemed University, Pune for support in the implementation of the research scheme.

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