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Research paper

Effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets

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Abstract

Controlled delivery of drugs has been achieved successfully by use of asymmetric membranes. In our study, we have evaluated the influence of various preparation parameters such as concentration of the polymer, concentration of the pore former and temperature of the precipitation bath on the permeability and the release characteristics of propranolol. Propranolol tablets were prepared by direct compression and were coated with varying concentrations of cellulose acetate and glycerin. The coat was precipitated in water, maintained at various temperatures, followed by air drying of the coat. Scanning Electron Microscopy (SEM) was used to characterize the asymmetric structure of the membrane. The influence of various preparation parameters on the release of propranolol from asymmetric coated tablets was evaluated. SEM confirmed the asymmetric nature of the membrane. A zero order release of propranolol was obtained from the coated tablets of propranolol. Various preparation parameters studied significantly affected ($p < 0.05$) the release of propranolol hydrochloride from the asymmetric membrane coated tablets and the release was independent of the pH and the rate of agitation of the dissolution medium ($p > 0.05$). Asymmetric membranes can be successfully utilized in the controlled delivery of highly water soluble drugs like propranolol and by modifying preparation parameters like polymer concentration, pore former concentration and temperature of the precipitation bath, desired release rates can be obtained.

Keywords: Propranolol hydrochloride; Asymmetric membrane; Osmosis; Osmotic drug delivery system; Controlled porosity membranes; Cellulose acetate

1. Introduction

Osmotic pressure has been successfully employed as the driving force to generate a constant release of a drug from a device, provided a saturated solution of the drug is available inside the device. However, once the concentration of the drug falls below saturation, the rate of release declines parabolically towards zero [1]. Different methods have been employed to evaluate the principles of osmosis in the drug delivery systems. One of the methods is to have coated tablets with semi-permeable membrane and a laser drilled orifice to osmotically release the drug [1,2]. These systems offer advantages in terms of zero order release, independence from pH, solubility and the speed of agitation on the release rates and have shown good *in vivo–in vitro* correlation [2–4].

Owing to the dense structure of the coat, the application of this kind of a delivery system for drugs with low solubility is limited. To overcome this problem mini osmotic pumps were developed, which successfully delivered the drugs with low aqueous solubility. However, in the case of irritating drugs, these systems could result in potential side effects of the gastrointestinal tract and also, occasionally the single orifice of these osmotic tablets can clog, resulting in an inconsistent release [4]. These mini pumps require a very complex production procedure of drilling a laser-drilled hole, resulting in an increased cost of production

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and a need for additional quality control testing of the finished product. To overcome these limitations tablets coated with a membrane of controlled porosity have been described [5–7]. These membranes consist of a leachable material, which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. This system is well suited for very soluble drugs and core excipients with high osmotic pressure. However, due to the relatively low permeability of the dense coatings, the osmotic delivery of the drugs with moderate to low solubility is limited.

Use of asymmetric membrane coating in the drug delivery has been described [8–10]. These membranes are used in pressure-driven membrane processes, such as reverse osmosis and ultrafiltration, where their unique properties i.e., (a) high mass transfer rates, and (b) good mechanical strength have been successfully utilized [11]. An asymmetric membrane is a bi-layer system consisting of a very thin (0.1–1μm) polymeric layer (skin of the membrane) on top of a highly porous and thick (100–200 μm) sub-layer [11]. The thin polymeric layer represents the actual barrier membrane. The highly porous sub-layer serves only as a support for the very thin and fragile skin and has no or very little effect on the separation characteristics and the mass transfer rate of the membrane [11]. Since the mass transfer rates are inversely proportional to the thickness of the barrier membrane, the separation characteristics are determined primarily by the nature of the skin polymer and/or the pore size. As a result, one of the main advantages of the asymmetric membrane is the higher rate of water influx, allowing the release of the drug even with a low osmotic pressure or poor solubility [9].

The permeability of the coat can be tailored by controlling the structure of the membrane, consequently allowing control on the release kinetics without altering the coating material or significantly varying the coating thickness. In addition, the porosity of the skin can also be controlled thus minimizing the time lag before drug delivery begins and allowing the drug to be released from a large number of delivery ports, which are formed during the coating process [12]. Tailored release can be obtained from asymmetric membrane coatings by modifying certain preparation parameters. So far there are no published references which have evaluated the effect of various formulation parameters on release characteristics of a highly water soluble drug from Asymmetric membranes. Thus, the major objective of this research was to formulate an osmotic drug delivery system for propranolol hydrochloride, a water soluble drug, utilizing asymmetric membranes and to study the effects of various preparation parameters on the release characteristics of propranolol from the membrane.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride B.P. was generously given by ICI Pharmaceuticals, India. Cellactose® 80 (a proprietary blend of lactose and cellulose, 75:25) and Kollidone® 30 (Povidone K 30) were obtained from Meggle, Wasserburg, Germany and BASF Corporation, Florham Park, NJ, USA, respectively. Acetonitrile, acetone, triethylamine, potassium phosphate monobasic and phosphoric acid were all HPLC grade and were purchased from the Fisher Scientific Co., Pittsburgh, PA, USA. Cellulose acetate (CA 398-10) was a gift from FMC Corporation, Philadelphia, PA, USA. Magnesium stearate, stearic acid, dibutyl phthalate, sodium chloride, and glycerin were purchased from Spectrum chemicals, Gardena, CA, USA. All the chemicals were used as obtained and were not purified.

2.2. Preparation of propranolol hydrochloride tablets

Propranolol hydrochloride tablets were prepared by direct compression method. The ingredients of the tablet are summarized in Table 1. All the ingredients except the lubricants (magnesium stearate and stearic acid) were mixed in a cube mixer (Hobart manufacturing company, Troy, OH, USA) at 37 rpm for 10 min. Lubricants were then added to the blend and mixed for another 5 min. Tablets were made on a single punch tablet press (Stokes, model # 518-1, Pennwalt chemical corp., Warminster, PA, USA) equipped with 3/8 inch, biconcave punch. The uncoated tablets were subjected to several quality control tests including weight variation, hardness, drug content, and release studies to ensure quality and reproducibility.

2.3. Preparation and composition of the coating solution

Coating solution was prepared by mixing varying concentrations of the polymer (cellulose acetate) and glycerin as a pore former along with other excipients like the plasticizer (dibutyl phthalate) and a solvent (acetone), giving approximately 15% total solids content. The composition and the various concentrations of the ingredients used are listed in Table 2.

2.4. Preparation of asymmetric membrane coat on the tablet

Asymmetric membrane was formed on the propranolol hydrochloride tablets by dip coating and wet precipitation technique. Tablets were dipped in the coating solution, removed and were allowed to precipitate in a precipitating

Table 1
Formula for the optimized propranolol HCl tablet

Ingredients	(%) w/w	Per tablet (mg)
Propranolol hydrochloride BP	22	80
Cellactose 80	63.5	230.91
Sodium chloride USP	10	36.34
Kollidone 30 USP	4	14.55
Magnesium stearate NF	0.25	0.91
Stearic acid NF	0.25	0.91
Total	100	363.62

Table 2
Composition of the coating solution

Ingredients	(%) w/w
Cellulose acetate NF	14–16
Glycerin USP	5.0–7.5
Dibutyl phthalate NF	0.6
Acetone NF	q.s.

bath, for 3 min. These precipitated tablets were blow-dried at 80 ± 2 °C for about a minute to remove the excess water and then air dried at ambient room temperature for 24 h. The coated tablets were subjected to several quality control tests including weight variation, weight gain, coating thickness, drug content, and release studies to ensure quality and reproducibility.

2.5. Solubility studies

Solubility of propranolol hydrochloride was accessed in the two different dissolution fluids namely Simulated Gastric Fluid without enzymes (pH 1.2) and Simulated Intestinal Fluid without enzymes, pH 6.8. An excess amount of propranolol hydrochloride was added to each dissolution fluid in glass tubes. Tubes were closed and placed in a shaker maintained at 37 °C and rotated at 60 rpm for 24 h. The samples were collected at the end of 24 h, filtered, diluted and analyzed by a HP 1100 series HPLC (Palo Alto, CA).

2.6. Scanning electron microscopy

Scanning Electron Microscopy (model AMR-1000, Amray instruments, Bedford, MA, USA) was used to confirm the asymmetric structure of the coat and also to compare various compositions of the coat. Samples for SEM were prepared by dipping the tablets in liquid nitrogen and then fracturing it to show the transverse section of the coat.

2.7. Analysis of propranolol hydrochloride in coated tablets and in the dissolution fluids

Propranolol hydrochloride was analyzed by HPLC using Zorbax SB-CN column (5 μm, 4.6 × 150 mm). The mobile phase consisted of 20 mM potassium phosphate buffer (pH 3.6)/acetonitrile/triethylamine, 75:25:0.2 v/v. The flow rate was 1.0 ml/min and the drug was detected at 229 nm. The HPLC method of analysis for propranolol hydrochloride in the tablets was validated for linearity, precision, specificity, sensitivity, and reproducibility.

2.8. In vitro release analysis

In vitro release studies were performed on the coated tablets to evaluate the effect of various preparation parameters on the release rate of the drug. Dissolution was conducted in USP dissolution test apparatus I (SR8 plus, Hanson Research, Chartsworth, CA, USA), at 100 rpm and 37 °C for a period of 16 h (duration of dissolution was selected on the basis of preliminary studies, data not shown, which showed almost complete drug release in about 16 h). The dissolution fluid used was 900 ml Simulated Gastric Fluid (SGF), without enzymes, for the first 2 h followed by 900 ml Simulated Intestinal Fluid (SIF), without enzymes, for the next 14 h. Samples (5 ml) were withdrawn every hour for the first 4 h, followed by every 2 h interval for up to 16 h. Every time the sample was withdrawn it was replaced with an equal volume of the dissolution medium. Following the collection, each sample was filtered through 0.2 μm Acrodisk® CR 25 mm syringe filter (Pall corporation, East Hills, NY, USA). The filtrate was analyzed for propranolol hydrochloride concentration using HPLC.

2.9. Statistical analysis

Statistical analysis was carried out on the data obtained from the release profiles of various formulations. One-way ANOVA was carried out on the release rate constants, k (obtained from the slopes of the release curves until approximately 80% of the drug was released). All experiments were done in triplicate ($n = 3$).

3. Results and discussion

Results of the quality control tests performed on the coated and uncoated tablets are listed in Table 3. Effect of various parameters like polymer concentration, pore former concentration and the precipitation temperature were studied. Comparative studies were carried out in two different dissolution mediums to mimic the environment of the gastro-intestinal tract. Unless stated otherwise, the coating solution consisted of cellulose acetate (CA) 15.0% w/w, glycerin (Gly) 5.0% w/w, dibutyl phthalate 0.6% w/w, dissolved in acetone and the temperature of precipitation of the coat was 20 °C.

Solubility studies of propranolol hydrochloride were performed in both the dissolution mediums SGF (pH 1.2) and SIF (pH 6.8) to confirm that "sink conditions" will be maintained during dissolution studies. The solubility of propranolol hydrochloride was found to be 33.79 ± 0.09 and 57.23 ± 1.08 mg/ml in the dissolution flu-

Table 3
Result of the quality control (QC) tests on the coated and uncoated tablets

QC test	Coated		Uncoated	
	Mean	SD	Mean	SD
Weight gain (mg)	28.26	1.95	–	–
Coat thickness (mm)	1.06	0.07	–	–
Drug content (mg)	79.71	1.8	80.34	2.56
Weight variation (mg)	393.9	3.51	366.7	6.42

Mean of 10 determinations.

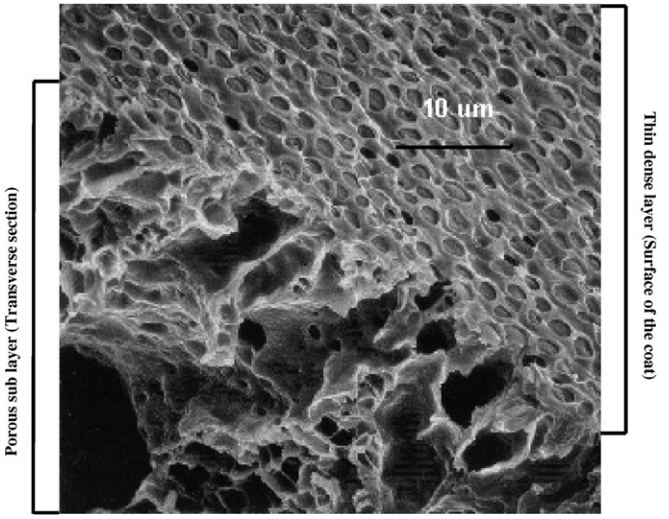

Fig. 1. SEM of the surface of the coat precipitated at 20 °C (magnification 2000×).

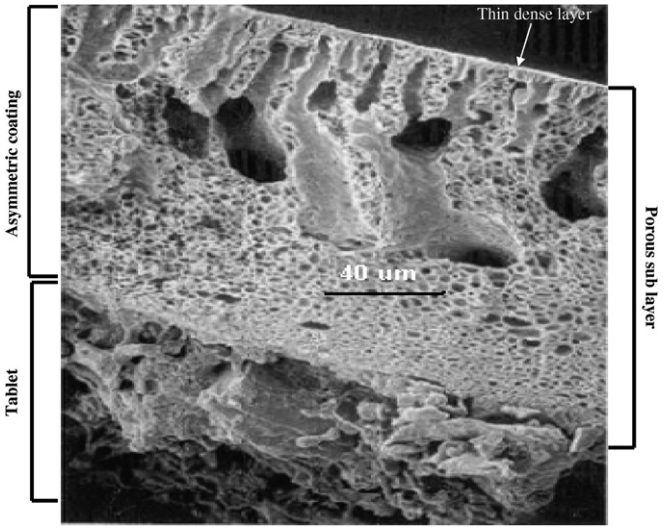

Fig. 3. SEM of the transverse section of the coat precipitated at 20 °C (magnification 500×).

ids SGF (pH 1.2) and SIF (pH 6.8), respectively. These concentrations were much higher (~100×) than the concentrations required to maintain the sink conditions during dissolution.

The asymmetric nature of the coat was confirmed by SEM analysis. SEM pictures showed that there was a thin and dense layer on the top, resting on a porous sub-layer (Figs. 1–4). Analysis of the coat revealed the effect of coating formulation on the structure/pore size of the coat. It is clear from the SEMs that the temperature of the water, used for precipitation, had an effect on the permeability (measured in terms of pore size and the number of pores) of the coat. The coat precipitated at a temperature of 20 °C had significantly fewer pores (Fig. 3) on the surface and had smaller pore size (1.246 ± 0.40 μm) as compared to the coat precipitated at 37 °C (2.48 ± 0.45 μm). The reason for this difference in permeability at different temperatures of coating could be due to a faster precipitation at the lower temperature, which would lead to an immediate increase in the polymer concentration on the surface and would inhibit diffusion of the precipitant into the membrane, leading to the formation of a denser membrane. The mean coat thickness was 1.06 ± 0.07 mm and there was no significant change in the thickness of the asymmetric coat as a result of changing preparation parameters (i.e., polymer concentration, concentration of the pore former, and the temperature of the precipitation bath).

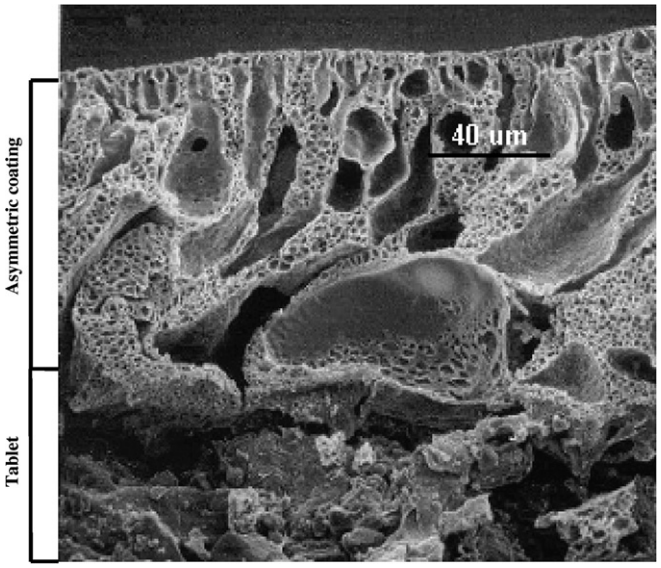

Fig. 4. SEM of the transverse section of the coat precipitated at 37 °C (magnification 500×).

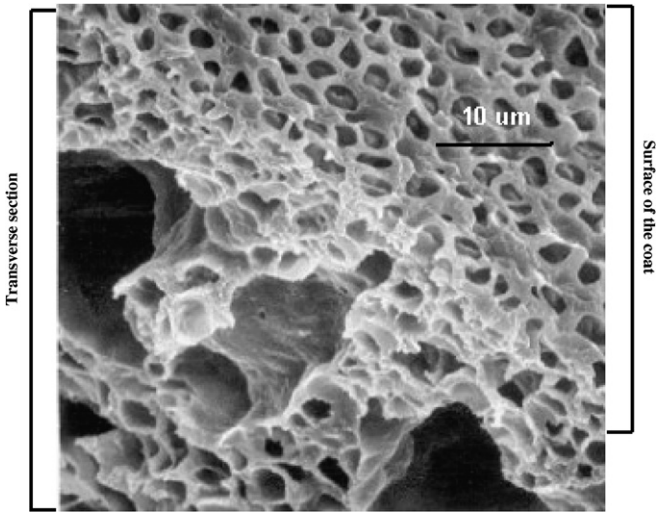

Fig. 2. SEM of the surface of the coat precipitated at 37 °C (magnification 2000×).

Asymmetric membrane coatings were applied on the propranolol hydrochloride tablets. Release of propranolol hydrochloride from asymmetric membrane coated tablets

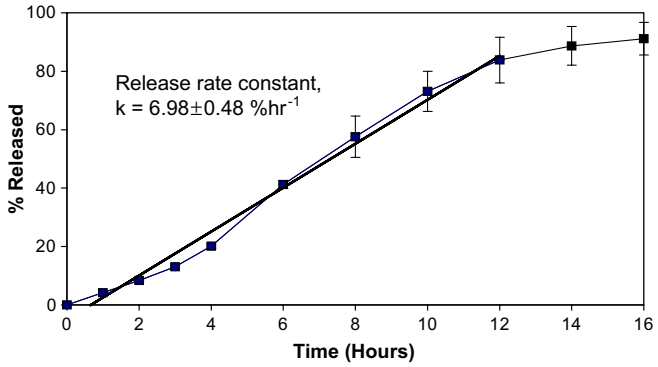

Fig. 5. Release of propranolol hydrochloride from asymmetric membrane coated tablets. Release rate constant (k) is represented as mean ± SD ($n = 3$).

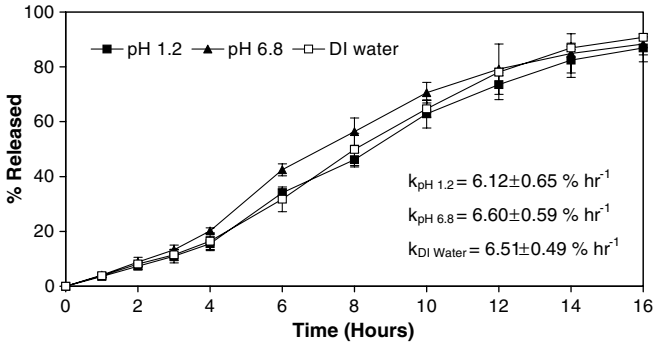

Fig. 7. Release of propranolol hydrochloride from asymmetric membrane coated tablets – effect of pH of the dissolution media. Release rate constant (k) is represented as mean ± SD ($n = 3$).

was evaluated using USP dissolution test apparatus I as mentioned earlier. The percent of drug released was calculated and plotted against time. Kinetic analysis was performed to access the order of release. It was found that the release from the asymmetric membrane coated tablets followed zero order kinetics for first 12 h ($r^2 = 0.99$) (Fig. 5). After about 12 h, when more than 80% of the drug was released, the release rate declined parabolically probably because there was not enough drug available in the core to provide the saturation concentration resulting in decline in the osmotic driving force. These results are in accordance with already published reports [1].

The role of the porous sub-layer as a barrier to flow was assessed as opposed to the skin (top layer) of the asymmetric membrane. For this, propranolol hydrochloride tablets were coated with asymmetric membrane coating and the skin of the coat was scrapped off and the tablets were then subjected to dissolution studies. The release profile was compared with that of a coated and uncoated tablets (Fig. 6). It was found that the skin of the membrane offered significant resistance to the release of the drug (release rate constant of the coated tablet with the top layer vs. without top layer: $6.98 \pm 0.48\%$ vs. $8.67 \pm 0.61\%$ h^{-1}, $p < 0.05$). This can be explained by the asymmetric structure of the membrane, which has a dense outer skin (with a low permeability) supported on a highly porous structure (Figs. 1–4). However, there also was significant resistance caused by the porous sub-layer as well (release rate constant of the tablet without top layer vs. uncoated tablet: $8.67 \pm 0.61\%$ vs. $400.1 \pm 4.2\%$ h^{-1}). The reason for the significant resistance offered by the porous sub-layer could be the presence of the unstirred layer around the tablet core due to the long and tortuous channels of the precipitated polymer. Additionally, the method of scraping the top layer was manual and there is a possibility that there was an incomplete removal of the top layer.

To investigate the effect of pH on the release rates from asymmetric membrane coated tablets, the release of propranolol hydrochloride was studied in two different dissolution fluids. Coated tablets were placed in dissolution medium SGF (pH 1.2), SIF (pH 6.8), and deionized water (pH 7.2). The dissolution profile of the coated tablet in dissolution mediums of varying pH is shown in Fig. 7. We found that there was no significant difference ($p > 0.05$) in the release rates of the drug with changing the media pH. The effect of rate of stirring was also studied on the release of the drug. Three rates of stirring were employed, i.e., 50, 75, and 100 rpm. Drug release was found to be independent of stirring rate (Fig. 8) ($p > 0.05$). These results confirm the osmotic nature of the release, which is independent of the pH and the rate of agitation of the dissolution medium.

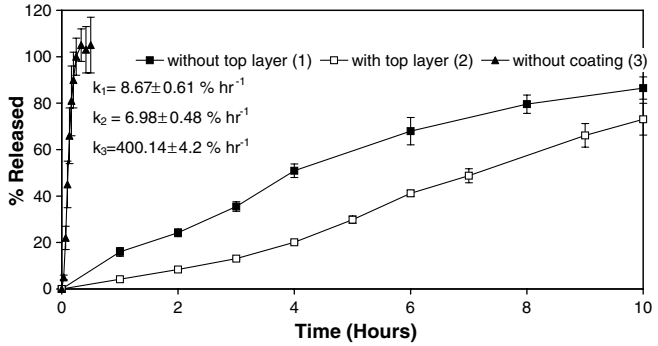

Fig. 6. Role of the porous sub-layer of the asymmetric membrane coating in drug release. Release rate constant (k) is represented as mean ± SD ($n = 3$).

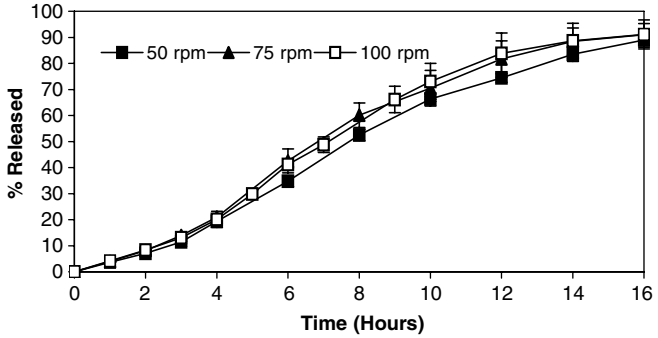

Fig. 8. Release of propranolol hydrochloride from asymmetric membrane coated tablets – effect of rate of stirring during dissolution. Release rate constant (k) is represented as mean ± SD ($n = 3$).

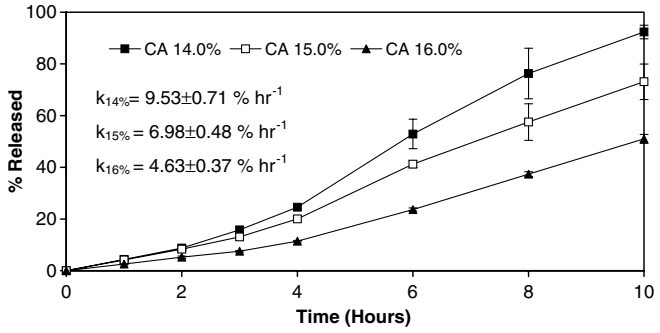

Fig. 9. Release of propranolol hydrochloride from asymmetric membrane coated tablets – effect of cellulose acetate (CA) concentration, Release rate constant (k) is represented as mean ± SD ($n = 3$).

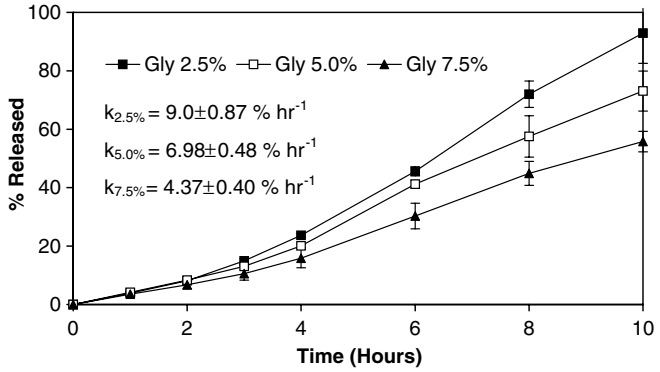

Fig. 10. Release of propranolol hydrochloride from asymmetric membrane coated tablets – effect of glycerin (Gly) concentration. Release rate constant (k) is represented as mean ± SD ($n = 3$).

To determine the effect of polymer concentration on the release rates of the drug, the concentration of the coating polymer, Cellulose Acetate (CA 398-10), was varied from 14.0% w/w to 16.0% w/w. As the concentration of the polymer in the coat was increased, the release rates were significantly reduced ($p < 0.01$) (Fig. 9). During coating of the tablets, it was observed that as the polymer concentration was increased there was a marked increase in the viscosity of the coating solution, which could be responsible for the reduction in the release rates. An increase in viscosity of the coating solution would result in less diffusion of precipitant into the concentrated polymeric layer and hence a less porous film will be formed, resulting in reduction of the release rates. At different concentration levels, there was no significant increase in the weight of the tablets (data not shown).

The effect of pore former, glycerin, was investigated by varying the concentrations of glycerin from 2.5% w/w to 7.5% w/w. Theoretically, it was expected that as the concentration of the pore former will increase, there should be an increase in the release rates, but an opposite effect was observed (Fig. 10). As, the concentration of glycerin was increased there was a significant reduction ($p < 0.01$) in the release rates. As the glycerin concentration was increased a marked increase in the viscosity of the coating solution was observed. With increase in the viscosity of the coating solution there would be a reduction in the penetration of the precipitant in the coat, resulting in decreased membrane permeability. Also, no change in the thickness of the coat was observed with the increasing concentration of the glycerin.

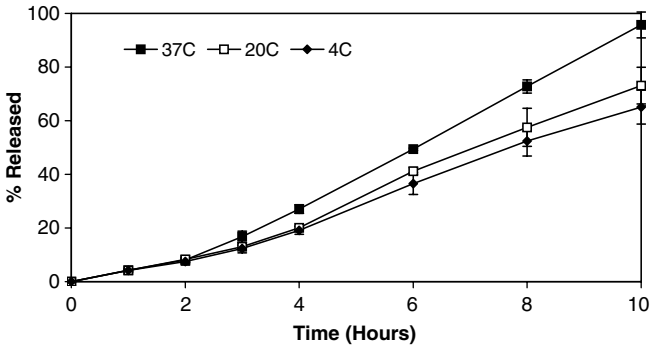

Fig. 11. Release of propranolol hydrochloride from asymmetric membrane coated tablets – effect of temperature of precipitation. Release rate constant (k) is represented as mean ± SD ($n = 3$).

The effect of precipitation temperature on the permeability of the coat was evaluated. Tablets coats were allowed to precipitate over a wide range of temperatures, from 4 to 37 °C. Increase in the temperature of the precipitation resulted in marked increase in the permeability of the tablet coat (Fig. 11). Theoretically, as the temperature of precipitation will increase, the precipitation would occur at a slower rate and the skin of the membrane will not form (which controls the rate of release rate). Without the skin, the coat would be highly porous, thereby increasing the release rates. These results were also supported by the SEM picture of the coat (Figs. 1–4). The release of drug from formulations precipitated at 37 °C was found to be significantly higher ($p < 0.05$) as compared to the formulations precipitated at 4 and 20 °C, whereas, no statistically significant difference was observed ($p > 0.05$) in case of formulations precipitated at 4 and 20 °C.

4. Conclusions

An osmotic drug delivery system for propranolol hydrochloride was successfully developed using asymmetric membrane coatings, a zero order release was achieved and it was established that the release rates were unaffected by the pH of the medium and the speed of agitation. The preparation parameters like concentration of the polymer, concentrations of the pore former and the temperature of precipitation had a significant effect on the permeability of the asymmetric membrane structure and the release profile. Asymmetric membranes can be successfully utilized in the controlled drug delivery of soluble drugs, like propranolol, and by modifying some preparation parameters like polymer concentration, concentration of the pore former, and temperature of precip-

itation, the structure of the asymmetric coat can be modified, resulting in modified release of the drug.

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