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# POLYMERIC PSEUDOLATICES DISPERSION BEARING ISOSORBIDE DINITRATE FOR TRANSDERMAL APPLICATION

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## ABSTRACT

A pseudolatex based system for transdermal delivery (PL-ISDN-D) of isosorbide dinitrate (ISDN) was developed for its prolonged and controlled systemic availability. To achieve the desired and controlled release rate, different combinations of Eudragit RL-100 and polyvinylpyrrolidone were used in the preparation of pseudolatices polymeric dispersions. These preparations were evaluated for in-vitro release and permeation of the drug across human cadavar skin. The designed systems exhibited linear relationship between drug release (Q) Vs 0.80 function of time ($t^{0.80}$).

The product exhibiting required skin permeation (500 mcg/h/100 mg) calculated to achieve an effective plasma concentration was selected for the in-vivo performance evaluation. The drug plasma profile was compared with the plasma profile obtained following the administration of conventional oral dose of isosorbide dinitrate.

The study revealed that designed pseudolatex transdermal drug delivery system of isosorbide dinitrate could be used successfully with improved performance.

## INTRODUCTION

The dermal route of drug delivery offers its own advantages over other routes of drug administration. Beside convenience

enhanced and controlled therapeutic response has been recorded (1). Recent progress in transdermal delivery system (TDS) is represented by the development of nitroglycerine transdermal delivery system such as, Transderm-Nitro (2), Nitro-Dur (3) and Nitrodisc (4). These systems were designed to regulate the release of the drug from the system and absorption of released drug across the skin. Recently the topical preparations of lidocaine, ephedrine and diclofenac based on pseudolatices (5-8) have been discussed. The drug in such systems is known to be dispersed at molecular level offering precised and controlled drug delivery. The pseudolatex dispersion following applications on skin, dries and offers the opportunity to produce a highly substantive clear, continuous and virtually invisible film containing molecularly dispersed drug (9).

The present study was an attempt to evaluate the transdermal pseudolatex based system of isosorbide dinitrate. Isosorbide dinitrate is a drug of choice in the treatment and management of angina pectoris, with short biological half-life i.e., $3.8 \pm 0.5$ hours (10). Therefore 5 to 20 mg of drug is recommended to be administered thrice a day. Inspite of good bioavailability on frequent oral administration contraindicated manifestations are associated with isosorbide dinitrate therapy. An appreciable transdermal permeability of isosorbide dinitrate has recently been established and a therapeutic system to provide a prolonged and continuous transdermal infusion of isosorbide dinitrate was explored (11). The prepared system was found to release the drug at a defined and controlled rate over an extended period i.e. for 24 hours.

## MATERIALS

Isosorbide dinitrate (Nicholas Laboratories India Ltd.); Eudragit RL-100 (Rohm Pharma Darmstadt FRG); Polyvinylpyrrolidone (BHC Chemicals Ltd. Poole, England); Tween 80 (Polysorbate 80) (Kochelight Chemical Lab., England); Dibutyl phthalate (Flueka A.G., Switzerland); Liquid paraffin (Loba Chemie Ind. Co. Bombay) and all other ingredients were of Analar grade and were used as received (Glindia, a chemical division of Glaxo India Ltd., Bombay, India).

**Table 1.** Compositions of Isosorbide Dinitrate Bearing Pseudolatices

| Ingredients | Percent concentration (w/w) Formulation | | | | |
|---|---|---|---|---|---|
| | PL-ISDN-A | PL-ISDN-B | PL-ISDN-C | PL-ISDN-D | PL-ISDN-E |
| Isosorbide dinitrate (based on polymer weight) | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| Eudragit RL-100 | 10.00 | 9.00 | 8.00 | 7.00 | 6.00 |
| Polyvinylpyrrolidone | 0.00 | 1.00 | 2.00 | 3.00 | 4.00 |
| Liquid paraffin | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Dibutyl phthalate | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| Tween-80 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Water | 30.00 | 30.00 | 30.00 | 30.00 | 30.00 |



## METHODS

### Preparation of Pseudolatex

The isosorbide dinitrate pseudolatex bearing polymeric dispersions were prepared by solvent removal method (9). The drug and polymer solution in chloroform containing 10% w/w polymer (Eudragit RL-100 and PVP in different weight fractions), 7.5% w/w drug (based on polymer weight), 2% w/w liquid paraffin (based on polymer) and 5% w/w dibutyl phthalate (based on polymer weight) was emulsified with an aqueous solution of surfactant (Tween 80, 10% w/w) (Table 1). The prepared emulsion was well stirred and kept in a vacuum oven at 45°C for 8-10 hours in order to evaporate the organic solvent in internal phase completely and water of external phase partially (Ca:30% w/w initially incorporated weight).

The drug concentration in pseudolatex was determined spectrophotometrically. The preparation was dried to a constant weight under vacuum and dissolved in methanol. The absorbance was measured at 200 nm using a Shimadzu UV-180 spectrophotometer (12).

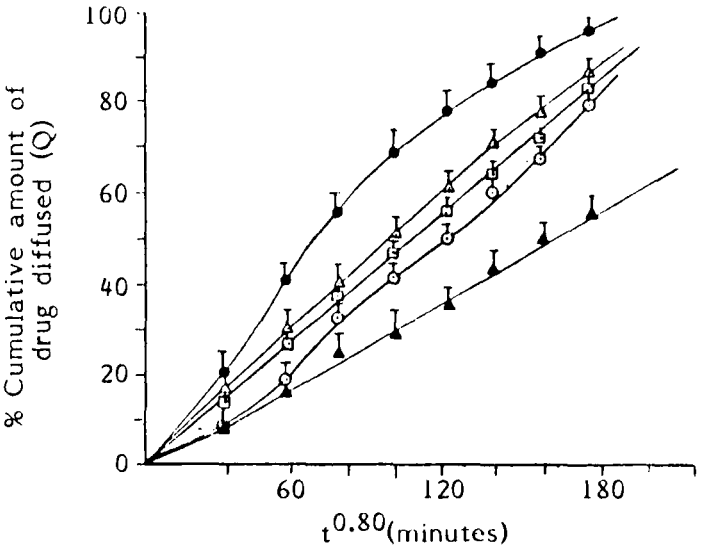


**Fig 1 :** In-vitro diffusion profile of isosorbide dinitrate in phosphate saline buffer (pH 7.4). ▲—▲ - PL-ISDN-A; ○—○ - PL-ISDN-B; □—□ - PL-ISDN-C; ●—● - PL-ISDN-D; Δ—Δ - PL-ISDN-E; Bar at data points indicates mean deviation ( ± S.D.).

## In-vitro Drug Diffusion

In-vitro drug release from pseudolatex preparation was determined in order to quantify the availability of drug for absorption on the skin using Franz diffusion cell (Crown Glass Co., New Jersy, U.S.A.). The contents of the donar compartment (pseudolatex) and the receiver compartment (isotonic PBS of pH 7.4 containing 20% v/v PEG-400) were separated by cellophane membrane (Spectropore) membrane with 5000-7000 mw cut-off (Spectrum Medical Industry, Loss Angels CA, U.S.A.). In this study, the solution of receptor compartment was withdrawn completely at the scheduled time and replaced with the fresh phosphate buffer (containing 20% v/v PEG-400). The temperature of the receiver compartment was maintained at 37± 1°C (Fig. 1).

The drug concentration in the samples was determined spectrophotometrically at 200 nm using method reported by Tingstad et al. (12).

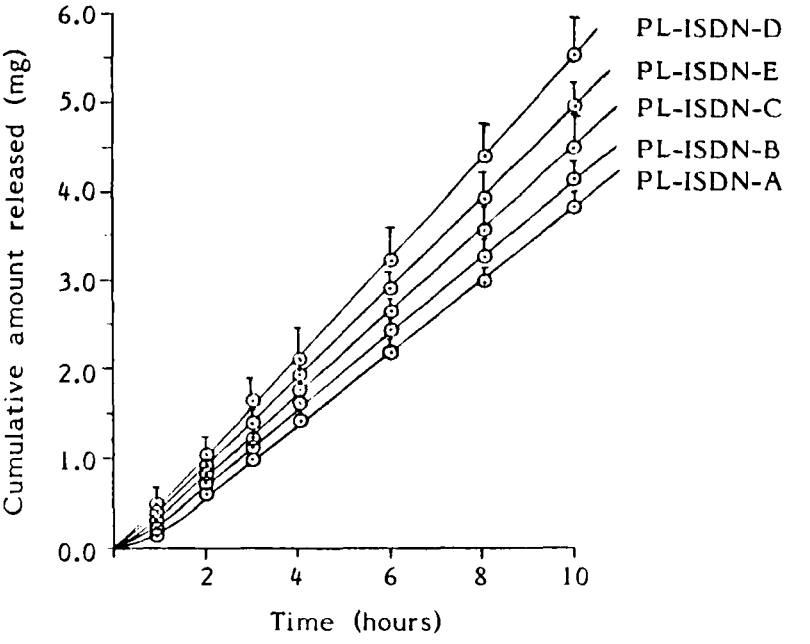


**Fig 2:** In-vitro skin permeation profile of isosorbide dinitrate from different pseudolatices. Bar at data points indicate standard deviation ( ± S.D.).



## In-vitro Skin Permeation

In-vitro skin permeation of isosorbide dinitrate from prepared pseudolatex was studied using Franz diffusion cell. The preparation (100 mg) was applied directly to the stratum corneum side of (freshly excised and undermatomed) human cadavar skin. Skin bearing pseudolatex preparation was mounted in between the donar and receptor compartment of the cell. In this system clinical conditions were simulated by controlling the receptor compartment temperature at 37± 1°C while allowing the donar compartment to be exposed to the ambient temperature (30°C). The receptor compartment contained isotonic PBS (pH 7.4) containing 20% PEG-400.

0.5 ml of sample was withdrawn from the receptor compartment at the time interval of 0, 1, 2, 3, 4, 6, 8 and 10 hours and samples were replaced with equal volume of fresh buffer. The samples were assayed for isosorbide dinitrate content spectrophotometrically at 200 nm. (Fig. 2).

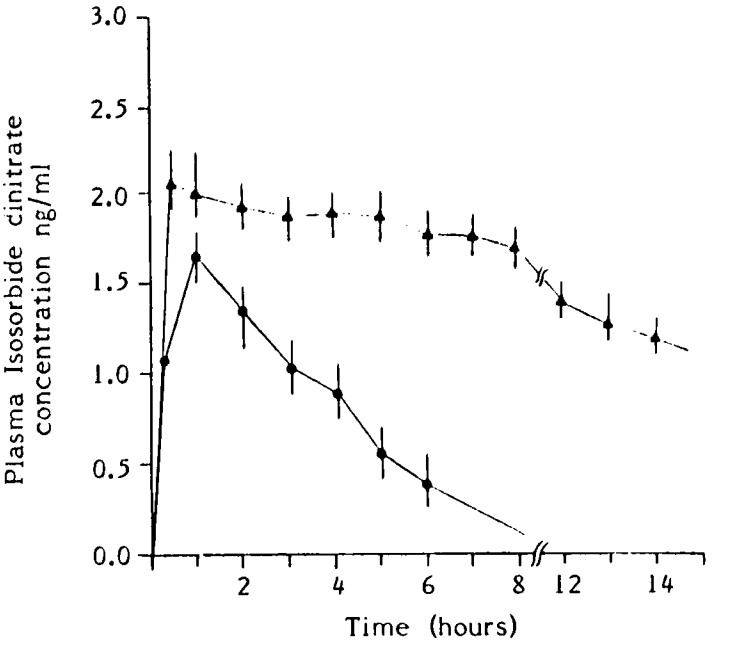


**Fig 3:** Mean plasma levels of isosorbide dinitrate following oral treatment ISORDIL$^R$ 5 mg. ( o—o ) and transdermal pseudo-latex PL-ISDN-D application ( ▲—▲ ). Bar at data points indicate standard deviation ( ± S.D.).



## In-vivo Performance

On the basis of the in-vitro skin permeation the formulation PL-ISDN-D (that released the drug at the rate 500 mcg/h/cm$^2$) was selected for in-vivo evaluation.

The studies were carried out on ten male human volunteers (Age: 25± 5 years, Average weight 60± 2 kg) who signed the consent form. Subjects passed for normal haemotological and urinary bio-chemical investigations. These subjects possess no history of having taken any drug during the preceding week as well as during these studies. The subjects were fasted with water at libitum for 12 to 14 hours prior to administration of the drug.

To each subject ISORDIL$^R$ equivalent to 7.5 mg of isosorbide dinitrate (Treatment 1) administered orally with 300 ml of water. Pseudolatex transdermal preparation (100 mg equivalent to 7.5 mg

of plain drug) (Treatment II) were applied topically at the cleaned forearm region at least one week apart following over night fasting. Blood (2 ml) was collected periodically from forearm vein with help of a hypodermal syringe. The transdermal preparations were removed 14 hours after application. Plasma was separated from the sample and isosorbide dinitrate content was estimated using gas liquid chromatography method reported by Sherber et al. (13), using Hewlett-Packard 5710A gas chromatograph. Mean plasma levels were computed and drug plasma profiles following treatment (I) and (II) were constructed (Fig. 3).

## RESULTS AND DISCUSSION

The pseudolatex polymeric dispersion prepared by solvent removal method was physically stable, uniform in size and demonstrated formation of an invisible and highly substantive clear film when applied to the skin.

The in-vitro release profile recorded for pseudolatex are shown in Fig. 1. The release from pseudolatex has shown a linear relationship between the cumulative amount of drug released (Q) and 0.80 exponent of time ($t^{0.80}$) which indicates non fickian diffusion dependent release profile. The slope of the plot was used to calculate the release rate constant of isosorbide dinitrate. An initial lag time of 20 min was observed (Fig. 1). The lag time could be accounted for by the time taken by the drug to diffuse across the cellophane membrane (used to support the pseudolatex). A linear increase in release rate of drug with increasing concentration of PVP in polymer matrix of the pseudolatex was recorded (Fig. 1).

The released isosorbide dinitrate from the pseudolatex appeared in the receptor compartment following a monophasic kinetics. It may be observed that as the concentration of hydrophilic polymer (PVP) increases from 10 to 30% w/w (based on total polymer weight) the permeation rate increased from 348 mcg/h/100 mg to 485 mcg/h/100 mg. The cumulative amount of drug permeated (Q) across the skin was plotted as a function of time (h). A linear portions were obtained after a lag period of 30-40 min. The higher permeation rate from pseudolatex could be attributed to the uniform and fine dispersion of drug in the coalesced structure of the pseudolatices. Moreover the use of a surfactant in

the preparation of pseudolatex may also enhance the drug penetration through skin (Fig. 2) (14).

On the basis of in-vitro skin permeation studies the product (PL-ISDN-D) was selected for in-vivo studies as the drug permeation rate constant across the human cadavar skin recorded 485 mcg/h/100 mg for product PL-ISDN-D was almost equal to the calculated permeation rate (required rate to achieve an effective drug plasma concentration). In-vivo performance of the transdermal product (Treatment II) was compared with orally administered tablet ISORDIL$^{R}$ treatment I. Fig. 3 shows the mean plasma Vs time profile of ISDN following the application of treatment I and treatment II. The plasma concentration of ISDN gradually increased and attained an average steady state level. The average plasma ISDN concentration remained nearly constant for 14 hrs. To examine intersubject variation resulting from either treatment, the peak plasma level values were normalized at $C_{max}$ and for all other sampling time the concentration were related to the values as described by Willis et al. (15). However, in the case of oral treatment with conventional tablet of ISDN the effective plasma level was reached within 0.3 hr. (Fig. 3).

The insignificant ($P > 0.5$) variation in drug plasma levels following PL-ISDN-D application could be accounted for by the skin permeation characteristics of the drug which are possibly the same for all subjects. The significant intersubject variation ($P < 0.5$) in plasma levels recorded in subjects receiving conventional tablets orally could be related to the gastric residential time and gastro-intestinal absorption which could noticeably vary from subject to subject.

Finally the pharmacokinetic parameters $C_{max}$, $t_{max}$, AUC and $T_{lag}$ were calculated from the plasma drug profiles of oral and transdermal treatments.

The improved performance of the designed transdermal drug delivery system of isosorbide dinitrate was established. The most effective behaviour was recorded for the pseudolatex based transdermal treatment ($AUC_{0-14}$) 24.80±1.20 ng/h/ml. It was better than the oral treatment ($AUC_{0-14}$) 9.80±0.8 ng/h/ml whilst the drug was given in equal doses.

It is concluded that pseudolatex dispersion of isosorbide dinitrate can be prepared using Eudragit RL-100:PVP (7:3) containing 7.50 w/w drug. Absorption across the skin of ISDN following the application of Polymer dispersion was at a controlled rate. The plasma levels of isosorbide dinitrate following the topical application could be maintained for prolonged period with insignificance intersubject variation.

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