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Case Study *Open Access*

Formulation development and in-vitro evaluation of repaglinide loaded transferosomal gels

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ABSTRACT

Bisoprolol is a drug belonging to the group of beta-blockers, a class of medicines used primarily in cardiovascular diseases. More specifically, it is a selective type β1 adrenergic receptor blocker. The U.S. Food and Drug Administration (FDA) approved an application by Duramed Pharmaceutical for Zebeta Oral Tablets (bisoprololfumarate) as a new molecular entity on July 31, 1992. In current work buccal drug delivery of Bisoprolol was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. buccal patches was prepared by using polymers Eudragit-L100, HPMCk_4M and HPMCk15M. by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. all the formulations prepare (F1-F9)were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions.

Keywords: Beta-blockers,Patches,Buccaldelivery,Bisoprolol.

INTRODUCTION

Transdermal drug delivery systems (TDDSs) offer a number of potential advantages over conventional methods such as injectable and oral delivery. However, the major limitation of TDDS is the permeability of the skin; it is permeable to small molecules and lipophilic drugs and highly

impermeable to macromolecules and hydrophilic drugs. The main barrier and ratelimiting step for diffusion of drugs across the skin are provided by the outermost layer of the skin, the stratum corneum. Several strategies

have been developed to overcome the skin's resistance, including the use of prodrugs, ion pairs, liposomes, microneedles, ultrasound, and iontophoresis. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, in case of lipophilic drug near to 90%. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well as topical delivery of drug. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives[1-10].Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short-acting insulin secretagogues, which act by binding toβ cells of the pancreas to stimulate insulin release. Repaglinide induces an early insulin response to meals decreasing postprandial blood glucose levels. It should only be taken with meals and meal-time doses should be skipped with any skipped meal. Approximately one month of therapy is required before a decrease in fasting blood glucose is seen. Repaglinide activity is dependent on the presence functioning β cells and glucose. In contrast to sulfonylurea insulin secretatogogues, repaglinide has no effect on insulin release in the absence of glucose. Rather, it potentiates the effect of extracellular glucose on ATP-sensitive potassium channel and has little effect on insulin levels between meals and overnight. As such, repaglinide is more effective at reducing postprandial blood glucose levels than fasting blood glucose levels and requires a longer duration of therapy (approximately one month) before decreases in fasting blood glucose are observed[18].

MATERIALS AND METHODS FORMULATION OF TRANSFERSOME GEL

Preparation of Transfersomes by Modified Hand shaking lipid film hydration technique: Six Transfersome formulations were prepared by thin film hydration method using Repaglinide, Soya Lecithin, and different concentrations of surfactants (Span-80, Tween80). The amount of drug is kept constant (8 mg) in all the formulations. Different formulations were prepared by using different ratios of phospholipid and surfactants in different ratios. The details about the surfactants used and amount of lecithin and surfactant used in each formulation are given in the table. Lecithin, surfactants and the drug are dissolved in 5 ml of organic solvent (Chloroform: Methanol 3:1). The organic solvent is then removed by evaporation while hand shaking above lipid transition temperature (430c). Final traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the phosphate buffer (pH 6.8) by rotation at 60 rpm for 1 hour at room temperature. The resulting vesicles are swollen for 2 hours at room temperature. The multilamellar lipid vesicles (MLV) are then sonicated using sonicator for 30 minutes.Quantity of substances taken for preparation of transfersomes

Table 1

Formulation	Repaglinide (mg)	Lecithin (mg)	Tween 80 (mg)	Span 80 (mg)
R1	2	95	5	--

R2	2	90	10	--
R3	2	85	15	--
R4	2	80	20	--
R5	2	90	-	10
R6	2	95		5
R7	2	85	-	15
R8	2	80	-	20

In each of the formulation, 5ml of chloroform and methanol ratio were added separately.

Preparation of topical transfersome gel

As a vehicle for incorporation of transfersomes for topical delivery, carbopol gels were prepared. Transfersomes aqueous dispersion was utilized for the formulation of topical gel. Gel polymer such as Carbopol 940 was utilized to prepare transfersome gel. 2g of Carbopol- 940 powder was dispersed into vigorously stirred) distilled water (taking care to avoid the formation of in dispersible lumps) and allowed to hydrate for 24 hrs. The dispersion was neutralized with tri ethanolamine to adjust the pH 6.8 by using pH meter.

OPTIMIZATION OF FORMULATION

There are various process variables which could affect the preparation and properties of the transfersome. The preparation procedure was accordingly optimized and validated. The preparation of transfersome containing Repaglinide involves various process variables such as effect of Lecithin: Surfactant ratio and effect of surfactant, optimization was done by selecting in vitro release of drug as optimizing parameter. During the preparation of a particular system, the other variables were kept constant.

CHARACTERIZATIONOF TRANSFERSOMES

Transfersome suspension

Vesicle shape and type: Transfersomes vesicles can be visualized by SEM and optical microscope. The Morphological characterization of transfersome vesicle such as shape and surface feature were projected by using optical microscope and SEM

Optical microscope method: A drop of transfersome suspension was placed over the slide and Photo micrograph was taken at 10x resolution Transfersome gel

Determination of pH: The value of pH of topical transfersome gels was measured by using digital pH meter at the room temperature.

Determination of entrapment efficiency percentage: The amount of Repaglinide entrapped in transfersome gel was estimated by centrifugation method. 1gm of Transfersome gel was taken and diluted with 10ml phosphate buffer (pH 6.8). This suspension was sonicated using bath sonicator for 20 minutes. Later this solution was placed in centrifugation tube and centrifuged at 14000 rpm for 30 minutes. 0.5ml of supernatant was withdrawn and diluted before going for absorbance measurement using UV spectrophotometer (UV-3200 Lab India) at 241nm. This gives us the total amount of unentrapped drug. Entrapment efficiency is expressed as the percent of drug trapped.

$$\% \text{ Entrapment} = \frac{\text{Total drug} - \text{Diffused drug}}{\text{Total drug}} \times 100$$

% Drug content: 1g of transfersome gel formulation was taken and the vesicles were lysed with 25 ml of methanol by sonication [citizen, India] for 15 min. Later this solution was placed in centrifugation tube and centrifuged at 14000 rpm for 30 minute. Then 10 ml of solution was diluted to 100 ml with phosphate buffer pH 6.8. Aliquots were withdrawn and drug content was calculated for Repaglinide by using UV spectrophotometer at 241nm.

$$\% \text{ Drug Content} = \frac{\text{Amount of Drug obtained after centrifugation}}{\text{Amount of drug taken}} \times 100$$

In-vitro drug release studies Modified Franz diffusion cell with a receiver compartment volume of 18 ml and effective diffusion area of 2cm^2 was used for this study. In-vitro drug study was performed by using egg membrane in phosphate buffer solution (pH 6.8). To perform in-vitro drug release study, egg membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2 cm^2 and capacity of receptor compartment was 30ml. The receptor compartment was filled with 30 ml of phosphate buffer (pH 6.8) maintained at 37± 0.50C and stirred by a magnetic bar at 100 rpm. Transfersome gel formulation equivalent to 8mg drug was placed on the cellophane membrane and the top of the diffusion cell was covered. At appropriate time intervals 5 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 6.8) to maintain sink conditions. The samples were analyzed spectrophotometrically at λ max 241nm.

RESULTS

CHARACTERIZATIONOF TRANSFERSOMES

Transfersome suspension

Vesicle shape and type

The surface morphology was studied by Optical Microscopy The shapes of most of the containing Repaglinidetransfersomes were found to be spherical from SEM analysis as shown in figures.

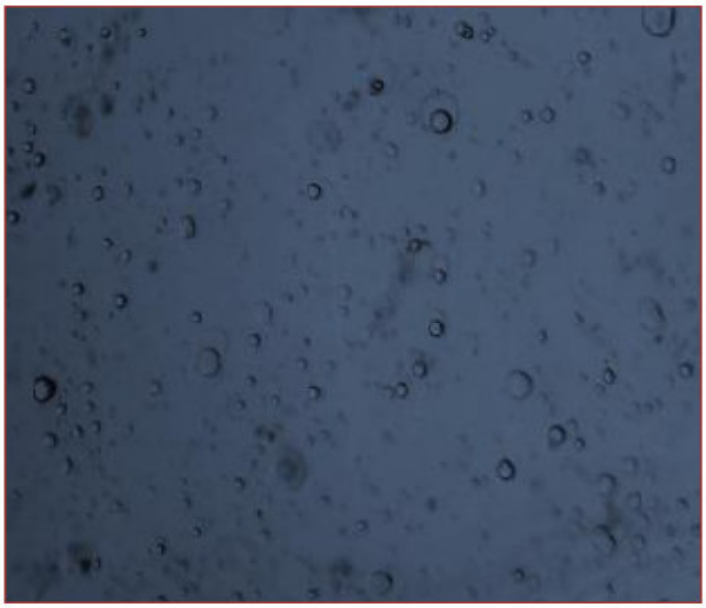

Fig . 1 Photomicrograph of Repaglinide loaded transfersome (RT7) at 10X

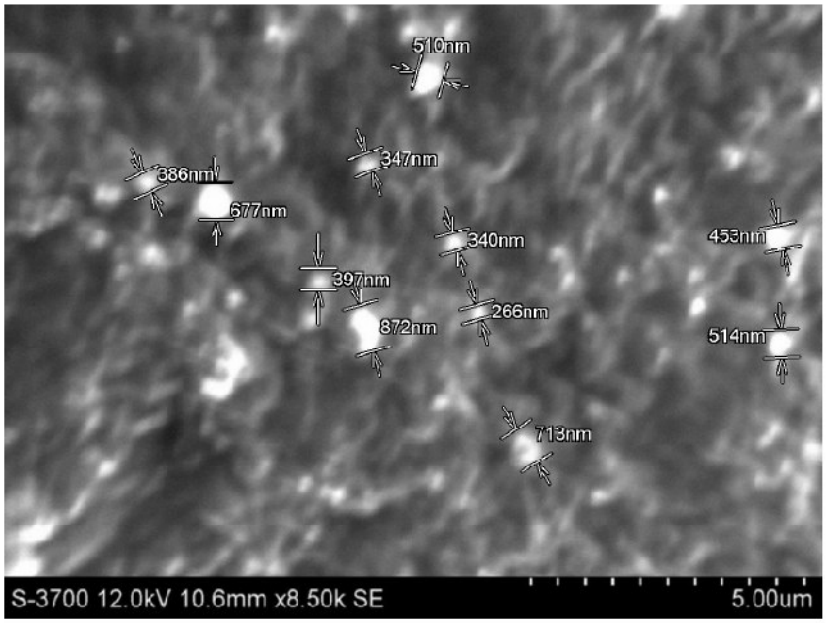

Fig . 2 SEM analysis of optimized formulation (RT7)

Entrapment efficiency

The % entrapment efficiency of deformable vesicles formulations were found to be in the range of 82.48 to 88.41 Entrapment efficiency of the R7 formulation was high.

% Drug content

% drug content of transfersome formulations (R1to R8) were determined according to procedure. The results obtained shows 86.45 - 94.56% drug content in the formulations. The results obtained are shown in table.

% Drug entrapped and % Drug content in transfersomes

Table 2

Formulation	% Entrapment Efficiency	% Drug content
R1	82.48	86.45
R2	84.26	92.02
R3	85.12	89.64
R4	84.21	87.29
R5	85.16	89.46
R6	86.27	92.24
R7	88.41	94.56
R8	87.29	92.41

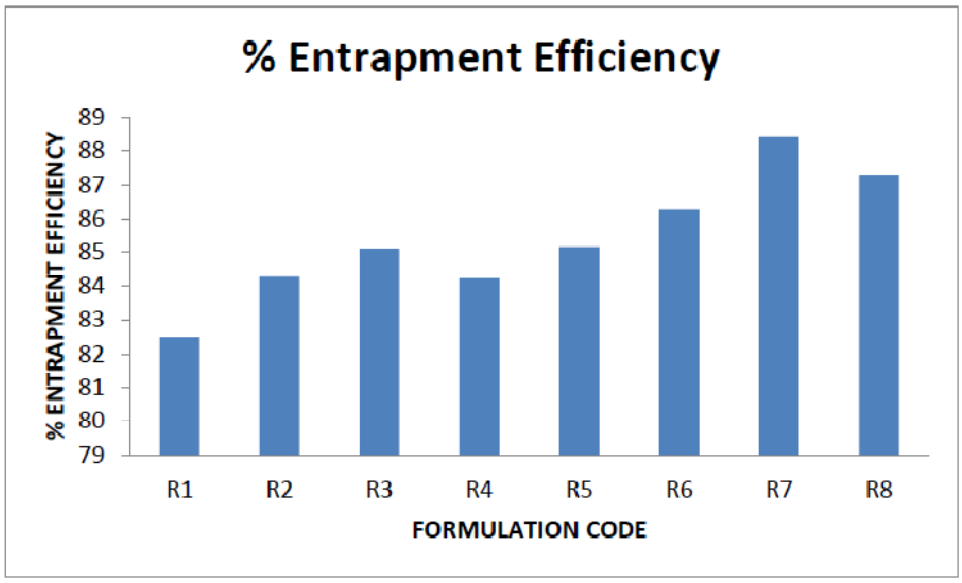

Fig .3 % Entrapment efficiency for Repaglinide all formulations(R1-R8)

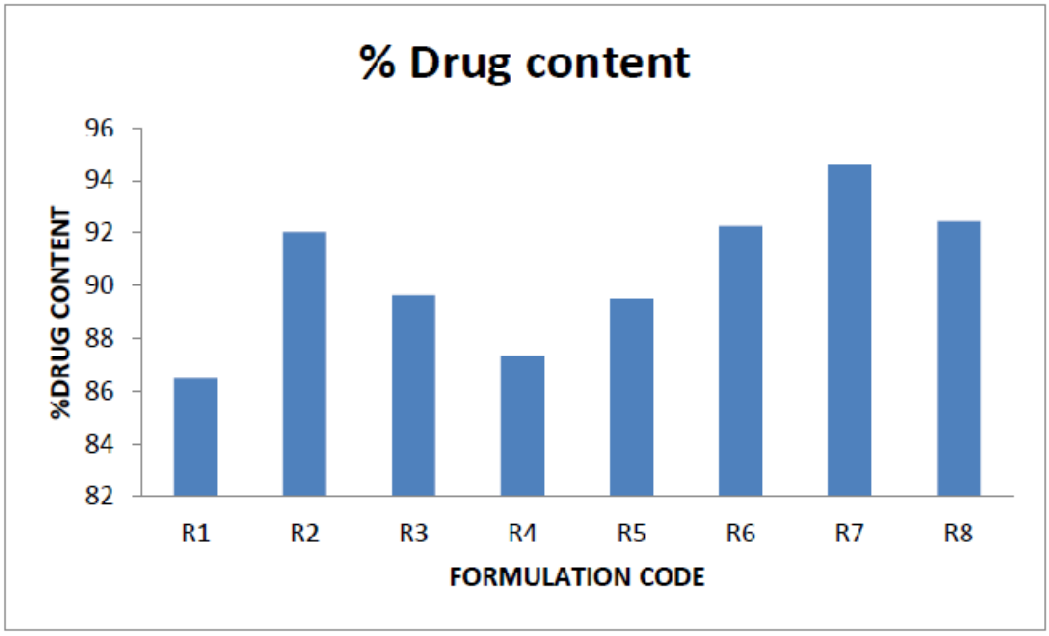

Fig .4 % Drug Content for Repaglinide all formulations (R1-R8)

In-vitro drug release study

The in-vitro diffusion study in phosphate buffer pH 6.8 were carried out using Franz diffusion cell according to procedure explained.

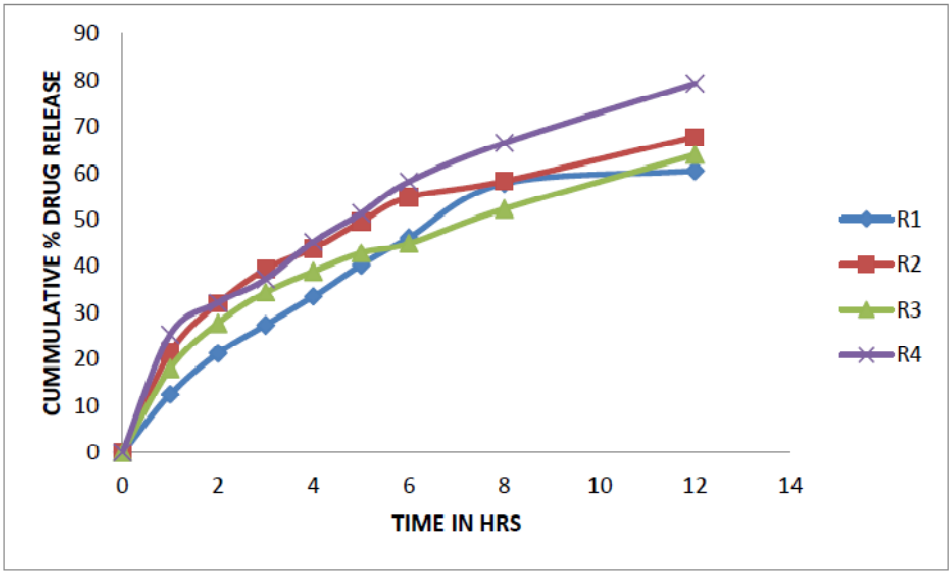

Fig . 5 In-Vitro drug release study for transfersome gel formulation R1-R4

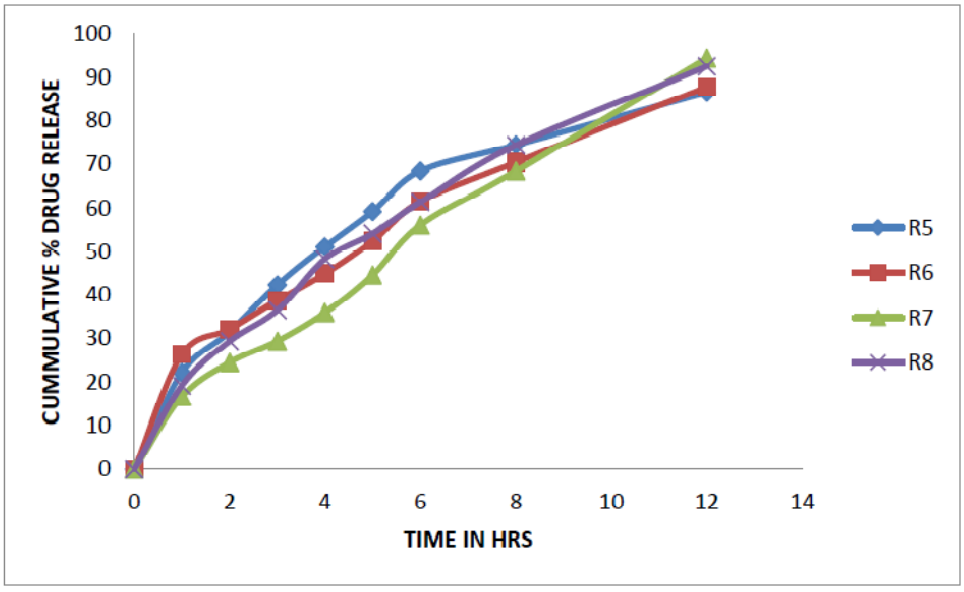

Fig . 6 In-vitro drug release study for transfersome gel formulation R5-R8

DISCUSSION

The percentage entrapment of repaglinide was found to be maximum with formulation R7 because of the increase in the ratio of lipid volume in the vesicles as compared to the encapsulated aqueous volume. The effect of phospholipids and edge activator ratio in the lipid components of vesicles on the entrapment efficiency of lipophilic drug, the efficiency increased with increasing surfactant concentration and thus increased with increasing lipid concentration. The results obtained shows 86.45 - 94.56% % drug content in all the formulations, which shows that there is no degradation of the drug in the process. Comparison of results obtained from diffusion studies for all six formulations have been done. It was found that formulation R7 shows higher drug release rate than other formulations. This result of dissolution profile showed slight initial burst release. This is probably caused by the release of drug absorbed on the transfersome surface or precipitated from the superficial lipid layer. Prolonged release in the later stage can be attributed to the slow diffusion of the drug from the lipid vesicle. It is clear from the results obtained that the

transfersomes have shown the minimum drug lost at refrigerated condition, and fairly high retention of drug inside the vesicles was observed. At this low temperature condition percentage remaining drug entrapped and drug content was good over a period of months. While, storage at higher temperatures 25±2^{o}C and 37±2^{o}C leads to less percentage remaining drug entrapped and drug content over a period of 3 months respectively. The higher amount of drug leakage at elevated temperature may be due to the degradation of lipids constituting bilayers resulting in defects in membrane packing and loss of overall rigidity that makes them leaky. With the increase in temperature, there is also increase in the fluidity of lipid bilayers, due to phase transition phenomenon. So it can be inferred from the above discussion that the transfersomes formulation should be stored at lower temperature to minimize the drug loss and increase the stability of drug.

CONCLUSION

The Transfersomes gel improve the transdermal delivery, prolong the release, and improve the site specificity of the drug Repaglinide. Transfersomes creates a new opportunity for the well-controlled transdermal delivery of a number of drugs that have a problem of administration by other routes.

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