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ORIGINAL ARTICLE

Improved bioavailability of timolol maleate via transdermal transfersomal gel: Statistical optimization, characterization, and pharmacokinetic assessment

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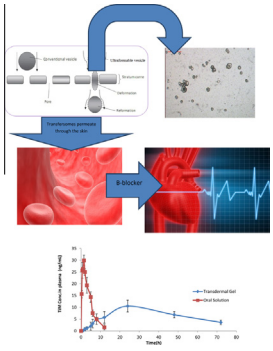
GRAPHICAL ABSTRACT



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ABSTRACT

Timolol maleate (TiM), a nonselective β-adrenergic blocker, is a potent highly effective agent for management of hypertension. The drug suffers from extensive first pass effect, resulting in a reduction of oral bioavailability (*F*%) to 50% and a short elimination half-life of 4 h; parameters necessitating its frequent administration. The current study was therefore, designed

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to formulate and optimize the transfersomal TiM gel for transdermal delivery. TiM loaded transfersomal gel was optimized using two 2^3 full factorial designs; where the effects of egg phosphatidyl choline (PC): surfactant (SAA) molar ratio, solvent volumetric ratio, and the drug amount were evaluated. The formulation variables; including particle size, drug entrapment efficiency (%EE), and release rate were characterized. The optimized transfersomal gel was prepared with 4.65:1 PC:SAA molar ratio, 3:1 solvent volumetric ratio, and 13 mg drug amount with particle size of 2.722 μm, %EE of 39.96%, and a release rate of 134.49 μg/cm^2/h. The permeation rate of the optimized formulation through the rat skin was excellent (151.53 μg/cm^2/h) and showed four times increase in relative bioavailability with prolonged plasma profile up to 72 h compared with oral aqueous solution. In conclusion, a potential transfersomal transdermal system was successfully developed and the factorial design was found to be a smart tool, when optimized.

Introduction

Timolol maleate is a β-adrenergic blocking agent that exhibits an anti-hypertensive activity, protects against angina pectoris, and myocardial infarction. Due to its short elimination half-life (4 h), it is orally administered twice daily. Additionally; because of poor bioavailability (50%), a high oral dose of 10–60 mg/day was required. As an adverse effect, bronchospasm was reported in some patients [1].

Transdermal delivery represents an attractive solution to oral problems. It bypasses the liver first pass effect; hence the bioavailability is expected to be increased. Additionally, it can be simply terminated and removed from the skin, if any of the side effects show up. Furthermore, the use of the vesicular system in the transdermal drug delivery may sustain the release of the drug, thus lowers its frequency of administration [2]. Despite the many advantages of the skin as a site of drug delivery, only few drugs are currently available in the market as transdermal delivery systems. This is because the inherent limitation of transdermal drug absorption, which is imposed by the outermost layer of the skin, the stratum corneum (SC) [3]. From 1991, several researches were focused on transfersomes in transdermal drug delivery system to overcome this intrinsic barrier. Transfersomes can penetrate efficiently various transport barriers, even through the pores or constrictions that would be confining for other particulates of comparable size. This capability is due to the self-adaptable and extremely high deformability of the transfersomes' membrane [4]. In contrast to other methods permeating the skin; transfersomes create drug depots in the skin that can slowly and gradually deliver the material under the skin and/or the systemic circulation without invasion [5]. Transfersomes are complex aggregate, composed of phospholipids, surfactant, and water; prepared by thin film hydration or modified hand shaking, lipid film hydration technique [5].

Analysis and understanding the appropriate combination of independent process and/or formulation variables (factors), which produce the optimized product can be established by statistical design of experiment tools, such as factorial designs. It is considered as the most effective way in estimating the influence of individual process variables with minimum experimentation and time, where all factors are tested in all possible combinations [6]. The aim of the present study was therefore, to develop timolol maleate transfersomal gel formulation by thin film hydration method for transdermal uses. Two 2^3 full factorial designs were employed to optimize and explore the effect of three formulation variables; including phosphatidylcholine: surfactant molar ratio, the solvent volumetric ratio, and the drug amount using two different surfactants (Tween 80 and Span 80). The aforementioned effects were evaluated on each of the particle size of the vesicles, the percentage entrapment efficiency of the drug, and the release rate through synthetic membrane. The optimized formulation was subjected to permeation studies using shaved rat skin and in vivo pharmacokinetics studies were carried out on Wistar rats on the optimized formulation; comparing the results with the oral solution.

Material and methods

Materials

Timolol maleate (TiM) was a gift from Sedico Company (Giza, Egypt). L-α-phosphatidylcholine (PC) (type IV-S) and Span 80 (S80) were purchased from Sigma Aldrich (St. Louis, MO, USA). Tween 80 (T80) was obtained from Scharlau Chemie (Sentmenat, Spain). Carbopol® 934 was supplied by Lubrizol Corporation (Ohio, USA). Naproxen sodium powder was a generous offer from El-Nile Pharmaceutical Chemical Company (Cairo, Egypt). All other chemicals and solvents were of pharmaceutical grade.

Preparation of transfersomes

Transfersomes were prepared by dry thin film hydration method [7]. A mixture of PC and surfactant (SAA) with different ratios was dissolved in 12 mL mixture of chloroform and methanol to form 5% w/v solution. The solvent was removed by rotary evaporation at 55 °C under reduced pressure (Heidolph 2, Schwabach, Germany) till a thin film is produced. The film was hydrated with 10 mL of phosphate buffer saline (PBS) pH 7.4, containing the drug. The formed suspension was subsequently sonicated for 10 min using bath type sonicator at 900H at temperature 25 °C (Jiotech UC-10, Serangoon, Singapore). The suspension was left overnight for maturation of vesicles and kept under vacuum to ensure the removal of residual solvent.