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Synthesis and *in vitro* characterization of chlorpheneramine-laden liposomes for topical applications

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Abstract: This study was aimed at synthesizing liposomes for the topical delivery of chlorpheneramine maleate using three-level factorial design. Each experiment consisted of a varying proportion of cholesterol, lecithin and a permeation enhancer mixture of Tween80 and polyethylene glycol (PEG1000), and resultant liposomes were extensively characterized. The drug release study was conducted at 6.0 pH, 37±1°C temperature and 100 rpm rotation speed utilizing a cellophane membrane pouch in a USP type II dissolution apparatus. Among formulations, L5 was considered as the optimal formulation because of high drug loading (99.05%), 87.71% drug release within 4 hours, high drug loading and the optimized formulation was found to be stable during stability testing. This high drug loading and release was achieved at low level of cholesterol and lecithin (0.1: 0.3g) and high level of permeation enhancer mixture (0.2g) as revealed by the surface plots. The drug release from the optimized formulation followed Fickian diffusion as revealed by Korsmeyers–Peppas kinetic model. In summary, combination of PEG1000 and Tween80 with lecithin and cholesterol can be successfully used to develop liposomes that efficiently incorporated chlorpheneramine. This formulation therefore has the potential to be used as a topical anti-allergic product.

Keywords: Chlorpheniramine maleate, drug release, factorial design, irritation, lecithin, liposomes.

INTRODUCTION

Transdermal drug delivery system (TDDS) is intended for delivering drugs across the dermis or skin into blood circulation to produce systemic effect by topical application. It offers various benefits including avoidance of hepatic first pass metabolism, ease of application and termination of therapy and often more effective than oral therapy for certain clinical issues (Dragicevic and Maibach, 2017, Marwah *et al.*, 2016). For the purpose of drug delivery into and through the skin, different types of pharmaceutical carriers have been used such as nanoparticles, nanoemulsions, microemulsions, liposomes, niosomes, ethosomes and many more (Das Kurmi *et al.*, 2017, Rai *et al.*, 2018, Sinico and Fadda, 2009, Xie *et al.*, 2018). Every carrier has its own advantages and disadvantages and are often chosen on the basis of physicochemical properties of drugs and intended use of the formulation. Liposome is one of the novel drug carrier system comprising of lipid bi-layered structure and are essentially capable of entrapping hydrophilic and hydrophobic drugs at one time (Li *et al.*, 2019). Drugs with high lipophilic properties will be entrapped in lipid domain, whilst hydrophilic drugs will stay in the hydrophilic core of liposomes (Benson, 2017). Conventional liposomes can deliver drugs to skin more efficiently as compared to their counterparts such as nanoparticles. Liposomes can also be made elastic by tweaking the phospholipids and cholesterol contents, and such liposomes withstand stress due to elasticity in the lipid bi-layer and can squeeze through narrow pores of the stratum corneum (Dar *et al.*, 2020, Mishra *et al.*, 2006). Generally, liposomes can cross the stratum corneum, which is the main barrier of skin that controls the ingress of chemicals (Shahzad *et al.*, 2015, Shahzad *et al.*, 2013); however, evidence of liposomes reaching the deeper tissue without breaking is scarce (Benson, 2017). Nevertheless, liposomes remained as the excellent carriers for delivering drugs into and through the skin (Kilian *et al.*, 2015).

Chlorpheniramine maleate (CPM), a first-generation antihistaminic drug, is an amphiphilic amine drug with hydrophobic ring structure and hydrophilic side chains carrying cationic amine groups as depicted in Fig. 1 (Varshosaz *et al.*, 2005). CPM has a mild sedative and good anti-allergic properties; thereby its topical formulations are typically used for the management of sun burns, urticaria, pruritus, angioedema and insect bites (Advenier and Queille-Roussel, 1989). CPM has a molecular weight of 390 Da, an aqueous solubility of 0.55g/100ml at 20°C, a low oral bioavailability 25 – 50% and an extensive hepatic metabolism, which makes it a suitable model drug to be encapsulated in liposomes for topical drug delivery (Soliman *et al.*, 2010).

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