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Development and optimization of pluronic® F127 and HPMC based thermosensitive gel for the skin delivery of metoprolol succinate

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ABSTRACT

The aim of the present investigation was to prepare and optimize suitable combination of polymers hydroxypropyl methylcellulose (HPMC) and pluronic® F127 (PN F127) for the development of thermosensitive gel of Metoprolol succinate (MS) using central composite design (CCD). The effect of formulation factors (concentration of HPMC and PN F127) on responses such as cumulative percentage release (CPR) of MS, bioadhesive force (BF) and viscosity was measured statistically. Quadratic model was found to be best fit model among different models used in the study. The optimum conditions were found to be 0.92% of HPMC and 15% of PN F127. Under these conditions, the predicted CPR, BF and viscosity were found to be 84.94 μg/cm^2, 41.56 gf and 48.94 Pa s, respectively. Ex vivo permeation of MS from optimized thermosensitive gel across abdominal skin of rat demonstrated highest flux (64.35 μg/cm^2/h) for the gel formulation containing 1,8-cineole (5% w/w). The hypotensive activity was performed on normotensive rabbits and the results showed that the optimized formulation prolonged the activity up to 12 h. The above findings indicated that thermosensitive gel of MS for skin application exhibited strong potential against hypertension and expected to provide a better alternative to oral MS formulations.

1. Introduction

Gels are semisolid systems in which a liquid phase is constrained within a three dimensional polymetric matrix (natural or synthetic). The matrix is introduced with a high degree of physical or sometime chemical cross-linking [1]. Based on the liquid medium entrapped, gels are classified in to hydrogel and organogel. Hydrogels are three-dimensional polymeric networks capable of imbibing large amounts of water or biological fluids due to the presence of a large number of hydrophilic groups or domains [2,3]. The main advantage of hydrogel is its biocompatibility, which is due to their high water content and soft consistency similar to natural tissue [2]. Hydrogels can be classified in to thermal gel, cryogel, complex coacervate gels etc. depending on the method of preparation [4].

Thermal gels/thermoreversible gels are the one which undergoes phase transition i.e., solid to liquid/liquid to solid or swelling/shrinking of polymer network with the change in temperature above or below certain temperature called sol-gel transition temperature or critical transition temperature. Pluronic®/poloxamers (PN) are such a group of polymers which exhibits thermoreversible property in aqueous solutions. PNs consist of hydrophobic PPO blocks at the center and hydrophilic PEO blocks on either side to produce a tri-block structure as PEO–PPO–PEO [5]. Among the various grades, PN F127 (poloxamer 407) is widely used as gelling agent in the concentration range of 20–30%. The gelation of PN depends upon both temperature and concentration. The total gelling process of PN is typically divided into two steps. The first step occurs when the temperature is increased in order to reach the critical micelle temperature that resulted in the aggregation of PN monomers to form spherical micelles. In the second step a further increase in the temperature packs the micelles in an orderly manner to form gels [5]. At very low concentrations, PN molecules exist as monomers in solution. Increasing PN concentration up to 10^{-4}% to 10^{-5}% (w/w) leading to critical micelle concentration, where spherical micelles are built up. Further increase in PN concentration results in a tightly packed system with a gel consistency [6,7].

MS is widely used in the treatment of hypertension, angina pectoris, and arrhythmias, due to its β-selective adreno-receptor blocking property [8]. The drug is freely soluble in water and is administered at a dose of 100 mg daily. The half-life of MS is about 3–4 h and it has oral bioavailability of about 50% [9], which is due to

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first-pass metabolism it undergoes by several oxidative pathways including a-hydroxylation, O-demethylation and *N*-dealkylation [10]. Papp et al. (2009) prepared matrix-type patches of metoprolol tartrate (5% w/w) using polymers such as acrylate and two types of metolose and observed that the metolose structure containing hydroxypropoxyl groups (Metolose 90 SH 100.000 SR) form H-bonds with water molecules which initiate the water penetration through the patches thus increasing their free volume holes and consequently the rate and extent of drug [11]. Agrawal and Munjal (2007) developed films composed of different polymers and the results indicated that the maximum release (44%) for metoprolol tartrate was obtained at 48 h and there was a reduction in 27% drug permeation across cadaver skin compared to rat abdominal skin [12]. Currently there is no transdermal gel formulation of MS available in the market with sustained release effect.

Multivariate statistical techniques such as artificial neural networks and response surface methodology (RSM) are being used in different field of research with an intention to minimize the number of experimental trials, to explain the impact of independent variables in the process and finally to obtain the most appropriate formulations with target goals [13,14]. Among the various designs used in the pharmaceutical field, CCD is one of the extremely useful and most popular types of sequential second order experimental design that is used to reduce the number of experimental runs, predicts possible nonlinear affect of each parameter and also linear and quadratic interactions among them [15]. Thus in the present study, a trial was made to develop thermal bioadhesive gel of MS employing CCD and optimize it using Derringer's optimization tool. Further to enhance the permeation of MS various chemical penetration enhancers (PEs) were incorporated in to optimized thermal gel. Finally, in vivo antihypertensive activity was performed on normotensive rabbits.

2. Materials and methods

2.1. Materials

MS was obtained from Poly Drug Laboratories Pvt. Ltd., Maharashtra, India. PN F127 and HPMC K100 M were received as gift samples from Lupin Pharma. Pvt. Ltd., Aurangabad, India and Ranbaxy Laboratories Pvt. Ltd., Gurgaon, Haryana, India, respectively. Dialysis membrane was procured from Hi-media Laboratories Pvt. Ltd., Mumbai, India. All other reagents and chemicals obtained commercially were of analytical grade and used as received.

2.2. Fourier transform-infrared spectroscopy (FT-IR)

The interaction study between drug and polymers was performed by FT-IR method (α-FT-IR spectrophotometer, Bruker Optics, Germany). Individual samples such as MS, HPMC K100 M, and PN F127, physical mixture e.g., MS with HPMC K100 M and MS with PN F127, and finally, the optimized thermal gel sample were analyzed by using KBr pellets technique. Spectral scanning was taken in the wavelength range between 4000 and 500 cm^{-1}.

2.3. Differential scanning calorimetry (DSC)

Differential scanning colorimeter (DSC Q10 V9.4 Build 287, Shimadzu, Tokyo, Japan) was used to perform thermal analysis of pure MS, PN F127, HPMC K100 M and optimized thermal gel in nitrogen atmosphere (50 ml/min). The samples were heated in an aluminum pan from 0 °C to 400 °C at a rate of 10 °C/min.

2.4. Preparation of HPMC K100M – PN F127 gel containing MS

PN F127 possesses reverse thermal gelling property and therefore cold method was adopted to prepare the gel [16]. Weighed PN F127 was slowly added to 4 °C cold distilled water (DW) with continuous stirring. Simultaneously, HPMC K100 M was dissolved in normal DW and stirred. Then, HPMC K100 M solution was added to PN F127 solution with continuous stirring at 4 °C. Accurately weighed MS (5% w/w) was added to above mixture with continuous stirring at 400 ± 10 rpm. The volume was made up to 100 gm with DW. The prepared gel was kept for 24 h at refrigerator temperature until complete dissolution of PN F127. PEs were added just before the evaluation.

2.5. Experimental design

A CCD was used to study the effect of formulation variables on dependent variables and statistically optimize the formulation factors [17,18]. All the independent and dependent variables were mentioned in Table 1. A trial version of Expert-Design software (Version 9.0.3.1, Stat-Ease Inc., Minneapolis, MN, USA) was employed for the statistical analysis. Experimental design of different batches of thermal gel and the obtained responses were presented in Table 2. The optimized formulation batch was selected for further study.

2.6. Drug content uniformity of thermal gels

All prepared gels were analyzed for MS content for desired range of 100 ± 10% [19]. Briefly, 100 mg of gel was taken in 10 ml of DW and mixed for 15 min. After filtration, the filtrate was suitably diluted with DW and the absorbance of the solution was measured at 222 nm spectrophotometrically. The experiments were performed in triplicate.

2.7. pH measurement

The pH was measured using digital pH meter (ELICO LI120, India) by dipping the probe in gel and allowing it to equilibrate. The pH was measured in triplicate.

2.8. Viscosity study of prepared gel

The samples were equilibrated for 30 min in beaker prior to measuring the viscosity. The viscosity determinations of the prepared gels were carried out by Brookfield viscometer (Model DV I PRIME) fitted with spindle 64 at angular velocity of 10 rpm at room temperature (25 °C) and expressed in Pa s.

2.9. Determination of bioadhesive force

Modified balance technique was used to measure the BF of the

Table 1
Variables and their levels in CCD.

Variables	Levels			Star points (α)	
	Low (−1)	Medium (0)	High (+1)	- α	+ α
Independent variables (factors)					
A = HPMC K100 M	0.5%	0.75%	1%	0.39644	1.10355
B = PN 127	15%	20%	25%	12.9289	27.0711
Dependent variables (response)					
R1 = CPR (%)	Maximizing				
R2 = BF (gf)	Maximizing				
R3 = Viscosity (Pa.s)	In the range				