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Formulation optimization and characterization of transdermal film of simvastatin by response surface methodology

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ABSTRACT

Matrix type of simvastatin transdermal film (SSTF) was developed with poly(vinyl alcohol) (PVA) and eudragit RL100 (EG) using response surface methodology (RSM) to investigate combined effect of the selected process variables like SS concentration, PVA:EG ratio and the dibutyl phthalate (DBT) concentration at different levels on dependent variables such as tensile strength and flux, with an aim to optimize a suitable combination of drug, polymer and plasticizer ratio. The study reveals that the effect of DBT concentration was highest on tensile strength, while SS concentration exhibited pronounced effect on SS flux through the abdominal skin of rat. According to Derringer's desirability prediction tool, the composition of optimized film was found to be 2% of SS, 2:1 ratio of PVA:EG and 40% of DBT. Under these conditions, the SSTF exhibited a predicted value of tensile strength and flux of 11.871 MPa and 43.569 μg/cm^2/h, respectively. The in vivo hypolipidemic study conducted for 14 days in hyperlipidemia induced Sprague–Dawley rats reveals that the optimized SSTF exhibited significant lowering of blood lipid level. The absence of skin irritation indicates that the prepared film was safe and well tolerated as transdermal formulation. Thus, the film may serve as an alternative therapy to oral dosage form of SS.

1. Introduction

Hypercholesterolemia is a well-known risk factor for cardiovascular mortality and morbidity among middle-aged and young elderly people [1]. Several studies such as the Framingham Heart Study [2], Multiple Risk Factor Intervention Trial, Johns Hopkins Precursor Study and Bogalusa Heart Study revealed that there is a positive relation between blood cholesterol level and coronary heart disease (CHD) [3]. The high level of blood cholesterol is characterized by elevated level of low density lipid (LDL) (130–159 mg/dl) and triglycerides (TGs) (>150 mg/dl) [4]. The higher blood level of above lipids along with low levels of high density (HDL) has the main role in occurrence of atherosclerosis [5], which in turn lead to CHD. It is well accepted that LDL is the primary target, and non-HDL and apolipoprotein B are secondary targets for hypercholesterolemia [6]. Generally statins are regarded as the drug of choice for the primary and the secondary prevention of hypercholesterolemia [1]. They act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby reduces the biosynthesis of cholesterols [7,8]. Among various statins, SS (chemically referred to as (1S-(1α,3α,7β,8β(2S*,4S*),8αβ))-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4 hydroxy-6 oxo-2H-pyran-2-yl)ethyl)-1-naphtalenyl-2,2-dimethylbutanoate) [9] has been widely used in the treatment of dyslipidemia and hypercholesterolemia [10].

SS belongs to class II of Biopharmaceutics classification system [11] and has poor aqueous solubility (6.3 μg/ml, pH 1–7, at 25 °C) [12], thus exhibiting dissolution rate limited absorption. Due to its slow dissolution rate in the gastro-intestinal tract coupled with extensive first-pass metabolism, about 95% of an oral dose is excreted in feces [13]. In addition, the ideal properties of SS such as molecular weight of 418.566, log p value of 4.7 [14], melting point of 135–138 °C [15], and short oral half-life of 2 h have made the drug a suitable candidate for transdermal delivery.

It was reported that topical or systemic administration of statins may be used in the treatment of various inflammatory dermatological disorders such as alopecia areata, vitiligo, erythema multiform, toxic epidermal necrolysis and psoriasis [16]. A topical ointment formulation of SS was developed and tested for anti-inflammatory activity in acute and chronic models of mice skin inflammation and the result showed a comparable effect to that of produced by dexamethasone [17]. Subsequently, a nanostructured lipid carrier (NLC) was successfully developed for the transdermal co-administration of olanzapine and SS for the treatment of psychiatric disorder associated with dyslipidemia [15]. This NLC formulation took 10 h to reach steady state plasma concentration in rat model and maintained sustained release for next 48 h. The same group of researcher successfully developed NLC of SS in combination with penetration enhancers such as ethanol and limonene and found flux enhancement ratio of 21 times compared to NLC without penetration enhancers [14]. However, the NLC formulation suffers from the limitation that it may lead to degradation of drug and

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carrier and the formulation of super cooled melt which may largely be due to the use of high pressure homogenization techniques and the high percentage of emulsifier used in NLC, respectively [18]. Further, the use of solid lipid makes the formulation costlier. So, a need for a cost effective transdermal formulation, which could deliver SS in sustained manner formed the basic objective of the present investigation.

Among various transdermal systems including membrane moderated, matrix, adhesive matrix, microreservoir, and membrane-matrix hybrid, matrix type transdermal system remains most popular because of its easy manufacturing [19]. PVA is a hydrophilic, nontoxic and biocompatible copolymer of vinyl acetate and vinyl alcohol [20]. Because of its excellent film forming property, PVA is widely used to develop films in combination with other polymers containing number of drugs such as nitrofurazone [21], clindamycin [22], minocycline [23], and gentamycin [24]. In recent years, eudragit acrylic resins, particularly EG and eudragit RS 100, have been widely used to prepare transdermal system because; (i) it has the ability to retain high percentage of active ingredients, (ii) it is well tolerated by the skin [25], and (iii) it has controlled release properties [28]. In addition, they are the zwitterionic copolymers of acrylic and methacrylic esters with pH-independent properties. Thus, a number of drugs such as bromhexine, diclofenac and isosorbide dinitrate, felodipine [26], and pinacidil monohydrate [27] were formulated with EG and eudragit RS 100.

Therefore, the present study was carried out to develop matrix type of transdermal film of SS utilizing RSM and investigated the systemic effect of SS in the lowering of blood lipid level in rat model. The overall RSM consists of two steps. In the first step designing of experimental trials using Box–Behnken 3-level, 3-factorial design technique was carried out, while in the second step optimization of best composition of variables for the transdermal patch was performed employing Derringer's desirability functional method. SS concentration, level of PVA:EG ratio, and DBT concentration were selected as independent variables and tensile strength and flux were chosen as dependent variables. Design-Expert software was used to design trials and to obtain optimized formulation by analyzing response surface plots [28,29].

2. Materials and methods

2.1. Materials

The drug sample of SS (purity >99%) was received as gratis sample from Ranbaxy Laboratories Pvt. Ltd., Gurgaon, Haryana, India. EG was received as gift sample from Evonik Degussa India Pvt. Ltd., Mumbai, India. PVA was procured from Arrow Chemicals Pvt. Ltd., Mumbai, India. Methanol and acetonitrile obtained from Merck Specialties Pvt. Ltd., Mumbai, India. DBT was purchased from Loba Chemie, Mumbai. All other chemicals used in experiment were of analytical grade.

2.2. Thermal analysis

The interaction study was performed by thermal analysis using a differential thermal analyzer (DTG-60, simultaneous TGA/DTA Analyzer, Shimadzu, Japan) with a nitrogen purge of 50 ml/min. Thermal analysis of SS, PVA, EG and the optimized SSTF was performed by heating the samples from 0 °C to 600 °C at a rate of 10 °C/min.

2.3. Experimental design

Preliminary study indicated that the factors such as drug concentration, proportion of PVA and EG and percentage of DBT were majorly influencing the mechanical property of film and flux through the abdominal skin of rat. Therefore, in the present study Box–Behnken statistical design was adopted to optimize the above formulation factors and to evaluate the main effect on responses such as tensile strength of film and flux of SS. All the independent and dependent variables were mentioned in Table 1. Statistical analysis for the present study was performed employing 45 day trial version of Design-Expert software (Version 9.0.3.1, Stat-Ease Inc., Minneapolis, MN, USA). Experimental design of different batches of matrix film and the obtained responses is presented in Table 2.

2.4. Preparation of matrix film

Different batches of matrix film of SS were prepared by solvent casting method as per the composition stated in Table 2. At first, different concentrations of PVA solutions were prepared by heating specified amounts of PVA in 20 ml of HPLC grade water at 90 °C under stirring till a clear and transparent solution was obtained [30,31]. Required quantities of SS, EG and DBT were separately dissolved in solvent mixture of methanol and acetonitrile (50:50) over a period of 2 h. This drug solution was added slowly to previously prepared PVA solution while cooling followed by mixing them thoroughly. The resulted solution was then poured on to mercury layer present in a petri dish. The solvent mixture was allowed to evaporate at room temperature for four days. The dried matrix films were cut into required dimension and wrapped in aluminum foil before being kept in a desiccator.

2.5. Evaluation of physicochemical properties

2.5.1. Drug content uniformity

The drug content analysis was performed by placing films of known area (equivalent to 2 mg of SS) in 10 ml of volumetric flask containing casting solvent mixture. The flasks were shaken in a water bath at 37 °C for 24 h. The solution was then filtered through a Whatman Filter Paper No. 1 and suitably diluted. Measurement of drug content was done with a UV–Vis spectrophotometer (UV-1800, SHIMADZU, Japan) at 238 nm.

2.5.2. Thickness and weight variation

A Digital Vernier Caliper (Mitutoyo, Japan) was used to measure the thickness of the prepared films at different places and then the mean was determined [32]. Weight variation studies were carried out with randomly selected six films (3.141 cm^2) from each batch using analytical balance (Shimadzu, Japan).

2.5.3. Folding endurance

A strip of film of specific area (4 cm × 2 cm) was cut and folded repeatedly at one place till it broke. The number of times the film could be folded at the same place without breaking/cracking was considered as folding endurance [33].

2.6. Mechanical property study

For the measurement of mechanical properties such as ultimate tensile strength (UTS), Young's modulus and elongation at break (EB), film specimen of specific dimension (3 cm × 1 cm) was fixed between two clamps of an Universal tensile testing machine (INSTRON 3366, USA Inc.). The clamps of the tester were covered with silicon gum to prevent slippage of the films during the test. Then, the films were driven

Table 1
Variables and their levels in 3^3 level factorial experimental design.

Variables	Levels		
	Low (−1)	Medium (0)	High (+1)
Independent variables (factors)			
A = SS (%)	0.5%	1%	2%
B = PVA:EG	1:2	1.5:1.5	2:1
C = DBT (%)	20%	30%	40%
Dependent variables (response)			
R1 = tensile strength (MPa)	Maximizing		
R2 = flux (μg/cm^2/h)	Maximizing		