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In vitro permeation and stability studies on developed drug-in-adhesive transdermal patch of simvastatin

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ABSTRACT

The transdermal drug-in-adhesive (DIA) patch of simvastatin (SM) was developed using acrylic adhesives such as DURO-TAK® 87-9301, DURO-TAK® 87-4287, DURO-TAK® 87-235A. The patches were evaluated for in vitro drug permeation across the pork ear skin using diffusion cell and stability studies. Among the three acrylic adhesives used, DURO-TAK® 87-9301 exhibited maximum flux (5.18 ± 0.23 μg/cm^2/h). To further enhance the drug permeation, isopropyl myristate (IPM), D-limonene and 1,8-cineol as penetration enhancers (PEs) were incorporated into the DIA patch prepared from DURO-TAK® 87-9301. Out of those, IPM containing patch exhibited a flux of 16.45 ± 1.67 μg/cm^2/h revealing that IPM is the best PE. The stability study was carried out on optimized fresh (SA4) and 6 months old patches stored at room and at accelerated condition (40 ± 2 °C/75 ± 5%RH) using FTIR, DSC and SEM techniques. Significant shift of peaks were not observed in FTIR spectra and DSC thermograms of the patches after the stability period. SEM micrographs of patches did not show any evidence of recrystallization indicating the presence of drug in the molecular form throughout the adhesive matrix. The investigation reveals that the DIA patch studied as above is stable and may serve as a potential drug delivery system for simvastatin.

1. Introduction

The formulations applied onto the skin surface are broadly categorized into two groups viz. topical and transdermal. Topical formulations deliver drug into local area of skin without systemic exposure. In contrary, transdermal formulations deliver effective concentrations of drugs into systemic circulation and thereby minimizing local effect [1]. With regard to transdermal application, a patch is the most convenient formulation with reference to productivity, cost involved in manufacturing and ease of application [2]. Furthermore, patches meant for transdermal application are usually widely accepted and represent a better replacement when oral administration is difficult such as in case of patient unable to swallow, or may results in erratic absorption (e.g. nausea, vomiting), or is in coma [3].

Transdermal patches are basically classified into three types viz. reservoir, polymer matrix monolithic or multi-laminate drug-in-adhesive (DIA) and microreservoir. A monolithic DIA patch is composed of an active ingredient, additives, pressure-sensitive-adhesive (PSA) [4,5] backing film and release liner [2]. DIA patch system has advantage over other patches due to its small size and thickness, better flexibility, uncomplicated production process, straightforward design and patient choice [6–8]. Moreover, dose adjustment, for example for patients with impaired hepatic or renal functions, can easily be attained by cutting/dividing the patch [9]. In case of DIA patch system, drug incorporated adhesive layer is in contact with the skin surface after application. Therefore, the selection of a suitable adhesive is important. Frequently used PSA polymers in transdermal DIA patch are polyisobutylenes, silicones and acrylics [10–12].

The outer layer of skin is stratum corneum (SC), which only allow lipophilic drugs with small molecular weight (< 500 Da) to penetrate via passive diffusion to reach systemic circulation in desired concentration [13]. As a result only a limited number of transdermal therapeutic systems (TTS) are available commercially. Presently, two approaches such as chemical and physical have been employed to enhance permeation of drugs across the skin in order to attain therapeutic concentration in blood. The chemical approach using penetration enhancers (PEs) has been considered most often for the development of successful DIA patches [2].

Simvastatin (SM) belongs to statin class of hypolipidemic drug whose mechanism of action is to inhibit 3-hydroxy-3-methylglutaryl

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coenzyme A (HMG-CoA) reductase and thereby decreases the biosynthesis of cholesterol [14]. SM exhibits poor aqueous solubility of 6.3 μg/ml at 25 °C, leading to poor absorption across the gastro-intestinal tract [15]. SM is considered as suitable candidate for transdermal drug delivery as it undergoes substantial pre-systemic metabolism in liver. In addition, it has molecular weight less than 500 Da (418.566), low melting point of 135–138 °C, [16] and short oral half-life of 2 h [17]. Extensive review of literature could not show any appreciable work on DIA patch of SM.

In the earlier investigation the researchers have successfully developed the matrix [17] and reservoir [18] type of transdermal drug delivery system (TDDS) of SM. The matrix patch of SM was prepared with polyvinyl alcohol (PVA) and eudragit (EG) in different ratio as polymer and dibutyl phthalate (DBT) as plasticizer using Box-Behnken design. At the optimum condition of 2% of SM; 2:1 ratio of PVA:EG; and 40% of DBT, values of tensile strength and flux (dependent variables) were found to be 11.871 MPa and 43.569 μg/cm^2/h, respectively. In the later study the effect of independent variables such as percentage of SM, poloxamer 407 (PX 407), and D-limonene on Q48 (cumulative amount of drug permeated per unit area after 48 h of permeation study) were studied employing Box-Behnken design. The highest Q48 (76.94 μg/cm^2) of SM across full thickness human cadaver skin was exhibited by the formulation composed of 1.5% w/w of SM, 25% w/w of PX 407 and 10% w/w of D-limonene. Furthermore, SM permeation was found to be increased with the increase in SM and D-limonene concentration. Recently, a monolithic DIA patch for co-delivery of SM and olanzapine was developed, wherein the drugs were encapsulated in nanostructured lipid carrier (NLC) and then incorporated into patch [19]. In the present study, both passive (using NLC and PEs) and active methods (pre-treatment of skin with dermaroller) were used and the result showed that propylene glycol as PE exhibited highest permeation rate.

One of the major problems of these patches is the crystallization of drug in the matrix upon storage. According to Fick's law of diffusion, the amount of dissolved drug in the matrix determines the drug release. Thus, drug re-crystallization can have a grave consequence on the drug release and eventually the therapeutic efficacy suffers. Furthermore, re-crystallization of drug may have effect on the adhesive properties of the patch. It was observed from the previous studies that the adsorption of drug such as ethyl estradiol and levonorgestrel onto the insoluble carrier cross-povidone (CPVP) prevented the drug re-crystallization [10,20]. This was attributed to the formation of hydrogen bond between the drug and CPVP thereby prevented the drug molecules from forming nuclei and subsequently crystal formation.

The concept of stability in pharmaceutics is understood as the ability of a pharmaceutical product to retain its properties within the specified limits throughout its declared shelf life [21]. Investigations/tests must be carried out according to international standards to define shelf life of a drug which provide information about various aspects of stability such as chemical, physical and microbiological [22]. Therefore, there is an intense need to study the stability aspects of drug in different types of patches along with other characterization. The objectives of the current research were to develop DIA patches of SM employing three different grades of acrylic adhesives and to study the effect of PEs on in vitro permeation of SM across ear skin of pig and assess the stability potential of selected patch at room and accelerated conditions for six months so as to throw some light on the shelf life of the formulation apart from conducting mechanistic study on treated and untreated skin specimens using histopathology technique.

2. Materials and methods

2.1. Raw materials and chemicals

SM (99.1% w/w) was a generous gift of Ranbaxy Laboratories Pvt. Ltd., Gurgaon, Haryana, India. Acrylic adhesives such as DURO-TAK® 87-9301, 87-4287, 87-235A were received as gift samples from Henkel electronic material LLC, 825 Cedar springs RD, Salisbury, NC 28147, US. The properties of acrylic adhesives were made supplementary. Polyster film laminate (ScotchPak™ 1012) backing layer, fluoropolymer coated polyster film (ScotchPak™ 1022) release liner were received as gift sample from #M Pharmaceuticals (St. Paul, MN, USA). Isopropyl myristate (IPM) was purchased from Sisco Research Lab., Mumbai, India. 1, 8-Cineole was procured from Merck Specialties Pvt. Ltd., Mumbai, India and D-limonene was obtained from Loba Chemie, Mumbai, India. Remaining chemicals used in the investigation were procured from standard and reliable sources.

2.2. Pre-formulation study

2.2.1. FTIR analysis

In order to investigate possible interaction between SM and PSAs, FTIR study was performed on pure drug and physical mixtures of drug with PSAs (1:1) employing α-FTIR, Bruker Optics, Germany. The analysis was performed by KBr pellet method with frequency ranges from 4000 to 400 cm^{-1}. The samples were dried prior to the analysis. The FTIR study was also performed on selected fresh patch, and patches before and after stability study.

2.2.2. DSC study

DSC measurements on SM and its physical mixtures with PSAs, and selected DIA patch before and after stability study were performed using a Differential scanning calorimeter (DSC Q10 V9.4 Build 287 with TDA), Shimadzu, Japan. Upon removal of the moisture from the sample by heating, accurately weighed (5 mg) sample was transferred into a standard aluminium crucible. Empty pan was used as reference. Heating of samples was done at a rate of 10 °C/min over a temperature range of 20–400 °C [10].

2.3. Preparation of patch

SM incorporated transdermal patches were prepared with various acrylate adhesives viz. DURO TAK® 87-9301, 87-4287, 87-235A and PEs such as IPM, D-limonene, 1,8-cineole by solvent evaporation technique [2,7] as per the details furnished in Table 1. Weighed amounts of SM and PEs were dissolved in ethyl acetate. PSAs were added to the above solution and agitated at room temperature for 30 min and the mixed solution was cast at a thickness of 400 μm on a polyster film (ScotchPak™ 1022) release liner with a micrometer adjustable film applicator (Culture Instruments, Bangalore, India). They were kept at room temperature for 24 h for evaporation of the residual solvent. The patches were then laminated with polyster film laminate (ScotchPak™ 1012) backing layer and cut into cut into suitable sizes (figure was made supplementary), packed in aluminium foil, and stored at ambient temperature until further study. The final dry thickness of the DIA matrix was fixed at 100 μm. The PEs were incorporated to the selected patches containing DURO TAK® 87-9301.

Table 1
Formulation of different DIA patches of SM.

Ingredient (% w/w)	Formulation code					
	SA1	SA2	SA3	SA4	SA5	SA6
SM	2	2	2	2	2	2
DURO TAK® 87-9301	98	–	–	93	93	93
DURO TAK® 87-4287	–	98	–	–	–	–
DURO TAK® 87-235A	–	–	98	–	–	–
IPM	–	–	–	5	–	–
D-Limonene	–	–	–	–	5	–
1, 8-Cineole	–	–	–	–	–	5

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