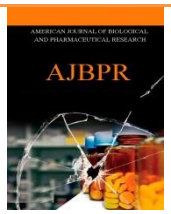
e - ISSN - 2348 - 2184
Print ISSN - 2348 - 2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr



EFFECT OF PERMEATION ENHANCERS IN DUAL RELEASE TRANSDERMAL PATCH

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Article Info

Received 25/12/2013
Revised 15/01/2014
Accepted 18/01/2014

Key words: Dual Transdermal Patch, Permeation enhancers, Dimethyl sulfoxide, HPMC.

ABSTRACT

Dual Release Transdermal patch containing Metoprolol tartarate and Metformin hydrochloride was prepared by using Hydroxy Propyl Methyl Cellulose as a polymer by solvent evaporation method. In this study the main objective was to investigate about the effect of permeation enhancers in Dual release transdermal patch. Due to the hydrophilic drugs used in the formulation there was in need to enhance the permeability of drugs through the skin. by using permeation enhancers like Dimethyl sulfoxide (DMSO), Pluronic F68 and Propylene glycol, six dual release transdermal patches were formulated excluding control batch i.e., patch without permeation enhancers. The formulated dual transdermal patches were evaluated for the invitro drug permeation studies. From the results is was concluded that the patch with 10 % DMSO shows best invitro drug permeation datas through the mice skin, it permeated most efficiently than other patches containing Propylene glycol and Pluronic F68 as enhancers. So it was concluded that DMSO was the best optimized permeation enhancer for dual release transdermal patch.

INTRODUCTION

Permeation enhancers are the compounds can promote skin permeability by altering the skin as a Barrier to the flux of a desired penetrant. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They modify the protein -lipid packaging of stratum corneum, by this chemically modifying the barrier functions leading to enhanced permeability. The drug permeation across the skin obeys Fick's first law [1]

$$\frac{dm/dt = J = DC_0 P}{h}$$

where, J= steady-state flux
D= diffusion coefficient of the drug in the stratum corneum
h= length or membrane thickness
P= partial coefficient between the stratum corneum and the vehicle
C_0= applied drug concentration.
where D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as the membrane resistance.
Enhancement of flux across membranes reduces to considerations of:

- Thermodynamics (lattice energies, distribution coefficients)
- Molecular size and shape
- Reducing the energy required to make a molecular hole in the membrane

The permeation enhancers are classified as follows

Solvents: These compounds increase penetration possibly by swelling the polar pathway. Examples include water

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alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide, dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyil, 2-pyrrolidone; laurocapram (Azone) miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. These compounds are, however, skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactants can penetrate and interact strongly with the skin. Once these surfactants have penetrated the skin, they can induce large alterations. Cationic surfactants are reportedly more irritant than the anionic surfactants, the nonionic have long been recognized as those with the least potential for irritation and have been widely studied. Examples of commonly used surfactants are:

Anionic surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic surfactants : Pluronic F127, Pluronic F68, etc

Bile salts : These systems apparently open up the heterogeneous multi-laminate pathway as well as the continuous pathways. Examples include: propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid

Miscellaneous chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-tolumide; calcium thioglycolate; anti-cholinergic agents.

In all transdermal patches, the drug is stored in a reservoir that is engulfed on one side with an impermeable backing laminate and has an adhesive layer on other side. In some designs drug is dissolved in a liquid or gel-based reservoir, which can simplify formulations and permit the use of liquid chemical enhancers like ethanol. These designs composed of four layers: an impermeable backing membrane followed by drug reservoir with a semi-permeable membrane that may serve as a rate-limiting barrier; and an adhesive layer at the bottom.[2]

The first-generation approach to transdermal drug delivery is limited primarily by the barrier posed by skin's outermost layer called stratum corneum, which is 10 to 20 µm thick. Underneath this layer is the viable epidermis, which measures 50 to 100 µm and is avascular. Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Closer examination of the stratum corneum barrier reveals a brick and mortar structure, where the bricks represent non-living corneocyte cells composed primarily of cross-linked keratin and the intercellular mortar is a mixture of lipids organized largely in bilayers. Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.[1,2]

The second generation of transdermal drug delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should have the following characters like increase skin permeability by reversibly disrupting or altering the stratum corneum structure, providing an added driving force for transport the drug into the skin. However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-conventional methods like ultrasound, have struggled with the balance between achieving increased delivery of drug across stratum corneum, simultaneously protecting deeper tissues from damage. As a result, this second generation transdermal delivery systems has advanced and novel clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and systemic applications.

Conventional Chemical Enhancers

Recognizing the need to increase skin permeability, second-generation delivery strategies have turned efficiently to the development of chemical enhancers. Many effective chemical enhancers disrupt the highly ordered bilayer structures of the intracellular lipids found in stratum corneum by inserting amphiphilic molecules into these bilayers to disorganize or alter the molecular packing or by extracting lipids using solvents and surfactants to create lipid packing defects of nanometer dimensions. Hundreds of different chemical enhancers have been studied, including off-the-shelf compounds and others specifically designed and synthesized for this purpose, such as Azone (1-dodecylazacycloheptan-2-one) and SEPA (2-n-nonyl-1,3dioxolane).

Liposomes, dendrimers and microemulsions have also been used as chemical enhancers with supramolecular structure that can not only increase skin permeability, but also increase drug solubilization in the formulation and drug partitioning into the skin. Their supramolecular size generally precludes penetration into the skin and thereby helps localize effects to the stratum corneum. These approaches have found success for enhanced delivery of some small molecules, especially for topical

dermatological and cosmetic applications. A highly deformable liposome formulation is currently in clinical trials for insulin delivery.

Another transdermal delivery approach that has been applied is the use of prodrugs. Through the addition of cleavable chemical groups that typically increases drug lipophilicity, such prodrugs can facilitate the transfer of a drug across the skin. This is accomplished by adding, for example, alkyl side chains with enzymatically cleavable linkers, such as esters or carbonates. One prodrug approach relies on the linkage of either two of the same or two different small molecule drugs to each other by a labile bond, which reduces their hydrophilicity, albeit at the expense of increasing molecular weight.

Because the prodrug approach is based on altering drug structure, as opposed to skin structure, prodrugs can avoid skin irritation. Even so, advancement of this field has been limited by the complexity of prodrug design, the applicability of the approach only to small molecule drugs and the need to gain US Food and Drug Administration (FDA) approval of the prodrug as a new chemical entity (rather than approval only of the transdermal delivery route for an already approved drug) [1-3].

MATERIALS AND METHODS

Material Used

Metformin hydrochloride, Metoprolol tartarate samples are obtained as a gift sample from Microlabs pvt ltd., Hosur, India., Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose (EC), Poly Ethylene Glycol (PEG), Chloroform and Propylene glycol, Pluronic F 68 , DMSO (Dimethyl sufoxide) are used as permeation enhancers was received from Chem. scientifics, Chennai. All the other solvents and chemicals used in this project are belongs to analytical grade.

Formulation of Dual Transdermal patch by Solvent evaporation method

Dual Transdermal patches of Metformin hydrochloride and Metoprolol were prepared by solvent evaporation technique. This was prepared separately by using different types of polymers like HPMC and EC with different concentration along with suitable solvent and permeation enhancers. The polymers are dissolved in suitable solvent to get polymer solution; and then Metformin Hcl and Metoprolol tartarate was added in the ratio of 1:1to the above polymer solution and stirred continuously until both the drugs and polymer are soluble to get a clear solution. To this polymer drug solution add poly ethylene glycol (PEG) used as plasticizer to increase the plasticity of the transdermal patch. And then add permeation enhancers like Dimethyl sulfoxide (DMSO), Pluronic F68, Propylene glycol with different concentration with continuous stirring to this solution. To avoid air bubbles keep the solution in bath sonicator for half an hour. Glass petridish was taken with a partition made by aluminium foil at the center equal half was taken and lubricated. Then the prepared solution i.e., Metformin and Metoprolol containing polymer solution was spread separately uniformly in this petridish, so that two solution separated by the aluminium foil partition. The mould was kept for one day and then the dried patches were then detached from the petridish and were stored in desiccators for further use. The formulation are shown in table no 1. [4].

EVALUATION OF PERMEATION ENHANCERS EFFECT IN DUAL TRANSDERMAL PATCH

Drug content uniformity

The uniformity of drug content of the dual transdermal film was determined, based on dry weight of drug and polymer used by means of a UV/VIS spectrophotometer method. The formulated patch was cut into pieces and dissolved in 10 ml of ethanol. The resulting solution was quantitatively transferred to volumetric flasks, and appropriate dilutions were made with phosphate buffer pH 6.8 and filtered through 0.22 µ filter and analyzed for Metformin hydrochloride content at 276 nm and Metoprolol tartarate content at 274 nm by using UV/VIS spectrophotometer. 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then dual transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the dual transdermal patches pass the test [5,6].

Invitro Permeation study

The *invitro* diffusion study of formulated dual transdermal patches of Metformin-Metoprolol was carried out by using excised mice abdominal skin and Franz diffusion cell. The skin was sandwiched between donor compartment and receptor compartment of the diffusion cell. A 2.2 cm^2 diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon star headed bead was placed in the receptor compartment filled with 12ml of 6.8 Phosphate buffer. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5˚C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24h; simultaneously replacing equal volume by phosphate buffer pH 6.8 after each withdrawal should be done to maintain a sink condition.

The samples were analyzed spectrophotometrically at 276nm for Metformin hydrochloride and 274 nm for Metoprolol tartarate. And the reading are tabulated and graphed by using prism software [6-9].

Primary skin irritation Study

The patches were tested for their potential to cause skin irritation in mice. Transdermal systems (blank and drug loaded) were applied onto nude skin of animals and observed for any sign of redness, itching, erythema and edema for a period of 24 hr. A 0.8% v/v aqueous solution of formalin was applied as standard irritant. The animals were applied with new patch/ formalin solution each day up to 7 days. Finally the application sites were graded according to a visual scoring scale, the erythema results was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. And the edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. Finally the skin of animal was send for histological examination if necessary [7-11].

RESULT AND DISCUSSION

***Invitro* skin permeation studies**

Dual transdermal patch containing Metformin hydrochloride and Metoprolol tartarate was attempted. All the patches were found to be most elegant, thin, flexible, smooth, and transparent. The mean (n = 3) cumulative amounts of drug diffuse through the sliced mice skin (*in vitro* skin permeation) were performed for 12 hours ,analyzed and their results are shown in Figure no:1. Among this six formulation P4 shows better release or skin permeation pattern i.e., 84.45±2.54% for Metformin Hydrochloride and 88.24±2.40% for Metoprolol tartarate in 12 hrs, this shows that P4 containing permeation enhancer i.e., DMSO 10% produce better permeability of drug through the skin than other patches. The invitro skin permeation for other patches are shown in table no 2 & 3.

Drug content Uniformity

The drug content uniformity was determined using UV spectrophotometric method for all the five formulations and the results of the drug content of formulated Dual Transdermal patches varies between 72.84±2.38% to 85.94±4.50% for Metformin hydrochloride and 82.68±4.80% to 89.54±4.28 % for Metoprolol tartarate. It concludes that the drug content is uniform throughout all the patches and maximum amount of drug was undergone in matrix formation with HPMC polymer.

Skin irritation studies

Primary skin irritation studies revealed that after 24 hrs there is no stain, inflammation or rashes in the mice skin, which was shown in Figure no: 2.It shows that the patches with permeation enhancers are biocompatible with the skin.

Table 1. Dual transdermal patches Formulation

Sl. no	Formulation code	Ingredients in mg and %					
		Metformin	Metoprolol	HPMC	DMSO	Propylene Glycol	Pluronic F68
1	P0	20	20	1:1	-	-	-
2	P1	20	20	1:1	5 %	-	-
3	P2	20	20	1:1	-	5%	-
4	P3	20	20	1:1	-	-	5%
5	P4	20	20	1:1	10%	-	-
6	P5	20	20	1:1		10%	
7	P6	20	20	1:1	-	-	10%

Table 2. Effect of Permeation Enhancers in Metformin *invitro* permeation Studies - P1-P6 Dual Transdermal Patch

Time in hrs	Formulation													
	P0 (Without Permeation enhancers)		P1 (5% DMSO)		P2 (5% PG)		P3 (5% Pluronic F68)		P4 (10% DMSO)		P5 (10% PG)		P6 (10% Pluronic F68)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	2.26	1.20	5.15	1.45	5.25	0.25	5.56	1.24	6.40	1.43	6.40	1.43	6.40	1.43
2	4.15	1.05	11.87	1.02	10.89	1.24	10.89	1.92	20.24	1.88	16.24	1.88	16.24	1.88
4	8.29	2.19	28.36	1.30	14.43	2.23	12.45	2.00	30.40	2.32	26.40	2.32	26.40	2.32
6	16.36	2.36	32.87	2.00	26.31	2.00	25.90	2.48	44.62	2.64	35.62	2.64	35.62	2.64
8	23.80	2.00	44.14	2.14	30.67	2.08	32.98	2.62	54.00	2.00	44.00	2.00	44.00	2.00
12	31.28	3.48	62.78	2.78	43.10	2.00	56.20	2.00	**84.45**	**2.54**	62.44	2.00	74.44	2.00

Table 3. Effect of Permeation Enhancers in Metoprolol *invitro* permeation Studies - P1-P6 Dual Transdermal Patch

Time in hrs	Formulation													
	P0 (Without Permeation enhancers)		P1 (5% DMSO)		P2 (5% PG)		P3 (5% Pluronic F68)		P4 (10% DMSO)		P5 (10% PG)		P6 (10% Pluronic F68)	
	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean
1	1.54	1.20	5.60	1.45	3.80	1.66	4.68	2.00	8.54	1.56	6.98	2.34	6.74	1.88
2	3.64	1.05	10.84	2.00	8.24	2.00	9.82	1.92	22.86	2.04	18.54	2.08	20.64	1.56
4	4.28	2.19	28.36	1.45	22.56	2.23	26.00	2.00	32.80	2.32	25.83	2.70	28.94	2.00
6	13.48	2.36	32.87	2.00	28.90	2.08	30.54	2.60	48.64	2.64	35.88	2.06	44.82	2.54
8	19.78	2.00	42.38	2.20	32.84	2.08	46.62	2.86	68.90	2.08	46.94	2.00	56.24	2.60
12	36.54	2.00	66.94	2.66	40.62	2.54	54.44	2.00	**88.24**	**2.40**	64.80	2.54	78.38	2.40

Figure 1. Effect of Permeation Enhancers in *Invitro* Diffusion Studies

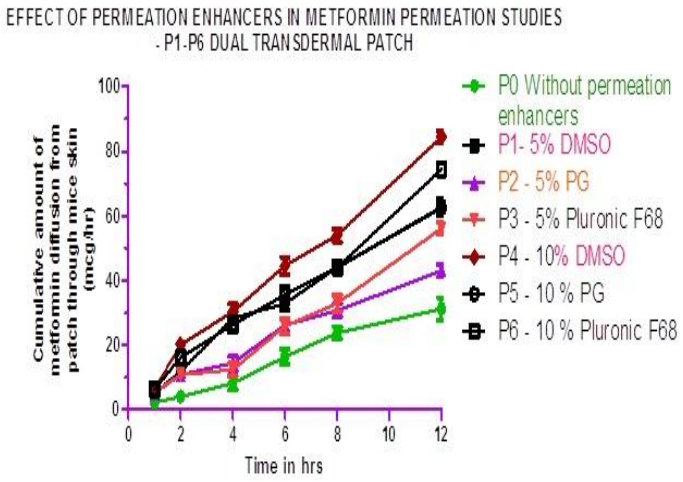
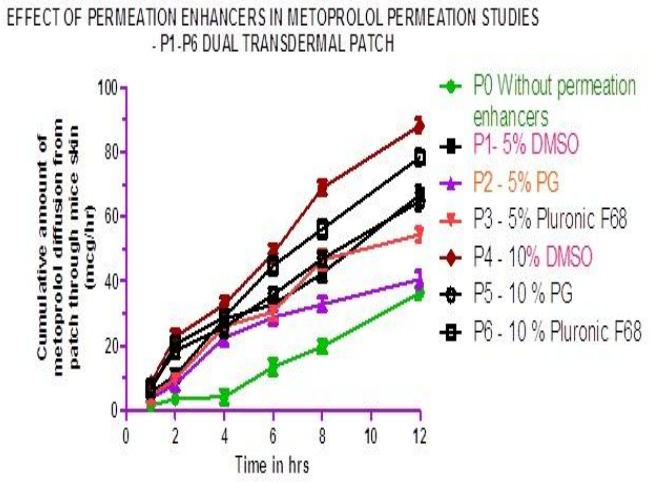
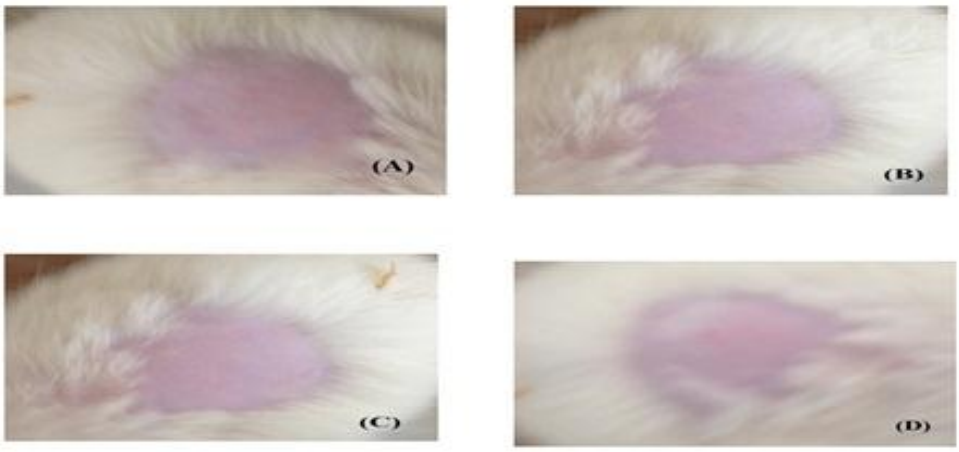


Figure 2. Skin irritation studies – Showing no rashes or edema after removal of patch from mice skin



Photographs of rats showing the skin irritation test for Best formulation M 1. (After removing the patch)
(A) control and (B) after 1 h (C) After 24 h and (D) after 48 h



CONCLUSION

From the results is was concluded that the patch with 10 % DMSO shows best invitro drug permeation datas through the mice skin, it permeated most efficiently than other patches containing Propylene glycol and Pluronic F68 as enhancers. So it was concluded that DMSO was the best optimized permeation enhancer for dual release transdermal patch.

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