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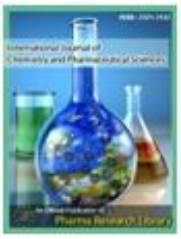

Research Article **Open Access**

Formulation and Evaluation of Microemulsion Based Gel System for the Transdermal Delivery of Isradipine

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A B S T R A C T

Isradipine (ISDP) is an effective calcium channel blocker used in the treatment of hypertension. It undergoes extensive first pass metabolism and bioavailability through the oral route is only about 15 to 24%.The purpose of the present study was to formulate and evaluate the microemulsion based transdermal therapeutic system for isradipine (ISDP). Pseudo ternary phase diagrams were constructed to determine the region of existence of microemulsions prepared using phase titration method. The formulations were developed using isopropyl myristate, tween 80 and PEG 400. Optimization of formulations was done based on solubility studies. The microemulsion was gelled using carbopol 934 as the gelling agent. The formulations were evaluated for percent drug content, pH, particle size, zeta potential, polydispersity index, conductivity, viscosity, percent transmittance, in vitro and ex vivo diffusion studies. The formulations B1 and B2 exhibited satisfactory physicochemical characteristics. The cumulative amount of isradipine permeated after 24 h was found to be 4270.11±59.85 µg/hr/cm^2. The calculated flux for ISDP was found to be higher than the target flux based on which it can be further evaluated for pharmacokinetic and pharmacodynamic studies.

Keywords: Isradipine, carbopol 934, microemulsion

A R T I C L E I N F O

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1. Introduction

Transdermal Drug Delivery

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation. Topical drug administration is localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system For the topical treatment of dermatological diseases as well as skin care, a wide variety of vehicle ranging from solids to semisolids and liquid preparation is available to clinician and patients. Within the major group of semisolid preparations, the use of transdermal gels has expanded both in cosmetics and in pharmaceutical preparations.

Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compared to creams and ointments. [1] Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.

Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.[2]

Microemulsions

In 1959, Schulman et al. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions". Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co surfactant with a droplet size usually in the range of 20-200 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. Microemulsions as drug delivery tool show favorable properties like thermodynamic stability (long shelf-life), easy formation (zero interfacial tension and almost spontaneous formation), optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity) and very small droplet size. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion. Microemulsions are easy to administer to children and to people who have difficulty swallowing solid oral dosage forms. A self microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions. It has also been referred to as microemulsion preconcentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility. The nanosized droplets have very high surface to volume ratios which are able to efficiently solubilize the drug. The drug is released in a more reproducible manner which will become less dependent on the GI physiology and the fed/fasted state of the patient. Since the drug delivery system should be mild and biocompatible, the choice of excipients is, however, limited.

2. Materials and Methods

Materials: Isradipine, Oleic acid, Iso propyl myristate, Iso propyl alcohol, Propylene glycol, Polyethylene glycol 400, Polyethylene glycol 600, Sunflower oil, Tween 20, Tween 80, Glycerol, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium chloride, Carbopol 934, Triethanolamine, Methyl paraben, Methanol, Dialysis membrane.

Methodology

Formulation Optimisation

a. Selection of method of preparation

Microemulsions were prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed.

b. Selection of oil

Literature survey revealed the use of oleic acid, isopropyl myristate and sunflower oil for preparation of microemulsion. Isopropyl myristate was selected as oil because of its easy availability and low cost.

c. Selection of surfactant

Literature survey revealed the use of tweens (tween 20 and tween 80) as surfactants. Tween 80 was selected as a surfactant for the preparation of microemulsion. Selection of surfactant was done on the basis of solubility criteria**.**

d. Selection of co-surfactant

Literature survey revealed the use of isopropyl alcohol, glycerol, and propylene glycol, polyethylene glycols (PEG 400 and PEG 600) for preparation of microemulsion. PEG

400 was selected as a co-surfactant. Selection of co-surfactant was done on the basis of solubility criteria.

Optimized method for preparation of Microemulsion:

The isradipinemicroemulsion was prepared by phase titration method employing isopropyl myristate as oil, tween 80 as surfactant and PEG 400 as co-surfactant. Oil phase, Isradipine, co-surfactant and surfactant were mixed to form an emulsion. To this mixture, water was added drop wise under continuous mechanical stirring.

Preparation of ME based Gel:

Microemulsion gel was prepared using carbopol 934 as the gelling agent. Methyl Paraben was dissolved in sufficient amount of water with the aid of heat at 37^{O}C and allowed to cool. Carbopol was hydrated by soaking in water for a period of 24 hours and was added to paraben. Triethanolamine was then added to the swollen polymer to form a gel. Microemulsion was gelled by adding the aqueous portion (gelling agent) to the nonaqueous portion (microemulsion) with continuous mechanical stirring.

3. Results and Discussion

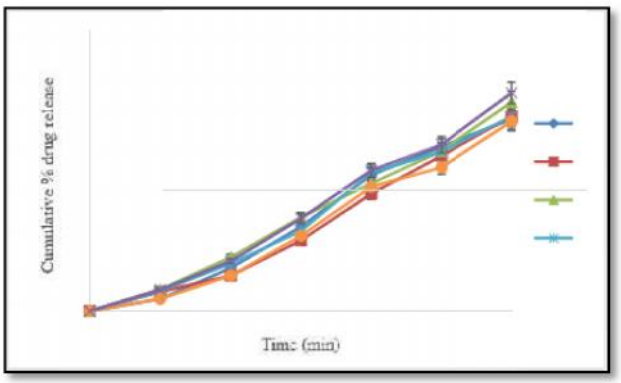

Figure 1: *In-vitro* release profile of isradipine from formulations

In vitro drug release study was performed for 6 formulations from A1 to C1 which showed the sustained release of drug. Based on these study formulations B1 and B2 which showed maximum % drug release of 89.2% and 93.14% respectively were selected for further evaluation tests.

Percentage drug content:

The drug content of microemulsion formulation was determined by using the U.V spectrophotometer keeping blank microemulsion as control at wavelength 328 nm.

Particle size distribution, polydispersity index, zeta potential and conductivity: Physical characteristics of microemulsion (particle size distribution, polydispersity index, zeta potential and conductivity) were determined by using Dynamic light scattering (DLS) method using a zetasizer. Fig. 15, 16, 17 and 18 show particle size distribution and zeta potential of the formulations B5 and B4 respectively. Table 15show particle size distribution, polydispersity index, zeta potential and conductivity of the formulations.

Ex vivo permeation studies

The results of *ex vivo* drug permeation studies from ME formulations were shown in Table 17, 18 and Fig. 19. The formulation B2 exhibited the greatest (4270.11±59.85µ g/hr/3.14cm^2) cumulative amount of drug permeation, which was significantly different compared to the lowest value observed with the formulation B1 (4011.12±58.83µg/hr/3.14cm^2) in 24 hrs. The flux obtained with formulation B2 was found to be maximum (43.16±1.33µ g/hr/cm^2) and the permeability coefficient was maximum (5.75±0.37cmh^{-1} x10^{-2}) as shown in table 19.

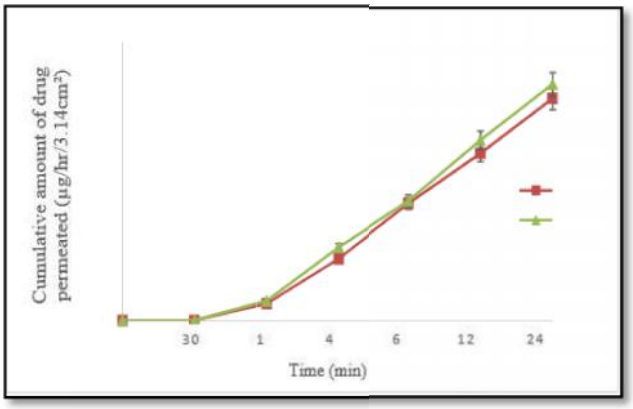

Figure 2: Ex vivo permeation profile of isradipine from formulations B1 and B2

Ex vivo permeation profile of ISDP was carried out on the optimized microemulsion formulations B1 and B2 after considering their *in vitro* release profile and the results have been shown in Figure 19. After 24hrs, the cumulative amount of drug permeated from the microemulsion formulation B1 and B2 was 4011.12 and 4270.11 µg/hr/cm^2 respectively. From this study, it can be concluded that the extent of diffusion of ISDP from the microemulsion may be due to the penetration enhancing effect of surfactant and co-surfactant present within the microemulsion formulation. The rather small particle size of the microemulsion formulation can also help this matter. The sustained profile of drug permeated observed may be due to the fact that drug is present within the oil phase and hence has a higher partition coefficient. The calculated target flux for ISDP was 36.68 µg/hr/cm^2. The flux value for formulations B1 and B2 were found to be higher than the target flux.

Table 1: *In-vitro* % drug release from the formulations

Time	% Drug release					
	A1	A2	B1	B2	B4	C1
0	0	0	0	0	0	0
30	5.1±0.18	8.21±0.29	9.13±0.34	9.14±0.37	8.56±0.29	5.23±0.26

1	18.4±0.54	15.12±0.45	23.0±1.1	21.32±1.11	20.3±1.63	15.2±1.43
4	36.11±2.1	30.13±1.98	40.0±2.43	39.53±2.65	34.11±2.11	32.19±2.40
6	58.12±2.98	50.1±2.01	54.43±2.66	60.01±2.16	59.12±2.95	53.03±2.11
12	70.1±3.1	66.29±2.87	68.32±2.98	71.05±3.10	68.12±2.99	61.38±2.67
24	82.0±4.13	83.1±4.65	89.2±5.12	93.14±5.93	83.1±4.12	81.05±4.11

Table 2: Drug content of Microemulsions

Formulation	% drug content
B1	99.6±0.41
B2	99.3±0.35

Table 3: Particle size, PI, zeta potential and conductivity

Formulation	Particle size	Polydispersity index	Zeta potential	conductivity
B2	24.0 nm	0.075	-25.6mV	0.082mS/cm
B1	261.9 nm	0.301	-21.0mV	0.075mS/cm

4. Conclusion

Microemulsions were prepared using isopropyl myristate as oil phase, tween 80 as surfactant and PEG 400 as co-surfactant. Pseudoternary phase diagrams were used to determine the region of existence of Microemulsions prepared using phase titration method. Optimization of formulations were done based on solubility studies. The prepared Microemulsion systems were evaluated for physicochemical characteristics, mainly *in vitro* release and *ex vivo* permeation. The *ex vivo* permeation studies were carried out across rat abdominal skin using Franz diffusion cell. The formulations B1 and B2 exhibited satisfactory physicochemical characteristics and their calculated flux was more than the target flux based on which it can be further evaluated for pharmacokinetic and pharmacodynamic studies.

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