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Review Article

A REVIEW: NANOEMULSION AS VEHICLE FOR TRANSDERMAL PERMEATION OF ANTIHYPERTENSIVE DRUG

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ABSTRACT

Hypertension is a chronic disease which required lifelong therapy. But most of antihypertensive drugs available today, showed extensive first-pass metabolism and low oral bioavailability which can be overcome by preparing its Transdermal Drug Delivery Systems. It enhances the drug permeation through the skin which can be achieved by using chemical enhancers and various solvents. Use of chemical enhancers is limited for its chronic application as it causes irritation at the site of application. It is therefore desirable to develop a topical vehicle instead of chemical enhancers for formulating transdermal drug delivery system. Microemulsion or nanoemulsion technique proved to be one of the most promising techniques for enhancement of transdermal permeation of drugs. The present article reviewed the transdermal (nanoemulsion or microemulsion) formulation of various antihypertensive drugs and their methodology in detailed.

Keywords*:* Transdermal Drug Delivery Systems, Nanoemulsion, Antihypertensive drug

INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are one of the most rapidly advancing areas of novel drug delivery, which are designed to deliver a therapeutically effective amount of drug across a patient's skin [1]. The first commercially available TDDS patch of scopolamine was approved by the U.S Food and Drug Administration in December 1979 for treatment of motion sickness.

Advantages of Transdermal Drug Delivery System [2, 3,4]

- It avoids GIT side effect, inactivation of drug by GIT enzymes, interaction of drug with food and first-pass metabolism of drugs in GIT.
- It provides controlled and sustained release of the medicament.
- It improves the bioavailability of drug.
- It provides uniform drug plasma concentration.
- It improves the patient's compliance.
- It can be administered to non- responsive, unconscious and nauseating patient.
- It provides easy termination of drug in case of toxicity by removal of the formulation from the skin.

Disadvantages of Transdermal Drug Delivery Systems[5]

- Transdermal drug delivery system is unsuitable for a drug that causes irritation at the site of application.
- It is suitable for potent drugs only.
- It is limited for the drugs which are imposed by skin permeability.

Hypertension refers to the prolonged and persistent elevation of blood pressure above the normal range. If not treated, hypertension can cause severe complication such as stroke, coronary heart disease and kidney failure. Patient with hypertension must take antihypertensive drug on a long term basis. Although such drugs cannot give a radial cure, they can prevent heart failure and acute stroke induced by hypertension. The medical practitioner often facing a major problem is that the patients on oral antihypertensive do not follow proper drug regimen. Furthermore, patient with high blood pressure are treated with number of drugs at a time. In addition, oral antihypertensive therapy has many disadvantages such as

1. It undergo extensive first-pass metabolism.
2. Shows unpredictable or low bioavailability.
3. Dose dumping.
4. Sustained toxicity.
5. Dose inflexibility and increase in the cost of product.

The complexity of the treatment and the problem of patient compliance with oral antihypertensive drugs increase as the patients with high blood pressure have to renew their prescription more often. Formulating transdermal patches of antihypertensive drugs provide greater patient compliance[6]. In addition, in two American states such as Florida and South Carolina an organization such as Medicaid claims that though the cost of transdermal patch was higher as compared to multi-drug regimen, it saved hypertensive patient from hospitalization and diagnostic costs and results in reduced overall health expenditure[7]. Also it provides overall saving of cost for medical care of hypertensive patients[8]. Present article reviewed the transdermal (nanoemulsion or microemulsion) formulation of various antihypertensive drugs and their methodology. To the best of our knowledge no article has been published in scientific journal which can give comprehensive information on TDDS of antihypertensive drugs.

Enhancement of drug penetration through the skin [9,10,11,12]

Both the desired and the undesired effect of a drug are dependent on the concentration of the drug at the site of action, which in turns depends upon the dosage form. In transdermal delivery, the goal of dosage design is to maximize the flux through the skin into the systemic circulation. There are two pathways such as tansappendageal and intercellular pathway by which drug can cross the skin and reach the systemic circulation. In the transappendageal route the drug substances penetrate via the sweat glands and the hair follicle. But this route is not an appropriate pathway of penetration for most molecules because it has smaller surface area (less than 0.1%). Also it lack suitable animal model for drug testing. Skin contains an uppermost layer epidermis, which has basal layer, spiny layer, stratum granulosum and upper most layer stratum corneum. The stratum corneum consists of corneocytes which is 200-300 nm thick, 30-50 um in diameter and hexagonal or polygonal in shape. It consists of alternating cell and lipid layers and is only 6-10 um thick which equivalent to about 14-18 cellular layers. The majority of molecules that cross the epidermis must partition into the stratum corneum before diffusing across the viable epidermis. Therefore, the major pathway for a compound is highly dependent upon its partition coefficient. Hydrophilic compounds may preferably partition into the intracellular domain, while lipophilic ones may cross the stratum corneum through the Intercellular route. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavorable for most drugs. Therefore, the major challenge in topical administration is to

increase the drug penetration into the skin. Moreover, the most of the pharmaceutical substances are lipophilic in nature. The clinical efficacy of such drug is being impeded by their low aqueous solubility resulting in poor penetration and absorption when they are designed for transdermal administration.

There has been a continue interest during recent years for modifying drug penetration into and through the skin. It can be possible by use of physical or chmical means of penetration enhancement. Physical means of penetration enhancement include use of iontophoresis, Sonophoresis and microneedle. Chemical means of penetration enhancement include use of chemical penetration enhancers[13]. The physical means are relatively complicated to use and will affect patients compliance. Most of the topical vehicles contain chemical enhancers and non-friendly solvents to achieve improved permeability[14]. But these vehicles usually results in various degree of irritancy and permanent damage to skin in case of chronic treatments.

Therefore it is desirable to develop topical vehicles that do not use chemical enhancers to facilitate drug penetration into and through the skin[15]. One of the most promising techniques for enhancement of transdermal permeation of drug is to develop microemulsion or nanoemulsion[16]. Microemulsions are quaternary systems composed of an oil phase, a water phase, and surfactant in combination with cosurfactant[17]. These spontaneously formed systems pose specific physicochemical properties such as transparency, optical isotropy, low viscosity and thermodynamic stability. In stable microemulsion, droplet diameter is usually within the range of 10-100 nm (100-1000A^0), and therefore this system is also termed as nanoemulsion (NE) [18].

Due to unique physicochemical properties, NE offer advantages over traditional topical and transdermal drug delivery formulation. Many studies have shown that NE formulation possess improved transdermal drug delivery properties both *in-vitro* [19-23] as well as *in-vivo* [24-26]. One of the unique characteristics of the NE technology is the relatively high percentage of total particle volume occupied by the internal hydrophobic oil core of the droplets. This provides high solubilization of lipophilic compound as compared to other lipoidal vehicle such as liposomes[27]. Both increase in solute concentration and the tendency of the drug to favor partitioning into stratum corneum make NE a useful vehicle to enhance transdermal drug permeability[28].

As demonstrated by recent publication[29], these systems themselves act as penetration enhancers and there is no need of incorporation of the conventional chemical enhancers.

Nanoemulsion Assisted Transdermal Permeation of Antihypertensive Drugs

Nifedipine[30]

Though nifedipine is a potent antihypertensive drug, it has extensive first pass metabolism and low bioavailability. K. Panduranga Rao et al prepared oil/water microemulsion of nifedipine by incorporating six lipophilic skin penetration enhancers such as ylang ylang oil, lavender oil, cinnamon oil, cineole, menathone and menthol. Ethanol was used as emulsifying agents. Three vehicle systems were used for developing microemulsion TDDS of nifedipine; first containing 25% ethanol, second system containing 50% ethanol and third system consisting of solutions of penetration enhancers in 100% ethanol saturated with nifedipne. The concentration of the penetration enhancers were kept same in all preparation. It was observed that maximum percutaneous nifedipine flux obtained with microemulsions containing 50% aqueous ethanol as compared to formulations consisting of 100% ethanol. It was also found that the formulation which contain cinnamon oil was the most efficient. Thus the result indicates that penetration enhancers when used as microemulsions are more efficient than their solution form.

Ramipril[31]

Ramipril a potent antihypertensive drug is almost completely converted to its active metabolite ramiprilat (a dicarboxylic acid) by hydrolytic cleavage of the ester group in the liver. It has about 6 times the angiotensin-converting enzyme inhibitor activity of ramipril. It is a lipophilic, poorly water soluble drug with variable oral absorption.

Shaikh Shafiq-Un-Nabi et al explain the basis for calculation and construction of pseudoternary phase diagram and also explain the selection of the formulation from the phase diagrams to avoid metastable formulations having minimum surfactant concentration in the least possible time. They had prepared nanoemulsion by spontaneous emulsification method by using Safsol 218 as oil, Cremophor EL as surfactant and Carbitol as cosurfactant. Pseudoternary phase diagrams were developed to select best formulation which contains 20% oil, 27% Smix and 53% aqueous phase. Best nanoemulsion region were selected for incorporation of Ramipril. 5mg of ramipril was selected as a dose for incorporation into the oil phase. The selected formulation was subjected to different stress test such as centrifugation, heating- cooling cycle and freeze-thaw cycle test. The stable nanoemulsion formulation was evaluated for droplet size and for viscosity. The result showed the uniformity of droplet size i.e. 34.5 nm and the lowest viscosity because of its lower oil content.

Carvedilol[32]

Carvedilol is used in the long term treatment of hypertention and angina pectoris. It has α_1 and β-receptor blocking activity. It is well absorbed from the gastrointestinal tract, but it is subjected to considerable first pass metabolism in the liver which lead to low oral bioavailability (25-30%). It is highly lipophilic and practically insoluble in water.

Mohammed Aquil designed nanoemulsion as a possible vehicle for transdermal therapeutic system of carvedilol. For fabrication of nanoemulsion, solubility of carvedilol in oil, surfactant and co-surfactants was employed. They had selected Miglyol 810 as an oily phase as it showed the highest solubility. Whereas Acconon CC6 and Co-20 were selected as a surfactact and co-surfactant respectively. The pseudo-ternary phase diagrams were developed for various nanoemulsion formulations composed of surfactant/cosurfactant ratio 1:1. The optimized nanoemulsion system was evaluated for *in-vitro* flux through an excised wistar rat skin using Franz diffusion cell. The result of their study showed that the formulation which contain 0.25% w/w carvidilol, 12.5% w/w Miglyol 810, 50% w/w Acconon CC6/Co-20 (1:1) and water has the maximum skin permeation rate (161.53 ug/cm^2/h). The nanoemulsions were also evaluated for their physiochemical characterization. The result of which revealed that nanorange size of oil globules provide intimate contact with skin layer which would help in achieving effective drug concentration.

In addition, to this, Sanjula Baboota et al [31] also developed and evaluated nanoemulsion for increasing the solubility and determine the *in-vitro* drug release of carvedilol. By using oleic acid and isopropyl myristate (IPM) (1:1) as the oil, Tween 80 as surfactant and Transcutol P as cosurfactants, various nanoemulsion formulations were prepared. For optimization of nanoemulsion formulation, pseudoternary phase diagrams were developed. The optimized formulation consists of 0.5% w/w of carvidilol, 6% w/w of oleic acid: IPM (1:1), 22.5% w/w of Tween 80, 22.5% w/w of Transcutol P and 49% w/w of distilled water in which the solubility of drug is higher. The optimized nanoemulsion formulation was evaluated for *in-vitro* flux through rat abdominal skin by using Keshany-Chein diffusion cell. It shows the highest value for different permeability parameters. Prepared nanoemulaion were subjected to determine physical parameters such as P^H, conductivity, viscosity, droplet size, droplet shape and refractive index. The stability and irritation studies encourages conducting a clinical study to determine nanoemulsion based carvidilol could become a new product in treatment of hypertension.

Nicardipine Hydrochloride[34]

Nicardipine hydrochloride a dihydropyridine calcium channel antagonist is used in the treatment of angina pectoris and hypertension. The oral bioavailability ranges from 20 to 30% because of extensive hepatic first pass metabolism. The elimination half-life is also very short i.e about 1 hour.

Nanoemulsion vehicles for enhanced and sustained transdermal delivery of Nicardipine were developed by using isopropyl myristate (IPM) as oil, surfactant mixture of tween 80 / span 80 and / or Tween 80 / Span 20, co-surfactant (ethanol) and aqueous phase respectively. The components for nanoemulsion were selected on the basis of high solubilization capacity of drug, nanoemulsifying ability of surfactants and area of NE from pseudo-ternary phase diagrams. The area of nanoemulsion isotrop region was larger in presence of ethanol as compared to in absence of ethanol. The mean droplet size was ranged from 70-123 nm and the droplet size became smaller with addition of ethanol. The selected NE from pseudo- ternary phase diagrams was finally optimized for high flux by *in-vitro* skin permeation studies. On the basis of the highest *ex-vivo* skin permeation profile, lowest droplet size and lowest viscosity, the nanoemulsion formulation was said to be optimized. It contains 52% IPM, 35% surfactant mixture and 13% water and had higher permeation rate through rat skin above 122.53 ± 1.87µg/cm^2/h. Thus the developed nanoemulsion has been successfully prepared and was expected to develop a teansdermal delivery system.

Amlodipine[35]

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 h and a bioavailability of 60-65%. It undergoes extensive first pass metabolism.

M. Aquil et al prepared oil-in-water nanoemulsion system for transdermal delivery of amlodipine. The solubility of amlodipine in oil and surfactant was evaluated to identify potential excipient. Various microemulsions were prepared using oleic acid as oil phase, Tween 20 as surfactant and Transcutol P as co- surfactant. The microemulsion existence ranges were defined through the construction of the pseudo-ternary phase diagram. The optimized nanoemulsion was characterized for its morphology, viscosity, pH, globule size and skin permeation of amlodipine through excised rat skin using a Franze diffusion cell. It was observed that increasing the concentration of oil and S (mix) decreases the flux; it was believed that due to increased globule size and decreased thermodynamic activity of drug at higher surfactant mixture concentration. Thus it was found that at low oil and S (mix) concentration the highest permeation rate and permeability coefficient obtained. The optimized nanoemulsion formulation shows maximum skin permeation rate of 49.681 ± 1.98 mg/cm^2/h and permeability coefficient of 0.497± 0.056 cm^2/h which contains 2% oil, 20% surfactant, 10% co-surfactants [S (mix) 2:1] and water. The result suggest that with poorly water soluble drugs such as amlodipine, topical delivery using nanoemulsion system may hold a great deal of promise for transdermal drug delivery system.

Felodipine[36]

Felodipine is a calcium channel blocker (calcium antagonist), a drug used to control hypertenaion. Felodipine is well absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism, resulting in an absolute bioavaolability of 13 to 16% in fasted individual.

Dasco R. et al designed and evaluated felodipine oil / water microemulsion which containing benzyl alcohol and isopropyl myristate as oil phase. Two suspension systems were developed as an aqueous drug suspension and a drug suspension in an apparent external phase of a microemulsion. Microemulsion was compared with this system for its skin permeation activity by using Franz diffusion cell. The *in vitro* skin permeation study revealed that the skin permeability of the microemulsion with the highest solubility of felodipine has the maximum flux. Whereas it was observed that the permeation rate decreases over time from the suspension in the apparent external phase. It was also found that the flux obtained from aqueous suspension was 10-15 times less than its microemulsion. The result obtained in this study suggest that microemulaion with benzyl alcohol would be a suitable vehicle for transdermal drug delivery in the management of hypertension.

Lacidipine[37]

Lacidipine is a calcium channel blocker used in the treatment of hypertension and atherosclerosis. Lacidipine is completely metabolized in the liver by cytochrome P450 3A4 to pharmacologically inactive metabolite. It undergoes extensive first-pass hepatic metabolism and has a mean absolute bioavailability of about 10%.

Madhusudan Rao Yamsani et al Prepared and evaluate elucidate mechanistic effects of microemulsion formulation components on transdermal permeation of the drug through the skin. Based on the solubility results pseudo-ternary phase diagram were constructed for various microemulsion formulation, which includes isopropyl myristate, Tween 80 and Labrasol as oil, surfactant and co-surfactant respectively. In his study for optimization of microemulsion formulation, the Box-Behnken statistical design was used to investigate permeation across the rat skin in 24hr (Q_{24}), flux and lag time. The optimum selected microemulsion was based on the maximum value of Q_{24}, maximum flux and low value of lag time. The optimized formulation was formulated as microemulsion gel using hydroxyl propyl methyl cellulose at 4%w/v in the microemulsion. The flux of microemulsion gel was found to meet the target flux (12.16 µg/cm^2/h). The bioavailability study of microemulsion gel was compared to the oral suspension. The bioavailability result revealed that Lacidipine is released and permeated well from microemulsion gel by transdermal route as compared to the oral suspension. A good *ex vivo- in vivo* correlation was obtained. The irritation studies suggested that the optimized microemulsion gel was a non-irritant transdermal delivery system.

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