



A Brief Review on Amlodipine Besylate Transdermal Patch

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Abstract

This review article provides an overview of the development and evaluation of a transdermal drug delivery system for amlodipine besylate, a medication commonly prescribed for hypertension and angina. The article highlights the importance of safe and effective drug delivery systems and discusses the formulation of the transdermal drug delivery system, including its ingredients, preparation method, and physicochemical properties. Various in-vitro evaluation methods, such as diffusion and skin permeation studies, were used to assess the performance of the system. The potential advantages and disadvantages of transdermal drug delivery systems are also discussed. In conclusion, this study provides evidence of the effectiveness of transdermal drug delivery systems for amlodipine besylate and suggests future research directions that could lead to further improvements in transdermal drug delivery systems for other medications.

Keywords

Transdermal Drug Delivery, Amlodipine Besylate, Calcium channel blocker.

INTRODUCTION AND BACKGROUND

Amlodipine besylate is a calcium channel blocker commonly prescribed for the treatment of hypertension and angina. While oral administration is the traditional route of drug delivery, it can lead to side effects and reduced efficacy due to first-pass metabolism. Transdermal drug delivery provides an alternative method of administration that bypasses the gastrointestinal tract and first-pass metabolism, potentially improving patient compliance and reducing side effects. Matrix-based transdermal drug delivery systems have been developed to sustain drug release and maintain therapeutic plasma levels over extended periods. In this review article, we will provide an overview of the formulation and in-vitro evaluation of matrix-based transdermal drug delivery of Amlodipine besylate and its potential clinical applications.

[7] Amlodipine (AD) is a calcium channel blocker with improved vascular selectivity and longer duration of

action. It offers smooth onset of action and 24-hour blood pressure control. Once-daily dosing enhances patient compliance and minimizes side effects. AD is suitable for a wide range of hypertensive patients, including the elderly, black individuals, and those with concurrent diseases. Numerous formulations of AD have been developed to enhance efficacy and stability. A comprehensive review of these formulations can aid pharmaceutical scientists and formulators in selecting and developing the most appropriate dosage form for AD.

[10] Transdermal delivery offers several potential advantages when compared to other routes of administration. One notable advantage is its ability to decrease the effects of first-pass metabolism often associated with oral delivery. Additionally, transdermal delivery is generally less painful than traditional injection methods. However, the stratum corneum (SC), which serves as the outermost layer of the skin, poses a challenge by limiting the passive

diffusion of larger or ionic molecules to the underlying layers. Consequently, it becomes necessary to employ safe methods that can permeabilize the SC effectively, allowing for the transdermal delivery of such molecules. Techniques for enhancing skin permeabilization can be categorized into passive/chemical and active/physical methods. Passive methods involve modifying drug-vehicle interactions and optimizing formulations to alter the structure of the stratum corneum, which is commonly employed in transdermal patches. However, passive methods may result in a lag time in drug release, particularly for rapid-onset drugs like insulin.

[10] Chemical penetration enhancers are widely used passive approaches to facilitate drug permeation across the skin without causing long-term damage. These enhancers increase drug partitioning into the stratum corneum's barrier domain through various mechanisms, such as increasing fluidity of lipid bilayers, interacting with intercellular proteins, disrupting, or extracting intercellular lipids, enhancing drug thermodynamic activity, and increasing stratum corneum hydration. Penetration enhancers include alcohols, sulphoxides, azone, pyrrolidones, essential oils, terpenes, terpenoids, fatty acids, water, and urea. However, their efficacy is often limited by the potential for skin irritation. Gels, including proniosomes and microemulsion gels, have been utilized in transdermal drug delivery (TDD) as penetration enhancers. Proniosomes are non-ionic surfactant vesicles that require hydration before drug release and permeation through the skin. Proniosomal gels enhance drug permeation from the skin barrier. Upon hydration, proniosomes convert into niosomes, which diffuse across the stratum corneum and adhere to the cell surface, creating a high thermodynamic activity gradient of the drug at the vesicle/stratum corneum interface. This gradient acts as the driving force for the penetration of lipophilic drugs across the skin.

[13]. The transdermal route of drug administration offers improved systemic bioavailability by bypassing the hepatic first-pass effect. However, the success of transdermal drug delivery relies on the drug's ability to penetrate the skin adequately for therapeutic

levels. Various methods have been reported to enhance drug penetration, including the use of penetration enhancers. Ideal enhancers should be pharmacologically inactive, non-irritating, and non-damaging to the skin. Chemical enhancers such as dimethyl sulfoxide, surfactants, alcohols, and urea derivatives have been investigated but are limited by adverse effects. Natural compounds like terpenes, derived from essential oils, have gained popularity as safe and non-irritating enhancers. D-limonene, a cyclic terpene, has been successfully used to enhance transdermal delivery of multiple drugs. Matrix patches containing Eudragit RL100 (ERL) and hydroxypropyl methyl cellulose (HPMC) have also been reported.

Advantages of TDDS

- Avoids vagaries associated with gastrointestinal absorption due to pH, enzymatic activity, drug-food interactions etc.
- Substitute oral administration when the route is unsuitable as in case of vomiting, diarrhea.
- Avoids hepatic "first pass" effect.
- Avoids the risks and inconveniences of parenteral therapy.
- Reduces frequency of doses, thus improving patient compliance.
- Rapid termination of drug effect by removal of drug application from the surface of the skin.
- Administration of medication in emergencies. (e.g., Non-responsive, unconscious, or comatose patient)
- Enhance therapeutic efficacy, reduced side effects due to optimization of the blood concentration-time profile and elimination of pulsed entry of drugs into the systemic circulation.
- Provide predictable activity over extended duration of time and ability to approximate zero-order kinetics. Improved control of the concentrations of drug with small therapeutic indices
- Minimize inter and intra-patient variation.
- Suitability for self-administration.

Advantage of Transdermal drug delivery system in comparison to Oral and Intravenous (IV) Formulation

Advantages	IV	Oral	TDDS
Reduced first pass effect	Yes	NO	YES
Self-administration	NO	YES	YES
Unrestricted Patient activity	NO	YES	YES
Non-invasive	NO	YES	YES

Disadvantages of TDDS

- The drug must have some desirable physicochemical properties for penetration through stratum corneum. If the drug dosage required for therapeutic value is more than 10mg/day, transdermal delivery becomes very difficult.
- Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age. Hence the rate of drug delivery may vary from site to site.
- Many drugs especially with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Types of Transdermal Patch

There are four types of transdermal drug delivery system:

1. Membrane permeation Controlled systems

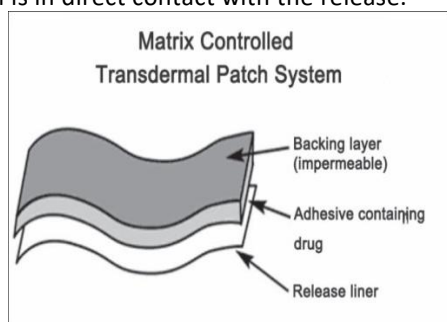
2. Matrix diffusion-controlled system

3. Adhesive dispersion- type system

4. Micro-reservoir type or micro-sealed dissolution-controlled systems.

Matrix diffusion-controlled system:

This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release.



Components of TDDS:

The components of transdermal devices include:

- a. Backing membrane.
- b. The polymer matrix or matrices that regulate the release of the drug.
- c. The drug substance.
- d. Enhancers and other excipients.

e. Adhesives.

(a) Backing membrane

The materials used as the backing membrane must be inert and impermeable to drugs and enhancers. The most used backing materials are metalized polyester laminated with polyethylene, alupoly and polyes. Excipient compatibility also must be seriously considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients. The most comfortable backing membrane may be the one that exhibits the lowest modulus or high flexibility good oxygen transmission, and a high moisture-vapor transmission rate.

(b) Polymer matrix

The development of transdermal systems requires judicious selection of a polymeric material or a series of polymers whose diffusive characteristic will be such that a desirable permeation rate of specific drug or another bioactive agent can be obtained. In addition, the solute size and polymer structure controls the solute diffusion coefficient. The polymer should meet the following requirements:

- The molecular weight, glass transition temperature and chemical functionality of polymer must allow proper diffusion and release of the specific drug.
- The polymer should not chemically react with the drug.
- The polymer and its degradation products must be non-toxic.
- The polymer should not decompose on storage or use of the device.

(c) The drug substances

In transdermal drug delivery system, the choice of drug substance is the most important decision in successful development. The important drug properties as shown in Table below, that affect its diffusion through the device as well as the skin. Diffusion of the drug in adequate amount to produce a satisfactory therapeutic effect is of prime importance. Other parameters such as skin irritation and clinical need should be considered before a drug is chosen for transdermal medication. The drug should be nonirritating and non-allergic to human skin. The drug should be stable in the skin environment.

Parameters	Properties
Dose	Less than 20 mg per day
Half-life	< 10 hrs.
Molecular weight	<400 Daltons
Melting point	<200°C
Partition coefficient	1 to 4
Aqueous Solubility	>1 mg/ml
pH of the Aqueous saturated solution	5-9
Skin Permeability Coefficient	>0.5X10 ⁻³ cm/h
Skin Reaction	Non irritability and non-Sensitizing
Oral Bioavailability	Low

(d) Enhancer

These are compounds which promote the skin permeability by altering the skin as barrier to the flux of a desired penetrate.

Ideal properties of penetration enhancers:

- Controlled and reversible enhancing action
- Chemical and physical compatibility with drug and other pharmaceutical excipients
- Should not cause loss of body fluids, electrolytes, or other endogenous materials.
- Non-toxic, non-allergic, non-irritating
- Pharmacological inertness
- Ability to act specifically for predictable duration.
- Odourless, colourless, economical, and cosmetically acceptable.

(e) Adhesive

A Pressure Sensitive Adhesive (PSA) is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemical and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device or in the back of the device and extending peripherally.

LITERATURE REVIEW

Amlodipine besylate is a calcium channel blocker used to treat high blood pressure and angina. Transdermal drug delivery systems (TDDS) are an attractive option for amlodipine besylate delivery due to their ability to provide controlled drug release, minimize side effects, and improve patient compliance. In this literature review, we will examine the current research on amlodipine besylate TDDS.

Kimura et al. in 2004 Prepared a matrix-type TDDS using ethyl cellulose as a polymer and evaluated its in vitro and in vivo performance. The TDDS showed a sustained release of amlodipine besylate for 24 hours in vitro, and in vivo studies showed a significant reduction in blood pressure in hypertensive rats.

Lee et al. in 2009, where they developed a matrix-type TDDS using a combination of polymers, namely, polyvinylpyrrolidone and hydroxypropyl methylcellulose. The TDDS showed a sustained release of amlodipine besylate for up to 72 hours in vitro and in vivo studies on rats showed a significant reduction in blood pressure over a period of 24 hours.

In 2012, Li et al. developed a bilayer TDDS of amlodipine besylate using an acrylic adhesive and ethyl cellulose as polymers. The TDDS showed a sustained release of amlodipine besylate for up to 72 hours in vitro, and in vivo studies on rabbits showed a significant reduction in blood pressure over a period of 48 hours.

Khodaverdi et al. in 2019 developed a TDDS of amlodipine besylate using a polyvinylpyrrolidone-covinyl acetate copolymer as a polymer. The TDDS showed a sustained release of amlodipine besylate for up to 48 hours in vitro, and in vivo studies on rats showed a significant reduction in blood pressure over a period of 24 hours.

C. M. M. Cunha: Cunha et al. (2019) developed a TDDS for amlodipine besylate using a blend of Eudragit RL100 and RS100 polymers. The researchers optimized the formulation by evaluating various parameters, including drug release, skin permeation, and adhesion.

S. M. Sayed: Sayed et al. (2020) prepared a transdermal patch containing amlodipine besylate and olmesartan medoxomil for the treatment of hypertension. The researchers used various permeation enhancers, including propylene glycol, oleic acid, and lauric acid, to improve drug delivery.

S. Y. Jang; Jang et al. (2020) developed a novel TDDS for amlodipine besylate using a combination of microneedles and iontophoresis. The researchers evaluated the patch's performance by measuring skin permeation, pharmacokinetics, and blood pressure reduction in rats.

A. H. Soliman; Soliman et al. (2021) developed a TDDS for amlodipine besylate using a blend of ethylcellulose and Eudragit RS100 polymers. The researchers optimized the formulation by evaluating drug release, skin permeation, and adhesion. They also conducted in vivo studies to assess the patch's pharmacokinetics and antihypertensive activity.

N. N. Alharbi; Alharbi et al. (2021) developed a TDDS for amlodipine besylate using a blend of chitosan and hydroxypropyl methylcellulose polymers. The researchers optimized the formulation by evaluating various parameters, including drug release, skin permeation, and stability. They also conducted in vivo studies to assess the patch's pharmacokinetics and antihypertensive activity.

In conclusion, amlodipine besylate TDDS has been extensively researched and has shown promising results in terms of sustained release and efficacy. The use of different polymers and TDDS designs has led to the development of TDDS with varying release rates and durations, providing a potential option for the treatment of hypertension and angina.

RATIONALE

Amlodipine is slowly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90%. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound. Formation of transdermal patch helps to avoid first pass metabolism and avoid vagaries associated with GI absorption. It also reduces the frequency of doses thus improving patient compliance.

EVALUATION OF TRANSDERMAL DELIVERY SYSTEM OF AMLODIPINE

SOLUBILITY MEASUREMENT

Solubility of amlodipine will be determined at several pH. Amlodipine will be added briefly to 10 ml of saline phosphate buffer solutions the samples stirred in a conical flask for 24 h maintained at 37°C. The pH of the samples will be checked after the studies. The suspensions will be filtered using a 0.45-micron Whatman filter paper and the filtrate will be determined spectrophotometrically.

PARTITION COEFFICIENT

Determination of the partition coefficient of the Amlodipine will be done in 1-octanol and buffer system (pH 7.4).

DRUG-EXCIPIENTS INTERACTION STUDY

FTIR Studies:

Infrared spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug and other excipients that will be used in the formulations. Samples are powdered and intimately mixed with 10 mg of drug powdered potassium bromide (KBr). The powdered mixture will be taken in a diffuse reflectance sampler and the spectrum will be recorded by scanning in the wavelength region of 4000-400 cm^{-1} in an FTIR spectrophotometer. The IR spectrum of the drug will be compared with that of the physical mixture of check for any possible drug-excipients interaction.

PERMEABILITY STUDIES

a. Preparation of porcine ear skin:

Taking the fresh full thickness pig ear porcine skin and the skin will be immersed in buffer for a period of 10-15 minutes. Hair removal will be done without damaging the epidermis using a trimmer. The subcutaneous layer is carefully separated from the dermis and then either used or stored frozen (for not more than 48 h) on an aluminum foil.

b. Permeability studies using modified Franz diffusion cell:

The permeability study of the drug will be carried out across the isolated porcine epithelial layer using a standardized modified Franz type diffusion cell. Drug having different concentration with 50% ethanol and 50% 7.4 pH phosphate buffer is taken in donor compartment. The skin will mount on the space between the donor and the receptor compartments. The receptor cell contains 50% ethanol and 50% phosphate buffer of pH 7.4 as the medium. The samples will be withdrawn 0, 1, 2, 3, 5, 8, 12, 24 hours. The medium is magnetically stirred at 600 rpm for uniform drug distribution and will be maintained at temperature of $37 \pm 1^\circ\text{C}$. The amount of drug diffused will be estimated spectrophotometrically at 225 nm.

Permeability coefficient (P): is the velocity of drug passage through the membrane in cm/h. The permeability coefficient was calculated from the slope of graph of percentage of drug transported v/s time as

$$P = \text{Slope} \times V_d / S$$

V_d = Volume of donor solution

S = Surface area of tissue

Flux (J): Flux is defined as the amount of material flowing through a unit cross sectional barrier in unit time. It is calculated by,

Flux (j) = P × CD

CD = Concentration of donor solution

P = Permeability

Diffusion coefficient (D): A factor of proportionality representing the amount of substance diffusing across a unit area through a unit concentration gradient in unit time.

Diffusion coefficient (d) = P × Thickness / partition coefficient

EVALUATION OF TRANSDERMAL FILMS

All the prepared transdermal patches will be evaluated for the following parameters.

(a) Thickness determination:

The thickness of the formulated films will be measured at four different points of different films using Vernier caliper and the average of four readings will be calculated.

(b) Uniformity of weight:

This will be done by weighing the three different patches of the individual batch of the same size at random and calculating the average weight. The individual weight should not deviate significantly from the average weight of three.

(c) Moisture loss:

The film will be weighed and kept in desiccator containing calcium chloride at 40°C in a dish, dried for at least 24 h. Then the film will be weighed again and again until it shows a constant result.

(d) Moisture uptake:

A weighed film kept in a desiccator at 40°C for 24 h will be taken out and exposed to two different relative humidity of 75%RH (saturated solution of sodium chloride) and 93%RH (saturated solution of ammonium hydrogen phosphate) in desiccator. The weights will be measured periodically till a constant weight is achieved.

(e) Drug content:

Transdermal patches of specified area will be cut into small pieces and taken in a 50 ml volumetric flask. Addition of about 10 ml of ethanol and shaking on a orbital shaker to get a homogenous solution and filtered. Then 0.5 ml solution will further be diluted to 10 ml saline 7.4 pH phosphate buffer. The absorbances of the solution will be measured at 225nm by UV spectrophotometer.

IN-VITRO DISSOLUTION STUDY

The performance of a matrix-based transdermal drug delivery system can be evaluated using various in-vitro methods. These methods are essential for assessing the drug release kinetics, drug penetration through the skin, and physical and chemical stability of the system.

Diffusion studies are used to determine the rate and extent of drug release from the transdermal drug delivery system. A Franz diffusion cell apparatus is used, which consists of two compartments separated by a membrane. The drug delivery system is placed on the donor compartment, and the receptor compartment is filled with a suitable medium. Samples are collected at regular intervals, and the drug concentration is analyzed using UV Spectroscopy or high-performance liquid chromatography (HPLC).

Skin permeation studies are used to determine the amount of drug that penetrates the skin and enters the receptor compartment. Human or animal skin is used as the membrane, and a Franz diffusion cell apparatus is used. Samples are collected at regular intervals, and the drug concentration is analyzed using UV Spectroscopy or HPLC.

Stability studies are conducted to evaluate the physical and chemical stability of the transdermal drug delivery system over time. These studies involve storing the drug delivery system under various conditions, such as high temperature, humidity, and light exposure, and assessing its stability using techniques such as UV, HPLC, Fourier-transform infrared spectroscopy, and scanning electron microscopy.

In addition to these methods, other evaluations can be conducted to assess the adhesive properties, mechanical strength, and drug content uniformity of the transdermal drug delivery system. These evaluations can help to optimize the formulation and improve the performance of the drug delivery system.

CONCLUSION

In conclusion, transdermal drug delivery systems have emerged as a promising alternative to oral administration of drugs for treating hypertension. Amlodipine besylate, a commonly prescribed calcium channel blocker, has shown great potential in transdermal drug delivery due to its lipophilic nature and long half-life. Various transdermal drug delivery systems, including patches and gels, have been developed for amlodipine besylate, and their efficacy and safety have been extensively evaluated. Overall, transdermal delivery of amlodipine besylate offers several advantages over oral administration, including improved patient compliance, reduced side effects, and better therapeutic outcomes. However, further studies are required to optimize the formulation and delivery of amlodipine besylate through transdermal drug delivery systems, and to investigate their long-term safety and efficacy.

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