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Review Article

A comprehensive review on transdermal patch of ciprofloxacin hydrochloride.

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ABSTRACT

Transdermal patches are now widely used as cosmetic, topical, and transdermal delivery systems. These patches represent a key outcome of the expansion in skin science, technology, and expertise developed through trial and error, clinical observation, and evidence-based studies that go back to the first existing human records. transcutaneous delivery provides variety one edge over injectables and oral routes by increasing patient compliance and avoiding initial pass metabolism severally. transcutaneous delivery not solely provides controlled, constant administration of the drug, but additionally permits continuous input of drugs with short biological half-lives and eliminates periodical entry into circulation, which regularly causes undesirable side effects. Ciprofloxacin may be a very popular fluoroquinolone having a broad spectrum of activity and diverse therapeutic prospects. the explanations for its wide use include multiseriate pathogens susceptible only to ciprofloxacin. The available clinical evidence suggests the doubtless enhanced efficacy of this drug in the treatment of various community-acquired and nosocomial infections, e.g. skin infections, and sexually transmitted diseases. As compared to other agents of its class, the pharmacokinetic profile of ciprofloxacin demonstrates equivalent or greater bioavailability, higher plasma concentrations, and increased tissue penetration, as reflected within the greater volume of distribution. The aim of the present review is to explore the importance and utilization of Transdermal patches of Ciprofloxacin hydrochloride begins with the earliest topical therapies and traces topical delivery to the present-day transdermal patches, describing along the way the initial trials, devices, and drug delivery systems that underpin current transdermal patches and their actives.

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INTRODUCTION

Innovations in transdermal delivery systems (TDS) have made important contributions to practice by providing advances in the delivery of treatment with existing and novel drugs. Today about 74% of medicine are taken orally and are found not to be as effective as desired. to enhance such character's transdermal drug delivery system emerged. Drug delivery through the skin to realize a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery [1]. A transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drugs are delivered through the skin at a predetermined and controlled rate. Skin is that the important site of drug application for both the local and systemic effects. Transdermal drug delivery system (TDDS) has several advantages over the traditional system; TDDS offers sustained drug release, avoidance of first-pass effect, patient

compliance, simple application, and removal just in case of toxicity as well decrease in the side effects as compared with conventional therapy [2]. The corneum acts as a barrier that limits the penetration of substances through the skin and this limitation can be overcome by permeation enhancing techniques.

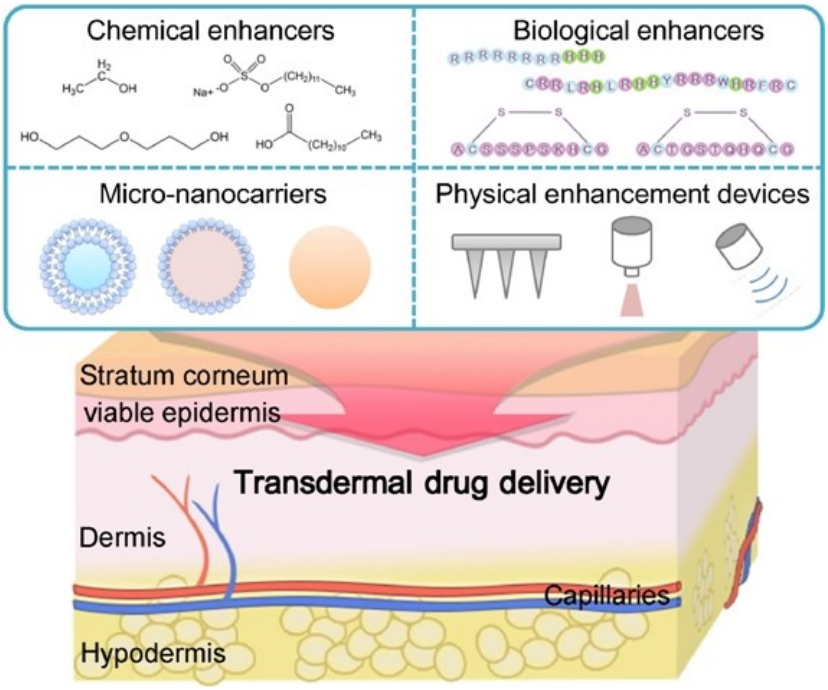

Figure 1. Schematic diagram of transdermal drug delivery system.

During the past 25 years, antimicrobial agents are introduced at a rate exceeding our ability to integrate them into clinical practice. Since their introduction, fluoroquinolones became a mainstay in the treatment of serious bacterial infections [3]. These are synthetic antibacterial agents structurally associated with nalidixic acid5. They depict several favorable properties like excellent bioavailability, good tissue penetrability, and a comparatively low incidence of adverse and toxic effects [4]. These drugs are potentially utilized in the treatment of urinary tract infections and prostatitis. they're also employed against bacterial enteric infections, biliary tract infections, sexually transmitted diseases, and prophylaxis within the immunocompromised neutropenic host. one among the most successful and widely used compounds of the class [5], ciprofloxacin, was patented in 1983 by Bayer A.G. and subsequently approved by the us Food and Drug Administration (US FDA) for use in the United States in 1987. Ciprofloxacin is marketed worldwide, with overflow 300 different brand names, and since its introduction, the worth of fluoroquinolones for their respective uses has been recognized. The licensed uses for ciprofloxacin within the United States are quite limited, and it's to be considered a drug of the final resort when all other antibiotics have failed. There are 10 approved uses of this drug within the adult population and two approved uses in the pediatric population, also as a variety of veterinary uses (as documented within the package inserts). Being not approved by the FDA, its other uses are often considered off-label. Ciprofloxacin may interact with variety of other drugs, some herbal and natural supplements, and certain thyroid medications [6]. Ciprofloxacin (Figure 2) has proved to be a blockbuster drug for Bayer A.G., generating billions of dollars in additional revenue. In 1999, ciprofloxacin was the 11th most prescribed drug within the United States, supported new prescriptions, and ranked 20th in total us sales. In 1999, Bayer′s gross revenue of ciprofloxacin in the United States were approximately $1.04 billion. The sale of ciprofloxacin increased dramatically following the anthrax scare of 2001 [7].

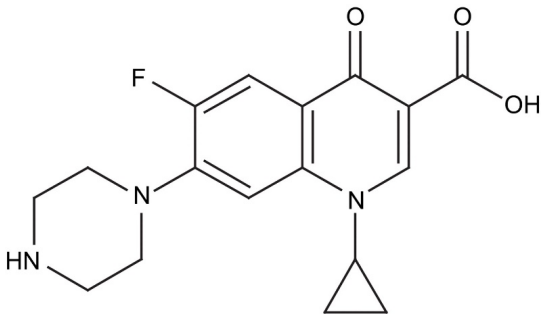

Figure 2. Structure of ciprofloxacin.

Ciprofloxacin hydrochloride (3-quinoline acid , 1-cyclopropyl- 6- fluoro- 1, 4- dihydro- 4- oxo- 7-(1-piperazinyl)-, mono-hydrochloride, monohydrate) (CP) may be a quinolone carboxylic acid derivative with high

antibiotic activity against gram-positive and gram-negative bacteria. the event of a controlled release system for CP is very interesting for post-surgery prophylaxis, for combating skin infections, soft tissues, joints, and bones. Inhibition of topoisomerase (DNA gyrase) enzymes, inhibits the relief of supercoiled DNA and promotes the breakage of double-stranded DNA [8].

Currently, intensive research is underway to formulate CIP into different nanocarriers to treat several diseases. Some examples are collected in Table 1.

Table 1. Ciprofloxacin-loaded nanocarriers under investigation with the aimed indication.

Type of Nanocarrier	Excipients Applied in Nanocarrier	Aimed Indications	Targeted Organs
Polymeric nanoparticles (NP) in nanofibers (NF)	PLGA and PCL–NP PEOT/PBT–NF	tissue engineering	middle ear
Nanoparticles and coated nanoparticles	PLGA and chitosan (coat)	root canal infection	tooth
Composite nanoparticles	synthetic nano-HA and sodium alginate	tissue engineering	bone
Microspheres	PLGA	osteomyelitis, orthopaedic infections	bone
Microparticles	calcium carbonate, sodium hyaluronate	lung infections	lungs
Nanocrystals inside liposomes	HSPC, cholesterol	lung infections	lungs
Amorphous nanoparticle Complex	dextran sulfate	non-cystic fibrosis bronchiectasis	Lungs
Lipid-core nanocapsules	PCL, sorbitan monostearate, oleic acid, polysorbate 80	cystic fibrosis	Lungs
Nanofibers	PVP	wound infections	Skin
Nanofibers	PVA, chitosan, graphene oxide	wound infections	skin

Abbreviations: HA–hydroxyapatite; HSPC–hydrogenated soy phosphatidylcholine; PCL-poly("-caprolactone); PEOT/PBT–Poly(ethylene oxide terephthalate)/poly(butylene terephthalate) copolymer; PLGA–poly(D,Llactide- co-glycolide); PVA–poly(vinyl alcohol); PVP poly(vinyl pyrrolidone).

Selection of drug candidate for transdermal delivery

The transdermal route of administration can't be employed for a large number of drugs. Judicious choice of the drug substance is that the most important decision in the successful transdermal system [9].

Advantages of transdermal drug delivery over the traditional dosage forms

1. The Transdermal drug delivery system (TDDS) are often defined as a delivery device, which upon application on an appropriate skin surface will be able to deliver the drug into the systemic circulation at sufficient concentration to ensure therapeutic efficacy, a further limitation to oral drug delivery, are often avoided with transdermal administration.
2. Steady permeation of drug across the skin, allowing consistent serum drug level, often a Goal of therapy.
3. Almost like intravenous infusion, it also achieves consistent plasma levels, but non-invasive in nature.
4. In addition, if toxicity develops from a drug administered transdermal, the consequences could be moderated by removing the patch.
5. Transdermal drug delivery are often used as an alternative delivery system for patients who cannot tolerate oral dosage forms.
6. It's of great advantage in patients who are nauseated or unconscious.
7. Drugs that cause gastrointestinal upsets are often good candidates for transdermal delivery because this method avoids direct effects on stomach and intestine.
8. Topical patches are an easy , non-invasive thanks to deliver substances directly into the body.
9. Topical patches over a controlled, steady delivery of medication over long periods of your time.
10. Topical patches have fewer side effects than oral medications or supplements.

Disadvantage to transdermal delivery systems stems

Disadvantage to transdermal delivery systems stems from the very fact that the skin is a very effective barrier; as a result, only medications whose molecules are sufficiently small to penetrate the skin can be

delivered in this method. a good variety of pharmaceuticals are now available in transdermal patch form. Characterization of skin patch is use to check its quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity &cutaneous toxicological studies [10, 11].

Factors affecting transdermal permeation

Biological factors

1. Skin condition

The skin itself acts as a barrier many agents like acids alkali penetrates through the skin. Methanol chloroform is that the solvents that remove lipids fraction by making tiny shunts on skin.

2. Skin age

It is seen that skin of adult and young ones are more susceptible compared to old ones. Some acids like steroids, boric acid and hexachlorophene have several side effects on children.

3. Blood supply

Any quite change in blood circulation affects the transdermal absorption.

4. Regional skin site

This factor effects the penetration. Nature of skin, thickness and density of skin layers vary from site to site these effects significantly penetration.

5. Species differences, skin thickness keratinization of skin vary from species to species so, it's effecting the penetration.

Physicochemical factors

1. Skin hydration

Generally, when skin absorbs water, it swells it softens the skin, and therefore the ability to pass through the skin increases for the drug.

2. Temperature and pH

The penetration rate varies as temperature varies. If the temperature is a smaller amount penetration is also less. Weak acids and weak base dissociate depending upon pH and pka values. Temperature and pH are the important factor for the skin penetration.

3. Drug concentration

Flow of drug is proportional to concentration gradient across the barrier concentration gradient are going to be more when the concentration of drug will be more across the barrier.

4. Molecular size and shape

Small particles will penetrate easily than large particles

Drug substance

For developing the transdermal drug delivery system drug should be administered with great care. Following are the desirable properties for transdermal delivery [12].

Physicochemical properties

The molecular size of the drugs should be but 1000 Daltons more than 1000 Daltons drugs are suitable for TDDS.

- The drug should have both lipophilic and hydrophilic phase.
- The drugs should be of low freezing point.
- Apart from these properties the drug should be potent.
- The drug should have short half-life.
- It should be non-irritating.

Recent innovations in transdermal drug delivery system

Iontophoresis

It involves permeation of ionized drug molecule under the influence of electrical current. Here the cationic drug is placed under anode and cationic under the cathode [13]. it's responsible for the movement of ions across the membrane with the small externally applied potential difference. this system is used in in Vivo transport of ionic and non-ionic drugs by the application of electrochemical potential gradient [14]. Polarity, valency and mobility of the drug molecules will affect the iontophoresis the efficacy will get effect by this factor [15]. Iontophoresis is that the electronic means of reminding to the patient to changes the dosage if needed.

Electroporation

High voltage within the form of direct current [100 volts] are applied on the skin for a very short period of time [milliseconds] which indies formation of transient pores. These pores allow the usage of macromolecules from the surface of the cell to the intracellular space via combination of diffusion and electrophoresis [16]. this is often very safe and painless procedure. It's having disadvantages like small delivery loads sometimes death heating damage.

Sonophoresis

The technique is employed to increase the skin permeation using ultrasonic energy (20 KHz to 20MHz). The drug is mixed with solvents placed on the skin Beneath the probes after applying coupling to skin.

Waves are generated by applying AC electrical signal to make the crystal then the crystal undergoes rhythmic deformation to produce ultrasonic vibrations [17]. the specified range of ultrasound frequencies generated by device can improve transdermal drug delivery [18] low frequencies are more effective [19]. The accurate mechanism for this system is still incomplete the problems with this device are availability, treatment cycles for delivery and undesirable side effects.

Microneedle

The first micro needle was discovered in the year 1976. Recently ALZA Corp has commercialised technology name Macro-flux. Macro-flux has advantage that it can be used either in combination with other drug reservoir or drug coating [20]. The drug is distributed through the needle it is most popular and Novel type of transdermal drug delivery system [21]. The needle could be of different types such as solid micro needle and micro needle patches with different mechanism of action [22]. For the Manufacturing of dissolving/hydrogel microneedle this method is mainly used [23].

Abrasion

It involves the removal of upper layer of skin to ensure the permeation of applied medicaments. Some of the devices are used by dermatologist ex. Microdermabrasion treatment of acne's, scar other skin marks [24].

CONCLUSION

One might draw the conclusion that transdermal patches could be used for transdermal ciprofloxacin delivery. It could be concluded that the transdermal patches have potentiality in transdermal administration of ciprofloxacin. All formulation showed good physicochemical properties like thickness, weight variation, and drug content. The in-vitro release results demonstrated that the diffusion mechanism was crucial to the drug release from the patch formulation. According to studies on the effects of penetration, concentration is a penetration enhancer. Thus, the transdermal patches we made could provide the delivery of drug at a controlled rate across intact skin and might be used in clinical situation.

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