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Review Article

Enhance Penetration Of Diclofenac Gel With Using Hemp Seed Oil As A Penetration Enhancer: A Review

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ABSTRACT

The transdermal route of administration offers an alternative pathway for systemic drug delivery with numerous advantages over conventional routes. Regrettably, the stratum corneum forms a formidable barrier that hinders the percutaneous penetration of most drugs, offering an important protection mechanism to the organism against entrance of possible dangerous exogenous molecules. Different types of penetration enhancers have shown the potential to reversibly overcome this barrier to provide effective delivery of drugs across the skin.

Diclofenac gel is a topical medication that contains diclofenac, which is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac work by inhibiting the production of prostaglandins, which are substances in the body that play a role in inflammation and pain.

In this review we investigate the formulation and evaluation of the biopharmaceutical behaviours of the transdermal gel containing Diclofenac with an attempt of use of hemp seed oils as permeation enhancers for transdermal applications.

INTRODUCTION

Transdermal drug delivery offers a very advantageous route for drug delivery compared with the other routes of drug administration having advantages such as bypassing the hepatic first pass metabolism, and longer duration of action [1,2]. However, the barrier function of the skin outermost layer, the stratum corneum (SC) is one of the main limitations to it, and for this reason, skin penetration enhancers are gaining the greatest interest in pharmaceutical research [3]. Penetration enhancers help in the permeation of the desired drug (penetrant) through the skin by lowering the impermeability of the skin [4]. Some properties which are desired in permeation enhancers are the must be pharmacologically inert, nonirritating, nontoxic, nonallergic, compatible with drugs and excipients, odorless, tasteless, colorless, and inexpensive and also have good solvent properties [5,6].

Diclofenac gel is a topical medication that contains diclofenac, which is a nonsteroidal anti-

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inflammatory drug (NSAID) [7]. It is commonly used to relief pain, inflammation, and swelling caused by various conditions such as arthritis, sprains, strains, and other musculoskeletal injuries [8]. Diclofenac work by inhibiting the production of prostaglandins, which are substances in the body that play a role in inflammation and pain[9,10].

This review article describes the natural penetration enhancers that have been employed to enhance the transdermal permeation of diclofenac

1. Gels : Topical dosage forms:

The word "Gel" was first applied to some semisolid materials in the late 1800s, based more on physiological characteristics than molecular makeup. Gels consist of high amount of diluted crosslinked networks that exhibit non-steady state flow. (11) They have a two-part semisolid structure that is filled with liquid. Among its common distinctive features include continuous structure which resemble properties of solids. Gels are increasing rapidly as the formulation of choice for topical drug delivery due to the molecular stability, arrangement, and biocompatibility of the bioactive ingredient involved in the formulations. (12) Organic polymers are employed in the majority of topical skin preparation, with carbomers that makes the product a nice, glittery, transparent and make it easy to remove the product from the skin by use of water depending on the type of foundation being utilized. The type of base used for topical medications for dermatology composition has a substantial effect on its effectiveness. Bases with high concentrations of oleaginous compounds give dry, irritated skin emollient properties. (13) More specifically, occlusive barriers (which stop moisture from escaping into the atmosphere) can be formed on the skin by bases containing non-volatile oleaginous compounds, including hydrocarbon bases. (14) Consequently, moisture seeps into the space between the stratum corneum and the coating of ointment, moisturising it. To make it easier for medication molecules to go through intracellular and intercellular channels and pathways, the stratum corneum is hydrated. The medicine serves as both the cream's foundation and its usual dispersion as microscopic particles in the moisture layer. Because only the dissolved substance applied topically will pass through the corneum stratum as a single molecular entity, More skin occlusion typically leads to improved absorption of percutaneous medicine. (15)

The integrity of the gel is determined by the solvent affinity of the polymer. The classical gel theory distinguishes between three different kinds of solvents:

i. A free and mobile solvent.

ii. A solvent bound salvation layer, usually through hydrogen bonding; and

iii. A solvent trapped inside the network structure.

a) DIFFERENT GELS FORMULATION: (16)

Gels can be categorised according to the type of solvent and colloidal phase.

i) Colloidal Phase-Based:

They are divided into

(One-Phase System) Organic

Inorganic (System in Two Phases)

- **Organic (Single Phase System) :**

On the twisted strands, there are sizable organic molecules that are continuously dissolved. The majority of organic gels are single-phase solutions made up of organic liquids like Plastibase and gelling agents like carbomer and tragacanth.

- **Inorganic (Two Phase System) :**

To avoid the formation of floccules in the formulation it is necessary that in the formulation the size of partition in dispersed phase is relatively large and develops a three dimensional structure in the formulation of gel throughout. If the system has small particles instead of larger molecules the formulation of gel will remain unstable.

Thixotrophy is its primary requirement, which means that when disturbed, they transform from a semisolid to a liquid. Examples include bentonite magma and aluminium hydroxide gel.

ii) Based on the Nature of Solvents: (17)

➢ **Hydrogels (Water Based):**

An arrangement of hydrophilic polymers arranged in three dimensions that retains its structural integrity while submerged in water is called a hydrogel. This is possible because individual polymer chains have been chemically or physically cross-linked to create the hydrogel. Examples of hydrophilic colloids are silica, sodium alginate, tragacanth, bentonite, and pectin. The hydrogel can be utilised as an ECG medical electrode, rectal medication delivery system, and sustained release drug delivery system.

➢ **Using a non-aqueous solvent (organogels):**

Gels with away from water solvent known as organogels are a type of gel in which there is three-dimensional, cross-linked network encloses a liquid organic phase. The addition of a polar solvent causes the lecithin solution in organic solvents to organogellate, or gel.

➢ **Xerogels :**

Xerogels are gels with a solid shape that are created by combining gradual, room-temperature drying with uncontrolled shrinking. Viscose sintering takes place when a xerogel is heated over a certain point, causing the porous gel to solidify into a thick glass. A few examples are ribbons made of tragacanth, dry cellulose, and polystyrene. Gels are sometimes categorised as plastic, pseudo-plastic, and thixotropic gels according to their non-Newtonian flow.

Formulation of Gel: (18)

The following elements could be present in the topical gel:

a) Polymer or gel-forming agent

b) Substances used in drugs

c) Enhancer of penetration

i) Organic polymers

Proteins: Xanthum gum, collagen, gelatin, etc. Polysaccharides: such as guar gum, pectin, tragacanth, agar, and alginic acid

ii) Polymers that are semi-synthetic Cellulose derivatives, including methyl cellulose, carboxymethyl cellulose, hydroxypropyl methylcellulose, and hydroxyethyl cellulose.

iii) Man-made Polymers Polyacrylamide, Polyvinyl Alcohol, Polyethylene, and its copolymers are examples of carbomers. Other examples are Carbopol-934, Carbopol940, and Carbopol-941.

iv) Inorganic Substances Examples consists of Aluminum hydroxide along with Bentonite.

v) Surfactants: Sodium lauryl sulphate, and Cetosteryl Alcohol are most commonly used surfactants.

b) Properties of Drug : (19)

Drug compounds are important in the topical product's formulation. The following are some crucial medication characteristics that affect how readily it diffuses through gels and skin:

i) Physiochemical Properties of Drugs for gels : (20)

- The medication's molecular weight should be under 400 daltons.
- Strongly alkaline or acidic medications are not ideal for topical application.
- The medication needs to be sufficiently lipophilic
- Candidates for drugs should have a pH between 5 and 9.

ii) Biological consideration of Drugs for gels: (21)

- The medication shouldn't irritate skin.
- The GI tract-degradable medications can be applied topically.
- Drugs shouldn't provoke a skin immunological response.

c) Permeation Enhancers : (22)

As chemicals that can facilitate the entry of pharmaceuticals into the skin, accelerants and

sorption promoters are other names for penetration enhancers. (23) Ideally, a penetration booster would have the following characteristics : -

- It ought to be inert chemically and pharmacologically.
- It should not be poisonous, irritating, or allergic.
- It ought to be cheap, tasteless, colourless, and odourless.
- It should act quickly and last for a predictable amount of time. (24)

2. Hemp Seed

Hemp seed oil (Hemp oil), obtained from the seeds of *Cannabis sativa* is known for its nutritive, health-enhancing properties and bioactivity. Hemp oil contains essential fatty acids (EFAs): Omega-6 fatty acids including linoleic acid, omega-3 containing the anti-inflammatory gamma linoleic acid (GLA) and omega 9. The ratio of omega-3 and omega-6, which are present in Hemp oil, is in the preferred ratio of 1:3 [25] for medical applications. Indeed recently Hemp oil has been found to exert antioxidative [26] [27] [28] , and anti-inflammatory [29] [30] effects.

As to skin health, Hemp oil with the abundance of its fatty acids is an excellent choice for nourishing the skin and protecting it from inflammation, oxidation, and other causes of aging [31] [32] . Hemp oil does not contain tetrahydrocannabinol (THC), which is the psychoactive component of marijuana.

Hemp seeds contain approximately 40% oil, 30% fibers and 25% proteins [33,34]. Those oils are rich in triacylglycerols (TAGs) represented by 18 different molecules; the predominating tags were LLL and OLLD with respective values of 23 and 19% [35].

Moreover, those oils contain high amounts of polyunsaturated fatty acids, which represent approximately 80% total fatty acids [36]. The fatty acid composition is characterized by the predominance of linoleic acid with range values of 45–60%, followed by oleic acid and palmitic with respective range values of 15–40% and 5–6% [37,38].

Hemp seeds contains also considerable amounts of polyphenols and tocopherols [39], the hydroalcoholic extract of Cannabis seeds contained many polyphenols such as gallic acid (12.9 ± 18.3 mg/100 g) and catechin (6.0 ± 5.2 mg/100 g) [40] reported the presence of additional polyphenols, namely quercetin-o-glucoside, n-trans-caffeoyltyramine and rutin.

Moreover, another sub-class of polyphenols known as cannabisins have been reported on the seed hydroalcoholic maceration [41]. The last authors described the presence of 11 molecules, namely cannabisin A, B, C, D, E, F, G, I, M, N and O, although these compounds have not been quantified. Concerning the tocopherols, four different isomers have been identified: the lead tocopherols are γ- and δ-tocopherols with 426 and 33 mg/kg, respectively [42,43].

3. Hemp Seed Oil Characterization[44]

Recorded GC-MS chromatograms and spectra of both unsaponifiable matter and saponifiable fatty acid methyl esters in saponifiable matter (Figure 1A,B) revealed the compositional features of the working sample of hemp seed oil described here in.

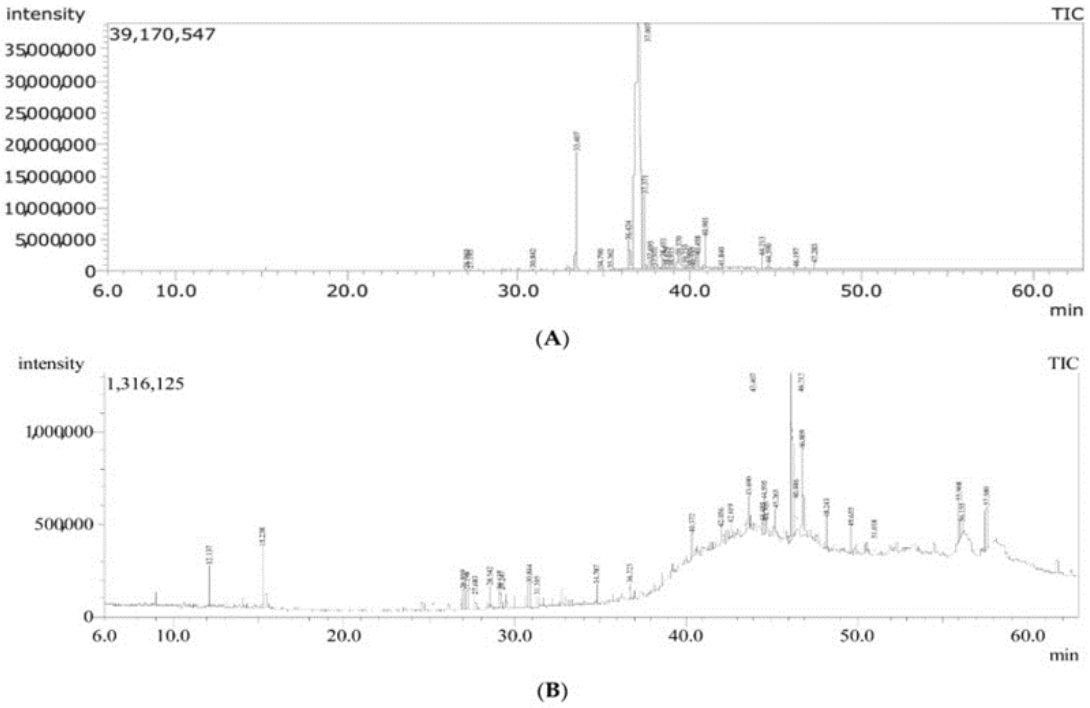

Figure1: Total ion chromate grams (TICs) of GC-MS/MS analysis of hemp seed oil working sample: (A)TIC of saponifiable matter, (B) TIC of un saponifiable matter.

1. PERMEATION STUDIES

The estimation of percutaneous absorption of a molecule is a very important step in the evaluation of a molecule of TDDS [45]. Moreover, in both pharmaceutical and cosmetic research, to support the development of TDDS skin permeation rates, evaluation has become a very important step [46]. The various ways by which the transdermal permeations of a drug molecule can be studied are.

2. In vitro release studies

Franz diffusion cell is used for carrying out in vitro release studies wherein the donor compartment the circular patch is mounted, the receptor compartment of which is filled with phosphate buffer saline (pH - 7.4), and the whole assembly is maintained at 32°C by the warm water circulation through the water jacket and is stirred at 40-50 rpm. The patch was kept in contact with the receptor liquid. About 0.5 ml of sample was withdrawn at regular intervals for 8 hrs and was replaced with the same amount of the medium. The samples were subjected to filtration, diluted, and analyzed spectrophotometrically [47]. In vivo release studies Animal models Hairless rat, hairless rhesus monkey, guinea pig, and rabbit are the most commonly used species used for evaluating transdermal drug. One of the most reliable models for in vivo evaluation of transdermal delivery in man is the rhesus monkey [48]. Animals in small scale are preferred for in vivo studies because of economic factors and availability [49].

2.1.Human volunteers

Clinical phase is one of the important stages in the development of a transdermal device, and in this stage, the formulation is tested in human volunteers for the collection of pharmacokinetic and pharmacodynamics data which are required to evaluate the generation of toxic effect during application of formulation. C14 radioisotope is used for labeling of drug to determine percutaneous absorption in human and measuring the radioactivity in excreta, but for knowing, amount residing in a body and amount excreted by other route attention is required [50].

2.2.In vivo dermal absorption study

For in vivo dermal absorption test, the dorsal surface (approximately 4 cm × 3 cm area) of the rabbit skin is first clipped free for the application of the test substance and this is done before 24 hrs of starting the test. The requisite amount of the test substance was applied to the area after that check it up to 24 hrs to see periodically there is any itching, redness or swelling.

CONCLUSION

The field of transdermal drug delivery due to its advantages has been rapidly developing and which has stimulated various researches to incorporate more and more drugs through transdermal route. Skin serves a limitation for permeation of drugs, and hence, permeation enhancers are used to increase the permeability of the poorly absorbed drugs and hence maintain its bioavailability. The review article summarizes Using hemp seed oil as a penetration enhancer in diclofenac gel could potentially be effective. Hemp seed oil has been studied for its ability to enhance the penetration of various compounds through the skin due to its composition of fatty acids, particularly linoleic acid and oleic acid. These fatty acids can help to soften the skin and improve its permeability, allowing for better absorption of medications like diclofenac gel.

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Conflict of Interest:

None

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