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Formulation and characterization of naproxen transdermal patch for Sustained drug delivery system

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Abstract
Considering that most inflammatory diseases occur locally and near the body surface, transdermal drug delivery of non-steroidal anti – inflammatory drug (NSAIDs) may be an interesting strategy for delivering these drugs directly to the diseased site. Naproxen, a potent non-Steroidal anti-inflammatory drug (NSAID) inhibits arachidonic acid metabolism by cyclo-oxygenase and lipo-oxygenase. The compound has been widely used in the treatment of rheumatoid arthritis, osteoarthritis, as well as a mild to moderate painkiller. In these study naproxen transdermal patches were prepared by solvent evaporation method using polymer HPMC and PEG 400.Propylene Glycol used as plasticizer. The prepared patches will evaluated for thickness, folding endurance, tensile strength, flatness, drug content uniformity, *In-vitro* permeation study, *In-vitro* release study was performed by using Franz-diffusion cell.

Keywords: naproxen transdermal patch, transdermal drug delivery system (TDDS)

Introduction

Transdermal Drug Delivery System (TDDS)

Transdermal patches comprise a method of delivering medication through the skin in a non-invasive manner. During transdermal drug delivery, a patch is adhered to a patient's skin. The patch contains the medication prescribed to the patient and is designed in such a way that the medication permeates the skin in a controlled fashion thus attaining more steady levels of the drug in the body. Patches are presently being marketed which can be worn anywhere from as little as eight hours to as long as seven days, depending on their therapeutic indication. These patches are secured with adhesives, which are designed to adhere comfortably to the skin which in turn allows a patient to use the patches for as long as is indicated by his or her physician. The markets of the world are replete with medications designed to ease and/or cure the symptoms associated with thousands of conditions. Traditional medication delivery methods, such as pills, capsules, liquids, powders, and intravenous needles, are often inefficient or invasive and can lead to undesirable side effects. Amongst the newer methodologies for administration of medicines is the use of transdermal approaches, including gels and patches for the treatment of many of the more common ailments.

Transdermal Patches

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.

The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method. A wide variety of pharmaceuticals are now available in transdermal patch form. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness [1, 2]. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it over comes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems.

So, this Transdermal Drug Delivery System has been a great field of interest in the recent time. Many drugs which can be injected directly into the blood stream via skin have been formulated. The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin. A Transdermal Patch has several components like liners, adherents, drug reservoirs, drug release membrane etc. which play a vital role in the release of the drug via skin. Various types of patches along with various methods of applications have been discovered to delivery the drug from the transdermal patch. Because of its great advantages, it has

become one of the highly research field among the various drug delivery system. Here, a general view over the transdermal patch has been discussed along with its advantages, disadvantages, methods of applying, care taken while applying, types and applications of transdermal patch and recent advances along with recent patents and market products

Fig 1: Sample transdermal patches.

On left is a 'reservoir' type, on the right a 'Single-layer Drug-in-Adhesive' version. Both contain exactly the same level of the same active ingredient with identical release rates.

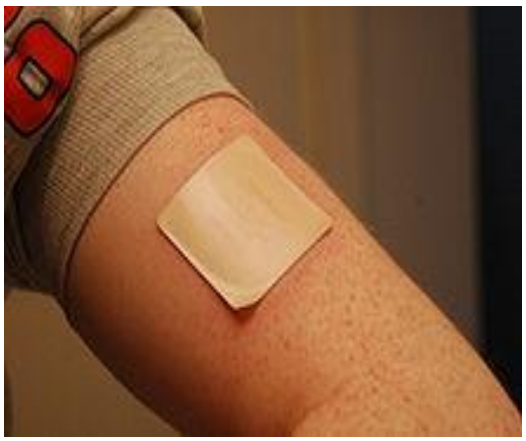

Fig 2: Nicoderm CQ patch

Fig 3: Contraceptive patch

Disadvantages of TDDS

1. Drugs with high molecular weight (> 500 Da) are difficult to penetrate the stratum corneum.
2. Drug dose is a limiting factor.
3. Drugs with partition coefficients in either of the extremities (low or high) fail to reach the systemic circulation.
4. Bioavailability of a drug through transdermal route is greatly reduced for the drugs which get metabolized in liver.
5. Skin permeability is also a limiting factor.
6. Drugs requiring higher blood levels are difficult to formulate as transdermal drug delivery systems.
7. May lead to skin irritation and allergic response.

Factors Affecting Transdermal Permeation

Penetrate concentration

Increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a long period of time.

Partition coefficient

A lipid/water partition coefficient value of 1 or greater is required for optimal transdermal permeability. It may be altered by chemical modification without affecting the pharmacological activity of the drug.

PH conditions

Applications of solutions whose pH values are either in high or low extremities can be destructive to the skin. With moderate pH values, the flux of ionizable drugs is affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

Release characteristics

Solubility of the drug in the vehicle affects the release rate. The mechanism of drug release depends on the following factors:

a) Whether the drug molecules are dissolved or suspended in the delivery systems.
b) The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
c) pH of the vehicle

Composition of the drug delivery system

The composition of the drug delivery system which includes boundary layers, thickness, polymers and vehicles which not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Uses of TDDS

The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans).
- Hormonal patches
  - Estrogen patches are sometimes prescribed to treat menopausal symptoms (as well as post-menopausal osteoporosis) and to transgender women as a type of

hormone replacement therapy.
- Contraceptive patch (marketed as Ortho Evra or Evra) and
- Testosterone CIII patches for both men (Androde) and women (Intrinsa).

- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- Transdermal scopolamine is commonly used as a treatment for motion sickness [4].
- The anti-hypertensive drug clonidine is available in transdermal patch form [5] under the brand name Catapres-TTS [6].

Materials and Method of Preparation for TDDS

Drug Profile

Drug Selection Criteria for Transdermal Patch

- The drug to be incorporated should have low dose up to few mg.
- The drugs with smaller and moderate molecular weight are preferable.
- Good solubility in organic solvent as well as also good stability.

Physical and Chemical Characteristics

Naproxen is a white or almost white odourless powder. It is soluble in organic solvents such as chloroform and slightly soluble in water.

Naproxen transdermal patch

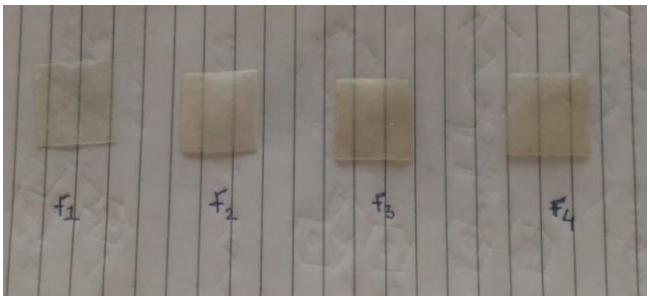

Fig 4

Result and Discussion

Melting point

Table 1: Melting point of Naproxen

Sr. No	Parameters	Naproxen
1	Melting point (°C) (Test sample)	151-153
2	Melting point (°C) (Reference)	152-155

Melting point of naproxen was found to be in the range of 151-153°C, while in the standard literature it is reported in the range of 152-155°C. So it can be concluded that naproxen was in pure state.

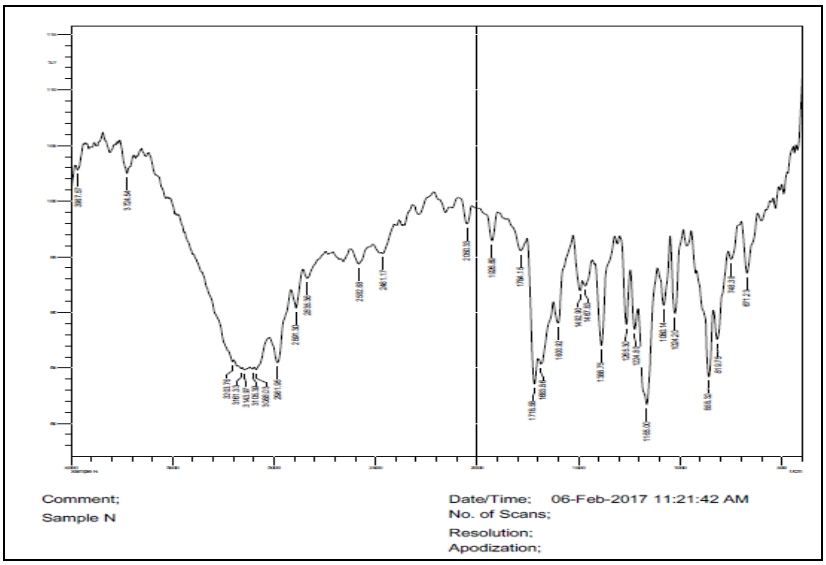

Fig 5

In vitro diffusion study

The *In vitro* diffusion study is carried out by using a Franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60ml and effective surface area of permeation 3.14 sqCms. The egg membrane is mounted between the donor and the receptor compartment. A weighed amount of transdermal patch is placed on one side of membrane is phosphate buffer Ph 7.4. The receptor compartment surrounded by water jacket to maintain the temperature at 37 ±5 ◦c. Heat is provided using a thermostatic hot plate with a magnetic stirred by Teflon coated magnetic stirrer. During each sampling interval samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each Occasion. The samples withdrawn are analyzed spectrophotometrically at 230nm. The drug release study was performed.

In vitro released profile of naproxen transdermal film F1, F2, F3 & F4

Table 2

Sr.no	Times(h)	F1(% drug release)	F2(% drug release)	F3(% drug release)	F4(% drug release)
1	0.5	4.50	3.50	3.90	4.11
2	1	8.30	6.60	5.50	7
3	2	16.16	10.40	11.20	12
4	3	25.16	17.75	15.50	18
5	4	33.10	24.92	25.25	27
6	5	40.15	30.67	30.70	32.10
7	6	45.36	38.80	40.10	40
8	7	54.81	46.55	47	49
9	8	65.41	55.68	56	57.10
10	9	71.31	64.71	65.10	66

Percentage drug release of f1 and f2

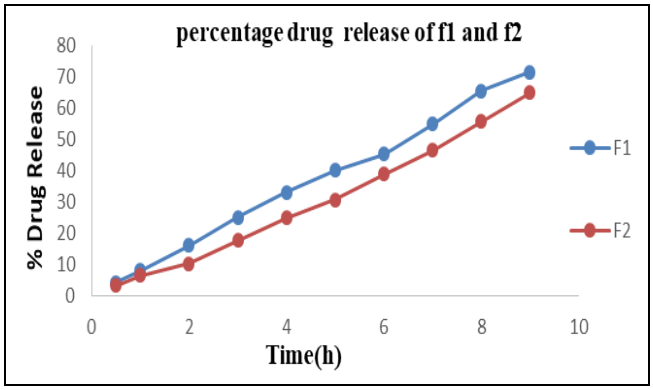

Fig 6

Percentage drug release of f3 and f4

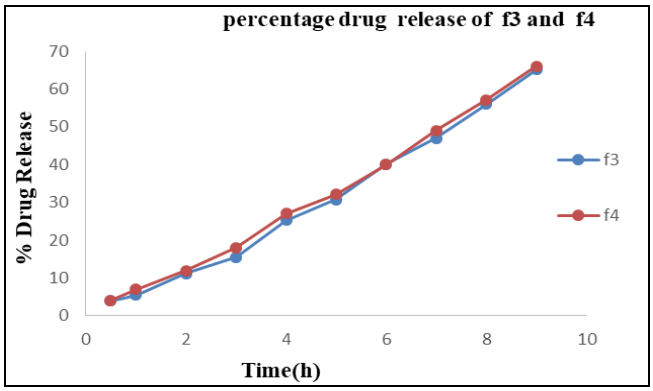

Fig 7

Calibration curve of naproxen

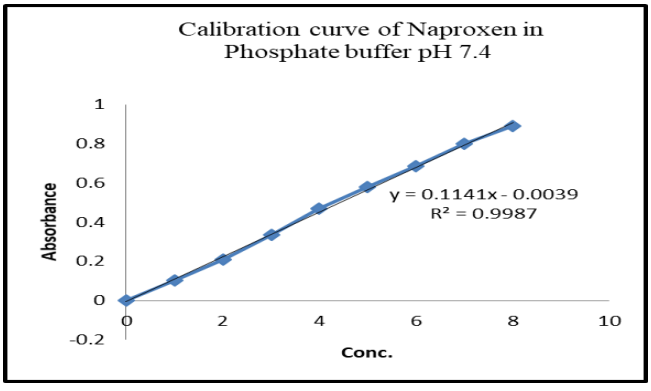

Fig 8

Composition of batches of transdermal patches of Naproxen

Table 3

Batch	Drug (Naproxen) mg	Polymer (HPMC:PEG 400)	Plasticizer (propylene Glycol) ml	Casting solvent (water) Ml
F1	10	1:1	1	10
F2	10	1:1	2	10
F3	10	1:1	1	10
F4	10	1:1	2	10

Thickness, folding endurance, drug content, flatness and weight variation of batches of Naproxen transdermal patch

Table 4

Batch	Thickness (mm)	Folding endurance	Drug Content (%)	Flatness (%)	Weight Variation (mg)
F1	0.24	315	98.33	100	92
F2	0.32	300	93.88	100	92
F3	0.36	310	91.38	100	99
F4	0.30	320	88.88	100	95

Conclusion

TDDS is very helpful to the patients suffering from the dreadful diseases, where the localization of the specific target becomes difficult during therapy. This review article provides valuable information regarding the transdermal patches and its evaluation process details as a ready reference for the research scientists who are involved in TDDS. TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. The application of TDDS has increased because of high end technology and devices.

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