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The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(6): 74-77

www.thepharmajournal.com
Received: 20-06-2015
Accepted: 22-07-2015

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Formulation and evaluation of transdermal patch of Cefdinir with various polymers

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Abstract
Cefdinir is an antibiotic used to treat certain infections caused by bacteria, such as pneumonia, bronchitis, ear infection, sinusitis, pharyngitis, tonsillitis, and skin infections. In this study, Cefdinir was used to prepare transdermal patches using various polymers such as Cellulose derivatives, polyvinyl alcohol, Polyethylene, Polypropylene, Polyvinylpyrrolidone and Polymethyl methacrylate with their different concentration. Patches were prepared by the solvent evaporation technique by using PEG-400 as plasticizer. Dimethyl sulphoxide was used to enhance the transdermal permeation of Cefdinir. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance and percentage of moisture content. All prepared formulations indicated good physical stability.

Keywords: Antimicrobial Activities, Bio Adhesive Strength, Cefdinir, Transdermal Patches, Transdermal Film, Permeation Enhancer, *in-vitro* Permeation Study.

1. Introduction [1, 2, 3]

Transdermal drug delivery systems, or transdermal patches, represent relatively new and very advanced administration systems for pharmaceutically active agents.

Transdermal drug delivery systems, where applicable, offer several advantages over other conventional dosage forms. Using TDDS, it is possible to achieve the following:

- Avoidance of the 'first pass effect'
- A stable and controlled blood level
- Comparable characteristics with intravenous infusion
- Termination of further administration, if necessary
- Long-term duration (ranging from a few hours to one week)
- No interference with gastric and intestinal fluids
- Administration of drugs with:

→ A very short half-life
→ Narrow therapeutic window
→ Poor oral absorption.

(2) Various types of patch designs

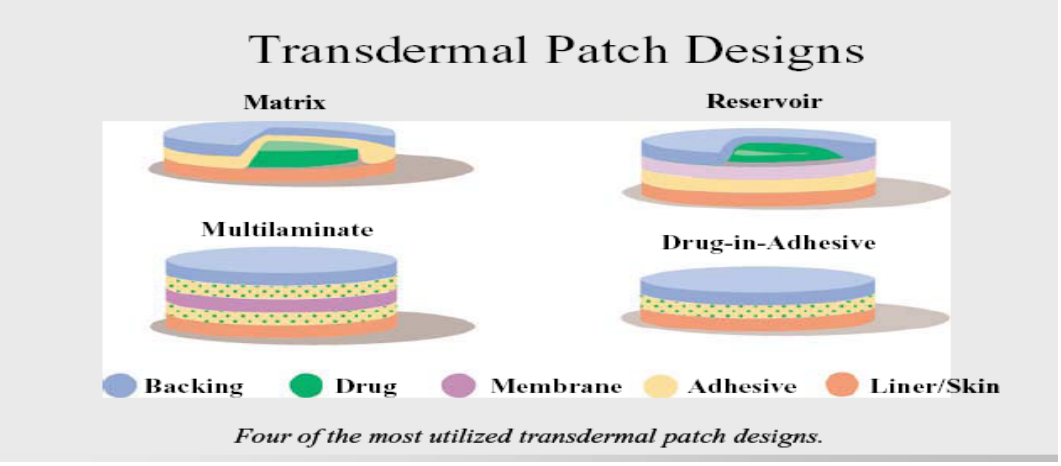

Fig 1: Transdermal patch designs

A) ***Drug in matrix***
Skin-controlled transdermal system with no membrane, which incorporates a drug-in-matrix layer between release liner and backing layers. In general, this type of system relies on characteristics of the skin to control the rate at which the drug diffuses into the body.

B) ***Drug in reservoir with a membrane***
A transdermal system that contains a rate-controlling membrane, with the drug in a reservoir. In general, this type of system is used when the delivery compound is of higher molecular weight and therefore more difficult to deliver transdermally.

C) ***Drug in adhesive***
A system in which the drug is incorporated directly into the adhesive, rather than as a separate layer. This system is used for smaller molecular compounds, which are among the easiest compounds to deliver via transdermal means.

D) ***Multi-layer Drug-in-Adhesive System***
Transdermal system, which tailors the rate of delivery of a drug via the use of layers of drug, membranes and adhesives. This type of system is particularly useful when prolonged drug delivery is desired.

(3) Basic Components of TDDS
Both matrix patches and liquid reservoir patches consist of several components. Some of these are similar in both classes, while others are class-specific.
Those common to both include:
a) Backing films
b) Release liners
c) Pressure-sensitive adhesives
d) Active ingredient(s)
e) Permeation enhancers
f) Other additives
g) Microporous or semi-permeable membranes
h) Pouching materials

→ Although the pouching materials do not represent a direct component of patches, I have included them because,
Firstly, a patch is never fully isolated from its pouching material. Secondly, they play a critical role in the patch's stability, and finally, they protect children (in cases of Nicotine and Fentanyl) from a very strong and dangerous active.

1. Backing Films
Backing films play a critical role in the TDDS (as long as they are packaged in their pouch), as well as during the use of the system.

The role of such a film is
- To protect the active layer and safeguard the stability of the system, and
- To affect skin permeation and tolerance, depending on occlusion or breathability.
- Because of the huge variety of ingredients, the release liner must be fully inert to the ingredients in order to avoid any type of incompatibility.
- It must also be flexible, comfortable and must present good affinity with the adhesive, as well as excellent printability.

The most common materials used as release liners are
- Polypropylene,
- Polyethylene (both high and low density),
- Saran,
- Polyesters,
- PVC, and
- Nylon.

2. Release Liners
A release liner is a film covered with an anti-adherent coating.

The role of the release liner is
- To protect the system as long as it is in the package, and it is removed just before the adhesion of the TDDS to the skin.
- Release liners play a crucial role in the stability of the product and in its safe and functional use. The release liner must therefore be chosen very carefully.
- An incorrect release liner does not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life.

There are several combinations of film and anti-adherent coating that are suitable, and the choice made depends on the ingredients of the system.

The most common films used as release liners are
⇨ Paper-Based,
⇨ Plastic Film-Based And
⇨ Composite films.

The two major classes of coating are
⇨ Silicones and
⇨ Fluor-polymers.

3. Pressure-Sensitive Adhesives
For both classes of TDDS, pressure-sensitive adhesives (PSAs) play a major role,
- Serving as the matrix that carries everything active (such as additives and permeation enhancers) and
- The means for making the patch stick to the skin.

There are several classes of PSA and each one is used for a very specific reason. The PSA must stick to the skin immediately and stay there for as long as it is needed. The correct choice of PSA has a critical effect on the stability of the system, the release of the active, the dermatotoxicity potential, and the accurate administration of the drug.

There are three major families of PSAs
⇨ Rubber-based psas,
⇨ Acrylic psas in the form of acrylic solutions,
⇨ Emulsion polymers or hot melts, and silicon PSAs.

Each class of adhesive has several pros and cons (see *Table)*. For each family of adhesives there are several sub-categories that give the required flexibility to the formulator. Each active is different and the choice of adhesives is critical for the success of the final product. There are several examples, such as:

⇨ **Acrylics**
→With or without functional groups
→Cross-linked or not
→ Solutions, hot melts or emulsions

Silicon-Based Adhesives
→ Standard
→ Amine-compatible

Rubbers with different
→ Testifiers
→ Cross-linkers
→ Stabilizers and plasticizers

Materials and Methods
The materials used in this study were following: Cefdinir as drug, HPMC K4M, HPMC K100M, polyvinyl alcohol, Polyethylene, Polypropylene, Polyvinylpyrrolidone and Polymethylmethacrylate as polymers and PEG-400 as plasticizer. Dimethylsulphoxide was used to enhance the transdermal permeation of Cefdinir. Whole preparation was done by solvent casting technique. All other laboratory materials were of analytical grade.

Preparation of Transdermal Patches [4, 5]
- The patches were prepared by solvent evaporation technique using Cefdinir, plasticizers and penetration enhancer.
- 5 mg Cefdinir was dissolved in 5 ml ethanol in a beaker followed by addition of 6 ml of PEG 400.
- The mixture was stirred continuously until a solution was formed.
- Now add 0.5 gm polymer in formed solution and allow to stir for 10 min.
- Finally add the penetration enhancer 2 ml in above solution and make up the volume up to 20 ml.
- This dispersion was properly stirred and poured into castor oil lined petri dish.
- A funnel of suitable size was inverted over the petri dish to minimize solvent evaporation.
- Casting solvent was then allowed to evaporate 48 h to obtain dry films.
- After 48 hours, patches were scrapped with knife and cut in to uniform pieces of 2 × 2 cm.
- The patches were stored between sheets of wax paper in a desiccator until further analysis.

Table 1: Formulations of Transdermal Patches

No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Cefdinir	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
2	HPMC K4M	0.5 gm	-	-	-	-	-	-
3	HPMC K100 M	-	0.5 gm	-	-	-	-	-
4	Polyvinyl Alcohol	-	-	0.5 gm	-	-	-	-
5	Polyethylene	-	-	-	0.5 gm	-	-	-
6	Polypropylene	-	-	-	-	0.5 gm	-	-
7	Polyvinylpyrrolidone	-	-	-	-	-	0.5 gm	-
8	Polymethylmethacrylate	-	-	-	-	-	-	0.5 gm
9	PEG-400	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml
10	Dimethylsulphoxide	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml
11	Ethanol	Up to 20 ml	Up to 20 ml	Up to 20 ml	Up to 20 ml	Up to 20 ml	Up to 20 ml	Up to 20 ml

Evalauation [6, 7, 8]

Thickness of patch
The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Drug content
An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution by appropriate dilution is estimated spectrophotometrically.

Percentage Moisture content
The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24h. The films are weighed again after a specified interval until the show a constant weight. The percent moisture content is calculated as the difference between final and initial weight with respect to final weight.

Percentage of moisture uptake
A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to
84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Tensile Strength [9]
To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation;

Tensile strength= F/a.b (1+L/l)
F is the force required to break;
a is width of film;
b is thickness of film;
L is length of film;
l is elongation of film at break point.

Content uniformity test [10]
10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal

patches pass the test of content uniformity. But if 3 patches have content the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. 0% constriction is equivalent to 100% flatness.

% Constriction =$L_1 – L_2/L_1$X 100

L2 = Final length of each strip

L1 = Initial length of each strip

Rolling ball test

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Result

Table 2: Resultive value of all formulations

Parameter	F1	F2	F3	F4	F5	F6	F7
Thickness (µm)	385±12	300±11	415±8	398±10	401±12	411±5	391±15
% Drug Content	97±1.2	99±0.2	96±1.1	98±1.3	98±0.8	96±1.3	97±0.8
% Moisture content	1.6±0.2	1.9±0.5	2±0.2	1.8±0.9	1.5±0.12	1.9±0.2	1.8±0.9
% Moisture uptake	2.5±0.5	2.6±0.7	2.4±0.3	2.5±0.2	2.4±0.3	2.9±0.1	2.6±0.2
Tensile Strength (dyne cm-2)	78.15±0.2	85.90±0.5	81.23±0.3	79.55±0.4	76.95±0.6	77.95±0.4	79.88±0.2
% Weight Uniformity	98±1.3	99±0.1	94±1.3	97±1.6	94±0.3	92±1.5	96±0.6
Folding Endurance	195±5	245±6	185±9	199±4	204±5	175±6	115±5
% Flatness	98±0.8	99±0.5	98±1.1	96±1.3	98±0.2	98±1.5	98±0.6
Rolling ball test (cm)	10	6	12	9	13	10	11

Conclusion

All the polymers were preparing transdermal patches, but among all the polymeric formulations, HPMC K100 M was showing best result. According to result all the evaluation parameter::s of transdermal patches were satisfactory given by F2 formulation. So it was concluded that among various polymers HPMC K100M was the best polymer used to prepare transdermal patches.

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