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FORMULATION AND EVALUATION OF CEFTRIAXONE TRANSDERMAL PATCH

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ABSTRACT

The ever increasing bacterial resistance is the motivation for the present work. Transdermal patch of ceftriaxone acts as a best alternative to oral administration to combat the rising bacterial resistance against antibiotics, reduce the risk of systemic side effects. A matrix type transdermal patch was developed containing ceftriaxone antibiotic as active pharmaceutical Ingredient. Different polymers and permeation enhancers like HPMC, PPG, and PEG-400 are used to formulate the patch. The compatibility of the drug and the polymers were studied by infrared spectroscopy which suggested absence of any incompatibility. Various parameters like drug content, thickness, folding endurance, % moisture content, % moisture gain, weight uniformity, drug content uniformity, invitro permeation were assessed for the prepared Transdermal films. The results obtained suggested that F4 formulation showed better physico-chemical properties and drug release compared to other formulations. It also showed excellent antimicrobial properties against Gram Negative (*E.Coli*) and Gram positive (*Staphylococcus aureus*) Bacteria.

INTRODUCTION

Transdermal drug delivery gained interest in administration of drugs through the skin for both local effect as well as systemic delivery of drugs. Transdermal patches improve bioavailability and patient acceptance. This system of drug delivery offers various advantages like reducing systemic adverse effects, avoidance of first pass metabolism.[1] Antibiotic patches can be prepared to increase drug loading efficiency.[2] Ceftriaxone is widely used in inflammatory disorders, pyelonephritis, severe acute bacterial rhino sinusitis etc. in the dose range of 250 mg to 2 g. The formulation of antibiotic patch is a novel approach to subside the drug toxicity by reducing the dose as well as dosing frequency.[3] In general antibiotics are routinely administered orally or systemically which involves use of high dose and ceftriaxone is not an exception to that.[4] Additionally, patch formulations can serve as better alternative to reduce antibiotic resistance.[5] Transdermal films prepared using polymeric solutions in different ratios can extend the drug release.[6]

In Matrix type Transdermal drug delivery system the commonly employed polymers are HPMC, EC, and PEG. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer and EC is hydrophobic in nature.[7-10] Hence both the polymers are used for the preparation of Ceftriaxone transdermal patch. The intention behind current research is to prepare a transdermal of Ceftriaxone Antibiotic which increases patient acceptance with a low dose and increased bioavailability.

There are reports describing the use of hydroxyl propyl methyl cellulose (HPMC) in transdermal patches and ophthalmic preparations[7-9] and ethyl cellulose (EC) in transdermal delivery systems as well as other dosage forms for controlled release of drugs[10-12] HPMC is freely water soluble, whereas EC is hydrophobic. So the transdermal delivery systems were prepared using HPMC and EC to study the effect of hydrophilic and hydrophobic nature of polymer on release of Ceftriaxone.

MATERIALS AND METHODS

Materials

Ceftriaxone was a gift sample obtained from Aurobino Pharma Ltd. Hyderabad HPMC, EC, PEG and Starch were procured from SD fine chemicals Pvt. Ltd. Other chemicals used in patch preparation like Urea, glycerin, chloroform, methanol, Tween 80 are of Analytical Grade.

Methods

Drug and polymer compatibility

The physicochemical compatibility between Ceftriaxone and polymers used in the Transdermal films was studied by using Fourier transform infrared (Perkin Elmer/Spectrum 2 LITA) spectroscopy. The Infrared

Spectra in the scan range of 400–4000 cm-1 at a resolution of 4 cm^{-1} were recorded by KBr pellet method. The comparison of spectra was carried out for the IR spectra obtained for ceftriaxone, polymers, and physical mixtures of ceftriaxone with polymers. The physical mixtures are prepared by simple trituration process.

Preparation of ceftriaxone transdermal patch

Ceftriaxone -loaded matrix-type transdermal films were prepared by using solvent casting method. A petri dish of total surface area of 56.7 cm^2 was used. The polymers were weighed accurately and dissolved in solvent mixture (chloroform: methanol) at 1: 4 ratio and allowed to stand until a clear solution was obtained. Ceftriaxone was dissolved in the solvent-polymer mixture to obtain clear solution. Polyethylene glycol 400 was used as a plasticizer and Polypropylene glycol was used as permeation enhancer which can act synergistically with PEG.[11-12] The petridish was lubricated with glycerin and the prepared solution was poured on PVA backing membrane and set aside for drying at room temperature for 24 hr. For slow setting of the transdermal film an inverted funnel was placed over the petridish. After the specified time the dried patches were carefully taken out and stored in desiccator until further evaluation.[13] Different formulations prepared were tabulated[Table 1].

Table 1: Design of Transdermal Formulation.

S. No	Ingredients	F1	F2	F3	F4	F5
1	Drug	50mg	50mg	50mg	50mg	50mg
2	Urea	0.2g	0.2g	-	-	-
3	Glycerine	1.2ml	1.2ml	1.2ml	0.2 ml	0.2ml
4	Chloroform	1ml	1ml	1ml	1ml	-
5	Methanol	4ml	4ml	4ml	4ml	-
6	Starch	-	-	0.2 g	-	1 g
7	Ethyl cellulose	-	-	0.4g	-	0.4 g
8	PEG-400	-	-	1.2 ml	1.2 ml	1.2 ml
9	HPMC	-	-	-	0.4gm	1.6 g
10	PPG	-	-	-	1 ml	1 ml
11	Tween 80	-	-	-	0.1ml	0.1 ml

Various parameters like drug content, thickness, folding endurance, % moisture loss, % moisture gain, weight uniformity, in vitro drug release, in vitro permeation were assessed for the prepared Transdermal films.

Physicochemical characterization of transdermal films

i. **Thickness of the patch:** The thickness of the prepared patch was measured by using a digital micrometer at different point of patch and the average thickness was recorded for the prepared patch.[14]

ii. **Weight uniformity: P**repared patches were dried before testing weight uniformity. A specified area of patch was cut in different areas of the patch and weighed in digital balance. The average weight was calculated from the individual weights.[15]

iii. **Folding endurance:** A 2 x 2 inch strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking is recorded.[16]

iv. **Percentage moisture content:** The prepared patches were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs. The films are to be reweighed and the percentage moisture content was determined.[17]

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100.$$

i. **Percentage moisture uptake:** The prepared patches were weighed individually and kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs. The films are to be reweighed and the percentage moisture uptake was determined.[17]

ii. **Drug content uniformity:** The amount of drug that is preset all over the patch was determined by dissolving certain area of patch in 100ml of phosphate buffer solution (pH 7.4). The drug was allowed to diffuse from patch by placing on shaker for about 30 mins-1 hr. A blank was prepared using a drug-free patch treated similarly. The solution was then filtered and drug content was calculated spectrophotometrically at 241nm by proper dilution.[18]

iii. **In vitro skin permeation studies:** An *in vitro* permeation study can be carried out by using Franz diffusion cell. Full thickness abdominal skin of goat weighing 50-100 gm. was used. Hair from the abdominal region was removed carefully by using an electric clipper. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment. The isolated goat skin piece was mounted between the donor and receptor compartments of the diffusion cell with the epidermis facing upward. The patch formulation was sandwiched between the compartments above the

goat skin. The entire setup with a magnetic bead was placed on a magnetic stirrer. The temperature of the cell was maintained at 37 ± 0.5°C using a thermostatically controlled heater. Samples of definite volume were removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are filtered through filtering medium and analyzed spectrophotometrically (Thermo electron Corporation-Nicolet e -100) at 241 nm.[19]

iv. **Anti-microbial activity of the drug:** The nutrient agar medium was prepared. The prepared patches were evaluated for antibacterial activity against Gram-positive (*S.aureus*) and Gram-negative (*E.coli*) bacterial strains. The standardized cultures previously quantified as 10^4 cfu/ml were inoculated on to the sterile Nutrient Agar medium. Equal area of patches were placed gently on plates and incubated at 37^0 C for 24 hr. The experiment was carried out in triplicate. Average Zones of Inhibition were measured.

RESULTS AND DISCUSSION

Drug- excipient interaction study

The FTIR spectrum showed that there were no physical interactions between the drug and excipient as the bands in the spectra represented all the functional groups in individual component. The band at 3252 cm^{-1} shows N-H stretching. The band at 1503cm^{-1} signifies C-N stretching. Appearance of broader bands at 3375 represents O-H stretching. Based on the bond stretching vibrations observed in the FTIR Spectra there were no incompatibilities observed for the combination of drug and excipients.

The organoleptic charecteristics of the formulation are tabulated [Table 2].

Table 2: Morphological characteristics of the transdermal patches.

Formulation code	Physical Appearance
F1	Thin, transparent, sticky, smooth
F2	Thin, nontransparent, flexible, smooth
F3	Thick, nontransparent, flexible, smooth
F4	Thin, transparent, uniform, soft
F5	Thick, nontransparent, sticky, smooth

All the prepared patch formulations appeared to be within the limit of patient compliance. All the formulations appear to be smooth and odorless. F1 and F4 formulations were observed to be transparent comparatively. The other physicochemical properties of the prepared formulations are shown [Table 3]. The antimicrobial activity of the prepared patches are tabulated. [Table 4].

Table 3: Physicochemical parameters.

Formulation code	Weight uniformity (mg)	Thickness (mm)	Drug content uniformity (%)	Moisture gain (%)	Moisture loss (%)	Folding endurance
F1	293±0.12	0.17±0.013	93±0.55	2.31±0.21	1.29±0.24	261
F2	295±0.14	0.19±0.015	95±0.65	2.21±0.26	1.20±0.51	242
F3	294±0.11	0.18±0.014	97.50±1.12	2.12±0.34	1.10±0.32	260
F4	299±0.09	0.16±0.012	98.96±0.68	2±0.32	1±0.12	265
F5	298±0.12	0.17±0.017	97.35±0.66	2.05±0.20	1.12±0.25	259

All the values are expressed as Mean± SD

Table 4: Antimicrobial activity of prepared patches.

Formulation code	Zone of Inhibition(mm)	
	E.Coli	***S.aureus***
F1	35±1.12	29±1.62
F2	34±1.16	28±0.72
F3	33±1.14	28±0.85
F4	36±0.52	27±0.62
F5	32±0.62	26±0.72

All the values are expressed as Mean± SD

Permeation of the drug: The in-vitro skin permeation studies of prepared Ceftriaxone Transdermal patches predicts the in vivo drug release profile. The in-vitro skin permeation studies using Goat skin are shown in Figure. F4 formulation showed maximum 74.652 ± 1.632 % drug release compared to all the other formulations. F4 formulation represented more cumulative amount of drug permeation compared to F1, F2, F3, & F5 formulations [Fig 1]. The hydrophilic polymer containing Formulation showed a faster release rate compared to hydrophobic polymer containing patch. Thus the nature of the polymer has a good influence on release of the drug.

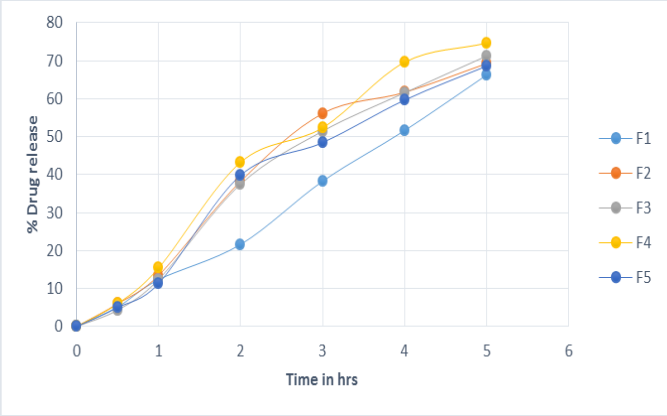

Fig. 1:% Drug release of different formulations.

CONCLUSION

By keeping in view the rise in popularity of noninvasive methods the developed transdermal formulation can achieve wide acceptability. All the transdermal patches were evaluated for various parameters such as physical appearance, thickness, weight variation, drug content, moisture content, moisture uptake, antimicrobial activity and in-vitro diffusion studies. The present work of ceftriaxone antibiotic transdermal patch can serve as a model to bypass the gut bacteria and skip the bacterial resistance which can sustain the activity of currently available antibiotics. Thus the transdermal patch helps in easy administration of drug into the systemic circulation for prolonged period of time and acts as best alternative to fight against bacterial resistance. Further studies can be done to increase the drug release by using different permeation enhancers.

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