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Preparation and Optimization of Transdermal Patch Using Antiviral Drug Acyclovir

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Abstract:

Acyclovir is an antiviral drug used for the treatment of herpes simplex virus infections, with an oral bioavailability of only 10-20% and half-life of about 3 h, and is soluble only at acidic pH (pKa 2.27). Mucoadhesive polymeric nanodrug delivery systems of acyclovir have been designed and optimized using 2(3) full factorial design. Poly (lactic-co-glycolic acid) (PLGA) (50:50) was used as the polymer along with polycarbophil as the mucoadhesive polymer and pluronic F68 as the stabilizer. From the preliminary trials, the constraints for independent variables X(1) (amount of PLGA), X(2) (amount of pluronic F68) and X(3) (amount of polycarbophil) have been fixed. The dependent variables that were selected for study were particle size, % drug entrapment and % drug release in 12 hrs. The derived polynomial equations were verified by check point formulation. The application of factorial design gave a statistically systematic approach for the formulation and optimization of nanoparticles with the desired particle size, % drug release and high entrapment efficiency. Drug: Polymer ratio and concentration of stabilizer were found to influence the particle size and entrapment efficiency of acyclovir-loaded PLGA nanoparticles. The release was found to follow Fickian as well as non-Fickian diffusion mechanism with zero-order drug release for all batches. In vitro intestinal mucoadhesion of nanoparticles increased with increasing concentration of polycarbophil. These preliminary results indicate that acyclovir-loaded mucoadhesive PLGA nanoparticles could be effective in sustaining drug release for a prolonged period.

Keywords: Acyclovir, Bioadhesive polymers, Transdermal Patch, Evaluation parameters

INTRODUCTION:

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative way for administrating medication. This device allowed for pharmaceuticals to be delivered across the skin barrier [1]. Simple theory behind transdermal permeation is that a drug is applied in a relatively high dosage at the surrounded by of a patch or other system, which is worn on the skin for an extended period of time. Throughout a diffusion course, the drug inters in the blood stream directly through the skin. Since there is elevated concentration on the patch and small concentration in the blood, the drug will keep diffusion in to the blood for a long episode of time; maintain the unchanging concentration of drug in the blood flow [2]. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the blood stream [3]. The basic components of any transdermal delivery system include the drugs dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that an chores the patch to the skin [4]. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin. Drugs administered via- skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed entry into systemic circulation which often causes undesirable side effect [5, 6].

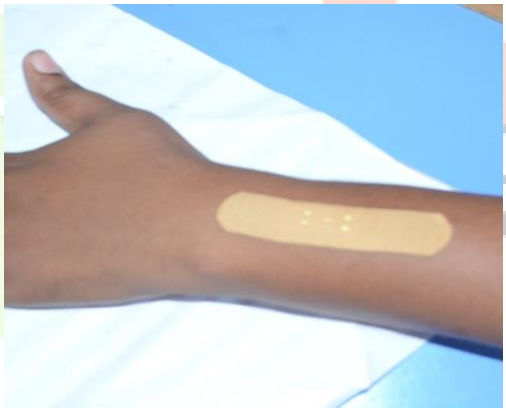

Fig. no. 1 - Transdermal patch

PREPARATION OF TRANSDERMAL PATCH

Solvent Evaporation Method:

Preparation of backing membrane

The 4 gm polyvinyl alcohol (PVA) is dissolve in 100 ml of distilled water to prepare 4% of polymeric solution with continuous magnetic stirring. After the 4% polymeric solution is pour in 4 open glass mould at same proportion and transfer in hot air oven at 60 ^{o}C for 6 hrs. Before pouring of polymeric solution in open glass mould few drop of glycerin is pour in glass mould [7, 8].

Preparation of casting solution:

Casting solution is prepared by the using suitable solvent (ethanol), ethyl cellulose, polymer (polyvinyl pyrolidone) and plasticizer (dibutylpthalate) is added slowly-slowly with continuous stirring [9]. The selected drug is also added slowly with continuous stirring of casting solution up to 45 min. Then dried backing membrane glass Petridis is removed from hot air oven after overnight [10]. The prepared casting solution pour in open glass contain dried backing membrane and transfer in to hot air oven at 60 ^{o}C for 6 hrs. After the complete drying of transdermal film the dried film is removed from glass mould [11].

MATERIALS AND METHODS:

Acyclovir was a gift sample from Ajanta Pharmaceutical Limited (Mumbai India); poly (D, L lactide-co-glycolide) (PLGA 50:50 and PLGA 85:15) were obtained as gift samples from Indena Ltd. (Rome, Italy); pluronic F68 and polycarbophil (Noveon AA-1) were procured from Strides Arcolab, (Bangalore, India) as a gift; acetone and cellophane membrane were purchased from S. D. Fine Chem. Ltd. (Mumbai, India). All other reagents and chemicals used in this study were of analytical grade.

Table no. 1 - Formulation of Transdermal patch

S. no.	Ingredients	Working Formula
1.	Acyclovir	75 mg
2.	Poly vinyl pyrollidone	860 mg
3.	Ethyl cellulose	140 mg
4.	Di butyl phthalate	30 mg
5.	Poly vinayl alcohol	4 gm/100ml
6	propylene glycol	2ml

Fig no. 2 - Transdermal patch acyclovir

Fig no. 3 - Transdermal patch acyclovir

EVALUATION OF TRANSDERMAL PATCH

Physical appearance

The prepared patches are physically examined for colour, clarity and surface texture [12].

Thickness of the patch

The thickness of the drug loaded patch is calculated in different points by using a digital micrometer, or travelling microscope, dial gauge, screw gauge, and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch [13]. Patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated [14].

Moisture content

Individually weighed patches are kept in the desiccators having fused calcium-chloride at room temperature for 24 hours. After 24 hrs the patches are to be reweighed and percentage moisture content is calculated by the formula [15, 16] -

$$\% \text{ Moisture content} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Final weight}}$$

Moisture uptake

The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in instruct to maintain 84% RH [17]. After 24 hrs the films are to be reweighed and determined the percentage moisture uptake from the mentioned formula [18].

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}}$$

Folding Endurance

This was determined by repeatedly folding the film at the same place until it broke [19]. The number of period the films could be folded at the same place without breaking/ cracking gave the value of folding endurance [20].

Drug Content

A specified area of patch (2 cm×2 cm) was dissolved in 5mL DMSO and upto 100ml distils water shaken continuously for 24 h. Then the whole solution was ultra-sonicated for 15 min [21]. After filtration, the drug was estimated spectrophotometrically at wavelength of 243 nm and determined the drug content [22, 23].

In vitro drug release

By using USP type 1 dissolution test apparatus, Drug release from the prepared TD patch was studied using 8 station dissolution rate test apparatus (Labindia, DS 8000) employing a paddle stirrer at 50 rpm and at 37±1°C [24-26]. Phosphate buffer of pH 7.4 (500 ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 12 h [27, 28]. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 243 nm for acyclovir using UV spectrophotometer machine 1800 (shimadzu) double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate [29].

RESULTS AND DISCUSSION

Pre-Formulation Studies of Acyclovir
Melting Point Determination:

Melting point of acyclovir was determined by using open capillary tube method. Digital malting point apparatus used to determination of melting point acyclovir drug show the Pre-formulation studies of Acyclovir drug is show melting point range is (**245-268** ^{o}C).“Practically Results Melting point is (255^{o}C) using digital melting point apparatus”.

Table no. 2 - Different solvent system solubility in Acyclovir drug

S. No.	Solvent system	Acyclovir Drug(Soluble / Insoluble)
1.	Chloroform	Insoluble
2.	Ethanol	Insoluble
3.	Distilled water	Slightly soluble
4.	Dimethylsulphaoxide(DMSO)	Soluble

I have study the acyclovir like drug and perform the solubility of different solvent as above the table discus the below:-

- ✓ Drug is Slightly Soluble in water solvent
- ✓ Should be soluble in DMSO as a co-solvent and soluble in water.
- ✓ Should be insoluble in Chloroform and Methanol solvent
- ✓ I have study the solubility of acyclovir and result is DMSO are used as co-solvent than soluble in different organic solvent and water of this drug.

Partition coefficient
Calculation:

Two phase system, hydrophobic (top) and hydrophilic (bottom) for measuring the partition coefficient of compounds.

$$K_{(pc)} = C_o/C_w k = 1.63$$

k = Equibrium constant

C_o = Equibrium constant of substance in organic phase

C_w = Equibrium constant of substance in aqueous phase.

The pKa influences the key physical properties of a drug-like mole molecule: Solubility Lipophilicity Permeability. Pka study of drug is important as care of solubility Lipophilicity Permeability of Acyclovir The pka show **(1.63 logP).**

UV studies of calibration standard curve and spectrum pics point of acyclovir
Spectrum of Acyclovir:

The ultra violet spectroscopy of Acyclovir drug and spectra show above the "graph (**ƛ=242**) nm". ACV standard curve in different concentration like - 10, 20, 30, 40, 50, 60µg/ml observe UV absorbance show in table and plotted graph. Study ten different concentration of UV spectra and 2% concentration show maximum absorbance **(0.399)** show in table .and plotted graph.

Table no. 3 - High absorbance of acyclovir drug

S. No.	Wavelength (nm)	Absorbance
1	242	0.399

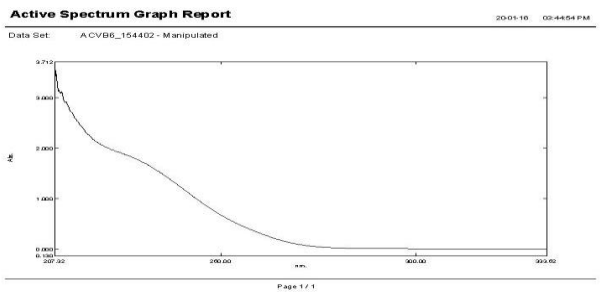

Fig. no. 4 - Spectrum graph of Acyclovir

Table no. 4 - Standard curve of acyclovir drug

S. No.	Concentration µg/ml	Absorbance
1.	10	0.228
2.	20	0.462
3.	30	0.688
4.	40	0.901
5.	50	1.139
6.	60	1.377

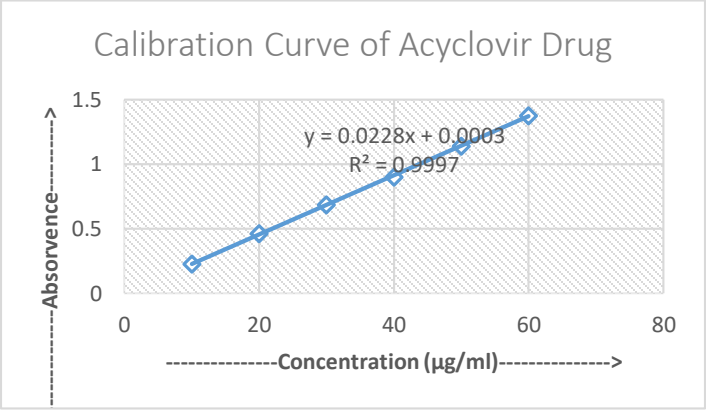

Fig. no. 5 - Calibration Curve of Acyclovir drug

Assay of Acyclovir:

0.15 g of Acyclovir was accurately weighed and dissolved in 60 ml of anhydrous glacial Acetic acid. A blank titration was carried out. The end point was determined by titrating with 0.1 M perchloric acid using potentiometric method. 100ml of 0.1 M perchloric acid is equivalent to 0.02252 g of $C_8H_{11}N_5O_3$. There is one report in the literature for the titrimetric assay of ACV in pharmaceuticals. The method involves the titration of the drug with perchloric acid and end point was detected either visually using crystal violet indicator or potentiometrically. The method was applicable over a range of 2-20 mg. following table - Average % purity of acyclovir drug (0.11 %).

Table no. 5 - Acyclovir drug assay observation table

S. No.	Volume of acyclovir solution (ml)	Burette reading		Volume of 0.5 perchloric acid (ml)
		Initial (ml)	Final (ml)	
1	10	0	4	3
2	10	4	6	2
3	10	6	8	2

EVALUATION OF TRANSDERMAL PATCH OF ACYCLOVIR

Physical Appearance:

All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness.

Thickness:

Patch thickness was measured using Vernier calliper at three different places, and the mean value was calculated.

Table no. 6 - Thickness determination of formulation

S. No.	Thickness (mm)	Average
1	0.03	0.03
2	0.02	
3	0.03	

Moisture content:

Individually weighed patches are kept in the desiccators having fused calcium-chloride at room temperature for 24 hours. After 24 hrs the patches are to be reweighed and percentage moisture content is calculated –

Table no. 7 - Evaluation of Transdermal Patch in Moisture Content

S. no.	Moisture content %	Average %
1	0.97	
2	1.02	2.286
3	0.95	

Moisture uptake:

The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in instruct to maintain 84% RH. After 24 hrs the films are to be reweighed and determined the percentage moisture uptake.

Table no. 8 - Evaluation of Transdermal Patch in Moisture Content

S. no.	Moisture uptake %	Average %
1	1.11	
2	1.36	1.32
3	1.49	

Folding endurance:

Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied.

Table no. 9 - Folding endurance determination of formulation

S. No.	Folding Endurance	Average
1	250	250
S	230	
3	270	

Drug Content:

A specified area of patch (2 cm×2 cm) was dissolved in 5mL DMSO and upto 100ml distils water shaken continuously for 24 h. Then the whole solution was ultra-sonicated for 15 min. After filtration, the drug was estimated spectro-photometrically at wavelength of 243 nm and determined the drug content.

Table no. 10 - Drug content study of transdermal patch

S. no.	Absorbance	Drug content (mg/ml)	% of Drug
1	0.4582	44..04	58.72

In Vitro Drug Release:

In vitro drug release: Acyclovir release from al the prepared TDD patch was slow and spread over more than 12h and depended on the polymer concentration used as shown inthe release data were analyzed. The correlation coefficient (r) values in the analysis of release.

Table no. 11 - In-vitro drug release study

S. no.	Time (in Min)	Absorbance	Concentration In 10 ml	Concentration in 900 ml	Cumulative concentration	Concentration ug (mg)	(%) Drug release
1	30	0.2847	7.580	6822	6822	6.822	9.096
2	60	0.3124	9.426	8484	15306	15.306	20.408
3	120	0.3561	12.340	11106	26412	26.412	35.216
4	180	0.3987	15.180	13662	40074	40.074	53.432

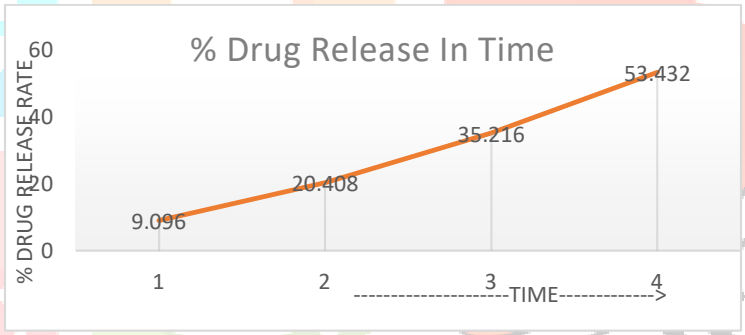

Fig. no. 6 - Drug release rate

CONCLUSION:

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative way for administrating medication. Throughout a diffusion course, the drug inters in the blood stream directly through the skin. Going concentration of drug in the blood flow. A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Simple theory behind transdermal permeation is that a drug is applied in a relatively high dosage at the surrounded by of a patch or other system, which is worn on the skin for an extended period of time. Acyclovir has previously been known for its use an anti-viral activity, for which it remains safe and effective. Due to its competitive binding, this drug is being considered for other uses for more severe conditions. On the bases of Acyclovir research paper and pre formulation study for different parameters as solubility, melting point, pka, UV. firstly melting point

determination of using capillary tube method by digital melting point machine show 255c.and Solubility of drug are soluble in DMSO as co-solvent and soluble in water, ethanol, and other solvent. Pka are determine organic phase / aqueous phase separation method uv range determine 1.63 log P . UV show wavelength of Acyclovir at (ƛ=242) nm and maximum absorbance is (0.399). I studied Acyclovir Pre-formulation and done the practical works as anti viral drug. Transdermal patches of acyclovir drug were successfully prepared by using ethyl cellulose and poly vinyl pyrollidone. Prepared patches were found to have smooth and uniform surface when they are functional onto skin. TDDS of acyclovir were prepared by solvent evaporation method and evaluated for different parameters. Evaluated for, physical appearance, thickness was found to be 0.35mm, moisture content was found to be 0.956%, moisture uptake was found to be 1.32%, and folding endurance was found to be 250. And drug content 44.04 mg/ml in 58.72% drug avleble then in vitro drug release in lover 9.04% and higher % is 53.45% Shows satisfactory results. This research work highlights that may be incorporated into the transdermal drug delivery system for their suitable and convenient use.

Evaluation factor:

Transdermal patches of acyclovir were successfully prepared by using ethyl cellulose and poly vinyl pyrollidone. Prepared patches were found to have smooth uniform surface when they are functional on to skin. TDDS of acyclovir drug were prepared by solvent evaporation method and evaluated for different parameters. Evshows satisfactory result.

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