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RESEARCH ARTICLE

PREPARATION AND EVALUATION OF ACECLOFENAC SODIUM PRONIOSOME TRANSDERMAL PATCHES

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ABSTRACT

Proniosomes are one of the important novel drug delivery carriers of various drug molecules. Aceclofenac potent analgesic anti inflamatory agent used for the treatment of inflammation. The main objective of the study was to develop proniosomal containing aceclofenac for transdermal delivery using different ratios of cholesterol and non-ionic surfactants in order to achieve a sustained release of drug on topical administration. Proniosomes were prepared by using slurry method and evaluated for angle of repose, entrapment efficiency, thickness, folding endurance, percent moisture loss and absorption, drug content and in-vitro diffusion studies. As the concentration of the cholesterol decreases the entrapment efficiency decreases due to the low vesicle size formation the in-vitro diffusion and kinetic analysis were done for proniosomal patches. It showed the release of 51.28% at 8th hr and fitted into Zero order and follows non-fickian diffusion mechanism. The best formulation (F6) was composed of cholesterol and surfactant in the ratio of 1:2 showed the better sustain action. From the study it was observed that proniosomal transdermal patches are very stable and promising sustained delivery system for Aceclofenac

INTRODUCTION

Over the decade treatment of illness accomplished by administration of drugs to the body through various routes like oral, rectal, parental & topical. Topical administration defined as application of a drug contained medicament to the surface of the skin to treat diseases as drug directly reaches systemic circulation. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the invassiveness of iv treatment and the altered conditions like absorption are advantages of topical delivery. [1-2].

Pronisomes[3]

Proniosome technology offers novel solution for poorly soluble drugs. Proniosome is a dry free flowing, granular product that could be hydrated immediately before use and would avoid many of the problems associated with aqueous noisome dispersions and problem of physical stability and uniform in size.

Components of pro niosomes

1. Different components of proniosomes: Surfactants, Carrier material, Membrane stabilizer, Solvent and Aqueous phase, Polymer matrix or matrices, Permeation enhancers, Other excipients

Table 1 List of Surfactants

Non-ionic Amphiphiles	Examples
Alkyl ethers and alkyl glyceryl ethers	Polyoxyethylene 4 lauryl ether, Polyoxyethylene cetyl ethers, Polyoxyethylene stearyl ethers.
Sorbitan fatty acid esters	Span 20, 40, 60, 80
Polyoxyethylene fatty acid esters	Tween 20,40,60,80

Preparation Of Proniosomes[5]

Slurry method

Proniosomes are prepared by addition of the carrier and the surfactant solution in a round bottomed flask which is rigid to rotary flash evaporator and vacuum pressure was applied to form a arid and free flowing fine particles and resulting powder should be stored in tightly closed container under refrigeration

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in light. The time required for Proniosome production is independent of the ratio of surfactant and the carrier.

Slow spray coating method

This method involves the spraying of surfactant in organic solvent onto the carrier and then evaporating the solvent. As the carrier is soluble in organic solvent the evaporation is repeated until the required surfactant loading is achieved.

Coacervation phase separation method

Mainly Proniosomal gels are prepared by this method. In this the surfactant, lipid and drug in a wide mouthed glass vial with small amount of alcohol. The mixture is warmed over water bath at 40-700 ^{0}C for 5min until the surfactant &carrier is dissolved completely and cool it. Then aqueous phase is added with all the ingredients and warmed until a clear solution is formed which is then converted into powder.

Backing membrane

This forms a good bond with drug reservoir and prevents the loss of drug from the top. It is impermeable substance that guard the product during use on the skin.eg metallic plastic laminate, occlusive base plate (alluminium foil), adhesive foam pad (flexible polyurethane) etc

Transdermal Drug Delivery[6]

Transdermal drug delivery is defined as self-contained, discrete dosage form which when apply to unbroken skin deliver the drug through the skin at controlled rate to the systemic circulation. The transdermal patches use a polymer to control the rate of drug delivery from the reservoir through the skin and into the blood stream.

Skin status or conditions for drug permeation[7]

Hydration, Broken or Irritated skin, Temperature, Sunburn Psoriasis, Skin peels

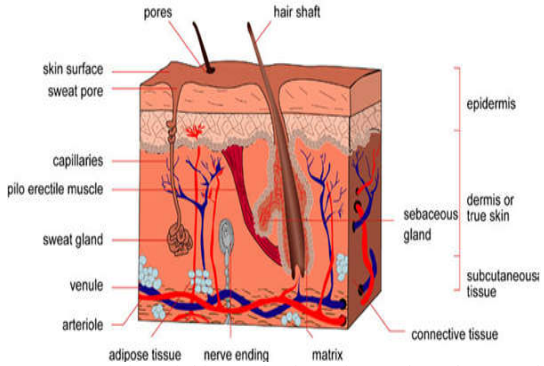

Fig 1 Cross section of skin Mechanism of Transdermal Permeation

Transdermal Patches

This route of drug delivery becoming the most popular route. It is a medicated adhesive patch which is placed on the skin for the delivery of certain dose of medication through the skin and directly into the bloodstream. The patches uses polymer to control the rate of drug delivery from the reservoir to the skin and into the bloodstream. Some of the drugs to be combined with solvents, like alcohol as this increases their penetrability through the skin.

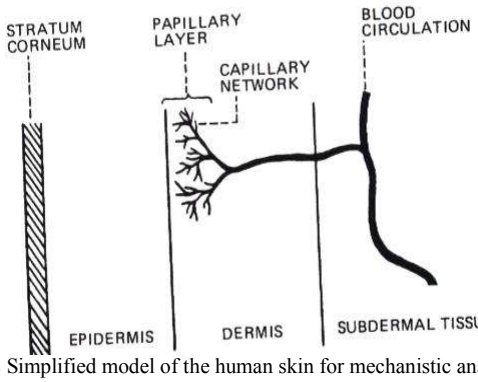

Figure 2 Simplified model of the human skin for mechanistic analysis of Skin Permeation

Table 2 Polymers for Transdermal drug delivery system

Natural polymers	Synthetic Elastomers	Synthetic polymers
Cellulose derivatives Zein, Gelatin, Shellac, Waxes, Natural rubber, Starch	Polybutadiene, Hydrine rubber, Polysiloxane, Silicone rubber, Neoprene	Polyvinyl alcohol, Polyethylene, Polyurea, Polymethyl methacrylate, Polyamide

Applications Of Transdermal Patches[9, 10]

- Nicotine patch which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Nitro-glycerine patches are prescribed for the management of Angina.
- The first antidepressant patch developed was Selegiline.

Based on the literature review observed we had planned to develop proniosomes in transdermal patches and evaluated. The prepared batches were evaluated and reported in this thesis.

Table 3 List of Carriers

S. No.	Carrier materials investigated
1	Maltodextrin
2	Sorbitol
3	Mannitol
4	Spray dried lactose
5	Glucose monohydrate
6	Lactose monohydrate
7	Sucrose stearate

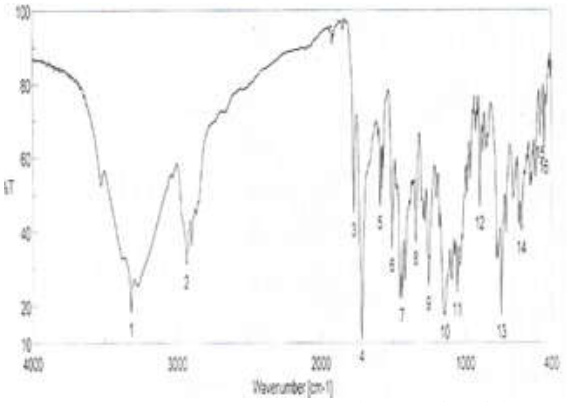

Figure 3 FT-IR spectra of Drug and Excipient

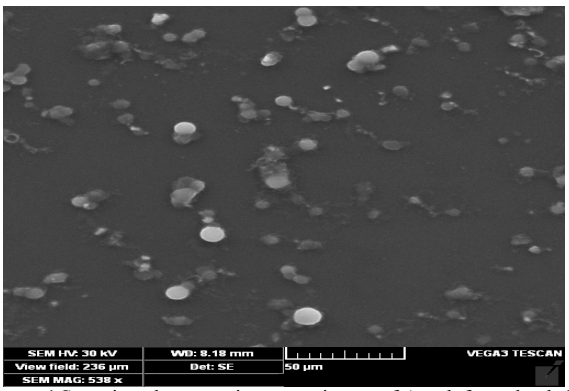

Figure 4 Scanning electron microscope image of Aceclofenac loaded proniosomal derived niosomes

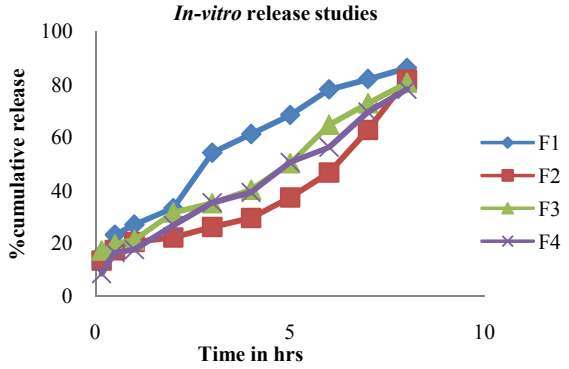

Figure 5 In-Vitro drug release studies of different concentrations of Span 40

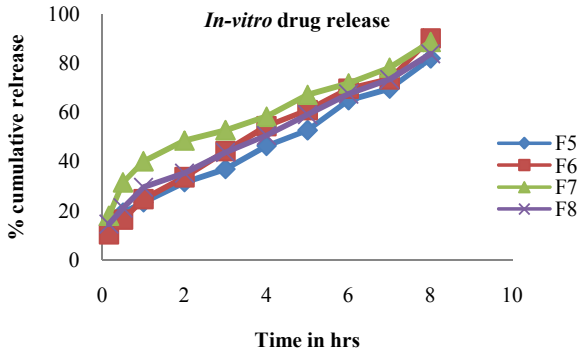

Figure 6 In-Vitro drug release studies of different concentrations of Span 60

Table 4 Drug excipients compatibility

Drug and Excipients	Interprepation			
	2^0 NH	C=O stret	Ar-c-cl stret	Di-subt Ar ring
Aceclofenac	3318	1716	1056	609
Aceclofenac+S40+S60 +T60+lactose+Chol	3318	1716	1056	609
Aceclofenac+HPMC	3319	1716	1142	608

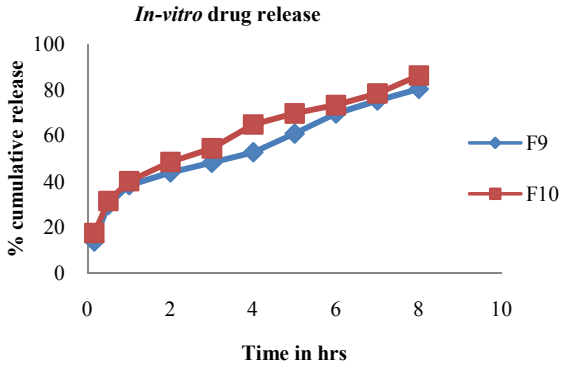

Figure 7 In-vitro drug release studies of different concentrations of tween 60

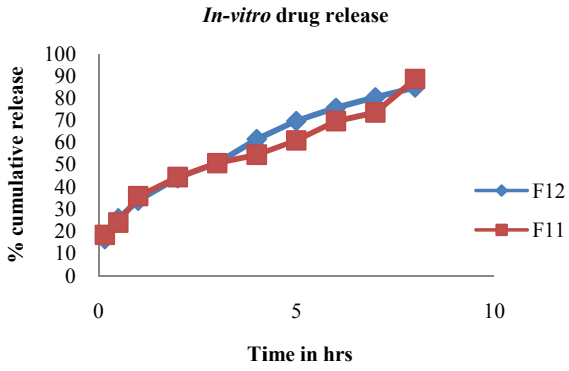

Figure 8 In-vitro drug release studies of different concentrations of drug

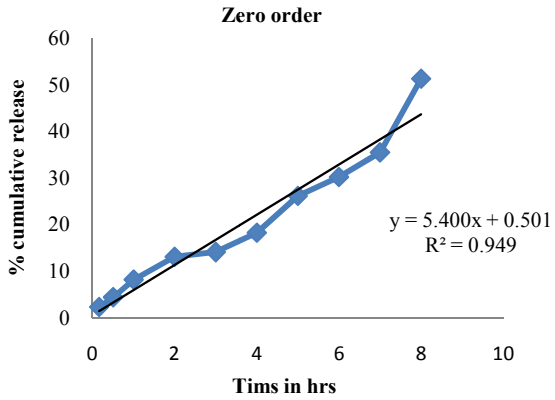

Figure 9 Zero Order Plot of Formulation F6

MATERIALS AND METHODS

Location and duration of study

This study was conducted at pharmaceutics lab, Sri Krishna Chaitanya College of pharmacy Madanapalle.

Table 5 Formulations of Proniosomes

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	100	100	100	100	100	100	100	100	100	100	200	400
Cholesterol(mg)	1000	1000	500	250	1000	1000	500	250	1000	1000	1000	1000
Span40 (mg)	1000	2000	2000	2000	-	-	-	-	-	-	-	-
Span60 (mg)	-	-	-	-	1000	2000	2000	2000	-	-	2000	-
Tween60 (mg)	-	-	-	-	-	-	-	-	1000	2000	-	2000
Lactose (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Diethyl ether (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Methonal (ml)	5	5	5	5	5	5	5	5	5	5	5	5

Table 6 Parameters of all formulations

Formulation code	Angle of repose	Thickness (mm)	Drug content	Percent entrapment efficiency	Folding endurance	% moisture absorption	% moisture loss
F1	33.1	0.203	83.7	72.45	108	3.87	0.77
F2	35.52	0.205	86.4	73.33	112	4.95	0.82
F3	32	0.201	88.2	75.29	103	5.79	0.72
F4	30.96	0.208	92.7	78.28	106	5.47	0.68
F5	33.06	0.204	93.6	79.06	117	5.19	0.64
F6	30	0.202	96.3	89.13	121	3.75	0.63
F7	32	0.21	91.8	84.21	104	6.47	0.71
F8	35.52	0.206	95.4	78.57	98	5.40	0.90
F9	33.1	0.204	89.1	68.38	94	5.38	0.76
F10	35.52	0.202	90.9	63.83	108	6.03	0.86
F11	32	0.208	84.6	92.36	113	6.97	0.77
F12	34.25	0.204	86.4	71.16	99	5.03	1.25

Table 7 Dissolution profiles of different batches

Time (hrs)	0.16	0.5	1	2	3	4	5	6	7	8
F1	3.93	8.86	14.74	19.50	22.94	27.86	35.24	37.21	38.55	58.07
F2	2.43	4.34	8.49	12.67	16.85	24.97	31.64	35.29	43.96	56.26
F3	3.37	6.04	10.58	14.76	17.44	20.48	22.95	33.30	44.31	59.08
F4	5.06	8.69	12.11	16.47	20.28	24.45	27.88	34.68	46.58	54.42
F5	2.81	6.03	10.76	14.76	18.75	21.99	27.29	35.23	44.34	53.46
F6	2.25	4.34	8.12	13.04	14.04	18.18	26.11	30.15	35.46	51.28
F7	3.37	6.42	10.21	14.19	17.43	23.29	27.30	33.17	40.18	52.65
F8	1.87	8.46	14.36	18.37	20.11	24.07	27.50	35.42	39.46	54.83
F9	3.93	8.49	12.86	16.48	18.59	22.55	25.61	32.77	43.93	62.83
F10	8.62	15.86	22.14	26.16	28.09	31.68	37.54	39.30	52.26	60.87
F11	4.31	10.55	15.70	20.83	25.58	31.27	35.28	43.96	52.70	56.38
F12	12.18	16.47	19.34	21.63	23.34	29.55	33.76	37.57	41.93	55.86

Table 8 data of kinetic model

Formulation	Zero order R^2	First order R^2	Higuchi's model R^2	Korsmeyer-peppas model R^2	N
F6	0.949	0.905	0.870	0.976	0.755

Active was received as a gift sample from Biophore India pvt. Ltd Andhra Pradesh, India, Span 40, Span 60, Tween 60, Cholesterol, HPMC, were recived from Lobachemie pvt. Ltd, mumbai, Lactose SD fine chemicals mumbai. Completion of this work Lasted for a period of three months

Formulation of Proniosomes

Proniosomes are developed using slurry method. In this method drug, cholesterol, surfactant were dissolved in a round bottom flask heat until a clear solution formed then the carrier was added and stirr contineously which is fixed to the rotary evaporator and vaccum was appiled until a dry powder forms.

Preparation of Transdermal Patches

Transdermal patches were prepared by using solvent evaporation method. In this polymer was dissolved in the methanol and the drug equivalent to 100 mg was weighed and dispersed in the the solution of the polymer to get the clear dispersion and then 2-3 drops of plasticizer was added to the polymer solution and air dried for 24 hrs in petridish with the help of inverted funnel and then the film was taken out.

Evaluation Of Proniosomes

Angle of Repose

The proniosomal powder was measured by funnel method. In this method the funnel was fixed at the height of 1.5 cm above the surface. Then the powder was poured through the funnel and to flow down the funnel to form the cone on the surface. Then the angle of repose was calculated by measuring the height of the cone and the diameter of its base.

Evaluations of Transdermal Patches

Thickness Uniformity

The thickness of the formulated film was measured at 3 different points using a Vernier calliper and average thickness was calculated.

Folding Endurance

It was measured manually a strip of film 1cm^2 was cut and repeatedly folded at the same place untill it break. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Percentage Moisture Absorption

The patches are weighed and placed in desiccator containing 100 ml of saturated solution of potassium chloride. After 3 days, the films were taken out and weighed. Then the percentage moisture absorption was calculated

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

The patches are weighed and placed in the desiccator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. Then the percentage moisture loss was calculated.

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content

1 cm^2 area of the films was cut and dissolved in methanol. The volume was made up to 100ml.The absorbance was measured at 274nm.From the absorbance and the dilution factor, the drug content in the film was calculated

In-vitro drug diffusion studies

In-vitro diffusion studies are carried out using Franz diffusion cell with a 25 ml capacity of receptor compartment. The cellophane membrane was placed between donor and receptor compartments. The patches are cut into size of 2 cm^2 and placed over the membrane and the receptor compartment was filled with buffer pH 6.8. Then it was placed on the magnetic stirrer and the solution was stirred using magnetic bead at 50 rpm. The sample were withdrawn at time interval of 10 mins ,30mins, 1, 2, 3, 4, 5, 6, 7 and 8 hrs then and it was replaced with same amount of fresh fluid and analyzed for spectrophotomerically at 274 nm.

Drug Release kinetics

To know the release kinetics the data obtained from the *in-vitro* release profile was fitted into various models like zero, first orders and Higuchi's model. Study the release kinetics; data obtained from *in vitro* drug release studies were plotted. In various kinetic models: zero order as cumulative amount of drug released Vs. time, first order as log cumulative percentage of drug remaining vs. time, And Higuchi's model as cumulative percentage of drug released vs. squareroot of time.

Evaluations Of Transdermal Patches

Thickness uniformity[11]

The thickness of the formulated film was measured at 3 different points using a Vernier calliper and average thickness was calculated.

Folding endurance[12]

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Percentage moisture absorption[13]

The patches are weighed and placed in desicators containing 100 ml of saturated solution of potassium chloride. After 3 days, the films were taken out and weighed. Then the percentage moisture absorption was calculated

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Drug Release kinetics[17]

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Zero Order

A plot was drawn cumulative drug release vs time in hrs

$$\mathbf{C = K_0\, t}$$

Where
K_0 : is the zero-order rate constant concentration/time
t**:** is the time in hours.

First Order

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$\mathbf{LogC = LogCo - kt/2{:}303}$$

Where
$\mathbf{C_0}$**:** is the initial concentration of drug,
K**:** is the first order constant, and t is the time.

Higuchi's Model

$$\mathbf{Q = Kt^{1/2}}$$

Where
K**:** is the constant design variables of the system
t**:** is the time in hours.

Hence, drug release rate is proportional to the reciprocal of the square root of time. To evaluate the drug release with changes in the surface area and the diameter of the tablets, the data were

also plotted using the Hixson-Crowell cube root law

$$3\sqrt{Q_0} - 3\sqrt{Q_t} = kHC - t$$

Where
Q_t is the amount of drug released in time t
Q_0 is the initial amount of the drug in the tablet

KHC is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs. time.

Korsmeyers-peppes Equation

It is to evaluate the release mechanism in this a plot of Log cumulative percentage of drug release vs Log the exponent n calculated through the slope of the straight line.

$$Mt - M\infty = Kt^n$$

Where
$Mt/M\infty$ =The fractional solute release.
t= the release time.
K = kinetic constant characteristic of the drug

Stability Studies

The best formulation was tested for its stability. This formulation was stored three temperatures at 4° ± 2°, 25° ± 2°/ 60 % RH ± 5 % RH and 37° ± 2°/ 65 % RH ± 5 % RH in humidity control oven. After 45 days the sample was evaluated for the physical appearance, entrapment efficiency, and *in-vitro* drug release was determined by spectrophotomerically.

CONCLUSION

The present study revealed that Slurry method followed by evaporation in rotary evaporator produced Aceclofenac loaded proniosomes. The formulation containing non-ionic surfactant and cholesterol with 1:2 ratios is found to be better when it's characterized for various pharmaceutical characters. The entrapment study also showed that the significant amount of drug was entrapped in proniosomal powder. The optimized proniosomes formulation showed maximum release at 8th hr. The formulation was incorporated into HPMC transdermal patch respectively. The incorporation of powder into patches showed more suatained release in the formulation with ratio of 1:2 of cholesterol and non-ionic surfactant. The release kinetics analysis indicated that most of the formulations fit into Zero order & release mechanism was based on non-fickian diffusion. In conclusion, the noval proniosomal formulations of Aceclofenac Sodium could be used for transdermal delivery in better treatment of rheumatoid arthritis . The results of stability study showed no significant alteration in physical and chemical parameters. Further studies using animal model will throw more light on the effectiveness of the formulation

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