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Original Research Article

Formulation and Evaluation of Antihistaminic Activity of Proniosome Based Transdermal Patches

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ABSTRACT

The objective of the present work was to develop transdermal patches loaded with proniosomes of Chlorpheniramine maleate to improve the bioavailability and to study the effect of different surfactants on drug release. Proniosomes were prepared using different ratios of surfactants, lecithin and cholesterol by coacervation phase separation method. Drug polymer interactions were studied using FTIR analysis. The formulated proniosomes were evaluated for their physical nature, particle size, pH, Spreadability, encapsulation efficiency and carried out in vitro study. Among all these, formulations containing span60 i.e. F2, F5, F8 shows higher encapsulation efficiency & % CDR, these were selected & converted into reservoir type transdermal patches. These patches were fabricated using backing layer & rate controlling membrane. Evaluation studies like weight variation, percentage moisture content, thickness, flatness, folding endurance, drug content, in vitro studies were carried out. The formulation TP2 showed maximum drug release of 96.42% and drug content of 98.27%. At last concluded that transdermal patch TP2 loaded with proniosome F5 was the optimum formulation.

Keywords: Transdermal drug delivery, Proniosomes, Encapsulation, In vitro study

INTRODUCTION

The basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body to promptly achieve and then maintain desired drug concentration in order to produce desired effect. Recently in the field of pharmaceutical science great efforts are being directed towards the refabrication of existing drug and drug delivery system into solve the problem related to poor solubility, poor bioavailability, dosing problem, stability, toxicity etc. This technique of working has led to the development of new drug and new delivery system in a more perfect form. [1]

Transdermal drug delivery

Transdermal drug delivery is defined as self-contained, discrete dosage form which when applied to intact skin deliver the drug at a control rate to the systemic circulation and maintains the drug concentration within the therapeutic window for prolonged period of time. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. These devices allow for pharmaceuticals to be delivered across the skin barrier. Theoretically, transdermal patches works in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time.

Though a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. [2]

Advantages

- They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
- They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
- To avoid the first pass effect e.g. Transdermal Nitro-glycerin. It is rapidly metabolized by the liner when taken orally.
- They are non-invasive, avoiding the inconvenience of parenteral therapy.
- They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine.

Disadvantages

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation
- Only potent drugs are suitable candidates or transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable
- Long-time adhere is difficult.
- The major barrier to transdermal delivery of drugs is stratum corneum. Vesicular delivery via skin is beneficial in that drugs, which permeate via skin and reaches systemic circulation. For transdermal delivery, proniosomes are the best vesicular system. [3]

Proniosomes

Proniosomes are non-ionic based surfactant vesicles, which may be hydrated immediately before use to yield aqueous niosomes dispersions. Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes. Proniosomes are semisolid liquid crystal (gel), prepared by techniques such as coacervation phase separation, slurry method and spray drying, upon subsequent hydration by means of incorporation in hydrophilic gel or by absorbing moisture from site of administration turns to niosome. [4] Proniosomes are more stable and convenient than niosomes and also provide following advantages viz. ease in transportation, distribution, storage, dosing, and sterilization. The release profile of both proniosomes and niosomes indicate that proniosomes derived niosomes are at least effective as conventional niosomes. Some researchers have also showed some results for particular drug where proniosomes show better permeation than niosomes. This may be justified on the basis of less relative concentration of non-ionic surfactants. The formulation of drugs into proniosomes also helps in better physical and chemical stability of the drug and the vesicular nature of the delivery system helps the drug to permeate through skin with an ease and helps in reaching systemic circulation and the target site without losing any drug activity and providing better therapeutic efficacy. [5]

MATERIALS & METHODS

Chlorpheniramine maleate, Lecithin, Sodium hydroxide, Polyvinyl alcohol & n-butyl benzyl phthalate were purchased from Yarrow Chem Products, Mumbai. Cholesterol & Potassium dihydrogen orthophosphate were purchased from Nice Chemicals Pvt. Ltd, Cochin. Sorbitan esters (Span 20, 60, 80) & Chloroform were obtained from Molychem. Ethyl cellulose from Balaji drugs & Ethanol from Travancore Sugars &Chemicals, Thiruvalla, Kerala.

PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of a dosage form of the drug substance. The overall objective of the study is to generate information that is useful in developing stable dosage forms. Organoleptic properties, melting point & solubility of drug was determined. Solubility was determined in the solvents like distilled water, Ethanol and Chloroform

ANALYSIS OF CHLORPHENIRAMINE MALEATE

FT-IR Spectroscopy of Chlorpheniramine maleate

The FT-IR spectrum of the obtained sample of drug and polymer were compared with the standard functional group frequencies of Chlorpheniramine maleate, Lecithin, Cholesterol, Ethyl cellulose & Poly vinyl alcohol respectively.

PREPARATION OF CALIBRATION CURVE OF CHLORPHENIRAMINE MALEATE

Preparation of stock solution (100µg/ml);

A weight of accurately 10mg of Chlorpheniramine maleate was taken and dissolved, then made up to 100ml with pH 7.4 phosphate buffer.

Preparation of working standard solution

From the stock solution different volumes of 5ml, 10ml, 15ml, 20ml, and 25mlwere taken and diluted up to 100ml in a volumetric flask with pH 7.4 phosphate buffer to give the concentrations of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml respectively. The absorbance was measured at 261nm in UV-Visible spectrophotometer against phosphate buffer pH 7.4 as blank and standard curve was plotted taking concentration vs. absorbance.

FORMULATION OF CHLORPHENIRAMINE MALEATE LOADED PRONIOSOMES

Proniosomes were prepared by coacervation phase separation method. The weighed amount of surfactant, lipid (cholesterol), protein (egg lecithin) and drug were taken in a clean dry wide mouth glass container. The ethanol was used as a solvent, it was added to 2.5ml of above mixture and warm it. After warming all the ingredients were mixed well with a glass rod, open end of the glass bottle was covered with the lid to prevent the loss of solvent. The temperature should be maintained at 60-70ºC for (5 min) until the surfactant mixture dissolved completely. After dissolving the mixture, aqueous phase 1.6ml of phosphate buffer pH 7.4 was added and warmed it till a clear solution was formed this was converted into proniosomal gel on cooling. The proniosomal gel was preserved in air tight container and stored in a dark place. [6]

Table: 1: Formulation trials of proniosomes

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorpheniramine maleate(mg)	100	100	100	100	100	100	100	100	100
Lecithin (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cholesterol(g)	0.2	0.2	0.2	0.15	0.15	0.15	0.3	0.3	0.3
Span 20(g)	0.75	-	-	1	-	-	0.5	-	-
Span 60(g)	-	0.75	-	-	1	-	-	0.5	-
Span 80(g)	-		0.75	-	-	1	-	-	0.5
Ethanol (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Phosphate buffer pH7.4 (ml)	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

EVALUATION OF PREPARED PRONIOSOMES [7]

Physical properties: Proniosome formulations were inspected visually for their color, odor and appearance.

Particle size analysis: The mean particle sizes of proniosomes were determined using an optical microscope.

Determination of pH: The pH of the prepared proniosome formulations were determined by using a digital pH meter.

Determination of encapsulation efficiency: [8] 0.2g of proniosomal gel was taken with 10ml of phosphate buffer. The above mixture was sonicated in a sonicator bath. After that solution placed in centrifuge

for centrifugation at 20,000 rpm at 20oC for 30 minute. The supernatant was collected and diluted with phosphate buffer pH7.4, the resulting solution was assayed by UV spectroscopy at 261nm. The percentage of encapsulation was calculated by following equation:

Encapsulation efficiency= $\frac{Ct-Cr}{Ct} \times 100$

Where,

Ct is the concentration of total drug

Cr is the concentration of free drug

Determination of Spreadability: The spreadability of formulations was measured by placing a weighed quantity (1 g) of proniosome gel was placed within a circle of 1 cm diameter pre-marked on a glass plate (10 X 10 cm). Another glass plate (10 X 10 cm) was placed on the gel. A weight of 500 g was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to gel spreading was noted. [9]

Spreadability= m ×l /t

Where,

m = weight placed to the upper slide (500g)

l =increase in diameter

t =time taken in seconds

In vitro release study: This study was carried out by using Franz diffusion cell. The formulation was taken in the donor compartment and phosphate buffer pH 7.4 was taken in the receptor compartment. The cellophane membrane, previously soaked overnight in the diffusion medium (phosphate buffer pH 7.4) was placed between the donor and receptor compartment. 1 g of the formulation was spread uniformly on the cellophane membrane, which is in contact with the receptor medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer with continuous stirring and the temperature of the medium was maintained at 37 ± 0.5ºC. At specific intervals, 1 ml of sample was withdrawn from the receptor compartment and replaced with an equal volume of phosphate buffer pH 7.4. After suitable dilutions were made, the absorbance of the sample was determined at 261 nm by UV-visible spectrophotometer.

FORMULATION OF PRONIOSOME LOADED TRADERMALPATCHES [10]

- Preparation of backing layer

4 gm. of Poly vinyl alcohol was dissolved in 100 ml water, and the solution was poured on to the petridish and dried at 60°C for 3 h.

- Preparation of rate controlling membrane

Rate controlling membrane was prepared by solvent evaporation method. 0.5 mg of ethyl cellulose polymer weighed and dissolved in 10ml of chloroform with n-butyl benzyl phthalate as plasticizers. Then the solution is poured on the horizontal surface of Petri dish and left for evaporation of solvent in order to obtain a thin film.

- Fabrication of Proniosomes loaded transdermal patches

For the fabrication of proniosome 3*2 cm backing membrane was cut out then three edges of the backing layer were then sealed with the edges of rate controlling membrane using adhesive tape. The weighed quantity (1 g) of gel was transferred into the reservoir patch. After filling, the unsealed edge was sealed using adhesive tape. The obtained reservoir patch was then pasted to an adhesive plaster (The backing layer should face to the plaster). A release liner was placed over the adhesive coated rate controlling membrane

Table 2: Formulation of proniosome loaded transdermal patches

Batch code	Loaded proniosome	Rate controlling membrane			Backing layer	
		Ethyl cellulose (g)	Chloroform (ml)	n-butyl benzyl phthalate (mg)	Poly vinyl alcohol (g)	Distilled water (ml)
TP1	F2	0.5	10	0.15	4	100
TP2	F5	0.5	10	0.15	4	100
TP3	F8	0.5	10	0.15	4	100

EVALUATION OF PRONIOSOMES LOADED TRANSDERMAL PATCHES

Physical appearance: Transdermal patches were visually inspected for color, clarity, flexibility and smoothness

Weight uniformity: [11] Prepared patches were dried in an oven about 4 hours. Specified area (1cm2) of dried patch was cut in different parts and weighed on digital balance.

Percentage of moisture content: The films were weighed individually and stored in desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

$$\text{Percentage moisture content} = \frac{W1-W2}{W2} \times 100$$

Where,
W1-intial weight
W2- final weight

Thickness: The thickness of the patches was measured at three different places using a screw gauge and average was calculated.

Folding endurance: [12] Specified area of patch was cut accurately and repeatedly folded at the same place till it was broken. The number of times patch folded in the same place without breaking gave the value of folding endurance

Flatness test: Longitudinal strips were cut out from each patch, one from the center and another from either side. The length of each strip was measured and the variation in length due to non-uniformity in flatness was measured by determining percent constriction, considering 0% constriction equivalent to 100% flatness.

$$\text{Percent constriction} = \frac{L1-L2}{L2} \times 100$$

Where,
L1-intial length
L2-final length

Drug content uniformity: [13] A specified area of patch (1cm2) was mixed with 100ml phosphate buffer pH 7.4 & stirred in a magnetic stirrer for 12 hours. Then it was filtered and absorbance of the solution was measured after suitable dilutions.

In vitro drug release study: [14] Study was carried out by using Franz- diffusion cell. In this method pre hydrated cellophane was used as the model membrane. The membrane was placed between the donor compartment and the reservoir compartment (phosphate buffer pH7.4). The patch was placed on the membrane, and the compartments clamped together. The receptor compartment was filled with phosphate buffer pH 7.4 and hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. Samples were withdrawn and replaced with receptor medium and assayed spectrophotometrically at 361nm and the amount of drugs released at various time intervals were calculated.

Stability studies: [15] The patches were wrapped in aluminium foil and kept in humidity chamber maintained at 30 ± 2°C/ 65 ± 5 % RH and 40 ± 2°C / 75 ± 5 % RH for one month. At the end of studies, samples were analyzed.

RESULTS

PREFORMULATION STUDIES

Organoleptic properties of the drug: The drug Chlorpheniramine maleate was white in color, odorless &melting point was 132ºC. It was freely soluble in distilled water & Ethanol. Drug was slightly soluble in Chloroform

FT-IR Spectroscopy of Chlorpheniramine maleate

The FT-IR spectrum ofChlorpheniramine maleateis shown in figure 1, which complies with standard functional group frequencies.

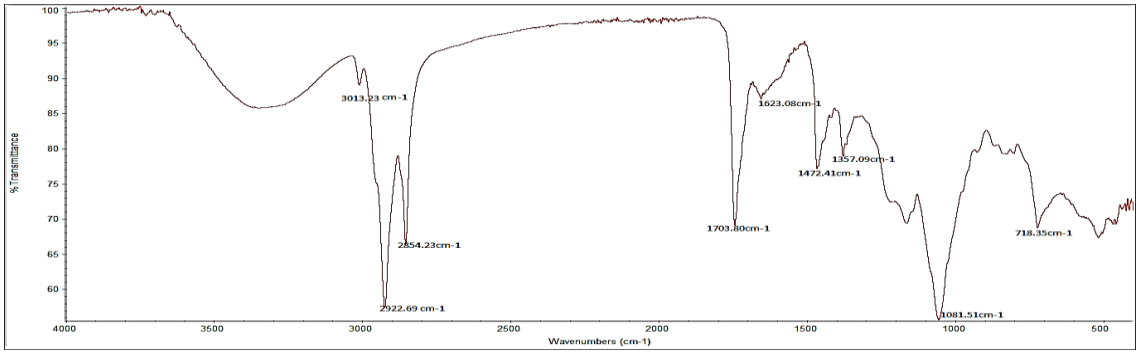

Figure1: FT-IR spectrum of Chlorpheniramine maleate

The peaks analyzed in the Table 3 indicate the most characteristic frequencies of functional group of Chlorpheniramine maleate which are C-H, OH,C-C & C-Cl were confirmed and comply with the reported frequencies.

Table 3: IR frequencies of Chlorpheniramine maleate

Functional group	Characteristic wave number	Chlorpheniramine maleate-observed wave number
CH stretching	3040-3010	3013.23
OH bending	1410-1310	1357.08
C-Cl stretching	800-700	718.35
C-N stretching	1090-1020	1081.51

Compatibility between drug and polymer

Combination of Chlorpheniramine maleate with excipients are shown in figure 2.

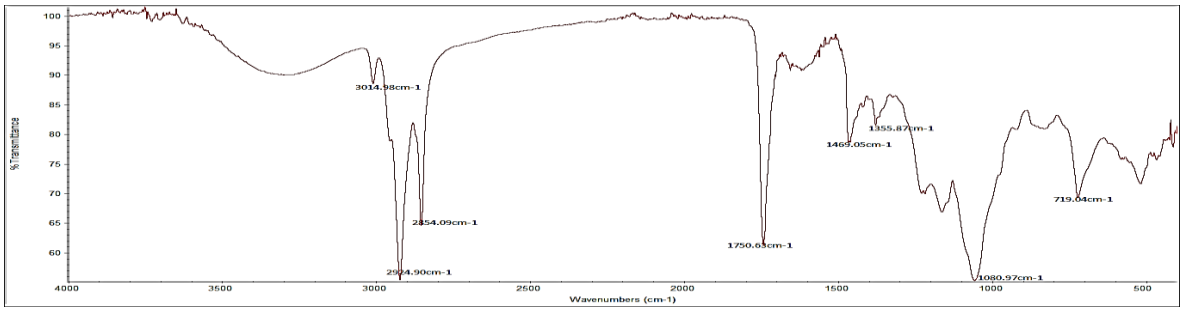

Figure 2: FT-IR spectrum of physical mixture of Chlorpheniramine maleate with excipients

Table 4: IR frequencies of Chlorpheniramine maleate with excipients

Functional group	Characteristic wave number	Chlorpheniramine maleate-with excipients observed wave number
CH stretching	3040-3010	3014.98
OH bending	1410-1310	1355.87
C-Cl stretching	800-700	719.04
C-N stretching	1090-1020	1080.97

The compatibility between drug-polymer was carried out using FT-IR peak matching method. All major peaks present in the spectrum of pure drug were observed in the spectrum of drug-polymer mixture. This suggests the absence of any chemical interaction and it concluded that there was no incompatibility between drug and polymers.

PREPARATION OF STANDARD CALIBRATION CURVE

Preparation of phosphate buffer pH7.4

Phosphate buffer pH 7.4 was prepared pH was measured using digital pH meter and was found to be 7.4

Preparation of standard calibration curve of Chlorpheniramine maleate

Standard calibration curve of Chlorpheniramine maleate was determined in phosphate buffer pH 7.4 by measuring the absorbance of the standard solutions at 261 nm using double beam UV

spectrophotometer. Table 5.6shows the absorbance of Chlorpheniramine maleate standard solutions containing 5-25 µg/ml of drug in phosphate buffer pH 7.4 at 261nm.

Table 5: Absorbance of Chlorpheniramine maleate standard solutions at 261 nm

Concentration (µg/ml)	Absorbance (nm)
0	0
5	0.192
10	0.412
15	0.602
20	0.823
25	0.992

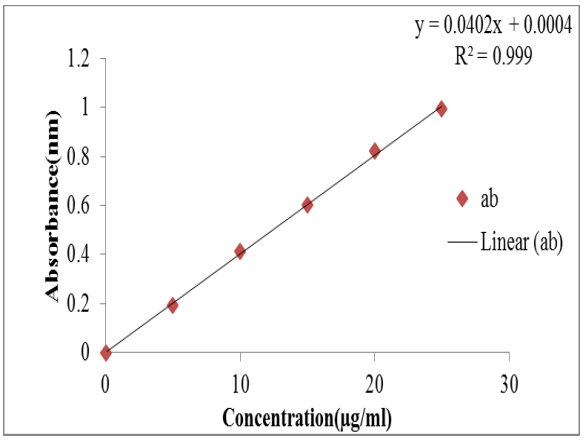

Figure.3: Standard calibration curve of Chlorpheniramine maleate

Figure showed slope, regression coefficient and intercept of 0.040, 0.999, and 0.0004respectively. The calibration curve was found to be linear in the range of 5-25 µg/ml at λmax261 nm.

EVALUATION OF CHLORPHENIRAMINE MALEATE LOADEDPRONIOSOMES

Physical properties: All proniosome formulations were yellow in color, having characteristic odor and semisolid appearance.

Table 6: Physical properties of Chlorpheniramine maleate loaded proniosomes

Formulation code	Colour	Odour	Appearance
F1	Yellow	Characteristics	Semisolid
F2	Yellow	Characteristics	semisolid
F3	Yellow	Characteristics	semisolid
F4	Yellow	Characteristics	semisolid
F5	Yellow	Characteristics	semisolid
F6	Yellow	Characteristics	semisolid
F7	Yellow	Characteristics	semisolid
F8	Yellow	Characteristics	semisolid
F9	yellow	Characteristics	semisolid

Particle size and pH: The mean particle size of Chlorpheniramine maleate loaded proniosomes ranged from 27.83- 41.23 µm. Skin compatibility is the primary requirement for a good transdermal formulation, it was found that the pH of all the formulations were in the range of 4.8 to 5.8 that suits the skin pH, signifying skin compatibility.

Table 7: Particle size & pH of Chlorpheniramine maleate loaded proniosomes

Formulation code	Particle size(µm)	pH
F1	36.19	4.8
F2	29.04	5.6
F3	35.17	5.5
F4	38.94	5.2
F5	27.83	5.8
F6	37.96	5.1
F7	31.72	5.4
F8	30.54	5.7
F9	41.23	5.4

Determination of encapsulation efficiency: The encapsulation efficiency is one of the main parameters in a plan of the Proniosomal formulations. The encapsulation efficiency relies on the stability of the vesicle which is greatly dependent on the type and amount of surfactant forming the bilayers, the amount of both cholesterol and lecithin. The percentage Encapsulation Efficiency of proniosomal formulations F1-F9 was determined. The encapsulation efficiency ranges from 74.59%- 94.56% and shown in the table7.Higher encapsulation efficiency was found in the formulation F5. In the proniosome formulation F5 has span 60 as surfactant & the lecithin, surfactant ratio was found to be 1:2.

Table 8: Encapsulation efficiency (%) of proniosomes

Formulation code	Encapsulation efficiency (%)
F1	76.07
F2	90.61
F3	80.82
F4	82.34
F5	94.56
F6	84.17
F7	86.35
F8	87.09
F9	74.59

Spreadability: The spreadability studies showed that all formulation have better spreadability ranges from 7.66-9.33 g cm/s

Table 9: Spreadability of proniosomes

Formulation code	Time(s)	Increase in diameter (cm)	Spreadability (g cm/s)
F1	300	5	8.33
F2	300	5.5	9.16
F3	300	4.6	7.66
F4	300	5.1	8.5
F5	300	5.6	9.33
F6	300	5.1	8.5
F7	300	5.2	8.66
F8	300	5.3	8.83
F9	300	4.7	7.83

In vitro drug release study

The in vitro drug release studies were carried out using Franz diffusion cell for 12 hrs. The percentage of drug released from the formulations F1-F5 were tabulated in table 7and F6-F9 were tabulated in table 8

Table 10: Percentage cumulative drug release data for formulations F1-F5

TIME (Hrs.)	F1 (%CDR)	F2 (%CDR)	F3 (%CDR)	F4 (%CDR)	F5 (%CDR)
1	16.74±0.34	22.32±0.29	15.11±0.47	21.16±0.76	23.72±0.69
2	22.43±0.57	26.02±0.41	19.37±0.18	27.86±0.51	30±0.57
3	25.89±0.78	32.81±0.86	23.7±0.38	32.83±0.27	33.3±0.42
4	30.35±0.21	41.36±0.66	27.19±0.91	36.72±0.34	37.52±0.36
5	36.74±0.62	47.97±0.52	33.06±0.67	43.93±0.41	44.28±0.48
6	45.58±0.94	52.13±0.16	48.22±0.72	47.33±0.53	52.1±0.72
7	50.16±0.33	62.88±0.45	49.15±0.38	52.16±0.73	61.21±0.54
8	59.24±0.17	72.19±0.49	52.63±0.81	55.22±0.61	70.03±0.26
9	68.01±0.28	76.1±0.28	60.42±0.26	63.76±0.98	74.44±0.39
10	76.02±0.91	80.51±0.63	72.63±0.63	71.81±0.81	81.53±0.65
11	81.82±0.75	87.77±0.44	80.01±0.39	79.15±0.76	86.26±0.66
12	87.95±0.48	93.06±0.81	86.81±0.22	89.16±0.49	94.23±0.41

Table 11: Percentage cumulative drug release data for formulations F6-F9

TIME (Hrs.)	F6 % CDR	F7 % CDR	F8 % CDR	F9 % CDR
1	14.65 ±0.17	22.79±0.74	20.23 ±0.15	13.72± 0.66
2	19.82± 0.62	25.8 ±0.18	22.49 ±0.39	17.71 ±0.71
3	24.63 ±0.27	29.56 ±0.23	27.35 ±0.61	22.25 ±0.44
4	33.02 ±0.38	35.48 ±0.65	33 ±0.99	28.49 ±0.62
5	37.14 ±0.88	39.65 ±0.48	43.63± 0.46	32.06 ±0.57
6	44.13 ±0.72	45.52 ±0.77	47.72 ±0.51	38.02 ±0.72
7	48.24 ±0.31	48.23 ±0.38	53.97 ±0.28	47.11 ±0.25
8	53.55 ±0.56	56.56 ±0.42	60.32 ±0.39	53.34 ±0.53
9	62.43 ±0.91	64.99 ±0.26	70.6 ±0.34	63.26 ±0.49
10	71.04±0.74	69.73 ±0.37	78.56 ±0.56	70.86 ±0.37
11	79.31 ±0.47	77.73 ±0.41	84.4 ±0.78	76.58 ±0.42
12	88.65 ±0.61	84.23 ±0.63	90.57 ±0.92	82.62 ±0.86

FORMULATION OF PRONIOSOME LOADED TRADERMALPATCHES

Based on higher encapsulation efficiency & % CDR, formulations F2, F5 & F8 were selected & converted into reservoir type transdermal patches. These patches are fabricated using backing layer & rate controlling membrane.

EVALUATION OF PRONIOSOMES LOADED TRANSDERMAL PATCHES

Physical appearance: The prepared patches were physically evaluated for their properties and the results are shown in the table 5.14. All the patches were transparent, flexible & the surface was found to be smooth.

Weight uniformity: The weights of these batches ranged between 0.108g to 0.131g & it was shown in the table 5.15.The weight variation study showed that no significant difference in average weight among each batch indicating that the patches are uniform throughout.

Table 12: Weight uniformity of transdermal patches

Batch code	Weight (g)
TP1	0.126 ± 0.23
TP2	0.131 ± 0.17
TP3	0.108 ± 0.35

Percentage of moisture content: The moisture content in different batches were low, ranged from1.91%to 2.11%and shown in the table 5.16.The transdermal patch containing F5 proniosome having lowest

moisture content. Low moisture content in patches could protect the formulations from microbial contamination &reduce bulkiness.

Table 13: Percentage moisture content of transdermal patches

Batch code	Moisture content (%)
TP1	2.06
TP2	1.91
TP3	2.11

Thickness: The thickness of different batches is almost identical ranged from 0.516mm to 0.518mm and shown in the table 5.17

Table 14: Thickness of transdermal patches

Batch code	Thickness(mm)
TP1	0.516 ± 0.24
TP2	0.518 ± 0.32
TP3	0.521 ± 0.17

Folding endurance: The folding endurance values of patches ranged from 76 to 91 & shown in table 5.18.The patch TP2 shows highest folding endurance i.e., 91±0.75. The result of this study showed that all the patches have a satisfactory strength and they did not break easily upon application

Batch code	Folding endurance
TP1	76 ± 0.86
TP2	91 ± 0.75
TP3	87 ± 0.54

Table 15: Folding endurance of transdermal patches

Flatness: In this study, the patches shows satisfactory flatness value & it ranged from 94.74% to 97.68%.The flatness values shown in table 5.17& it reveals that the surface of all patches were smooth &could be maintained when applied to the skin.

Table 16: Flatness of transdermal patches

Batch code	Percent constriction (%)	Flatness (%)
TP1	5.26	94.74
TP2	2.32	97.68
TP3	4.76	95.24

Drug content: The drug content in the different batches of formulations loaded with proniosomes was found to be in the range of 92.77 - 98.27 % as shown in table 5.20. From this it was found that the drug remains in encapsulated form in proniosomes and is uniformly distributed in the patches.

Table 17: drug content of transdermal patches

Batch code	Drug content (%)
TP1	94.4 ± 0.25
TP2	98.27 ± 0.39
TP3	92.77 ± 0.17

In vitro drug release studies: The in vitro drug release studies were carried out using Franz diffusion cell for a period of 12 hrs. The percentage of drug released from the formulations TP1-TP3 were tabulated in table 5.21

Table 18: Percentage cumulative drug release data for formulations TP1-TP3

Time (Hrs.)	TP1 % CDR	TP2 %CDR	TP3 %CDR
0	0	0	0
1	20.68±0.84	16.74±0.25	18.82±0.98
2	25.29±0.35	25.55±0.34	22.70±0.87
3	36.72±0.21	29.08±0.36	28.49±0.35
4	41.86±0.35	37.78±0.38	32.53±0.58
5	48.01±0.87	46.18±0.78	47.58±0.97
6	53.80±0.97	49.85±0.94	53.14±0.27
7	59.23±0.28	58±0.62	58.8±0.81
8	63.12±0.65	69.07±0.54	62.68±0.75
9	74.29±0.76	75.06±0.19	69.20±0.56
10	79.60±0.31	81.74±0.68	75.12±0.47
11	83.13±0.47	87.87±0.73	80.66±0.33
12	90.41±0.75	96.42±0.61	86.74±0.71

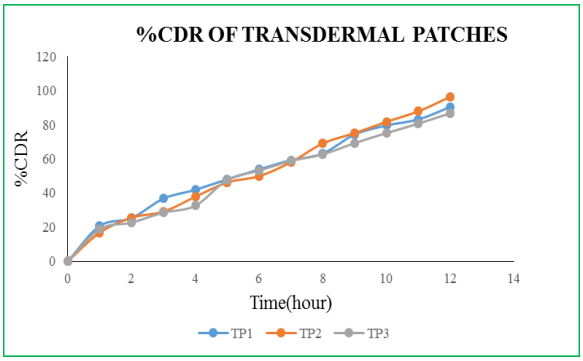

Figure 6: Percentage cumulative drug release data for formulations TP1-TP3 5.6.11 Kinetics of in vitro drug release

Kinetics of in vitro drug release: The results obtained of in vitro release studies were attempted to fit into various mathematical models

Table 19: Kinetic study of formulations TP1-TP3

Batch code	Release kinetics				
	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2	n
TP1	0.9761	0.9375	0.9752	0.9834	0.617
TP2	0.9919	0.841	0.9489	0.9828	0.7192
TP3	0.981	0.962	0.9599	0.9639	0.6711

The in-vitro drug release data was subjected to goodness of fit by linear regression analysis, according to zero order, first order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release. The result of linear regression analysis of data including regression coefficient are summarized in above table 5.22. When the regression coefficient 'R^2' values of zero order and first order plots were compared, it was observed that the drug release from the formulations is more likely to follow zero order kinetics.Based on the values of regression coefficient, it was concluded that the formulation TP2 strictly follows zero order kinetics compared to other formulations.

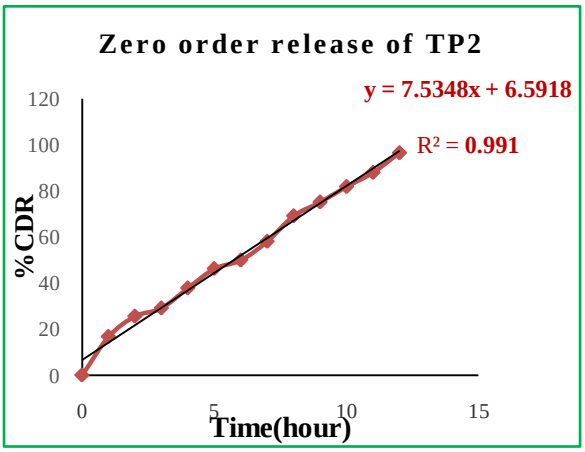

Figure 7: Zero order plot of TP2

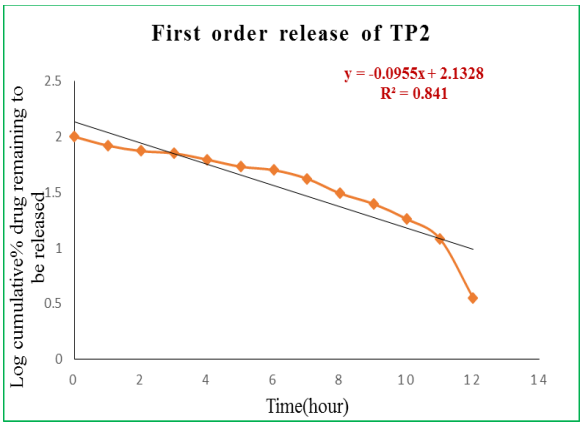

Figure 8: First order plot of TP2

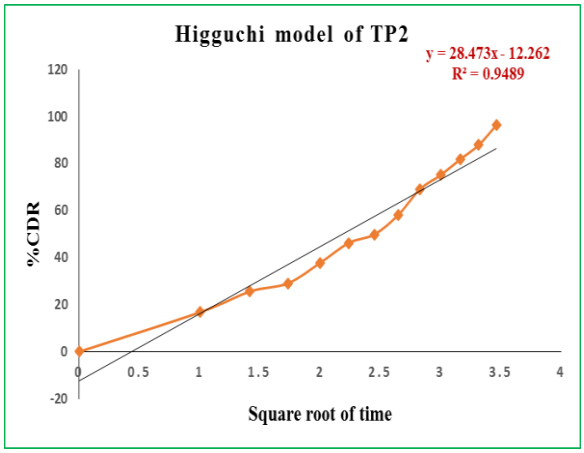

Figure 9: Higuchi model of TP2

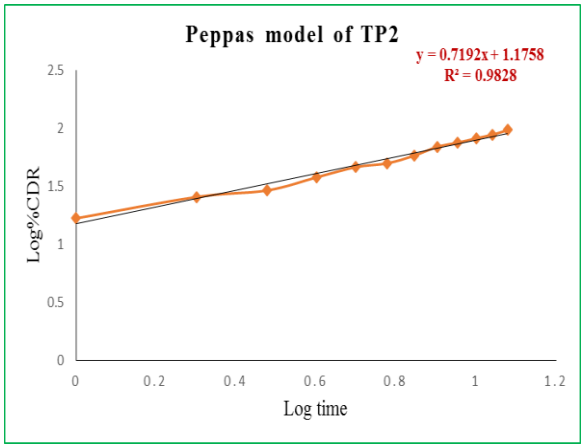

Figure 10: Peppas model of TP2

The best fit model for all the formulations were calculated and was observed that the formulation followed zero order kinetics. The diffusion exponent 'n' values ranged from 0.617-to 0.719 as per Korsmeyer and Peppas model. And also the n value indicating that the drug release is by non-Fickian mechanism.

Stability studies

Stability studies were carried out on formulations TP2 for a period of 1 month and comparison of the parameters before and after stability studies were reported in the table.

Table20: Comparison of physical parameters & drug content before and after stability

	Appearance	Drug content (%)
Before stability study	Transparent, flexible, smooth	98.27
After stability study	Transparent, flexible, smooth	96.31

Table 21: Drug release determination after stability

Time (hrs)	%CDR	
	Before stability study	After stability study
0	0	0
1	16.74	14.51
2	25.55	23.89
3	29.08	27.92
4	37.78	35.73
5	46.18	43.03
6	49.85	47.86
7	58	56.12
8	69.07	65.09
9	75.06	72.46
10	81.74	78.91
11	87.87	86.74
12	96.42	94.32

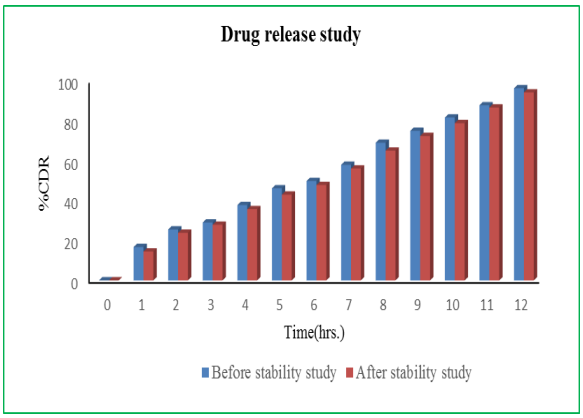

Figure 11: Graphical representation of % CDR before & after stability studies.

The results obtained from the stability studies showed that the optimized formulation TP2 loaded with proniosome F5 showed slight change in the smoothness and flat surface after one month stability study. The drug content of the formulation was slightly decreased into 96.31% and the % CDR was reduced into 94.32%. From the stability studies it was confirmed that the optimized formulation of Chlorpheniramine maleate loaded proniosome based transdermal patch remained stable at 40°C and 75% relative humidity.

DISCUSSION

In the present study, Proniosomes were prepared by coacervation phase separation method with different ratio of surfactant, lecithin & cholesterol. The formulated proniosomes were visually inspected for their physical nature, then the particle size was measured using optical microscope & it ranged from 27.83 to 41.23µm. The pH of all formulations was found to be suitable to skin pH. All the formulations showed good spreadability in the range of 7.66-9.33 g cm/s. The drug encapsulation efficiency (%) was studied for all proniosomes & it was found to be in the range of 74.59 to 94.56 %. Higher encapsulation efficiency was found in the formulation F5. In the proniosome formulation F5 has span 60 as surfactant & the lecithin, surfactant ratio was found to be 1:2. The cholesterol content was high in the formulation F5 that also influence the encapsulation efficiency. The cumulative drug release (%) of all proniosome formulations was determined by in vitro diffusion study & it ranged from 82.62-94.23%.The proniosomes having span 60 as surfactant shows higher %CDR. Based on higher encapsulation efficiency & % CDR, formulations F2, F5 & F8 were selected & converted into reservoir type transdermal patches. These patches were fabricated using backing layer & rate controlling membrane. Evaluation studies like weight variation, percentage moisture content, thickness, flatness, folding endurance, drug content, in vitro studies were carried out. According to these studies, found that the prepared patches have uniform weight, flat surface, sufficiently thick, low moisture content & did not break easily. The formulation TP2 loaded with proniosome F5 showed higher drug content i.e. 98.27%. The in vitro drug release study was carried out using Franz diffusion apparatus & the % CDR ranged from 86.74 to 96.42%.The formulation TP2 showed maximum drug release of 96.42% and drug content of 98.27%. All the formulations follow zero order kinetics among this TP2 possess highest regression co-efficient. The 'n' value of optimized formulation TP2 indicated that the drug release follows non-Fickian release. It was confirmed from the stability studies that the optimized formulation remained stable at 40°C and 75% relative humidity.

CONCLUSION

Based on higher drug content & drug release, it was concluded that the

transdermal patch TP2 was considered as the optimized formulation.For transdermal delivery, proniosomes are the best vesicular system because they act as a drug reservoir for a prolonged period of time and increases skin permeation. The findings of results revealed that the poor bioavailability & gastric side effects on oral administration can be overcome by applying Chlorpheniramine maleate transdermally in the form of patches. Proniosomal gel transdermal patches were highly stable, more rate of drug release and reducing the drug degradation when compared to other type of transdermal patches.

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