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Formulation and Evaluation of Transdermal Patch Containing Cyproheptadine

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ABSTRACT
The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix.
Matrix type systems were developed in the present study. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Cyproheptadine with different concentration of various polymers alone using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F3formulation has been selected as the best formulation among all the other formulations. The in-vitro drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the in-vitro release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows Higuchi release kinetics model release by diffusion technique from the polymer.
Keywords: Cyproheptadine,Transdermal drug delivery, Diffusion, Penetration enhancers, Higuchi release.

I. INTRODUCTION

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

They are noninvasive, avoiding the inconvenience of parenteral therapy.Transdermal drug delivery has manyadvantages over conventional drug delivery and can be discussed as follows.

Cyproheptadine is chemically 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine. The structure of cyproheptadine is shown in Figure 1.

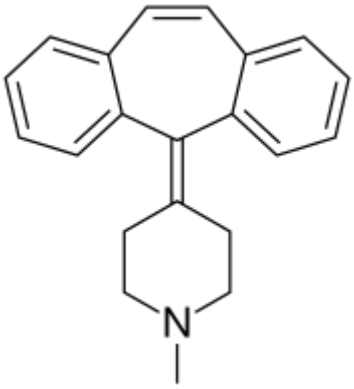

Fig . 1: Structure of Cyproheptadine drug

Cyproheptadine is a class of medications called **antihistamines**. It works by blocking the action of histamine, a substance in the body that causes allergic symptoms. Blocking histamine helps reduce allergy symptoms, such as sneezing, stuffy/runny nose, and itchy eyes/skin. It is a first-generation antihistamine with additional anticholinergic, antiserotonergic and local anesthetic properties. It is sold under brand name = Periactin.

II. MATERIALS AND METHODS

2.1. Materials

Cyproheptadine drug sample was Provided was by the **SURA LABS,**Dilsukhnagar, Hyderabad.Excipients used are Polyvinyl Alcohol,Polyvinylpyrrolidone,PEG-200(ml),Dimethylsulphoxide,Methanol(ml) were procured from Merck Specialities Pvt Ltd. Equipments used in the study are Double beam UV VisibleSpectrophotometer procured from Lab India UV 3000 , Digital weigh balance by Sartourious, FTIR Spectrophotometer by Bruker and Magnetic Stirrer 2MLH , Franz diffusion cell procured from Remi Equipments,Mumbai, India.

III. METHODS

1.Preformulation studies of drug

2. Identifcation of drug

3.1. Organoleptic properties:

The drug sample was evaluated for its Colour, Odour and Appearance.

3.2. Determination of Melting point:

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

3.3. Determination of solubility:

The solubility of Cyproheptadine was determined by adding excess amount of drug in the solvent. The Cyproheptadine has very low aqueous solubility. Its solubility is not reported in any official book, so determination of solubility is important. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Cyproheptadine prepared using 10 ml of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 283 nm and 285 nm for phosphate buffer and distilled water respectively.

3.4. Determination of UV scan:

A 100mg of Cyproheptadine was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-400nm.

3.5. Calibration curve of Cyproheptadine :

A 100mg of Cyproheptadine was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in

concentration range of 5,10,15,20 and 25 µg /ml. The absorbance of these solutions were determined spectrophotometrically at 283 nm.

IV. FORMULATION OF TRANSDERMAL PATCHES:

4.1. Preparation of blank patches:

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

4.2. Formulation of Drug Incorporated Transdermal Patches:

The matrix-type transdermal patches containing Cyproheptadine were prepared using different concentrations of HPMC K100 M, Polyvinyl Alcohol and Polyvinyl pyrrolidone. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG-200 was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78cm^2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 8 mg. the formulation table is given in Table no.4.2.

Table 4.2: Formulation of Cyproheptadine Patches

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cyproheptadine	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
HPMC K100 M	**50**	**100**	**150**	**-**	**-**	**-**	**-**	**-**	**-**
Polyvinyl Alcohol	**-**	**-**	**-**	**50**	**100**	**150**	**-**	**-**	**-**
Polyvinylpyrrolidone	**-**	**-**	**-**	**-**	**-**	**-**	**50**	**100**	**150**
PEG-200 (mL)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Dimethylsulphoxide (mL)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Methanol (mL)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**

4.3. EVALUATION PARAMETERS OF PATCHES

All the prepared transdermal patches were evaluated by the following parameters:

4.4. Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

4.5. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

4.6. Weight variation

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

4.7. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously shaked for 12hrs, and then Sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number whatmann filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam UV-Visible spectrophotometer to determined drug content at λ_{max} 283 nm. Respected Placebo patch was taken as a blank solution.

4.8. 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 centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = I1 - I2 \text{ X } 100$$

I2 = Final length of each strip
I1 = Initial length of each strip

4.9. In-vitro Drug Diffussion Study:

The in vitro study of drug permeation through the semi permeable membrane was performed using a Franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This

membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5^{0}C. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 283

V. DRUG RELEASE KINETICS:

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

5.1. Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released vs time

$$C=K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

5.2.First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$Log C = Log C o - k t / 2.303$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

5.3. Higuchi Model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t 1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

5.4. Kors meyerPeppas equations:

Korsmeyerpeppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

$Mt/M\infty=Ktn$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

VI. COMPATIBILITY STUDY

6.1. FTIR study:

The infrared spectrum of the pure Cyproheptadine sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

VII. RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

7.1. Analysis of drug:

A. UV scan:

The lambda max of Cyproheptadine was found to be 283 nm.

B. construction of calibration curve:

Table 7.1: Standard graph of Cyproheptadine

Concentration(µg/ml)	Absorbance (at 283nm)
0	0
5	0.123
10	0.254
15	0.369
20	0.492
25	0.607

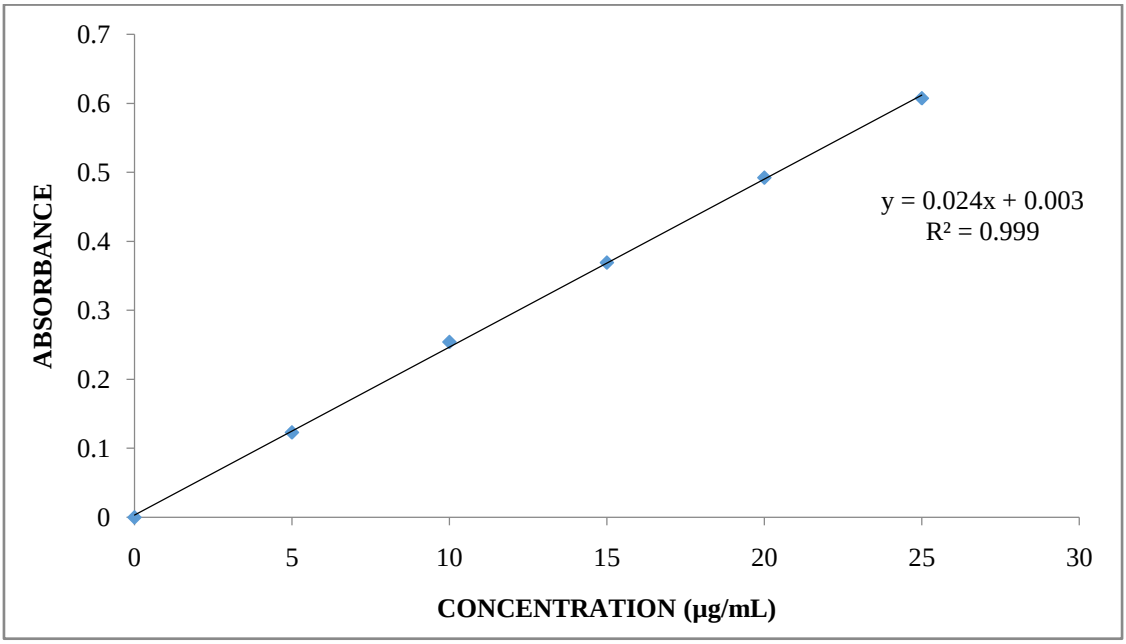

Figure 7.1: Standard calibration curve of Cyproheptadine

7.2. Preformulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Cyproheptadine transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 7.2: Results of identification tests of drug

Parameter	Cyproheptadine
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 7.3: Results of melting point determination tests of drug

Drug	Reported melting point
Cyproheptadine	163 ^{0}C

C. Determination of solubility:

Table 7.4: Solubility Determination

solvent	Drug solubility(mg/ml)
Distilled water	0.0403

Ph 7.4 phosphate buffer	78.3

7.3 Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.043 ±0.002 to 0.051±0.004 mm.

All formulations from F1 to F 9 Shows weight variation in between 95±3.19 to 100±6.95mg.

Folding endurance from formulations F1 to F9 was found to be in between 71 ± 2.15 to 77 ± 2.34 which can withstand the folding of the skin.

All formulations showed % drug content from 95.32 ± 9.25 to 99.87 ± 1.98.

Table 7.5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness (%)	% Drug Content
F1	98±3.15	0.043 ±0.002	74 ± 0.14	97	Transparent	95.32 ± 9.25
F2	99±1.59	0.049±0.006	73 ± 2.10	99	Transparent	97.25 ± 5.14
F3	95±3.19	0.051±0.002	75 ± 3.17	97	Transparent	99.87 ± 1.98
F4	100±6.95	0.046±0.006	76 ± 3.11	98	Transparent	97.12 ± 5.29
F5	96±1.86	0.048±0.001	77 ± 2.34	96	Transparent	98.43 ± 1.75
F6	98±1.15	0.050±0.005	71 ± 2.15	95	Transparent	99.69 ± 0.59
F7	99±4.72	0.049±0.003	75 ± 2.36	99	Transparent	96.78 ± 3.14
F8	99±1.96	0.047±0.002	74 ± 2.04	99	Transparent	99.24 ± 6.97
F9	97±2.98	0.051±0.004	75 ± 2.96	97	Transparent	98.39 ± 5.69

In vitro diffusion study:

All the formulation in vitro diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 ^{o}C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 7.6: In vitro drug permeation of Cyproheptadine containing different concentrations of HPMC K100 M

Time (hr)	F1	F2	F3
0	0	0	0
1	20.62	15.73	12.08
2	29.91	23.30	19.18
3	41.16	36.32	26.94
4	52.18	47.59	38.58
5	65.30	56.24	46.44
6	76.18	63.31	55.76
7	88.97	72.08	64.99
8	99.72	83.68	71.23
9		92.08	78.47
10		97.99	87.63
11			93.01
12			98.87

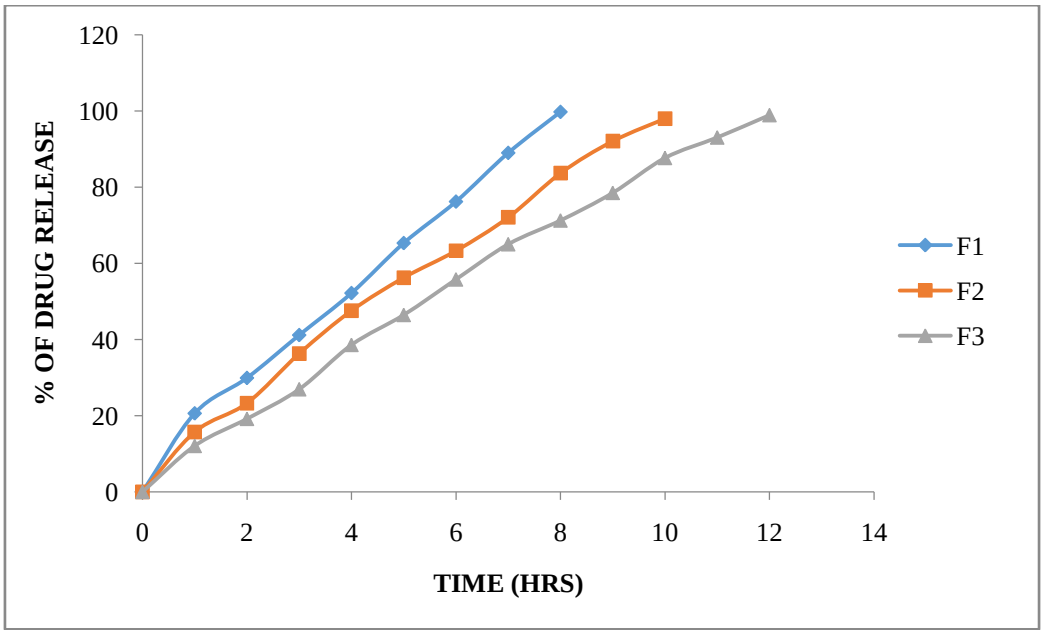

Figure: 7.2 Cumulative % drug permeation of Cyproheptadine patch (F1, F2, F3)

The formulations F1 to F3 were prepared by different concentrations of HPMC K100 M (50, 100, 150mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 8 hours it was total amount of drug was permeated.

Table 7.7: In vitro drug permeation of Cyproheptadine containing different concentrations of Polyvinyl Alcohol

Time (hr)	F4	F5	F6
0	0	0	0
1	26.34	17.34	13.27
2	40.74	24.36	20.34
3	51.48	35.27	27.23
4	69.74	43.45	35.47
5	72.19	58.46	40.19
6	81.48	65.63	47.28
7	86.18	70.28	53.37
8	92.29	76.29	61.46
9	97.21	82.32	70.28
10		87.48	77.37
11		95.64	85.21
12			89.36

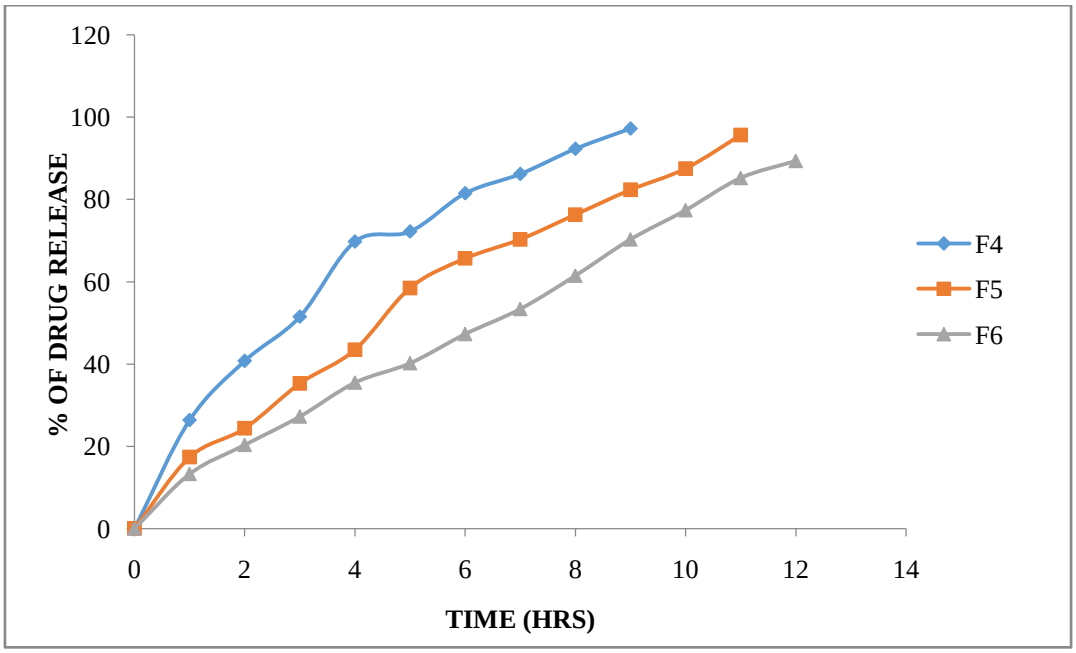

Figure: 7.3 Cumulative % drug permeation of Cyproheptadine patch (F4, F5, F6)

The 50mg concentration of polymer was showed maximum drug released at 9 hours 97.21 %. The 60mg concentration of polymer was showed maximum drug release 95.64 at 11 hours. Hence in that 3 formulations F6 formulations showed total drug release at desired time period.

Table: 7.8 In vitro drug permeation of Cyproheptadine containing different concentrations of Polyvinylpyrrolidone

Time	F7	F8	F9
0	0	0	0
1	15.47	13.15	10.28
2	24.03	22.06	19.46
3	34.43	30.52	26.52
4	42.56	39.37	30.47
5	51.27	47.46	36.61
6	59.84	55.08	42.07
7	67.34	62.31	50.36
8	78.25	70.49	56.13
9	89.38	79.30	61.23
10	98.04	86.21	68.31
11		91.55	75.43
12		98.12	81.37

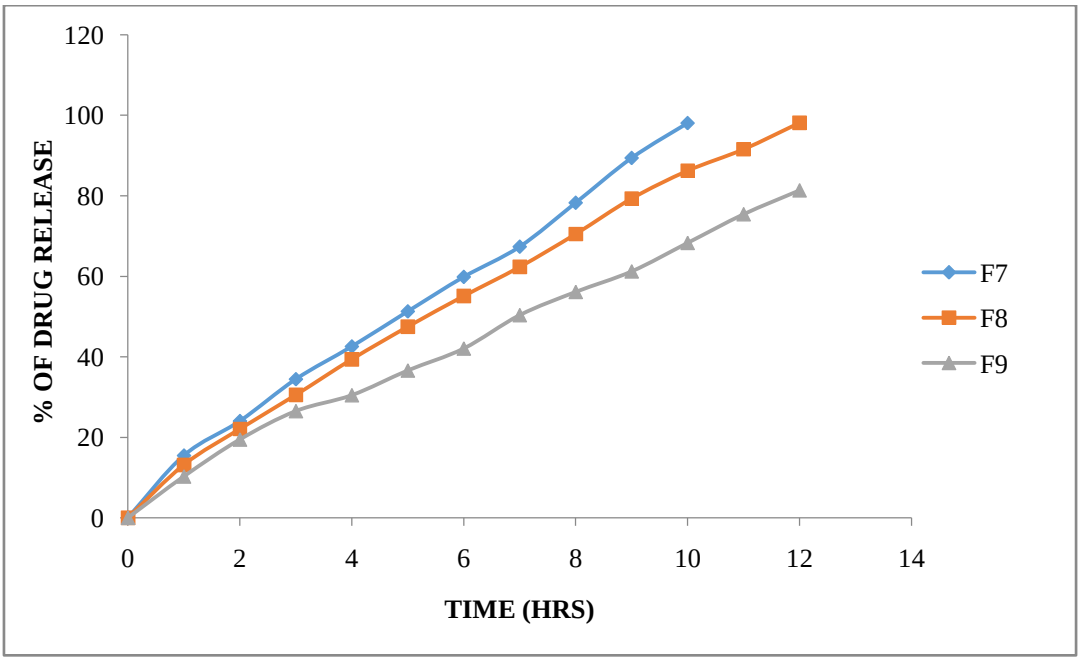

Figure: 7.4 Cumulative % drug permeation of Cyproheptadine patch (F7, F8, F9)

The formulations F7 to F9 were prepared by different concentrations of Polyvinylpyrrolidone (50, 100, 150mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 50mg (F7) concentration of polymer was showed maximum drug release 98.04 within 10 hours. The 100mg (F8) concentration of polymer was showed maximum drug released at 12 hours 98.12 %. The 150mg (F9) concentration of polymer was showed less drug release 81.37 at 12 h.

Among all 9 formulations F3 formulation showed good drug permeation from the patch.
Among all in vitro evaluation parameters F3 formulation passed all evaluation parameters.

7.4 Kinetic models for Cyproheptadine

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table: 7.9 Kinetics data of F3 Cyproheptadine patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
12.08	1	1.000	1.082	0.000	1.944	12.080	0.0828	-0.918	87.92	4.642	4.447	0.195
19.18	2	1.414	1.283	0.301	1.908	9.590	0.0521	-0.717	80.82	4.642	4.324	0.318
26.94	3	1.732	1.430	0.477	1.864	8.980	0.0371	-0.570	73.06	4.642	4.180	0.461
38.58	4	2.000	1.586	0.602	1.788	9.645	0.0259	-0.414	61.42	4.642	3.946	0.696
46.44	5	2.236	1.667	0.699	1.729	9.288	0.0215	-0.333	53.56	4.642	3.769	0.872
55.76	6	2.449	1.746	0.778	1.646	9.293	0.0179	-0.254	44.24	4.642	3.537	1.105
64.99	7	2.646	1.813	0.845	1.544	9.284	0.0154	-0.187	35.01	4.642	3.271	1.370
71.23	8	2.828	1.853	0.903	1.459	8.904	0.0140	-0.147	28.77	4.642	3.064	1.577
78.47	9	3.000	1.895	0.954	1.333	8.719	0.0127	-0.105	21.53	4.642	2.782	1.860
87.63	10	3.162	1.943	1.000	1.092	8.763	0.0114	-0.057	12.37	4.642	2.313	2.329
93.01	11	3.317	1.969	1.041	0.844	8.455	0.0108	-0.031	6.99	4.642	1.912	2.730
98.87	12	3.464	1.995	1.079	0.053	8.239	0.0101	-0.005	1.13	4.642	1.042	3.600

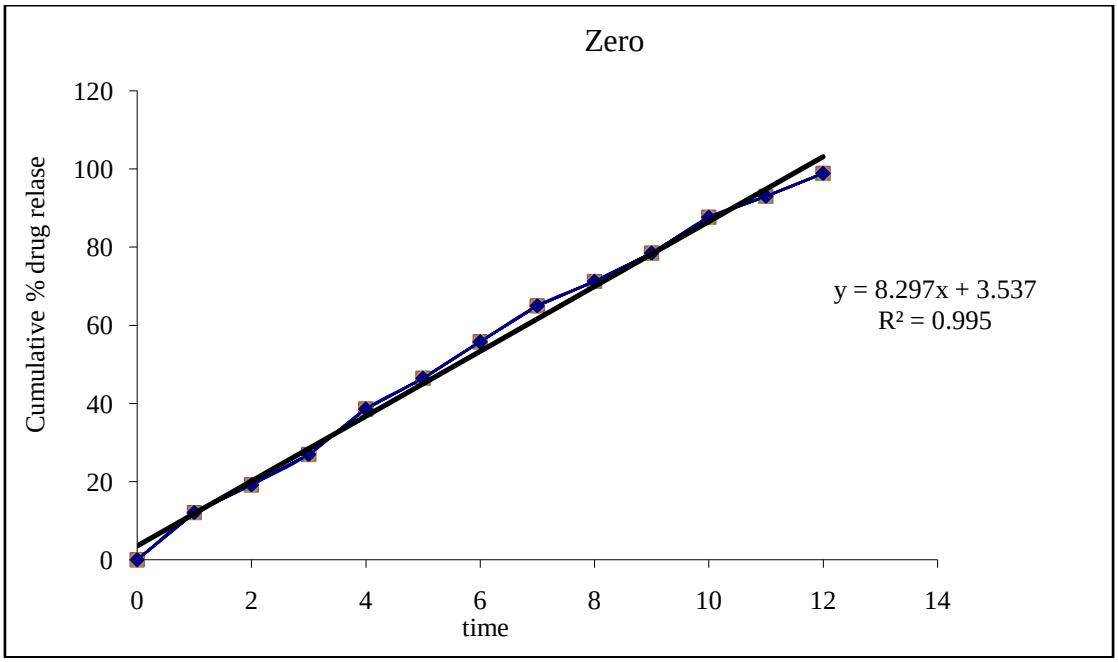

Figure: 7.5 Graph of Zero order kinetics

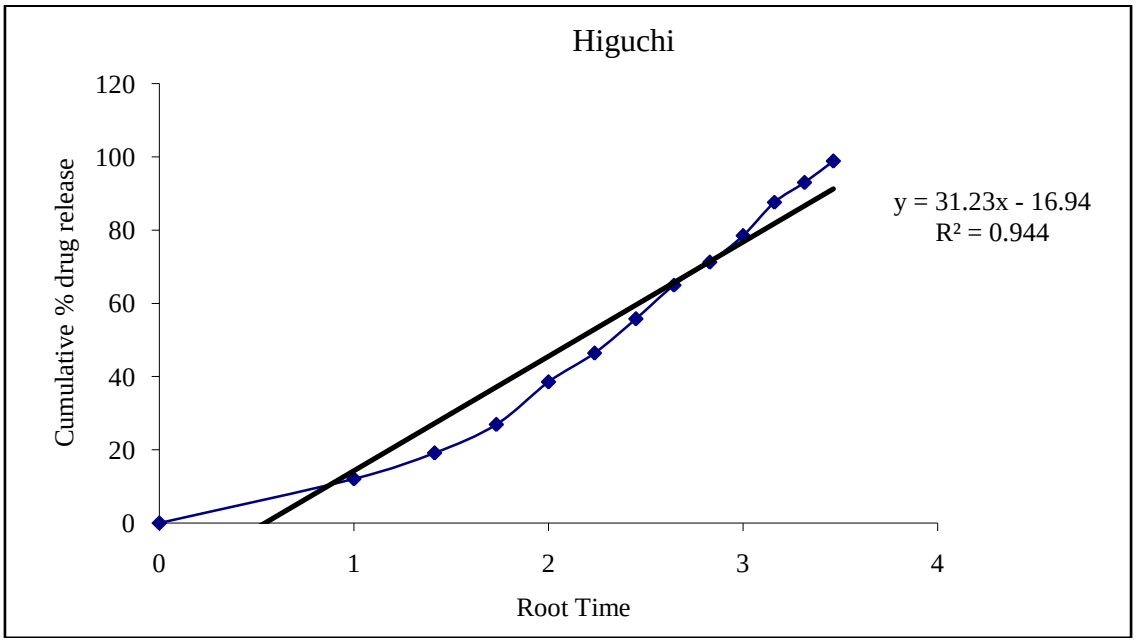

Figure: 7.6 Graph of Higuchi release kinetics

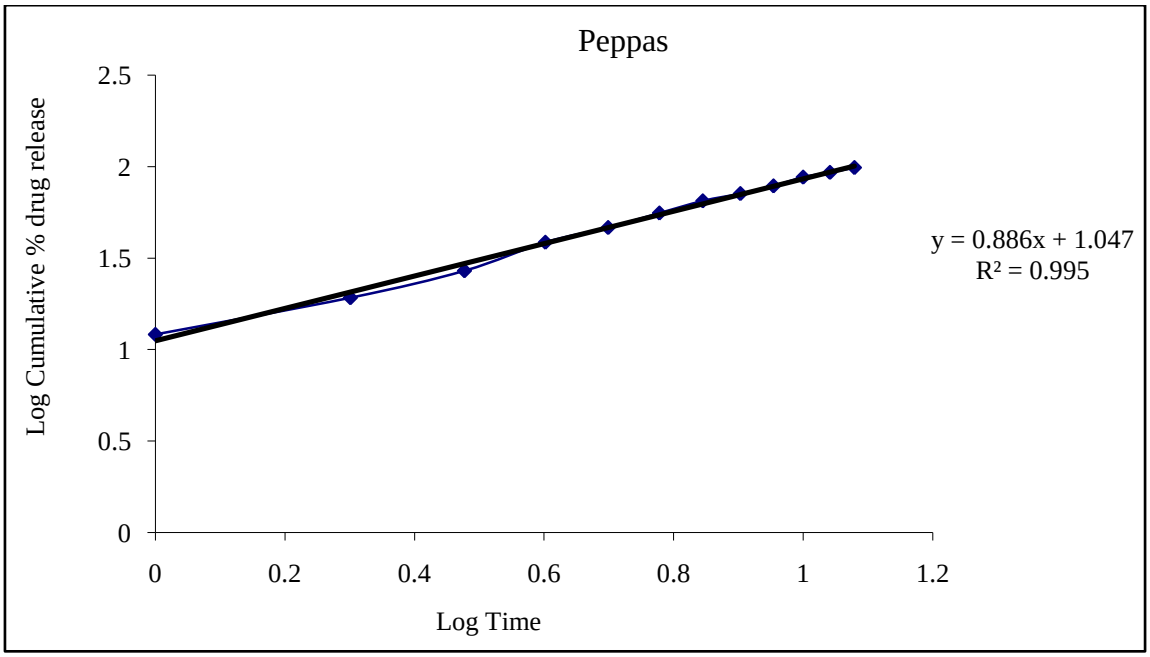

Figure : 7.7 Graph of peppas release kinetics

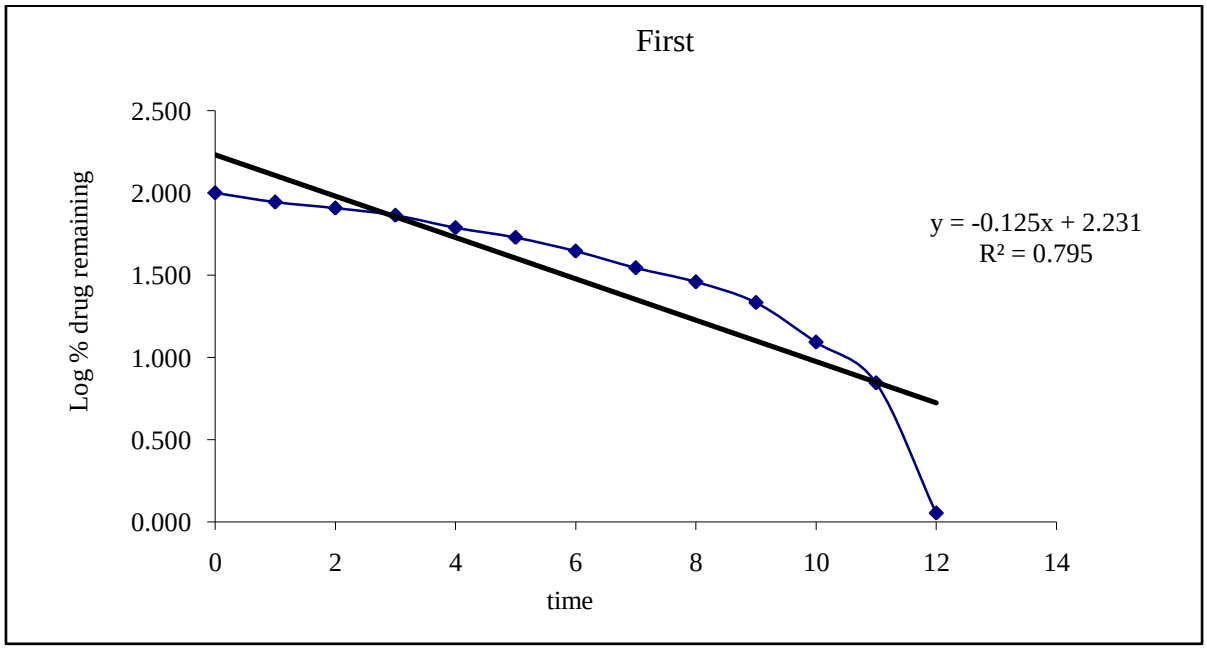

Figure: 7.8 Graph of First order release kinetics

From the above data the optimized formulation followed Higuchi release kinetics model rule.

7.2. Compatibility studies:
IR SPECTROSCOPY:

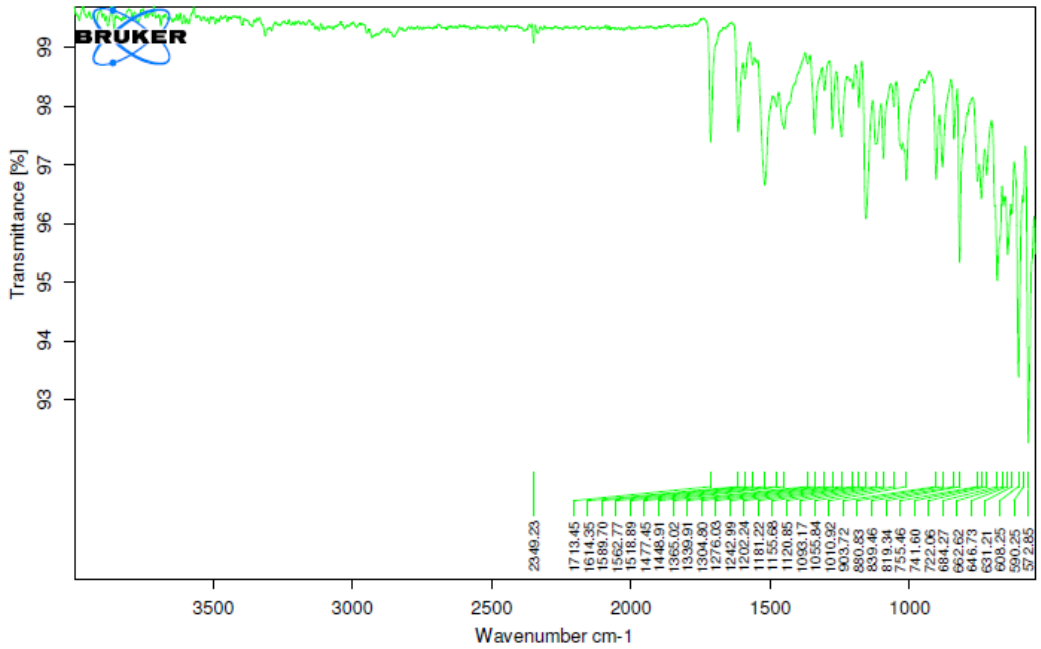

Figure7.9: FTIR Spectrum of pure Cyproheptadine drug

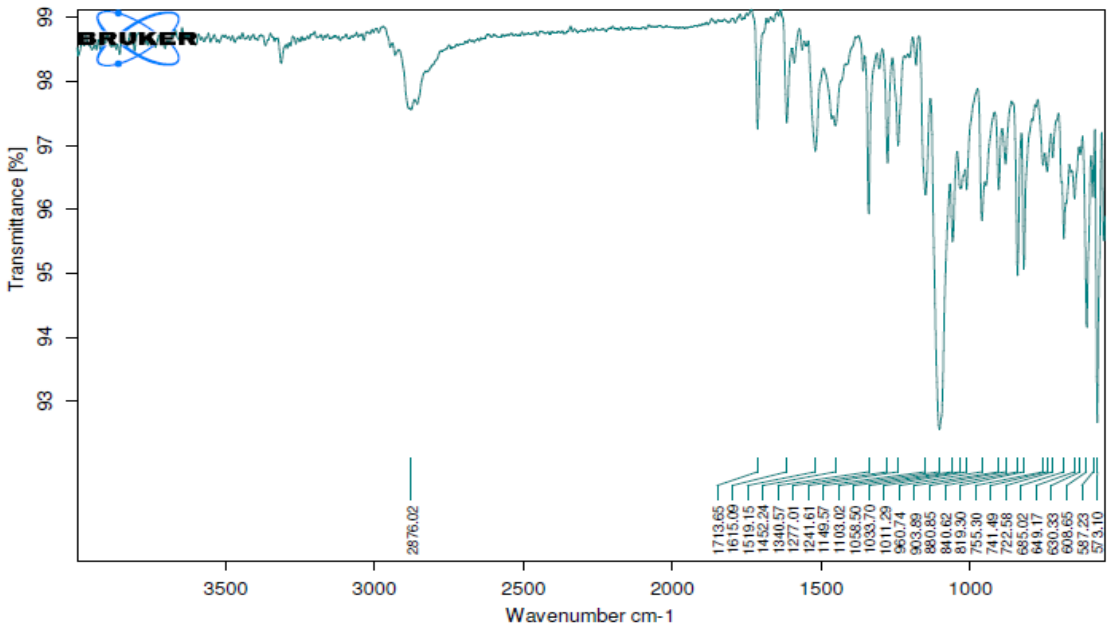

Figure 7.10: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

VIII. CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Cyproheptadine patches using different types of polymers by solvent evaporation technique method. The drug used is the best studied for therapy in treating various allergic symptomatologies - including dermatographia, rhinitis, conjunctivitis, and urticaria - as well as adjunctive therapy in the management of anaphylaxis following treatment with epinephrine.

Cyproheptadine was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.
From the experimental results obtained, F3formulation has been selected as the best formulation among all the other formulations. The in-vitro drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.
The data obtained from the in-vitro release studies were fitted to various kinetic models like zero order, first order, Higuchi model and Pappas model.
From the kinetic data it was found that drug release follows Higuchi model release by diffusion technique from the polymer.
Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Cyproheptadine patches was found to be successful in the release of the drug for an extended period of 12 hrs.

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