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PREPARATION AND EVALUATION OF TRANSDERMAL PATCH CONTAINING DRUG DIACEREIN

Srinivas Reddy. Cheedipudi*[1], Dr.Shaik Harun Rasheed[2], Sainath Kadam[3], Rohit Kumar Deo[4], Sahin Shaikh[5], Rehola T Yimchunger[6], Sakshi Baghel[7]

Department of Pharmaceutics, Gurunanak School of Pharmacy, Rangareddy, Telangana[1].

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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 Diacerein 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. F4formulation 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 zero order model release by diffusion technique from the polymer.

Keywords: *Transdermal drug delivery, hydrophobic polymers and Diacerein.*

Corresponding author:

Srinivas Reddy. Cheedipudi,

Department of Pharmaceutics,
Gurunanak School of Pharmacy,
Rangareddy, Telangana.
Email Id- srinivasch269@gmail.com

QR code

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INTRODUCTION:

Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other[1].the difference between sustained release and controlled release is shown by fig.1.

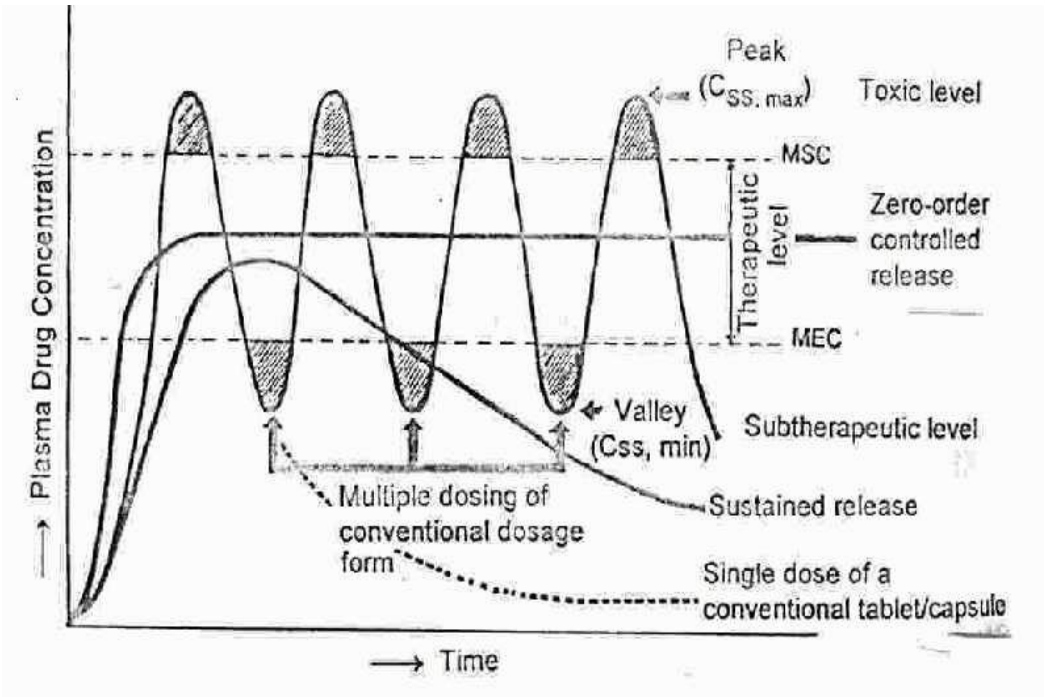

Figure 1. 1: Comparative graphs of conventional, sustained- and controlled release delivery systems.

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

Transdermal drug delivery: An 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.

Definition: 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.

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

Advantages [2,3,4,5]:

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of s drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
9. They are used for drugs with narrow therapeutic window. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

Disadvantages [3,4,6]:

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Structure of skin:

An average adult skin has a surface area of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97+/-0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, and cushion internal structures [7,8]

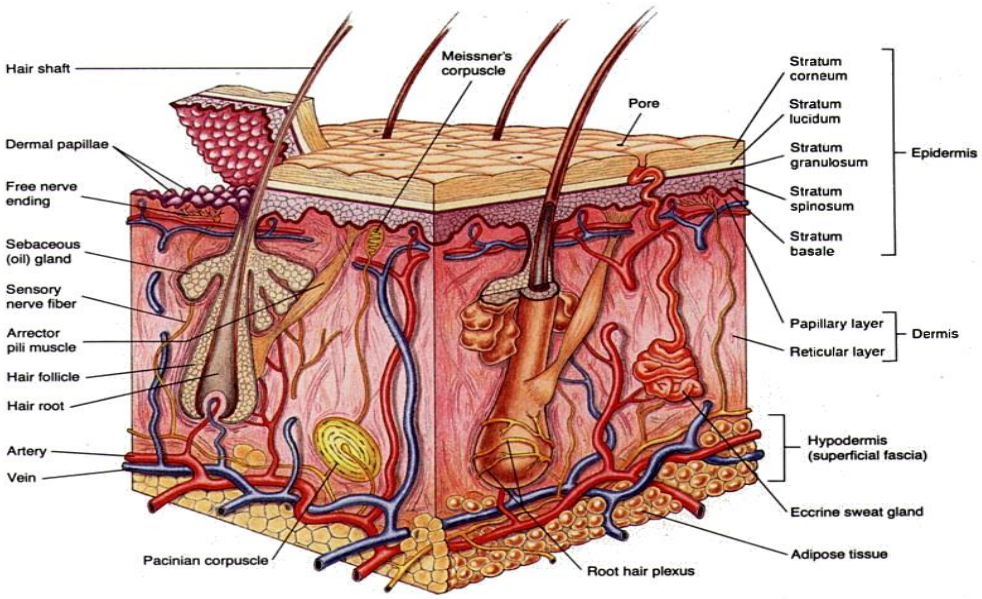

Figure 1.2: Structure of skin

The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers. [6,9,10]
The epidermis – thin protective outer layer.
The dermis – the tough elastic second layer.
The hypodermis – layer of fatty and connective tissue.

The Epidermis:
The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer):
The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer):
As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer):
As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

Stratum lucidum:
In the palms and the soles an anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer immediately above layer immediately above the granular layer. This region is the stratum lucidum.

Stratum corneum (horny layer):
As the final stage of differentiation, epidermal cells construct the most the superficial layer of the epidermis, the stratum corneum. On general body areas the membrane provides 10-15 layers of much flattened, keratinized dead cells (corneocytes). Ultimately these cells are sloughed off through desquamation. A keratinocyte's journey from basal layer to horny layer takes about 14 days. The cell travels through the layers of stratum corneum for

another 14 days before it is finally shed. So the normal turnover rate of the epidermis is atleast 28 days. The stratum corneum plays a crucial role in controlling the percutaneous absorption of drug molecules.

The barrier nature of stratum corneum depends critically on its unique constituents; 75-80% is protein, 5-15% is lipid with 5-10% unidentified on a dry weight basis. The protein is located primarily within the keratinocytes and is predominantly alpha-keratin (around 70%) with some beta-keratin (approximately 10%) and a proteinaceous cell enveloping (around 5%). Enzymes and other proteins account for approximately 15% of the protein component. The cell envelop protein is highly insoluble and is very resistant to chemical attack. This outer keratinocytes protein has a key role in structuring and ordering the intercellular lipid lamella of the stratum corneum; the keratinocytes is bound to a lipid envelop through glutamate moieties of the protein envelop. The lipid envelop thus provides an anchor to the keratinocytes and links the proteinaceous domains of the keratinocytes to the intercellular lipid domains. Human stratum corneum is a unique mixture of lipids and, for most permeates; the continuous multiply bilayered lipid component of the stratum corneum is key component in regulating drug flux through the tissue. It is clear that the lipid content of the stratum corneum varies between individuals and with body site, but major components of the domain include ceramides, fatty acids, cholesterol, and cholesterol sulfate and sterol/wax esters.

MATERIALS:

Diacerein -Procured From Sanofi Aventis Pharma, Ltd, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Ethyl Cellulose -Merck Specialities Pvt Ltd, HPMC -Merck Specialities Pvt Ltd, Acetone-Merck Specialities Pvt Ltd, Dichloromethane -Merck Specialities Pvt Ltd, Dibutyl phthalate -Merck Specialities Pvt Ltd, Glycerine-Merck Specialities Pvt Ltd.

METHODOLOGY:

Analytical method development:

A.UV scan:

A 100mg of Diacerein 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 100µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10µg/ml solution was scanned from 200-400nm.

B. Construction of calibration curve:

A 100mg of Diacerein 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's of these solutions were determined spectrophotometrically at 270 nm.

Preformulation study:

A. Colour, Odour, Taste and Appearance:

The drug sample was evaluated for its Colour, odour and appearance.

B. Melting point determination:

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

C. Determination of solubility:

The solubility of Diacerein was determined by adding excess amount of drug in the solvent.

The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Diacerein 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 270 nm and 273 nm for phosphate buffer and distilled water respectively.

Formulation of transdermal patches:

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.

Formulation of drug incorporated transdermal patches:

The matrix-type transdermal patches containing Diacerein were prepared using different concentrations of Ethyl Cellulose, and HPMC polymers. 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. Dibutyl phthalate was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch. The formulation table is given in table no. 7.1.

Table 7.1: Formulation of Diacerein patches

INGREDIENTS	FORMULATION CHART							
	F1	F2	F3	F4	F5	F6	F7	F8
Diacerein (g)	1	1	1	1	1	1	1	1
Ethyl Cellulose (g)	0.2	0.5	1	1.5	-	-	-	-
HPMC (g)	-	-	-	-	0.2	0.5	1	1.5
Acetone (mL)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Dichloromethane (mL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Dibutyl phthalate (mL)	1	1	1	1	1	1	1	1
Glycerine (mL)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

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.

Analysis of drug:

A. UV scan:

The lambda max of Diacerein was found to be 256 nm.

B. construction of calibration curve:

Table 8.1: Standard graph of Diacerein

Concentration (µg/ml)	Absorbance (at 256 nm)
0	0
5	0.121
10	0.225
15	0.334
20	0.439
25	0.546

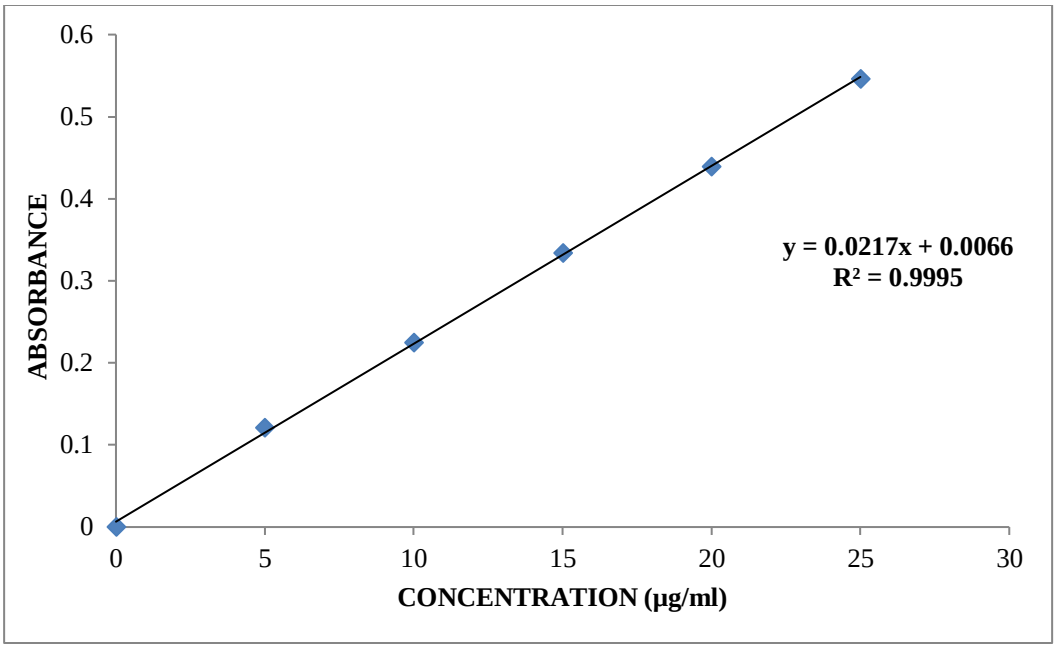

Figure 8.1: Standard calibration curve of Diacerein

8.2. Preformulation study

Totally, Eight formulation trials were done with the aim to achieve the successful matrix type Diacerein 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 8.2: Results of identification tests of drug

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

B. Melting point determination:

Table 8.3: Results of melting point determination tests of drug

Drug	**Reported melting point**
Diacerein	216.6 °C

C. Determination of solubility:

Table 8.4: Solubility Determination

solvent	**Drug solubility(mg/ml)**
Distilled water	4.93
Ph 7.4 phosphate buffer	78.3

8.3 Evaluation of Patch

The formulations F1 to F8 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 0.041±0.007 to 0.051±0.004 mm.

All formulations from F1 to F8 shows weight variation in between 70 ±9.58 to 79 ±4.69 mg.

Folding endurance from formulations F1 to F8 was found to be in between 81 ± 0.15 to 89 ± 2.15 which can withstand the folding of the skin.
All formulations showed % drug content from 95.1 ± 2.61 to 99.74 ± 1.57.

Table 8.5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F1	75±1.05	0.046 ± 0.003	81 ± 0.15	100	Transparent	97.1 ± 2.10
F2	78 ±5.36	0.049±0.008	86 ± 1.39	99	Transparent	98.28 ± 0.45
F3	71 ±2.84	0.051±0.004	85 ± 2.26	100	Transparent	97.69 ± 2.21
F4	75 ±5.41	0.041±0.009	80 ± 1.84	100	Transparent	95.1 ± 2.61
F5	77 ±9.18	0.049±0.004	82 ± 3.10	99	Transparent	99.2 ± 3.87
F6	79 ±4.69	0.041±0.007	89 ± 2.15	100	Transparent	98.35 ± 0.59
F7	70 ±9.58	0.047±0.001	84 ± 2.36	99	Transparent	99.11 ± 2.34
F8	76 ±3.86	0.045±0.009	87 ± 2.04	100	Transparent	99.74 ± 1.57

***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 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8.6: *In vitro* drug permeation of Diacerein

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	37.81	32.14	27.38	22.65	20.31	19.38	18.38	16.21
2	41.20	35.63	35.79	26.16	25.23	25.43	26.45	20.07
3	44.39	45.82	42.88	34.98	26.96	36.86	29.59	25.17
4	57.85	51.40	48.54	45.29	36.35	38.75	38.83	38.56
5	62.34	55.09	59.17	56.73	41.02	47.46	44.26	41.58
6	67.13	63.46	66.62	68.22	54.75	56.13	55.15	50.27
7	79.91	75.02	71.93	75.73	68.13	64.16	66.29	56.68
8	83.28	78.59	75.87	78.40	78.84	68.77	69.76	64.37
9	95.96	81.36	83.26	86.01	88.22	76.85	75.27	73.77
10	96.21	85.11	89.15	89.58	95.09	84.49	76.19	78.42
11	97.56	90.78	90.02	96.96		88.88	87.64	81.12
12		96.19	98.14	99.63		90.16	91.49	89.28

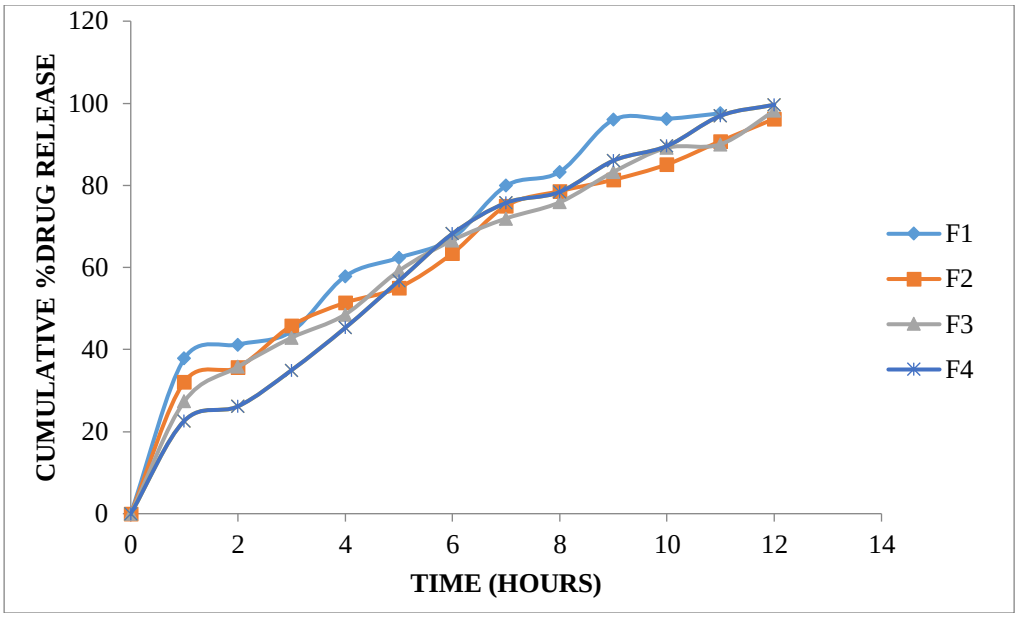

Figure: 8.2 Cumulative % drug permeation of Diacerein patch (F1 to F4)

The formulations F1 to F4 were prepared by different concentrations of Ethyl Cellulose (0.2, 0.5, 1 and 1.5g) in 2*2 cm^2patch, 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 12 hours it was total amount of drug was permeated. The 1.5 g concentration of polymer was showed maximum drug released at 12 hors 99.63%. Hence in that 4 formulation showed total drug release at desired time period.

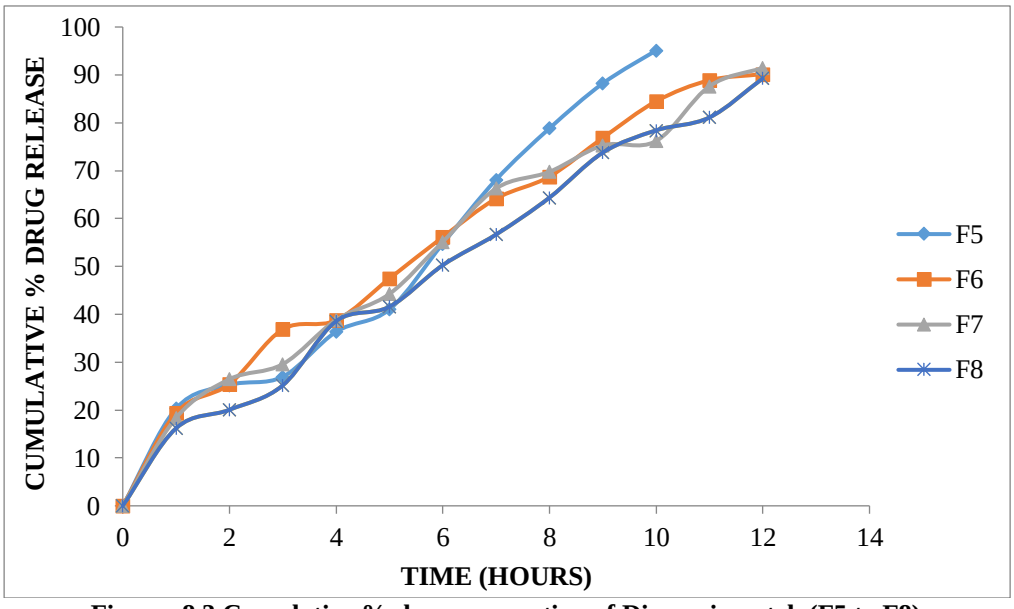

Figure: 8.3 Cumulative % drug permeation of Diacerein patch (F5 to F8)

The formulations F5 to F8 were prepared by different concentrations of HPMC (0.2, 0.5, 1 and 1.5g) in 2*2 cm^2 patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 1g (F7) concentration of polymer was showed maximum drug release 91.49 within 12 hours.

The 1.5g (F4) concentration of polymer was showed maximum drug released at 12 hours 99.63%.

Among all 8 formulations F4 formulation showed good drug permeation from the patch.
Among all *in vitro* evaluation parameters F4 formulation passed all evaluation parameters.

Kinetic models for Diacerein:
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: 8.7 Kinetics data of F4 Diacerein 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
22.65	1	1.000	1.355	0.000	1.888	22.650	0.0442	-0.645	77.35	4.642	4.261	0.381
26.16	2	1.414	1.418	0.301	1.868	13.080	0.0382	-0.582	73.84	4.642	4.195	0.446
34.98	3	1.732	1.544	0.477	1.813	11.660	0.0286	-0.456	65.02	4.642	4.021	0.620
45.29	4	2.000	1.656	0.602	1.738	11.323	0.0221	-0.344	54.71	4.642	3.796	0.845
56.73	5	2.236	1.754	0.699	1.636	11.346	0.0176	-0.246	43.27	4.642	3.511	1.131
68.22	6	2.449	1.834	0.778	1.502	11.370	0.0147	-0.166	31.78	4.642	3.168	1.474
75.73	7	2.646	1.879	0.845	1.385	10.819	0.0132	-0.121	24.27	4.642	2.895	1.746
78.4	8	2.828	1.894	0.903	1.334	9.800	0.0128	-0.106	21.6	4.642	2.785	1.857
86.01	9	3.000	1.935	0.954	1.146	9.557	0.0116	-0.065	13.99	4.642	2.410	2.232
89.58	10	3.162	1.952	1.000	1.018	8.958	0.0112	-0.048	10.42	4.642	2.184	2.457
96.96	11	3.317	1.987	1.041	0.483	8.815	0.0103	-0.013	3.04	4.642	1.449	3.193
99.63	12	3.464	1.998	1.079	-0.432	8.303	0.0100	-0.002	0.37	4.642	0.718	3.924

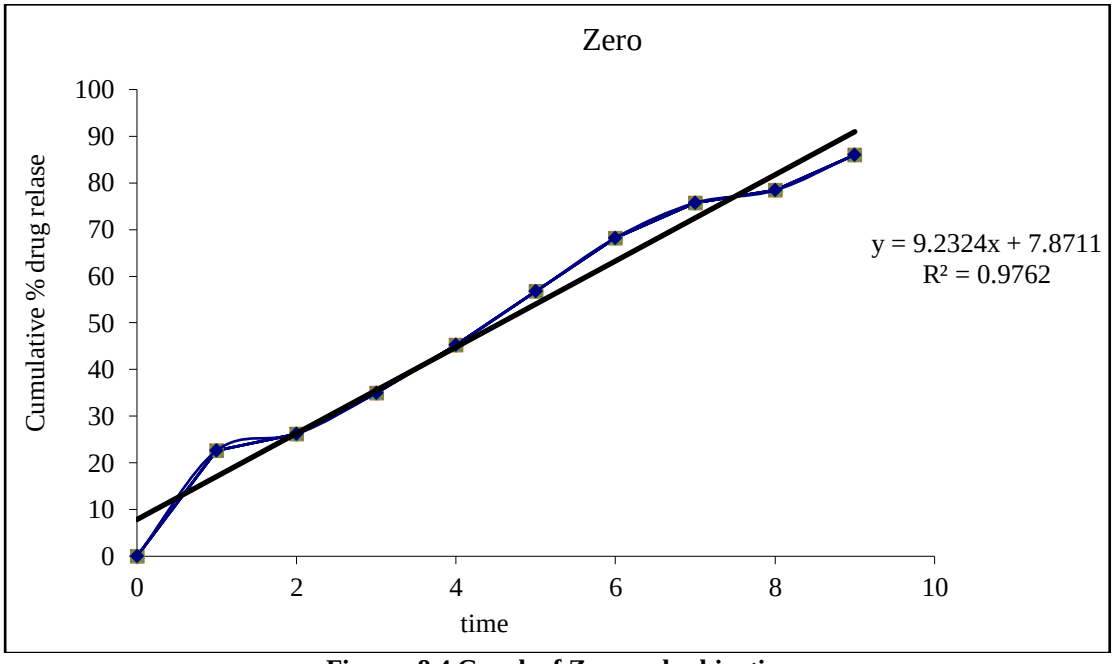

Figure: 8.4 Graph of Zero order kinetics

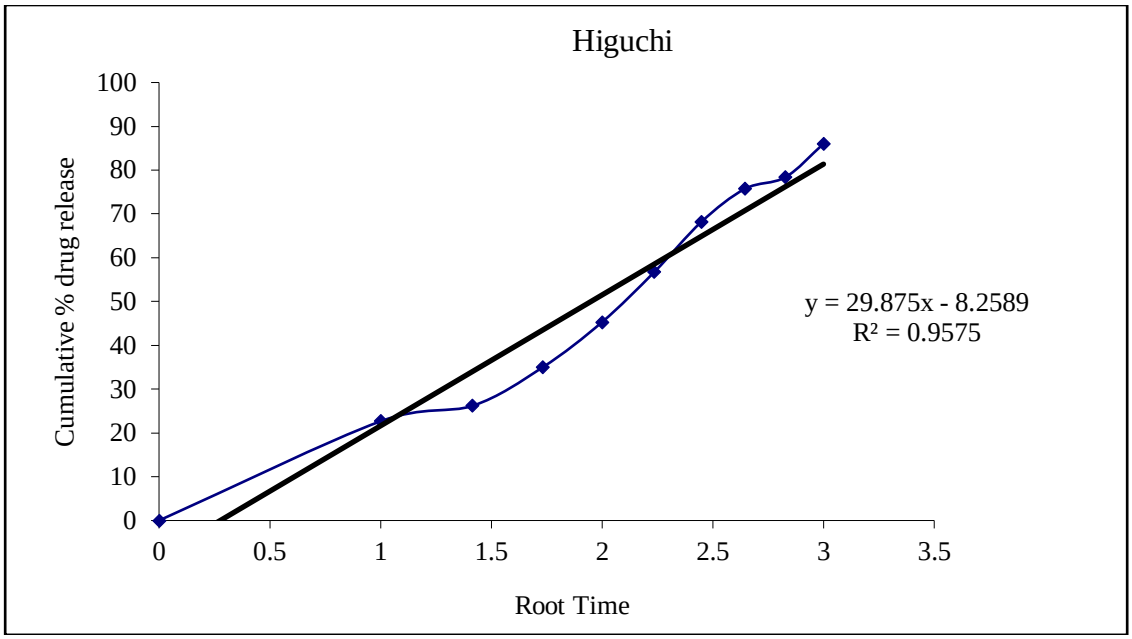

Figure: 8.5 Graph of Higuchi release kinetics

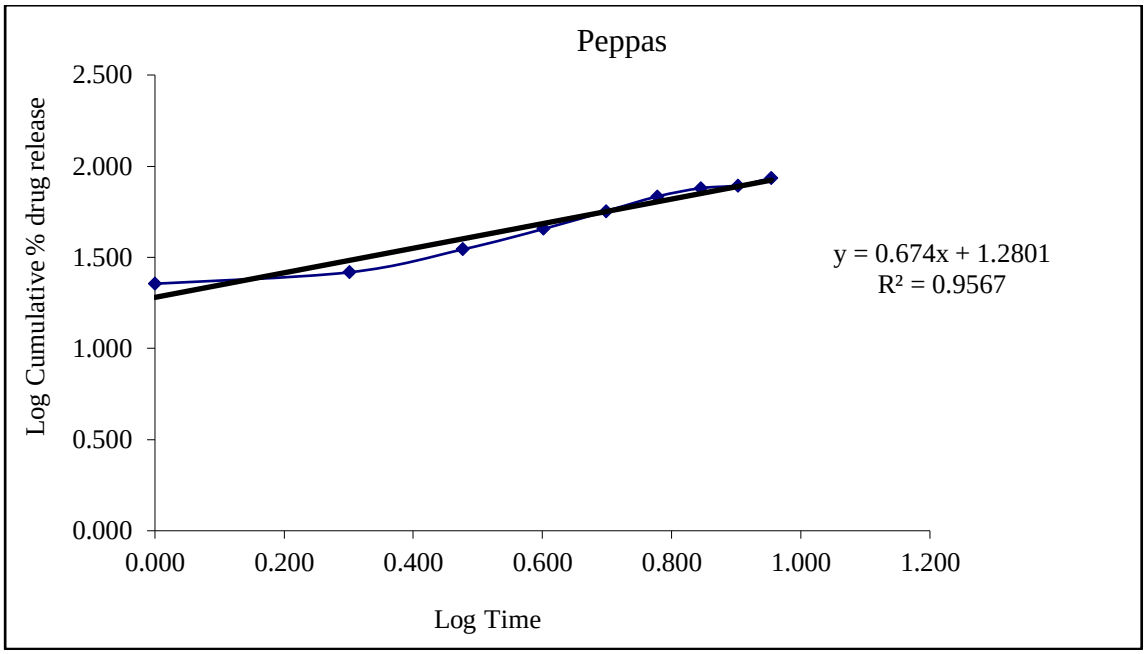

Figure: 8.6 Graph of peppas release kinetics

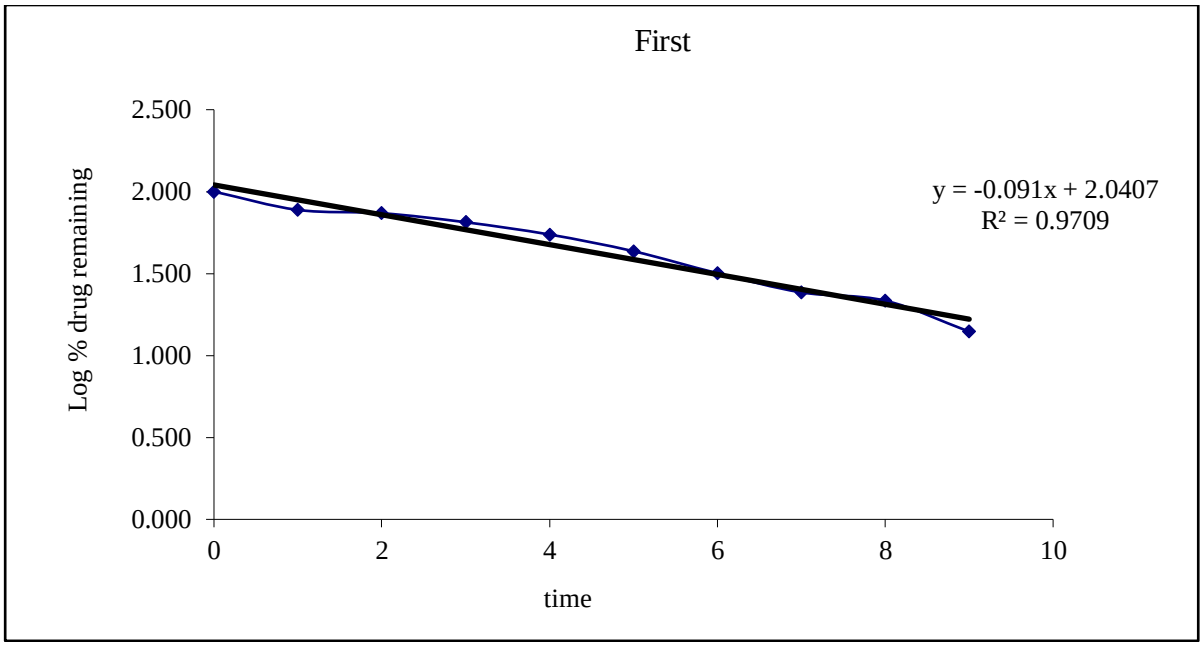

Figure: 8.7 Graph of First order release kinetics

From the above data the optimized formulation followed Zero order model rule.

Compatibility studies:

IR SPECTROSCOPY:

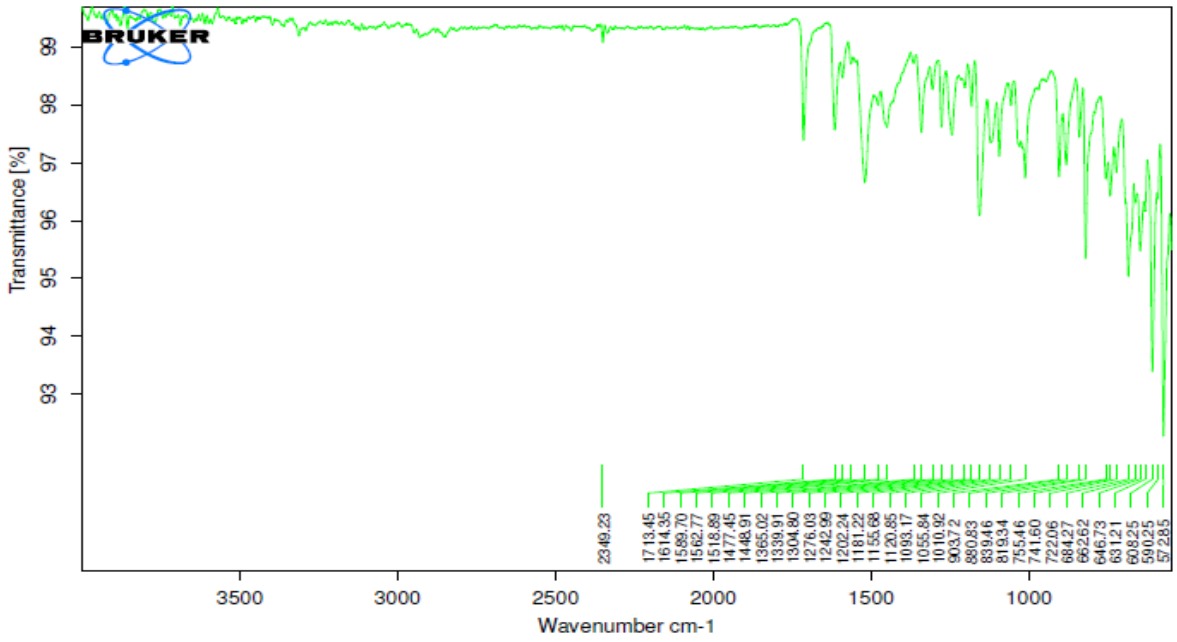

Figure: 8.8 FTIR Spectrum of pure Diacerein drug

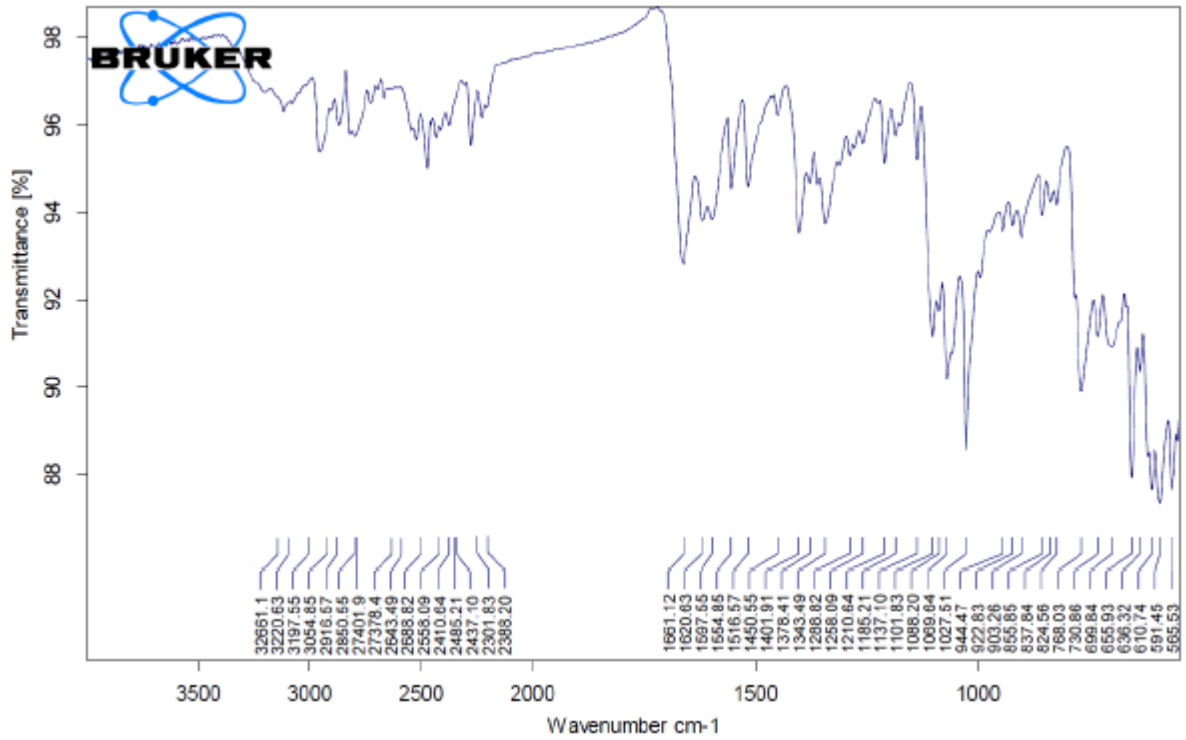

Figure: 8.9 FTIR of Optimized formulation

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

CONCLUSION:

In the present investigation an attempt has been made to design and develop the formulation of Diacerein patches using different types of polymers by solvent evaporation technique and mercury substrate method. The drug used is the best studied for therapy in treating osteoarthritis.

Diacerein was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.

From the experimental results obtained, F4formulation 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 Zero order 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 Diacerein patches was found to be successful in the release of the drug for an extended period of 12hrs.

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