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Research Article

**FORMULATION AND EVALUATION OF TRANSDERMAL
DRUG DELIVERY SYSTEM OF HESPERIDIN****Gandham Archana*, M. Mounika, Dr. D. Venkata ramana.**

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Abstract:

The present study focuses on the formulation and evaluation of a transdermal drug delivery system (TDDS) of Hesperidin, a natural bioflavonoid known for its antioxidant, anti-inflammatory, and Vaso protective properties. Due to its poor oral bioavailability and extensive first-pass metabolism, the transdermal route was selected to enhance systemic absorption and ensure sustained therapeutic action. Transdermal patches were prepared using various combinations of polymers such as Ethyl Cellulose, HPMC and Eudragit RSPO, along with suitable plasticizers. The formulations were evaluated for physicochemical properties including thickness, weight variation, folding endurance, moisture content, drug content uniformity, and in vitro drug release. The optimized formulation exhibited good mechanical strength, satisfactory drug content, and a sustained drug release profile over 12 hours. The study concludes that Hesperidin-loaded transdermal patches can serve as a promising alternative to conventional dosage forms, potentially improving patient compliance and therapeutic efficacy.

Keywords: Hesperidin, Ethyl Cellulose, HPMC and Eudragit RSPO

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1. 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 other¹.

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.

1.1 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 a 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 drug having a 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.

MATERIALS AND METHODS:

Materials

Hesperidin Procured From Torrent Pharma, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad.

Ethyl Cellulose Merck Specialities Pvt Ltd

HPMC Merck Specialities Pvt Ltd

Eudragit RSPO Merck Specialities Pvt Ltd

PEG-400 (ml) Merck Specialities Pvt Ltd

Chloroform Merck Specialities Pvt Ltd

Dimethylsulphoxide Merck Specialities Pvt Ltd

Dibutyl phthalate Merck Specialities Pvt Ltd

7. METHODOLOGY:**7.1. Analytical method development:****A.UV scans:**

A 100mg of Hesperidin 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 I 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 Hesperidin 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 I 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 10,20,30,40 and 50µg /ml. The absorbances of these solutions were determined spectrophotometrically at 330 nm.

7.2. 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 Hesperidin 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 Hesperidin 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 330 nm and 333 nm for phosphate buffer and distilled water respectively.

7.3. 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 Hesperidin were prepared using different concentrations of Ethyl Cellulose, HPMC and Eudragit RSPO 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 cm² patches. Drug incorporated for each 2x2 cm² patch. The formulation table is given in table no. 7.1.

Table 7.1: Formulation of Hesperidin patches

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hesperidin	25	25	25	25	25	25	25	25	25
Ethyl Cellulose	25	50	75	-	-	-	-	-	-
HPMC	-	-	-	25	50	75	-	-	-
Eudragit RSPO	-	-	-	-	-	-	25	50	75
PEG-400 (ml)	10	10	10	10	10	10	10	10	10
Chloroform	15	15	15	15	15	15	15	15	15
Dimethylsulphoxide (ml)	2	2	2	2	2	2	2	2	2
Dibutyl phthalate* (ml)	7	7	7	7	7	7	7	7	7

8. 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.

8.1. Analysis of drug:

A. UV scan:

The lambda max of Hesperidin was found to be 330 nm.

B. construction of calibration curve:

Table 8.1: Standard graph of Hesperidin

Concentration (µg/ml)	Absorbance (at 330 nm)
0	0
10	0.107
20	0.226
30	0.334
40	0.449
50	0.556

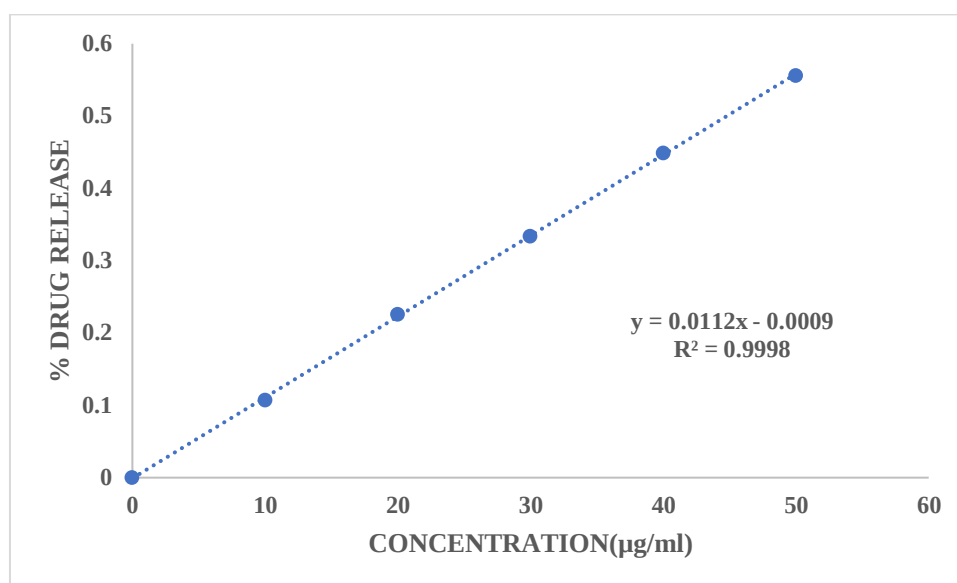


Figure 8.1: Standard calibration curve of Hesperidin

8.2. Preformulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Hesperidin 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	Hesperidin
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
Hesperidin	305-306 °c

C. Determination of solubility:**Table 8.4: Solubility Determination**

solvent	Drug solubility(mg/ml)
Distilled water	48.93
Ph 7.4 phosphate buffer	60.31

8.3 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 0.041 ± 0.007 to 0.051 ± 0.004 mm.

All formulations from F1 to F9 shows weight variation in between 80 ± 9.85 to 89 ± 4.96 mg.

Folding endurance from formulations F1 to F9 was found to be in between 70 ± 1.84 to 79 ± 2.51 which can withstand the folding of the skin.

All formulations showed % drug content from 97.1 ± 2.10 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	85 ± 1.51	0.046 ± 0.003	71 ± 0.51	100	Transparent	97.1 ± 2.10
F2	88 ± 5.63	0.049 ± 0.008	76 ± 1.93	99	Transparent	98.28 ± 0.45
F3	81 ± 2.48	0.051 ± 0.004	75 ± 2.62	100	Transparent	97.69 ± 2.21
F4	85 ± 5.14	0.041 ± 0.009	70 ± 1.84	100	Transparent	98.1 ± 2.61
F5	87 ± 9.81	0.049 ± 0.004	72 ± 3.11	99	Transparent	99.2 ± 3.87
F6	89 ± 4.96	0.041 ± 0.007	79 ± 2.51	100	Transparent	98.35 ± 0.59
F7	80 ± 9.85	0.047 ± 0.001	74 ± 2.63	99	Transparent	99.11 ± 2.34
F8	86 ± 3.68	0.045 ± 0.009	77 ± 2.04	100	Transparent	99.74 ± 1.57
F9	84 ± 7.92	0.048 ± 0.006	72 ± 2.69	100	Transparent	98.48 ± 0.44

***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 °C. 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 Hesperidin

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.22	8.04	6.18	4.86	5.65	3.71	6.41	8.92	5.89
2	13.75	15.07	11.73	8.92	12.23	8.47	9.66	12.36	10.53
3	17.87	22.61	25.02	14.04	17.44	15.45	13.37	17.31	22.07
4	21.09	29.57	33.31	21.16	23.08	21.02	18.56	24.08	37.47
5	29.77	32.24	40.34	35.86	39.88	28.44	24.22	28.01	42.88
6	37.28	41.52	48.71	39.03	45.44	34.78	31.94	36.45	49.81
7	55.39	49.77	53.93	46.49	52.63	41.67	37.37	41.18	53.99
8	67.57	54.24	56.54	55.22	68.97	51.26	45.03	49.12	61.04
9	74.73	61.83	64.19	67.53	77.53	59.63	54.01	68.06	67.87
10	81.21	72.68	70.83	74.37	83.51	63.97	67.83	79.01	74.02
11	85.96	87.91	84.99	88.11	95.46	73.08	78.99	83.46	80.12
12	92.26	91.22	89.15	93.62	99.73	82.23	85.15	87.87	85.25

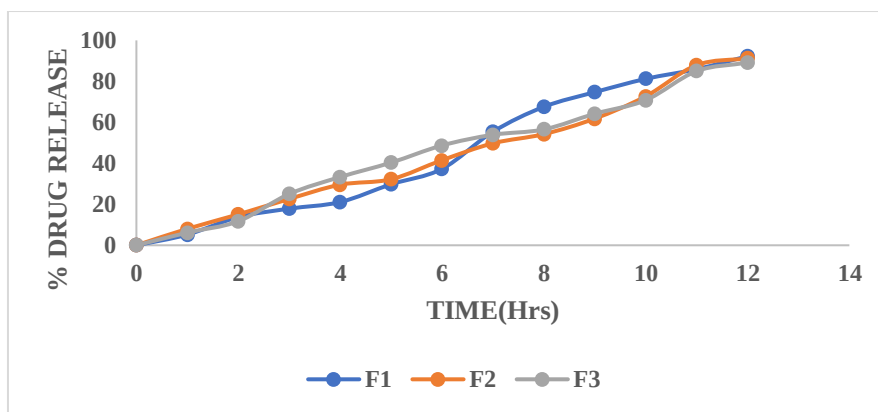


Figure: 8.2 Cumulative % drug permeation of Hesperidin patch (F1, F2 and F3)

The formulations F1 to F3 were prepared by different concentrations of Ethyl Cellulose (25, 50 and 75mg) in 2*2 cm² patch, 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 25 mg concentration of polymer was showed maximum drug released at 12 hors 92.26%. Hence in that 3 formulation F1 formulations showed total drug release at desired time period.

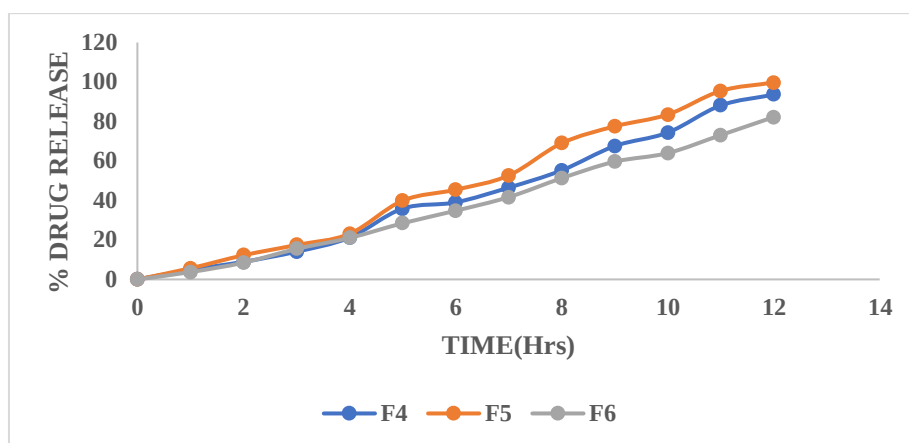


Figure: 8.3 Cumulative % drug permeation of Hesperidin patch (F4, F5 and F6)

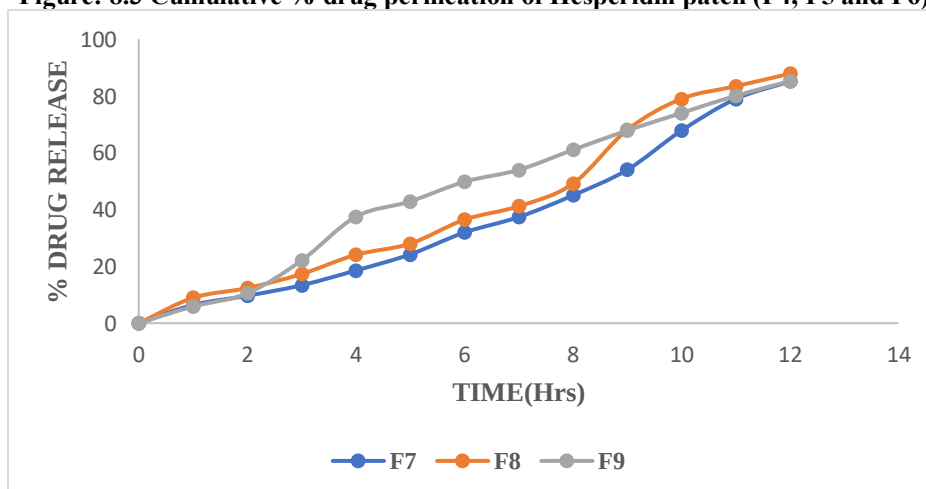


Figure: 8.4 Cumulative % drug permeation of Hesperidin patch (F7, F8 and F9)

The formulations F4 to F6 were prepared by different concentrations of HPMC (25, 50 and 75mg) in 2*2 cm² patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 50mg (F5) concentration of polymer was showed maximum drug release 99.73 within 12 hours.

The 1000mg (F9) concentration of polymer was showed maximum drug released at 12 hours 89.25%.

Among all 9 formulations F5 formulation showed good drug permeation from the patch.

Among all *in vitro* evaluation parameters F5 formulation passed all evaluation parameters.

8.4 Kinetic models for Hesperidin

Various models were tested for explaining the kinetics of drug release. To analyse 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 F5 Hesperidin patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	% RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE E / 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
5.65	1	1.000	0.752	0.000	1.975	5.650	0.1770	-1.248	94.35	4.642	4.552	0.089
12.23	2	1.414	1.087	0.301	1.943	6.115	0.0818	-0.913	87.77	4.642	4.444	0.198
17.44	3	1.732	1.242	0.477	1.917	5.813	0.0573	-0.758	82.56	4.642	4.354	0.287
23.08	4	2.000	1.363	0.602	1.886	5.770	0.0433	-0.637	76.92	4.642	4.253	0.389
39.88	5	2.236	1.601	0.699	1.779	7.976	0.0251	-0.399	60.12	4.642	3.917	0.724
45.44	6	2.449	1.657	0.778	1.737	7.573	0.0220	-0.343	54.56	4.642	3.793	0.849
52.63	7	2.646	1.721	0.845	1.676	7.519	0.0190	-0.279	47.37	4.642	3.618	1.023
68.97	8	2.828	1.839	0.903	1.492	8.621	0.0145	-0.161	31.03	4.642	3.142	1.499
77.53	9	3.000	1.889	0.954	1.352	8.614	0.0129	-0.111	22.47	4.642	2.822	1.820
83.51	10	3.162	1.922	1.000	1.217	8.351	0.0120	-0.078	16.49	4.642	2.545	2.096
95.46	11	3.317	1.980	1.041	0.657	8.678	0.0105	-0.020	4.54	4.642	1.656	2.986
99.73	12	3.464	1.999	1.079	0.540	8.311	0.0100	-0.001	0.27	4.642	0.646	3.995

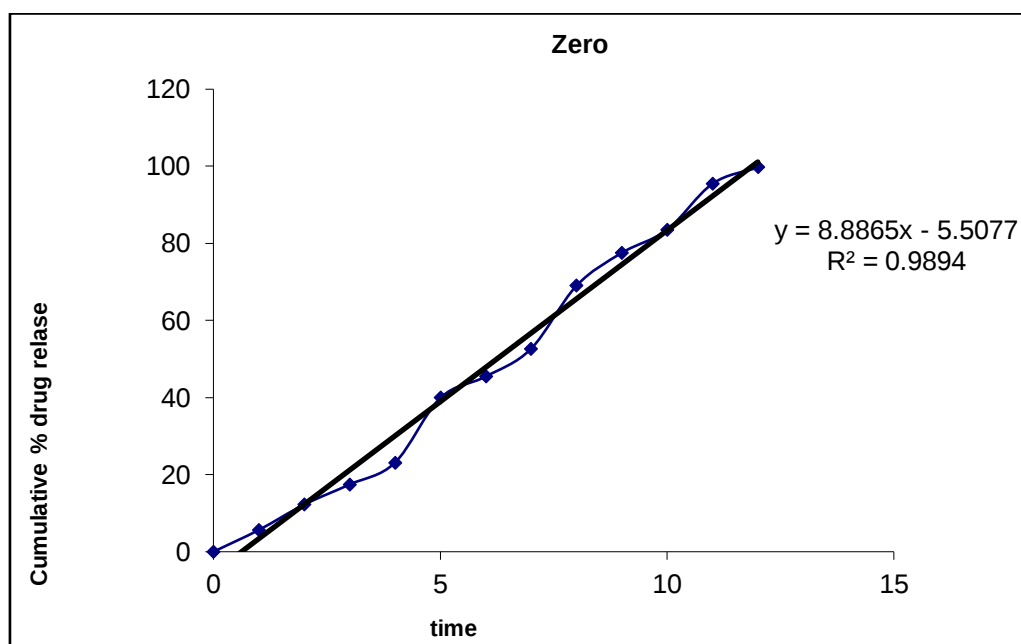


Figure: 8.5 Graph of Zero order kinetics

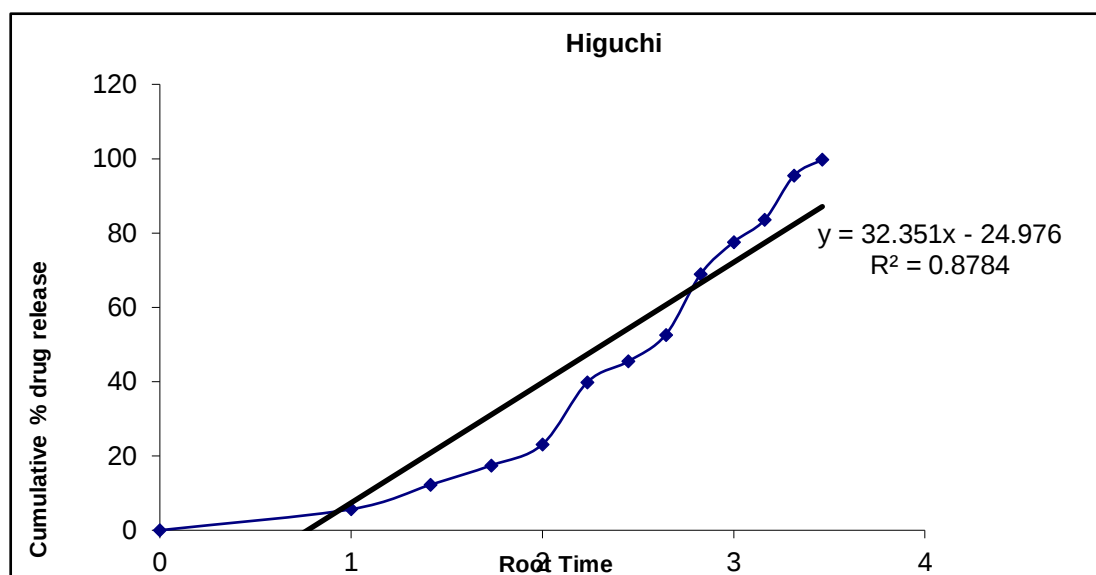


Figure: 8.6 Graph of Higuchi release kinetics

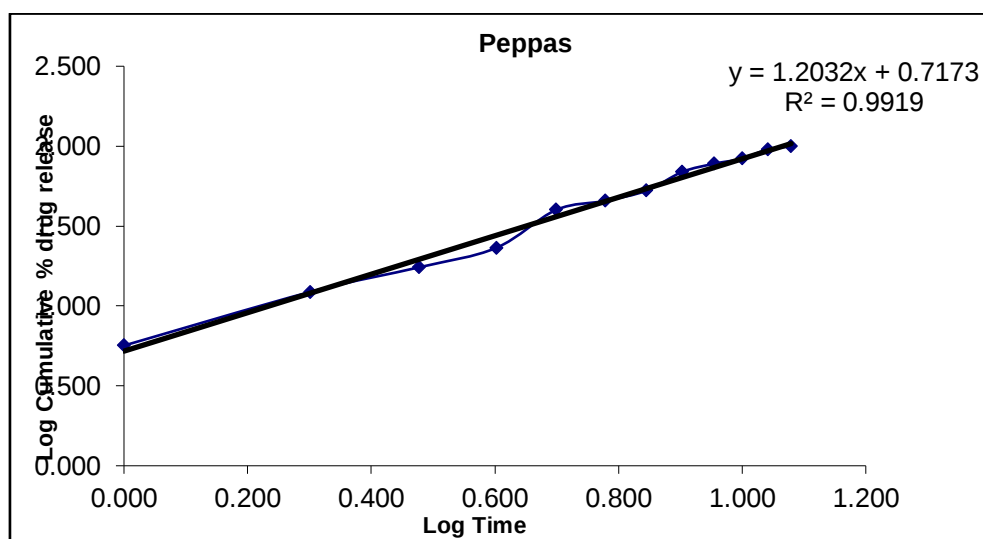


Figure: 8.7 Graph of peppas release kinetics

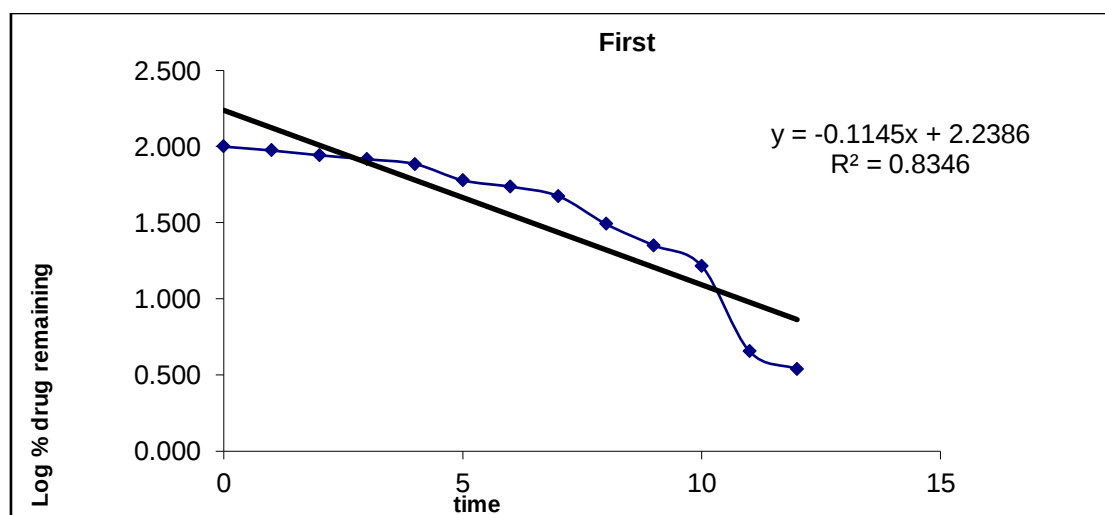


Figure: 8.8 Graph of First order release kinetics

From the above data the optimized formulation followed peppas model rule.

8.2. COMPATIBILITY STUDIES: IR SPECTROSCOPY:

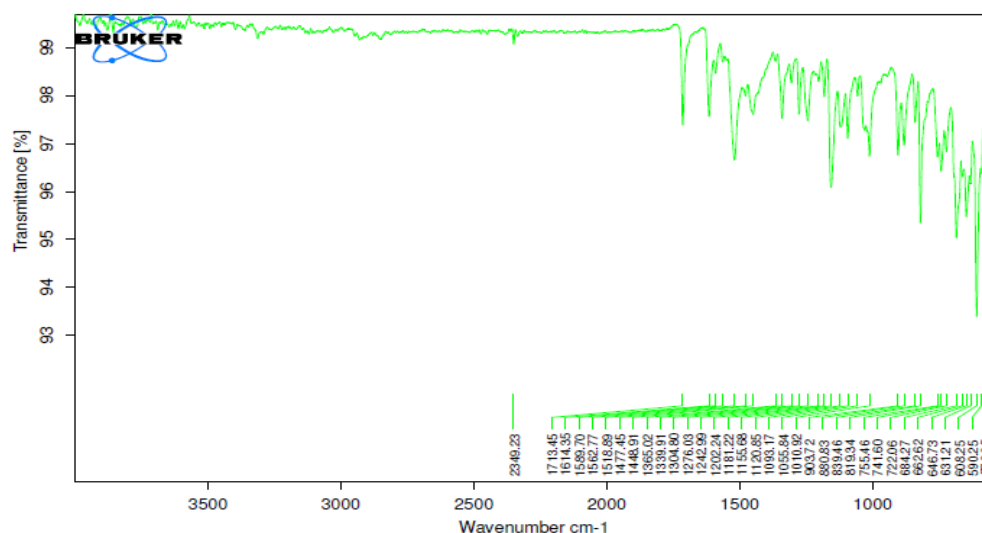


Figure: 8.9 FTIR Spectrum of pure Hesperidin drug

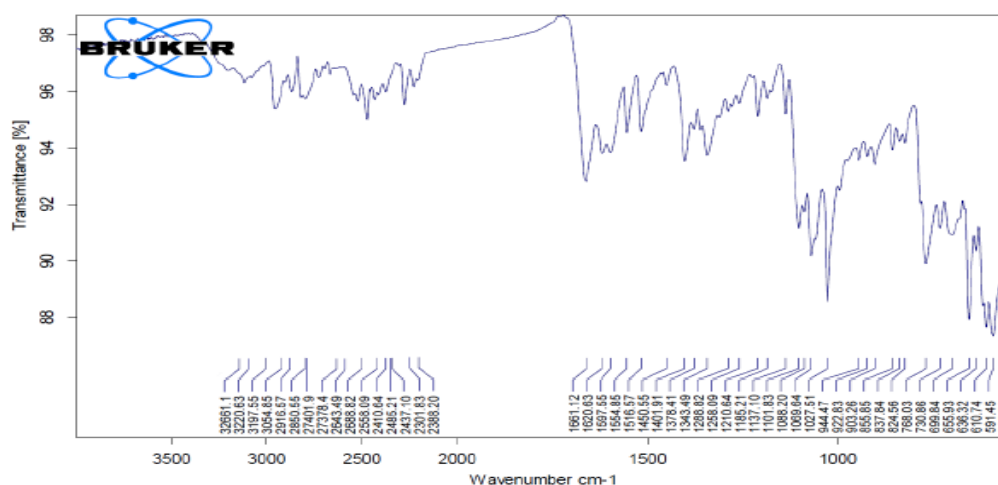


Figure: 8.10 FTIR of Optimized formulation

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

9. CONCLUSION:

The present study was successfully conducted to formulate and evaluate a transdermal drug delivery system (TDDS) of Hesperidin, aiming to improve its bioavailability and provide sustained drug release. Various formulations were prepared using suitable polymers and plasticizers, and evaluated for physicochemical parameters such as thickness, tensile strength, moisture content, drug content uniformity, and in vitro drug release. Among the

developed formulations, the optimized batch demonstrated desirable mechanical properties and a controlled drug release profile over an extended period, indicating its potential for effective transdermal delivery. The results suggest that Hesperidin can be effectively delivered through the transdermal route, potentially overcoming its limitations related to poor oral bioavailability and enhancing therapeutic efficacy.

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