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Formulation and Evaluation of Oxyphentabutazone Loaded Transdermal Patches

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ABSTRACT

The present study focuses on the formulation and evaluation of oxyphenbutazone-loaded transdermal patches intended to provide sustained drug delivery and enhance patient compliance. Oxyphenbutazone, a non-steroidal anti-inflammatory drug (NSAID), is associated with gastrointestinal side effects when administered orally; hence, transdermal delivery offers a promising alternative. The patches were prepared using the solvent casting technique with various polymers such as HPMC, PVA and SCMC in different ratios. The formulated patches were evaluated for physicochemical parameters including thickness, weight variation, folding endurance, surface pH, moisture content, moisture uptake, drug content, and in vitro drug release. Among the formulations, the optimized patch exhibited desirable properties and sustained drug release for up to 12 hours. The drug release kinetics followed controlled release behaviour, indicating the potential of the developed patch as an effective transdermal drug delivery system for oxyphenbutazone. This approach may reduce the frequency of dosing and minimize systemic side effects, thereby improving overall therapeutic outcomes.

Keywords: Formulation of Oxyphenbutazone-Loaded Transdermal Patches, HPMC ,PVA.

INTRODUCTION

Transdermal drug delivery has become an increasingly significant area of pharmaceutical research because it offers a unique combination of therapeutic convenience, safety, and controlled drug administration. Unlike oral dosage forms, which must undergo first-pass hepatic metabolism and are often associated with fluctuations in plasma concentration, transdermal systems deliver the drug through the skin directly into systemic circulation. This approach provides a sustained release of medication over an extended period, reduces dosing frequency, minimizes gastrointestinal irritation, and enhances overall patient compliance. The skin, although a highly protective barrier, offers an accessible and pain-free route for drug administration when the physicochemical properties of the molecule and the formulation are appropriately optimized. With advancements in polymer science, permeation enhancers, and fabrication techniques, transdermal patches have evolved into reliable, stable, and patient-friendly drug delivery devices. A transdermal patch typically consists of a backing layer, drug-loaded matrix or reservoir, adhesive layer, and protective liner. Among these, matrix-type systems are widely used because they are simple to formulate, flexible, and capable of providing controlled drug release based on polymer composition and drug–polymer interactions. The ideal transdermal system should not only allow uniform drug distribution

but must also be non-irritating, non-sensitizing, and mechanically stable under conditions of daily wear. Parameters such as moisture content, moisture uptake, elasticity, folding endurance, and uniformity of thickness determine the performance and acceptability of the patch. Additionally, the choice of polymers and plasticizers significantly influences the mechanical strength, drug release rate, and permeation behavior of the final product. NSAIDs are frequently studied for transdermal delivery due to the well-known problems associated with their oral administration, such as gastric discomfort, ulcerogenic potential, and hepatic strain. Oxyphenbutazone, a potent non-steroidal anti-inflammatory and analgesic agent, is especially suitable for transdermal use because its therapeutic action is most beneficial when steady levels are maintained over time, particularly in painful inflammatory conditions. It exhibits effective anti-inflammatory properties but can cause adverse effects when administered orally over long periods. Delivering oxyphenbutazone through a transdermal system offers the possibility of achieving therapeutic concentrations at the site of action while reducing systemic side effects and avoiding high peak plasma levels. Furthermore, bypassing the gastrointestinal tract enhances safety in patients who require chronic therapy or those who experience difficulty tolerating oral NSAIDs. In the development of an oxyphenbutazone transdermal patch, several formulation factors play a critical role. The selection of polymers is crucial, as they govern drug distribution, flexibility, and release characteristics. Commonly used hydrophilic and hydrophobic polymers can be blended to obtain desirable permeability and matrix stability. Plasticizers are incorporated to improve film flexibility, prevent brittleness, and facilitate drug diffusion through the polymeric network. Permeation enhancers may be added to temporarily modify the skin barrier, allowing improved penetration of oxyphenbutazone through the stratum corneum. The solvent-casting technique is widely used for matrix patch preparation due to its simplicity, cost-effectiveness, and suitability for heat-sensitive drugs. Once formulated, the patches must undergo a series of physicochemical evaluations to ensure quality and reproducibility. Tests such as thickness measurement, weight variation, folding endurance, tensile strength, moisture absorption, moisture loss, and surface pH help determine physical stability and patient acceptability. Drug content uniformity ensures that each patch delivers a consistent dose. In-vitro release studies provide essential information about the drug diffusion profile, while ex-vivo permeation studies using biological or synthetic membranes simulate real-world skin absorption. These evaluations collectively help optimize the formulation for maximum therapeutic efficiency. The formulation and evaluation of a transdermal patch containing oxyphenbutazone, therefore, holds great potential in improving the clinical utility of this drug. By ensuring controlled release, minimizing side effects, and enhancing patient comfort, a well-designed transdermal system may serve as an effective alternative to conventional administration routes. The present study focuses on developing a stable, effective, and patient-friendly oxyphenbutazone transdermal patch and evaluating its physicochemical properties, release characteristics, and skin permeation behavior to establish it as a promising candidate for transdermal NSAID therapy.

METHODOLOGY:

Analytical method development:

A.UV scan:

A 100mg of Oxyphenbutazone 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 200-600nm.

B. Construction of calibration curve:

A 100mg of Oxyphenbutazone 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 2,4,6,8 and 10µg /ml. The absorbances of these solutions were determined spectrophotometrically at 282 nm.

Pre formulation 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 Oxyphenbutazone was determined by adding excess amount of drug in the solvent.

The Oxyphenbutazone 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 Oxyphenbutazone 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 analysed by using UV spectrophotometer at 305 nm and 282 nm for phosphate buffer and distilled water respectively.

Formulation of transdermal patches [47]

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 Oxyphenbutazone were prepared using different concentrations of HPMC, PVA and SCMC. 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. Glycerine and Acetone 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 was 8 mg. the formulation table is given in table no. 7.1s.

Table:1 Formulation of Oxyphenbutazone Patches

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Oxyphenbutazone (Mg)	100	100	100	100	100	100	100	100	100

HPMC (grams)	0.5	0.5	-	1	1	-	1	1	-
PVA (grams)	-	0.5	0.5	-	1	1	-	1	1
SCMC (grams)	0.5	-	0.5	1	-	1	1.5	-	1.5
Glycerine(ml)	1 -2	1 -2	1 -2	1 -2	1 -2	1 -2	1 -2	1 -2	1 -2
Acetone (ml)	10	10	10	10	10	10	10	10	10

Evaluation Parameters of patches

Physical evaluations

a. Thickness[47]

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

b. 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.

c. Weight variation[47]

The three disks of 2*1 cm^2 were 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.

d. 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 Whatman 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 λmax 282 nm. Respected Placebo patch was taken as a blank solution.

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.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

***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 aluminium 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 analysed for drug content spectrophotometrically at 282 nm

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.

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.

First order kinetics:

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

$L o g C = L o g C o - k t / 2.303$

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

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.

Kors meyer Peppas equations:

Korsmeyer Peppas 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-release.

Compatibility study

FTIR study:

The infrared spectrum of the pure Oxyphenbutazone 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.

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 Oxyphenbutazone was found to be 282 nm.

B. construction of calibration curve:

Table 1: Standard graph of Oxyphenbutazone

Concentration(µg/ml)	Absorbance (at 282 nm)
0	0
2	0.114
4	0.225
6	0.334
8	0.439
10	0.546

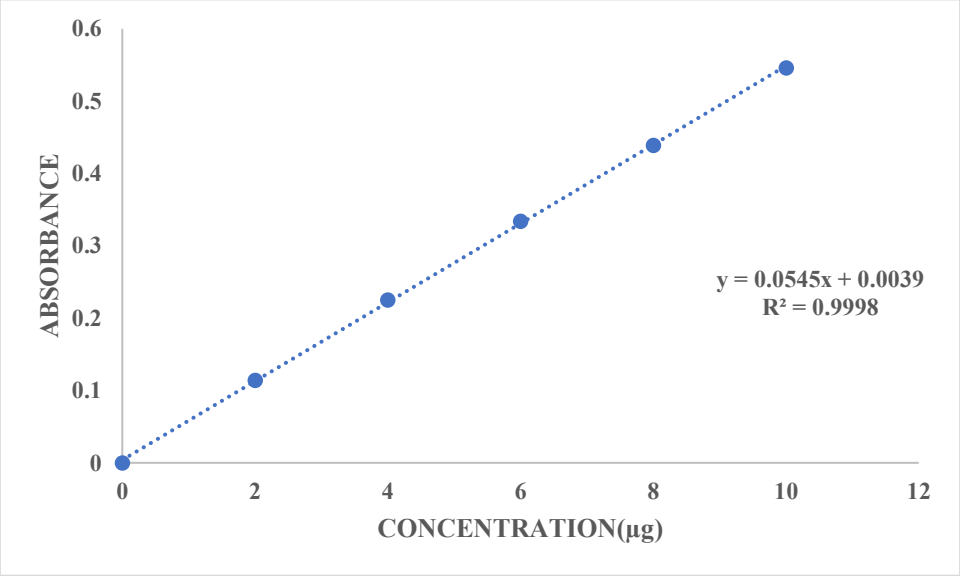

Figure 1: Standard calibration curve of Oxyphenbutazone

Pre formulation study

Totally, twelve formulation trials were done with the aim to achieve the successful matrix type Oxyphenbutazone HCL 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 2: Results of identification tests of drug

Parameter	Oxyphenbutazone HCL
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 3: Results of melting point determination tests of drug

Drug	Reported melting point
Oxyphenbutazone HCL	189-290 ^{0}c

C. Determination of solubility:

Table 4: Solubility Determination

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

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 1.061±0.004 to 1.079±0.008mm.

All formulations from F1 to F9 shows weight variation in between 145±1.05 to 150 ±9.58mg.

Folding endurance from formulations F1 to F9 was found to be in between 90 ± 1.84 to 99 ± 2.15which can withstand the folding of the skin.

All formulations showed % drug content from 95.1 ± 2.61 to 99.74 ± 1.57.

Table 5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F1	145±1.05	1.076 ± 0.003	95± 0.15	100	Transparent	97.1 ± 2.10
F2	148 ±5.36	1.079±0.008	93± 1.39	99	Transparent	98.28 ± 0.45
F3	146 ±2.84	1.061±0.004	94± 2.26	100	Transparent	97.69 ± 2.21
F4	145 ±5.41	1.071±0.009	90 ± 1.84	100	Transparent	95.1 ± 2.61
F5	147 ±9.18	1.069±0.004	93± 3.10	99	Transparent	99.2 ± 3.87
F6	149 ±4.69	1.071±0.007	99 ± 2.15	100	Transparent	98.35 ± 0.59
F7	150 ±9.58	1.077±0.001	95± 2.36	99	Transparent	99.11 ± 2.34
F8	146 ±3.86	1.075±0.009	98± 2.04	100	Transparent	99.74 ± 1.57
F9	144 ±7.29	1.078±0.006	93± 2.96	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 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 6: *In vitro* drug permeation of Oxyphenbutazone containing different concentrations of HPMC

Time (hrs)	F1	F2	F3
0	0	0	0
1	5.22	8.04	12.81
2	14.57	16.07	21.37
3	17.78	22.00	25.20
4	21.09	29.75	34.03
5	29.77	32.42	41.43
6	38.28	41.25	49.17
7	55.93	49.77	53.39
8	68.75	58.42	57.45
9	75.37	62.38	65.91
10	81.12	78.86	72.38
11	85.69	88.19	85.99
12	97.29	99.51	95.62

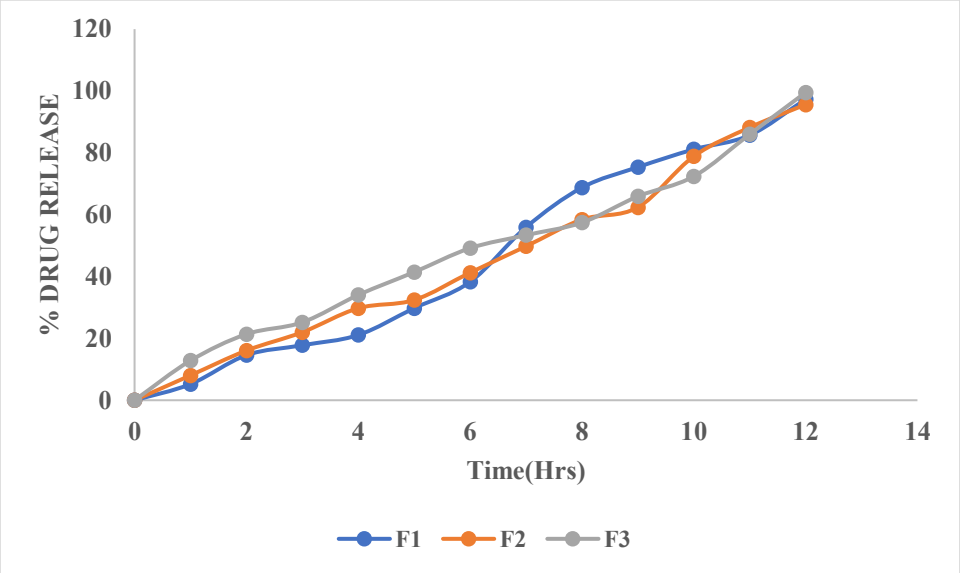

Figure: 2 Cumulative % drug permeation of Oxyphenbutazone patch (F1, F2 and F3)

The formulations F1 to F3 were prepared by different concentrations of HPMC (0.5) 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 0.5 mg concentration of polymer was showed maximum drug released at 12 hrs 99.51%. Hence in that formulation F2 formulations showed total drug release at desired time period.

Table 7 : *In vitro* drug permeation of Oxyphenbutazone containing different concentrations of PVA

Time (hrs)	F4	F5	F6
0	0	0	0

1	4.68	6.56	12.17
2	8.29	11.32	18.74
3	14.04	18.44	24.54
4	21.61	23.80	29.20
5	25.68	33.08	31.44
6	31.30	37.44	37.87
7	37.94	53.36	44.76
8	46.22	69.97	52.62
9	58.35	78.35	69.26
10	76.73	85.15	74.79
11	91.11	92.64	85.08
12	95.44	98.63	93.32

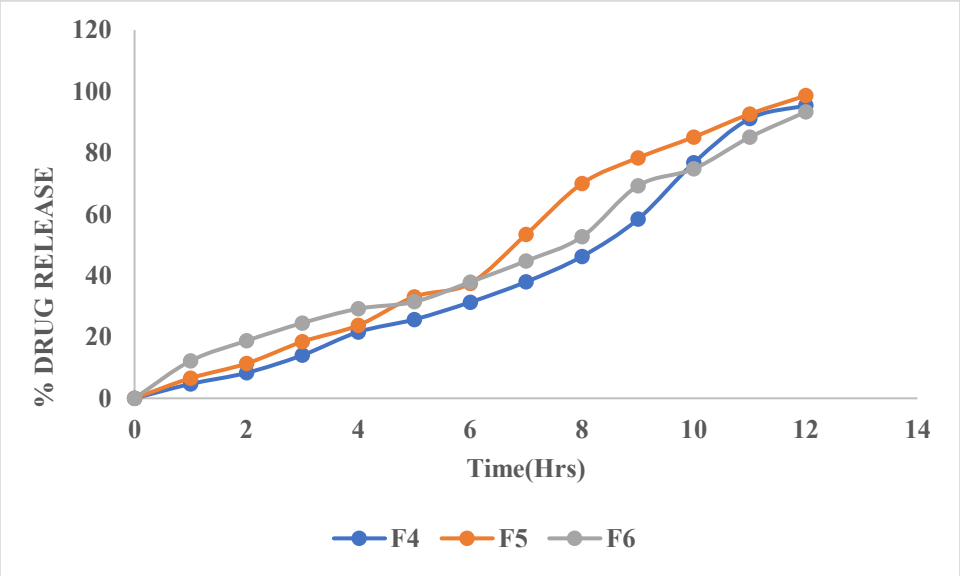

Figure: 3 Cumulative % drug permeation of Oxyphenbutazone patch (F4, F5 and F6)

The formulations F4 to F6 were prepared by different concentrations of PVA (1) in 2*2 cm^2patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 1mg (F5) concentration of polymer was showed maximum drug release 98.63 within 12 hours.

Table: 8 *In vitro* drug permeation of Oxyphenbutazone containing different concentrations of SCMC

Time	F7	F8	F9
0	0	0	0
1	6.14	9.29	5.98
2	9.66	15.63	11.35
3	14.73	18.13	25.70
4	18.65	24.80	38.74
5	25.22	31.10	45.88

6	34.49	37.54	52.18
7	38.73	43.81	56.99
8	46.30	49.21	62.40
9	56.10	67.06	69.78
10	68.08	79.10	75.20
11	81.99	85.64	83.21
12	87.43	88.78	96.52

Figure:8.4 Cumulative % drug permeation of Oxyphenbutazone patch (F7, F8 and F9,) The formulations F7 to F9 were prepared by different concentrations of SCMC (1.5) in 2*2 cm^2patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 1.5 mg (F9) concentration of polymer was showed maximum drug release 96.52 % within 12 hours. Among all 9 formulations F2 formulation showed good drug permeation from the patch.

Among all *in vitro* evaluation parameters F2 formulation passed all evaluation parameters.

8.4 Kinetic models for Oxyphenbutazone

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:9 Kinetics data of F2 Oxyphenbutazone patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	%) REL	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	0	0	0	0	0	0	0	0	0	0
8.04	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.000
16.07	2	1.414	1.206	0.301	1.924	8.035	0.0622	-0.794	83.93	4.642	4.378	0.263
22	3	1.732	1.342	0.477	1.892	7.333	0.0455	-0.658	78	4.642	4.273	0.369
29.75	4	2.000	1.473	0.602	1.847	7.438	0.0336	-0.527	70.25	4.642	4.126	0.515
32.42	5	2.236	1.511	0.699	1.830	6.484	0.0308	-0.489	67.58	4.642	4.073	0.568
41.25	6	2.449	1.615	0.778	1.769	6.875	0.0242	-0.385	58.75	4.642	3.887	0.754
49.77	7	2.646	1.697	0.845	1.701	7.110	0.0201	-0.303	50.23	4.642	3.690	0.952
58.42	8	2.828	1.767	0.903	1.619	7.303	0.0171	-0.233	41.58	4.642	3.464	1.177
62.38	9	3.000	1.795	0.954	0.477	6.931	0.0160	-0.205	37.62	4.642	3.351	1.291
78.86	10	3.162	1.897	1.000	0.500	7.886	0.0127	-0.103	21.14	4.642	2.765	1.877
88.19	11	3.317	1.945	1.041	0.521	8.017	0.0113	-0.055	11.81	4.642	2.277	2.364
99.51	12	3.464	1.998	1.079	0.540	8.293	0.0100	-0.002	0.49	4.642	0.788	3.853

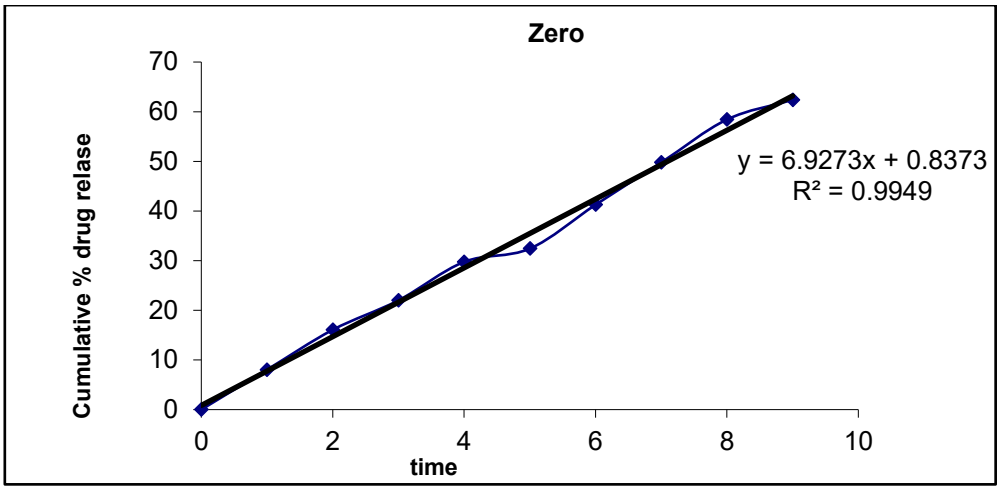

Figure: 4 Graph of Zero order kinetics

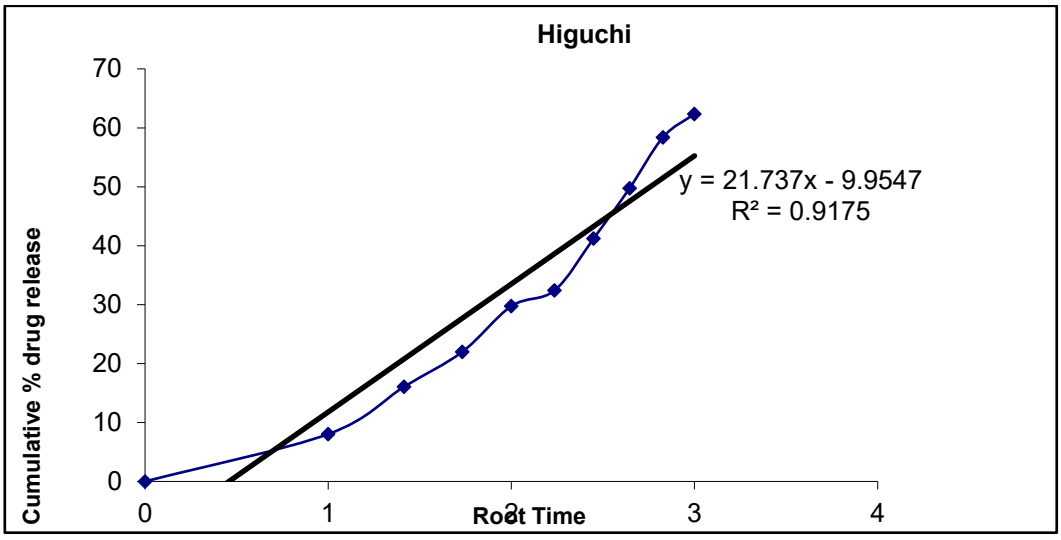

Figure: 5 Graph of Higuchi release kinetics

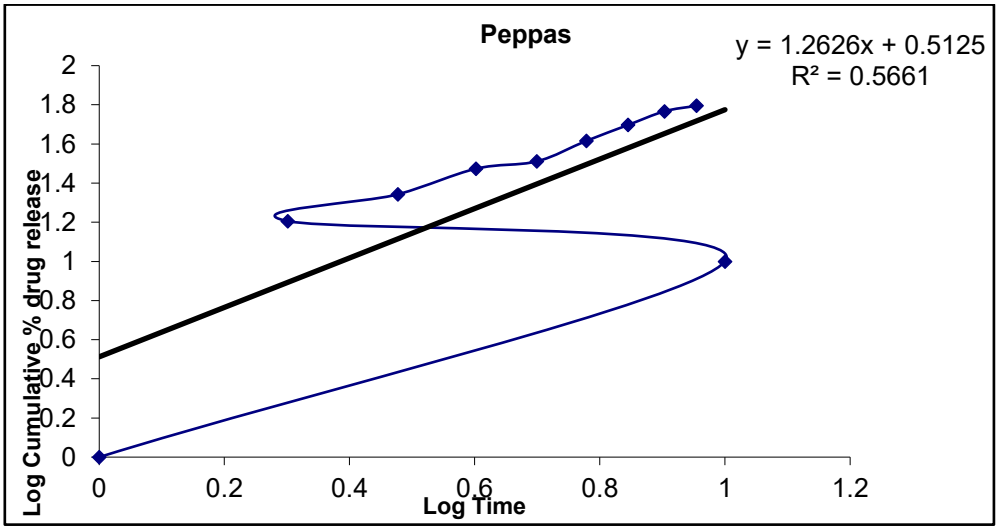

Figure :6 Graph of peppas release kinetics

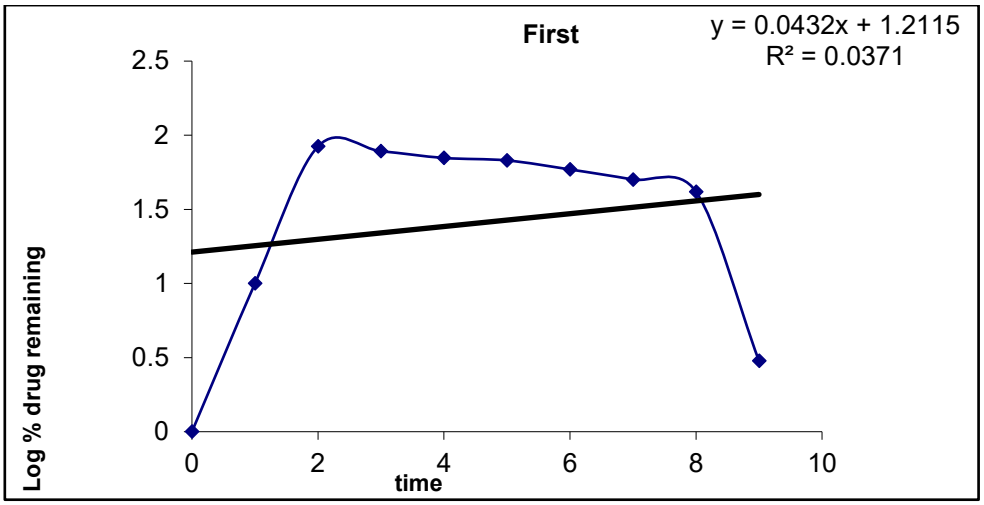

Figure: 7 Graph of First order release kinetics

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

Compatibility studies:

IR SPECTROSCOPY:

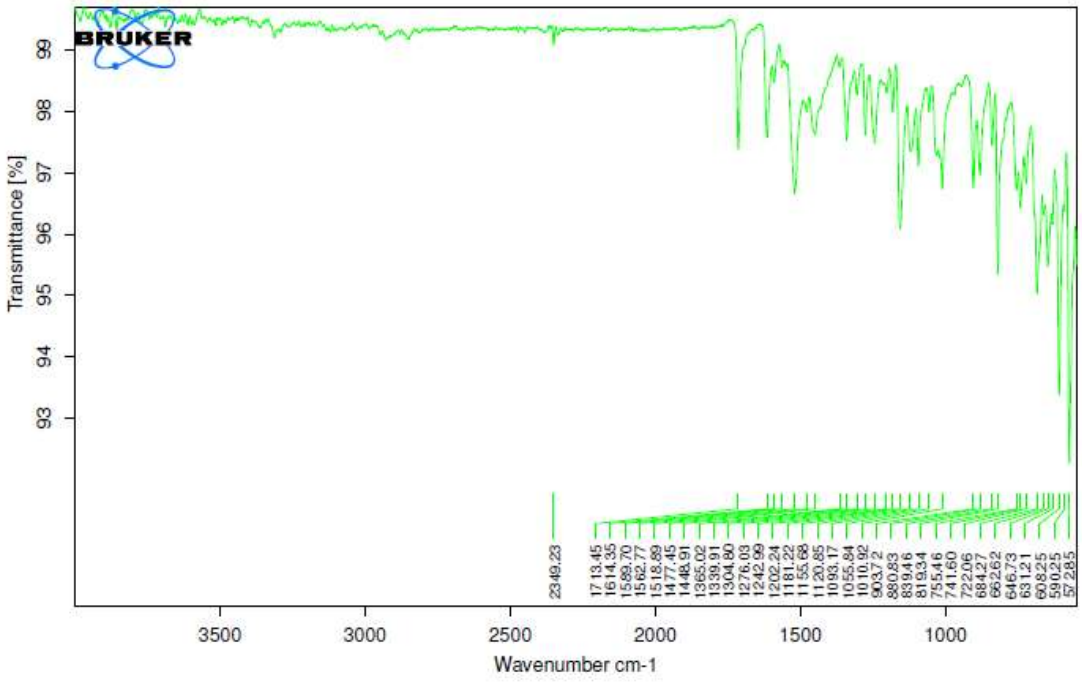

Figure 8.9: FTIR Spectrum of pure Oxyphenbutazone HCL drug

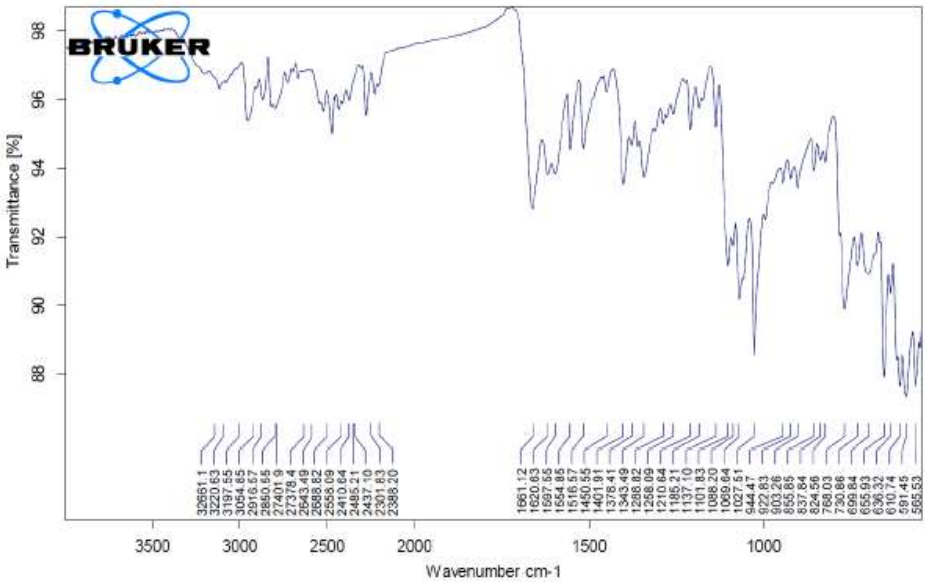

Figure : 10: FTIR of Optimized formulation

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

CONCLUSION

The present study successfully formulated and evaluated oxyphenbutazone-loaded transdermal patches using various polymers by the solvent casting method. All prepared formulations were subjected to comprehensive physicochemical evaluation, including thickness, weight variation, folding endurance, drug content uniformity, moisture content, moisture uptake, and in vitro drug release studies. Among all the formulations, the optimized patch exhibited satisfactory physicochemical characteristics and provided sustained drug release over a prolonged period. The in vitro release profile demonstrated that the selected formulation followed controlled release kinetics, indicating its potential to maintain consistent plasma drug concentration, thereby minimizing dosing frequency and enhancing patient compliance. Overall, the study concludes that transdermal delivery of oxyphenbutazone is a promising alternative to oral administration, offering improved therapeutic efficacy and reduced gastrointestinal side effects.

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