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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH CONTAINING CLOTRIMAZOLE AND TURMERIC OIL

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Abstract:-

Background :-*An antifungal medication with a biological half-life of two hours, clotrimazole has gastrointestinal adverse effects when used orally at doses of 500 mg twice daily. The goal of this study is to create a transdermal drug delivery system for Clotrimazole and turmeric oil that will deliver the medication to a specific site to treat a fungal infection and lessen any potential sensitization or irritation issues.*

Method:- *A turmeric oil is first extracted from the turmeric rhizomes, and then these transdermal patches were made using the solvent casting method using the placebo method. Different combinations of polymer were used with the solvents MDC and methanol in a 1:1 ratio, and polyethylene glycol 500 and propylene glycol were used as permeation enhancers and plasticizers. The manufactured patches were assessed for weight fluctuation, thickness, weight variation, moisture absorption, moisture uptake, folding endurance, flatness, drug content, and in-vivo permeation study during the analysis of the compatibility study*

RESULT:-*In vitro drug release studies for all formulations revealed that the first dose of drug was released in 2 to 2.5 hours, and the complete dose was released (95%) within 24 hours. The formulation were uniform in their physical characteristics combinations of three polymers HPMC, EC, and EUDRAGIT RS-100, implying excellent quality and uniformity in patch characteristics as compared to other combinations of polymers.*

Conclusion:- *Transdermal patches made of Clotrimazole and turmeric oil were successfully created, and their evaluation indicated good quality and uniformity in patch characteristics. These patches may have therapeutic effects and provide benefits such as lowering the frequency of doses required for treatment, increasing patient compliance, and increasing bioavailability.*

Keywords:-Clotrimazole, Turmeric oil, Eudragit RS 100,HPMC, EC, Transdermal drug delivery system

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1] INTRODUCTION:

An antifungal drug called clotrimazole and turmeric oil must be consumed orally twice daily to be effective in treating fungal infections. The current work's objective is to develop a Clotrimazole and turmeric oil controlled release dosage form that is not administered orally or via injection. Therefore, it was anticipated that Clotrimazole and turmeric oil transdermal patches would be created and tested using this non-invasive approach with the goal of achieving controlled and target-specific release of Clotrimazole and turmeric oil over an extended period of time in order to reduce the frequency of drug administration.

Transdermal drug delivery systems (TDDS) are self-contained, discrete dosage forms that are sometimes known as "skin patches" or "medical adhesive patches." Several drugs' therapeutic effectiveness can be increased through transdermal distribution by avoiding certain adverse effects, such as gastro-intestinal discomfort, poor absorption, and decomposition due to a hepatic "first-pass" effect. The formation of metabolites that cause side effects, the short half-life and need for regular dose, etc. A transdermal patch is a medicinal adhesive pad put to the skin with the goal of gradually releasing the active ingredient over the course of many hours to days. Transdermal patches are cutting-edge medicine delivery systems that affect the skin application systemically. Compared to other methods, the TDDS system has a number of clinical benefits.

Transdermal patch varieties

1.Single layer drug in matrix;
2. Multi layer drug in matrix;
3.Reserve type patches;
4. Matrix type patches; and
5. Vapour type patches.

When a drug is administered transdermally, penetration enhancers can help a drug's capacity to permeate the skin. Clotrimazole It is effective as a topical treatment for ringworm and other diseases. In cases treated for 2-4 weeks twice-daily, cure rates of 60–100% have been seen. Methanol and dichloromethane were used as the solvents in the same quantities, while propylene glycol was used as a plasticizer and penetration enhancer.[1-13]

2.1 Method of Extraction:-

In order to extract the oil from turmeric, fresh Curcuma longa plants were harvested. The rhizomes were gathered, rinsed under running water from the tap, and then cleaned with distilled water. We utilised sliced and peeled rhizomes. 250 G of sliced and peeled rhizome and 400 ml of distilled water were added to the 1000 ml round bottom flask. Using Guenther's approach Since 1948, extraction has been carried out at room temperature using hydro distillation. 7 The homogenate mixture was cooked in the RBF for 6 to 8 hours. The oil from the top layer of the Eppendorf tube was separated from the water and analyzed for curcumin content using a separating funnel.[14]

2.2] Formulation of patch:-Using the solvent casting process, film-forming polymers such Eudragit RS-100, Ethyl cellulose, Hydroxypropyl Methylcellulose (HPMC), plasticizer, and penetration enhancer, transdermal patches containing clotrimazole were produced.

Propylene glycol was used. It provides information on the specific chemical composition of the clotrimazole transdermal patch. The polymers Eudragit RS-100, HPMC, and ethyl cellulose were weighed accurately. Were each dissolved in a 1:1 mixture of methanol and dichloromethane (DCM).

Propylene glycol was then added as a plasticizer and penetration enhancer to the polymeric Solution after the medication had been dissolved in it. A magnetic stirrer was used to combine the solution. An inverted funnel was then employed to prevent sudden evaporation while the entire solution was carefully poured into the glass petridish. This solution was allowed to dry for 24 hours. At room temperature; the prepared film was kept into desiccators till evaluation test was done in self sealing plastic envelopes.

3] Materials:-

Clotrimazole was buyed from labchem and curcumin oil has been extracted and the solvents and other excipients (polymer, permeation enhancers, plasticsizer) was use as of analytical.

3.1] Preformulation studies :- It contains research on identification, melting point, UV absorption maximum, and interactions between drug excipients.[15]

Organoleptic characteristics of the active ingredient: Color, flavor, taste, and condition have all been recognised as organoleptic characteristics.
Calculating the melting point and boiling point of active ingredient:- Clotrimazole's melting point and curcumin oil's boiling point were discovered using the capillary technique, and the temperatures at which each substance dissolved were noted.

Calculating UV absorption maximum:- The maximum concentration of clotrimazole was discovered in the spectra at 242 nm, and the spectral data from this scan was used to prepare a calibration curve of clotrimazole. The UV spectrophotometric method was used to determine the active ingredient.[8]

Drug- excipients compatibility studies:- A vial containing a small amount of drug product with excipients was properly sealed and sealed from above with a rubber stopper. The same samples were stored at 60°C for approximately 2 weeks and then at 40°C for 2 months. After storage, the samples were physically inspected for liquefaction, solidification, odor or gas evolution, and discoloration.[16]

3.2] Method of preparation:-
Solvent casting is a technique used to create transdermal patches containing clotrimazole and curcumin longa. In this technique, a glycerin-coated glass Petri plate is filled with a homogenous combination of polymeric and drug solution (to make it easier to remove the patch after the solvent has evaporated). At normal temperature, solvent evaporation typically takes 24 to 36 hours (depending on the amount of solvent used), and after it has, the residue has dried into a uniform polymeric film, which is then preserved and kept for upcoming testing and stability criteria (it is wrapped in aluminium foil).[17]
3.2.a) Calculation of transdermal dose of the drug **:-** we can calculate the transdermal dose of the drug so that we can get appropriate content values for active ingredients should present in the ideal patch
To calculate the transdermal dose formula is ;oral dose multiply by bioavailability and divide by100

1) transdermal dose of the clotrimazole=500×5/100.=25mg
2) Transdermal dose of the curcumin longa oil =500×0.5/100.=1.85ml

To achieve the transdermal patch of 20 mg :-
Area of petridish = $(\pi r)^2$ =3.14×$(5)^2$ = 78.5sq. ;. Diameter of petridish is 10cm.
Area of patch/Area of petridish=7×3/78.5= 21/78.5= 3.73sq.cm(void area of petridish to fill active ingredients so;
3.73×our dose on patch =3.73×25=93.45 mg at petridish for 25 mg of clotrimazole Transdermal patch.[18]

3.2.b) Selection of polymer content for preparation of polymeric film by placebo method:-
Several polymeric combinations with various solvents are used to make transdermal patches without any active ingredients (hit and trial method), and then the patch that we want is chosen for the medication and curcumin extract integration. The table 1; contains the composition and characterization of placebo patches without any active ingredients using various polymers in varying ratios; the polymers utilised are HPMC, PVA,PVP,EC, and EUDRAGIT RS-100.

Sr. No	Polymers	Ratio	Physical appearance
1	PVP:EC	2:1	Non uniform film
2	PVA:EC:PVP	1:2:1	Non uniform film
3	PVA:EC	1:2	Non flexible film
4	HPMC:PVA:EC	2:2:1	Flexible and uniform film
5	HPMC:EUDRAGIT S-100:EC	3:1:1	Smooth transparent, uniform and flexible film.
6	HPMC:EC	3:1	Smooth transparent and flexible film

TABLE1):- Preparation of polymeric film by different placebo combination of polymers:-

3.2.c) Selection of solvent:- We attempted to create hydrophobic and hydrophilic transdermal patches in order to determine the best solvent. Table [2] comprises the solvent that was utilised in the above-mentioned varied polymeric ratios. Then, since more oven heating can cause the oil in turmeric to degrade, we decided to move forward with formulation code-5. Methanol and MDC are also practical to utilise since they quickly evaporate and produce a polymeric layer.[19,20]

Sr. No	Polymers	Ratio	Methanol and water (1:1)	Dichloromethanol and methanol (1:1)
1	PVP:EC	2:1	Non uniform and greasy film	Non uniform film
2	PVA:EC:PVP	1:2:1	Non uniform and greasy film	Tough and non uniform film
3	PVA:EC	1:2	Non uniform and greasy film	Smooth and non uniform film
4	HPMC:PVA:EC	2:2:1	Smooth and flexible film	Smooth and flexible
5	HPMC:EUDRAGIT S-100:EC	3:1:1	Smooth and flexible, greasy film	Smooth, transparent uniform film
6	HPMC:EC	3:1	Smooth and greasy film	Flexible and uniform film

TABLE:-2) choosing a solvent by observing physical appearance:-

3.2.d Plasticizer:- (PEG-400) (PEG-400) 30%W/W of polymeric content and 15%W/W of polymeric content in Permeation Enhancers (PG). [21,22]
The acquired transdermal patch of Curcumin longa was packaged in aluminium foil for storage and preservation.

Formula Code	Clotrimazole (Mg)	Curcumin Longa Oil (ml)	Solvent Methanol And MDC (1:1)	Plasticsizer (PEG-400)W/W	Permeation Enhancers(PG) W/W	Polymeric Combination	Ratio
F1	25	1.85	50ml	30%	15%	HPMC:PVA:EC	3:2:1
F2	25	1.85	50ml	30%	15%	HPMC:PVA:EC	2:1:1
F3	25	1.85	50ml	30%	15%	HPMC:EUDRAGIT S-100:EC	3:1::1
F4	25	1.85	50ml	30%	15%	HPMC:EUDRAGIT S-100:EC	3:2:1
F5	25	1.85	50ml	30%	15%	HPMC:EC	4:1
F6	25	1.85	50ml	30%	15%	HPMC:EC	2:1

4)Evaluation of Combination of transdermal patch was inspect on chemical, physical and drug release parameters:-

4.a] physical parameters:-The physical characteristics, homogeneity, absence of air bubbles, and drug precipitation of the patches were evaluated because these factors significantly affect a patient's willingness to accept the patch and its therapeutic efficacy.[23]

4.b] weight variation:-Following individual patch weighing, the average weight of 10 patches from each formulation was determined. A person's weight shouldn't deviate too much from the average weight.[25]

4.c] Thickness:-A vernier calliper was used to measure the thickness of each patch at four different spots on the drug-loaded patches. The average values and standard deviation values of the three readings were computed for each drug-loaded patch.[24]

4.d] Folding endurance:-The folding endurance is defined as the number of folds (number of times the film is folded at the same spot) required to either break the specimen or produce noticeable fissures. These tests are essential to determine the sample's folding resistance.[25] This also indicates how fragile

something is; brittleness is measured by how long something can be folded. A short (2 cm x 2 cm) piece of film was repeatedly folded until it broke to evaluate the film's folding resistance. How many times the film could be folded in the same location without breaking was used to measure folding endurance.[26]

4.e] Tensile strength:-Rectangular containers were used to capture the films. The films were cut into 15 centimeter-long, 1 cm-wide strips using a proportionate amount of the solution determined by area calculations. The films were fastened to the Tensile strength apparatus with the jaws initially 10 cm apart. Trials where the jaw cracked were ruled invalid, and the result was repeated on a different strip. The following equation was used to calculate the tensile strength: - Tensile strength is calculated as Break force [1 + change in length] / (width) (breadth) [original film length].[27]

The percent elongation was computed by taking a measurement of the length just before the break point and replacing it with the formula.

4.f] Flatness test:-The longitudinal strips of each formulation were cut into patches. Both from the middle and the opposite side of the patch. The length of each strip was measured, as well as the variance in length brought on by the non-uniformity of flatness. It was thought that 100% flatness meant 0% restriction. The formula below was used to determine flatness.[28,29]

L1-L2/L2 x 100 % constriction

Where L1 denotes a strip's initial length and L2 its final length

4.g] Moisture content:-For 24 hours, film was placed in a desiccator with calcium chloride while being weighed separately to ascertain its moisture content. The film is reweighted after a predetermined period of time until a steady weight is shown, and the percentage of moisture content is calculated using the formula below:[28]

4.h] Moisture uptake:-The individually weighed transdermal films were kept in desiccators with saturated potassium chloride solutions for 24 hours at room temperature. The created Polymeric films with loaded clotrimazole were reweighed 24 hours later, and the % moisture uptake was determined using the formula below.[30]

4.i] Drug content:-Accurately determine a 7x3cm section of the resulting film was removed, dissolved in 100 ml of methanol and MDC solution in a 1:1 ratio, and the mixture was then agitated using a magnetic stirrer for 24 hours. Before filtration, the entire solution is sonicated to ensure thorough dissolution. After that, a double-beam UV-Vis spectrophotometer was used to detect absorbance at 261 nm.[31]

Formulation code	Thickness (mm) ± S.D	Weight variation (gm) S.D	Flatness (%)	Folding endurance S.D	Tensile strength (kg/mm2) ±S.D
F1	0.128±0.003	168.25±32.05	99	98.05±3.24	2.288±0.015
F2	0.174±0.004	215.58±31.06	100	105.46±2.85	0.293±0.013
F3	0.168±0.005	256.38±21.03	100	108.68±2.28	0.343±0.031
F4	0.278±0.006	296.35±35.70	101	121.75±1.05	0.397±0.043
F5	0.288±0.007	295.82±20.31	101	98.13±3.24	0.415±0.060

Formulation code	Moisture uptake	Moisture content	Drug content (%)±S.D
F1	1.355±0.02	1.253±0.17	91.58v0.44
F2	2.525±0.05	2.315±0.48	89.01±0.13
F3	3.784±0.87	3.548±1.58	83.35±0.28
F4	4.001±1.25	3.705±2.45	91.25±1.58
F5	4.125±1.58	3.815±2.78	93.56±0.68

4.l] In vitro permeation study:-Egg shell membranes with 80 ml-capacity receptor compartments were used for in-vitro permeation testing. The egg shell membrane was sewn to the hollow tube's end to act as a donor compartment, and a beaker was also there to act as a receptor. Compartment. In the receptor compartment, there is a pH 7.4 phosphate buffer solution. The entire assembly was placed on the magnetic stirrer, which continually churned the fluid with the help of a magnetic bead. 1 ml of the sample was taken out at regular intervals and its drug concentration was calculated using a spectrophotometric measurement at 261 nm. 37 0.5 °C was maintained as the temperature.

RESULT AND DISCUSSION:

1)Pre-formulation studies:-

The preformulation study was conducted in order to establish various formulation parameters for transdermal patches and to assure the accuracy of the drug sample.

2)Identification of drug:-3 organoleptic properties of clotrimazole and curcumin longa oil.

Sr.no	Properties	Inference of clotrimazole	Inference of curcumin oil
1	State	Amorphous	Liquid
2	Color	White	Pale yellow
3	Odor	Odorless	Curry like earthy aroma

3)Melting point:- It was discovered that the medicine clotrimazole and curcumin oil had a melting point of 147±2°C, which was higher than the previously reported value (147 to 149°C), which suggested the drug sample was pure.

4)Boiling point :- The API curcumin oil's boiling point of 110°C, which was higher than the previously reported figure (109 to 113°C), proved that it was pure.

5)UV absorption maxima:-It was discovered the drug greatest absorbance in methanol occurred at 240nm

Sr.no	Concentration (µg/ ml)	Absorbance
1	0	1.320
2	4	0.621
3	8	0.312
4	12	0.182
5	16	0.085
6	20	0.047

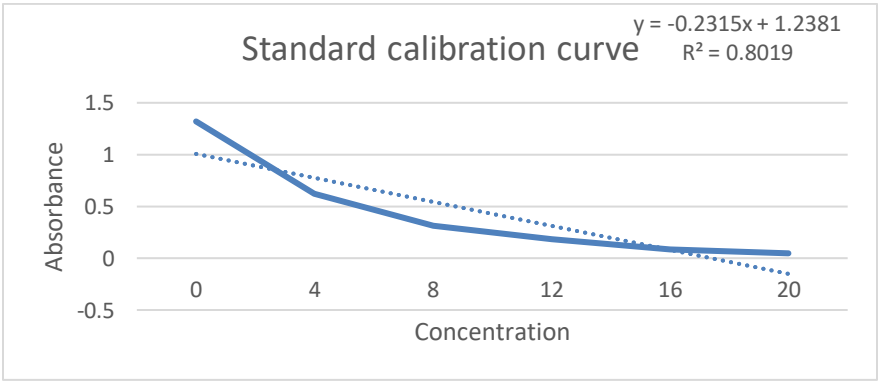


Table of formulation F1 toF5 data from a comparative in vitro permeation investigation for zero order release kinetics

			Cumulative drug release (%)		
Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
15	10.72	10.41	6.68	3.85	3.56
30	15.35	14.08	10.93	10.65	8.56
60	30.86	19.3	16.89	14.66	13.16
120	42.28	23.04	26.44	21.87	19.34
180	50.52	27.85	29.85	29.28	25.89
240	64.18	40.86	38.72	37.50	35.98
300	69.18	45.89	46.66	45.34	43.96
360	79.34	59.63	55.89	52.24	49.36
420	83.52	66.25	68.85	59.89	62.65
480	86.12	76.25	77.28	67.38	70.72
540	91.10	84.72	85.56	73.89	77.48
600	95.25	92.33	94.47	83.56	83.85

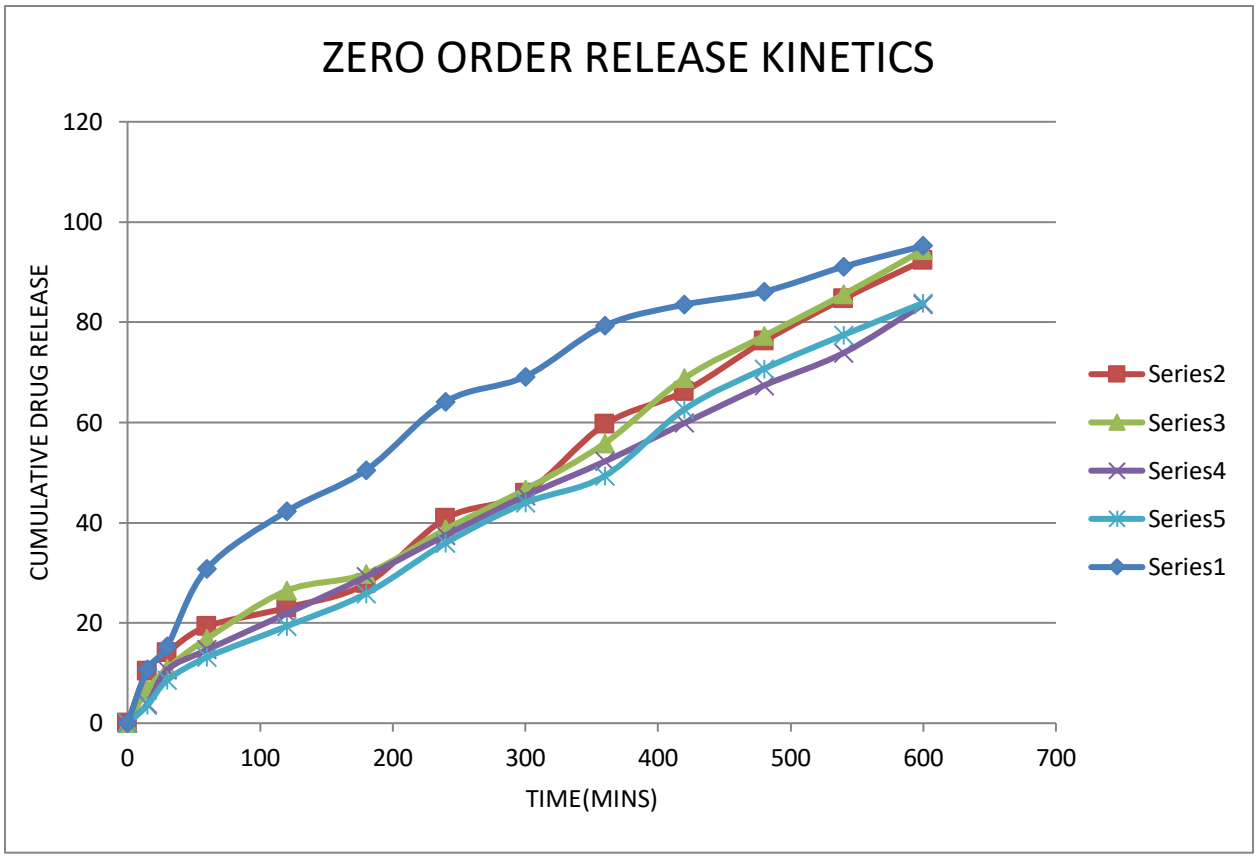


Figure no.1

-By cumulative drug release Vs Time (mins) graph of zero order kinetics release of patch is plotted as result shown in above figures.

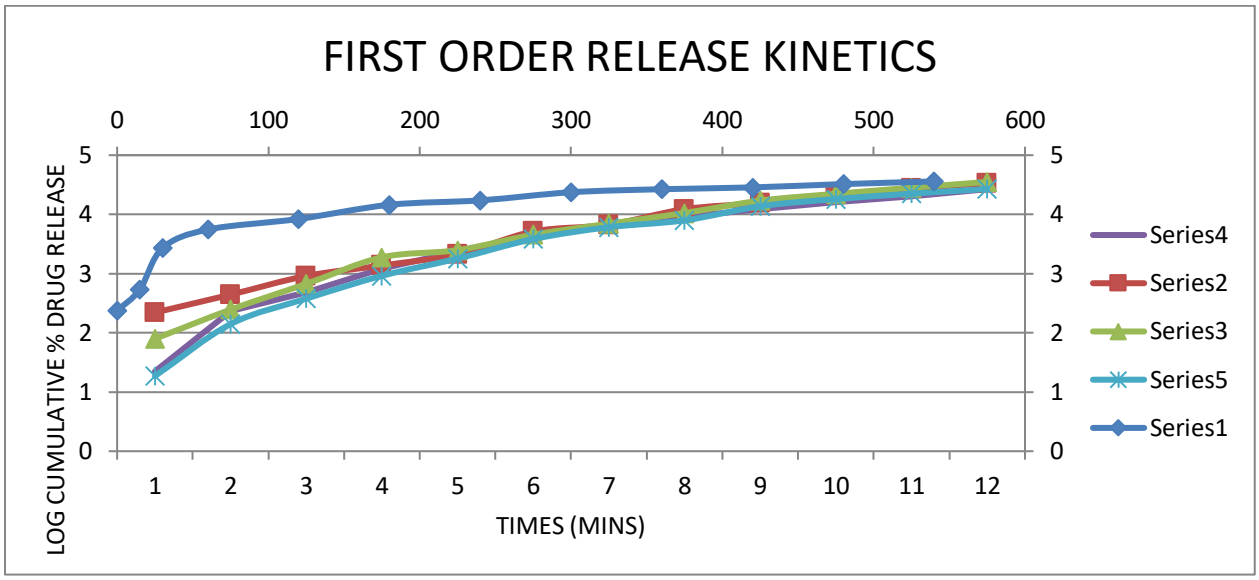
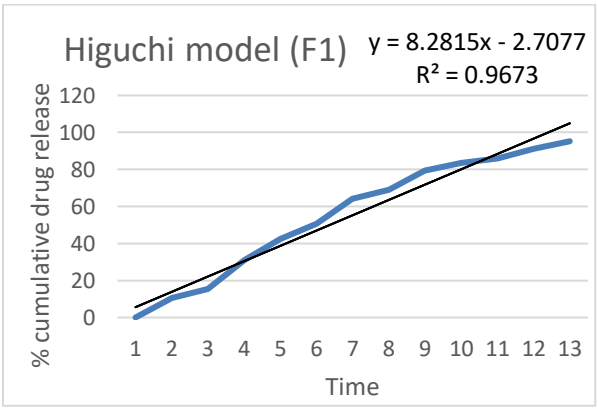
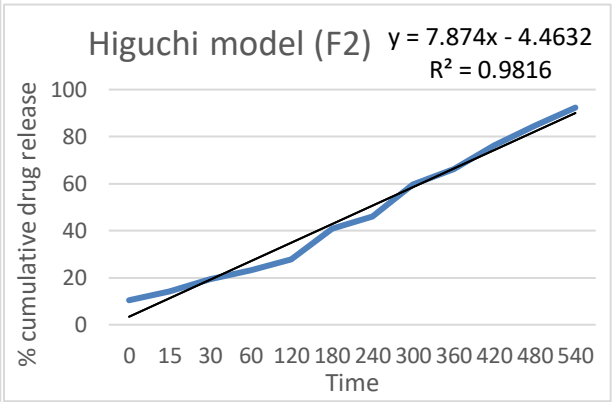
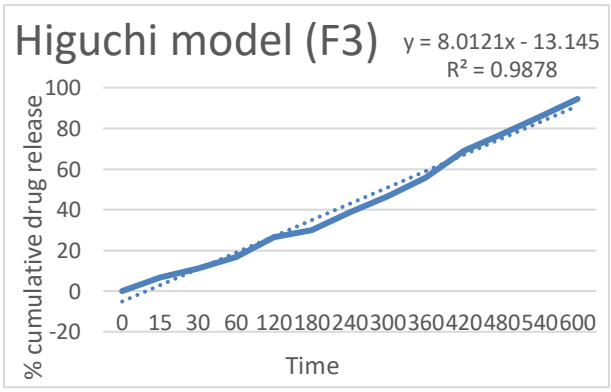


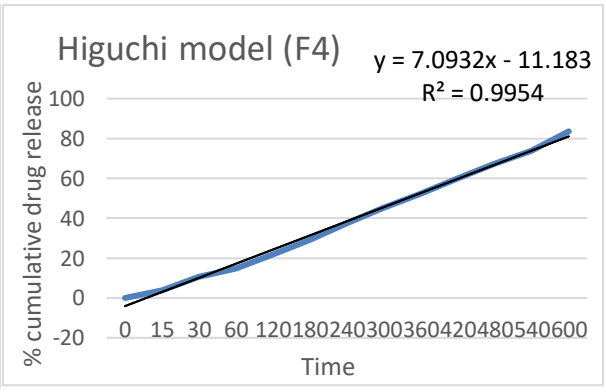
Figure no.2

Log Cumulative %drug release vs time(minutes) graph for first order release kinetics of patch is plotted as shown in above figures.









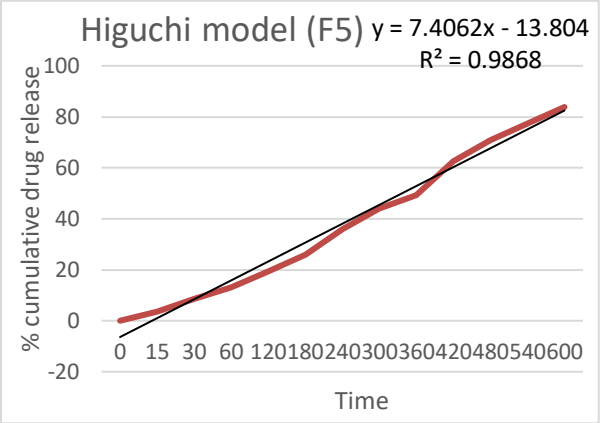


Figure no.3

% cumulative drugrelease vs the time(minutes) As demonstrated in the above figures, a graph for the release kinetics [diffusion] of clotrimazole transdermal patch is plotted.

Result:

Clotrimazole, a broad-spectrum antifungal medication, inhibits the permeability and functionality of the fungal cell membrane, preventing the production of ergosterol. to locally address vaginal yeast infections as well as skin conditions like jock itch and oropharyngeal candidiasis. The present work's objective was to create a transdermal patch for clotrimazole that also contained curcumin oil to lessen the skin's sensitivity and redness when the patch is applied. In the present study, the patches were made using the film-forming polymers Eudragit RS-100, HPMC, and EC. The solvent casting technique was used to make five different transdermal patch formulations. The use of propylene glycol as a plasticizer and a permeation facilitator. Before the transdermal patch is used, preformulation study, such as identification, physical characterization, and testing,

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