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# Formulation and Evaluation of Tacrolimus Transdermal Gel

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**Abstract:** The present study was aimed at the formulation and evaluation of Tacrolimus transdermal gel using different polymers in varying ratios to develop an effective transdermal drug delivery system with improved drug release characteristics. Tacrolimus is an immunosuppressive agent widely used in the management of inflammatory and autoimmune skin disorders. Transdermal delivery offers several advantages, including avoidance of first-pass metabolism, improved patient compliance, and sustained drug release.

Tacrolimus transdermal gels were prepared using different polymers such as Carbopol 934, HPMC K5, and HPMC K15, either alone or in combination at different concentrations and ratios. The prepared formulations were evaluated for various physicochemical parameters, including appearance, homogeneity, pH, viscosity, spread ability, and drug content. Compatibility studies confirmed the absence of any significant interaction between the drug and excipients used in the formulations.

All prepared formulations exhibited satisfactory physicochemical properties and complied with the acceptable limits specified by the Indian Pharmacopoeia (IP). The formulations were further subjected to in-vitro drug release studies to evaluate their release characteristics. The results indicated that the type and concentration of polymers significantly influenced the release behaviour of Tacrolimus from the gel matrix.

Among all the formulations, formulation F9 was identified as the optimized formulation based on its superior evaluation parameters and drug release profile. F9 exhibited the highest cumulative drug release of 97.82% within 300 minutes, demonstrating better release characteristics compared to the other formulations. The optimized polymer ratio provided an effective gel matrix that facilitated controlled and enhanced drug release.

The study concluded that Tacrolimus transdermal gel formulated with an optimized combination of polymers can serve as a promising alternative for transdermal drug delivery, offering improved drug release and potential therapeutic benefits.

**Keywords:** HPMC K 5 , HPMC K 15, Carbopal 934,Tacrolimus transdermal gel

## 1. INTRODUCTION

Innovations inthe areaof drugdelivery aretaking placeat amuch fasterpace ascompared withthe lasttwo decades. Improved patientcompliance andeffectiveness areinextricable aspectsof newdrug delivery systems. A more radical approach has been to explore newer interfaces on the body for introducing therapeutics.

One suchapproach, transdermaldrug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules. Transdermal drug deliverysystem (TDDS) isone ofthe systemslying underthe categoryof controlleddrug delivery, inwhich theaim isto deliverthe drugthrough the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devicesof definedsurface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation.[1]

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism respectively.Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular intervals, due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing.

The limitationsof theoral routecan beovercome andbenefits ofintravenous drug infusion such as to bypass hepatic "first pass" hepatic elimination (HEPE) tomaintain constantprolonged and therapeutic effective drug levels in the body can be closely duplicated, without its potential hazards, by transdermaldrug administrationthrough intact skin. Table1.1 representsthe advantagesand disadvantages of delivering drug across the skin for systemic therapy.

**Table 1.1:** Advantages and disadvantages of TDDS

| Advantages | Disadvantages |
|---|---|
| Self-administration is possible and continuous, sustained release of drug | Only small lipophilic drugs can be delivered currently through the skin |
| Avoids peak and trough drug levels and longer and multiday dosing intervals | Drug molecule must be potent because patch size limits the amount that can be delivered |
| Avoids first-pass hepatic metabolism and enzymatic degradation by the gastrointestinal tract and also avoids gastrointestinal irritation | Not suitable for high drug doses |
| Less frequent dosing improves patient compliance | Adhesion may vary with patch type and environmental conditions |
| Alternate route for patients who are unable to take oral medications | Adhesion may vary with patch type and environmental conditions |
| Dose delivery unaffected by vomiting or diarrhea | Skin irritation and hypersensitivity reactions may occur |
| Drug administration stops with patch removal | The barrier functions of the skin change from one site to another on the same person, from person to person and with age |

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms**.**

The transdermal route is indeed desirable, but there is one small obstacle: whereas the function of the GI tract is to render ingested material suitable for absorption, the skin's function is to keep things out of the body. The major barrier within the skin is the stratum corneum, the top layer of the epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells . Hygroscopic, but impermeable to water, it behaves as a tough, flexible membrane. The intercellular space is rich in lipids. The stratum corneum is about ten microns thick, but on the palms and soles it ranges up to 600 microns.

## ROUTES OF PENETRATION

here arecritically threeways inwhich adrug molecule can cross the intact SC: via skin appendages (shunt routes), through the intercellular lipid domains or by a transcellular route [Figure 1.2]. Physiochemical properties of the molecule govern theflux ofa particulardrug topermeate bya combination of these routes.[3]

### The appendageal route

The transappendagealroutes arealso knownas theshunt routes, and include permeation through the sweat glands and across the hair follicles with their associated sebaceous glands. Skin appendages provide a

continuous channel directly across the SC barrier. Recent studies have re-examined the long held assumption that the follicles occupy approximately 0.1% of the surfacearea ofthe human skin. Otberg et al. showed that the follicular number, opening diameter and follicular volume are important considerations in drug delivery through these appendagesand, indeed, theforehead provides 13.7 mm2/cm2 as the follicular infundibula, i.e. approximately 13.7% ofthe surfacearea ofthe foreheadis availableas follicles. Interestingly, the same study also showed that the historically held view of the follicles providing approximately 0.1% of the SC appears to be valid for forearm skin.

### Transcellular route

Drugs enteringthe skinvia thetranscellular routepass throughthe corneocytes. Corneocytes containinghighly hydratedkeratin providean aqueousenvironment from which hydrophilic drugs can pass. The transcellular pathway requires not only partitioning into and diffusion through the keratin bricks but also into and across the intercellular lipids.

### Intercellular route

The intercellular route involves drug diffusion through the continuous lipid matrix. This route is a significant obstacle for two reasons:

i. recalling the "bricks and mortar" model of SC, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.

ii. The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition intoand diffusethrough repeatedaqueous and lipid domains. This route is generally accepted as the most common pathfor smalluncharged moleculespenetrating the skin.

### Rationale for Transdermal Drug Delivery

Given thatthe skinoffers suchan excellentbarrier to molecular transport, the rationale for this delivery strategy needs tobe carefully identified. Clearly, thereare severalinstances inwhich themost convenientof drugintake methods (the oral route) is not feasible and when alternative routes must be sought.

Although intravenousintroduction ofthe medicament avoids many of these shortfalls (such as gastrointestinal and hepatic metabolism), itsinvasive andapprehensive nature (particularly for chronic administration) has encouraged the search for alternative strategies, and few anatomical orifices have notbeen investigatedfor theirpotential asoptional drugdelivery routes. Nevertheless, thetransdermal modeoffers severaldistinct advantages:

(1) The skinpresents a relatively large and readily accessible surface area (1–2 m2) for absorption;

(2) The application of a patch-like device to theskin surfaceis a non-invasive (and thusa patientcompliant) procedurethat allowscontinuous intervention (i.e., system repositioning, removal or replacement).

Further benefitsof TDDSshave emergedover thepast few years as technologies have evolved. These include the potential for sustained release (useful for drugs with short biological half-lives requiringfrequent oralor parenteraladministration) andcontrolled inputkinetics, whichare particularly indispensable for drugs with narrow therapeutic indices. Of course, the implementation of TDD technology. must betherapeutically "justified": drugs withhigh oral bioavailability and infrequent dosing regimens that are well accepted by patients do not warrant such measures. Similarly, transdermal administration is not a means to achieve rapid bolus-type drug inputs; rather, it is usually designed to offer slow, sustaineddrug deliveryover substantialperiods of time and, as such, tolerance-inducing drugs or those (e.g., hormones) requiringchronopharmacological management are, at least to date, not suitable. Nevertheless, there remains a large pool of drugs for which TDD is desirable but presently unfeasible. The natureof theSC is, inessence, thekey to this problem. The excellent diffusional resistance offered by the membrane means that the daily drug dose that can be systemically deliveredthrough areasonable "patch-sized" arearemains inthe 10mg range. This limitationimposes thefirst criterionfor asuccessful transdermal candidate: transdermal drugsmust bepharmacologically potent, requiringtherapeutic bloodconcentrations inthe ng/ml range, or less. The second criterion is that SC is very selective with respect to the type of molecule that can be transported across this outer covering, and not all molecules that pass the "potency" test will have the necessary physicochemical properties.[4]

## METHODOLOGY

### 7.1. Analytical method development:

### a). Determination of absorption maxima:

100mg of Tacrolimus pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e. 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). Scan the 10µg/ml using Double beam UV/VISspectrophotometer in the range of 200 – 400 nm

### b). Preparation calibration curve:

100mg of Tacrolimus pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e. 100µg/ml). From this take 10, 20, 30, 40, and 50ml of solution and make up to 100ml with 0.1N HCl to obtain 1, 2, 3, 4, and 5 µg/ml of Tacrolimus solution. The absorbance of the above dilutions was measured at 250nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient ($R^2$)which determined by least-square linear regression analysis. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated. The results of standard curve preparation are shown in Table-and figure

### 7.2. Drug – Excipient compatibility studies

### Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analysing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

## METHOD OF PREPARATION

### STEP1:

Preparation of emulsion using oil phase and water phase by emulsification method. Drug can be incorporated either in oil or aqueous phase depending upon its solubility.

### STEP2:

Formulation of gel base by using hydrocolloids by soaking in warm water.

### STEP3:

Third step after cooling, a prepared emulsion is incorporated into preformed gel and stir to uniform disperse emulsion into gel base.

### Preparation of Tacrolimus gel

Different formulations were prepared using varying amount of gelling agent. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel bases (Carbopol 934, HPMC-5 and HPMC15+Carbopol-934) were prepared by dispersing in distilled water separately with constant stirring at a moderate speed using mechanical shaker. Formulations F1, F2 and F3 were prepared by Carbopol 934; F4, F5 and F6 by HPMC-5; F7, F8, and F9 by HPMC15+Carbopol-934 as gelling agent. In formulations the gel were prepared by dispersing base in heated distilled water (75°C) and the dispersion was cooled and left overnight. The pH of all the formulations was adjusted to 5.5 to 6.5 using tri ethanol amine (TEA). The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben were dissolved in propylene glycol and mixed with aqueous phase Tacrolimus being hydrophobic was dissolved in oil phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The

obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the gel. The composition of different formulations has been discussed in Table 7.1.

**Table 7.1:** Composition of gel formulation

| COMPOSITION OF GEL FORMULATIONS (%W/W) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Tacrolimus | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Carbopol-934 | 50 | 75 | 100 | – | – | – | – | – | – |
| HPMC-5 | – | – | – | 50 | 75 | 100 | – | – | – |
| HPMC15+Carbopol-934 | – | – | – | – | – | – | 50 | 75 | 100 |
| Triethanolamine | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Liquid paraffin | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Alcohol | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Span 80 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Tween 80 in ml | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 1 | 5 |
| Propylene glycol | 5 | 5 | 5 | 5 | 5 | 5 | 55 | 5 | 5 |
| Methyl paraben | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Water | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |

**Characterization of Gellified Emulsion**

**1. Physical appearance**

The prepared Emulsion formulations were inspected visually for their colour, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter).

**2. Rheological Study**

The viscosity of the different gel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

**3. Spread ability**

Spread ability is determined by apparatus suggested by which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spread ability is measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground glass slide is fixed on this block. An excess of gel (about 2 gm.) under study is placed on this ground slide. The gel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel is scrapped off from the edges. The top plate is then subjected to pull of 80 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spread ability. Spread ability was calculated by using the formula,

$$S= M.L/T$$

Where, S = spread ability,

M = Weight tied to upper slide,

L = Length of glass slides

T = Time taken to separate the slides completely from each other.

**4. Extrudability study**

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating gel formulation for extrudability is based upon the quantity in percentage of gel and gel

extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 seconds. More quantity extruded better is Extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude gel from tube (in gm.) / Area (in cm)

### 5. Drug Content Determination

Drug concentration in Gellified Emulsion was measured by spectrophotometer. Drug content in Gellified Emulsion was measured by dissolving known quantity of Gellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV -1700 CE, Shimadzu Corporation, Japan).

### 6. *In Vitro* Release Study

Franz diffusion cell (with effectivediffusion area3.14 cm 2 and 15.5ml cellvolume) Was used for thedrug release studies. Gellified Emulsion (200 mg) was applied onto Thesurface ofegg membrane evenly. The eggmembrane was clamped between the donor andthe receptorchamber ofdiffusion cell. The receptorchamber was filled with freshly preparedPBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analysed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval .The cumulative amount of drug released across the egg membrane was determined as a function of time.

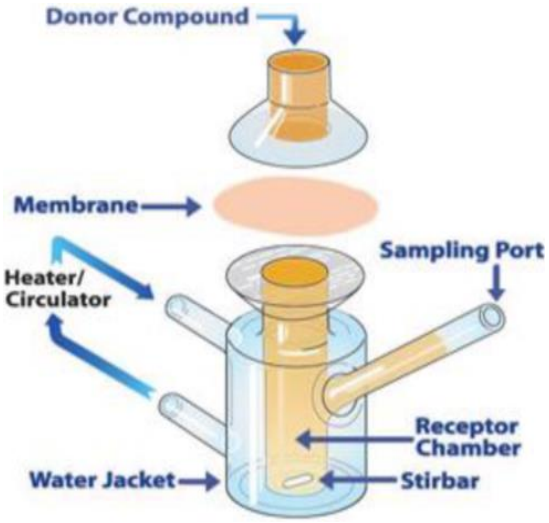


**Fig 7.2:** Franz diffusion cell

### Equation used to determine drug release

### 1. Higuchi's equation

$$Q = k2\sqrt{t}$$

Q = Percent of drugrelease at time t. k2= Diffusion rate constant.

### 2. Zero-order equation Q = k0t

Where-

Q = Amount of drug release at time t. k0 = Zero order release rate.

### 3. First-order equation In = (100-Q) = In 100 - k1t

Where-

Q = Percent of drug release at time t.

k1 = the first order release rate constant.

## RESULTS AND DISCUSSION

A unique feature of topical drug delivery is the direct accessibility of the skin as a target organ for diagnosis and treatment. Topical drug delivery system offers several advantages over oral drug delivery systems. Oral drug delivery system produced many sides effect so overcome the side effect of the oral dosage form, the drug was formulated in to topical drug delivery system i.e. gel. Gel formulation of Tacrolimus was prepared using 4 types of gelling agent: Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934 as polymers. Tacrolimus, used for the topical as vaginal yeast infections, oral thrush, diaper rash, tinea versicolor, and types of ringworm including athlete's foot and jock itch. In the present study, an attempt was made to formulate topical gel of DRUG for efficient delivery of drug across the skin.

### 8.1 Analytical Method

### 8.1.1 Standard graph of Tacrolimus in 0.1N HCl:

The scanning of the 10µg/ml solution of Tacrolimus in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at $\lambda_{max}$ as 250 nm. The standard concentrations of Tacrolimus (1-6) µg/ml) was prepared in 0.1N HCl showed good linearity with $R^2$ value of 0.998, which suggests that it obeys the Beer-Lamberts law.

**Table 8.1:** Standard Curve of Tacrolimus in 0.1 N HCl

| Concentration µg/ml | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.125 |
| 20 | 0.251 |
| 30 | 0.365 |
| 40 | 0.482 |
| 50 | 0.608 |

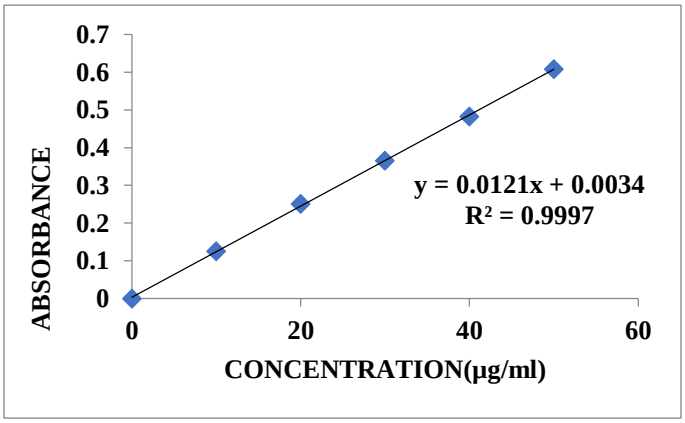


**Fig 8.1:** Standard Curve of Tacrolimus in Phosphate buffer pH 0.1N HCl

The scanning of the 10µg/ml solution of Tacrolimus in the ultraviolet range (200-400nm) against 6.8 pH the maximum peak observed at $\lambda_{max}$ as 250 nm. The standard concentrations of Tacrolimus (1-6) µg/ml) was prepared in pH 6.8 showed good linearity with $R^2$ value of 0.999, which suggests that it obeys the Beer-Lamberts law.

**Table 8.2:** Standard Curve of Tacrolimus in pH 6.8

| Concentration µg/ml | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.128 |
| 20 | 0.244 |
| 30 | 0.366 |
| 40 | 0.482 |
| 50 | 0.599 |

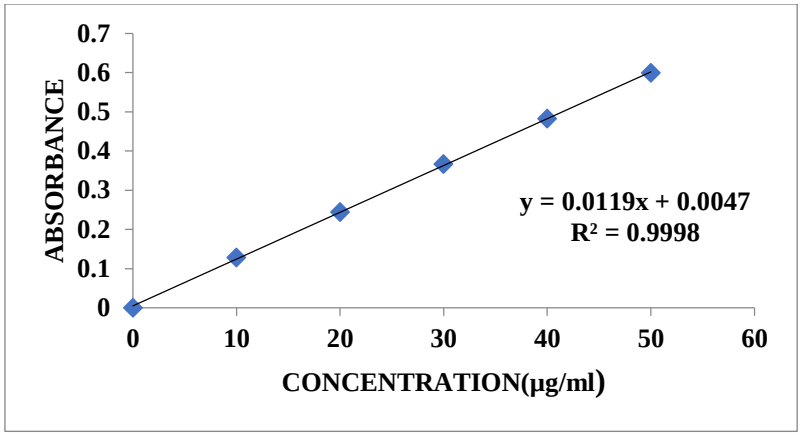


**Fig 8.2:** Calibration curve of Tacrolimus in pH 6.8 at 250nm

## 8.2 Drug and Excipient Compatibility Studies

### 8.2.1 FTIR study

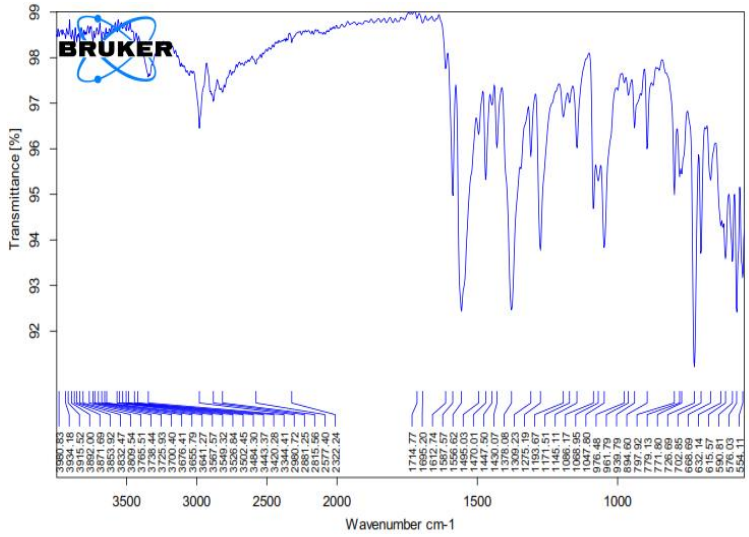


**Fig 8.3:** FTIR Graph of Pure Drug

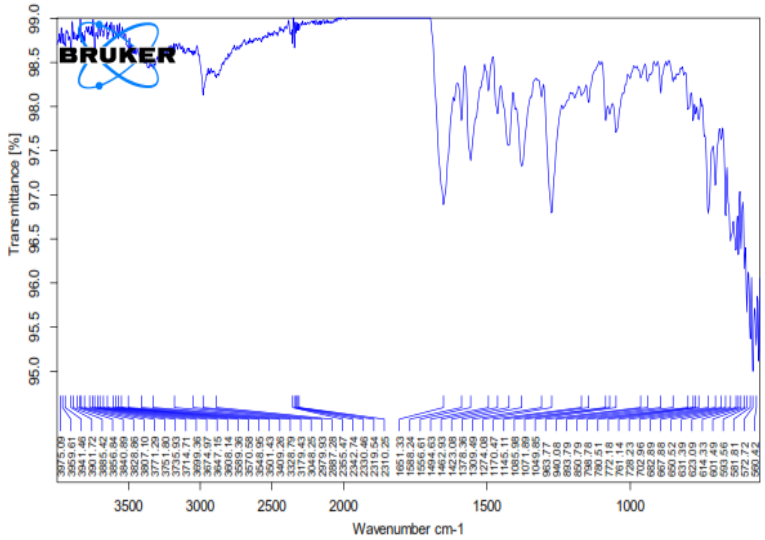


**Fig 8.4:** FTIR Graph of Optimised Formulation

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible

### Physical Examination

The prepared gellified emulsion formulations were white, viscous, and creamy preparations, with a smooth and homogeneous appearance, as given in table. Incorporation of propylene glycol as a humectant not only provided the optimum spread ability to the product, but also improved the aesthetic appearance. HPMC15+Carbopol-934 as a gelling agent helped to achieve the desired viscosity, thereby affecting the homogeneity as well as the spread ability of the final preparations. There was no sign of phase separation in any of the preparations.

**Table 8.3:** Physicochemical characteristics of gel

| S.No. | Formulation code | Color | Phase separation | Grittiness | Homogeneity | Consistency |
|---|---|---|---|---|---|---|
| 1 | F1 | White | None | - | Fair | + |
| 2 | F2 | White | None | - | Fair | + |
| 3 | F3 | White | None | - | Fair | + |
| 4 | F4 | White | None | - | Good | ++ |
| 5 | F5 | White | None | - | Good | ++ |
| 6 | F6 | White | None | - | Good | ++ |
| 7 | F7 | White | None | - | Excellent | +++ |
| 8 | F8 | White | None | - | Excellent | +++ |
| 9 | F9 | White | None | - | Excellent | +++ |

### Measurement of pH

The pH of gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and it was placed for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated. The pH of the gel formulations was in range which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The data is reported in Figure.

**Table 8.4:** Different formulations Parameters

| S. No. | Formulation code | pH | Viscosity | Spreading Coefficient | Extrudability | Drug content |
|---|---|---|---|---|---|---|
| 1 | F1 | 6.10 | 6892 | 16.6 | 10.8 | 98.19 |
| 2 | F2 | 6.15 | 7752 | 18.3 | 11.3 | 99.51 |
| 3 | F3 | 5.99 | 8125 | 16.9 | 13.6 | 98.36 |
| 4 | F4 | 6.12 | 3550 | 21.6 | 9.1 | 97.85 |
| 5 | F5 | 6.09 | 4218 | 28.1 | 10.5 | 98.11 |
| 6 | F6 | 6.15 | 5128 | 32.3 | 11.4 | 99.14 |
| 7 | F7 | 6.23 | 8972 | 33.3 | 12.3 | 99.35 |
| 8 | F8 | 6.18 | 9757 | 35.4 | 15.6 | 98.16 |
| 9 | F9 | 5.98 | 9818 | 39.8 | 17.6 | 100.05 |

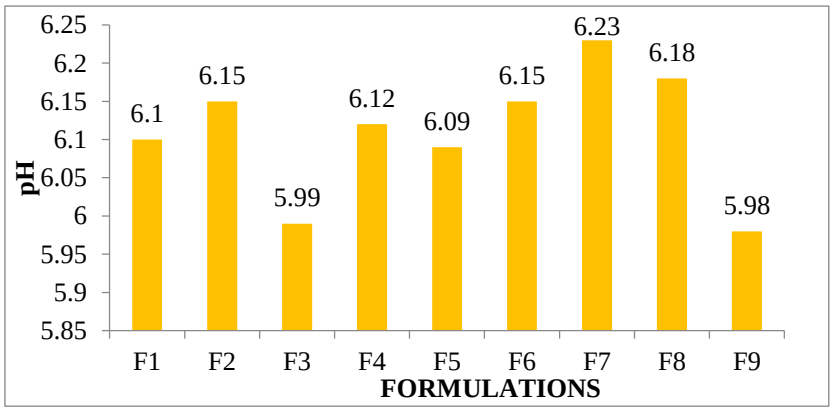


**Fig.8.5:** pH of different formulations F1-F9

### Viscosity of Gellified emulsions

All of the prepared formulations possessed optimum viscosity. Since, the type and quantity of the gelling agent in each formulation was the same, inclusion of different bases to have brought about some difference in the viscosity of the gellified emulsions. While F9 was the most viscous formulation, F4 had the least viscosity.

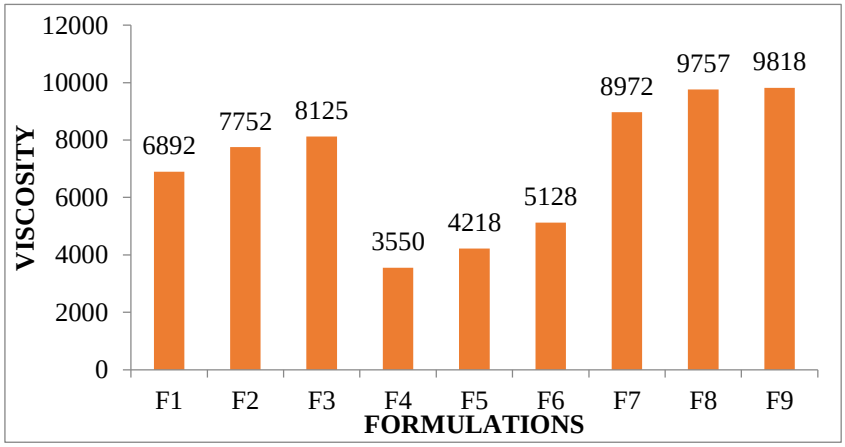


**Fig 8.6:** Viscosity of different formulations F1- F9

**SPREADABILITY:** The values of the spread ability indicated that the gellified emulsions were easily spreadable by small amount of shear. Formulation F9 gave the highest value for spread ability.

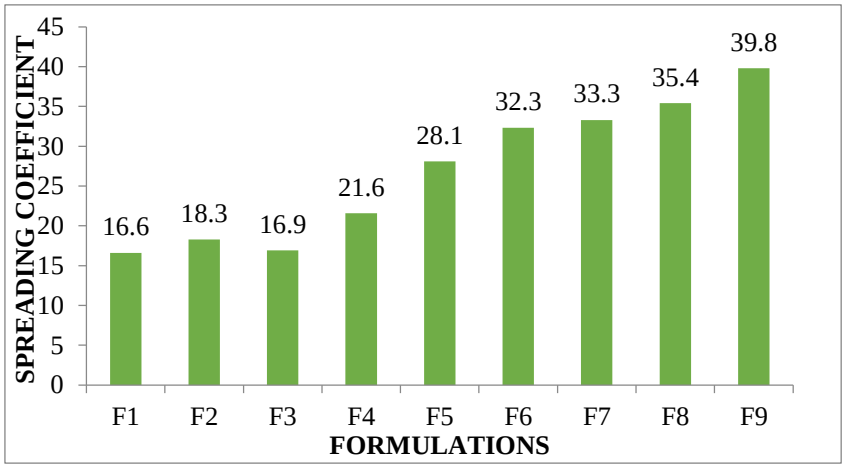


**Fig 8.7:** Spreading Coefficient of different formulations F1-F9

**Extrudability:** The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked and the results were shown in Table Figure

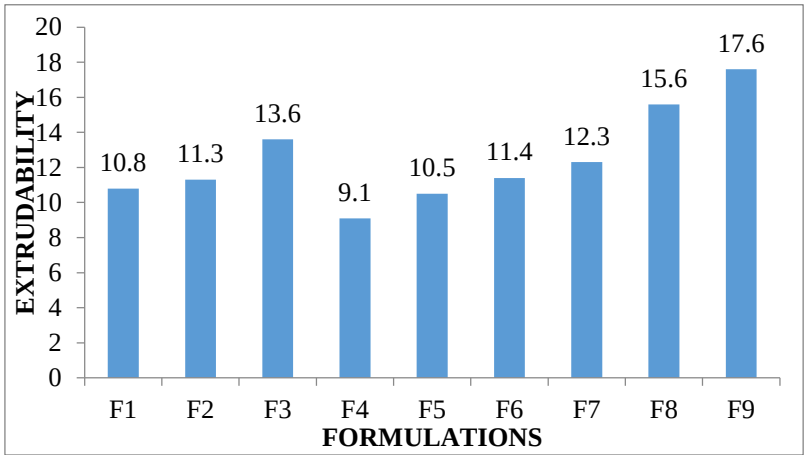


**Fig.8.8:** Extrudability of different formulations F1-F9

**Drug content:**

The percent drug content in gellified emulsions was found to fall in the range of 97.85 to 100.05.

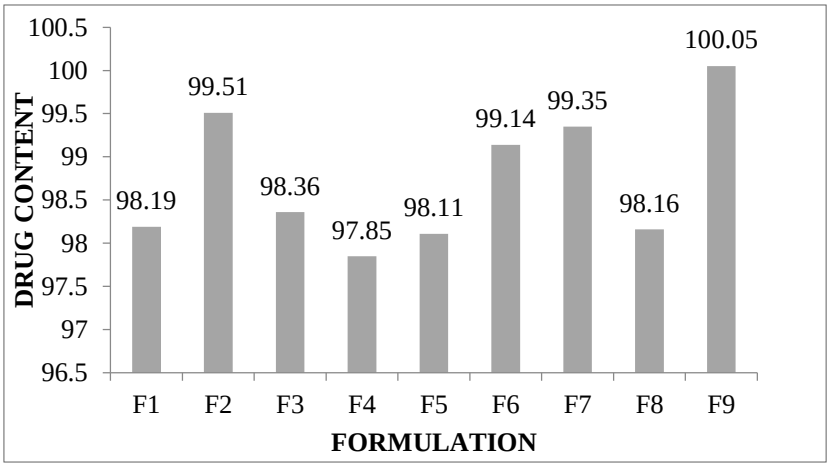


**Fig .8.9:** Percentage drug content of different formulations F1-F12

**Table 8.5:** Dissolution Data of gel containing Tacrolimus by using various polymers

| Time(Min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 32.39 | 26.13 | 20.03 | 42.80 | 34.19 | 33.31 | 25.94 | 19.96 | 22.14 |
| 30 | 46.62 | 34.81 | 36.53 | 58.93 | 44.11 | 42.29 | 35.63 | 31.13 | 32.91 |
| 45 | 53.78 | 49.94 | 45.24 | 63.46 | 57.89 | 53.64 | 42.80 | 36.31 | 38.01 |
| 60 | 70.31 | 57.43 | 52.90 | 76.04 | 68.23 | 60.72 | 51.99 | 47.60 | 45.20 |
| 90 | 76.10 | 63.97 | 58.18 | 86.57 | 76.85 | 68.34 | 59.12 | 53.96 | 51.63 |
| 120 | 87.32 | 71.08 | 67.49 | 91.94 | 87.98 | 75.87 | 66.54 | 61.83 | 57.76 |
| 150 | 90.89 | 78.50 | 73.91 | | 94.33 | 82.79 | 72.79 | 67.24 | 63.81 |
| 180 | 93.35 | 82.32 | 79.30 | | 95.19 | 88.64 | 76.52 | 74.06 | 71.56 |
| 210 | | 86.13 | 85.37 | | | 92.26 | 85.58 | 78.90 | 75.16 |
| 240 | | 93.69 | 92.16 | | | 93.83 | 91.40 | 84.23 | 80.26 |
| 270 | | 95.74 | 95.66 | | | | 93.76 | 92.61 | 86.51 |
| 300 | | | 96.81 | | | | | 95.90 | 97.82 |

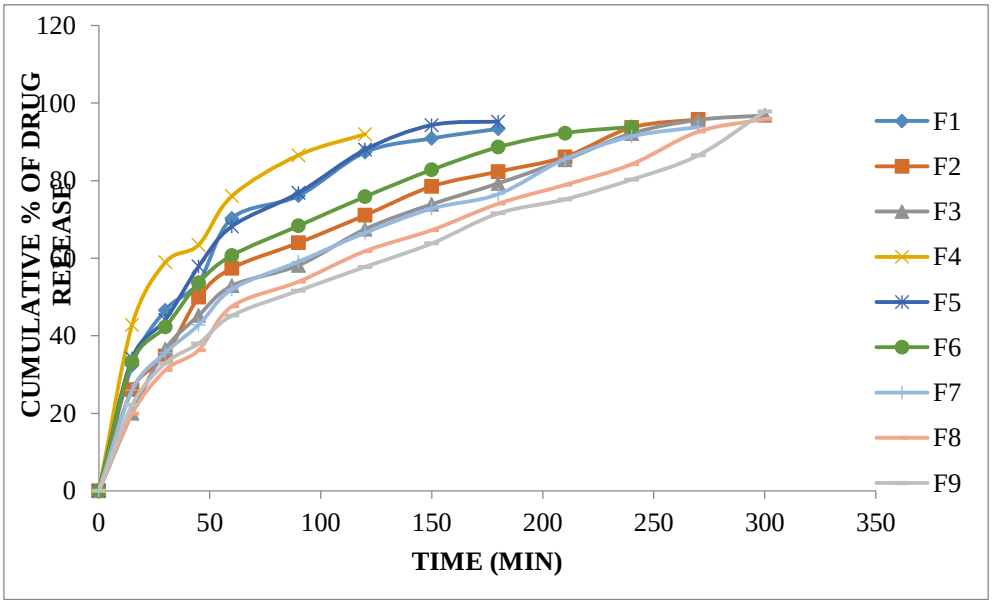


**Fig .8.10:** Diffusion study of gel containing Tacrolimus with Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934 (F1 to F9)

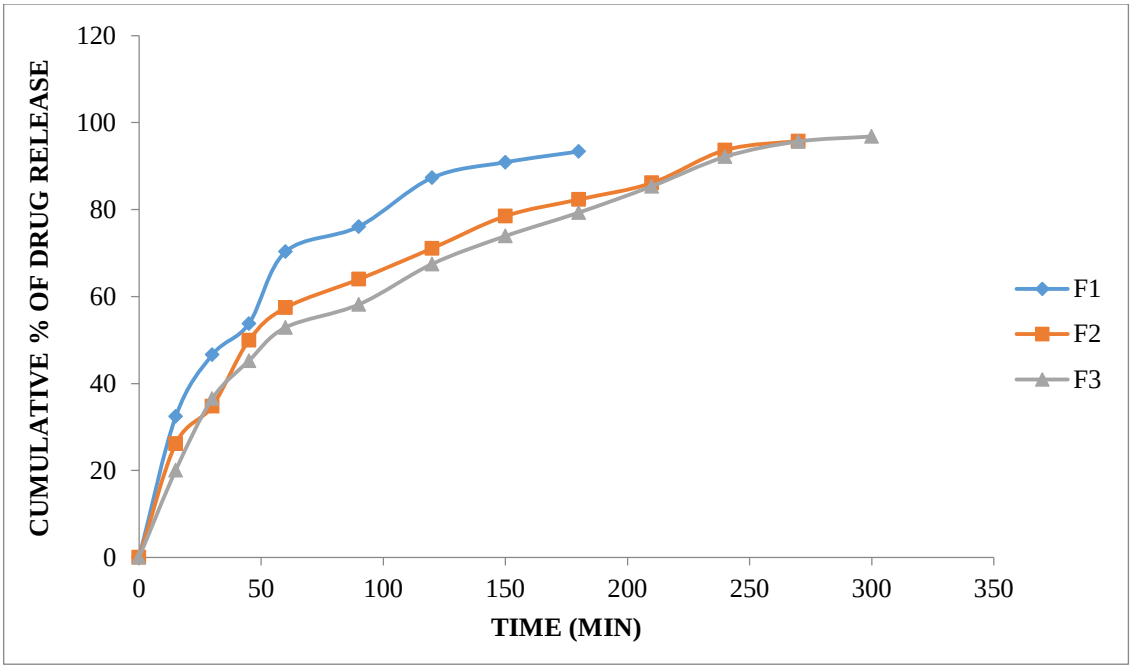


**Fig.8.11:** Diffusion study of gel containing Tacrolimus with Carbopol-934 (F1 to F3)

The % drug release of F1 to F3 formulations depends on concentration of polymer/gelling agent in the formulation. The **Carbopol-934** 1:1 and ratio was unable to retard the drug release up to desired time. The ratio of drug and **Carbopol-934** 1:1.5 was unable retard the drug release up to 5 hrs. In F3 formulations, **Carbopol-934** ratio is 1:3 showed maximum % drug release i.e. 96.81 at 5 hours.

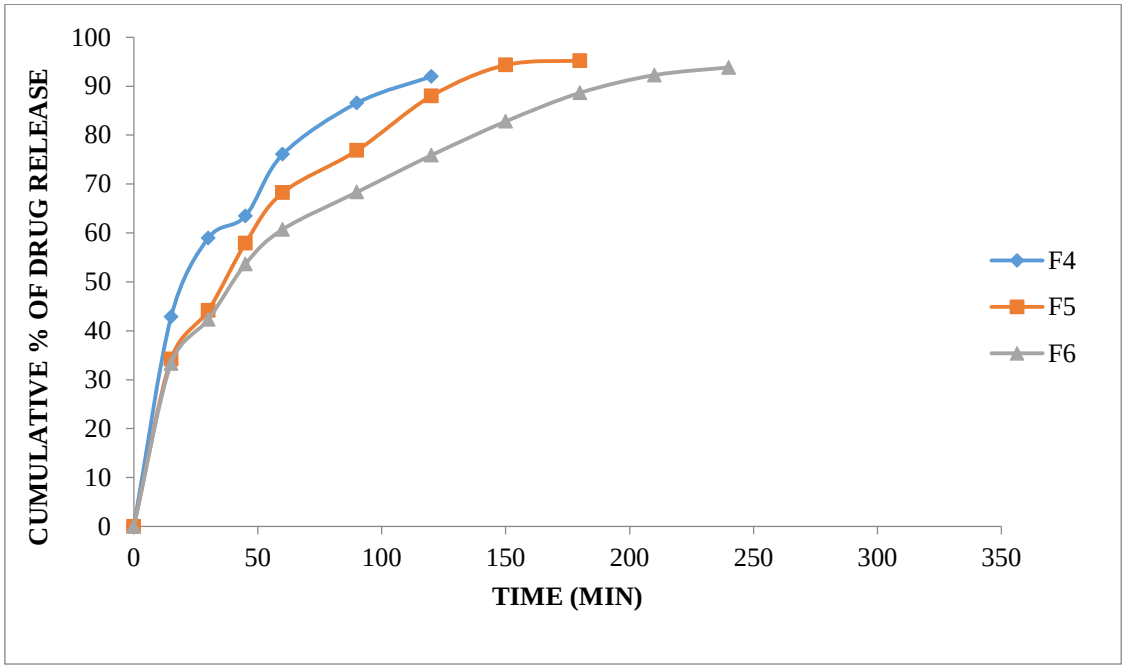


**Fig 8.12:** Diffusion study of gel containing Tacrolimus with HPMC-5 (F4 to F6)

The % drug release of F4 to F6 formulations depends on concentration of polymer/gelling agent in the formulation. The **HPMC-5** 1:1 and ratio was unable to retard the drug release up to desired time. When the ratio of drug and **HPMC-5** 1:1.5 was unable retard the drug release up to 3 hrs. In F6 formulations, **HPMC-5** ratio is 1:3 showed maximum % drug release i.e. 93.83 at 4 hours.

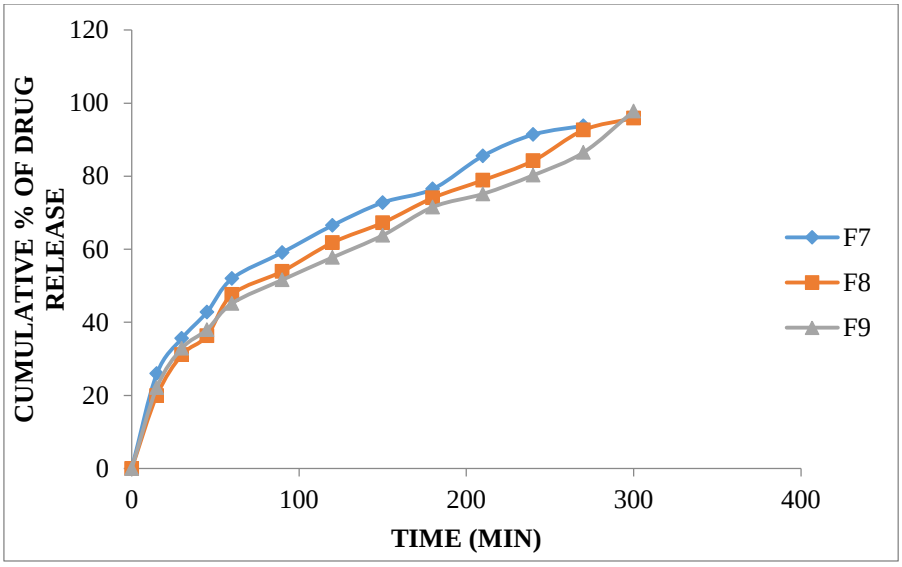


Fig.8.13: Diffusion study of gel containing Tacrolimus with HPMC15+ Carbopol-934 (F7 to F9)

The % drug release of F7 to F9 formulations depends on ratios of polymer in the Gel. The **HPMC15+ Carbopol-934** 1:1 ratio was unable to retard the drug release up to desired time. When the ratio of **HPMC15+ Carbopol-934** 1:3 was retard the drug up to desired time period i.e. 97.82% at 5 hours. In F9 formulations, **HPMC15+ Carbopol-934** is 1:2 ratios it is more retard the drug release.

Hence based on Diffusion data of 9 formulations, F9 formulation showed better release up to 5 hours. So F9 formulation is optimized formulation.

**Pharmacokinetics**

**Application of Release Rate Kinetics to drug diffusion Data**

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Tacrolimus release from Sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

**Table 8.6:** Release kinetics data for optimized formulation (F9)

| Time (T) | Cumulative (%) Release | Root (T) | Log (%) Release | Log (T) | Log (%) Remain | RELEASE RATE (CUMULATIVE % RELEASE / t) |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | |
| 15 | 22.14 | 3.873 | 1.345 | 1.176 | 1.891 | 1.476 |
| 30 | 32.91 | 5.477 | 1.517 | 1.477 | 1.827 | 1.097 |
| 45 | 38.01 | 6.708 | 1.580 | 1.653 | 1.792 | 0.845 |
| 60 | 45.2 | 7.746 | 1.655 | 1.778 | 1.739 | 0.753 |
| 90 | 51.63 | 9.487 | 1.713 | 1.954 | 1.685 | 0.574 |
| 120 | 57.76 | 10.954 | 1.762 | 2.079 | 1.626 | 0.481 |
| 150 | 63.81 | 12.247 | 1.805 | 2.176 | 1.559 | 0.425 |
| 180 | 71.56 | 13.416 | 1.855 | 2.250 | 1.454 | 0.398 |
| 210 | 75.16 | 14.491 | 1.876 | 2.322 | 1.395 | 0.358 |
| 240 | 80.26 | 15.492 | 1.904 | 2.380 | 1.295 | 0.334 |
| 270 | 86.51 | 16.432 | 1.937 | 2.431 | 1.130 | 0.320 |
| 300 | 97.82 | 17.321 | 1.990 | 2.477 | 0.338 | 0.326 |

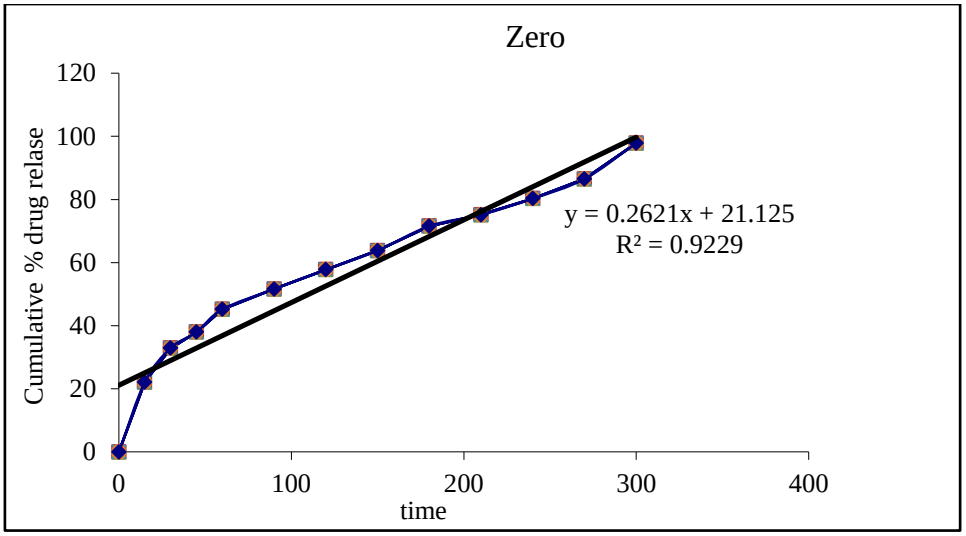


**Fig 8.15:** Graph of zero order kinetics

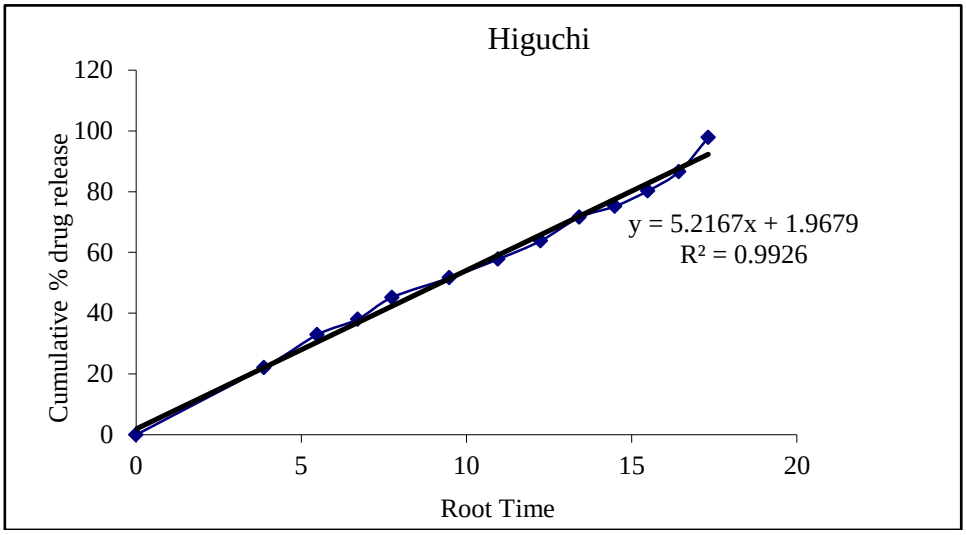


**Fig.8.16:** Graph of higuchi release kinetics

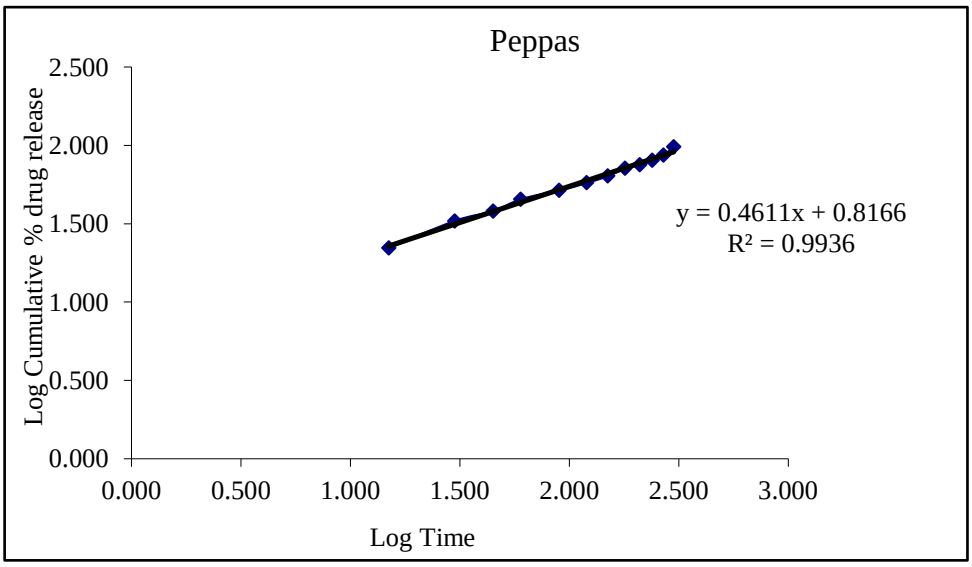


**Fig.8.17:** Graph of peppas release kinetics

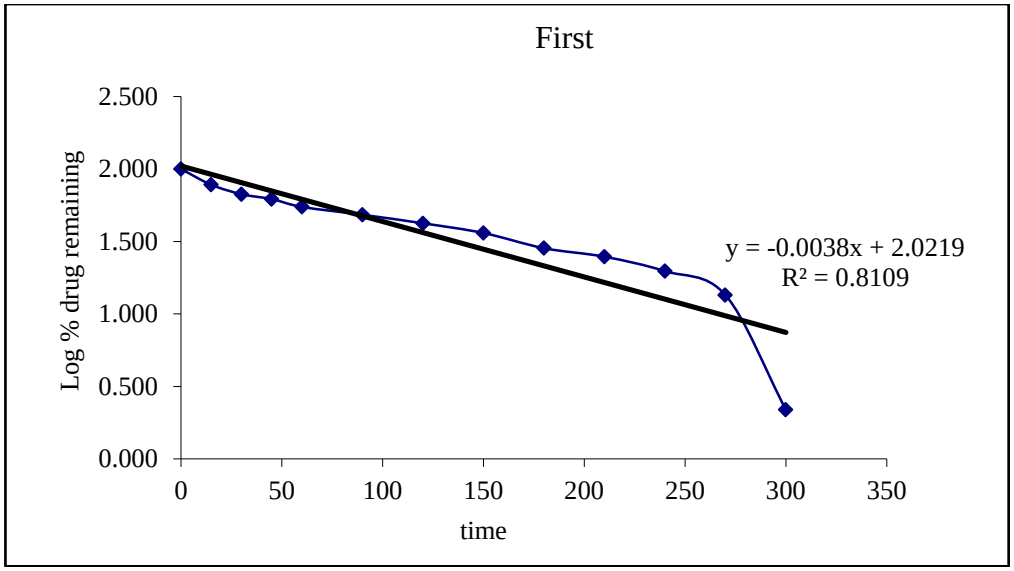


**Fig.8.18:** Graph of first order release kinetics

### Drug Release Kinetic Study

The release data analysis was carried out using the various kinetic models i.e. using cumulative % drug release vs. time (zero order kinetic model); log cumulative % drug remaining vs. time (first order kinetic model) and cumulative % drug release vs. square root of time (Higuchi model). The $R^2$ values are tabulated in table. All formulae showed best fitting to Peppas release kinetics.

## 9. CONCLUSION

The present study successfully formulated and evaluated Tacrolimus transdermal gel using different polymers and polymer combinations, namely Carbopol 934, HPMC K5, and HPMC K15 in combination with Carbopol 934 at different ratios. The prepared formulations were evaluated for various physicochemical parameters including appearance, pH, homogeneity, viscosity, spread ability, drug content, and in-vitro drug release.

The results demonstrated that the type and concentration of polymers significantly influenced the characteristics and performance of the transdermal gels. Formulations containing Carbopol 934 exhibited good gel strength and consistency, whereas HPMC-based formulations showed satisfactory spread ability and controlled drug release behaviour. The combination of HPMC K15 and Carbopol 934 produced gels with improved viscosity, enhanced stability, and sustained drug release compared to formulations prepared with individual polymers.

Among all the formulations, the optimized polymer ratio provided acceptable physicochemical properties, uniform drug distribution, and superior drug release characteristics, indicating its suitability for transdermal delivery of Tacrolimus. The study confirms that polymer blending can effectively modify the release profile and improve the overall performance of Tacrolimus transdermal gel.

Therefore, Tacrolimus transdermal gel formulated with an appropriate combination of HPMC K15 and Carbopol 934 may serve as a promising alternative for controlled and effective transdermal drug delivery.

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