E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/14.02.08

Research Article

Formulation and Development of Emulgel to Enhance the Transdermal Permeability of BCS Class II Drug (Tacrolimus)

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Received: 27.09.24, Revised: 30.10.24, Accepted: 21.11.24

ABSTRACT
Topical drug delivery systems significantly improve the therapeutic efficacy of drugs. The topical route of drug delivery is the most preferred route for administration of drugs. The rationale for the development of an emulgel formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition. Drug-release-retarding polymers are the key performers in such systems. The drug content was found to be in the range of 81.13 – 98.25 %. From the *in-vitro* drug release data, it was observed that the percentage cumulative drug release of Tacrolimus was shown by formulation F3. F3 released 99.37 % of the drug in 60 min. The 'n' value of optimized formulation F3 was found to be 0.717 which indicated that the drug was released by first order kinetics with anomalous (Non-Fickian) release. From the stability studies, formulation F3 doesn't show significant difference for physical properties, homogeneity, consistency, drug content and viscosity. Based on the above evaluation studies, it could be concluded that Tacrolimus can be used as an emulgel by mixing equal quantities of a gel and emulsion portions for acute bacterial skin infection.

Keywords: Topical, Emulgel, Drug Delivery, Therapeutic.

INTRODUCTION

Tacrolimus (also FK-506 or Fujimycin) is an immunosuppressive drug whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory uveitis after bone marrow transplants, and the skin condition vitiligo.[1]

However, the low solubility and bioavailability limits the effect and application of Tacrolimus. Emulgel based topical drug delivery systems, such as increasing the solubility of hydrophobic drugs and improving drug permeability, were established to overcome these shortcomings.[2] An increased range of drug under modification/ development of very less solubility in water and thus with bioavailability with poor class. Such nominated class II/ IV drugs. Novelty in formulation methods mandatory for producing complete drug product (for drug) which as adequate pharmacokinetics. The mutual approach of formulation along with this kind of compounds emphasis on generating and stabilizing small sized particles of drug in effort to rise surface area accessible in dissolution in vivo and henceforth dissolution rate and accordingly tissue or plasma levels for drug. Stability of shelf life and degradation (enzymatic) are principal areas of worry and design of formulation attentions on stabilizing drug during storage and for protection from enzyme (endogenous) degradation till it reach up to target **(**therapeutic). Such novel DDS well matched for bioactive formulation. Lipid DDS can engage for Phytomedicine delivery in case of oral/ topical administration that considered as leading ways of phyto medicinal administration. Such kind of applications grips countless potential in use and progress of Phytomedicine which consider complications of its carriage owed to particular properties of physicochemical.

MATERIALS AND METHODS

Materials

Tacrolimus was obtained as gift sample from Vama Pharma (Nagpur). Carbopol 940, Liquid Paraffin, Span 20, Tween 20 etc was obtained from Shree Sadguru Hitech Lab, Pune. All chemicals used were analytical grade.

Methods

Preparation of Tacrolimus Emulgel

Emulgel was prepared using carbopol 940, as gelling agents. The gels in formulations were prepared by dispersing carbopol in purified water with constant stirring at a moderate speed and then the pH are adjusted to around 6 using tri-ethanol amine. The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Finally the emulgel was prepared by mixing the both gel and emulsion in 1:1 ratio. The composition of different formulations has been discussed in Table no. 1.

Table No. 1: The Main Composition of Emulgel Formula

Formulation code (mg)	F1	F2	F3	F4	F5	F6
Tacrolimus	10	10	10	10	10	10
Carbopol 940	10	10	10	10	10	10
Liquid Paraffin	50	50	75	75	100	100
Span 20	10	15	10	15	10	15
Tween 20	5	10	5	10	5	10
Propylene glycol	50	50	50	50	50	50
Ethanol	25	25	25	25	25	25
Methyl Parabens	0.3	0.3	0.3	0.3	0.3	0.3
Ethyl Parabens	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of the Tacrolimus Emulgel Fourier Transform Infrared Spectroscopy (FTIR)

The primary objective of this investigation was to identify a stable storage condition for the drug in solid state and identification of compatible excipients for formulation.

Physical Properties of the Emulgel

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, and phase separation.

Measurement of PH

An emulgel solution prepared by dissolving 1gm of emulgel in 100 ml of deionized water and it was left for 2 hours. Then pH of the prepared emulgel solution was measured using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Spreadability study of Emulgel

To determine the spreadability of micro-emulsion based emulgel, 0.5 mg of emulgel is placed within circle of 1 cm diameter pre-marked on a glass plate, over which second plate is placed. A weight of 500 mg is allowed to rest on the upper glass plate for 5 min. The increase in diameter is observed due to emulgel, the spreading is noted.

Viscosity Measurements

The viscosity of different emulgel formulation was determined at 37ºC using a Brookfield viscometer. The samples were rotated using spindle 6 at 3, 5, 10, 20, 30, 50 and 100 rpm and the viscosities were measured. With 30 seconds between these successive speeds.

Drug Content Determination

One gram of emulgel was dissolved in 100 ml of phosphate citrate buffer (pH 5.5), filtered to obtain clear solution. The absorbance of the solution is determined using UV spectrophotometer at Tacrolimus λ_{max} (dilution is performed when needed). Concentration and drug content was determined by using the same standard plot.

Kinetics of Drug Release

The cumulative amount of Tacrolimus released from the selected formulas at sequential time intervals were fitted to zero order, first order kinetics, Higuchi and Korsmeyer–Peppas models to characterize drug release kinetics and propose a mechanism of drug release.

Selection of Optimum Formula

The prepared emulgel formulas were evaluated for their physical appearance, pH determination, and *in vitro* drug release and stability studies.

Stability Studies

The selected optimum formula of the prepared emulgel formulas was subjected to accelerated stability studies at 30°C, 40°C and 50°C for a period of 3 months. Samples were withdrawn at 15-days time intervals. In addition, it evaluated for physical appearance, pH, rheological properties and drug content.

FTIR Study

The FTIR spectrum of Tacrolimus is shown in figure. It showed that, functional group band frequencies of Tacrolimus were in resemblance to the reported range of standard Tacrolimus that authenticated that the obtained sample of Tacrolimus was pure.

RESULTS AND DISCUSSION

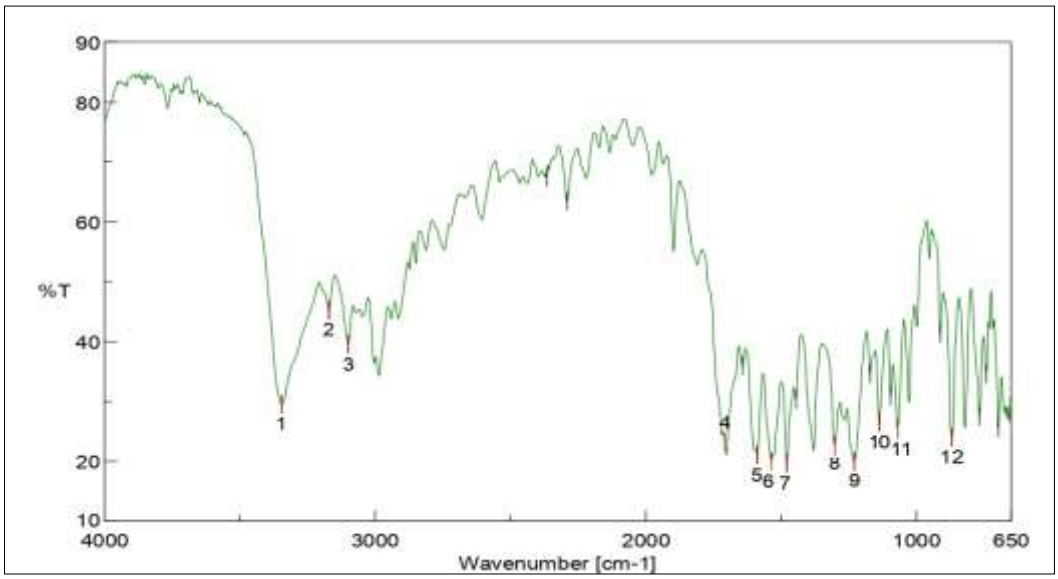

Figure No.1: FTIR spectroscopy of Tacrolimus with excipients

No.	Position	Intensity	No.	Position	Intensity
1	3346.79	29.508	7	1478.12	19.9701
2	3170.4	45.2375	8	1301.72	22.548
3	3089.05	39.5285	9	1239.05	19.9701
4	1707.66	23.2269	10	1136.83	26.531
5	1587.07	21.1235	11	1079.31	25.3767
6	1535.06	20.0654	12	869.739	23.9878

Physical properties

Emulgel formulations were viscous creamy preparation with a smooth homogeneous texture and glossy appearance. The physical properties of the prepared emulgel formulas are shown in table

Table No. 2: Physical Properties of Prepared Tacrolimus Emulgel

Formula No.	Homogeneity and Consistency	Phase separation
F1	Excellent	None
F2	Excellent	None
F3	Excellent	None
F4	Excellent	None
F5	Excellent	None
F6	Excellent	None

pH Measurement

pH of Prepared Emulgel were measured by using pH meter. The pH of the emulgel formulation was in the range of 5.76-6.23 which considered acceptable to avoid the risk of skin irritation upon application to skin.

Table No.3: pH Study of Emulgel

Formulation	pH

F1	5.83
F2	5.76
F3	6.19
F4	6.23
F5	5.80
F6	6.1

Spreadability study of Emulgel

Table No.4: Spreading study of Emulgel

Formulation	Spreadability (gm.cm/sec)
F1	18.8 ± 0.6
F2	29.2 ± 0.3
F3	35.5 ± 0.1
F4	32.3 ± 0.7
F5	30.2 ± 0.1
F6	21.6 ± 0.4

The Spreadability value of batch F1-F6 was depicted in the Table. The formulation F3 exhibited high spreading coefficient of 35.5 ± 0.1gcm/s. The Spreadability is dependent on the concentration of polymer and viscosity of the formulation. All formulation Spreadability results were acceptable.

Multi-Speed Viscosity Measurement

The maximum viscosity was observed in F3, that contains CP 940 and Liquid Paraffin, this could be explained by the higher molecular weight of the CP 940 in comparison with the other formulas and also refer to the addition of the neutralizing agent Triethanolamine in CP 940 formulas. In gel systems, consistency depends on the ratio of solid fraction, which produces structure, to liquid fraction. The profiles showed that as the share stress increased, the normally arranged molecules align their long axes in direction of flow orientation reduce the internal resistance of material and hence decrease viscosity .The results showed that within each type of polymer the viscosity increased as the concentration of polymer increased. Most of the prepared formulations are of good acceptable rheological profile ranged mentioned in many literatures, which is 3349-3584mPas. However, the attentiveness of viscosity increases with the understanding of the extent of increased viscosity on drug release retardation and stability of formulas prepared.

Drug content

The drug content of the formulated emulgel was estimated spectrophotometrically at 293 nm. The results were presented in table 7.7 and they were within the official limits.

Table No.5: Drug Content of Prepared Tacrolimus Emulgel

Sr. No.	Formulation	Drug content (%)
1	F1	96.82
2	F2	97.65
3	F3	98.25
4	F4	98.06
5	F5	92.07
6	F6	81.13

In-Vitro Drug Release Profile

We found that, the following order of the formula F3> F4 > F5> F1 > F2 > F6, the increased. highest percent of release over 60 min. The release percent was decreased when the concentration of the gel base

Table No.6: In Vitro Drug Release Profile of Prepared Tacrolimus Emulgel

Time (Min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
10	45.78± 0.76	62.31 ± 0.57	42.73 ± 0.56	46.98 ± 0.93	21.21 ± 0.69	51.79 ± 0.62
20	64.37 ± 0.70	71.35 ± 0.41	63.34 ± 0.44	58.60 ± 0.55	38.18 ± 0.55	55.78 ± 0.76
30	73.29 ± 0.61	80.93 ± 0.72	66.34 ± 0.67	64.37 ± 0.70	47.25 ± 0.51	59.21 ± 0.69
40	90.30 ± 0.47	90.41 ± 0.56	71.25 ± 0.51	70.29 ± 0.61	64.18 ± 0.54	63.17 ± 0.22
50	93.22 ± 0.51	94.30 ± 0.34	91.43 ± 0.92	81.88 ± 0.90	86.20 ± 0.46	90.30 ± 0.47
60	97.10 ±0.58	96.30 ± 0.17	99.37 ± 0.11	98.48 ± 0.66	97.28 ± 0.70	96.21 ± 0.46

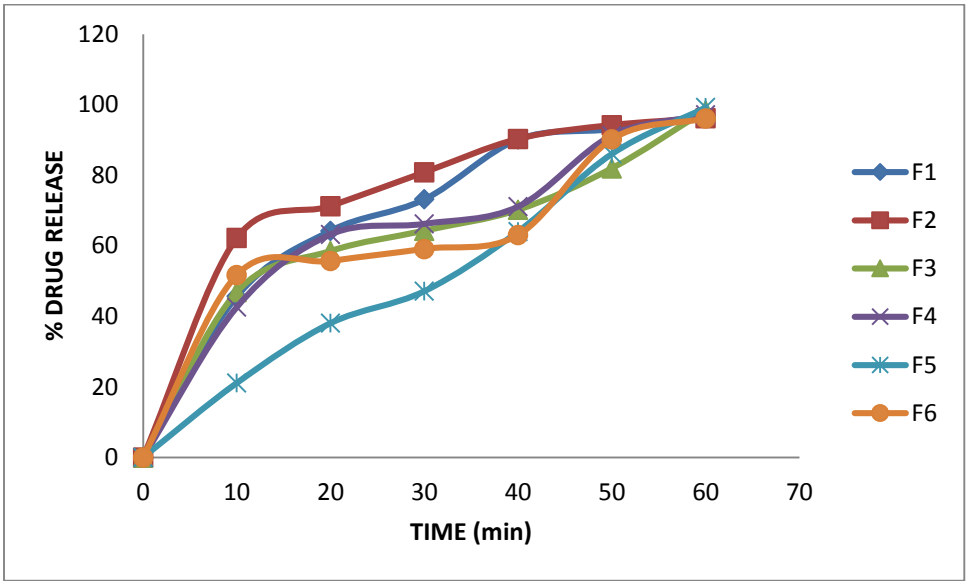

Figure No.2: Invitro Drug Release of Tacrolimus Emulgel Kinetics Release study

Table No.7: Release kinetics of Tacrolimus Emulgel

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
F1	0.852	0.981	0.986	0.922
F2	0.729	0.984	0.937	0.884
F3	0.992	0.717	0.919	0.987
F4	0.867	0.751	0.973	0.912
F5	0.876	0.885	0.979	0.923
F6	0.839	0.836	0.928	0.900

Selection of Optimum Formula

All the prepared formulas are subjected to characteristic's analysis. Stability on standings in order to select the optimum formula, Formula (F3) was selected as an optimum formula since it has the maximum release profile (99.37 %) after 60 min. in addition to pH value of (6.19) which is within the range of healthy skin pH. so, there is no irritation would be expected from this formula. Additionally (F3) has an acceptable physical properties, homogeneity, consistency, drug content and viscosity. In addition, for the selected formula (F3), the release fitted mostly on Zero order kinetics. The release rate is independent of the concentration of the drug. Their lease exponent value of First Order Kinetics equation (n) was 0.717 i.e. this suggests that the emulgel follows case anomalous (non-Fickian) diffusion (0.45< n<0.89).The Zero order kinetics, is considered a very desirable in drug release systems. Consequently, this formula was subjected to further studies like stability.

Stability Studies

The stability of Tacrolimus selected formula (F3) was studied at three different temperatures 30° C, 40° C and 50° C for three months. Samples the emulgel was taken at one month interval and was studied for drug content. After the stability study, formulation F3 doesn't show significant difference for physical properties, homogeneity, consistency, drug content and viscosity.

CONCLUSION

Tacrolimus is TLS (also FK-506 or Fujimycin) is an immunosuppressive drug which is mainly used in post organ transplant to reduce the activity of the patient's immune system against the risk of organ rejection. It is also used for atopic dermatitis, vitiligo and severe uveitis. Organoleptic properties, melting point determination, solubility studies, FT-IR frequencies showed that the Tacrolimus used was similar to the reported values. After the comparison of FTIR results, it was concluded that there was no incompatibility between drug and polymer. CP-940 was chosen as polymer of gel for the formation of Tacrolimus emulgel. In this study, six formulations were prepared by mixing equal quantities of a gel and emulsion portions. Each batch of the formulations was evaluated for melting point, FTIR study and the results were within the limit. The prepared formulations were also evaluated for physical properties and pH, Multi-speed viscosity measurement, drug content *in-vitro* drug release studies and stability study.

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