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R E S E A R C H A R T I C L E

Formulation and *In-Vitro* Evaluation of Tacrolimus Solid Dispersions

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A B S T R A C T

"In the present study Tacrolimus solid dispersions were formulated the standard curve of Tacrolimus was obtained and good correlation was obtained" with R^2 value 0f 0.999.the medium selected was pH 7.4 phosphate buffer. "Tacrolimus was mixed with various proportions of excipients showed no colour change at the end of two months proving no drug excipient interactions". The precompression mix of Tacrolimus solid dispersions were characterized with relevance angle of repose, bulk density, broached density, Carr's index and Hausner's magnitude relation. The precompression mix of all the batches indicating sensible to truthful flow ability and squeezability. Solid dispersions were ready with varied concentrations of carriers, the ready solid dispersions were compressed into pills by exploitation rotary tablet punching machine, and eight millimeter punch, with the hardness of four.5kg /cm2.The developed tablets were evaluated for varied internal control parameters. The tablets were passed all the tests. Among all the formulations F1 formulation containing, Drug and Peg 4000 within the magnitude relation of 1:0.25 showed sensible result that's ninety four.95 you bored with fifty minutes. Because the concentration of compound will increase the drug unleashes was faded. Whereas the formulations containing PEG 6000 showed less unleash. Therefore from the dissolution knowledge it absolutely was evident that F1 formulation is that the higher formulation.

Keywords: Tacrolimus, solid dispersions, PEG 4000, PEG 6000.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

The oral route of drug administration is the most common and preferred route of delivery due to convenience and ease of ingestion. From a patient's prospect, swallowing a dosage form is a comfortable means of taking medication. As a result, patient compliance is more effective with orally administered medications as compared with other routes of administration, for example, parenteral route. Although the oral route of administration is preferred, in case of many drugs it can be a problematic and inefficient mode of delivery for a number of reasons.

Limited drug absorption resulting in poor bioavailability is amongst the potential problems that can be overcome while delivering an active agent via the oral route. After administering a drug orally, it firstly dissolves in gastric media and then permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include:

- Enhancing solubility and dissolution rate of poorly water-soluble drugs and
- Enhancing permeability of poorly permeable drugs. Solubility is a predetermined and rate limiting step for absorption.

Drug has to enter in to the systemic circulation to exert its therapeutic effect. In recent technologies, innovation of combinatorial chemistry and high throughput screening (HTS) can effectively discover the new drugs which exhibit good pharmacological activities. However, 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility. In the Biopharmaceutical Classification System (BCS) (**table 1 and figure 1**) drugs with high membrane permeability and low aqueous solubility are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly for improving the oral absorption and bioavailability of BCS Class II drugs. Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi [1].

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. It was discovered in 1984 from the fermentation broth of a Japanese soil sample that contained the bacteria Streptomyces tsukubaensis. Tacrolimus is chemically known as a macrolide. It reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506 binding protein) creating a new complex. This FKBP12-FK506 complex interacts with and inhibits calcineurin thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription.

2. Materials and methods

Materials used in the work

Tacrolimus purchased from Dr. Reddys labs, PEG 4000, PE 6000, PVP K30 are purchased from Nihar traders pvt Ltd., Magnesium stearate, Aerosil, Microcrystalline Cellulose are purchased from Nihar traders pvt Ltd. Potassium dihydrogenortho phosphate from Finar chemicals Ltd. And Sodium hydroxide purchased from Himedia Laboratories.

Methodology

Preformulation Studies: Pre formulation involves the appliance of biopharmaceutical principles to the chemistry parameters of drug substance area unit characterized with the goal of coming up with optimum drug delivery system.

Drug-Excipients compatibility studies:

Drug Excipients compatibility studies were applied by combination the drug with varied excipients in several proportions (in 1:1 quantitative relation were ready to own most probability interaction between them) was placed during a phial, and closed with rubber stopper and sealed properly.

Analytical methodology development for Tacrolimus:

a) Determination of absorption maxima

A spectrum of the operating standards was obtained by scanning from 200-400nm against the chemical agent blank to mend absorption maxima. The λmax was found to be 235nm. Thus all additional investigations were applied at an equivalent wavelength.

b) Preparation of ordinary graph in pH seven.4 medium

100 mg of Tacrolimus was dissolved in fuel five metric capacity unit, volumetrical flask build up to one hundred metric capacity unit of Phosphate buffer of pH seven.4, from this primary stock ten metric capacity unit was transferred to a different volumetrical flask created up to 100ml with Phosphate buffer of pH seven.4, from this secondary stock was taken on an individual basis and created up to ten metric capacity unit with Phosphate buffer of pH seven.4, to supply ten,20,30,40 and fifty µg/ml severally. The absorbance was measured at 235 nm by employing a actinic radiation spectrophotometer.

Formulation Development: Solid dispersions were ready by solvent evaporation methodology. Fuel was used as solvent. Tacrolimus dose was taken as 20mg.Water soluble polymers like PEG 4000 and PEG 6000 were elect as carriers. Drug and polymers were taken in several ratios explicit within the formulation chart (Table 2). The ready solid dispersions were had the sieve no twenty to induce uniform sized particles. The solid dispersions were mixed with needed quantities of dilutant, material and glidant. The mix was evaluated for precompression parameters.

Evaluation of tablets:

Pre compression parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the

powder cone is measured and angle of repose is calculated using the following equation. [55]

$\tan \theta = h/r$ …… (1)

Where, h and r are the height and radius of the powder cone.

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula. [56]

Bulk density = M/V_0 ……..… (2)

M = Powder mass

V_0 = apparent unstirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula. [57]

Tapped density=M/V_f ..... (3)

M =weight of sample power taken

V_f=tapped volume

4. Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 …… (4)

5. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation. [58]

$H = \rho T / \rho B$ …….. (5)

Where ρT = tapped density, ρB = bulk density

Post compression parameters:

a) Thickness: The thicknes of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets were indiscriminately chosen from every batch and severally weighed. The common weight and variance 3 batches were calculated. It passes the check for weight variation check if less than 2 of the individual pill weights deviate from the common weight by over the allowed proportion deviation and none deviate by over double the proportion shown. it absolutely was calculated on Associate in Nursing electronic scales.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

Friability = ($[w_O - w] / w_O) \times 100$

Where;

w_O = weight of the tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions.

d) Assay:

The content of drug in five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in 0.1 N HCl by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectro-photometrically at 284 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Tacrolimus tablets

Drug unleash from Tacrolimus tablets decided by victimisation dissolution take a look at u. s. accumulation (USP) twenty four kind II (paddle). The parameters used for activity the dissolution were pH scale seven.4 medium because the dissolution medium of amount 900ml. the full study is being meted out at a temperature of 370 C and at a speed of 50rpm.

5ml aliquots of dissolution media were withdrawn whenever at appropriate time intervals (5, 10, 20 minutes.) and replaced with recent medium. Once retreating, samples were filtered and analyzed once acceptable dilution by UV photometer. The concentration was calculated victimisation normal standardization curve.

3. Results and discussion

Determination of λ max:

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 235 nm.

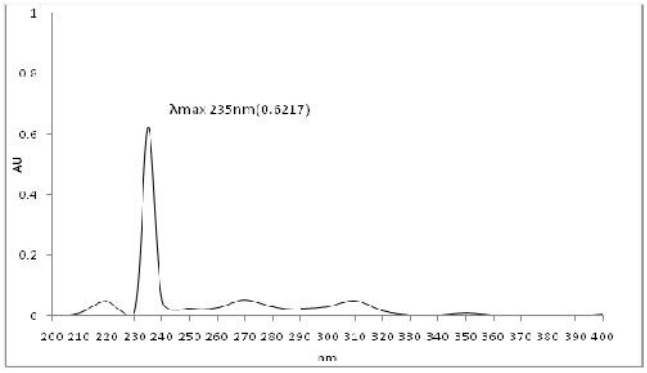

Fig6: Spectrum showing absorption maxima.

Calibration curve of Tacrolimus:

The standard curve of Tacrolimus was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 7.4 phosphate buffer. The standard graph values of Tacrolimus are tabulated as below.

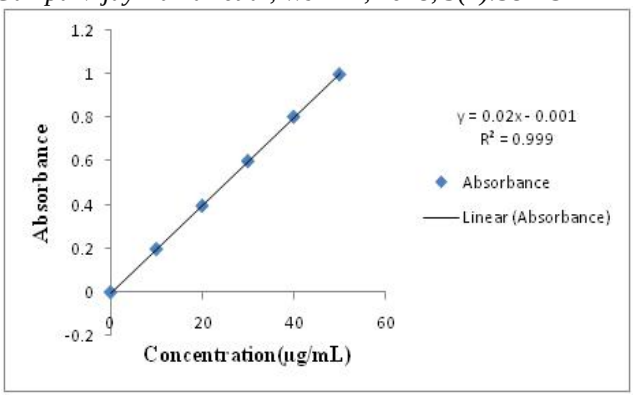

Fig no 7: Standard Curve of Tacrolimus

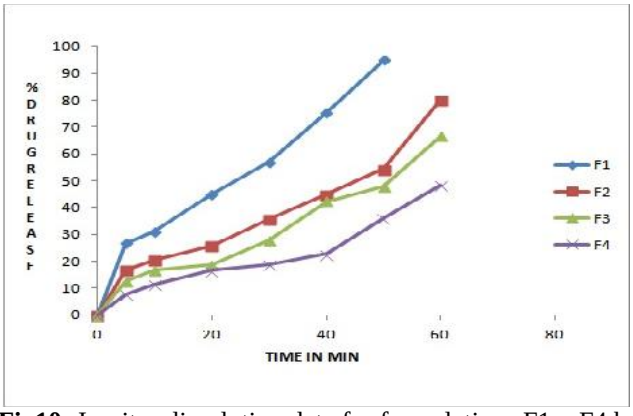

Fig10: In-vitro dissolution data for formulations F1 – F4 by using PEG 4000 Polymer

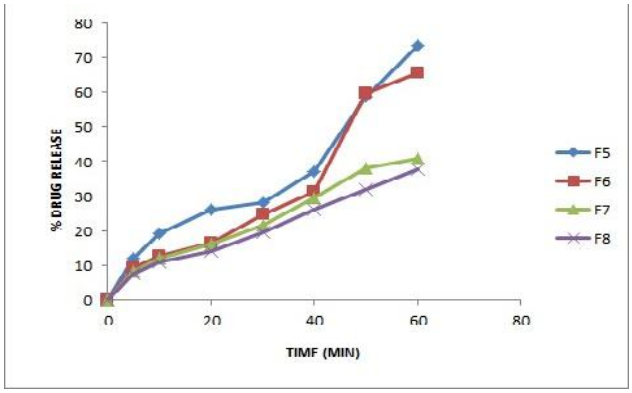

Fig 11: In-vitro dissolution data for formulations F5– F8 by using PEG 4000 Polymer

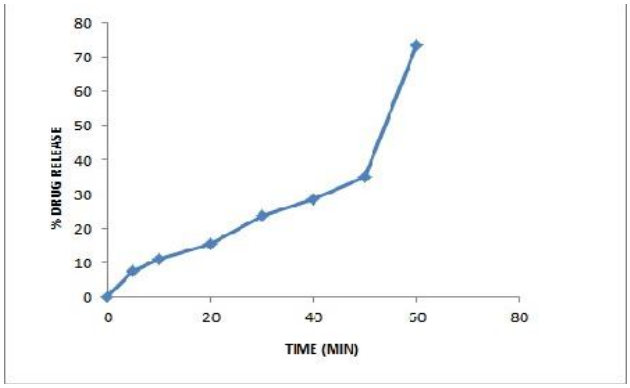

Fig12: In-vitro dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer.

Evaluation of Precompression Blend:

The precompression blend as solid dispersions was characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

In vitro release studies:

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 7.4 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 235nm.

Among all the formulations F1 formulation containing, Drug and Peg 4000 within the magnitude relation of 1:0.25 showed sensible result that's ninety four.95 you tired of fifty minutes. Because the concentration of compound will increase the drug unleashes was slashed. Whereas the formulations containing PEG 6000 showed less unleash. thus from the dissolution information it absolutely was evident that F1 formulation is that the higher formulation. The formulation containing combination of PEG 4000& 6000 was conjointly not manufacturing desired share drug unleash. The formulation is following zero order unleash dynamics.

4. Conclusion

The normal curve of Tacrolimus was obtained and smart correlation was obtained with R2 price zerof 0.999. The medium chosen was pH scale seven.4 phosphate buffer. Tacrolimus was mixed with numerous proportions of excipients showed no color amendment at the tip of 2 months, proving no drug-excipient interactions. The precompression mix of Tacrolimus solid dispersions were characterized with reference to angle of repose, bulk density, abroach density, Carr's index and Hausner's magnitude relation. The precompression mix of all the batches indicating smart to honest flowability and softness. Solid dispersions were ready with numerous concentrations of carriers, the ready solid dispersions were compressed into pills by exploitation rotary tablet punching machine, and eight millimetre punch, with the hardness of four.5kg /cm2.The developed tablets were evaluated for numerous internal control parameters. The tablets were passed all the tests. Among all the formulations F1 formulation containing, Drug and Peg 4000 within the magnitude relation of 1:0.25 showed smart result that's ninety four.95 you tired of fifty minutes. Because the concentration of compound will increase the drug unharness was shriveled. Whereas the formulations containing PEG 6000 showed less unharness. Thence from the dissolution information it absolutely was evident that F1 formulation is that the higher formulation. By conducting additional studies like in-vivo studies, diagnosis and clinical studies we are able to commercialize the merchandise.

Table 2 : Formulation table showing various compositions

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	5	5	5	5	5	5	5	5	5
PEG 4000	10	20	30	40					20
PE 6000					10	20	30	40	20
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

Total weight of tablets = 100 mg

The tablets were prepared by using 8 mm flat surfaced punch.

The hardness of the tablets was maintained as 4.5 kg/cm^2.

Table 3: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Table 4: Scale of Flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 6: Physical properties of pre compression blend

Formulation Code	**Angle of repose (Θ)**	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Carr's Index (%)**	**Hausner's ratio**
F1	25.10°	0.54±0.01	0.52±0.01	9.42±0.12	1.02±0.02
F2	25.43°	0.55±0.03	0.61±0.02	9.41±0.13	1.10±0.01
F3	25.41°	0.55±0.02	0.68±0.03	10.03±0.19	1.13±0.06
F4	26.40°	0.52±0.01	0.62±0.06	10.14±0.02	1.16±0.01
F5	27.12°	0.59±0.03	0.64±0.03	10.35±0.13	1.17±0.03
F6	25.31°	0.60±0.03	0.65±0.04	10.12±0.34	1.11±0.06
F7	26.11°	0.57±0.01	0.64±0.01	9.93±0.11	1.13±0.03
F8	26.15°	0.54±0.03	0.59±0.03	10.12±0.02	1.12±0.01
F9	26.10°	0.55±0.01	0.62±0.03	10.21±0.13	1.13±0.03

All the values represent mean ± Standard deviation (SD), n=3

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