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Formulation and evaluation of immediate release solid dosage of sirolimus drug

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ABSTRACT

By the application of factorial design a best formulation was optimised for the immediate release of Sirolimus drug. The optimised formulation was evaluated for its physicochemical evaluation and in vitro drug release, in which it showed better formulation when compared with the marketed product. The formulations F 11, followed first order kinetics, Krosmeyer-Peppas exponential coefficient „n" > 1 indicates that the release was governed by Super case II transport.

Keywords: Sirolimus; Immediate release; First order Kinetics.

1. INTRODUCTION

Sirolimus is an immunosuppressive agent. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*, 15*E*,17*E*, 19*E*, 21*S*,23*S*,26*R*,27*R*,34a*S*)- 9,10,12,13,14,21,22, 23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27 -dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl] -1-methylethyl]-10,21-dimethoxy -6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4] oxaaza cyclo hentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$.

Sirolimus (also known as rapamycin) is a macrocyclic lactone produced by *Streptomyces hygroscopicus* that inhibits interleukin (IL)-2 and other cytokine receptor-dependent signal transduction mechanisms [1]. Sirolimus is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged ≥ 13 years receiving renal transplants [2]. Unfortunately, sirolimus belongs to the biopharmaceutics classification system (BCS) class II drug category because of its low solubility and high permeability [3]. To improve the biological performance of sirolimus, various formulations, such as inclusion complexes with cyclodextrins, liposomal formulations, nanocrystals, and solid dispersion, have been developed [4–8]. In fact, the oral bioavailability of sirolimus can be improved by enhancing *in vitro* supersaturation via an amorphous solid dispersion. The present study aims to at developing an Immediate Release Tablet Dosage form of Sirolimus to improve the solubility profile of poorly soluble drug by converting into the surface solid dispersion.

2. EXPERIMENTAL

2.1. Materials

Sirolimus (purity 99.4%) and all other additives used were purchased from Sigma-Aldrich, India.

2.2. Development of Sirolimus immediate release tablet

Based on the previous report of us for the formulation of immediate release of Sirolimus tablet, we have optimised a best formulation using factorial design. Optimised formula was given in table 1.

Table - 1: List of Ingredients

Ingredients	F11
Neutral carrier	90
Model Drug	2
d-l-alpha tocopherol	0.2
Poloxamer 188	6
Kollidon K 30	1
Magnesium stearate	0.75
Kollidon CL	11.75
Avicel 200	38.3
Total	150

2.2.1. Preparation of drug dispersion

- The Model drug was weighed.

- DCM and Ethanol were weighed in combinational ratio of 4 parts to 1 & mixed.
- Poloxamer 188 was weighed (40#)
- Model drug and Poloxamer 188 was dissolved in the DCM and Ethanol in glass beaker with help of stirring by glass rod.
- D-l-alpha tocopherol and Kollidon K 30 was added to step 4 and dissolved.

2.2.2. Drug loading on Neutral carrier

- Neutral carriers were added to the FBP and were allowed to fluidize.
- The total quantity of drug dispersion was on to the fluidized carrier.

2.2.3. Preparation of lubricated blend

- Addition of extragranular Avicel 200 (30#) and Kollidon CL (30#) was done to the drug loaded carriers and blended for 10 mins.
- Magnesium stearate (60#) was added to the above blend and blended for 5 mins.

Blends were compressed into tablets on a rotary tablet compression machine.

2.3. Evaluation of tablets

The formulated tablets were evaluated for the following physicochemical parameters.

2.3.1. Hardness

Tablets require certain amount of strength to have a resistance from breakage, while transportation and handling before use. It was measured by Monsanto Hardness Tester (Tab machines, India)[9].

2.3.2. Friability

Friability was performed by using friability test apparatus (Electrolab, ET2, India). Specified number of tablets were weighed and placed in the tumbling chamber and rotated for four minutes at a speed of 25 rpm. During each revolution, tablets fall from a distance of 6 inches to undergo shock. After 100 revolutions the tablets are dusted and reweighed. The loss in weight indicates friability and loss of less than 1% in weight is considered to be acceptable [10]. It was determined by the following formula.

$$F = W1 – W2 / W1 \times 100$$

Where, W1 = Initial weight of tablets

W2 = Final weight of tablets

2.3.3. Disintegration time

The disintegration time was performed using an USP disintegration test apparatus (TD2, Tab machines, India) with distilled water at 37±0.5°C. The disintegration time was taken to be the time when no granules of any tablets were left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets were recorded and mean value was reported [11].

2.3.4. Dissolution study

Dissolution studies were conducted to determine the release pattern of the product. Dissolution test of all the batches were carried out using USP type II apparatus and estimation of Sirolimus by using the following HPLC Chromatographic condition.

The RP-HPLC with a variable wavelength ultraviolet spectrophotometric detector set at 278 nm. System Gold software was used for data acquisition and system Gold nouveau software was used for data reporting and analysis. For the preliminary analysis different columns in combination with different solvent systems were tried out. Analytical column used for analysis was Knauer ODS 5 mm, 4.6 × 150 mm. Column temperature was set at 55°C. The mobile phase was a mixture of 70% ACN and 30% ammonium acetate buffer (The buffer was prepared by dissolving 0.8 g ammonium acetate in 1000 ml water, adjusted to pH 5.8 with NaOH 1N). Injection volume was 150 µl which injected into the column using a Hamilton injector syringe and the isocratic flow rate was set at 1.5 ml/min. SRL was detected by UV absorption at 278 nm.

2.3.6. Release kinetics

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data. Mathematical models are

Zero Order Kinetics

The graph was plotted as cumulative % drug release Vs Time where the drug release rate is independent of its concentration.

$$C = K\theta t$$

Where,

$K\theta$ = Zero order rate constant expressed in units of concentration/time

t = Time in hours.

First order Kinetic model

The graph was plotted as log cumulative % of drug remaining Vs Time, where release rate is concentration dependent

$$\text{Log } C = \log C_0 - Kt / 2.3030$$

Where,

C_0 = Initial concentration of drug

K = First order constant

t = Time in hours.

Higuchi kinetics

Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The graph was plotted as cumulative % drug released Vs square root of time.

$$\mathbf{Q = Kt_{1/2}}$$

Where,

K = Constant reflection design variable system

$t_{1/2}$ = Time in hours.

Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one then the particular dosage form is considered to follow Higuchi kinetics of drug release.

Hixson-crowell erosion equation

It describes the drug release with changes in the surface area and the diameter of particles the data were plotted using the Hixson and crowell rate equation. The graph was plotted by cube root of % drug remaining in matrix Vs time.

$$\mathbf{Q_0^{1/3} - Q_t^{1/3} = KHCt}$$

Where,

Qt = Amount of drug released in time t

Q0 = Initial amount of drug in tablet.

KHC = Rate constant for Hixon crowell rate equation

Korsmeyer-Peppas equation

To find out the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$Mt / M\alpha = Kt\ n,$$

$$\text{Log } Mt / M\alpha = \log K + n \log t$$

Where,

Mt / Mα = Fraction of drug released at time

K = Kinetic rate constant

t = Release time

n = Diffusion exponent indicative of the mechanism drug release.

This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log Time.

3. RESULTS AND DISCUSSION

3.1. Formulation of Optimized Batch:

An optimized batch as per Stat-Ease was prepared with the following concentrations of the factors. The formulation was prepared as per table 1 .

Table - 2: Concentration of factors of Optimized batch

FACTOR 1 **A-Poloxamer 188**	FACTOR 2 **B-Kollidon CL**	FACTOR 3 **C-Magnesium Stearate**
4	10.5	0.5

3.2. Evaluation of Tablets of Optimized batch

Tablets were evaluated to predict the effect of 3 formulation factors on the overall characteristics of the finished product.

3.2.1. Physicochemical evaluation

The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and disintegration time. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The results were shown in table 3.

Table - 3: Evaluation of tablets of optimized batch F 11

Parameters	Model drug	Reference product
Weight (gm.)	154.9±0.3	155±0.40
Thickness (mm.)	3.43±0.20	3.42±0.20
Hardness (N)	48.0±0.90	50.0±0.70
Friability (%)	0.52±0.30	0.51±0.20
Disintegration time(sec.)	86.0±2.00	88.0±2.00

3.2.2. *In vitro* drug release studies

In vitro dissolution studies (Table 4 and Figure 1) of the formulation of immediate release sirolimus was carried out in pH 7.4 phosphate buffers for 120 mins. Optimized formulation F11 correlates with the marketed product. The

optimized batches were found to be close to that of the innovator tablets. The formulations F11, followed first order kinetics, Krosmeyer-Peppas exponential coefficient n > 1 indicates that the release was governed by Super case II transport (Table 5).

Table - 4: Dissolution Profile of Optimized batch

Batch No. F 11	10	20	30	45	60	120
Model drug	84.3	87	90.2	94.1	97.5	99.6
Reference Product	85.3	89.8	91.7	95.5	98.3	98.8

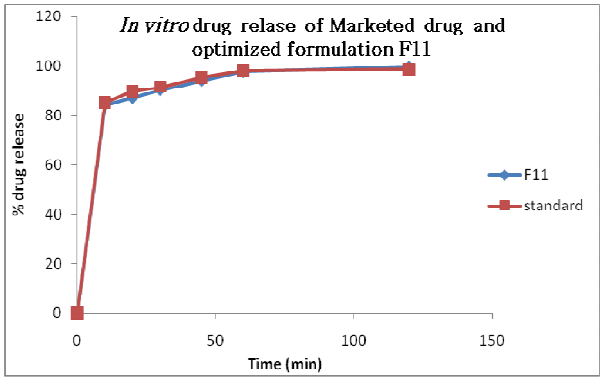

Figure - 1: Dissolution profile of optimized batch F 11.

Table - 5: Release kinetic parameters

Formulation		F11	Standard
Zero order r^2		0.987	0.947
First order r^2		0.997	0.974
Higuchi model r^2		0.964	0.976
Korsmeyer Model	n	0.059	0.066
	r^2	0.984	0.992
Hixson-Crowell Cube root r^2		0.991	0.966

4. CONCLUSION

From the above experimental results it can be concluded that immediate release tablets of Sirolimus can be prepared by using different proportion & combination of superdisintegrants and binder and we selected F11 as best formulation based on the optimization result. Formulation (F11) showed better drug release when compared to other formulations and showed fair flow properties. The formulations F11, followed first order kinetics, Krosmeyer-Peppas exponential coefficient „n" > 1 indicates that the release was governed by Super case II transport.

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