Original Article

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A Tablet Matrix with *Hibiscus rosa* Sinensis Leave Mucilage for Effective Treatment of Rare Lymphangioleiomyomatosis Using Sirolimus

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Abstract

Using a blend of herbal and synthetic polymers, the authors aim to extend the release of Sirolimus from the tablets. Sirolimus was used as a model drug, Hydroxy Propyl Methyl Cellulose was used as a synthetic polymer, and mucilage from *Hibiscus rosa* sinensis leaves was used as a natural polymer in this study. In addition to treating Lymphangioleiomyomatosis damage and suppressing body rejection toward transplanted organs, sirolimus is also an orphan drug. The Sirolimus matrix tablets are made with a combination of *H. rosa* sinensis leaf mucilage and Hydroxypropyl Methyl Cellulose. We assessed the flow properties of the blend and classified the designed tablets for official and non-official tests, including Sirolimus discharge. Sirolimus matrix tablets have passable pre- and post-formulation parameters with good Sirolimus content. A chemical interaction between Sirolimus and the polymers used in the study was not observed. Researchers also discovered that *H. rosa* sinensis leaf mucilage can be a good polymer in combination with other polymers for prolonged drug release.

Keywords: *Hibiscus rosa* sinensis, Matrix, Release, Sirolimus, Tablets.

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1. Introduction

In some parts of the world, orphan diseases are rare diseases that do not have a market large enough to attract support and funding for finding cures, except by the government granting economically advantageous conditions for creating and selling such treatments. A condition known as Lymphangioleiomyomatosis (LAM) damages the alveoli, making the blood unable to get enough oxygen (1). As of right now, there is no cure or drug available that can improve lung function LAM is an orphan disease. The only solutions to this problem are oxygen therapy and lung transplantation. But organ transplantation causes rejection by the body and needs immunosuppressive drugs (2, 3).

As the name implies, an orphan drug is a pharmaceutical agent developed to treat conditions that, because they are so rare, would not be economically feasible without government assistance. This type of disease is referred to as an orphan disease. After organ transplantation, sirolimus (SRS) is prescribed to patients as an immunosuppressant to prevent anti-rejection reactions in their bodies. The drug SRS is used to treat orphan diseases such as LAM, which is an orphan disease. SRS is a BCS class II drug with solubility problems (4).

Because of its many benefits, such as ease

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of administration, patient compliance, and cost-effectiveness, oral drug delivery is considered an effective method for treating a number of fatal diseases.

As the conventional dosage form have some issues like frequent dosing and difficult to maintain the drug concentration in the therapeutic window that can be resolved by sustained release systems.

Sustained release drug delivery has several advantages over conventional dosage forms, such as improving patient compliance because it requires less frequent administration of the drug, reducing fluctuations in steady-state drug levels, maximising the therapeutic effectiveness of potent drugs, and reducing healthcare costs.

Matrix tablets can be prepared by blending drug with release retarding polymers on the other hand membrane systems involves coating of drug core with release controlling membrane. The system for sustaining drug discharge from the tablet matrix is simple and effective, with no dose dumping.

Many polymers have been discovered and are available for making matrix systems, but they are costlier. Instead of going in search of new artificial polymers, exploring and finding a natural one is more economical and abundant. There are multiple techniques that can be used to realise extended drug delivery systems with controlled SRS discharge, but the matrix system is the simplest, cheapest, and most effective of these (5).

Hibiscus rosa sinensis belongs to the tribe Hibiscus of the family Malvaceae and is a species of tropical hibiscus. Tropical and subtropical regions are widely cultivated, but it is unknown where it comes from in the wild, so its native distribution is unknown. Most likely, it originated in tropical Asia. Tropical and subtropical regions cultivate this ornamental plant widely.

Herbal leaf mucilage of *Hibiscus rosa* sinensis leaves can be used instead of polymers because it is economical and easily available (6).

In this investigation, the authors used *H. rosa* sinensis leaves mucilage as a release retardant polymer to check its assets for sustaining the discharge of SRS from the matric tablets.

2. Materials and methods

2.1. Identification of Sirolimus

SRS was identified based on its physical appearance, melting point, and solubility (7).

2.2. Sirolimus calibration curve

Ten mg of SRS was dissolved and made the volume required in 50ml volumetric flask with methanol with an aid of 0.4% SLS. Solutions from 2-12 µg/ml were made and measured at 278 nm in UV-Vis spectrophotometer and the absorbance so obtained and the concentrations were used to plot calibration curve for the estimation of SRS.

2.3. Extraction of mucilage

As described by Ahad et al., the extraction and purification were performed. We boiled fresh H. rosa sinensis leaves after washing, soaking, and soaking them. Filtered, isolated with Acetone, dried, sieved with #80 (8).

2.4. Drug excipient compatibility studies

2.4.1. Differential scanning calorimetry (DSC)

SRS and the blend were analyzed by DSC using a Perkin Elmer FTIR spectrophotometer to check for drug-excipient interactions. In separate aluminum pans, samples were heated at 10 °C/min from 50-300°C under nitrogen at a flow rate of 50 ml/min.

2.4.2. FTIR study

FTIR spectra and distinctive peaks of SRS and SRS with excipient blend were made by the Bruker IR spectrophotometer.

2.5. Calibration curve

SRS calibration curve (9) shows a slope of 0.0745x-0.0099 with a regression (R2) value of 0.9996 (Figure 1).

SRS was mixed with HRLM, lactose and MCC with a starch paste to get a wet mass. Later, it passed through sieve #6/12 to get granules and dried, and talc and silicon dioxide were added and compressed to get tablets (table 1).

2.6. Pre formulation studies

The authors determined whether dried granules moved easily from hopper to tablet dyes for compression by checking flow patterns (10, 11).

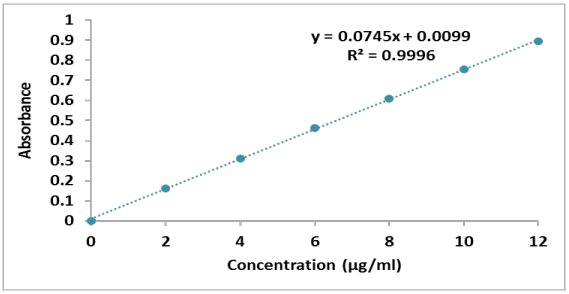

Figure 1. Calibration curve of Sirolimus.

Table 1. Composition of the Tablets.

Ingredients (mg)	Formulation					
	F-1	F-2	F-3	F-4	F-5	F-6
Sirolimus	1	1	1	1	1	1
Hibiscus rosa sinensis leaves mucilage	10	20	30	40	50	60
Lactose	15	15	15	15	15	15
Micro Crystalline Cellulose	64	54	44	34	24	14
Silicon dioxide (colloidal)	5	5	5	5	5	5
Talc	5	5	5	5	5	5
The weight of the tablets	100	100	100	100	100	100

2.7. Post formulation studies

The tablets were characterized for by following parameters(12, 13).

2.7.1. Thickness of tablets

A sliding caliper was used to measure the thickness of 5 tablets from each batch.

2.7.2. Uniformity of weight

Each batch was weighed based on the weight of 20 tablets, and the mean weight was also determined. Unorthodoxy was then calculated for individual weights.

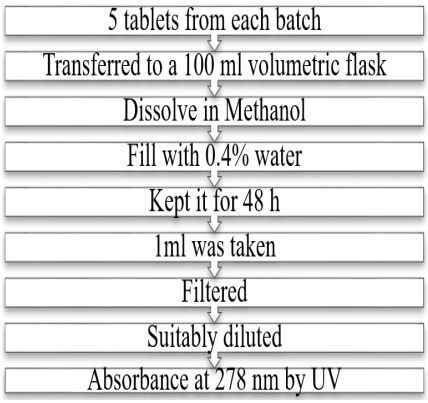

Figure 2. Procedure for determining the drug content in the tablets

2.7.3. Tablet hardness

From each batch, five tablets were randomly selected and their hardness was measured using a Pfizer tester.

2.7.4. The loss on friability

The authors allowed 10 pre-weighed tablets from each batch to fall 100 times (4 min) from 6 inches and weighed them after dusting.

2.7.5. Determination of drug content in tablets

SRS content in the PRT was hindered by the process explained in figure 2 (14, 15).

2.7.6. In vitro dissolution studies

The dissolution conditions adopted for drug dissolution(16) were concise in table 2.

3. Results

3.1. API characterization

SRS appearance, melting point, and solubility are listed in figure 3.

3.2. Compatibility studies

DSC thermograms so obtained with SRS and the excipient combination were represented in

Table 2. In vitro dissolution conditions.

Parameter	Description
Apparatus	USP-II
Rotation (rpm)	100
Medium	0.1 M HCl for first 2 h then in pH 6.8 phosphate buffer solution for 10 h
Volume	900 ml
Temperature	37±0.5°C
Sampling at	1, 4, 6, 8, 10 and 12 h
Wavelength	278 nm

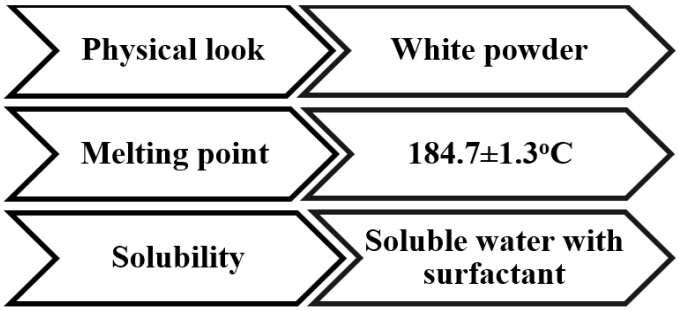

Figure 3. Sirolimus identification parameters.

Table 3. DSC thermograms details of drug and polymers.

DSC sample	Endothermic events (°C)			ΔH Fusion	Ref
	T onset	T peak	T end	Enthalpy (J)	
Sirolimus	178.4	185.5	195.6	-389.37	An endothermic peak
Sirolimus+ Polymers	171.3	181.8	193.7	-358.84	A shift in peak to left due to positive blending of Sirolimus with polymers

table 3.

According to the FTIR spectra, the typical SRS bands were not reformed in the physical mixtures, which implies that HPMC or HRLM have no negative relation with SRS.

3.3. Pre formulation studies

The flow parameters of the granules were illustrated in table 4.

3.4. Post formulation studies

According to the PRT, the drug and excipients are added and blended systematically, which is represented by a uniform thickness (5 mm) and weight. There was a 1% loss in friability, and the hardness was greater than 4 kg/cm2, indicating that the PRT is extremely strong. In PRT, the SRS content was satisfactory, according to specifications (Table 5). In vitro, it appears that SRS is released from the formulation in a controlled manner. F-5 was the only formulation to exhibit prolonged controlled discharge (Figure 4).

3.5. Discharge kinetics and mechanism

In order to understand the mechanism of discharge and kinetics of SRS-optimized formulations, F-5 was fitted into mathematical models, and n R2 values were obtained for zero-order, first-order, Hixson-Crwell's, and Korsmeyer-Peppa's models (Table 6). The results of this study indicate that no fickian discharge occurred from the devices, since the "n" value was > 0.5 and fit the Korsmeyer Peppas model.

4. Discussion

The SRS was in white, and the melting

Table 4. Flow parameters of the granules

	Flow properties				
Formulation	Angle of repose (o)	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F-1	26.37±0.04	0.521±0.05	0.545±0.02	4.403±0.09	1.046±0.01
F-2	29.55±0.11	0.522±0.03	0.569±0.03	8.260±0.15	1.090±0.02
F-3	24.38±0.21	0.489±0.04	0.521±0.04	6.142±0.04	1.065±0.03
F-4	28.49±0.12	0.456±0.09	0.501±0.04	8.982±0.12	1.098±0.05
F-5	27.01±0.19	0.465±0.06	0.510±0.02	8.823±0.02	1.096±0.01
F-6	26.17±0.16	0.415±0.04	0.451±0.07	7.982±0.19	1.086±0.06

Readings in mean ±SD; The number of trials (n=3)

Table 5. Physical Characteristics of the matrix table.

Formulation	Physical parameter				
	Uniformity of weight (mg)	Hardness (cm2)	Thickness (mm)	Friability (%)	Assay (%)
F-1	252.8±1.59	8.8±0.07	4.56±0.04	0.51±0.02	98.5±4.18
F-2	251.4±1.52	9.2±0.06	4.51±0.05	0.27±0.01	96.3±3.19
F-3	250.1±1.09	7.8±0.08	4.59±0.09	0.41±0.04	97.4±2.15
F-4	252.7±2.58	8.2±0.08	4.53±0.07	0.47±0.02	98.7±4.15
F-5	251.3±0.85	10.0±0.01	4.52±0.09	0.54±0.02	99.6±5.25
F-6	250.8±0.82	11.7±0.07	4.51±0.03	0.32±0.02	98.4±2.36

Values in mean ±SD; The number of trials (n=3).

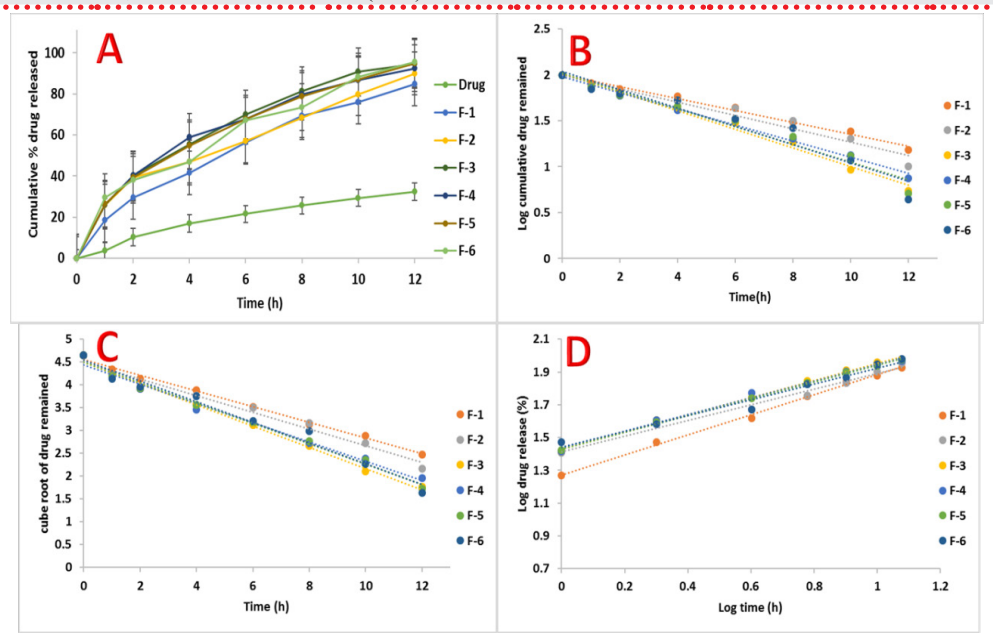

Figure 4. A) Zero-order, B) First-order, C) Hixon-Crowell's, and D) Korsmeyer Peppas plots of matrix tablets.

point and solubility confirmed that the gifted sample was as per the monograph of SRS (17).

In the DSC results, SRS showed a peak at 185.5 ºC, with a shift in peak to the left due to positive blending of SRS with polymers (peak at 181.8 ºC). No new peaks were observed in the DSC of the SRS thermogram when compared to pure SRS, indicating that SRS is not incompatible with the polymers used (18). Additionally, FTIR studies revealed that the characteristic peaks and stretch-

Table 6. Kinetic data of the matrix tablets.

Formulation	Model with correlation values				
	Zero-order	First order	Hixson Crowell's	Korsmeyer Peppas	Assay (%)
	R2	R2	R2	R2	n
PRT-1	0.9081	0.9916	0.9847	0.9994	0.5984
PRT-2	0.9315	0.9607	0.9729	0.9937	0.4958
PRT-3	0.9153	0.9757	0.9867	0.9974	0.5157
PRT-4	0.8877	0.9815	0.9915	0.9988	0.5245
PRT-5	0.9009	0.9767	0.9889	0.9958	0.5326
PRT-6	0.9158	0.9709	0.9873	0.9897	0.4925

es in SRS spectra were found undisturbed in the physical mixtures, which implies that HPMC and HRLM have no negative relationship with SRS.

The AR of formulations was <30, which represents the very good flow properties of the granules so made for compression (19). The flow properties were further confirmed with Hausner's ratio as these values were 1.10 (20).

The so-formed granules were compressed into tablets that were uniform in size and shape. The hardness was > 4 kg/cm2 and the loss on friability was 1%, which illustrates that the formed tablets were intact and mechanically strong (21). The tablets were also found to have satisfactory drug content.

When the results of drug release were studied using mathematical formulae, they indicated that no fickian discharge occurred from the devices since the "n" value was > 0.5 and fit the Korsmeyer-Peppas model.

5. Conclusion

In this study, the authors observed that Sirolimus matrix tablets cover the emission rate for a long period of time (> 12 h) with increased bioavailability and dose. It was also demonstrated that H. rosa sinensis leaf mucilage can be a good polymer that can function with HPMC for controlling drug discharge with reduced adverse effects and cost, and with improved patient satisfaction and effectiveness.

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Conflict of Interest

The authors have no conflict of interest.

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