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SOLUBILITY ENHANCEMENT OF RIFAMPICIN BY USING LIQUISOLID TECHNIQUE

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Abstract

Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include liquisolid technique, micronization, nanonization, sonocrystallization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, co-crystallisation, complexation and drug dispersion in carriers. The "Liquisolid" technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability. Rifampicin is an orally administered broad-spectrum anti tubercular drug. It is freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride. Liquisolid formulations were prepared by Avicel PH 102 as carrier material and Aerosil 200 as coating material. PEG 400, PG and Polysorbate 80 were used as liquid vehicle. Absence of significant drug-carrier interaction was confirmed by IR studies. High drug content and high dissolution rate were observed in F2.

INTRODUCTION:

Since the implementation of combinatorial chemistry and high throughput screening for the investigation of new chemical entities, the molecular weight and lipophilicity of drugs increase and this in turn decreases water solubility. Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption. Therefore, new technologies increasing the solubility and thus drug release are looked for [1]. Release enhancement of poorly soluble drugs may be achieved by an increase in the drug solubility, the drug surface area, or by formulating the drug in its dissolved state: Several methodologies such as micronization, co-grinding, formulation of inclusion complexes, solid dispersions, and lipid based formulations such as self-emulsifying drug delivery systems (SEDDS) have been introduced with different success. Adsorption of drugs to hydrophilic silica aerogels has been shown to be a promising technique for drug release enhancement. This methodology also allows a long-time stabilization of amorphous drugs. Upon contact with fluids, the structure of hydrophilic aerogels collapses and a fast release of the loaded drug take place [2].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medication may be converted into a dry looking, non-adherent, free flowing, and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. However, even though in the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to displayenhanced drug release properties,

and consequently, improved bioavailability [3].

Historically, liquisolid compacts are descendants of 'powdered solutions', an older technique which was based on the conversion of a solution of a drug in a nonvolatile solvent into a dry-looking, nonadherent powder by mainly adsorbing the liquid onto silicas of large specific surfaces [4]. Such preparations, however, have been investigated for their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later studies on powdered solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems [5, 6].

In these studies, however, large quantities of silicas were still being used, and the flow and compression properties of the products were never validated and standardized to industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they presented significant 'liquid- squeezing out' phenomena and unacceptably soft tablets, thereby hampering the industrial application of such systems [6, 7].

MATERIALS AND METHODS:

Materials:

Rifampicin was received as a gift sample from Cadila Pharmaceuticals Ltd., Ahmedabad. PEG400, Propylene Glycol (PG), Polysorbate 80, Avicel PH 102 and Aerosil 200 were purchased from Central Drug House (P) Ltd., New Delhi.

Methods [7, 8]:

In all the formulae 20mg of drug was added. First the liquid vehicle was taken into motor and the drug was added to it. The mixture was stirred well to make the drug dissolve or disperse into the liquid vehicle. Then the stated amount of carrier material was added to the liquid blend and stirred well until all the liquid gets absorbed into the carrier particles. Then added was the coating material and stirred for 10 minutes until the powder blend gets dry look.

EVALUATION

1. Melting Point [8, 9]

The melting point of the drug was determined by Thiele's tube method.

2. Drug Excipient Compatibility Studies [8, 9]

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation. To analyze the compatibility between drug and excipients, proposed to incorporate into the formulation, IR studies ware carried out taking the physical mixture of drug and other excipients as a test sample.

3. Solubility Studies [9]

The solubility study of the drug was carried out in distil water, 0.1N HCl, pH 6.8 Phosphate buffer, PEG 400, PG, Cremophor® EL and polysorbate 80. Excess amount of the drug was added to 10ml of these liquids and the solutions were kept for 48hrs in waterbath shaker. The solutions were then centrifuged and the supernatants were analyzed by UV spectrophotometry.

4. Determination of Flow Properties [10-13]

a. Angle of repose

The frictional force in the powder can be measured by the angle of repose. Angle of repose was determined by fixed funnel method.

Angle of repose can be calculated by using following formula:

$$\vartheta = \tan^{-1}(h/r)$$

b. Density Measurement

Granule density may influence compressibility, flowability, tablet porosity and other properties.

Bulk Density:

Weigh accurately 10gm of drug, which was previously passed through 20 # sieve, and transfer in 50 ml graduated cylinder. Carefully level the powder without compacting, and record unsettled volume. Calculate bulk density in gm/ml by following formula,

Bulk Density = Weight of Powder/Bulk Volume

Tapped density:

Weighed accurately 10 gm of drug, which was previously passed through 20 # sieve, and transfer in 50 ml graduated cylinder. Then mechanically tap the cylinder containing sample by raising cylinder and

allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. After 500 taps the volume of powder (Vo) was noted and again tapped for another 750 taps (Vf). If difference between Vo and Vf was more than 2% another 1250 taps were given repeatedly until the difference reduces to less than 2%.

Tapped Density = Weight of Powder / Tapped Volume

c. Carr's index

The Carr's compressibility index and Hausner's ratio are measurement for find out tendency of powders to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows:

%Carr's Index = (Tapped Density – Bulk Density) / Tapped Density * 100

d. Hausner's ratio

Hausner's Ratio = Tapped Density / Bulk Density

5. Calibration curve of Rifampicin [11, 12]

Observing the solubility profile of the drug, it was confirmed that the drug is practically insoluble in water and aqueous media like 0.1N HCl and 6.8 pH phosphate buffer. Therefore the caliberation curve of the drug was taken in chloroform. Calibration curve of rifampicin was prepared by taking 1mg/ml concentration of the drug into chloroform l as stock solution and the solution was further diluted to 2, 3, 4, 5 ppm solution and absorbance was recorded at 241.2nm.

6. Drug Content [13, 14]

50 mg of Liquisolid formulation was taken for content uniformity analysis. Liquisolid formulation was dissolved in 150ml of chloroform and the solution was stirred for 1.5hr then it was filtered through Whatmann filter paper. Amount of drug was detected by UV method.

7. In-Vitro Drug Release Study [14, 15]

Drug release studies were carried out using paddle type dissolution test apparatus (75 rpm, 37 °C) in 6.8 pH phosphate buffer as well as 0.1N HCl (900 ml). At the end of the each sampling time period 10 ml of the samples were taken and analyzed for drug content. A 10 ml Volume of fresh and filtered dissolution medium was added to make the volume after each sample

withdrawal. Sample was analyzed using UV method.

RESULTS AND DISCUSSION

1. Melting Point

The melting point of the drug was found to be 183^0C.

2. Drug Excipient Compatibility Studies

From the figure, one can see that there is no introduction of any new peak in the functional group region and there isn't removal of any peak, which is present in the spectra of individual compounds. This infers that no functional group present in the drug or excipients is degraded and there is no formation of any new functional group which indicates that all the excipients present in the tested sample are compatible with drug and also with each other.

3. Solubility Studies

From the solubility profile it can be judged that the drug is very soluble in all the non-polar liquid vehicles and very slightly soluble in water and other aqueous solutions. And amongst the non-polar liquid vehicles the drug has highest solubility in PEG 400.

4. Determination of Flow Properties of drug.

Flow properties of rifampicin:

From the table it can be confirmed that drug alone has very poor flowability. **Flow properties of formulation:**

From the results of the pre-compression evaluation parameters, it can be seen that F6, F7, F8 and F9 have poor flowability. The powder blends obtained after mixing of all the ingredients were wet for those formulations. The reason attributed for such wet powder blend was the higher viscosity of polysorbate 80. Due to higher viscosity of liquid, it could not be absorbed by Avicel PH 102 and whole powder blend remained wet. For other formulations the flow property of the powder blends was good.

5. Calibration Curve of Rifampicin

Three trials of calibration curve were taken and the average value of the three reading is taken along with standard deviation. This calibration curve was further used for assessment of dissolution data.

6. Drug content

7. In-Vitro Drug Release Study

In-vitro drug release study was carried out in both SIF and SGF. From the results of the test for screening design, we observed that in SGF more amount of the drug gets dissolved in comparison with that of in SIF. But in both SIF and SGF, F2 shows highest amount of drug dissolved i.e. the formulation with the PEG-400 as the liquid vehicle has the higher %CDR than PG. This is because of the higher solubility of the drug in PEG.

From these results, PEG-400 can be screened out as the best liquid vehicle for rifampicin amongst the three selected liquid vehicles. Dissolution study was carried out in both SGF and SIF for the optimization formulations. In both dissolution media, observing the %CDR profiles, it was confirmed that drug shows highest solubility from the F2 formulation. Then going from F3, F1, F5 and F6, the %CDR of the drug gets reduced gradually and the F7 formulation shows the least %CDR. The sole reason attributed for this decrease is the Molecular Fraction of the drug in the liquid vehicle. Molecular Fraction is the amount of drug in the solution/dissolved form in the liquid vehicle. As we go from the formulation F2 to F6 the amount of the liquid vehicle in the formulation gets reduced but the amount of drug remains same, that means molecular fraction of the drug will be decreased and more amount of the drug would remain in the suspended form which will not get dissolved in the dissolution media resulting in the decreasing %CDR

CONCLUSION:

Knowing that Rifampicin is very slightly soluble in water, an attempt was made to increase its solubility and dissolution by novel and highly promising Liquisolid technology. Preformulation studies suggested that the drug has highest solubility in PEG-400 amongst the selected liquid vehicles and that drug has no interaction with any excipient selected for preparation of Liquisolid compacts. The formulation prepared by using the Liquisolid technology, passed all the pre-compression evaluation parameters and was having dry look and free-flowing characteristic. The optimized formulation having PEG-400 containing 20mg drug (F2) which showed higher percent cumulative

drug release within 90 minutes. This suggests that Liquisolid technology is one of the breakthrough technologies for enhancement of the solubility and dissolution of poorly water soluble BCS Class-II drugs to be delivered orally.

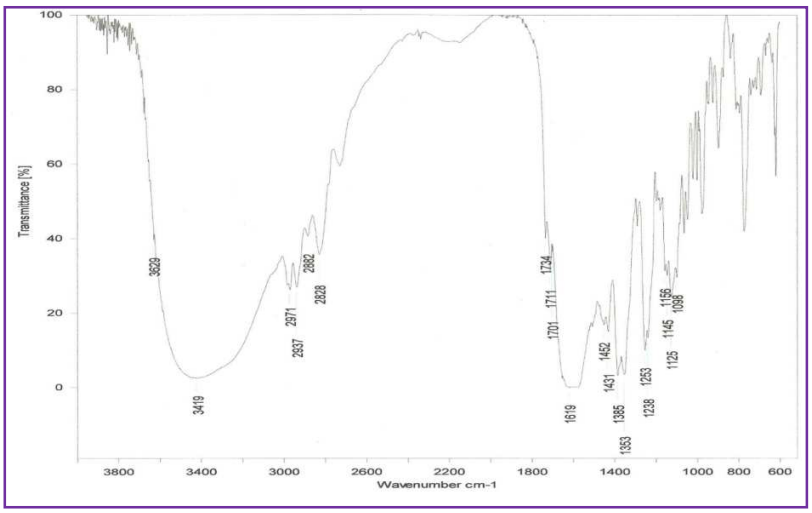

Figure 1: IR Spectra of Rifampicin.

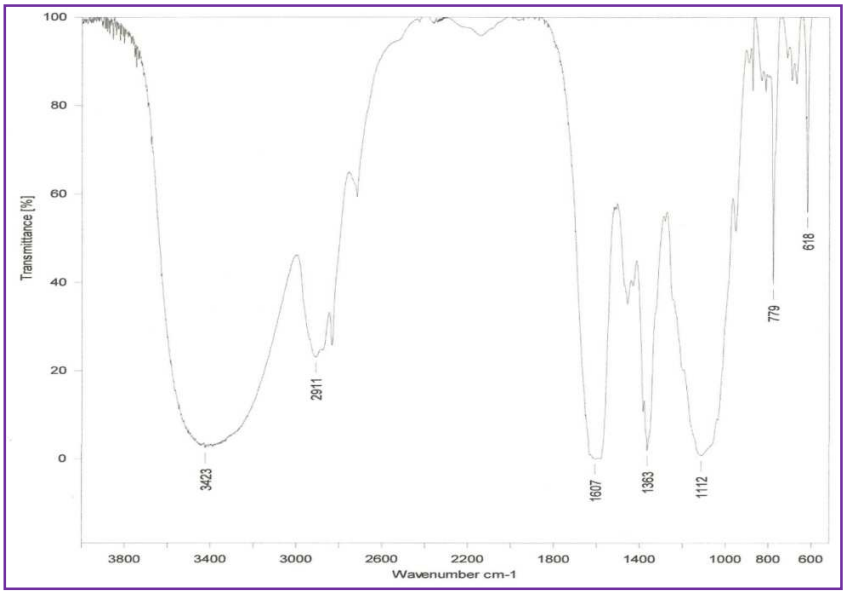

Figure 2: IR Spectra of Placebo.

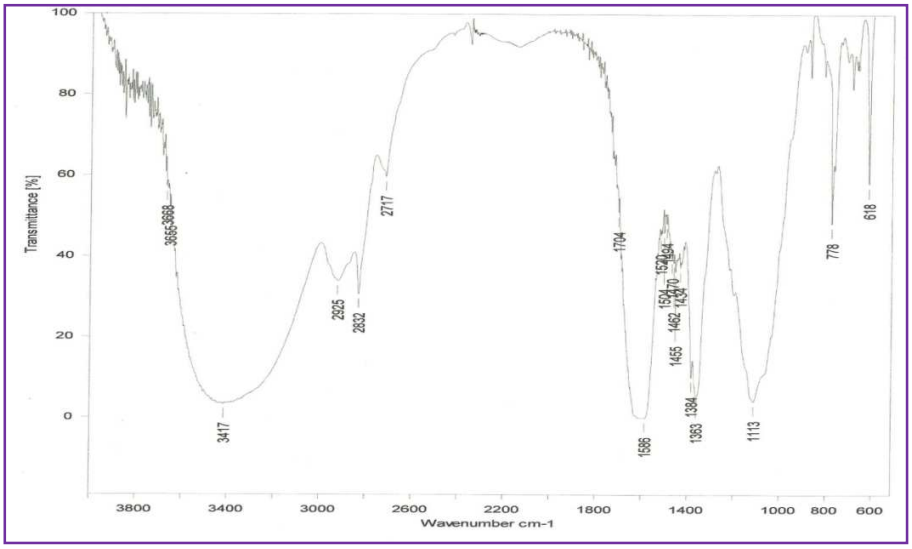

Figure 3: IR Spectra of Formulation.

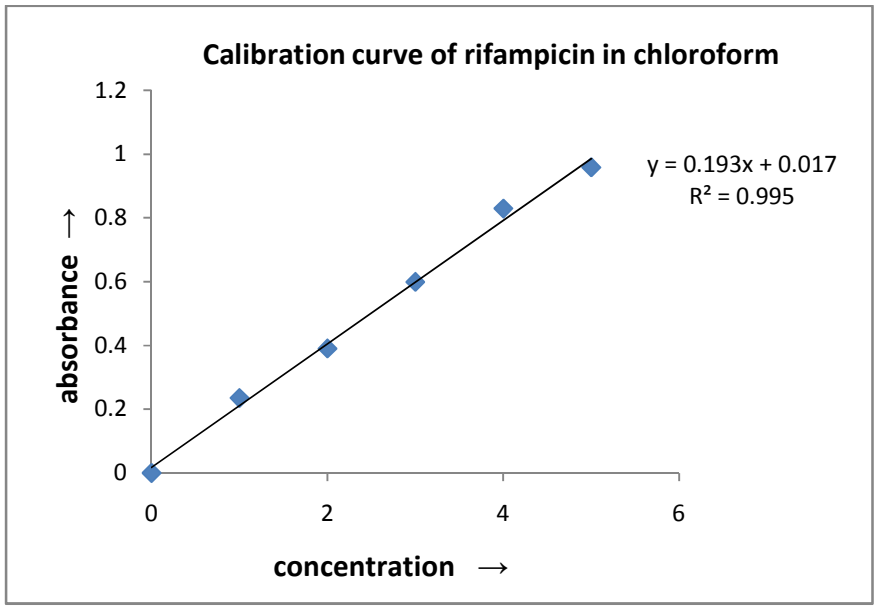

Figure 4: Calibration Curve of Rifampicin

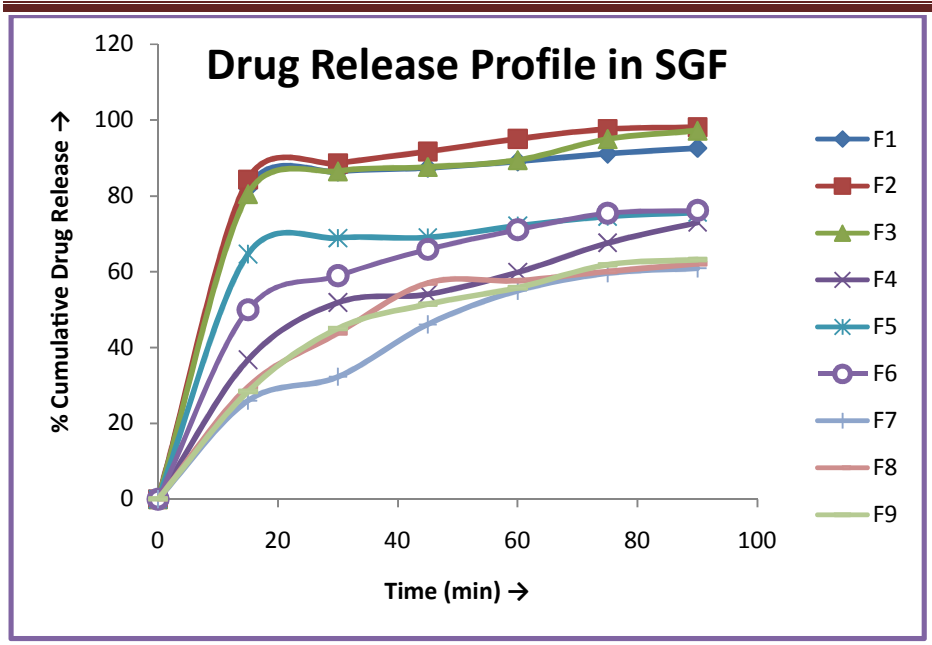

Figure 5: %CDR in SGF for Screening Design

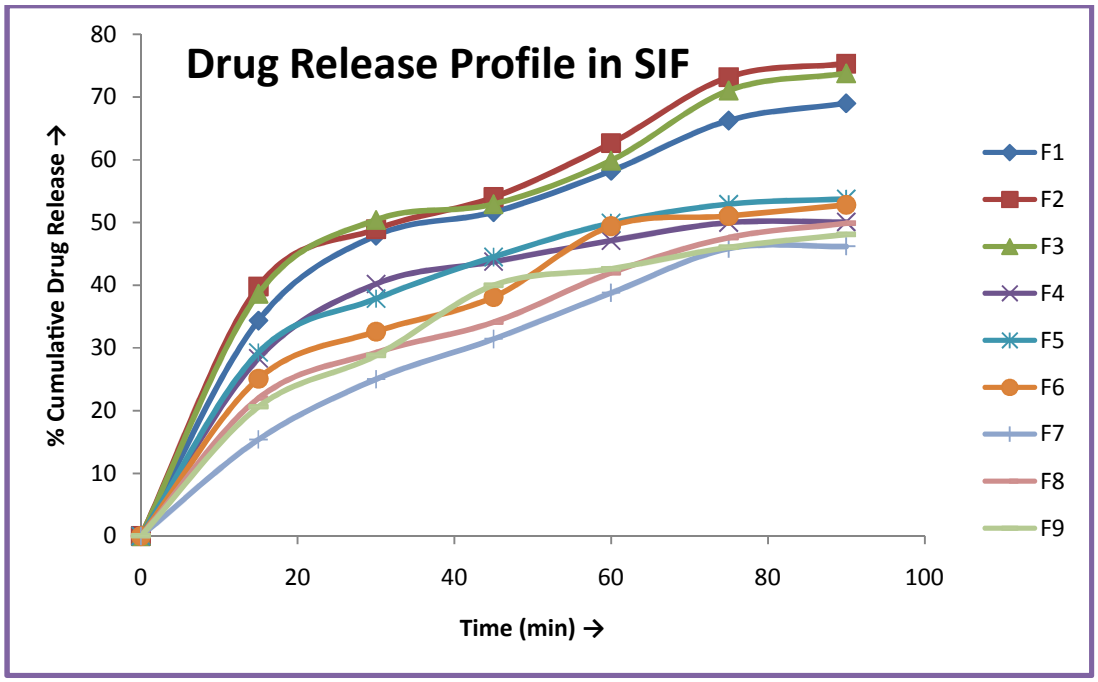

Figure 6: %CDR in SIF for Screening Design

Table 1: Formulations of liquisolid compact

Batch Code	Liq. Vehicle	Drug Conc.	Vehicle (mg)	Avicel PH 102 (mg)	Aerosil 200 (mg)	Unit Wt (mg)
F1	PEG400	20	50	360	20	450
F2		20	100	360	20	500
F3		20	150	360	20	550
F4	PG	20	50	360	20	450
F5		20	100	360	20	500
F6		20	150	360	20	550
F7	Polysorbate 80	20	50	360	20	450
F8		20	100	360	20	500
F9		20	150	360	20	550

Table 2: Solubility of Drug in Different Solvents

Liquid Vehicle	Solubility (w/w)
Cremophor® EL	4.966819 ± 0.227871
PEG 400	9.989659 ± 0.265720
PG	9.553540 ± 0.385571
Polysorbate 80	2.109716 ± 0.148579
Distil water	0.000871 ± 0.000014
0.1N HCl	0.000721 ± 0.000028
6.8 pH Phosphate buffer	0.000902 ± 0.000018

Table 3: Flow properties of rifampicin

Test	Result	Inference
Angle of Repose	38	Poor Flow
Bulk Density	0.33gm/ml	-
Tapped Density	0.54gm/ml	-
Carr's Index	38.89	Poor Flow
Hausner's Ratio	1.64	Poor Flow

Table 4: Flow properties of formulation

Batch Code	Angle of Repose	Carr's Index	Hausner's Ratio	Flowability
F1	29.94 ± 0.35	15.02 ± 0.63	1.18 ± 0.01	Good
F2	28.82 ± 1.14	15.45 ± 1.19	1.18 ± 0.02	Good
F3	30.77 ± 0.95	15.81 ± 0.74	1.19 ± 0.01	Good
F4	28.08 ± 0.53	17.68 ± 0.87	1.21 ± 0.01	Good
F5	29.84 ± 0.38	15.47 ± 0.11	1.18 ± 0.01	Good
F6	37.84 ± 0.95	18.68 ± 3.66	1.47 ± 0.08	Passable
F7	32.48 ± 0.37	16.46 ± 1.62	1.48 ± 0.03	Passable
F8	30.43 ± 0.73	15.97 ± 0.52	1.19 ± 0.02	Passable
F9	37.84 ± 0.95	20.68 ± 3.66	1.47 ± 0.08	Passable

Table 5: Calibration Curve of Rifampicin.

Sr. No	Concentration (µg/ml)	Absorbance
1	0	0
2	1	0.235
3	2	0.390
4	3	0.599
5	4	0.829
6	5	0.958

Table 6: Drug content

Batch Code	Drug Content
F1	98.10 ± 1.2
F2	99.72 ± 2.2
F3	93.20 ± 1.1
F4	91.47 ± 1.5
F5	94.02 ± 1.1
F6	88.80 ± 1.4
F7	92.68 ± 1.4
F8	87.44 ± 2.2
F9	81.45 ± 0.7

Table 7: %CDR in SGF for Screening Design

Time (min)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0.0	0	0	0	0	0	0
15	82.02	84.33	80.48	36.75	64.61	49.92	25.97	29.59	28.38
30	86.33	88.54	86.48	51.86	68.88	58.92	32.27	43.78	45.00
45	87.34	91.69	87.60	54.06	69.01	65.88	46.10	56.99	51.40
60	89.08	95.04	89.42	59.85	72.10	71.06	54.99	57.61	55.75
75	91.11	97.61	94.97	67.56	74.56	75.42	59.60	60.03	61.80
90	92.57	98.11	97.19	72.99	75.58	76.12	60.89	62.09	63.16

Table 8: %CDR in SIF for Screening Design

Time (min)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0	0	0
15	34.35	39.81	38.65	28.31	29.26	25.09	15.38	21.97	20.59
30	47.88	48.94	50.41	40.17	37.83	32.60	25.00	29.27	28.78
45	51.64	54.03	52.93	43.73	44.47	38.10	31.40	34.10	39.99
60	58.20	62.64	59.89	47.08	49.89	49.42	38.75	41.99	42.61
75	66.23	73.19	71.05	49.95	52.89	51.03	45.80	47.60	46.03
90	68.98	75.32	73.78	50.04	53.73	52.81	46.16	49.89	48.09

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