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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF RIFAMPICIN THROUGH LIQUID SOLID TECHNOLOGY

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Abstract: Rifampicin is poorly soluble in water and exist sufficient lipophilic property, it is beneficial to dissolve them in pre-dissolved state, e.g. in liquid formulation. In all the formulae 20 mg of drug was added. Avicel PH 102 was used as carrier material and Aerosil 200 as coating material. PEG 400, PG and Polysorbate 80 were used as liquid vehicle. 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 coating material was added and stirred for 10 minutes until the powder blend gets dry look. From the results of the pre-compression evaluation parameters, it can be seen that F6, F7, F8 and F9 had 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. The optimized formulation having PEG400 : PG; 100:50 containing 20mg drug (F14) which showed higher percent cumulative drug release within 90 minutes. This suggests that Liquisolid technology was one of the breakthrough technologies for enhancement of the solubility and dissolution of poorly water soluble BCS Class-II drugs.

Keywords: Liquisolid Technology, Rifampicin, Avicel PH 102, Solubility, Lipophilic Drugs



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INTRODUCTION

With the liquisolid technology as described by Spireas a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerin are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface, which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts^{1,2}.

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^{3,4}. 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 display enhanced drug release properties, and consequently, improved bioavailability^{1,5,6}.

MATERIALS AND METHODS:

Materials:

The following lists of materials that are best possible pharma grade available are used.

Table 1: Material used in the present investigation

Sr.no	Ingredients	Supplier/Manufacturer
1	Rifampicin	Intas pharmaceuticals
2	PEG 400	Astron Corporation
3	Propylene glycol	Phemodyes corporation
4	Polysorbate 80	Astron Corporation
5	Avicel 200	Phemodyes corporation

Method of Preparation^{7, 8}:

In all the formulae 20 mg of drug was added. Avicel PH 102 was used as carrier material and Aerosil 200 as coating material. PEG 400, PG and Polysorbate 80 were used as liquid vehicle.

Table 2: Formulations of liquisolid compact

Batch Code	Liq. Vehicle	Drug (mg)	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

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 coating material was added and stirred for 10 minutes until the powder blend gets dry look.

Preformulation studies:

A. Physical Appearance^{7, 8}: Appearance of Drug was observed visually.

B. Melting Point⁸: The melting point of the drug was determined by Thiele's tube method.

- C. Calibration curve of Rifampicin^{7, 9}:** Observing the solubility profile of the drug, it was confirmed that the drug was practically insoluble in water and aqueous media like 0.1N HCl and 6.8 pH phosphate buffer. Therefore the calibration curve of the drug was taken in chloroform. Calibration curve of rifampicin was prepared by taking 1 mg/ml concentration of the drug into chloroform as stock solution and the solution was further diluted to 1, 2, 3, 4, 5 ppm solution and absorbance was recorded at 241.2nm.
- D. Solubility Studies^{9, 10}:** 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.
- E. IR Spectrum of drug^{8, 9}:** FT-IR spectrum of the pure drug sample was recorded with Nicolet iS10, Thermo Scientific, India.
- F. Differential Scanning Calorimetry (DSC)^{7, 10}:** DSC of the pure drug sample was recorded with Mettler DSC 30 S (Mettler Toledo, UK). The samples were sealed in the aluminum crimp cell and heated at the speed of 10°C/min from 0 to 300°C in nitrogen atmosphere (60 ml/min).

Optimization of Liquisolid Compact:

Table 3: Optimization of liquisolid compact.

Batch Code	Drug	PEG 400	PG	Avicel 102 (mg)	PH (mg)	Aerosil 200 (mg)	Unit (mg)	Wt
F10	20	50	50	360	20	500		
F11	20	50	100	360	20	550		
F12	20	50	150	360	20	600		
F13	20	50	200	360	20	650		
F14	20	100	50	360	20	550		
F15	20	150	50	360	20	600		
F16	20	200	50	360	20	650		

EVALUATION:

Determination of Flow Properties

- A. Angle of repose^{11, 12}:** 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:

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

Where, θ = Angle of repose h = Height of heap in cm r = Radius of heap in cm

B. Density Measurement^{14, 15}:

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

- a. **Bulk Density:** Weigh accurately 10 gm 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

- b. **Tapped density:** Weigh 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 (V_o) was noted and again tapped for another 750 taps (V_f). If difference between V_o and V_f 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:

$$\% \text{Carr's Index} = (\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density} * 100$$

D. Hausner's ratio:

Hausner's Ratio = Tapped Density / Bulk Density

Drug Excipient Compatibility Studies^{9, 15, 16}:

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 were carried out taking the physical mixture of drug and other excipients as a test sample.

Scanning electron microscopy (SEM)^{11, 17}:

The surface characteristics of pure drug and the liquisolid formulation were studied by SEM (JSM-5610, Tokyo, Japan). The samples were mounted on double sided adhesive tape and coated with platinum sputter coater and then analysed.

Drug Content^{10, 18}:

50 mg of Liquisolid formulation was taken for content uniformity analysis. Liquisolid formulation was dissolved in 150 ml of chloroform and the solution was stirred for 90 min then it was filtered through Whatmann filter paper. Amount of drug was detected by UV method.

***In-Vitro* Drug Release Study^{15, 19, 20}**

Drug release studies were carried out using paddle type dissolution test apparatus (75 rpm, 37 °C) in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). 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 dissolution medium was added to make the volume after each sample withdrawal. Sample was analyzed by UV method. Simulated gastric fluid (SGF) was prepared by dissolving 2.0 g of sodium chloride and 3.2 g of purified pepsin, which is derived from porcine, with an activity of 800 to 2500 units per mg of protein in 7 ml of hydrochloric acid and sufficient water to make 1000 ml. This solution has a pH of about 1.2. Simulated intestinal fluid (SIF) was prepared by dissolving 6.8 g of monobasic potassium phosphate in 250 ml of water, mix and adds 77 ml of 0.2 N sodium hydroxide and 500 ml of water. Add 10.0 g of pancreatin mix and adjust the resulting solution pH with either 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 6.8 ± 0.1 , dilute with water to 1000 ml.

RESULTS AND DISCUSSION

Preformulation studies:

Physical Appearance: The drug was found to be in reddish brown crystalline powder.

Melting Point: The melting point of the drug was found to be 183°C.

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.

Table 4: Calibration Curve of Rifampicin.

Sr. No	Concentration ($\mu\text{g/ml}$)	Absorbance
1	0	0.000
2	1	0.235
3	2	0.390
4	3	0.599
5	4	0.829
6	5	0.958

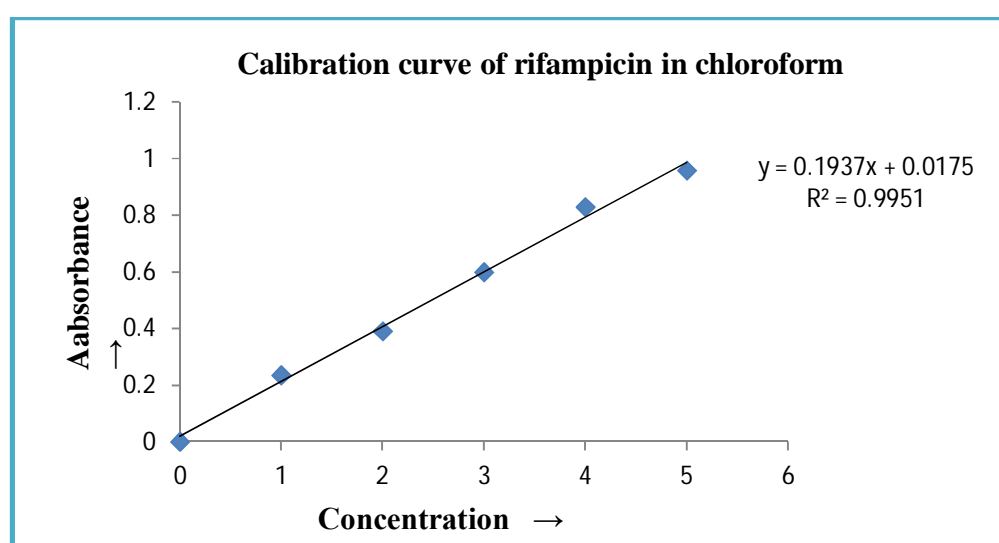


Figure 1: Calibration Curve of Rifampicin

Solubility Studies

Table 5: 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

From the solubility profile it can be judged that the drug was very soluble in all the nonpolar 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.

IR Spectrum of Drug

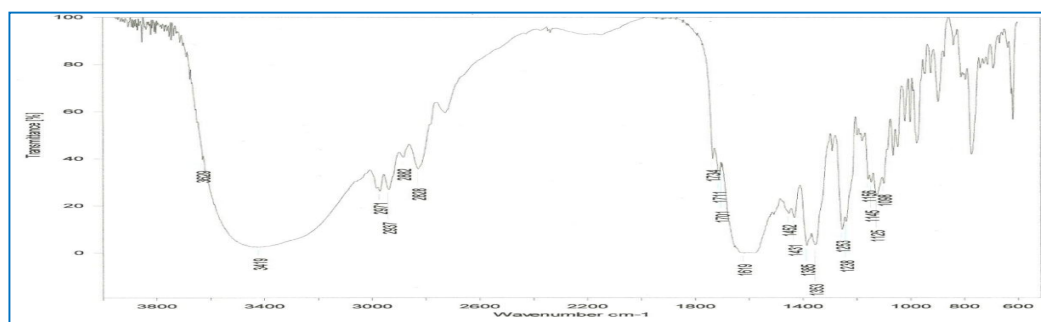


Figure 2: IR Spectrum of rifampicin

Table 6: FT-IR Interpretation of Rifampicin

Functional Group	Peak (cm ⁻¹)
-OH	3419
C=O (Ketone)	1711
-NH	2971
C=C (Aromatic)	1452
C-N	1125
C=O (Amide)	1619

From the spectrum of the drug it can be seen that all the characteristic peaks of rifampicin were present in the Table 6, which proves that the tested sample of the drug was rifampicin.

Differential Scanning Calorimetry (DSC)

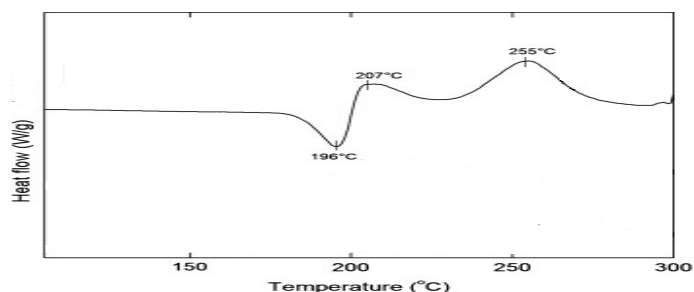


Figure 3: Differential Scanning Calorimetry of Rifampicin

DSC graph of rifampicin showed an endothermic peak around 196°C corresponding to its melting point. DSC graph also show exothermic peak at 207°C which represent subsequent recrystallization of the drug and gives amorphous form of drug. Further peak of exotherm at 255°C show decomposition of amorphous form.

Determination of Flow Properties:

Table 7: Flow properties of formulation

Batch Code	Angle of Repose (θ)	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

From the results of the pre-compression evaluation parameters, it can be seen that F6, F7, F8 and F9 had 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.

Table 8: Flow properties of Formulation

Batch Code	Angle of Repose (θ)	Carr's Index %	Hausner's Ratio	Flowability
F10	26.24 ± 0.55	14.01 ± 0.73	1.16 ± 0.21	Good
F11	26.92 ± 1.14	15.25 ± 1.29	1.19 ± 0.32	Good
F12	31.87 ± 0.95	14.21 ± 0.74	1.20 ± 0.01	Passable
F13	27.28 ± 0.63	17.88 ± 0.97	1.22 ± 0.0	Good
F14	27.92 ± 0.33	15.58 ± 0.51	1.18 ± 0.21	Good
F15	38.34 ± 0.55	16.78 ± 2.86	1.48 ± 0.06	Passable
F16	35.48 ± 0.66	17.56 ± 1.52	1.39 ± 0.06	Passable

From the results of the pre-compression evaluation parameters, it can be seen that F10, F11, F13, and F14 Had good flow property.

Drug Excipient Compatibility Studies.

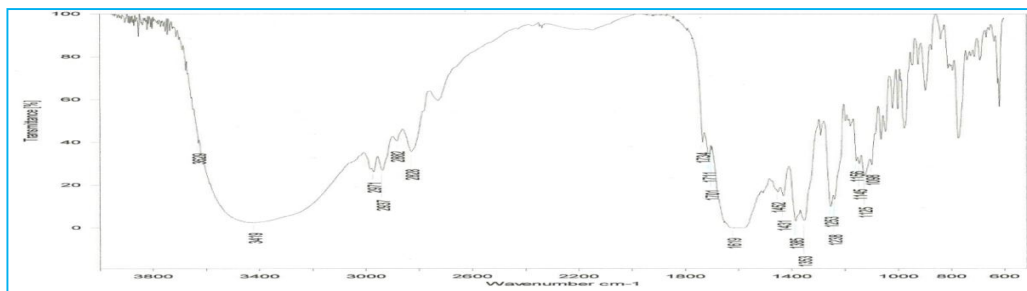


Figure 4: IR Spectra of Rifampicin

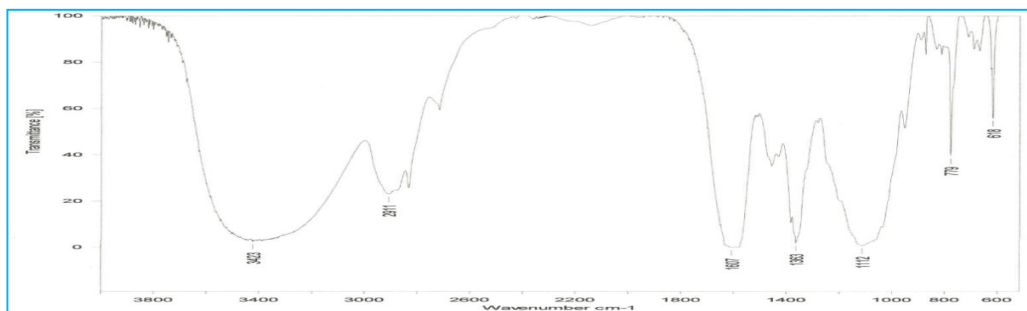


Figure 5: IR Spectra of Placebo

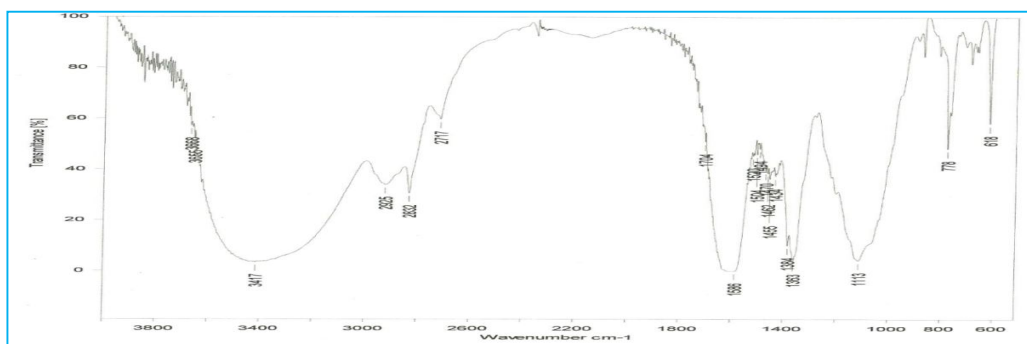


Figure 6: IR Spectra of Formulation

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.

Scanning electron microscopy (SEM)

The surface morphology of pure drug and liquisolid formulation are as displayed below.

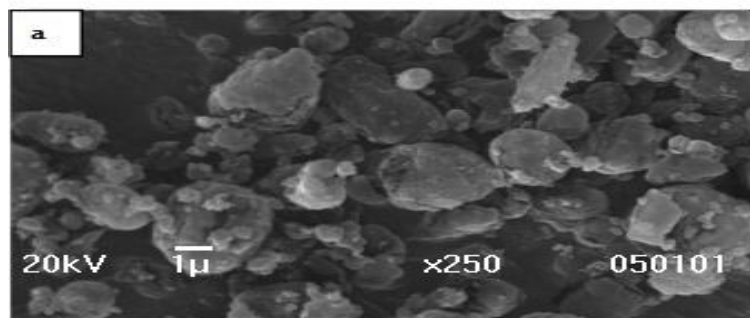


Figure 7: Scanning electron microscopy of pure drug

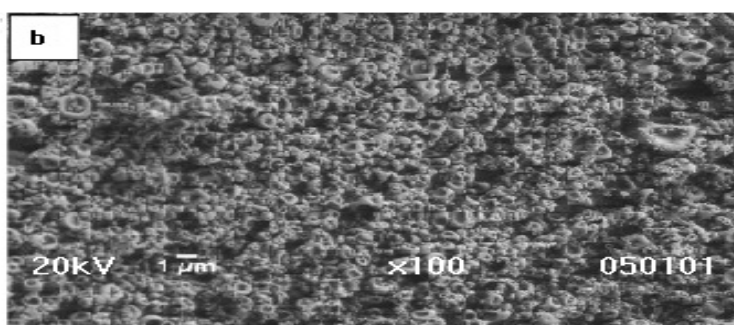


Figure 8: Scanning electron microscopy of liquisolid formulation F14

Drug Content

Table 9: 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

Maximum amount of drug was observed in F2, F1, F3, F5 formulation.

Table 10: Drug Content

Batch Code	Drug Content
F10	91.82 ± 2.6
F11	89.25 ± 6.2
F12	82.20 ± 1.1
F13	90.57 ± 1.2
F14	99.32 ± 1.2
F15	85.50 ± 1.6
F16	94.58 ± 1.3

Maximum amount of drug was observed in F14, F16, F10, F13 formulation.

5.2.5 *In-Vitro* Drug Release Study

To carry out *In-vitro* drug release study in both SIF and SGF first calibration curve of rifampicin was prepared in SGF and SIF. 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 was because of the higher solubility of the drug in PEG.

Table 11: Percentage CDR in SGF or 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	38.23	42.23	43.25	36.75	64.61	49.92	25.97	29.59	28.38
30	48.56	54.89	55.42	51.86	68.88	58.92	32.27	43.78	45.00
45	66.85	63.12	62.34	54.06	69.01	65.88	46.10	56.99	51.40
60	66.23	69.78	66.77	59.85	72.10	71.06	54.99	57.61	55.75
75	71.11	76.56	72.86	67.56	74.56	75.42	59.60	60.03	61.80
90	72.57	78.11	77.19	72.99	75.58	76.12	60.89	62.09	63.16

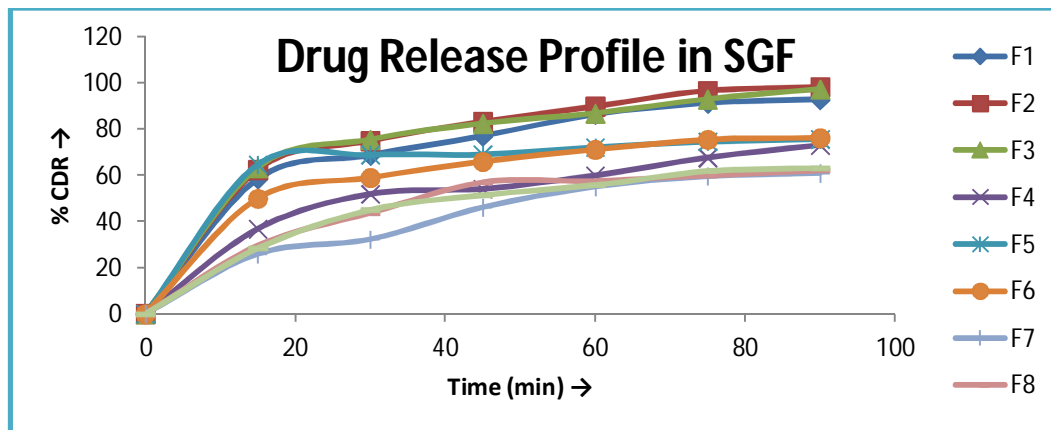


Figure 9: %CDR in SGF for Screening Design

Table 12: percentage 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

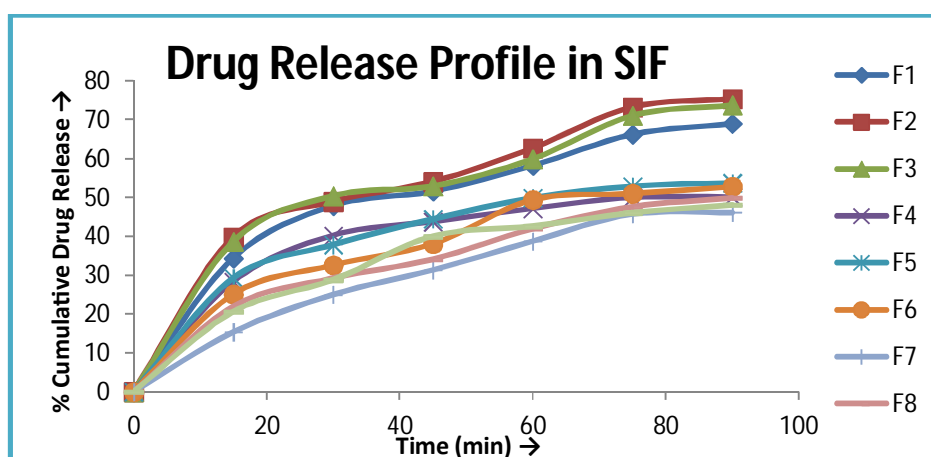


Figure 10: %CDR in SIF for Screening Design

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 was the Molecular Fraction of the drug in the liquid vehicle. Molecular Fraction was the amount of drug in the solution/dissolved form in the liquid vehicle.

Table 13: Percentage CDR in SGF For Screening Design

Time (min)	% Cumulative Drug Release						
	F10	F11	F12	F13	F14	F15	F16
0	0	0	0.0	0	0	0	0
15	39.25	42.25	41.69	32.65	40.32	48.25	28.27
30	45.52	50.89	55.42	52.76	55.88	59.60	30.97
45	55.85	60.12	60.75	59.06	72.82	64.20	42.41
60	62.53	68.28	68.82	62.98	78.68	72.88	52.89
75	70.51	75.26	75.72	70.22	82.46	79.25	58.80
90	69.87	75.51	77.19	79.89	89.11	87.68	86.00

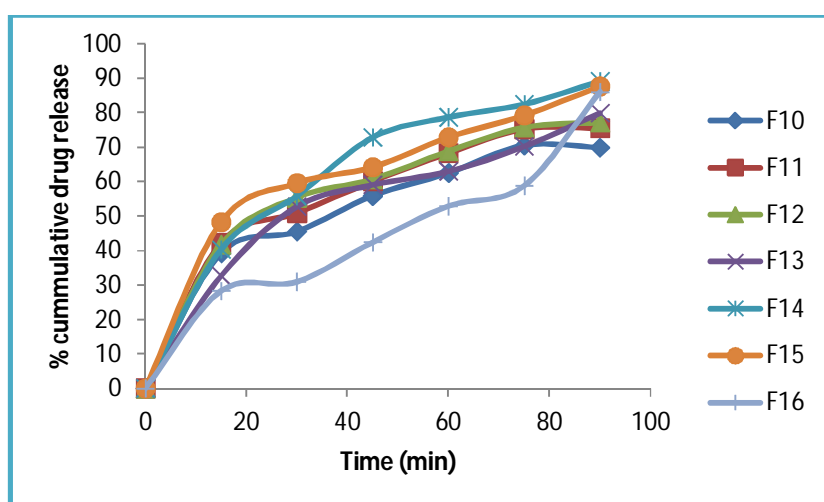


Figure 11: %CDR in SGF for Screening Design

Table 14: Percentage CDR in SIF for Screening Design

Time (min)	% Cumulative Drug Release						
	F10	F11	F12	F13	F14	F15	F16
0	0.00	0.00	0.00	0.00	0.00	0.00	0
15	35.32	37.80	38.55	25.61	39.81	28.00	20.39
30	42.89	45.92	48.39	51.09	49.64	38.26	24.10
45	50.63	49.01	52.83	56.93	59.23	42.20	39.30
60	58.21	52.62	58.79	59.20	67.84	56.32	48.85
75	62.22	62.10	65.15	66.89	71.89	68.33	66.90
90	64.95	67.41	70.78	72.23	77.92	76.21	76.16

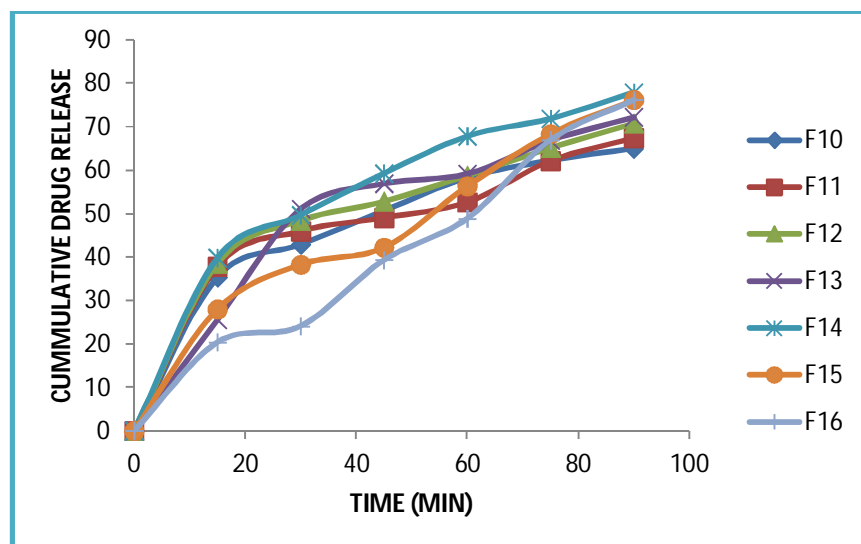


Figure 12: %CDR in SIF for Screening Design

From these results, Formula 14 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 F14 formulation. Then going from F15, F16, F13 and F12, the %CDR of the drug gets reduced gradually and the F10 formulation shows the least %CDR. The sole reason attributed for this decrease was the Molecular Fraction of the drug in the liquid vehicle. Molecular Fraction was the amount of drug in the solution/dissolved form in the liquid vehicle.

CONCLUSION:

Formulation prepared by using the Lquisolid technology, passed all the pre-compression evaluation parameters and was having dry look and free-flowing characteristic. The optimized formulation having PEG400:PG; 100:50 containing 20mg drug (F14) which showed higher percent cumulative drug release within 90 minutes. This suggests that Lquisolid technology was one of the breakthrough technologies for enhancement of the solubility and dissolution of poorly water soluble BCS Class-II drugs.

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