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Formulation and Optimization of Rifampicin and Quercetin Laden Liquisolid Compact: In-Vitro and In-Vivo Study

Devang Tandel[1,2]*, Kalpana Patel[2], Vaishali Thakkar[3], Tejal Gandhi[4]

[1]*Research Scholar, Gujarat Technological University, Ahmedabad, Gujarat, India.*
[2]*Department of Quality assurance, Anand Pharmacy College, Anand, Gujarat, India.*
[3]*Department of Pharmaceutics, Anand Pharmacy College, Anand, Gujarat, India.*
[4]*Department of Pharmacology, Anand Pharmacy College, Anand, Gujarat, India.*

***Email:** devangapc205@gmail.com*

ABSTRACT

The major objective of this study is to create rifampicin and quercetin-containing liquisolid compacts with improved gastrointestinal absorption and dissolving properties. Propylene glycol, PEG 200, and Tween 20 were chosen as ideal non-volatile liquid carriers to create the required formulations because of their increased drug solubility. In an attempt to create a free-flowing, compressible powder, the liquisolid formulations were then combined with a carrier and coating material. In order to create liquisolid powders with good flow qualities, Avicel pH-102, Aeroperl 200, and Aerosil 200 demonstrated good liquid retention potential values, demonstrating their efficiency as solid carrier and coating materials in the creation of liquisolid compacts. The medication and carrier had no discernible interaction, according to FT-IR spectra. The DSC and PXRD experiments proved that the crystalline form of the medication was absent from the liquisolid powders. Furthermore, the improved drug dissolving performance in liquisolid systems revealed that the drug had changed into a molecular or amorphous state. In-vivo rat pharmacokinetic investigations revealed the ability of non-volatile liquid carriers of liquisolid systems to enhance drug absorption from formulation and enhance the gastrointestinal absorption and dissolving rate of rifampicin and quercetin.

Key words: *Rifampicin (RIF), Quercetin (QUE), Liquisolid, Formulation, D-Optimal design*

INTRODUCTION

Dissolution of the drug, which is largely influenced by drug solubility, has an impact on bioavailability. The rate-limiting step of the absorption process is dissolution since the majority of recently created drugs are inefficient or insoluble in water (BCS class-II). As a result, absorption is inadequate. The pharmaceutical business and researchers are therefore faced with difficulty as a result of the high demand for better products [1-6].

The bioavailability and, therefore, the effectiveness of medicinal drugs are directly influenced by their physicochemical qualities. Therefore, raising the dissolution profile is a difficult issue for researchers [1-6]. For improving oral bioavailability, several dissolution enhancement techniques for rifampicin and quercetin have been reported in the literature. These techniques include solubilization in surfactant systems [7], solid dispersion [8-11], nanoparticle [12, 13], nanosuspension [14], solid lipid particle [15-17], and inclusion complex [18, 19].

The methods mentioned above, however, have several process-related shortcomings. For instance, using a sonicator to prepare polymeric nanoparticles and a spray dryer to dry them both require expensive equipment. The disadvantage of high saturation solubility and fast dissolving velocity is lost as a result of particle agglomeration caused by the unstable nature of nanosuspension formulation.

A very promising alternative for quick and thorough medication dissolution is Liquisolid technology. Additionally, it is a straightforward, easily scaled-up, and inexpensive formulation technique for enhancing the rate of dissolution of poorly water-soluble medicines. The drug particles in the Liquisolid compact are dissolved in a non-volatile liquid vehicle before being combined with the right carrier and coating excipients to create a non-adherent, free-flowing, and compressible powder mixture by being caught within the excipients' intrinsic matrix. A coating of carrier particles begins to form once the liquid drug has completely saturated the interior matrix. The surplus liquid that was left on the carrier material's surface is further absorbed by the coating layer, leaving the entire system dry and free-flowing. The liquisolid approach has produced encouraging results for a variety of medications [20-25].

Therefore, the Liquisolid compacts that contain insoluble pharmaceuticals encourage dissolution by facilitating the wetting process by increasing the net effective surface area, which leads to an increase in the availability of the drug for dissolution media [20-25].

A semi-synthetic antibiotic called rifampicin is made from *Streptomyces mediterranei*. It has a wide range of anti-bacterial action, including activity against different Mycobacterium species. It slows the start of RNA synthesis in sensitive species by inhibiting DNA-dependent RNA polymerase activity by creating a stable complex with the enzyme [26].

RIF is only 50–60% bioavailable in oral formulations, necessitating higher doses to achieve the necessary biological action. Additionally, the therapeutic regimen for TB is linked to the emergence of resistant TB strains, protracted treatment duration, subpar patient compliance, immune system degradation, and lung tissue loss [26]. Additionally, rifampicin causes neurotoxicity, hepatic, renal, hematological disease, and other adverse effects at hazardous levels [26].

Quercetin has been described in the literature as a bioenhancer that increases bioavailability while minimizing side effects from current tuberculosis treatments. According to the literature, herbal bio-enhancers have been used to improve the bioavailability and bio efficiency of various classes of medications, including antibiotics, antiviral, antifungal, and anti-tubercular medicines [27, 28].

Combining bio-enhancers aims to decrease the dose, toxicity, and treatment time. Additionally, quercetin has hepatoprotective and immunomodulatory effects that are helpful in the treatment of tuberculosis [9, 10]. Citrus fruits, vegetables, and plants contain the polyphenolic flavonoid quercetin. It functions by inhibiting CYP3A4 and the P-Gp efflux pump and displays anti-oxidant, anti-allergic, radical scavenging, anti-inflammatory, anti-tuberculosis, anti-bacterial, anti-neoplastic, and anti-atherosclerotic properties. Diltiazem, digoxin, verapamil, etoposide, and paclitaxel are just a few of the medications whose bioavailability, blood levels, and effectiveness have been demonstrated to be increased by quercetin [29, 30].

In view of the aforementioned facts, the goal of the research effort was to improve rifampicin's dissolution when it was combined with quercetin as a bioenhancer using the liquisolid compact technology and the DoE approach. Using Design Expert software, the crucial characteristics of liquisolid compact solubility and percent cumulative drug release were further examined, and an optimum batch was then chosen based on the desirability function.

For dose determination of quercetin, we performed an In-vitro Anti-tuberculosis bioassay of different ratios of RIF: QUE (1:1 and 1:0.5). We found that 1:1 ratio of RIF and QUE have significant activity against Mycobacterium tuberculosis H37Rv strain. So, we have selected 150 mg RIF and 150 mg QUE for further formulation development [31].

MATERIALS AND METHODS

Materials

Rifampicin and quercetin of analytical quality were bought from Swapnroop Drugs and Pharmaceuticals in Aurangabad, Maharashtra, India. Aeroperl 200 and Aerosil 200 were obtained as gratis samples from Evonik Pharma in Mumbai, India. Neusilin, Syloid XDP 3150, and Syloid 244 FP were obtained as gratis samples from Company KG, Germany. Hydrochloric acid, sodium hydroxide, and potassium hydrogen orthophosphate were all purchased from Merck in Mumbai, India. According to the Indian Pharmacopeia, 0.1 M of hydrochloric acid and a pH-6.8 phosphate buffer were created for investigation. Throughout the experiment, distilled water was used.

Saturation solubility study

Different non-volatile vehicles, such as propylene glycol, Tween 20, Tween 80, PEG 200, 400, and 600, were used for the saturation solubility investigation. To achieve saturation, extra Rifampicin and Quercetin have been

added to 1 ml of a non-volatile vehicle. Remi, India, vortexed the solution for fifteen minutes. Additional samples were centrifuged at 5000 rpm for 15 min, and the supernatant was collected and filtered through a membrane filter (0.45 m). The transparent drug solution was diluted with methanol before being examined by a UV spectrophotometer (Shimadzu Corp., Japan) at 365 cm and 470 cm for QUE and RIF, respectively. Three copies of each sample were analyzed [20-25].

Screening of Non-volatile vehicle and optimization using D-optimal mixture design

In propylene glycol, tween 20, and PEG 200, both medicines had the highest levels of solubility. Numerous combinations and varied non-volatile vehicle volumes were tested to increase the solubility of both medicines. According to the results of the initial screening batches, the optimal solvent mixture should still be adjusted using Tween 20 (0.1 to 0.2 ml), PEG 200 (0.3-0.7 ml), and PG (0.2-0.6 ml). The amount of medicine in its solubilized state depends on the solvent capacity of the non-volatile liquid carrier; hence optimizing the mixture of non-volatile solvents is a key consideration. Therefore, further D-optimal mixture design was used to improve the non-volatile vehicle combination. With Design Expert version 11, the experimental data were analyzed, and a total of 16 run randomized D-optimal mixture designs were created. The independent variables were Tween 20, PEG 200, and propylene glycol (X1, X2, and X3). The response variables for both medications' solubility in mg/ml and their percentage CDR at 60 minutes in 0.1 M hydrochloric acid were selected because they were viewed as crucial elements for Liqui-solid Compact to improve oral absorption of the poorly water-soluble drug [20-25].

Determination of flowable liquid-retention potential (Φ – value)

The fixed quantity of powder material (5 gm) was combined gradually with the liquid medication, and the resulting admixture was applied to one end of the polished metal plate. While keeping the opposite side on the ground, the metal plate was gradually raised from one side. The angle of the slide was defined as the angle created between the plate and the ground. The ideal flowable attribute of a powder excipient in relation to the specific liquid vehicle being employed is an angle of slide value of roughly 33 [20-25].

Liquid load factor

Once the Φ –value of carrier and coating material was measured, the liquid load factor for acceptable flowability was calculated by using the following equations.

$$Lf = (CA + CO)/R \quad (1)$$

$$R = Q/q \quad (2)$$

Here CA and CO are flowabilities liquid retention potential of carrier and coating materials, respectively. R is the excipient ratio as defined by Eq. (2). The R-value between 10 and 20 was shown to produce the best flow properties in studies published in many study journals, hence in this investigation, a mean of 15 was taken for calculation [20-25].

Screening of carrier and coating material for the non-volatile vehicle

Preliminary batches of Avicel pH-102, Lactose, Sorbitol, Dicalcium Phosphate, Aeroperl 200, Neusilin, Syloid XDP 3150, Syloid 244 FP as carrier material, and Aerosil 200 as coating material were chosen based on a survey of the literature. When using Avicel pH-102, Lactose, Sorbitol, and Dicalcium Phosphate, which cannot be used commercially as an oral formulation, the amount needed for full adsorption of 1 ml of liquid medication in first batches was greater than 1 gm. In contrast, the amount needed for full adsorption was over IIG limits in the cases of Aeroperl 200, Neusilin, Syloid XDP 3150, and Syloid 244 FP. As a result, various carrier and coating material combinations were tested. By measuring the angle of repose (θ), the flow characteristics of a liquid-solid particle were assessed [20-25].

Preparation of liquisolid formulation

In 5 ml RIA vials, the necessary quantity of the drug and the above-optimized composition of non-volatile solvents were added, and the vials were vortexed until the entire drug was solubilized. By carrying out the three stages outlined by Spireas *et al*., the liquid medication that resulted was placed into a mortar and combined with the ideal amount of carrier and coating components. In the first step, the liquid medication was distributed evenly

throughout the powder excipient by blending the two components for nearly a minute at an estimated mixing rate of one rotation per second. The liquid/powder mixture was applied uniformly as a layer to the surfaces of a mortar in the second step and allowed to stand for about five minutes to allow the drug solution to permeate the internal matrix of the powder material. The powder is removed from the mortar's surface in the third stage using an aluminum spatula, and it is then combined with the lubricant and glidant for another 30 seconds in the same manner as in the first stage. The final liquisolid formulation was produced and placed inside a 00-size capsule shell [20-25].

In-vitro dissolution study

Utilizing a dissolution device USP Type I, the dissolution rates of marketed formulations of RIF (R-cin 150, 150 mg Rifampicin capsule IP manufactured by Lupin Pharmaceutical Pvt, Ltd.) and QUE (Quercetin 100 mg capsule manufactured by Health vita) were determined. Dissolution investigations were conducted using 900 ml of 0.1 M hydrochloric acid and 0.1 M phosphate buffer pH-6.8 with 0.02% Vitamin C and 0.2% SLS as dissolution media at 50 rpm and 37 0.5 °C. At appropriate intervals of time (0, 15, 30, 45, and 60 min), appropriate aliquots were taken out and filtered through Whatman filter paper before being diluted with dissolving media. The investigation was conducted in sink circumstances. After that, the samples were examined using the newly designed UV/visible spectrophotometer technique. The dissimilarity factor (f_1) and similarity factor (f_2) were calculated by using the following equations [20-25].

$$f_1 = \frac{\sum R_t - T_t}{\sum R_t} \times 100 \quad (3)$$

$$f_2 = 50 \times \left\{ log \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} |R_t - T_t|^2 \right] - 0.5 \times 100 \right\} \quad (4)$$

Where Rt is drug release from reference at time t, Tt is drug release from reference at time t, n = number of sampling points.

Drug excipient compatibility study

Fourier transform infrared (FT-IR) spectroscopy

By using the traditional KBr pellet method, the infrared spectra of Rifampicin, Quercetin, Avicel pH-102, Aeroperl 200, and improved Liquisolid formulations were predicted using an FT-IR spectrophotometer (Bruker Optics, USA). The resolution was 4 cm^{-1}, and the scanning range was 4000-500 cm^{-1} [20-25].

Differential scanning calorimetry (DSC) studies

Using a differential scanning calorimeter, Rifampicin, Quercetin, Avicel pH-102, Aeroperl 200, and improved Liquisolid formulations underwent DSC analyses to determine the molecular state of the medication in the compacts (Perkin Elmer, USA). An aluminum crucible that was tightly sealed was heated to a temperature that ranged from 20 °C to 400 °C at a heating rate of 10 °C/min using a constant nitrogen gas flow of 30 ml/min [20-25].

Powder X-ray diffractometry (PXRD)

PXRD investigations were used to illustrate the drug's crystalline character in the formulation. The PXRD profile of the optimized liquisolid formulation, carrier, and pure API was acquired using an X-ray diffractometer (Bruker D2 phaser) that used CuK radiation at 30 kV voltage, 10 mA current, and an X'celerator detector [20-25].

Stability study

The optimized formulation was kept for three months at 40 °C, and 75% RH and measurements were made of its hardness, disintegration time, and percentage of drug release over that time (15 min, 30 min, 45 min, and 60 min was evaluated). The release profile of stability samples and freshly made liquisolid compact were examined [20-25].

An in-vivo pharmacokinetic study in the rat

Anand Pharmacy College's Institutional Animal Ethics Committee (IAEC) (Registration No. 277/PO/ReBi/2000/CPCSEA) and the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA) accepted the study's ethical conduct (Protocol no. 1928 dated 11 October 2019). In a room with a regulated temperature of 20°C 2°C and a 12-hour light/dark cycle, rats were kept in plastic cages with corn cob bedding. 4.0 mg/kg of RIF and QUE were administered orally by gavage to 250 10 g Wistar albino rats after they had been fasting for the previous 12 hours and had free access to water. Five groups of four rats each were created out of the total population of rats (n = 4). Each group was then separated into Groups A and B. The first group, designated as the control group, got CMC suspension; the second group, RIF pure API; the third group, RIF and QUE pure API; the fourth group, marketed formulation of RIF and QUE; and the fifth group, Liqui-solid formulation of RIF and QUE. Blood samples were drawn from the retroorbital vein and placed in Eppendorf tubes with disodium EDTA. Blood was drawn using the retro-orbital route at 0, 1, 2, 3, 4, 5, and 8 hours for the pharmacokinetic investigation. The plasma from the samples was immediately frozen at 20°C and kept for analysis after being immediately centrifuged at 5000 rpm for 10 minutes. Within 6-7 hours of the blood collection, the UPLC-MS/MS technique was used to estimate RIF and QUE in all of the samples. A non-compartmental methodology was used to calculate the pharmacokinetic parameters. The linear trapezoidal rule was used to compute the AUC, or area under the plasma concentration vs. time curve after oral delivery of pure API, market formulations, and liquid-solid formulations were calculated [20-25].

RESULTS AND DISCUSSION

Saturation solubility study

Solubility tests in several non-volatile solvents were conducted in order to choose the best liquid vehicle for the formulation of RIF and QUE Liquisolid compacts. Drug solubility at its highest level was tested in non-volatile vehicles. The likelihood of in vivo drug precipitation would eventually be reduced, and the weight of the final formulation would also be reduced by using a vehicle with high drug solubility. Due to the polarity of poorly soluble drugs, which favors solubilization in medium chain triglycerides/mono/diglycerides, propylene glycol (25 mg/ml for RIF and 35 mg/ml for QUE), PEG 200 (25 mg/ml for RIF and 40 mg/ml for QUE), and Tween 20 (10 mg/ml for RIF and 8 mg/ml for QUE) non-ionic surfactants demonstrated high drug solubility. The RIF and QUE solubility in Tween 80 (5 mg/ml for RIF and 7 mg/ml for QUE), PEG 400 (15 mg/ml for RIF and 20 mg/ml for QUE), and PEG 600 (10 mg/ml for both drug) were found to be insufficient to dissolve the medication directly. To prepare the compact, Tween 20 was used as a surfactant after the medication had been first dissolved in PEG 200, with Propylene glycol as a solvent.

Optimization of non-volatile vehicle mixture using D-optimal mixture design

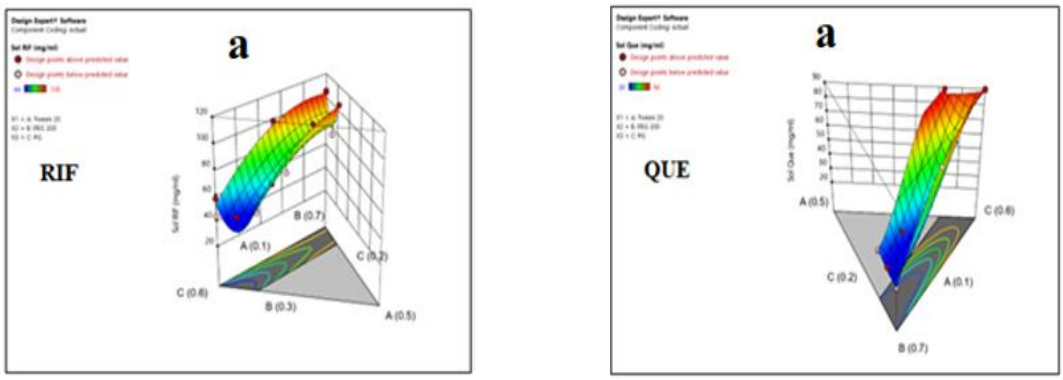
Table 1 explains the D-Optimal mixture design experimental runs and the effect of X on Y variables.

Table 1. The influence of D-optimal design output (16 batches) independent variables (X1 to X3) and independence variables (Y1 and Y2)

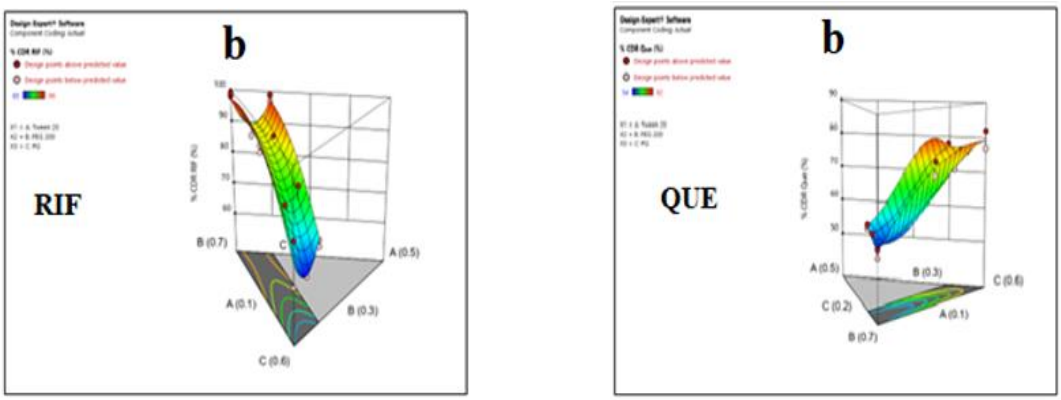
Batch	Tween 20 (ml) X1	PEG 200 (ml) X2	PG. (ml) X3	Solubility (mg/ml) Y1		% Drug release at 60 min Y2	
				RIF	QUE	RIF	QUE
1	0.20	0.30	0.50	52	85	73	76
2	0.17	0.39	0.44	62	75	85	74
3	0.12	0.39	0.49	60	70	82	72
4	0.20	0.30	0.50	50	89	71	78
5	0.20	0.60	0.20	105	35	99	60
6	0.10	0.30	0.60	58	90	79	82
7	0.15	0.47	0.37	61	41	82	63
8	0.10	0.70	0.20	106	31	99	54
9	0.10	0.70	0.20	105	30	98	56
10	0.20	0.60	0.20	105	34	97	59
11	0.15	0.30	0.55	45	84	65	76
12	0.10	0.30	0.60	44	89	65	77

13	0.10	0.50	0.40	99	74	94	72
14	0.17	0.54	0.28	95	35	91	60
15	0.10	0.50	0.40	96	79	92	76
16	0.15	0.65	0.20	75	34	86	59

The solubility of RIF and QUE increases with increasing PEG 200 and propylene glycol levels, according to a 3D contour plot **(Figure 1a)**. Similarly, for% CDR release of both medicines increases with increased PEG 200 and propylene glycol levels **(Figure 1b)**.



a)



b)

Figure 1. a) 3D contour plot of %CDR of RIF and QUE at 60 min, **b)** 3D contour plot of Solubility of RIF and QUE

When choosing a model, it was found that a quadratic for RIF and special quartic for QUE with an adjusted R2 value (0.9323 for RIF and 0.9958 for QUE) that was closer to 1 provided the greatest match. Analysis of variance (ANOVA) was used to validate the model, and all statistical parameters were in the range depicting the best fit of the model. A coefficient of variance (%CV) (5.12 for RIF and 3.09 for QUE) value was less than 10%. Adequate precision value (14.88 for RIF and 32.76 for QUE) was found to be more than 10. The model's P value (0.0001 for RIF and QUE) was less than 0.05; the ANOVA analysis revealed that the models were significant for all of the responses, solubility of both drugs, and %CDR of RIF and QUE.

In favor of achieving better desirability, several constraints were imposed for increased solubility and % CDR based on statistical data and ANOVA analysis. To validate the experimental design, three runs of the experiment were recommended by the Design Expert program. As further anticipated error was estimated, Batch-B [Tween 20(0.1 ml): PEG 200 (0.462 ml): PG (0.437 ml)] was chosen for further analysis since it showed the lowest error relative to the other two batches.

Determination of flowable liquid-retention potential

Aeroperl exhibited the highest flowable liquid retention potential of all the carrier materials tested at 1.98 ml. This means that 1.98 ml of liquid medication may be accommodated with 1 g of Aeroperl powder, and it still maintains its good flow characteristics (angle of slide = 34). However, the maximum daily intake of Aeroperl should not

exceed 200 mg in accordance with the Inactive Ingredient Limit. And to absorb the liquid medication for the proposed formulation, more than 500 mg was needed. Therefore, we are unable to adsorb the liquid medication using Aeroperl, Syloid 244 EP, Syloid XDP 3150, or Neusilin US2 separately. Another carrier material with a 0.76 liquid retention potential has been added. We have, therefore, further investigated various carrier material ratios to obtain good adsorption and good flow properties. Aerosil exhibited the highest flowable liquid retention potential of all the coating materials evaluated, with a capacity of 1.922 ml.

Liquid load factor

Equation (1) was utilized to determine the liquid load factor. The - value for Avicel pH-102/Aeroperl 200 (5:1) was determined to be 1.15 ml, as previously discussed in the section. Aerosil 200 achieved the a -value of 1.92 for the chosen coating material. R was determined to be 6. Equation (1)'s determined Load factor (Lf) value was found to be 0.51 by putting all these values in it. It suggests that we can add a substantial amount of liquid medication to the powder.

Screening of carrier and coating material for the non-volatile vehicle

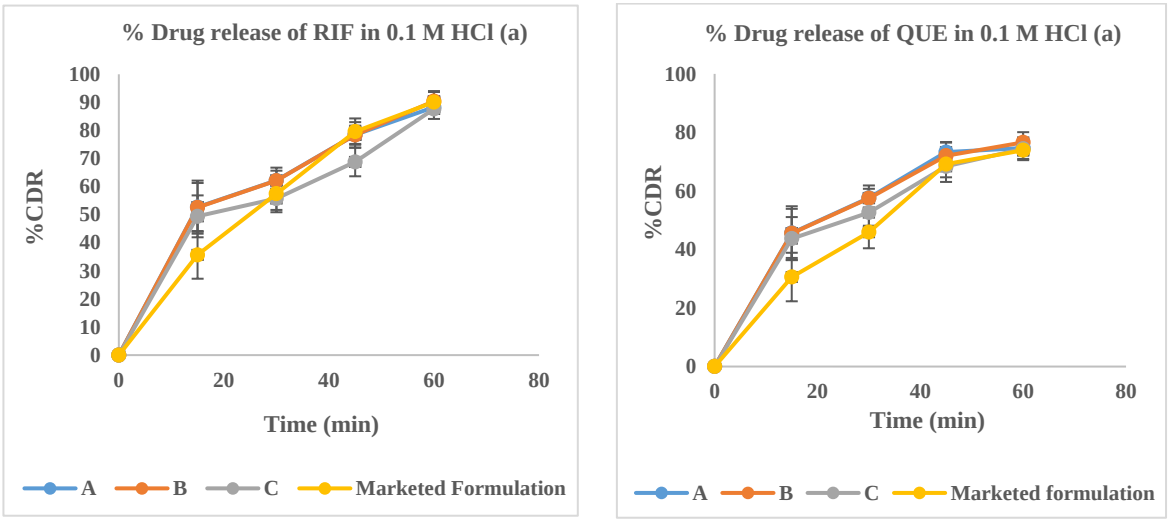
Based on the information in **Table 2**, we chose the carrier materials Avicel pH-102 and Aeroperl 200, and Aerosil 200 was chosen as the coating material to absorb 1 ml of liquid. To enhance the powder's flow characteristics, magnesium stearate and talc were added. The powder was then further filled into 00-size capsules to make it commercially viable.

Table 2. Selection of Carrier and coating material based on preliminary batches

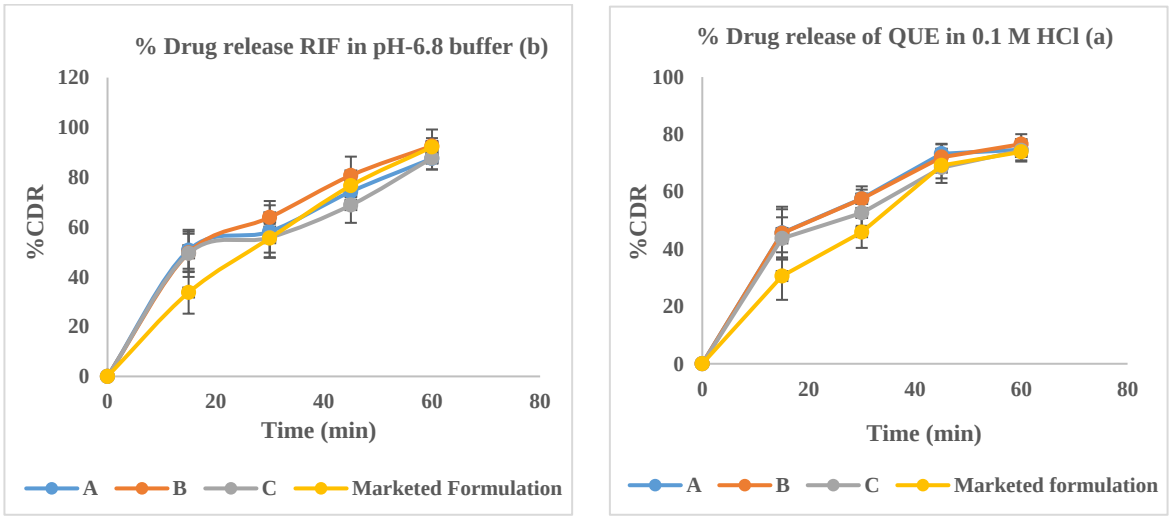
Batch	Avicel pH 102 (mg)	Lactose (mg)	DCP (mg)	Aeroperl 200 (mg)	Neusilin (mg)	Syloid XDP 3150 (mg)	Syloid 244 FP (mg)	Aerosil 200 (mg)	Magnesium Stearate & Talc (1:1) (mg)	Total Weight (mg)	Flow Property (Angle of Repose) θ
1	500	-	-	100	-	-	-	100	150	850	27
2	550	-	-	-	150	-	-	100	150	950	31
3	580	-	-	-	-	100	-	100	150	930	30
4	590	-	-	-	-	-	100	100	150	940	28
5	-	600	-	100	-	-	-	100	150	950	28
6	-	620	-	-	150	-	-	100	150	1020	28
7	-	610	-	-	-	100	-	100	150	960	29
8	-	610	-	-	-	-	100	100	150	960	29
9	-	-	630	100	-	-	-	100	150	980	27
10	-	-	640	-	150	-	-	100	150	1040	26
11	-	-	635	-	-	100	-	100	150	985	27
12	-	-	635	-	-	-	100	100	150	985	28

In-vitro dissolution studies

RIF and QUE were the subjects of a drug release investigation in 0.1 M HCl and phosphate buffer pH-6.8. For RIF, it was discovered that at 60 minutes, drug release was greater than 85% in 0.1 M hydrochloric acid and 90% in pH-6.8 phosphate buffer. In contrast, the drug release for QUE% was greater than 75% after 60 minutes in both pH-6.8 phosphate buffer and 0.1 M hydrochloric acids. For the commercial version of both medications, a similar release profile was seen **(Figures 2a and 2b)**.

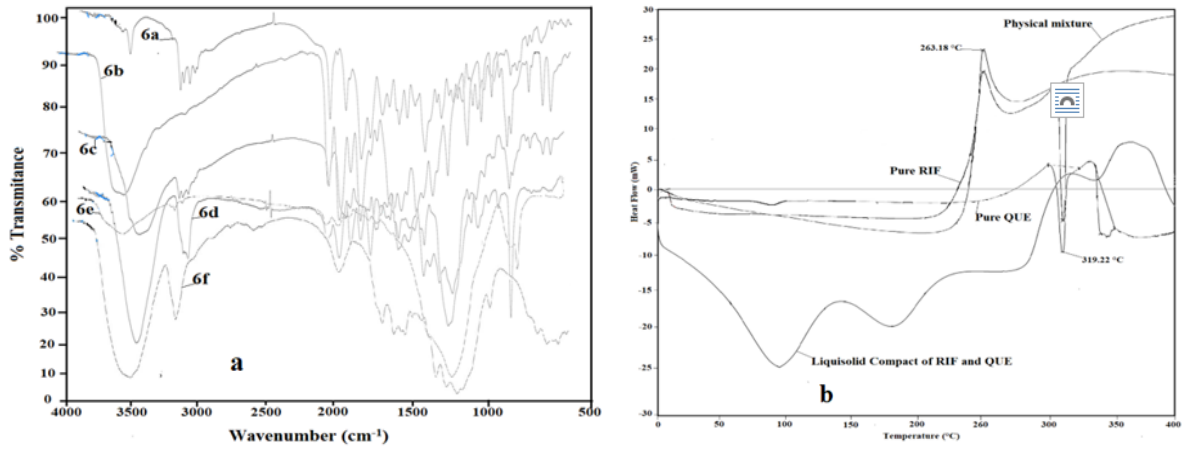


a)

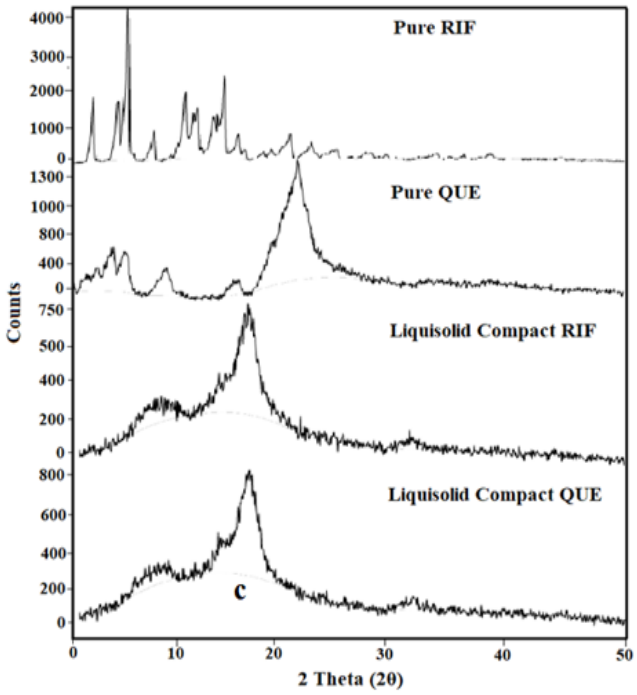


b)

Figure 2. a) The dissolution profile of RIF and QUE marketed product (MP)and test product (TP) in pH-6.8 phosphate buffer, **b)** The dissolution profile of RIF and QUE marketed product (MP)and test product (TP) in 0.1 M HCl



a) b)



c)

Figure 3. a) FT-IR spectra of Pure Rifampicin, Quercetin, and Liqui-solid formulation, **b)** DSC thermogram of Pure Rifampicin (a), Quercetin (b), Liqui-solid formulation (c), Avicel pH-102 (d), Aeroperl 200 (e), **c)** PXRD spectra of Pure Rifampicin, Quercetin, Aeroperl 200 and Liqui-solid formulation and Avicel pH-102.

Drug excipient compatibility studies

Fourier transform infrared (FT-IR) spectroscopy

Figure 3a displays the spectra of RIF. QUE, Avicel PH 102, Aeroperl 200, physical mixture, and liquid-solid compact. This study reveals that there was no significant change in the spectrum of liquisolid compacts when compared with the drug alone, as the incorporation of Rifampicin and Quercetin into the non-volatile liquid did not change the position of its functional groups. The absence of shifts in the wave numbers of the FT-IR peaks of the liquisolid formulations and prominent peaks observed for liquisolid compacts similar to a pure drug indicates the lack of significant interaction between the drug and the carrier in the mixture.

Differential scanning calorimetry (DSC) studies

Figure 3b displays the thermograms for RIF, QUE, Avicel PH 102, Aeroperl 200, the physical mixture, and the liquid-solid compact. The crystalline nature of the medication is confirmed by the DSC thermogram, which shows a clear, recognizable endothermic peak for rifampicin and quercetin at 263.18 and 319.22 °C to its melting temperature. The thermogram of the liquisolid compact in **Figure 3b** shows the complete disappearance of a peculiar peak. The absence of the distinctive peak clarified that the drug was in a solution form in the liquisolid system and was dispersed molecularly within the liquisolid compacts.

Powder X-ray diffractometry (PXRD)

RIF appears to be crystalline based on the several strong peaks at 2 of 11.67, 11.72, 11.77, 11.82, and 11.87. The numerous strong peaks at 2 of 11.21, 11.77, 11.87, 12.38, 12.53, and 13.09 also point to QUE's crystalline character. The non-volatile solvent was used to dissolve RIF and QUE, and the resultant solution was adsorbed by Avicel PH 102 and Aeroperl 200. Despite having peaks on the PXRD of the new liquisolid formulation at 11.72, 11.77, 11.87, 12.38, and 13.09, the peak intensity was significantly lower than that of the pure drug. This could be because the medication is present in an amorphous or solubilized state. Therefore, the constructive particular sharp peaks were missing from the liquisolid formulation's X-ray diffractogram **(Figure 3c)**.

Stability study

There was no significant change in the physicochemical properties of liquisolid powder after the stability period.

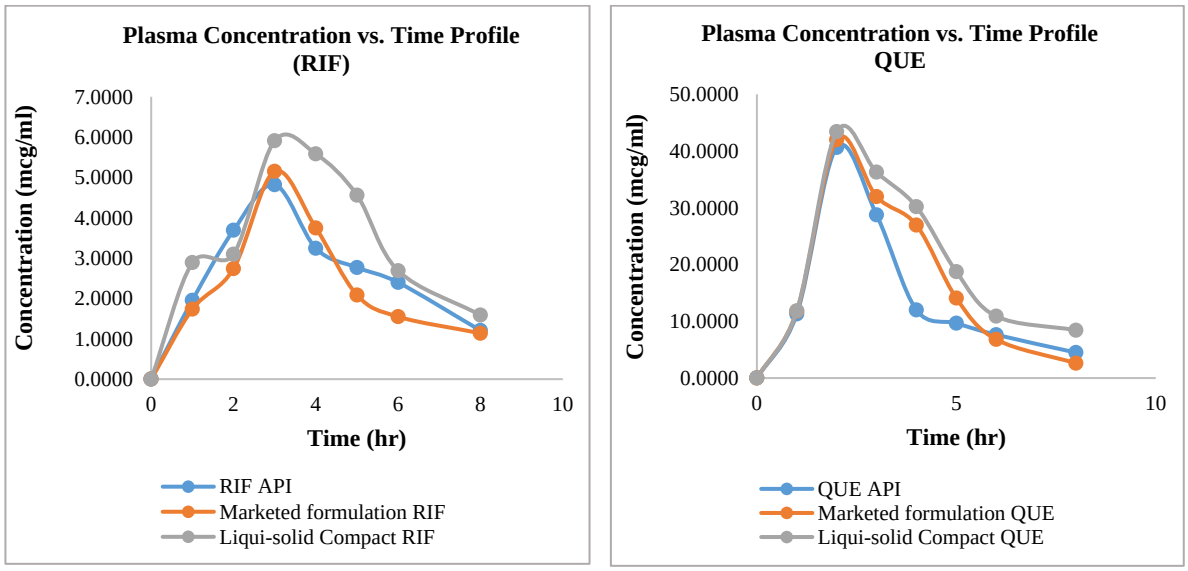
In-vivo pharmacokinetic study

RIF and QUE were found using the UPLC-MS/MS technique in rat plasma samples. The pharmacokinetic data make it abundantly evident that RIF and QUE absorption from Liqui-solid compact is comparable to those of the marketed formulation. When compared to the marketed formulation (5.15 µg/ml), the plasma concentration-time profile for RIF Liqui-solid compact (5.90 µg/ml) exhibited a similar Cmax. According to the Cmax value, the bioavailability and dissolution of the liquid-solid formulations RIF and QUE produce a blood level of bioavailability that is more similar to and does not significantly differ from the marketed formulation **(Table 3 and Figure 4)**.

Table 3. Pharmacokinetic parameters of spherical agglomerates and marketed formulation

Pharmacokinetic parameters	Liqui-solid compact		Marketed formulation		Pure API	
	RIF	QUE	RIF	QUE	RIF	QUE
AUC_{0-t} (µg.hr/ml)	27.65	165.72	18.91	139.58	19.67	118.28
$AUMC_{0-t}$ (µg.hr/ml)	108.82	587.38	71.11	452.01	79.02	379.81
MRT (hr)	3.93	3.55	3.75	3.23	4.01	3.21
C_{max} (µg/ml)	5.90	43.42	5.15	41.98	4.32	40.63
t_{max} (hr)	3	2	3	2	3	2
K_{ab} (hr^{-1})	0.49	2.22	0.62	1.03	0.96	0.80
K_{el} (hr^{-1})	0.32	0.31	0.28	0.53	0.26	0.33
$t_{1/2}$ (Absorption) (hr)	1.40	0.31	1.11	0.67	0.72	0.86
$t_{1/2}$ (Elimination) (hr)	2.11	2.18	2.46	1.29	2.58	2.05

AUC_{0-t}, area under the plasma concentration vs. time curve of last available measurement; $AUMC_{0-t}$, Area under the plasma concentration x time vs. time curve from 0 to time; MRT, Mean residence time; C_{max}, Maximum concentration; t_{max}, time of peak concentration; K_{ab}, Absorption constant; K_{el}, Elimination constant; $t_{1/2}$, Half-life



a) b)

Figure 4. Pharmacokinetic profile of RIF and QUE marketed product, Pure API and Liquisolid formulation in the rat.

CONCLUSION

The study shows that the liquisolid technique can be a tempting method for enhancing the dissolving profile of medications with high dose requirements and low water solubility. The drug release was enhanced by the addition of a non-volatile solvent and surfactant in a liquisolid compact. The use of the fractional factorial design approach has shown that different combinations of PEG 200, Propylene glycol, and Tween 20 have a substantial impact on drug release from the formulation. The better dissolution profile of the liquisolid compact was presumably caused by the medication being in an amorphous state or being molecularly disseminated in the liquisolid compact,

according to the results of DSC and XRD investigations. After a three-month storage period, stability testing showed that none of the formulation's key features had changed significantly. Pharmacokinetic studies revealed that the created formulation delivered more drugs to the bloodstream than the marketed product.

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