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Original article

Formulation and optimization of liquisolid compact for improving the dissolution profile of efavirenz by using DoE approach

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ABSTRACT

Efavirenz displays low and variable bioavailability because of its poor aqueous solubility and high log P-value. The present investigation was aimed to improve the dissolution profile of efavirenz by using a simple, scalable and cost-effective technique of liquisolid compact. The drug was dissolved in Trancutol-HP for preparing the liquid medicament which was subsequently mixed with carrier and coating material to make free-flowing and compressible powder. 3^2 full factorial design was used to optimize the formulation in which the Neusilin US2/Corn starch ratios and carrier/coating material ratio were selected as independent variables. The results of *in-vitro* dissolution test proved that liquisolid compacts have better dissolution profile compared to tablets containing pure drug. Results of DSC and XRD studies suggested that the high dissolution of the drug from the liquisolid compacts was possibly because of the drug either being in an amorphous state or being molecularly dispersed within the internal matrix of compacts.

1. Introduction

Efavirenz is a first-generation, non-nucleoside reverse transcriptase inhibitor recommended to be used in combination with two other reverse transcriptase inhibitors (tenofovir disoproxil fumarate + lamivudine + efavirenz) as a first-line treatment against HIV infection (Human Immunodeficiency Virus) (Organization, 2018). The daily recommended dose of efavirenz is 600 mg, to be given orally at empty stomach, preferably at bedtime for minimizing possible neuropsychiatric side effects (Vrouenraets et al., 2007). Efavirenz is currently available in 50 mg/200 mg capsules form and 600 mg film-coated tablet form. Efavirenz is BCS-II (low solubility, high permeability) drug having extremely low aqueous solubility (9.0 μg/ml) and low intrinsic dissolution rate (0.037 mg/min/cm^2). It is also a highly lipophilic drug with a log P value of 5.4. The drug molecules with an intrinsic dissolution rate of less than 0.1 mg/min/cm^2 often exhibit dissolution limited bioavailability problems when administered orally. (Kaplan, 1972) Due to these extreme properties (low water solubility and high lipophilicity), oral formulations of efavirenz display bioavailability only about 40–45% and it reaches the C_{max} within 3–5 h. Not only that but it also reported to have a very high intra (55–58%) and inter-subject variability (19–24%) (Fabbiani et al., 2009; Friedland et al., 2006).

This low bioavailability problem of efavirenz oral formulation has attracted many researchers to come up with better formulation strategies. Sathigari et al. have prepared inclusion complexes of efavirenz with ß-cyclodextrin (ß-CD), hydroxypropyl ß-CD (HPßCD), and randomly methylated ß-CD (RMßCD). The authors proved that physical and kneaded mixtures of efavirenz with CDs have better dissolution than that of the pure drug (Sathigari et al., 2009). Avachat et al. have prepared liquid crystal nanoparticles of efavirenz by sonication and spray drying methods. The prepared liquid crystal nanoparticles had a substantially high dissolution rate than the pure drug (Avachat and Parpani, 2015). Chiappetta et al. have prepared liquid aqueous formulation containing polymeric micelles of efavirenz for pediatric patients. (Chiappetta et al., 2010) Sathigari et al. have prepared a solid solution of efavirenz with Eudragit EPO and Plasdone-s-630 by hot-melt extrusion and proved that the dissolution rate of drug extrudes was substantially higher than that of the crystalline drug (Sathigari et al., 2012). Patel et al. have prepared efavirenz nanosuspension by using the media milling method and reported that oral bioavailability of efavirenz nanosuspension in rabbits

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was 2.19-fold higher than that of the marketed formulation (Patel et al., 2014).

Even though each of the previously attempted methods have good therapeutical potential, they all suffer from some of its own process related limitations. For example preparation of polymeric micelles by sonication and spray drying requires costly equipment like sonicator and spray dryer respectively. The formulation of a solid solution by hot-melt extrusion requires not only an expensive instrument such as a twin-screw extuder, but here the critical process parameters also need to be optimized very carefully for having uniform distribution of drug within the polymer matrix (Crowley et al., 2007). The stability of nanosuspension formulation is very challenging as the high surface energy of nanocrystals often leads to particle agglomeration and Oswald ripening. The formulations with aggregated particles loses the advantage of high saturation solubility and high dissolution velocity (Wu et al., 2011).

Compared to all of the above-mentioned techniques, the liquisolid compact system is simple, easy to scale up and low-cost formulation strategy for improving the dissolution rate of the poorly soluble drug. In the liquisolid compact, the drug particles are first dissolved, partially dissolved or suspended in the non-volatile liquid vehicle and subsequently adsorbed on the suitable carrier and coating excipients to make non-adherent, free flow and compressible powder mixture. When dissolved or suspended drug particles are mixed with carrier and coating excipients, they get entrapped into the internal matrix of excipients. Once liquid medication completely saturates the internal matrix then it starts to form a layer on the surface of carrier particles. This extra liquid remaining on the surface of the carrier material is adsorbed by coating material making the entire system dry and free-flowing (Spireas, 2002). In the light of above-mentioned facts, the primary aim of the present investigation was to prepare liquisolid compact of efavirenz for improving its dissolution profile.

Another key feature of this investigation is the application of DoE (design of experiment) approach to optimized the formulation compositions and to investigate the effect of change in the formulation compositions on the desirable product characteristics such as hardness, disintegration time and *In-vitro* percentage drug release at a specific time intervals. There are many excellent publications dealing with the preparation of liquisolid compacts for different drugs are available but in most the publications, the composition of the formulation was decided either by conventional trial and error method or by using information obtained from previously published articles (Chella et al., 2014, 2012; Hentzschel et al., 2012; Javadzadeh et al., 2009). In this investigation, 3^2 full factorial design was applied for exploring the effect of change in formulation composition on the key attributes of liquisolid compact. The optimized batch was selected by using the desirability function of Design expert software (trial version) based on composite desirability of selected responses.

2. Material and methods

Efavirenz was received as a generous gift from Bharat Parenterals Ltd., Vadodara, India. Transcutol HP, Capryol 90 and Labrasol were received as a gift sample from Gattefosse, France. Acrysol K140, Acrysol K150, Acrysol K160, and Kyron T314 were purchased from Corel pharma, Ahmedabad, India. Neusilin US2 and Fujicalin were purchased from Gangwal chemicals, India.

2.1. Solubility study of drug

Excess amount of drug was added in 10 ml selected non-volatile vehicles to form a supersaturated solution in a glass vial. The mixtures were vortexed for 15 min. to facilitate the mixing of drug and non-volatile solvent. The mixtures were kept in a shaker incubator at 25 °C for 48 h to achieve equilibrium. The samples were centrifuged at 5000 rpm for 30 min to sediment insolubilized drugs. The supernatants were diluted with methanol and analyzed for the drug content by using UV-spectrophotometer (Shimadzu UV-1800) at 247 nm.

2.2. Method for formulating liquisolid compact

The required amount of the drug and non-volatile co-solvent were added in 20 ml glass beaker and heated gradually until all the drug was solubilized. The resultant warm liquid medication was incorporated into the fixed amount of carrier and coating materials by the following the three steps as suggested by Spireas et al. In the first stage, the powder excipient and liquid medicaments were blended at an estimated mixing rate of one rotation per second for nearly one minute in order to have a uniform distribution of the liquid medication in the powder. In the second stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow the drug solution to get absorbed in the internal matrix of the powder material. In the third stage, the powder is scraped off from the surface of mortar by using an aluminum spatula and then mixed with the disintegrating agent for another 30 seconds in the same way as described in the first step. The yielded final liquisolid formulation was compressed in tablet form (Spireas, 2002).

2.3. Application of mathematical model for designing efavirenz liquisolid formulations

Spireas and Bolton have introduced a mathematical model for producing liquisolid compacts with acceptable flowability and compactibility. This model is based on the hypothesis that powder material can only accommodate a specific amount of liquid medicament (co-solvent + drug) in the inner matrix while preserving acceptable flowability and compatibility. Once the proportion of liquid exceeds the certain limit, the flow property and compactibility of the powder material starts to decline. This maximum amount of liquid which a powder material can retain while maintaining acceptable flowability and compatibility is known as flowable liquid-retention potential (Φ – number) and compressible liquid-retention potential (Ψ – number) respectively. The acceptable compactibility means the ability of powder material to produce cylindrical compacts of adequate crushing strengths (approximate 5–6 kg/cm^2) and acceptable friability without presenting any "liquid-squeezing - out" phenomena during compression. Once the inside matrix is saturated with liquid medication, the extra liquid will start to deposit as a layer on the surface of powder material. This extra layer of liquid is adsorbed by adding another powder excipients known as "coating material" that finally leaves the total powder material free-flowing, non-adherent and compressible. "Excipient Ratio" (R) is defined as the ratio of carrier and coating material **required** to make powder with acceptable flowability and compressibility.

$$R = Q/q \quad (1)$$

where Q = amount of carrier material and q = amount of coating material.

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

The liquid medicament was gradually added to the fix quantity powder material (10 gm) and this resulted admixture was placed at one end of the polished metal plate. The metal plate was gradually uplifted from one side while keeping the other side on the ground. The angle formed between plate and ground was consid-

ered as the angle of slide (Elkordy et al., 2013). The angle of slide value of around 33 represents the optimal flowable property of powder excipient with respect to the particular liquid vehicle used. (Tayel et al., 2008)

2.3.2. Determination of compressible liquid-retention potential (Ψ – value)

The liquid medicament was added gradually to 1 gm powder material for making uniform admixture. The admixture was compressed with specific hardness in the rotary tablet machine to make a tablet. In this investigation, the crushing strength value between 5 and 7 Kgf was considered as an acceptable one. During compression, it was also observed that there was no leakage of liquid medicament from the powder admixture (Spireas, 2002)

2.3.3. Liquid load factor

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

$$^{\Phi}\mathrm{Lf} = {}^{\Phi}\mathrm{CA} + {}^{\Phi}\mathrm{CO}\ (1/\mathrm{R})\ \text{for flowability} \quad (2)$$

$$^{\Psi}\mathrm{Lf} = {}^{\Psi}\mathrm{CA} + {}^{\Psi}\mathrm{CO}\ (1/\mathrm{R})\ \text{for compressibility} \quad (3)$$

Here $^{\Phi}$CA and $^{\Phi}$CO are flowability liquid retention potential of carrier and coating materials respectively and $^{\Psi}$CA and $^{\Psi}$CO are compressible liquid retention potential of carrier and coating materials respectively. R is the excipient ratio as defined by Eq. (1). According to studies published in different research articles, it was noted that the R-value between 10 and 20 resulted in optimal flow property and acceptable compactible property so in this investigation a mean of 15 was taken for calculation (Javadzadeh et al., 2007).

The liquid load factor can also be calculated by using the weight of liquid and carrier material as per the following equation.

$$Q = W/L_f \quad (4)$$

Q = Weight of carrier material and W = Weight of liquid medicament. Here between $^{\Phi}L_f$ and $^{\Psi}L_f$ whichever had the lower value was put in Eq. (4). Eq. (4) gave the weight of carrier material required to imbibe particular liquid medicament. The obtained value of Q was applied in Eq. (1) to calculate the value of the coating material required to adsorb the extra liquid layer from the surface.

2.4. Primary trial for selection of carrier and coating material.

The primary trials were conducted to identify the carrier and coating material which can accommodate maximum liquid medicament without losing flowability and compactibility. The methods used for screening are described in the above-mentioned section under the heading of ''Determination of Flowable liquid-retention potential" and ''Determination of compressible liquid-retention potential". The obtained values were put in Eqs. (3) and (4) for calculating the liquid loading factor.

2.5. Post compression evaluation parameters

2.5.1. Weight variation

Twenty tablets were randomly selected from each set and separately weighed. The average weight and standard deviation (SD) of three batches were calculated. The tablets considered passed weight of not more than two individual tablets weight varied from the average weight by more than 2.5% and no tablet deviated by more 5% of average weight.

2.5.2. Content uniformity

The content uniformity was measured by taking 10 tablets randomly from each batch. The tablets were weighted, crushed to powder and dissolved in methanol. The resulted solution was filtered through 0.45 μm membrane filter and analyzed using UV spectrophotometer at 247 nm.

2.5.3. Hardness

The hardness or crushing strength of the tablets was determined by using Monsanto hardness tester. Five different tablets from each batch were tested and the average hardness was calculated.

2.5.4. Friability

Friability was measured by using Roche friabilator. 10 tablets were weighted (W_0) and placed in the friabilator to be rotated at 25 rpm for 4 min. Tablets were collected, de-dusted, and weighed again. The difference in the initial weight and final weight (W_t) was used to calculate % friability.

2.5.5. Disintegration time

Six tablets were placed in the disintegration test apparatus and the time required for these tablets to completely disintegrate into fine particles was noted. The disintegration test was performed in 900 ml distilled water at 37 ± 0.5 °C temperature and at the rate of 30 ± 2 cycles/minutes.

2.5.6. In vitro dissolution study of formulation batches, marketed product, and pure drug-containing tablet

The drug release from liquisolid tablets, marketed formulation (Efcure® 200 mg, manufactured by Emcure Pharmaceuticals Ltd.) and tablets containing pure drug was measured by using USP type II paddle-type apparatus containing 900 ml of dissolution medium (0.1 N HCl + 0.5%w/v SLS) at 37 ± 0.5 °C. 5 ml aliquot was withdrawn after regular time intervals (0, 15, 30, 45 and 60 min.) and replaced with fresh medium. The aliquots were passed through 0.45 μm membrane filter and analyzed by UV–Visible spectrophotometer at 247 nm.

Dissimilarity factor (f_1) and similarity factor (f_2) were calculated by using the following equations.

$$f_1 = \frac{\sum R_t - T_t}{\sum R_t} * 100$$

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

where

R_t is drug release from reference at time t
T_t is drug release from reference at time t
n = number of sampling points

2.6. Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) study

The polymorphic properties of a drug can significantly affect the dissolution rate, bioavailability and therapeutic effectiveness of the formulation. Therefore, it was essential to study the polymorphic property of efavirenz in liquisolid formulations by DSC and XRD. For DSC study 5 mg samples of pure drug and liquisolid compact were sealed in standard aluminum pans. The samples were scanned at a rate of 5 °C/minutes from 20 °C to 350 °C. The empty pans were similarly sealed and used as a reference.

2.7. Stability study

The optimized formulation was stored at 40 °C and 75% RH for 3 months. The stored formulation was evaluated for key parameters like hardness, disintegration time and percentage drug release at the defined time period (15 min, 30 min, 45 min, and 60 min). The release profile of stored formulation was compared with freshly prepared liquisolid compact.

3. Results and discussion

3.1. Solubility study of drug

As depicted in Fig. 1, Transcutol HP (Highly purified diethylene glycol monoethyl ether) was able to solubilize the highest amount of drug followed by Capryol 90 and PEG-400. Transcutol HP is primary alcohol approved to use as a co-solvent in oral, topical and transdermal formulations. The practically determined solubility of efavirenz in water was around 0.008 mg/ml whereas in Transcutol-HP it was 739.29 mg/ml which was almost 92,000 × higher. The solubility of the drug in the non-volatile solvent is the primary determinant affecting the ability of liqiusolid compact to improve the dissolution rate. In fact, the previous study proved that the dissolution rate of the drug from liquisolid compact was directly proportional to the solubility of the drug in the non-volatile solvent (Nokhodchi et al., 2005). This is particularly important for drugs such as efavirenz, where high doses are required to accommodate in a unit dosage form.

3.2. Determination flowable liquid-retention potential

Among all the carrier materials screened, Neusilin US2 had the highest flowable liquid retention potential of 1.4 ml. This meant that 1 gm of Neusilin US2 powder was able to retain its good flow property even after accommodating 1.4 ml of liquid medicament with it (angle of slide = 33). This was followed by Compressil 101, Fujicalin and MCC respectively, thus Neusilin US2 was selected as carrier material. (Fig. 2). Among all the coating materials tested, aerosil had the highest flowable liquid retention potential of 1.6 ml. During initial the dissolution studies, it was observed that the liquisolid compacts containing only Neusilin US2 as carrier material were not able to release the drug completely. This was possibly because of the drug was entrapped firmly in the internal matrix of Neusilin US2. To overcome this problem corn starch was mixed with Neusilin US2. Starch is widely used as a disintegrating agent in tablets because of its swelling property. The swelling property of starch was expected to help the drug to get released easily from the high internal surface area of Neusilin US2. (Kottke et al., 1992). The angle of slide was again measured for three newly prepared mixtures of corn starch and Neusilin US2 with the ratios of 1:9, 2:8 and 3:7. It was practically observed that corn starch and Neusilin US2 in the ratio of 1:9 and 2:8 had the same liquid retention potential as for plain Neusilin US2 (1.4 ml). In the subsequent trials it was also observed that as the proportion of corn starch was further increased in the mixture, the liquid retention potential started to decrease drastically so it was decided to use Neusilin US2/corn starch mixture as the carrier material in the ratio of 9:1 and 8:2.

3.3. Determination of compressible liquid-retention potential (Ψ – Value)

During the compressibility test, it was observed that Neusilin US2/corn starch in the ratio of 9:1 and 8:2 was able to retain

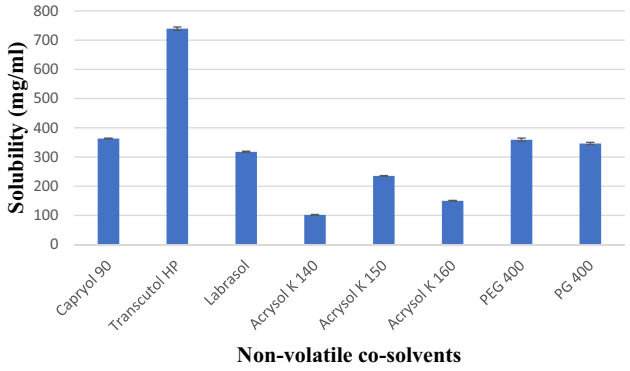


Fig. 1. Solubility of the drug in various non-volatile co-solvents.

1.4 ml of Transcutol HP without presenting any leakage problem and were also able to provide acceptable hardness.

3.4. Liquid load factor

The liquid load factor was calculated by using Eqs. (2) and (3). As described in the previous section, the Φ – value and Ψ – value for Neusilin US2/corn starch (9:1 and 8:2) were taken as 1.4 ml. For the selected coating material, aerosil 200 obtained Φ – value for was 1.6. The R-value as described in the introduction part was taken as 15. By putting all these values in equation (3) and (4), the calculated value of ${}^{\Phi}Lf$ and ${}^{\Psi}Lf$ were found to be 1.66 and 1.4 respectively. Since the ${}^{\Psi}L_f < {}^{\Phi}Lf$, the value of ${}^{\Psi}L_f$ was finally considered as a liquid load factor for this particular liquisolid system.

3.5. Determining the weight of liquid medication

The practically measured solubility of efavirenz in Transcutol HP was found to be 739.27 mg/ml. To dissolve 200 mg of efavirenz, 267.3 mg of Transcutol HP was required (density of Trasncutol HP is 0.99 gm/ml) which led to the total weight of liquid medicament at 467.4 mg. (Drug + co-solvent = 200 mg + 267.3 mg)

3.6. Determining the weight of carrier material

It was calculated by using Eq. (4), by putting the value of W = 467.3 mg (weight of liquid medicament) and L_f = 1.4 (Liquid load factor) in it. The weight of required carrier material was found to be 333.78 mg

3.7. Determining the weight of coating material

By using Eq. (1) the weight of the required coating material was calculated, it came to 22.25 mg.

3.8. Primary trial for selection of carrier and coating material.

The composition of preliminary batch is given in Table 1. The quantities for Transcutol HP, carrier material and coating material were taken as per calculation steps explained in the previous section. Kyron T-314 as disintegrant (4% w/w) and Magnesium Oxide (MgO) as a lubricant (1%w/w) were also added in the formulation. During preliminary trials it was observed that the Neusilin US2/-corn starch ratio and R-value (carrier/coating material) had a significant effect on the drug release from the liquisolid compact, so it was decided to use 3^2 full factorial designs for determining the extent of their impact on the desired product characteristics. Table 2 displays the coded and transformed values for selected

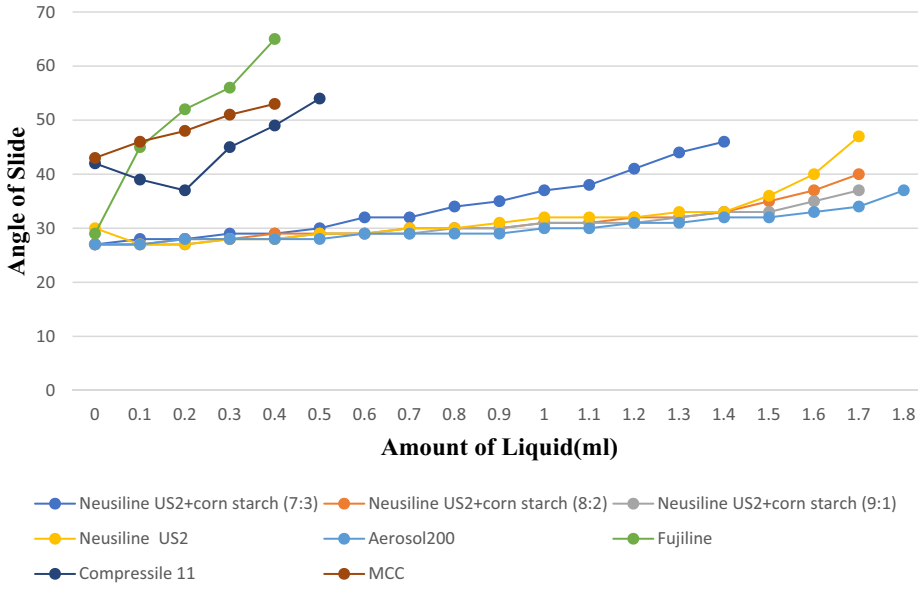


Fig. 2. Determination of Φ value for carrier and coating material.

Table 1
Composition of preliminary batch.

Efavirenz	Transcutol HP	Q (Neusilin US2)	q (Aerosil 200)	Kyron T 31	MgO
200 Total Weight = 911.56	267.3	333.78	66.75	34.71	9.02

*All the weights are in mg.

Table 2
Coadded and transformed value for design batches.

Batch code	Coadded value		Decoded value	
	X_1 (Neusilin US2 + CS)	X_2 (R value)	X_1 (Neusilin US2 :CS)	X_2 (R-value)
F-1	−1	−1	1:0	5
F-2	0	−1	9:1	5
F-3	1	−1	8:2	5
F-4	−1	0	1:0	10
F-5	0	0	9:1	10
F-6	1	0	8:2	10
F-7	−1	1	1:0	15
F-8	0	1	9:1	15
F-9	1	1	8:2	15

independent factors: X_1 - Neusilin US2/corn starch ratio and X_2 – Carrier/Coater ratio. The composition of all the design batches is given in Table 3.

Table 4 displays the results of the various physicochemical tests performed on design batches.

3.9. Post compression evaluation parameters for designed batches

3.9.1. Weight variation

The average weight of tablets from each prepared batch was well within the range of acceptable limits.

3.9.2. Content uniformity

The drug content in all the prepared formulations was more than 95%, within the range of acceptable limits.

3.9.3. Hardness

The prepared liquisolid compacts have hardness between 6.2 and 5.0 Kgf which was in the acceptable range for the conventional tablets.

3.9.4. Friability

No tested formulation has lost more than 1% weight during the friability test and no visible cracks were observed on the surface of any tablets.

3.9.5. Disintegration time

The disintegration time for all prepared liquisolid compacts was less than 3 min which is within the acceptable range.

3.9.6. In vitro dissolution study of formulation batches, marketed product, and pure drug-containing tablet

The dissolution profile of efavirenz liquisolid tablets (F1-F9), marketed formulation and pure drug-containing tablets is given

Table 3
Composition of design batches.

Batch Code	Efavirenz	Transcutol HP	Q (Neusilin + CS)	q (Aerosil 200)	Kyron T 314 (4%)	MgO (1%)	Total Weight
F1	200	267.3	333.78 (333.78 + 0)	66.75	34.71	9.02	911.56
F2	200	267.3	333.78 (300.40 + 33.38)	66.75	34.71	9.02	911.56
F3	200	267.3	333.78 (267.02 + 66.76)	66.75	34.71	9.02	911.56
F4	200	267.3	333.78 (333.78 + 0)	33.37	33.37	8.67	876.49
F5	200	267.3	333.78 (300.40 + 33.38)	33.37	33.37	8.67	876.49
F6	200	267.3	333.78 (267.02 + 66.76)	33.37	33.37	8.67	876.49
F7	200	267.3	333.78 (333.78 + 0)	22.25	32.93	8.56	864.82
F8	200	267.3	333.78 (300.40 + 33.38)	22.25	32.93	8.56	864.82
F9	200	267.3	333.78 (267.02 + 66.76)	22.25	32.93	8.56	864.82

*All the weights are in mg.

Table 4
Post-compression parameters of design batches.

Batch	Thickness (mm)	Hardness (Kgf)	Weight Variation (mg)	Drug Content (%)	Disintegration Time (sec.)	% CDR in 15 min (Y_1)	% CDR in 30 min (Y_2)
F-1	7.58 ± 0.031	6.2	910.7 ± 1.78	97.63 ± 1.17	67.33 ± 2.51	38.84 ± 0.84	69.51 ± 0.85
F-2	7.56 ± 0.026	5.8	910.1 ± 1.38	97.05 ± 1.31	65.66 ± 1.52	64.84 ± 1.68	90.33 ± 0.99
F-3	7.53 ± 0.032	5.6	910.7 ± 1.95	97.10 ± 1.42	67.66 ± 2.51	74.91 ± 1.52	98.02 ± 1.3
F-4	7.35 ± 0.030	5.4	874.3 ± 1.01	96.45 ± 0.96	76.33 ± 3.78	38.11 ± 0.39	71.25 ± 1.2
F-5	7.32 ± 0.026	5.4	875.6 ± 1.42	97.05 ± 1.65	74.33 ± 4.50	55.71 ± 1.60	91.90 ± 0.28
F-6	7.37 ± 0.044	5.6	875.4 ± 0.95	96.59 ± 1.06	74.00 ± 2.64	69.06 ± 1.77	92.33 ± 0.66
F-7	7.09 ± 0.050	5.0	864.7 ± 1.04	97.59 ± 1.14	80.33 ± 1.52	38.96 ± 0.18	63.80 ± 1.41
F-8	7.14 ± 0.044	5.2	863.3 ± 0.81	96.93 ± 1.23	77.00 ± 2.54	57.7 ± 0.99	86.8 ± 1.07
F-9	7.08 ± 0.040	5.0	864.0 ± 1.44	97.00 ± 1.70	76.33 ± 2.51	65.18 ± 1.17	84.74 ± 0.48

*n = 3 batches.

in Fig. 3. The cumulative drug release (CDR) from formulation F-1, F-4, and F-7 after 15 min was less than 40% whereas it was more than 55% for all other batches. At the same time, the marketed product was able to release around 60% drug. The high drug release from other batches was because of the presence of corn starch in their composition. Because the corn starch has excellent swelling property, it was able to quickly push and unlock the drug from the internal matrix of Neusilin US2. Compared to liquisolid tablets, pure drug-containing tablets was able to release only 15% drug in 15 min which was significantly lower ($f_2 < 50$) than prepared liquisolid compacts. After 30 min. the drug release from the batches F-1, F-4 and F-7 were around 70%, compared to that the drug release from other batches (F-2, F-3, F-5, F-6, F-8 and F-9) and marketed products was around 85% and 80% respectively. At 30 min time interval also, the percentage drug release from all the design batches was significantly higher than that of tablets containing the pure drug which was only around 30% ($f_2 < 50$). All the design batches were able to release almost 100% drug before the end of 60 min, where only 39% drug was released from pure drug tablets at the end of 60 min. The marketed product was able to release more than 90% drug in 60 min.

The improved dissolution profile of efavirenz from liquisolid tablets can be explained by using the modified "Noyes–Whitney" equation as mentioned below.

$$\frac{dC}{dt} = \frac{DS}{Vh}(Cs - C)$$

where dC/dt is the change in concentration of drug over time (dissolution rate), D is the diffusion coefficient, S is the effective surface area, surface area of the particles which is in contact with dissolution medium, V is the volume of the dissolution medium, h is the thickness of the diffusion layer, C_S is the saturation solubility (concentration of drug at dissolving surface) and C is the concentration of drug in the dissolution media at time t (Siepmann and Siepmann, 2013). During the dissolution test, all the tested formulations (design batches, marketed product, and pure drug tablet) had to experience the same external parameters such as temperature, composition and volume of dissolution medium. Based on that it could be assumed that dissolving particles from all the tested formulations had the same width of the diffusion layer around them. In the modified "Noyes–Whitney" equation, if D, V and h are assumed to be constant then the dissolution rate (dC/dt) becomes directly proportional to the effective surface area (an area of drug particles in direct contact with the dissolution medium) and difference in the concentration of drug in the diffusion layer and bulk dissolution medium.

The first step in the liquisolid system was to dissolve the drug in Transcutol HP where it was expected to either be molecularly dispersed or to have significantly lower particle size than the pure crystalline drug. This conclusion was verified by the results of the DSC and XRD studies given in Fig. 4(a) and (b) respectively. In DSC study, a single sharp exothermic peak for was observed at approximately 140 °C for the crystalline efavirenz where, in the case of the optimized batch, the peak was completely absent likely because the crystalline drug was converted into the amorphous form or the drug was being molecularly dispersed in the liquisolid compact (Zahedi and Lee, 2007). This finding was further supported by the XRD test, in which the pure drug exhibited the sharp diffraction peaks compared to no diffraction peaks for the optimized batch (Fig. 4(b)). It is a well-established fact that thermodynamically unstable amorphous form contains very high internal energy compared to stable crystalline form, resulting in a high dissolution rate of amorphous drug (Alonzo et al., 2010). In the second scenario where the drug is considered to be molecularly dispersed in the liquisolid compact, it is expected to get directly release at molecular level only in dissolution medium compared to large crystal form in case of pure drug containing tablet (Chella et al., 2012).

Another dissolution promoting feature of liquisolid compact is its ability to reduce the interfacial tension between the drug particles and the dissolution medium because of the presence of the non-volatile liquid. The non-volatile liquid acts as the bridge between the drug particle and dissolution medium, thereby promoting easy diffusion of the drug molecule from the dissolving surface. This kind of bridging mechanism is completely absent in tablets containing pure drug (Fahmy and Kassem, 2008). The pres-

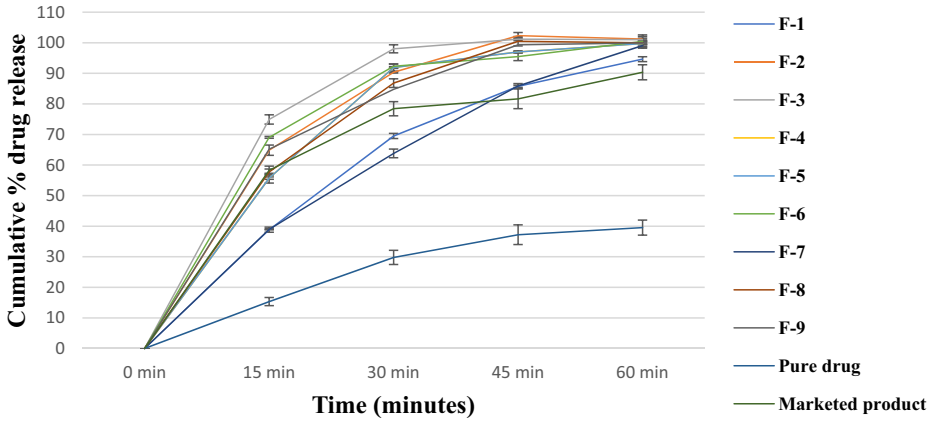
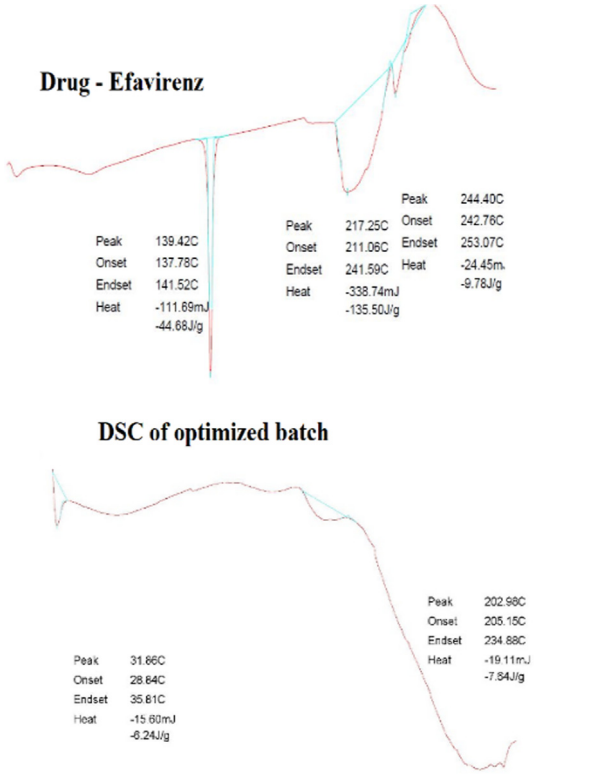


Fig. 3. *In vitro* dissolution study of design batches and pure drug-containing tablet.



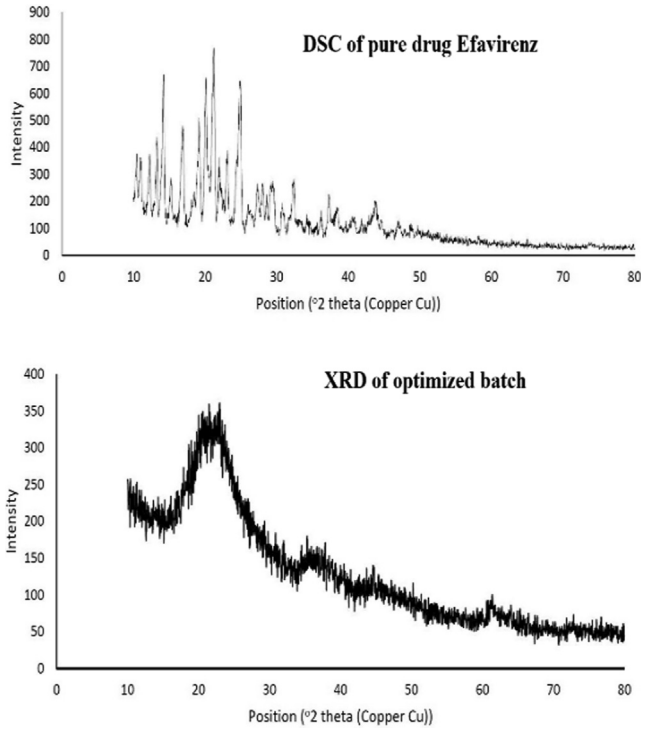


Fig. 4 (*continued*)

Fig. 4. (a) DSC of pure drug and optimized batch and (b) XRD of pure drug and optimized batch.

ence of non-volatile liquid around the particle in the liquisolid system may also have helped in dissolving more drugs in the stagnant diffusion layer, resulting in high concentration gradient (Cs-C) between the diffusion layer and bulk medium, leading to better dissolution of the drug according to modified "Noyes–Whitney" equation. (Burra et al., 2011).

3.10. Statistical analysis and graphical presentation of the obtained results

The primary objective of preparing liquidsolid compact was to improve the dissolution profile of efavirenz so cumulative drug release in 15 min (Y_1) and 30 min (Y_2) were selected as the response variables. The obtained R^2 value for both response variable Y_1 and Y_2 was 0.99 and 0.94 respectively which confirmed the excellent predictability of the regression model. For both the variables, $F_{calculated} \gg F_{tabulated,}$ with F significant value of less than 0.05 which proved the validity of the over-all models. The polynomial equations generated from the regression analysis for response variable Y_1 and Y_2 are mentioned below. The terms having a p-significant value of more than 0.05 were omitted from the equation.

$$Y_1 \text{ (\% CDR in 15 Minutes)} = 57.79 + 15.54X_1 - 2.78\,X_2 - 5.24\,X_{11}$$
$$Y_2 \text{ (\% CDR in 30 Minutes)} = 91.61 + 11.70X_1 - 3.60X_2 - 9.60\,X_{11}$$

For responses Y_1 and Y_2, the positive coefficient for term X_1 suggested positive effect of independent variable X_1 on response variables Y_1 and Y_2. It meant that as the value of X_1 (proportion of corn starch in the fixed weight mixture) increased, the percentage drug release in 15 min and at 30 min also increased. This was possibly because the corn starch was able to pushed the drug to get released

from the internal matrix of Neusilin US2 due to its high swelling property. The 3D response surface plot and contour plots depicted in Fig. 5(a) and (b), suggested how the response variables (Y_1 and Y_2) varied with respect to change in independent variables. The plots suggested that variable X_1 had higher influence on the amount of drug released at both time intervals than variable X_2. A clear linear relationship was observed between both the independent variables (X_1 and X_2) and response variable Y_1 where in the case of response variable Y_2 it is not exactly linear.

3.11. Desirability function for the selection of optimized batch

After fitting the mathematical model, the desirability function in Design Expert® software (trial version) was used to select the optimized batch. The software merges all the response variable in such a way that the final selected optimized batch has the right balance of all the desired properties. All the responses are bought to the same scale by assigning them a value between 0 and 1, depending upon the desirability of the response. A desirability value of 0 represents an unacceptable value for the responses, and a value of 1 the most desired one. The software assigned desirability for individual response and gave composite desirability value for each batch by taking the geometric mean of the desirability of all the responses. The constrained values selected for the optimized batch is given in Table 5.

The solutions suggested by the software are graphically represented as an overlay plot and desirability plot in Fig. 6(a) and (b) respectively. The software recommended batch F-3 with the highest overall desirability of 0.91 so it was selected as the optimized batch.

Table 5
Constrains value selected for the optimized formulation.

Responses	Constrains		
	Minimum	Maximum	Goal
% CDR at 15 min.	70	75	Maximum
% CDR at 30 min.	90	100	Maximum

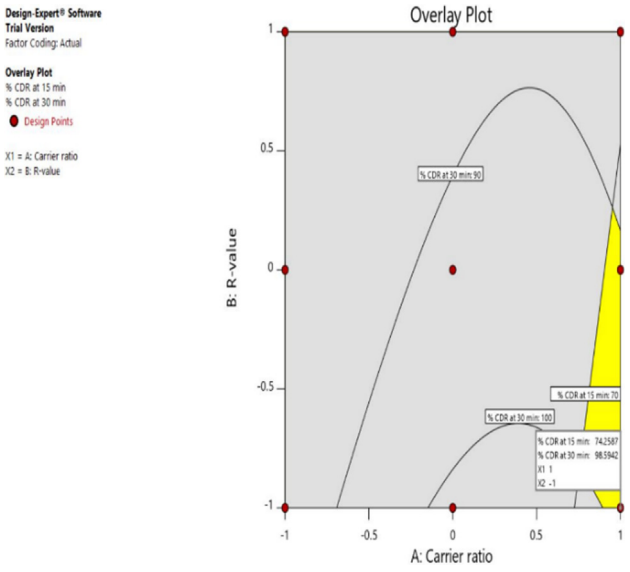


Fig. 6. (a) Overlay plot for response variable and (b) Desirability plot for optimized batch.

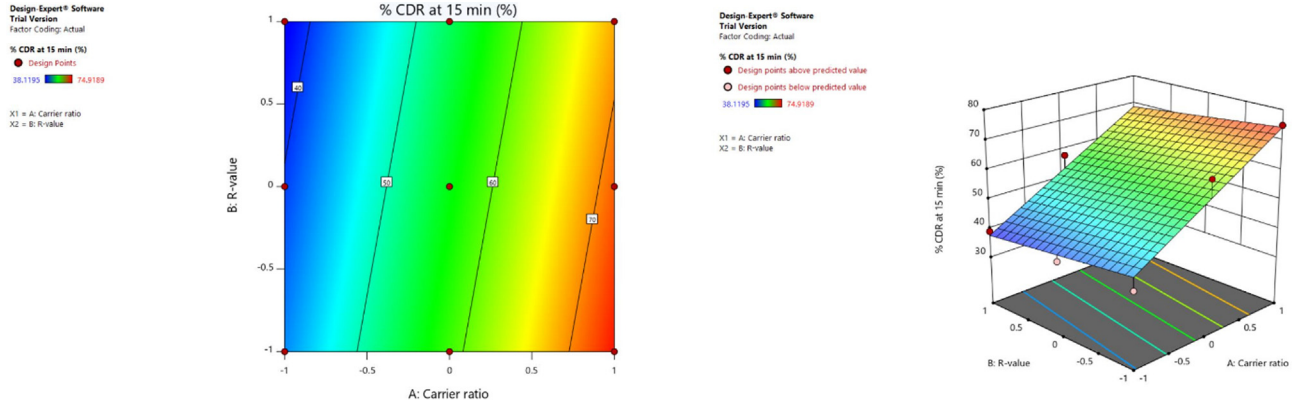


Fig. 5. (a) 3D response surface plot and contour plot of % CDR at 15 min. (Y1) and (b) 3D response surface plot and contour plot of % CDR at 30 min. (Y2).

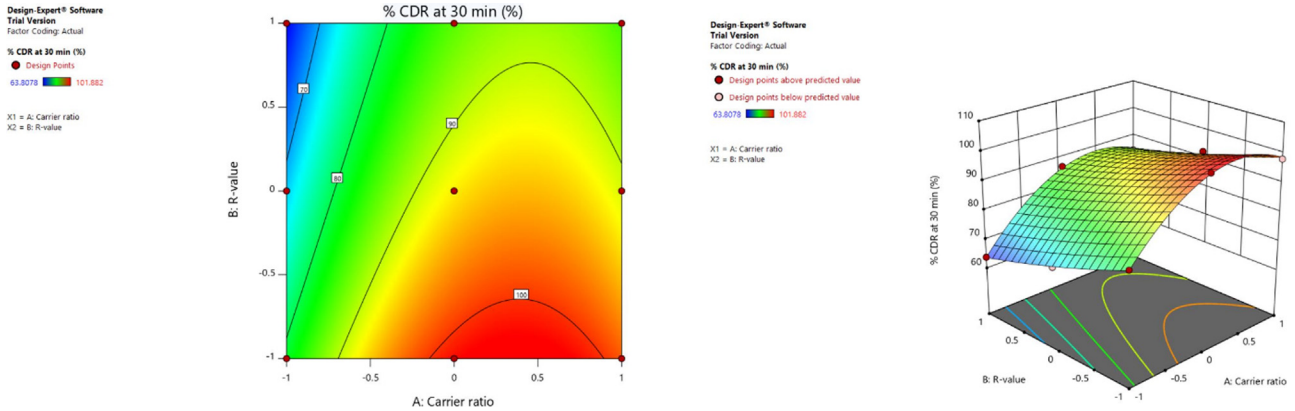


Fig. 5 (*continued*)

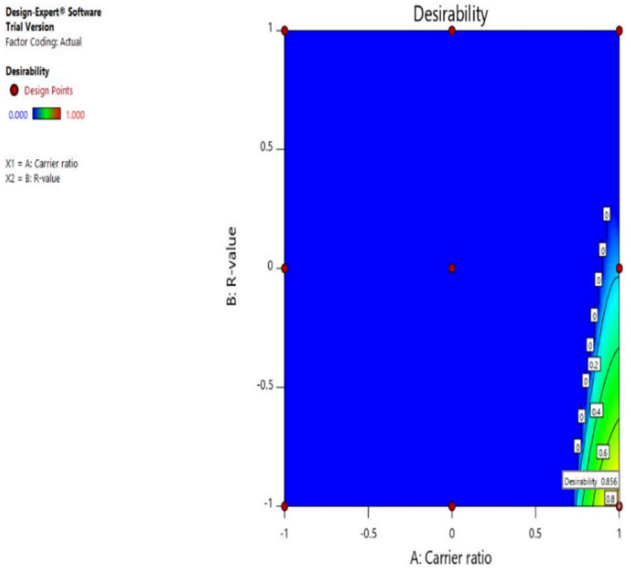


Fig. 6 (*continued*)

3.12. Stability study

There was no significant change in the physicochemical properties of liquisolid tablet after the stability period. There was a slight increase in disintegration time for the stored formulation but it was well within the acceptable limit of 15 min. DSC study suggested that there was slight recrystallization of the drug in liquisolid tablets at the end of the stability period, but it had no significant effect on the dissolution profile of optimized formulation.

4. Conclusion

The study proved that liquisolid technique can be an enticing approach for improving the dissolution profile of drugs having high dose requirements and low water solubility. The addition of corn starch in liquisolid compact was able to improve the drug release. Application of the DoE approach has revealed that carrier to coating ratio and mixing of corn starch with Neusilin US 2 have a significant effect on drug release from the formulation. The design batches have acceptable tableting properties such as flow property, compactibility, hardness, friability, content uniformity and disintegration time. The design batches had significantly high dissolution rate compared to pure drug-containing tablets at all the defined time intervals. The results of DSC and XRD studies suggested that the improved dissolution profile of liquisolid compact was possibly either due to the drug being in an amorphous state or molecularly dispersed in the liquisolid tablet. Stability studies revealed that there was no significant change in any pivotal characteristics of the formulation at the end of 3 months storage period.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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