Design, Formulation and optimization of liquisolid compact of Atazanavir by using DoE approach

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ABSTRACT

Because of its limited water solubility, the anti-HIV drug atazanavir requires a unique drug delivery mechanism to improve its therapeutic efficacy and safety. The primary purpose of this study was to develop a method for producing liquisolid powder compacts (LSPCs), which have been shown to be a promising solubility enhancement technique for effective oral administration of BCS class II drugs. Therefore, a unique LSPC formulation of the BCS class II drug atazanavir was developed in an effort to enhance its oral administration. Transcutol HP, propylene glycol, span 20, and span 80 were used in the solubility tests. Transcutol HP was used in the formulation of the LSPCs since it is a non-volatile solvent. In order to measure how various formulation factors affect LSPC performance, a 3^2-factorial design was used. Dependent variables were disintegration time and cumulative drug release percentage; independent variables were the percent of ataznavir in transcutol HP (X1) and the percent of sodium starch glycolate (X2). High dissolving profile with acceptable tablet characteristics were achieved in LSPCs of Atazanavir prepared with propylene glycol at the optimal drug concentration. No drug-polymer interactions were found using Fourier transform infrared spectroscopy (FTIR), and Atazanavir was converted from a crystalline to an amorphous state using differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The potential of LSPCs for increased permeation of Atazanavir over the rat intestinal barrier was also highlighted by permeation tests performed in isolated rat intestine. The better oral administration of Atazanavir shown by the increased penetration of clonazepam from LSPCs formulation through rat gut warrants further investigation.

Keywords: Atazanavir, Fourier transform infra-red spectroscopy, differential scanning calorimetry, liquisolid powder compacts, anti-HIV, 3^2 factorial design, Drug release studies.

INTRODUCTION

The oral route is the most preferred means of drug administration due to the ease, high patient compliance, and low cost of production. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT) when given orally [1,2]. In the case of poorly soluble drugs, dissolution is the rate-limiting step in absorption process. Generally, compounds with aqueous solubility lower than 100 mg/mL show dissolution-limited absorption and erratic and/or incomplete absorption from the gastrointestinal tract of animals and humans. Advancements in the fields of biotechnology and drug discovery have led to the discovery of increasingly large number of active molecules [3]. However, 40% of all newly developed drugs are poorly soluble or insoluble in water, leading to ineffective absorption and therapeutic failure. Various techniques are reported to improve the dissolution of poorly soluble drugs, including solid dispersions, crystal engineering, ball milling, complexation, self-emulsifying drug delivery systems and the use of mesoporous silica carriers [4,5,6]. Recently, the liquisolid technique has shown promise for improved dissolution. The concept of liquisolid tablets was developed from powdered solution technology that can be used to formulate liquid medication. A liquisolid system is defined as dry, non-adherent, free-flowing

and compressible powder mixtures converted from liquid drugs, drug suspensions or drug solutions in nonvolatile solvents with selected carriers and coating materials [7]. In this technique, the drug is dissolved in a non-volatile liquid and converted to dry, free flowing and compressible solid using carrier and coat materials. Since non-volatile solvents are used to prepare the drug solution/ suspension, the liquid is not evaporated and the drug is carried in a liquid system and is dispersed throughout the final product. A mathematical model by Spireas and Bolton was used to calculate the required quantities of carrier and coating material to be added to produce acceptable flow and compressibility [8].

In the light of above-mentioned facts, the primary aim of the present investigation was to prepare liquisolid compact of Atazanavir 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 [9,10]. The optimized batch was selected by using the desirability function of Design expert software (trial version) based on composite desirability of selected responses [11,12].

MATERIALS AND METHODS

Atazanavir was received as a generous gift from Hetero pvt. Ltd, India. Aerosil and Sodium Starch Glycollate were purchased from Loba Chemicals Mumbai, India. Propylene Glycol, Poly Ethylene Glycol (PEG) 200,300,400,600 were purchased from S.D fine chem. Limited. Tween 20 and 80; Span 20 and 80 were purchased from Corel pharma, Ahmedabad, India.

Solubility

Atazanavir solubility has been evaluated in a variety of solvents, including but not limited to: distilled water, Transcutol HP, PEG-200, PEG-400, and PEG-600; methanol; chloroform; phosphate buffer; and pH 1.2 and 6.8. was calculated using a magnetic stirrer at ambient temperature [13].

Formulation of Liquisolid Compacts

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 [14]. 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 [15]. 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.

Application of mathematical model for designing Atazanavir liquisolid formulations

In order to create liquisolid compacts with desirable flowability and compactability, Spireas and Bolton have presented a mathematical model [16]. This model is predicated on the assumption that a given quantity of liquid medicament (co-solvent + drug) in the inner matrix would not adversely affect the flowability or compatibility of the powder material. When the powder's liquid content rises over a particular threshold, its flow quality and compactability begin to degrade. Powders have a flowable liquid-retention potential (- number) and a compressible liquid-retention potential (- number) that indicate how much liquid they can hold without losing their flowability or compatibility. Powder materials with acceptable compactability are those that, when compressed, do not exhibit the "liquid-squeezing-out" phenomenon and instead form cylindrical compacts with suitable crushing strengths (about 5-

6 kg/cm2) and acceptable friability. The excess liquid drug will begin to accumulate as a coating on the surface of the powder after the inside matrix has been soaked [17]. Powder excipients known as "coating material" are used to adsorb the additional layer of liquid, making the final powder substance flowable, non-adherent, and compressible. To create a powder with suitable flowability and compressibility, the "Excipient Ratio" (R) is the proportion of carrier to coating material. [R] is defined in [R] =.

$$R = \frac{Q}{q}$$

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

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

The liquid drug was slowly added to the predetermined amount of powder material (10 gm), and the resulting admixture was then deposited at one end of the polished metal plate. One edge of the metal plate was raised off the ground while the other was kept in place [18]. The angle of slide was calculated as the distance between the plate and the ground. Powder excipients' flowability is maximized with regard to the liquid vehicle by having an angle of slide value close to 33.

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

To get a consistent admixture, 1 gm of powder was slowly infused with the liquid drug. Using the rotating tablet machine, the admixture was crushed to the desired hardness. Crushing strengths between 5 and 7 Kg f were found to be satisfactory in this study. No liquid drug was seen to escape from the powder admixture during compression [19].

Liquid load factor

The liquid load factor required for satisfactory flowability and compressibility was determined using the following equations after the - value and - value of the carrier and coating material had been determined.

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

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

The flowability liquid retention potential of the carrier material and the compressible liquid retention potential of the coating material are denoted by CA and CO, respectively [20]. With reference to Eq. (1), we denote this relationship as R, where R is the excipient ratio. The optimum flow property and acceptable compactible property were found to occur at an R-value between 10 and 20, and the mean of these values was used in this study's computation (R=15; p=.085).

$$Q = \frac{W}{Lf}$$

Weight of liquid drug (W) = Weight of carrier substance (Q)

Primary trial for selection of carrier and coating material.

Initial tests were done to determine which carrier and coating material could hold the most liquid drug while yet being easily dispensed and compacted [21]. See the subsections under "Determination of Flowable liquid-retention potential" and "Determination of compressible liquid-retention potential" for further information on the screening procedures that are used. The liquid loading factor was computed by plugging the results into Eqs. (3) and (4).

Precompression evaluation parameters

Bulk density

Atazanavir's bulk density was measured by carefully transferring 5.00gm from a glass funnel into a 20 ml graduated cylinder. The space taken up by each sample was measured [22].

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density

With the use of a funnel, a precisely measured sample of powder was introduced to the graduated cylinder [23]. Standard procedure is for noting the starting volume, then tapping the sample (50, 100, 150, or 250 times) until no further decrease in volume is noticed or the percentage change is less than 2%.

Tapped density = Wt. of sample in gm / Tapped volume

Compressibility Index and Hausner's ratio

Powder bulk density and tapped density were used to calculate the compressibility index and Hausner's ratio, respectively [24].

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{X100}$$

Hausner's Ratio = Tapped Density / Bulk Density

Angle of repose

The powder mixture's angle of repose was calculated using the funnel technique. A funnel was used to collect the precisely measured powder. The height of the funnel was modified such that its tip barely made contact with the peak of the powder mound. The angle of repose was determined by measuring the powder cone's diameter with the help of the formula [25].

$$\text{Tan } \theta = h/r$$

Where, h and r are the height of pile and radius of the pile.

Experimental design for designing liquisolid powder compacts

Two independent variables are each represented by three levels in a 3^2-factorial design. Nine separate iterations [26,27] were carried out based on this plan. The percentage of Atazanavir in the non-volatile solvent (Transcutol HP) and the percentage of super disintegrant (sodium starch glycolate) were chosen as the independent variables. The 12-hour drug release (%CDR) and the disintegration time (DT) were the dependent variables in this study. Table 1 shows the values for the independent and dependent variables. To calculate the value of the response (Eq. 3), a statistical model was utilized that included both interactive and polynomial elements.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2$$

where Xi is the factor being estimated, Y is the dependent variable, b0 is the mean of the 9 trials, and bi is the calculated coefficient. The primary impacts, denoted by X1 and X2, are the average outcomes of changing one element from its minimum to maximum values.

Post Compression Parameters

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 [28]. 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.

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 [29].

Friability

Friability was measured by using Roche friabilator. 10 tablets were weighted (W0) and placed in the friabilator to be rotated at 25 rpm for 4 min [30]. Tablets were collected, de-dusted, and weighed again. The difference in the initial weight and final weight (Wt) was used to calculate % friability

$$\text{Friability (\%)} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} X100$$

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 [31]. The disintegration test was performed in 900 ml distilled water at 37 ± 0.5 ºC temperature and at the rate of 30 ± 2 cycles/minutes

In vitro dissolution studies

The USP II dissolving equipment (DS 8000, Lab India, Mumbai, India) was used to perform the in vitro dissolution. dissolving of atazanavir LSPCs was carried out at 37 0.5 °C and 75 rpm in a vessel containing 900 ml of HPLC water as a suitable dissolving medium. Aliquots of 5 ml were removed and replaced with new dissolving media of the same volume at regular intervals of 5, 10, 15, 30, 45, 60, 90, and 120 minutes [32]. Millipore membrane filters (NYLON 66, Axiva, Lab filters, Delhi, India) with a pore size of 0.45 m were used in the drug release analysis, and the samples were analyzed using high performance liquid chromatography.

Solid state characterization

Fourier transforms infrared (FTIR) spectroscopy

Using a Fourier Transform Infrared Spectrophotometer (Bruker, Alpha-T, Ettlingen, Germany), spectra of pure Atazanavir, MCC PH 102, AEROSIL® 200, sodium starch glycolate, and optimized Atazanavir loaded LSPC were obtained. Using a hydraulic pellet press with a pressure of 10 t, KBr discs were used to prepare the samples. The range of scanning was from 4000 to 400 Cm1 for the samples. The OPUS-6.5 software [33] is used to analyse the spectra.

Differential scanning calorimetry (DSC)

Pure Atazanavir and Atazanavir-loaded LSPC subjected to DSC (Model: SIIO-6300, Japan) analysis of their respective thermograms. The thermal behavior of the samples was studied by scanning the temperature from 0 to 300 °C at a rate of 10 °C/min using nitrogen as the blanket gas [34].

X-ray diffraction (XRD)

Pure Atazanavir and optimized Atazanavir loaded LSPC X-ray diffraction (Model: Stereoscans S120, Cambridge, UK) patterns identified to further characterize their crystalline states. After loading the samples onto the diffractometer, they are irradiated with Cu-K radiation (40 kV 30 mA) and scanned at a scan rate of 0.05°/0.4 s [36] throughout a range of 2, values from 10 to 80°.

Stability studies

The Atazanavir-loaded LSPC formulation was stable after being stored for three months at 40 °C/75% 5% RH, as recommended by the International Conference on Harmonization (ICH). After 90 days, the samples were extracted for assay, disintegration time, and in vitro release tests [35].

RESULTS & DISCUSSION

Solubility

As can be shown in Fig. 13, the most drug was solubilized by Transcutol HP (Highly purified diethylene glycol monoethyl ether), followed by Capryol 90 and PEG-400. Atazanavir had a solubility of 0.008 mg/ml in water, but it was 25.360.12 mg/ml in Transcutol-HP.

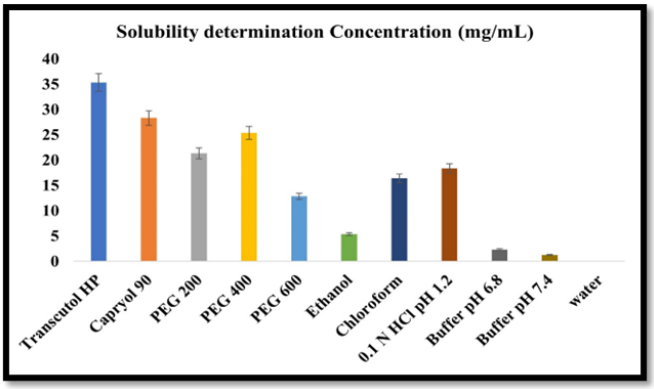


Figure 1: Solubility determination of different solvents and buffer mediums

Determination flowable liquid-retention potential

Avicel pH 102 showed the greatest flowable liquid retention potential (1.4 ml) of all the carrier materials tested. This means that after combining 1.3 ml of liquid drug with 1 gm of Avicel pH 102 powder (angle of slide = 33), the powder still had its excellent flow quality. After considering Compressil 101, Fujicalin, and MCC, we ultimately settled on using Avicel pH 102 as our carrier material. Aerosil' s 1.6 ml flowable liquid retention potential was the greatest of all the studied coating materials. It was found that liquisolid compacts made with solely Avicel pH 102 as the carrier material did not dissolve fully during the dissolving investigation. This might have happened because the drug was securely bound inside the Avicel pH 102 matrix. Sodium starch glycolate (SSG) was combined with Avicel pH 102 to solve this issue. Because of its swelling tendency, SSG is often utilized as a super disintegrating agent in tablets. The huge interior surface area of Avicel pH 102 was thought to facilitate the drug's release thanks to SSG's swelling properties. SSG and Avicel pH 102 solutions were made, and the angle of slide was again evaluated throughout a range of (0-4, 10-90%). It was found experimentally that a mixture of 2% SSG and 2% Avicel pH 102 had the same liquid retention potential as bare Avicel pH 102 (1.4 ml). Subsequent studies showed that adding more SSG to the combination substantially reduced the liquid retention potential, hence it was decided to utilize an Avicel pH 102 /SSG mixture in the range of 0% to 9% as the carrier material.

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

Avicel pH 102 /SSG in the ratio of 0-4 and 10-90 was found to hold 1.4 ml of Transcutol HP without showing any leakage issue and to offer satisfactory hardness during the compressibility test.

Liquid load factor

Using Eqs. (2), (3), we were able to get the liquid load factor. The - value and - value for Avicel pH 102 /SSG (0-4 and 10-90) were determined to be 1.4 ml, as mentioned before. The obtained - value for the chosen coating material, aerosil 200, was 1.6. According to the setup, we used an R-value of 15. The computed values of Lf and Lf were 1.66 and 1.3, respectively, after plugging all these numbers into equations (3) and (4). When calculating the liquid load factor for this liquisolid system, the value of Lf was used since it was less than Lf.

Primary trial for selection of carrier and coating material.

Transcutol HP, carrier substance, and coating material amounts were determined analytically. Drug release from the liquisolid compact was found to be significantly affected by the Avicel pH102/aerosil ratio and R-value (carrier/coating material) during preliminary trials; thus, 3^2 full factorial designs were implemented to assess the significance of these variables.

Table 1: Trail Formulation of atazanavir Liquisolid Compacts

F.Code	Drug in Conc.	Avicel pH102	Aerosil	R	Lf	SSG	Total weight
F1	10	300	15	20	0.033	0	345.033
F2	10	200	20	10	0.055	2	242.055
F3	10	210	10	21	0.047	4	255.047
F4	50	225	10	22.5	0.222	0	307.722
F5	50	220	15	8.8	0.227	2	296.027
F6	50	235	20	11.75	0.212	4	320.962
F7	90	240	15	16	0.375	0	361.375
F8	90	250	10	25	0.3	2	377.3
F9	90	260	20	13	0.346	4	387.346

Precompression studies of the prepared liquisolid systems

These numbers show that all powder mixes in each batch have acceptable micromeritic qualities, including adequate flow property and compressibility.

Table 2: Micromeritic properties of pre-compression Atazanavir liquid solid powders

Formulation	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's Ratio
F1	26.85 ± 0.16	0.496±0.001	0.569±0.002	11.247	1.147
F2	27.38 ± 0.37	0.326±0.005	0.396±0.013	17.676	1.214
F3	22.36 ± 0.52	0.695±0.031	0.722±0.024	3.739	1.041
F4	25.64 ± 0.65	0.415±0.002	0.491±0.013	15.47	1.183
F5	25.79 ± 0.40	0.352±0.013	0.403±0.002	12.655	1.144
F6	27.36 ± 0.14	0.428±0.002	0.489±0.001	14.698	1.142
F7	26.61 ± 0.08	0.395±0.001	0.415±0.016	4.587	1.050
F8	28.68 ± 0.14	0.402±0.002	0.436±0.035	7.798	1.084
F9	26.12 ± 0.25	0.36±0.001	0.412±0.042	12.62	1.144

Application of experimental design for designing liquisolid tablets

Table 3: Coded and transformed value for design batches.

Run	X1	X2	Y1	Y2
1	10	0	135.28±0.53	45.31±0.02
2	50	2	110.48±1.24	69.82±0.13
3	10	4	35.26±3.02	95.36±0.11
4	90	0	65.32±1.26	75.14±0.02
5	50	-0.828427	75.34±1.52	39.62±0.14
6	-6.56854	2	89.34±3.02	89.36±0.25
7	50	2	125.48±2.48	45.26±0.13
8	50	2	130.42±2.69	46.51±0.34
9	50	2	129.47±2.51	48.09±0.62
10	50	2	127.54±1.37	48.35±0.21
11	90	4	139.62±2.04	45.26±0.34
12	50	4.82843	65.42±1.38	49.82±0.16
13	106.569	2	95.34±2.03	80.32±0.25

Effect of formulation variables on disintegration time (Y1)

Disintegration time (Y1) is affected by formulation factors such as atazanavir percentage (X1) in Transcutol HP and sodium starch glycolate percentage (X2).

Disintegration time = +124.68 +5.36A -4.97B +43.58AB -13.04A2 -24.02B2

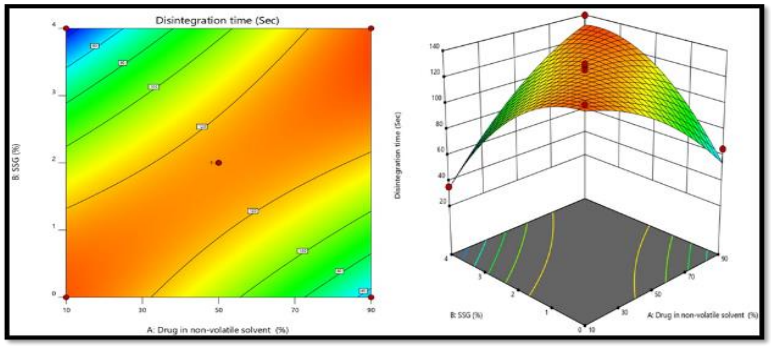


Figure 2: Response surface plot (A) and contour plot (B) showing effect of X1 and X2 on response disintegration time (Y1).

In Fig. 2, we see the combined impact of X1 and X2 on YQ15 and YDT. Disintegration time (Y1) was shown to decrease with increasing concentrations of atazanavir and sodium starch glycolate in Transcutol HP.

Effect of formulation variables on release profile (Y2)

An increase in the percentage of atazanavir in Transcutol HP (X1) results in a decrease in the amount of drug released at the 15-minute mark (Eq. 10), while an increase in the percentage of sodium starch glycolate (X2) results in an increase in the amount of drug released at the 15-minute mark (Eq. 10). Compared to the pure drug, which exhibited less than 10% drug release at Q15 at P 0.05, the optimized formulation of atazanavir loaded LSPC showed more than 85% drug release at Q15. In Eq. (10), we see how different formulation factors affect the 15-minute drug release (YQ15).

Drug release = +51.61 -4.13A +4.32B -19.98AB +16.74A2 -3.32B2

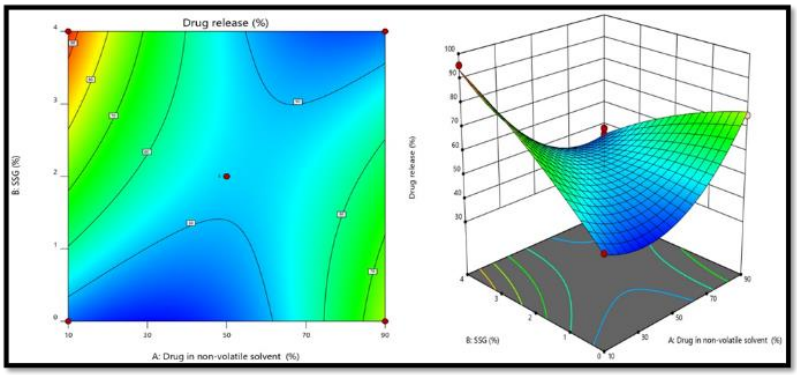


Figure 3: Response surface plot (A) and contour plot (B) showing effect of X1 and X2 on response disintegration time (Y2).

Desirability function for the selection of optimized batch

The optimal batch was chosen using the Design Expert® software's desirability function (12.0.3.0) after the mathematical model was fitted. The programme combines all the response variables to provide an optimised batch with an optimal distribution of characteristics.

Table 4: Composition, experimental vs. predicted value with percentage error of optimized Formulation

Variables	Optimum	Respons	Observed value	Predicted	Percentage

	composition	e	of response	value of response	Error
X1 (%)	10.00	Y1	35.26±3.02	33.706	1.554
X2 (%)	4	Y2	95.36±0.11	93.462	1.898

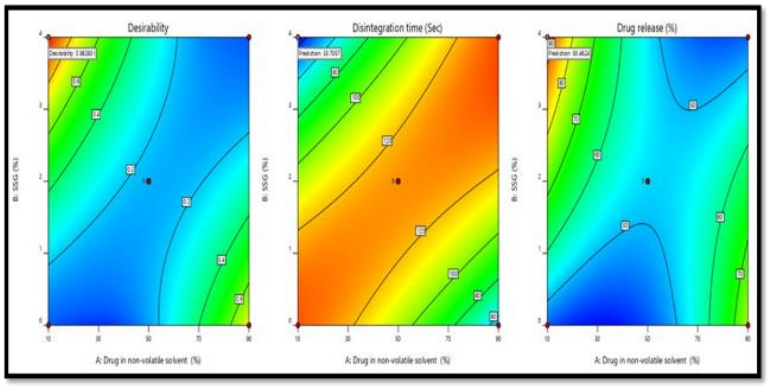


Figure 4: Desirability plot for optimized batch.

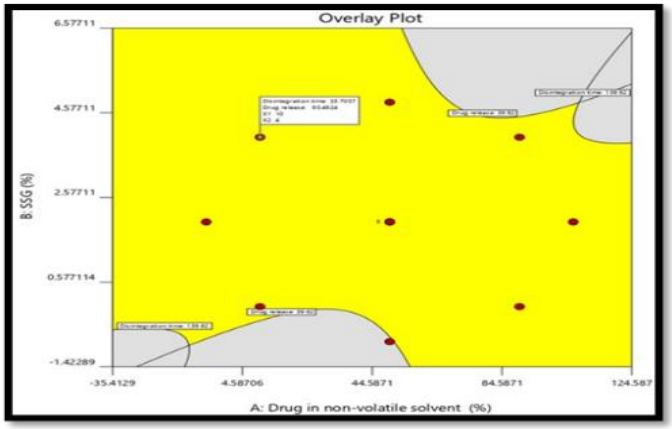


Figure 5: Overlay plot for response variable

Post compression evaluation parameter

Each batch's average tablet weight fell safely inside the allowable range. All of the finished products had a drug content of more than 95%, well within allowable parameters. The hardness of the ready liquisolid compacts ranged from 6.2 to 5.0 Kgf, which is within the allowable range for the standard tablets. There were no discernible surface fractures on any of the tablets subjected to the friability test, and no formulation lost more than 1% of its initial weight.

Table 5: Post compression evaluation parameters

Run	Thickness (mm)	Hardness (Kgf)	Weight Variation (mg)	Drug Content (%)	Friability%
1	7.36±0.01	3.26±0.21	345±2.35	94.32±0.26	0.81±0.02
2	7.23±0.03	3.25±0.13	323±1.26	95.82±0.43	0.78±0.01
3	7.49±0.01	3.01±0.14	312±2.34	99.61±0.21	0.64±0.03
4	7.38±0.02	3.24±0.25	295±2.10	98.57±0.16	0.35±0.11
5	7.65±0.04	3.25±0.13	301±3.06	97.52±0.26	0.64±0.13
6	7.34±0.01	4.26±0.16	326±2.53	96.51±0.42	0.52±0.02
7	7.83±0.02	4.05±0.2	342±2.31	98.03±0.13	0.82±0.14
8	7.59±0.11	4.31±0.01	315±1.06	96.31±0.41	0.43±0.13

9	7.35±0.03	3.69±0.03	328±0.98	97.03±0.36	0.39±0.01
10	7.26±0.11	4.25±0.12	315±2.75	97.34±0.12	0.58±0.02
11	7.12±0.21	4.13±0.11	325±3.56	98.16±0.25	0.36±0.13
12	7.35±0.01	3.26±0.02	336±2.43	98.43±0.42	0.52±0.12
13	7.05±0.12	3.58±0.12	342±1.38	99.02±0.13	0.49±0.02

Solid state characterization

Fourier transform infrared spectroscopy

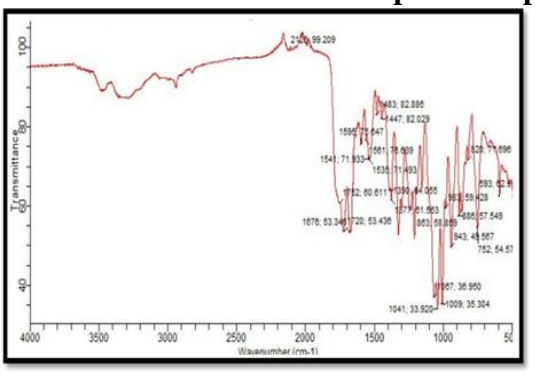


Figure 6: FTIR spectrum of Pure Drug

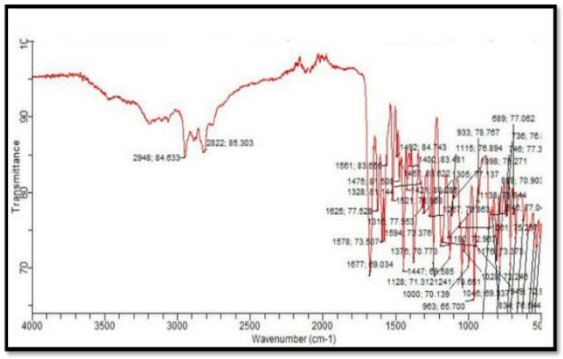


Figure 7: FTIR spectrum of F3

No peaks in the spectra were identified as belonging to any components other than Atazanavir and excipients, suggesting that the IR patterns of the optimized formulation of Atazanavir and the pure drug are identical.

Differential scanning calorimetry

Atazanavir's endothermic (melting) peak on the differential scanning calorimetry (DSC) curve was measured to be 202.15 degrees Celsius (Fig. 24, curve A). The DSC curve for the Optimized formulation of atazanavir liquisolid powder compacts showed no atazanavir peak, suggesting that the drug was less crystalline (more amorphous) in the final formulation.

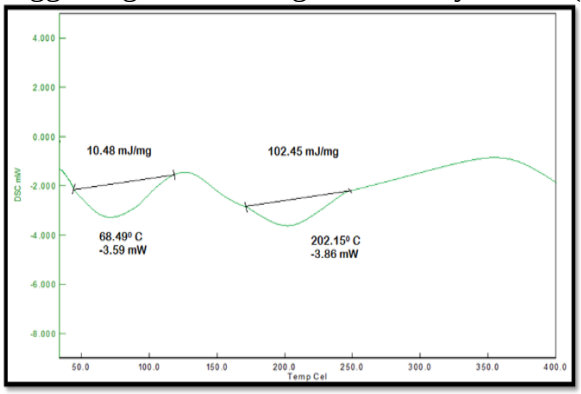


Figure 8: DSC thermogram of Pure drug

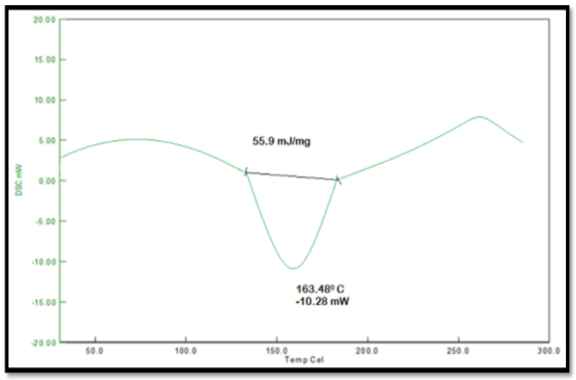


Figure 9: DSC thermogram of F3

X-Ray powder diffraction analysis

The crystallinity of the LSPC components was evaluated through X-ray powder diffraction (XRD) analysis. The 2 values of 11.86, 14.79, 15.06, 18.27, 18.54, 20.07, 20.49, 22.84, 23.95, 24.34, 26.11, 27.16, 27.48, 27.81, and 30.23° were found to be prominent for atazanavir. X-ray diffraction (XRD) analysis of the atazanavir-loaded optimized formulation showed that, with the exception of the 22.84° peak, all of the main peaks belonging to atazanavir had gone, indicating that the drug had been converted from its crystalline to its amorphous form. The amorphousness of a sample increases as its degree of crystallinity decreases.

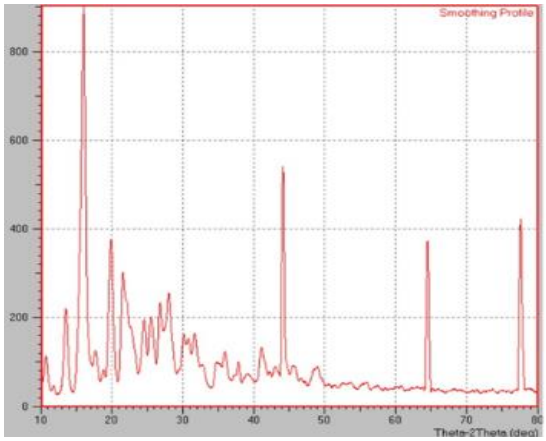


Figure 10: XRD of Pure drug

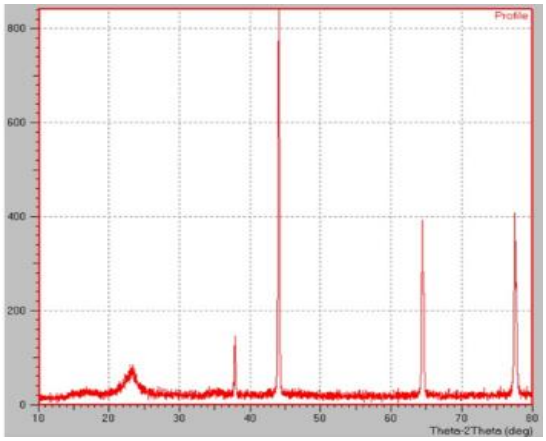


Figure 11: XRD of F3

Dissolution studies

After 15 minutes, the CDR was below 40% for formulations F-1, F-4, and F-7, but over 55% for all other batches. However, the commercially available version still managed to release around 60% of the active ingredient. Other batches had a high drug release rate because they included SSG. Due to the SSG's superior super disintegrant ability, the drug was rapidly pushed and released from the avicel pH 102 matrix. Pure drug tablets, in contrast to prepared liquisolid compacts, were only able to release 15% drug in 15 min, which was much lower (f2 50). The drug release from batches F-1, F-4, and F-7 was around 70% after 30 minutes, whereas the drug release from other batches and commercially available goods was approximately 85% and 80%, respectively. The proportion of drug released from all design batches was likewise considerably greater at the 30 min time period (f2 50) compared to pure drug tablets. Nearly all of the drug was released from all of the design batches in the first 60 minutes, but just 39% had been released from pure drug tablets over the same time period. The commercial product had a drug release efficiency of more than 90% in 60 minutes.

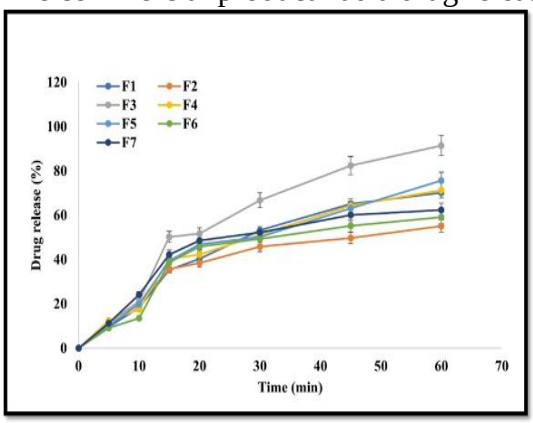


Figure 12: Dissolution profile of F1-F7

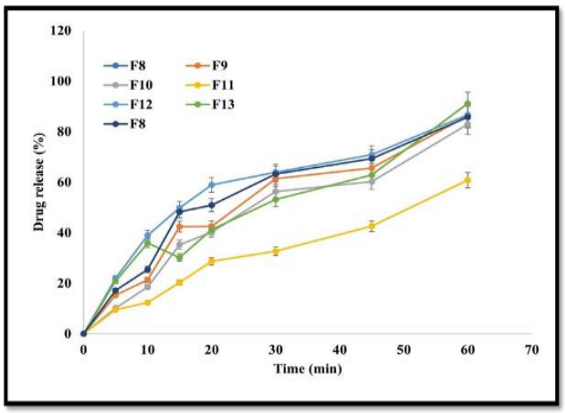
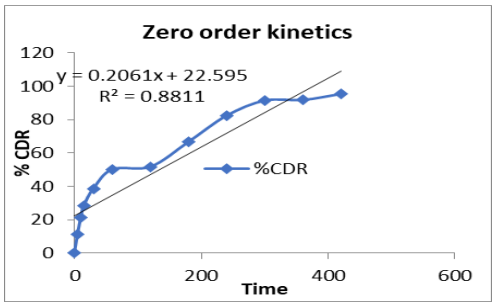


Figure 12: Dissolution profile of F8-F13

Drug release kinetics



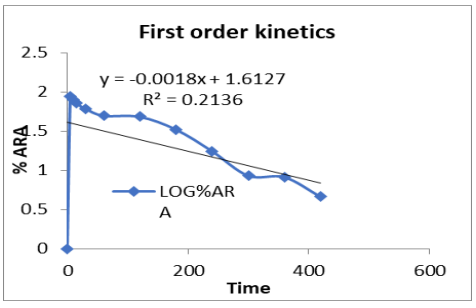


Figure 13: Zero order kinetics

Figure 14: First order kinetics

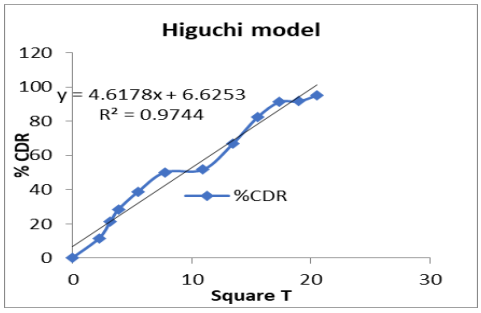


Figure 15: Higuchi model

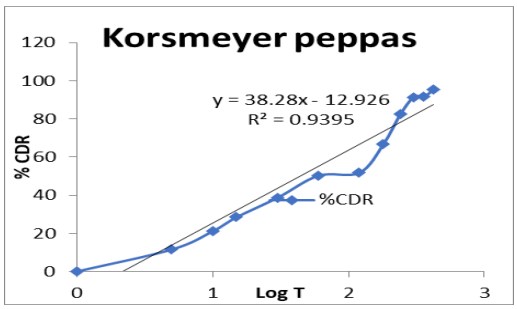


Figure 16: Korsmeyer Peppas model

Stability studies

After three months, Formulation F-1 showed no appreciable deterioration in its physical and chemical characteristics. Quantified parameters at many time points were shown.

Table 6: Results of stability studies of optimized formulation F-3

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^0C/60%RH	91.44	89.36	88.46	87.95	Not less than 80 %
F-3	30^0C/75% RH	91.44	88.62	85.62	80.13	Not less than 80 %
F-3	40^0C/75% RH	91.44	87.26	83.16	79.68	Not less than 80 %

Conclusion

Atazanavir was more soluble in the presence of Transcutol HP than in the presence of PEG or Tweens & spans, according to the solubility experiments. Poorly soluble drugs such as atazanavir may benefit from the liquisolid technology, which was recently shown to have this potential. In a liquisolid formulation, Atazanavir dissolution was greatly improved over the commercially available drug. Increases in particle wetting and surface area may explain the faster dissolving rate. Formulation F3 of Atazanavir liquisolid compacts was shown to be the optimal formulation based on XRD, FT-IR, drug content, and In Vitro dissolution tests. Bulk density, tapped density, Hausner's ratio, and compressibility index were only some of the physical properties tested on the powder mixture. After conducting dissolving testing, powder analysis by X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR), and stability investigations on the core tablets made from the powder, it was determined that formulation F3 was the most effective.

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