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FORMULATION AND EVALUATION OF LIQUISOLID COMPACT FOR ENHANCING DISSOLUTION PROPERTIES OF ATAZANAVIR

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Abstract:

To improve oral delivery of the BCS class II medication atazanavir, a special liquisolid powder compact (LSPCs), formulation was created. In the solubility tests, span 20, span 80, propylene glycol, and transcutol HP were employed. Because it is a non-volatile solvent, transcutol HP was utilised in the LSPC formulation. Propylene glycol was used to manufacture Atazanavir LSPCs at the ideal drug concentration, resulting in a high dissolving profile and excellent tablet properties. Using Fourier transform infrared spectroscopy (FTIR) revealed no drug-polymer interactions.

Keywords: *Atazanavir, liquisolid compact, Transcutol, FTIR, drug release.*

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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]. 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 [2]. 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 [3]. 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 [4]. 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 [5]. 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 [6].

MATERIALS & METHODS:

Materials:

Atazanavir was purchased from Hetero pvt. Ltd. Propylene Glycol, Poly Ethylene Glycol (PEG) 200,400,600 was purchased from S.D fine chem. Limited. Tween 20,80; Span 20,80 was acquired from Corel Pharma Chem., Ahmedabad, India.

Experimental studies:

Formulation of Liquisolid Compacts

The model drug is first diluted in various drug: vehicle ratios of non-volatile solvent systems (Propylene glycol, PEG 400) called liquid vehicles. After continuously mixing the aforesaid liquid for 10-20 minutes in a mortar, a carrier mixture (Micro crystalline cellulose pH 102) was added. Then, we added the coating substance (Aerosil powder) and stirred everything together. The carrier and coating materials used were adjusted in proportion to the R value. Disintegrants such cross povidone and other additives like Glidant (magnesium stearate) are often added to the aforementioned binary combination before being mortar-mixed for its respective applications. The combined ingredients were then compacted [7].

Using a mathematical model to create formulations for Atazanavir liquisolid

A mathematical approach has been proposed by Spireas and Bolton to design liquisolid compacts with desired flowability and compatibility [8]. It is assumed that a specific amount of liquid medication (drug + co-solvent) in the inner matrix will not negatively impact the powder material's compatibility or flowability. The "Excipient Ratio" (R), which is the ratio of coating material to carrier, is necessary to produce a powder with the right flowability and compressibility.

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

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

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

The prescribed quantity of powder material (10 gm) was gradually mixed with the liquid medication, and the resultant admixture was subsequently applied to one end of the polished metal plate [8]. While one edge of the metal plate remained in place, the other was lifted off the ground. By measuring the distance between the plate and the ground, the angle of the

slide was determined. **Determination of compressible liquid-retention potential (Ψ – value)**
The liquid medication was gradually added to 1 gramme of powder to make a uniform combination. To achieve the required hardness, the additive was crushed using the rotating tablet machine [9]. In this investigation, crushing strengths of 5 to 7 kg f were deemed adequate. During compression, there was no visible release of liquid medication from the powder admixture.

Liquid load factor
Once the - value and - value of the coating material and carrier were established, the following equations were used to calculate the liquid load factor [88].

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

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

CA stands for the carrier material's flowability liquid retention potential, whereas CO stands for the coating material's compressible liquid retention potential. We refer to this relationship as R in regard to Eq. (1), where R is the excipient ratio.
liquid load factor

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

Weight of liquid drug (W) = Weight of carrier substance (Q). In this case, the smaller of Lf and Lf

Primary trial for coating and carrier material selection.
The purpose of the initial research was to find the coating and carrier material that could carry the most liquid medicine while yet being compactible and easily dispensed [89].

Evaluation of Powder Blend
Bulk density:
Five grammes of atazanavir were carefully transferred from a glass funnel into a graduated 20 ml cylinder in order to determine its bulk density [10]. It was measured how much space each sample occupied.

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

Tapped density:
The LABINDIA density tester, which is essentially a graded cylinder, was a mechanical tapping device used to measure the density [11]. It is standard practice to record the initial volume and then tap the sample 50, 100, 150, or 250 times until the volume doesn't fall any more or the percentage change is less than 2%.

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

Compressibility Index and Hausner's ratio:
Powder flow properties may be predicted quickly and easily using the compressibility index or the closely related Hausner's ratio.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

$$\text{Hausner's Ratio} = \text{Tapped Density / Bulk Density}$$

Angle of repose:
The funnel approach was used to calculate the powder combination's angle of repose. A funnel was used to collect the accurately measured powder [12]. The top of the powder mound barely brushed the tip of the funnel since it was raised to the proper height.

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

Where, h and r are the elevation of pile and radius of the heap.

Evaluation of Tablets: (Post Compression Parameter)
Weight Variation:
The average weight was determined by randomly selecting and weighing 20 whole pills. The tablets' masses were measured [93]. The United States Pharmacopoeia (USP) specifies that no single tablet's weight may be less than 90% or more than 110% of the mean [13].

Hardness:
Test the Hardness of 10 tablets from the sample provided and record the findings in Kg/Cm2. Take a mean reading of the 10 samples and report that. The minimum acceptable density is 4.0 Kg/cm2.
Friability (core tablets):
Remove the dust from the sample of 13 pills provided. Weigh the pills and make a note of the total. Rotate the drum of the friability device for 4 minutes (100 revolutions) with the tablets inside. Use the device for the allotted time or revolutions per minute. Get the pills out of there and clean them up.

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

In vitro dissolution studies

For the in vitro dissolution, the USP II dissolving apparatus (DS 8000, Lab India, Mumbai, India) was utilized. In a vessel with 900 ml of buffer as an appropriate dissolving media, atazanavir LSPCs were dissolved at 37 ±0.5 °C and 75 rpm [14]. Five millilitre aliquots were taken out and replaced with fresh dissolving medium of the same amount at 5, 10, 15, 30, 45, 60, 90, and 120-minute intervals.

Stability studies

Following three months of storage at 40 °C/75% 5% RH, as advised by the International Conference on Harmonisation (ICH), the atazanavir-loaded LSPC formulation remained stable. Samples were taken out for assay, disintegration time, and in vitro release testing after 90 days [15].

RESULTS & DISCUSSION

Determination flowable liquid-retention potential

Aerosil's 1.6 ml capacity offered the most potential for flowable liquid retention of any coating material tested. Experimental research indicates that a 2% SSG and 2% Avicel pH 102 mixture may be able to store liquid as much as 1.4 ml of naked Avicel pH 102.

Calculating the potential for compressible liquid retention (Ψ-Value)

According to the results of the compressibility test, Avicel pH 102/SSG in the ratios of 0–4 and 10-90 could contain 1.4 ml of Transcutol HP without leaking while still providing a high enough level of hardness.

Liquid load factor

The obtained -value was 1.6 for the selected coating material, Aerosil 200. According to the setup, we used an R-value of 15. Upon entering each of these numbers into equations (3) and (4), the resulting Lf values were 1.66 and 1.3, individually.

Primary trial for selection of carrier and coating material.

Table 1: Formulation of atazanavir Liquisolid Compacts

F.Code	Drug in Conc.	Avicel pH102	Aerosil	R	Lf	SSG	Total weight
F1	10.0	300	15	20	0.033	0	345.033
F2	10.0	200	20	10	0.055	2	240.055
F3	10.0	210	10	21	0.047	4	255.047
F4	10.0	225	10	22.5	0.222	0	282.722
F5	10.0	220	15	8.8	0.227	2	256.027
F6	10.0	235	20	11.75	0.212	4	280.962
F7	10.0	240	15	16	0.375	0	281.375

Precompression studies

All formulations of powders have great flowability, as seen by Table 2, which displays angles of repose ranging from 22.36±0.52 to 28.68±0.14. Tapped density was found to be between 0.39 to 0.72 g/cm3, while bulk density ranged from 0.36 to 0.695 g/cm3. Carr's index (percent) and Hausner's ratio (1.041–1.214) were found to be 3.739–17.676 and 1.041–1.214, respectively.

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

Formulation	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner's Ratio
F1	25.45 ± 0.15	0.483±0.001	0.553±0.002	10.320	1.146
F2	26.36 ± 0.36	0.324±0.003	0.385±0.013	17.683	1.213
F3	23.38 ± 0.51	0.686±0.012	0.713±0.024	3.357	1.040
F4	24.53 ± 0.64	0.413±0.001	0.490±0.013	15.163	1.182
F5	25.64 ± 0.42	0.351±0.005	0.413±0.002	12.685	1.143
F6	26.32 ± 0.13	0.427±0.002	0.485±0.001	14.237	1.140
F7	27.38 ± 0.07	0.394±0.001	0.412±0.016	4.780	1.051

Post-compression evaluation parameter

The mean weight of the pills in each batch was safely within the permitted limit. The drug content of all the final products was over 95%, which was well within permissible limits. The ready liquisolid compacts had a hardness amid 6.2 and 5.0 Kgf, which is within the range that is permitted for regular tablets. None of the tablets that underwent the friability test showed any visible surface cracks, and none of the formulations lost more than 1% of their initial weight. Within three

minutes, all of the liquisolid compacts that were created broke up, which is well within the permitted range.

Table 3: Post compression assessment constraints

Formulation	Thickness (mm)	Hardness (Kgf)	Weight Variation (mg)	Drug Content (%)	Friability%
F1	7.36±0.01	3.26±0.21	345±2.35	94.32±0.26	0.81±0.02
F2	7.23±0.03	3.25±0.13	323±1.26	95.82±0.43	0.78±0.01
F3	**7.49±0.01**	**3.01±0.14**	**312±2.34**	**99.61±0.21**	**0.64±0.03**
F4	7.38±0.02	3.24±0.25	295±2.10	98.57±0.16	0.35±0.11
F5	7.65±0.04	3.25±0.13	301±3.06	97.52±0.26	0.64±0.13
F6	7.34±0.01	4.26±0.16	326±2.53	96.51±0.42	0.52±0.02
F7	7.83±0.02	4.05±0.2	342±2.31	98.03±0.13	0.82±0.14

Solid state characterization

Fourier transform infrared spectroscopy

The optimized Atazanavir loaded formulation of LSPCs (Fig. 23) showed the spectra of the excipient-characteristic peaks, and the Atazanavir peaks were also evident, but with a lower absorption strength, suggesting that the drug was trapped in the carrier matrix. There were no peaks in the spectra that could be attributed to anything other than Atazanavir and the excipients, indicating that the IR patterns of the pure medication and the optimized formulation of Atazanavir are the same.

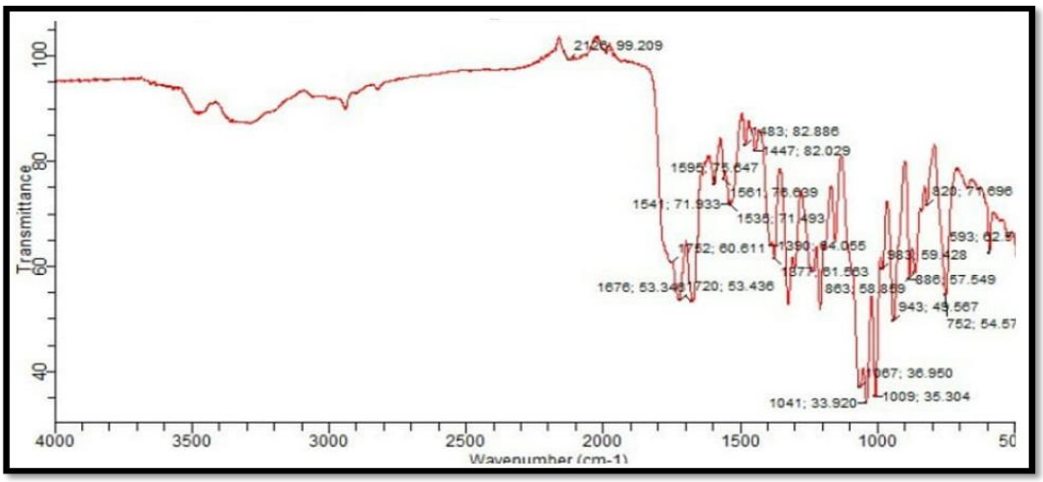

Figure 1: FTIR spectrum of Pure Drug

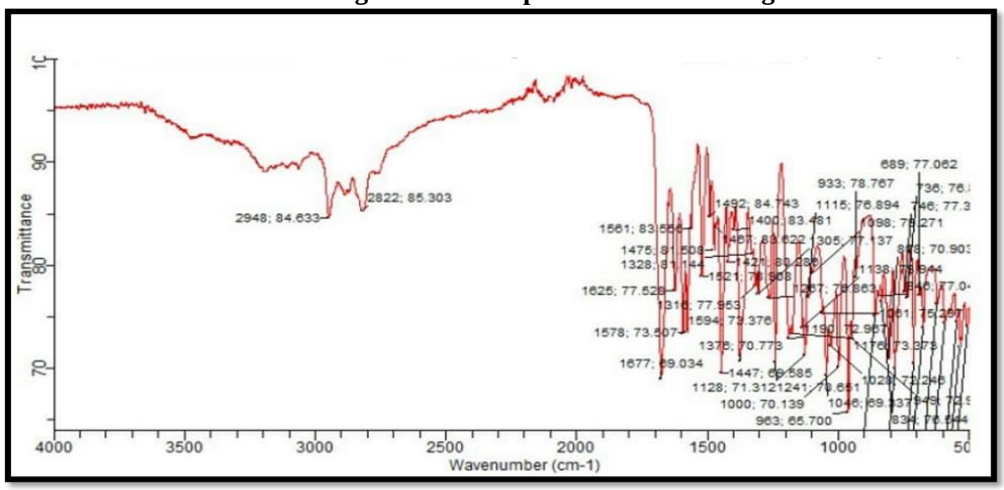

Figure 2: FTIR spectrum of optimized atazanavir liquisolid compact formulation (F3)

Differential scanning calorimetry

The endothermic (melting) peak of atazanavir was found to be 202.15 degrees Celsius on the differential scanning calorimetry (DSC) curve. In the optimized formulation of atazanavir liquisolid powder compacts, the medication was less crystalline (more amorphous) according to the DSC curve, which did not display an atazanavir peak. When LSPCs were produced, the medication changed from a crystal to an amorphous state, which indicated improved solubility and an increased dissolution release profile.

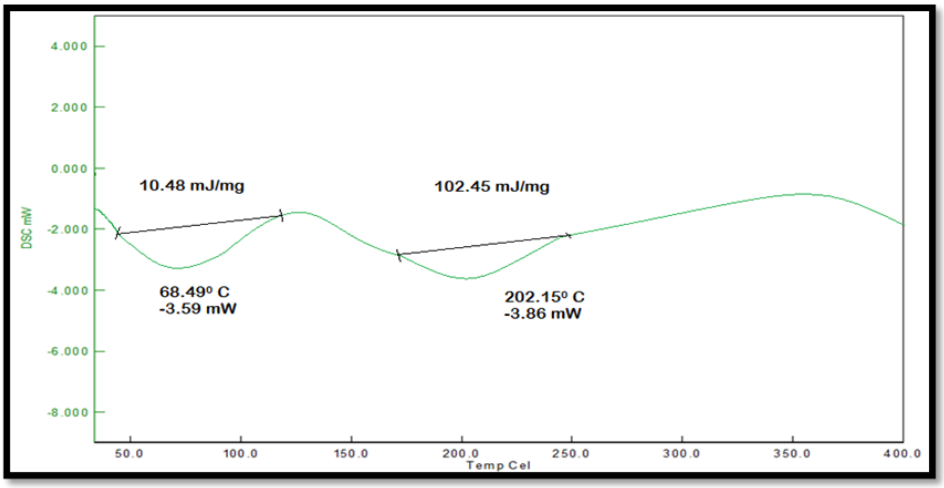

Figure 3: DSC thermogram of Pure drug

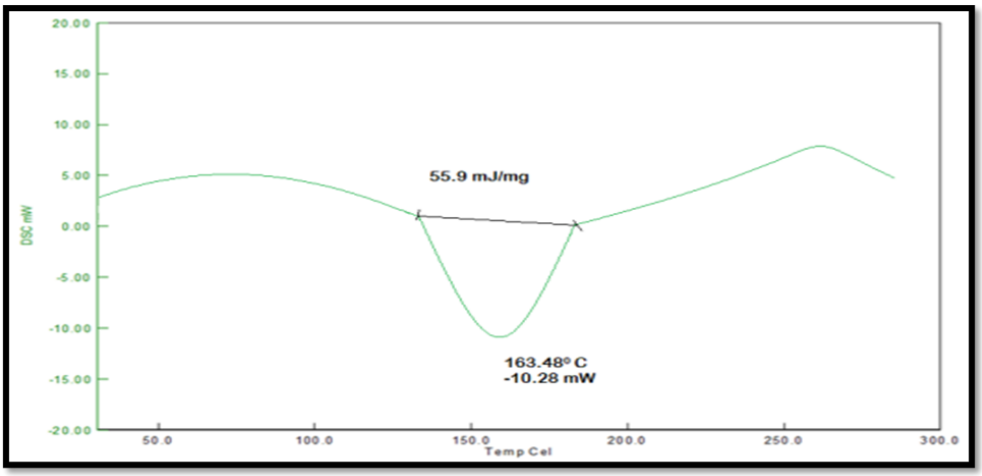

Figure 4: DSC thermogram of optimized formulation (F3)

Dissolution studies:

Formulations F-1, F-4, and F-7 had CDRs below 40% after 15 minutes, while all other batches had CDRs above 55%. Around 60% of the active component was nevertheless released by the commercially available form. Only 15% of the medication could be released from pure drug tablets in 15 minutes, which was significantly less than that of prepared liquisolid compacts (f2 50). The drug release from commercially available goods and other batches was approximately 80% and 85% after 30 minutes, respectively. Additionally, at 30 minutes, the proportion of medication released from all design batches was much higher than that of pure drug tablets (f2 50). During the first 60 minutes, only 39% of the drug was released from pure drug tablets, but almost all of the drug was released from all design batches. The commercial product's 60-minute medication release efficiency was over 90%

Table 4: Dissolution data of Atazanavir in different concentrations (F1-F7)

Time (min)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
5	9.63	10.26	11.54	12.36	10.28	9.15	11.28
10	18.26	20.21	21.15	17.58	19.86	13.56	24.15
15	35.26	35.68	50.24	40.28	39.48	38.64	42.18
20	40.26	38.48	51.75	42.23	46.89	45.81	48.63
30	53.26	45.86	66.74	51.18	50.18	49.38	52.18
45	65.15	49.68	82.44	64.31	63.15	55.18	60.15
60	70.15	55.15	91.44	71.25	75.63	59.16	62.35

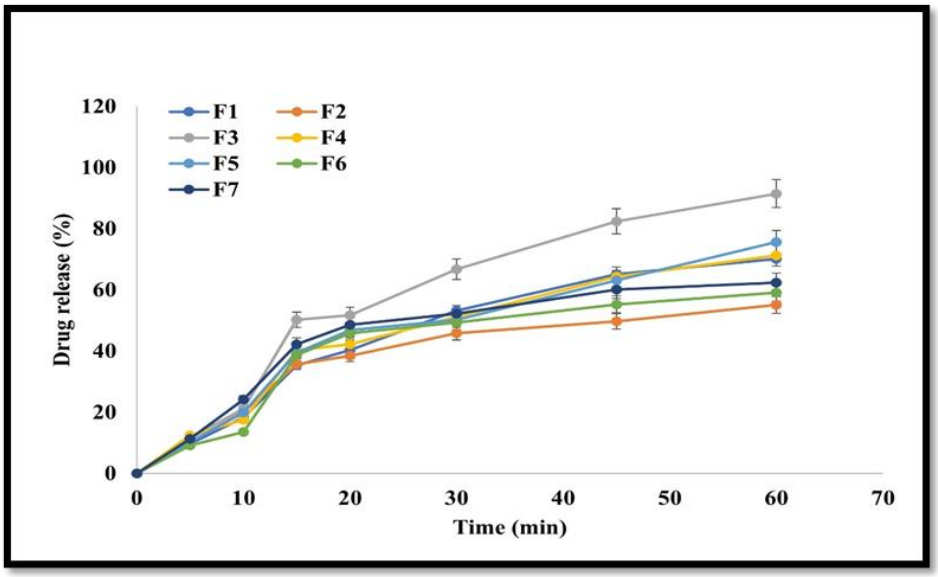

Figure 5: Dissolution profile of (F1-F7) formulations

Drug release kinetics

Zero order kinetics

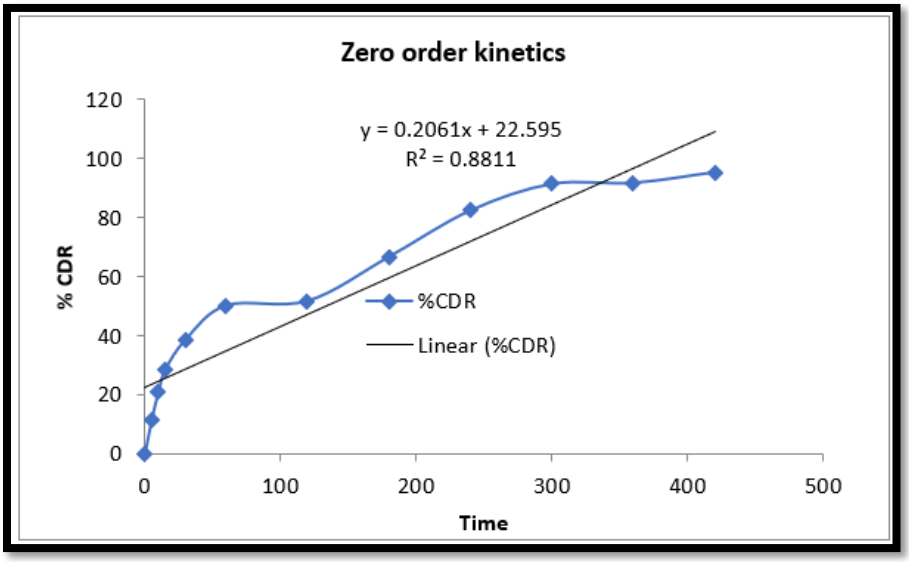

Figure 6: Zero order kinetics

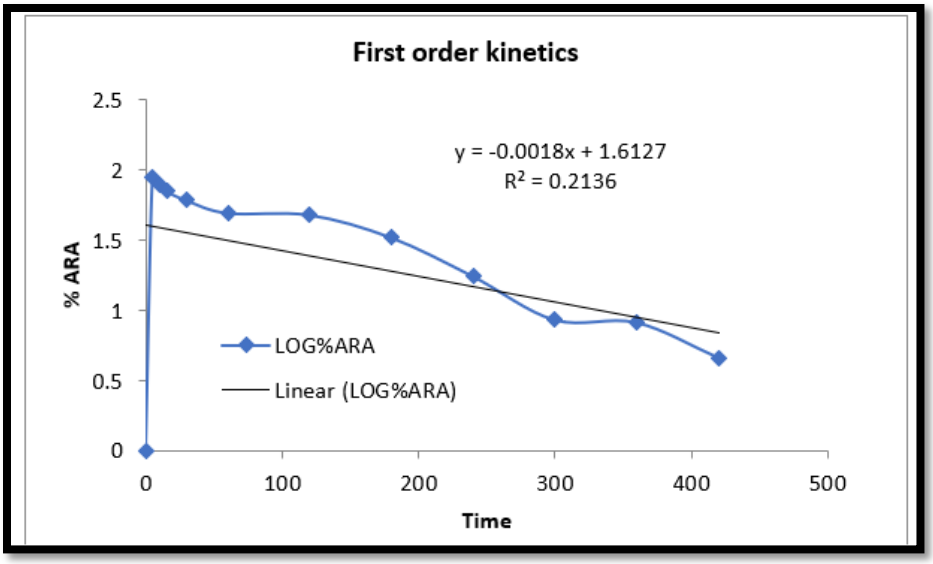

Figure 7: First order kinetics

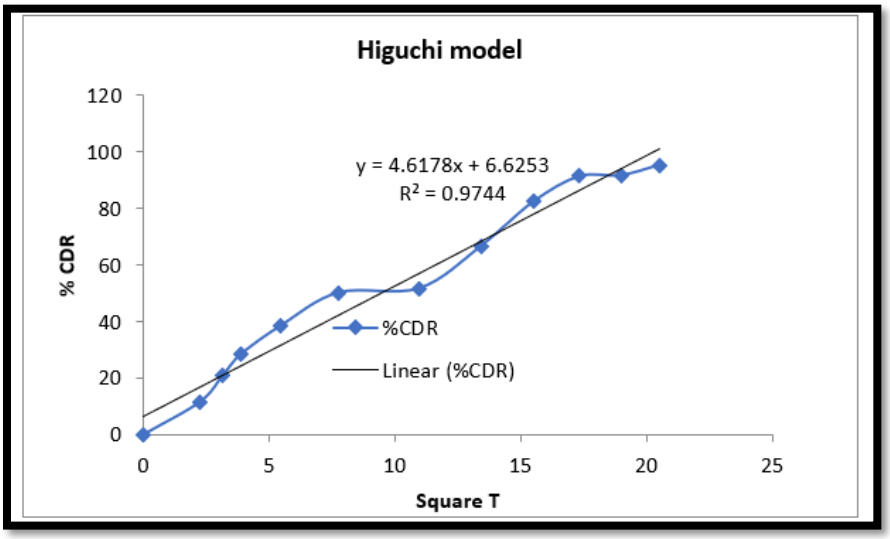

Figure 8: Higuchi model

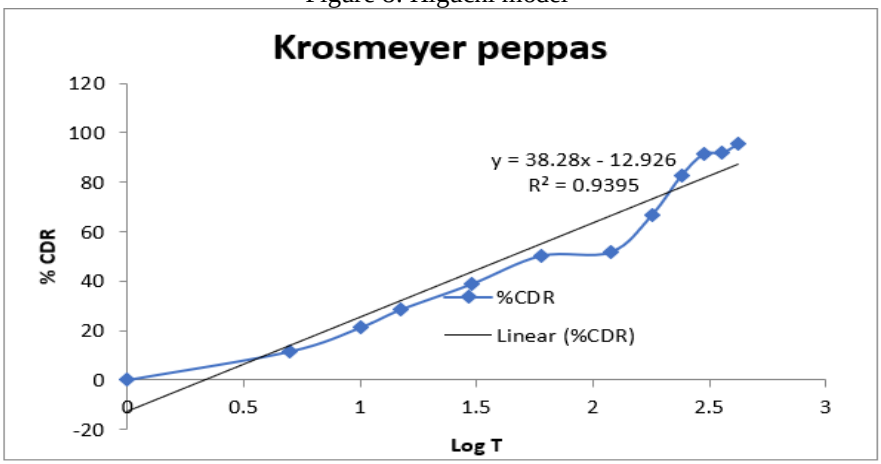

Figure 9: Korsmeyer Peppas

Stability studies:

The physical and chemical properties of Formulation F-1 did not significantly deteriorate after three months. There was multiple time points with quantified parameters displayed.

Table 5: 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 % Release	91.44	89.36	88.46	87.95	Not less than 80 %
F-3	30^0C/75% RH % Release	91.44	88.62	85.62	80.13	Not less than 80 %
F-3	40^0C/75% RH % Release	91.44	87.26	83.16	79.68	Not less than 80 %

SUMMARY & CONCLUSION:

According to the results of the solubility tests, atazanavir was more soluble when Transcutol HP was present than when PEG or Tweens & spans were present. Liquisolid technology has lately demonstrated the potential to be beneficial for poorly soluble medications like atazanavir. Atazanavir solubility was significantly better in a liquisolid formulation than in the currently available medication. The medicine and excipients did not react with one another, according to the IR spectra. Particle wetting and surface area increases could be the cause of the quicker rate of dissolution. FT-IR, drug content, and in vitro dissolution studies all indicated that formulation F2 of atazanavir liquisolid compacts was the best formulation. Among the physical characteristics of the powder mixture that were investigated were bulk density, tapped density, Hausner's ratio, and compressibility index. Following stability tests on the powder-based core tablets, dissolving testing, Fourier transform infrared spectroscopy (FT-IR), formulation F2 was found to be the most successful.

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