

Original Article

Optimization and Characterization of Co-Amorphous System for Ideal Drug Candidate

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Abstract: Newly discovered and under discover drug substance/ APIs have the poor water solubility hence making it bioavailable is challenging. How co-amorphous system can address such problem. Active pharmaceutical ingredients, which require being absorbed into the bloodstream, maybe challenged by multiple barriers and harsh condition in the gastrointestinal tract, leading to losses in bioavailability. Alternative to amorphous polymeric, is co-amorphous solid dispersions with solubility and stability improvements over the corresponding amorphous and crystalline drugs. This study determined the optimization and characterization of co-amorphous system for ideal drug candidate. Co-amorphous solid dispersion were prepared by dry milling technique with ball milling for 60 min to 120 min by taking 1:1M and 1:3M ratio of drug and coformer and evaluated the characterization of the particle size distribution, in-vitro drug release and drug content. Full factorial design was used to get the optimized formula using milling time and drug coformer ratio as variables and particle size distribution, in-vitro drug release and drug content as a responses. Results is not cleared which one and which ratio is optimum and best for the results please describe it concisely & wisely. The evaluation results from the study suggested that the optimized formulations showed that there are successfully increased in evaluation parameters compared to respective API's. Hence it was concluded that improvement of in-vitro pharmaceutical performance by co-amorphization technique using the artificial sweeteners as a coformer.

Keywords: dissolution, fluconazole-maltose, aceclofenac-aspartame, dissolution

1. INTRODUCTION

Oral route of drug administration is one of the most preferred routes of administration due to better patient compliance, lower manufacturing costs, and ease of administration. Moreover, oral administration is used for local and systemic delivery of a wide range of drug molecules, from small molecule drugs to large bio macromolecules [1]. Despite the above-mentioned advantageous features, oral administration faces several limitations, such as low solubility, low permeability, rapid degradation in the gastrointestinal tract, and inability to penetrate the protective mucosal barrier. Oral drug administration is the most accepted route for drug delivery among the various routes due to its advantages like non-invasive, painless, self-administration, and high patient compliance. Drug substances with low aqueous solubility are increasingly prevalent in the research and development speculations of discovery-oriented pharmaceutical companies [2]. In the last decade, a significant number of new chemical entities have emerged in the poorly soluble drug category, which generally

leads to low oral bioavailability. However, active pharmaceutical ingredients, which need to be absorbed into the bloodstream, may face multiple barriers and harsh conditions in the gastrointestinal tract, resulting in bioavailability losses [3]. For example, poorly soluble bioactive ingredients may result in low absorption, which certainly translates into low bioavailability and low therapeutic index. In oral drug delivery systems, gastrointestinal absorption significantly depends on the solubility and dissolution rate of drug molecules. However, at present, approximately 90% of new chemical entities and 40% of currently marketed drugs belong to classes II and IV of the Biopharmaceutical Classification System (BCS), which suffer from the problems of low water solubility and low bioavailability [4]. It is well established that dissolution is often the rate-limiting step in gastrointestinal absorption of a drug from solid dosage forms. Water solubility is a key parameter that influences biological activity, formulation, and biopharmaceutical properties in vitro and in vivo. However, many drugs currently in use and under development have low water solubility and belong to classes II and IV of the Biopharmaceutical Classification System (BSC), i.e., they have low solubility [5]. Consequently, numerous attempts have been made to modify the dissolution characteristics of these poorly water-soluble drugs in an effort to attain more rapid and more complete absorption performance. Approximately 70-90% of newly synthesized molecules are belonging to BCS class II and IV compounds [6]. A number of novel approaches for enhancing low aqueous solubility of drugs have been attempted and continued to evolve over a period. Reduction in particle size (Nano-drug delivery) and increased surface area, the use of alternative salt forms, Solubilization of drug in co-solvents or micelle solutions, complication with cyclodextrins or the use of lipid based vehicles for the delivery of lipophilic drugs to name few. Among these strategies, the amorphization of poorly water-soluble drugs has become one of the most effective approaches to improve their solubility and dissolution, and thus enhance drug bioavailability [7]. Compared to their crystalline counterparts, amorphous solids lack the long-range order of molecular packing and have higher internal energy. The amorphous solid state offers improved apparent solubility and dissolution rate due to the lower energy barrier required to dissolve the molecules, and hence transformation of crystalline drug into amorphous is widely employed for increasing solubility. However, thermodynamic instability due to the recrystallization tendency during processing, storage and in contact with the biological fluids, limits the potential application of amorphous systems [8]. Transformation of a crystalline drug to the amorphous form is a promising option for overcoming these challenges, since it has been shown to effectively increase the apparent solubility and dissolution rate of poorly soluble drugs. However, the use of amorphous drugs has been limited due to their poor physical stability (i.e. tendency to recrystallize) [9]. To stabilize the amorphous form, different glass solution subtypes, i.e. polymeric amorphous solid dispersions, mesoporous silicon or silica-based glass solutions, and co-amorphous formulations have been introduced [10]. The limited water solubility of new drug candidates presents a major problem during dosage form development, as these drugs are unlikely to result in poor absorption and thus poor bioavailability after oral administration. For an API to become orally bioavailable, it must dissolve in the gastrointestinal fluid, especially for drugs belonging to classes II and IV of the biopharmaceutical classification system. In order to increase the solubility of an API without changing its chemical structure, a co-amorphous system can be prepared, which uses a second small molecule instead of a polymer as a stabilizing agent. The amorphization technique is one of the available techniques to overcome the aqueous solubility of the API and the new chemical entity that belongs to classes II and IV of the biopharmaceutical classification system. Co-amorphous formulation is a binary or ternary system formed from low molecular weight crystalline materials such as sugar, surfactant, amino acid and organic acid. Aceclofenac is a non-steroidal anti-inflammatory drug, which is used in the prevention and treatment of rheumatoid arthritis and osteoarthritis. Aceclofenac belongs to class II drugs in the pharmaceutical classification systems, i.e. it has low solubility and high permeability. One of the main problems of this drug is its low aqueous solubility (i.e. 0.78 mg/ml in water), which results in bioavailability after oral administration. By

increasing the solubility of aceclofenac, its bioavailability is increased. Fluconazole is a synthetic antifungal agent belonging to the triazole group. It is one of the commonly used antifungal agents for most types of fungal infections including superficial and invasive fungal infections. It has known potential and competence to inhibit the synthesis of ergosterol, a major component of fungal cell membrane. Fluconazole is used to treat serious fungal or yeast infections such as vaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, other candida infections like urinary tract infections, peritonitis and fungal meningitis. This drug has been classified as a class I compound according to the Biopharmaceutical Classification System (BCS). Fluconazole is slightly soluble in water i.e. 4.363 g/l. By increasing the solubility of fluconazole, its bioavailability is increased.

2. MATERIALS & METHOD

2.1 List of Material Used

Table 01: List of materials used

Sl. No.	Materials	Suppliers
1	Aceclofenac	Karnataka Antibiotics and Pharmaceuticals Limited, Bangalore, India
2	Fluconazole	Orient Pharm, Mumbai, India
3	Aspartame	Yarrow Chem. Products, Mumbai, India
4	Maltose	Yarrow Chem. Products, Mumbai, India

Table 02: List of equipment's used

Sl. No.	Name of the equipment	Model /Company name
1	Electronic analytical balance	Shimadzu AUX -224
2	Ball mill	Rolex Ball mill Meter Driven
3	FTIR	Alpha broker
4	Dissolution Apparatus	Electro lab
5	UV-Visible Spectrophotometer	Shimadzu UV-Visible spectrophotometer. UV-1700, Japan.
6	Electronic Analytical balance	Shimadzu AUX-224, Japan
7	Melting point apparatus	µThermocal 10 Analytical instruments

Method of estimation for Fluconazole includes Estimation of Fluconazole ,Preparation of 0.1N HCl, Preparation of Standard Stock Solution,Preparation of working standard solution, Serial dilution of working standard solution to get beer's concentration and Standardization of Fluconazole. Method of estimation for Aceclofenac includes estimation of Aceclofenac, Preparation of phosphate buffer solution of 7.5, Preparation of Standard Stock Solution, Preparation of working standard solution,Serial dilution of working standard solution to get beer's concentration and Standardization of Aceclofenac. The following Preformulation studies were carried out for Aceclofenac and coformer;

- Morphology
- Determination of melting point of Aceclofenac
- Drug compatibility studies
- Differential Scanning Calorimetry
- In-vitro dissolution study
- Estimation of drug content

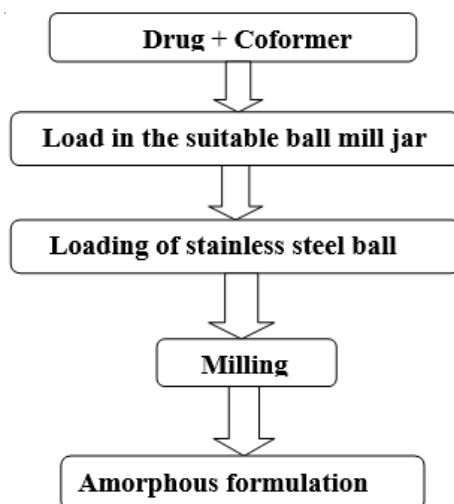


Figure 01: Preparation of co-amorphous formulation by ball milling technique

The optimization of the formulation was carried out by using Design Expert Software®, trial version. Full factorial design was performed with 2 variables i.e. Drug coformer ratio, milling time were select as critical process parameter or design factor and the milling speed, volume of milling jar, ball to powder ratio was kept constant in formulation. The responses like drug content, drug dissolution and particle size are recorded in 2 levels of variables. Total four of each experiment was conducted to obtain optimum formula of the drug.

Table 03: Optimization protocol

S.N	QbD	Co-amorphous formulation
1	Version	12.0.1.0
2	Design	Full factorial design
3	Model	2FI
4	Variables	Drug : coformer ratio, milling time
5	Level	High – low
6	Response	Drug content, Dissolution, Particle size

Table 04: Formulation design of Co-amorphous formulation of Aceclofenac

S.N	Formulation code	Aceclofenac : Aspartame (Molar ratio)	Milling time (min)
1	F1	1:1	120
2	F2	1:1	60
3	F3	1:3	120
4	F4	1:3	60

Table 05: Formulation design of Co-amorphous formulation of Fluconazole

S.N	Formulation code	Fluconazole : Maltose (Molar ratio)	Milling time (min)
1	F1	1:1	120
2	F2	1:1	60

3	F3	1:3	120
4	F4	1:3	60

Coamorphous production yield was determined by formula mentioned below.

$$\text{Percentage yield (\%)} = \frac{\text{Practical weight of coamorphous formulation}}{\text{Batch size}} \times 100$$

A weighed amount of blend was poured into a graduated cylinder and the volume (Vo) was noted. Then the graduated cylinder was fixed on the density apparatus and the timer knob is set for 100 tapping and after that volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated by using the following formula.

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_f$$

Where, W = weight of the powder.

Vo= Initial volume of the powder.

Vf= Final volume of the powder.

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular materials. Hausner's ratio was calculated from the bulk and tapped density using the following formula;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 06: Stability testing Conditions

Stability testing	Conditions	Time Period
Long term testing	25°C±2°C, 60%RH±5%	12 months
Accelerated testing	40°C±2°C, 75%RH±5%	6 months

3. RESULTS & DISCUSSIONS

Various responses like drug release, drug content and particle size was observed by altering the drug conformer ratio and milling time. The results obtained by the optimization software are as below.

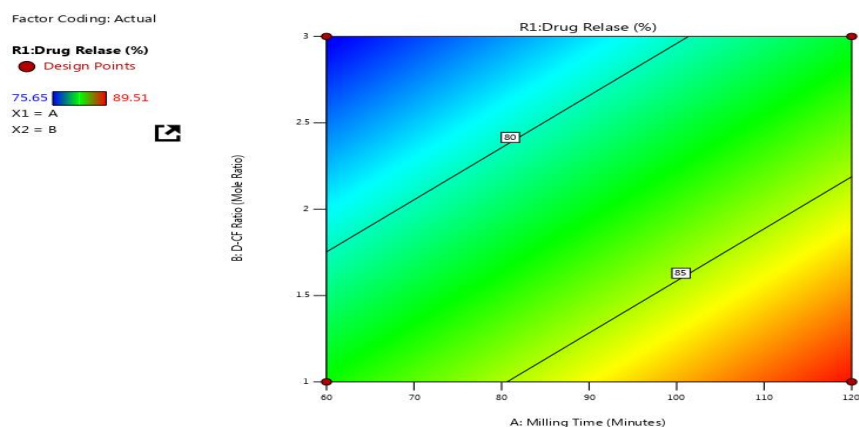


Figure 02: Response 1 Drug release, Contour plot

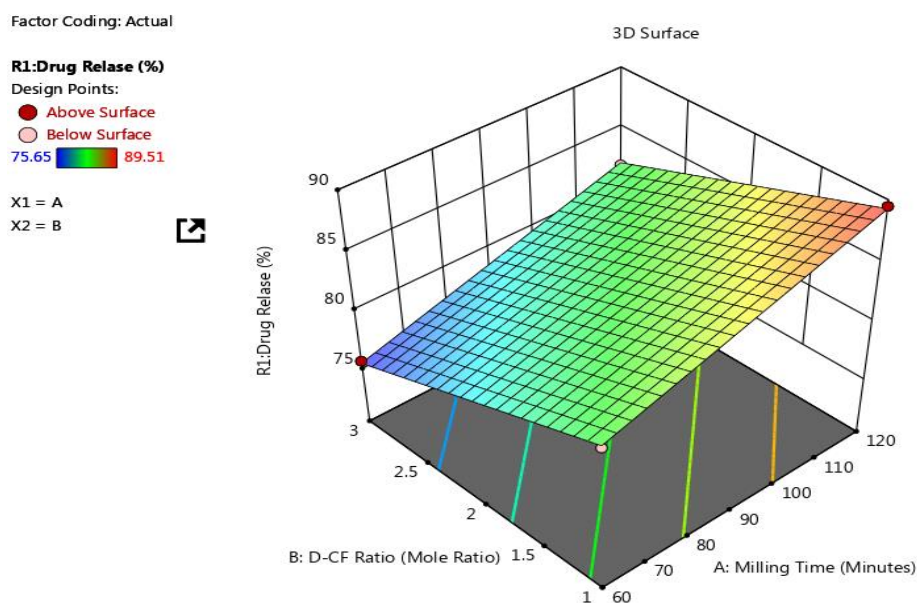


Figure 03: Response Surface Design

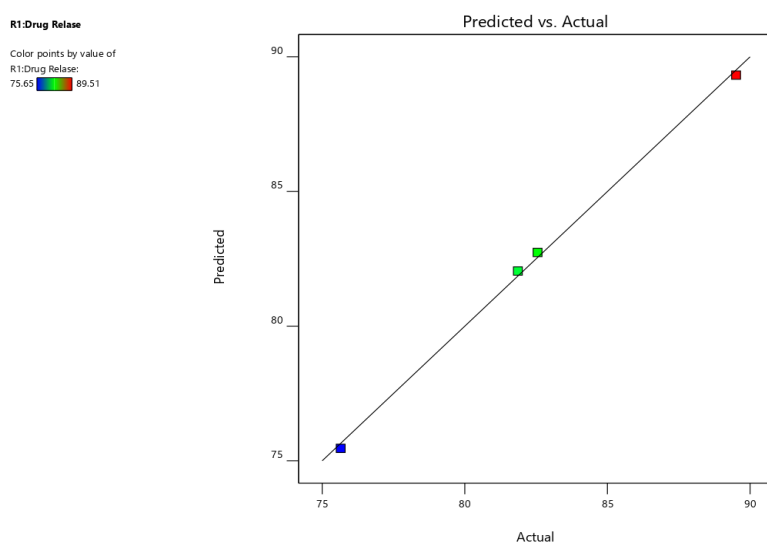


Figure 04: Predicted vs. Actual

Table 07: ANOVA for selected factorial model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	96.29	2	48.14	342.36	0.0382	significant
A-Milling Time	43.36	1	43.36	308.35	0.0362	
B-D-CF Ratio	52.93	1	52.93	376.36	0.0328	
Residual	0.1406	1	0.1406			
Cor Total	96.43	3				

The **Model F-value** of 342.36 implies the model is significant. There is only a 3.82% chance that an F-value this large could occur due to noise. **P-values less** than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

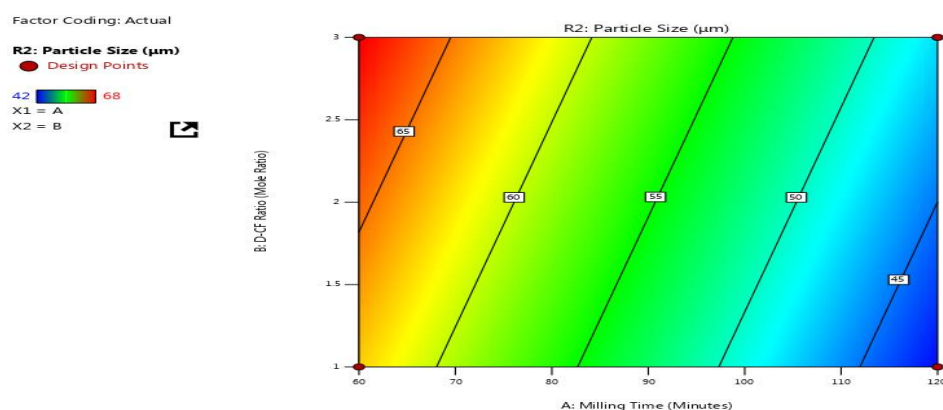
Table 08: Fit Statistics

Std deviation	CV%	R ²	Adjusted R ²	Adeq Precision
0.3750	0.4551	0.9985	0.9956	42.6777

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Noise ratio of 42.677 indicates an adequate signal.

3.1 Coefficients in Terms of Coded Factors

R1: Drug release = $82.39 + 3.29(A) - 3.64(B)$, By this data observation the final equation in term of coded factors represents as equation with 82.39 constant values of test A with 3.29 positive values and test B with 3.64 negative value suggested effect of factor consutigitively or orderly.

**Figure 05:** Response 2: Particle size, Contour plot

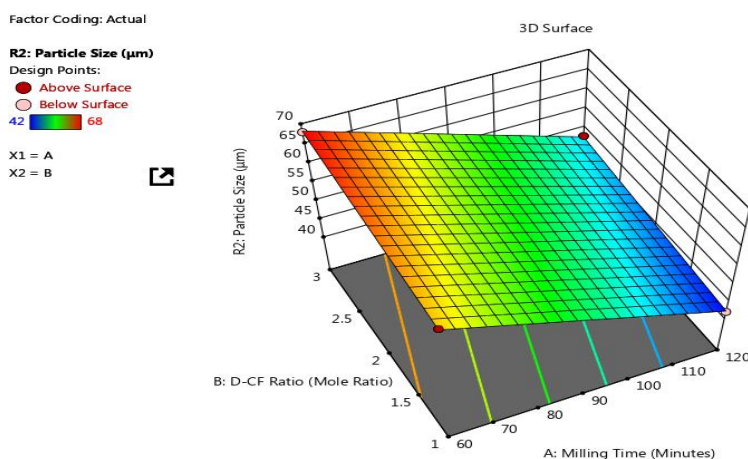


Figure 06: Response Surface Design

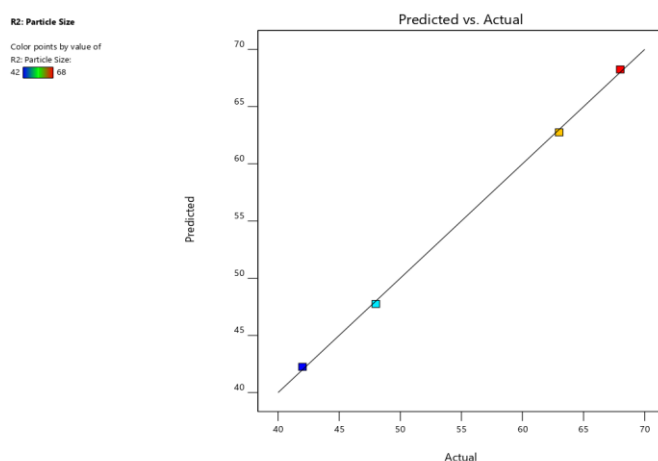


Figure 07: Predicted vs. Actual

Table 09: ANOVA for selected factorial model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	450.50	2	225.25	901.00	0.0236	significant
A-Milling Time	420.25	1	420.25	1681.00	0.0155	
B-D-CF Ratio	30.25	1	30.25	121.00	0.0577	
Residual	0.2500	1	0.2500			
Cor Total	450.75	3				

The **Model F-value** of 901.00 implies the model is significant. There is only a 2.36% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

Table 10: Fit Statistics

Std deviation	CV%	R ²	Adjusted R ²	Adeq Precision
0.5000	0.9050	0.9994	0.9983	60.0444

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Noise ratio of 60.044 indicates an adequate signal.

3.2 Coefficients in Terms of Coded Factors

R2: Particle size = $55.25 - 10.25(A) + 2.75(B)$, By this data observation the final equation in term of coded factors represents as equation with 55.25 constant values of test A with 10.25 negative values and test B with 2.75 positive value suggested effect of factor consutigatively or orderly.

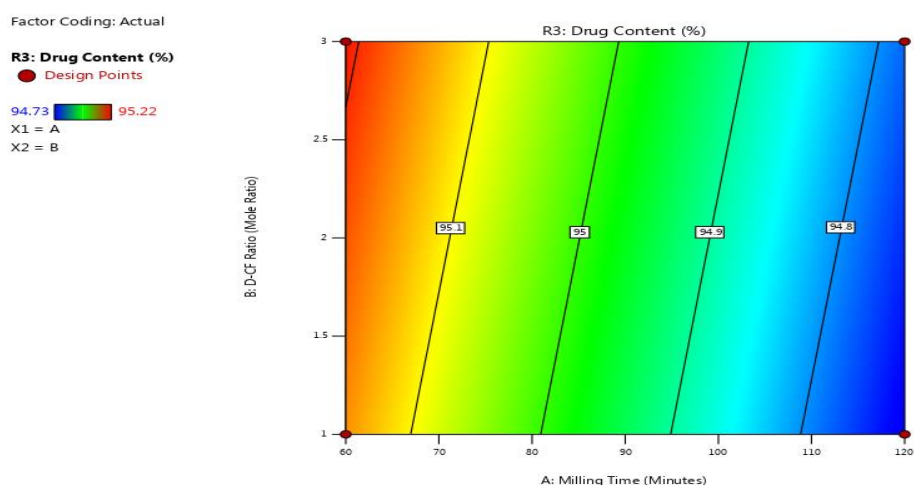


Figure 08: Response 3 Drug content, Contour plot

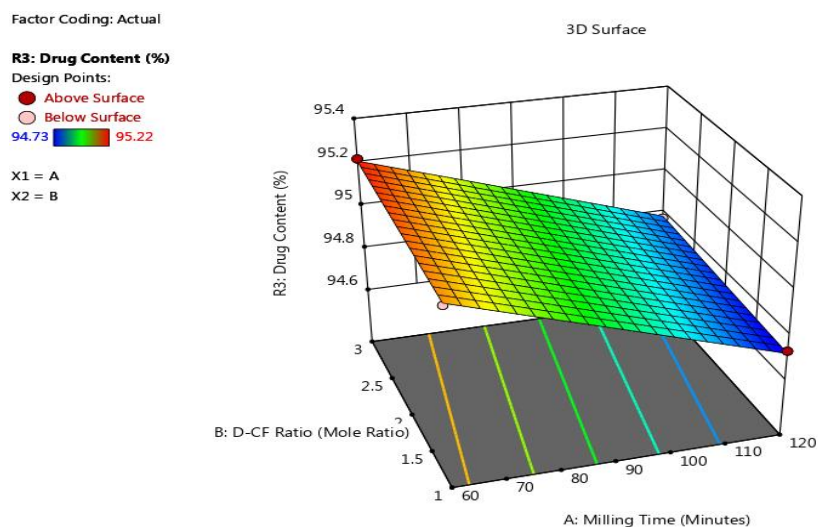


Figure 09: Response Surface Design

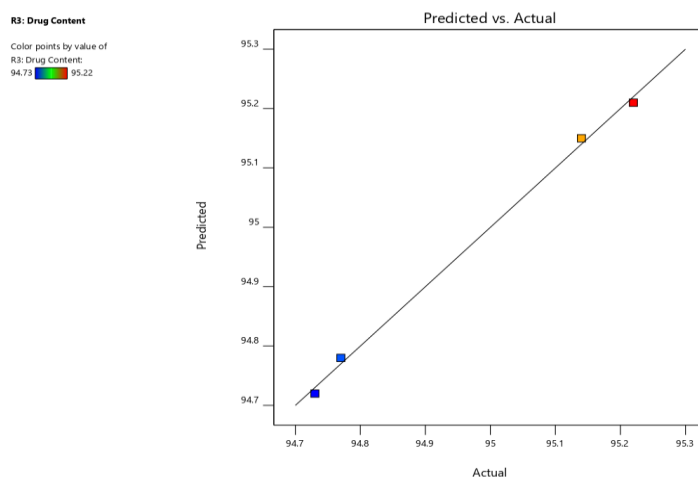


Figure 10: Predicted vs. Actual

Table 11: ANOVA for selected factorial model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.1885	2	0.0942	235.62	0.0460	Significant
A-Milling Time	0.1849	1	0.1849	462.25	0.0296	
B-D-CF Ratio	0.0036	1	0.0036	9.00	0.2048	
Residual	0.0004	1	0.0004			
Cor Total	0.1889	3				

The Model F-value of 235.62 implies the model is significant. There is only a 4.60% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

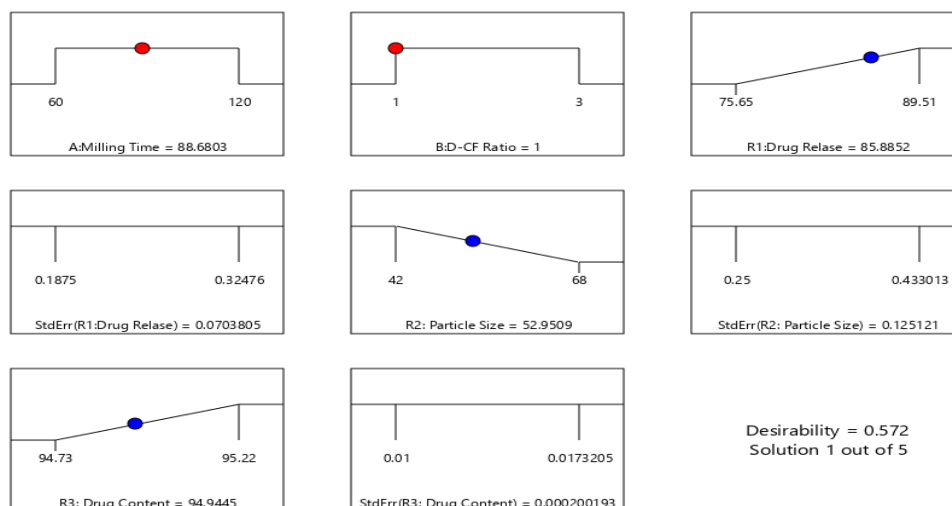
Table 12: Fit Statistics

Std deviation	CV%	R ²	Adjusted R ²	Adeq Precision
0.0200	0.0211	0.9979	0.9936	28.2902

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Noise ratio of 28.29 indicates an adequate signal.

3.3 Coefficients in Terms of Coded Factors

R3: Drug content = 94.97 – 0.2150(A) + (B), By this data observation the final equation in term of coded factors represents as equation with 55.25 constant values of test A with 10.25 negative values and test B with 0.0300 positive value suggested effect of factor consutigutively or orderly.



Factor Coding: Actual
 R1: Drug Release
 R2: Particle Size
 R3: Drug Content
 ● Design Points
 X1 = A: Milling Time
 X2 = B: D-CF Ratio

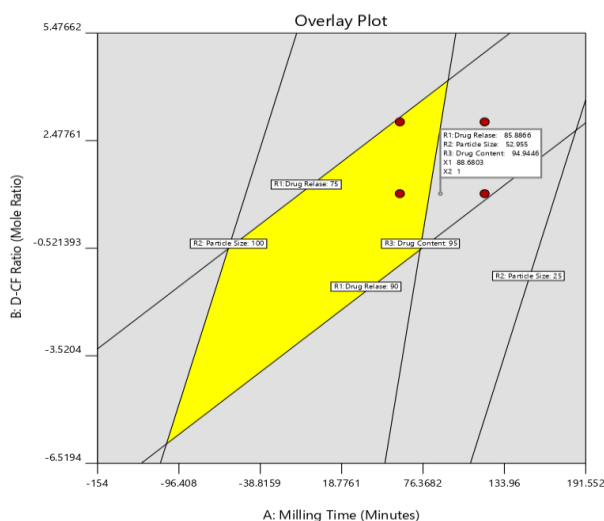


Table 13: Optimized formula given by Design Expert® of Fluconazole co-amorphous formulation (FFO)

Drug	Coformer	Formulation code	Drug : Coformer ratio (M)	Milling time (min)
Fluconazole	Maltose	FFO	1:1	88.68

Table 14: Response comparison of co-amorphous formulation (predicted vs. practical)

Optimized formulation (AFO)	Drug release (%)	Particle size (μm)	Drug content (%)
Theoretical(predicted)	82.393	55.25	94.97
Practical(actual)	82.40	57.34	93.21

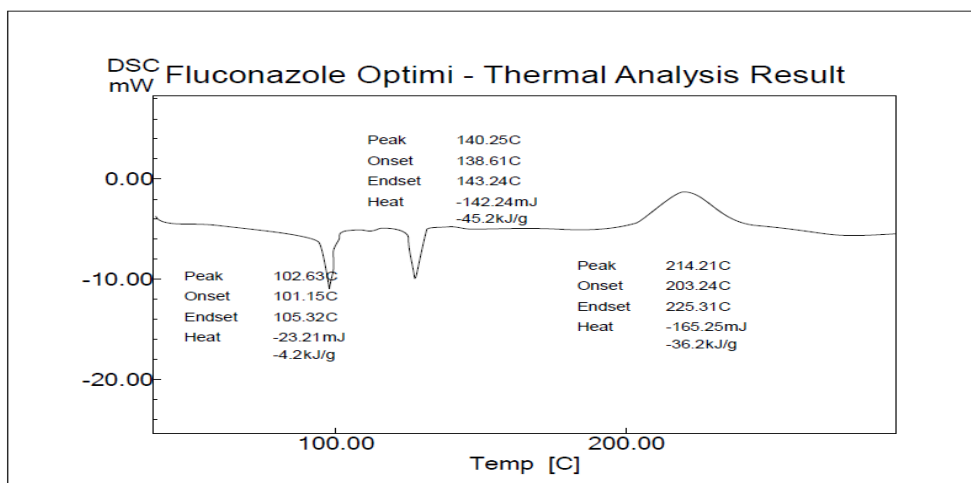


Figure 11: DSC thermogram of the fluconazole optimized formulation (FFO).

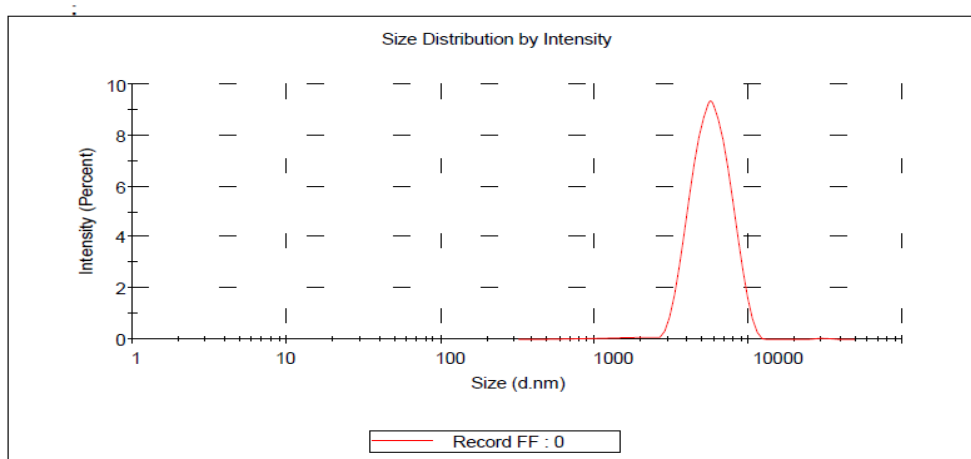


Figure 12: Particle size distribution of fluconazole optimized formulation (FFO)

Stability study at ambient conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $75\% \text{RH} \pm 5\%$) for fluconazole co-amorphous optimized formulation (FFO). A white or almost white, amorphous, free flowing amorphous powder.

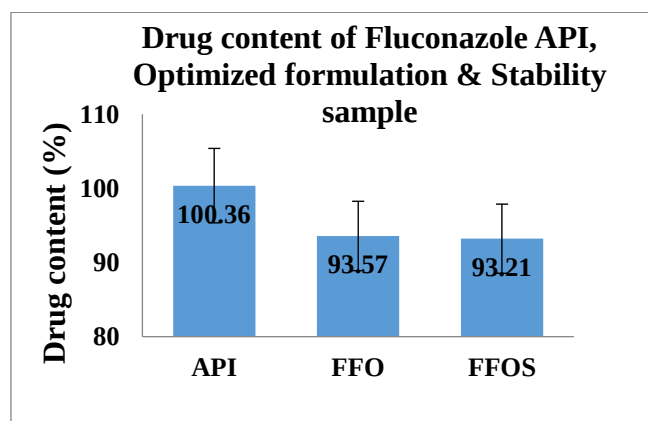


Figure 13: Comparison of drug content percentage of fluconazole API, optimized formulation & optimized formulation after stability

Table 15: Comparison of In-vitro drug release of fluconazole API, optimized formulation & optimization formulation after stability

Time (min)	CDR % API's	CDR % FFO	CDR % FFOS
0	0	0	0
30	12.85	14.46	13.82
60	29.96	32.87	32.22
90	43.56	43.58	43.25
120	54.88	63.88	63.24
150	62.34	78.46	76.85
180	67.52	82.4	81.43

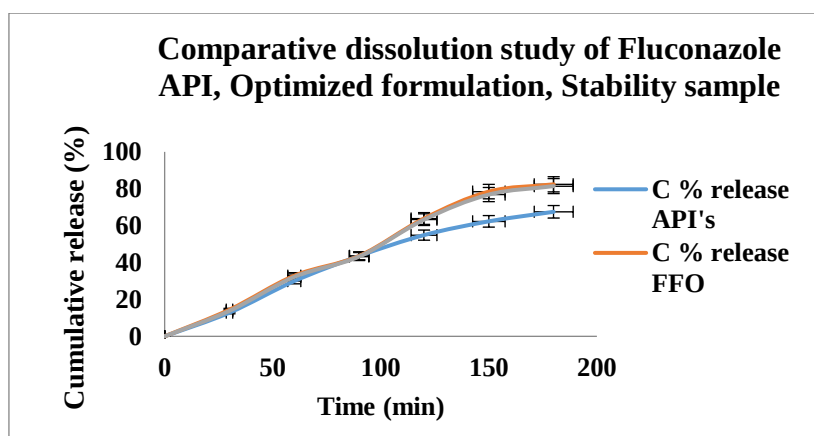


Figure 14: Comparison of In-vitro drug release of fluconazole API, optimized formulation & optimization formulation after stability

Different concentrations of Aceclofenac solutions were prepared using phosphate buffer pH 7.5 and absorption was measured at 274.65 nm. Graph was plotted using drug concentration at X- axis and absorbance at Y-axis.

Table 16: Standard calibration curve data for Aceclofenac in phosphate buffer pH 7.5

Standard calibration curve of Aceclofenac		
S.N	Concentration ($\mu\text{g/ml}$)	Absorption (nm)
1	10 $\mu\text{g/ml}$	0.115
2	20 $\mu\text{g/ml}$	0.172
3	30 $\mu\text{g/ml}$	0.314
4	40 $\mu\text{g/ml}$	0.443
5	50 $\mu\text{g/ml}$	0.587

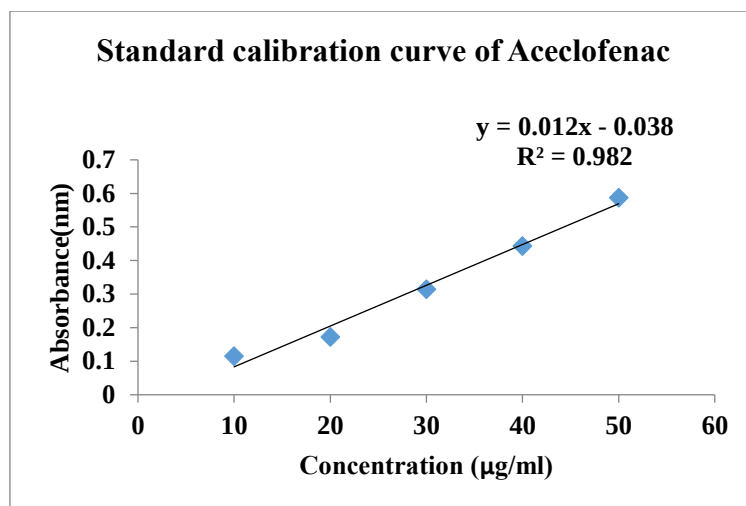


Figure 15: Calibration curve of Aceclofenac in phosphate buffer pH 7.5

The melting point of Aceclofenac was found to be 151.34°C (average) and according to IP 2007 the melting point of Aceclofenac was within the range of 149-153°C.

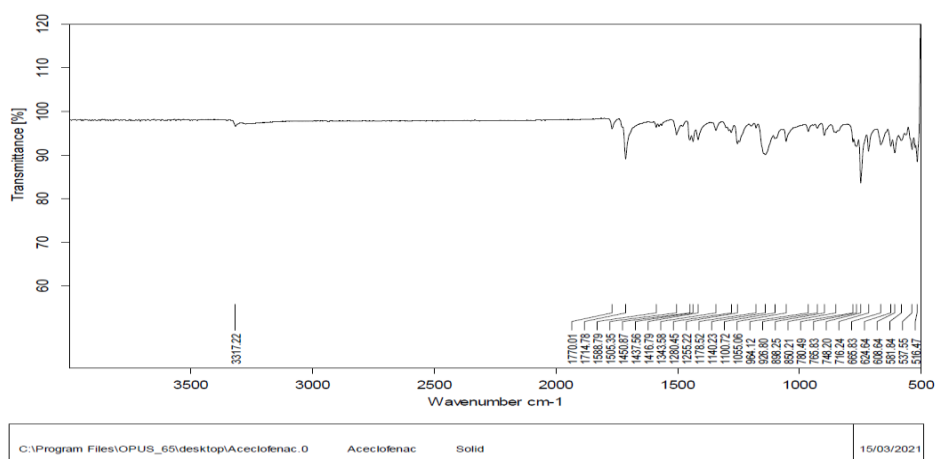


Figure 16: FTIR spectra of Aceclofenac

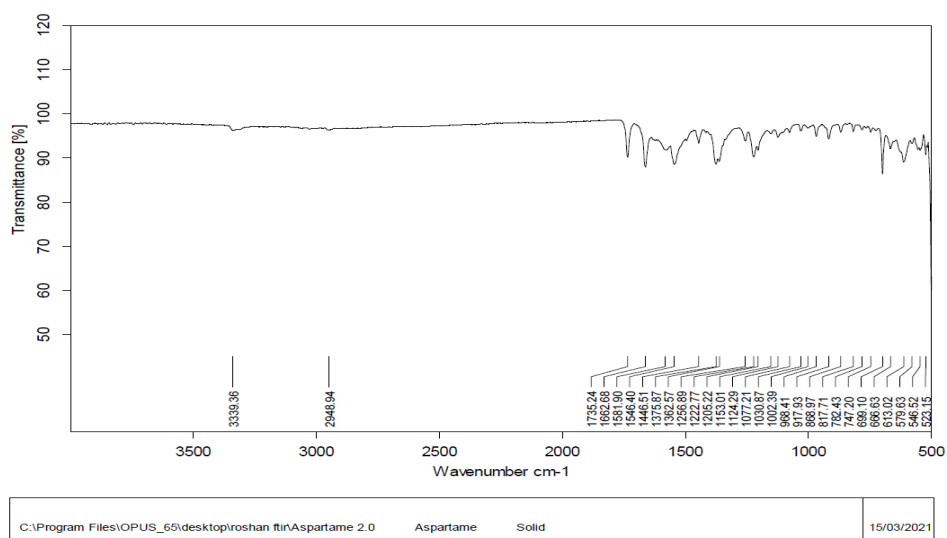


Figure 17: FTIR spectra of Aspartame

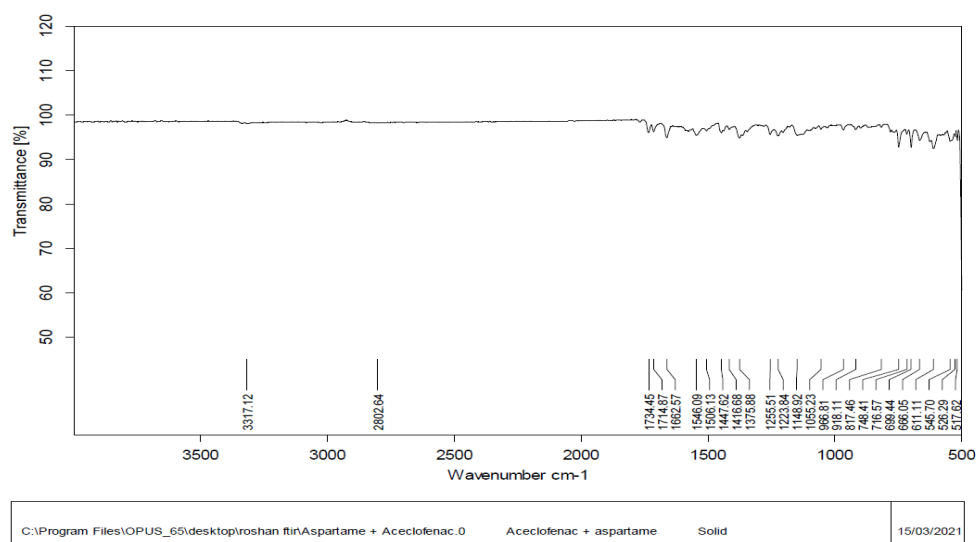


Figure 18: FTIR spectra of Aceclofenac + Aspartame

Table 17: IR interpretation of Aceclofenac

Functional group	Range (Cm ⁻¹)	Observed value in pure aceclofenac (Cm ⁻¹)	Observed value in aceclofenac + aspartame (Cm ⁻¹)
-O-H	3000-2500	2835	2802
-C=O	1780-1710	1770	1734
-Cl	850-515	716.24	716.57
-NH	3500-3300	1617	3317.12

Table 18: *In-vitro* drug release profile of aceclofenac API

Time (min)	CDR %
0	0
30	10.5
60	27.81
90	42.15
120	50.48
150	60.28
180	65.58

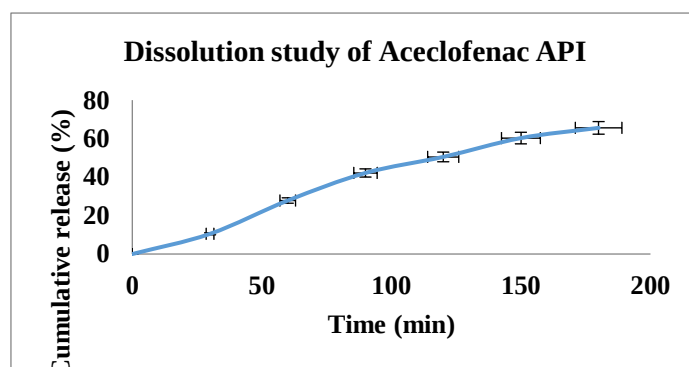


Figure 19: *In-vitro* drug release of Aceclofenac API

Table 19: Production yield of Aceclofenac co-amorphous formulation

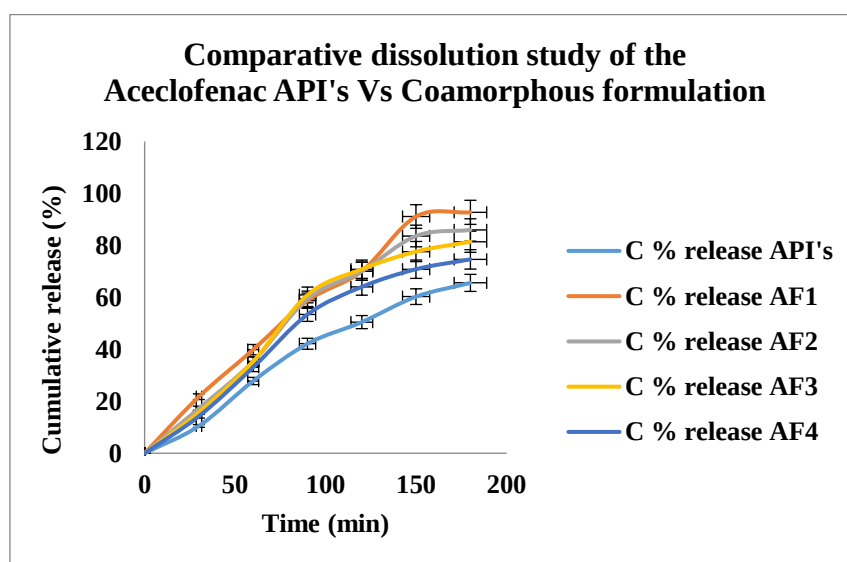
Sl. No.	Formulation	Yield (%)
1	AF1	90
2	AF2	88
3	AF3	92
4	AF4	90
5	AFO	92

Table 20: Micrometric properties of Aceclofenac co-amorphous formulation

Sl. No	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio
1	AF1	0.615	0.889	1.45
2	AF2	0.606	0.870	1.44
3	AF3	0.597	0.909	1.52
4	AF4	0.625	0.851	1.36
5	AFO	0.597	0.870	1.45

Table 21: Comparison of *In-vitro* drug release of aceclofenac API's and Co-amorphous formulation

Time (min)	CDR % API's	CDR % AF1	CDR % AF2	CDR % AF3	CDR % AF4
0	0	0	0	0	0
30	10.5	21.75	17.25	15.75	14.25
60	27.81	39.87	35.35	35.34	33.08
90	42.15	58.72	59.45	60.95	53.43
120	50.48	70.08	70.08	70.84	64.05
150	60.28	91.14	83.64	77.64	70.85
180	65.58	92.75	85.96	81.43	74.64

**Figure 20:** Comparative *In-vitro* drug release study of aceclofenac API's and Co-amorphous formulation.

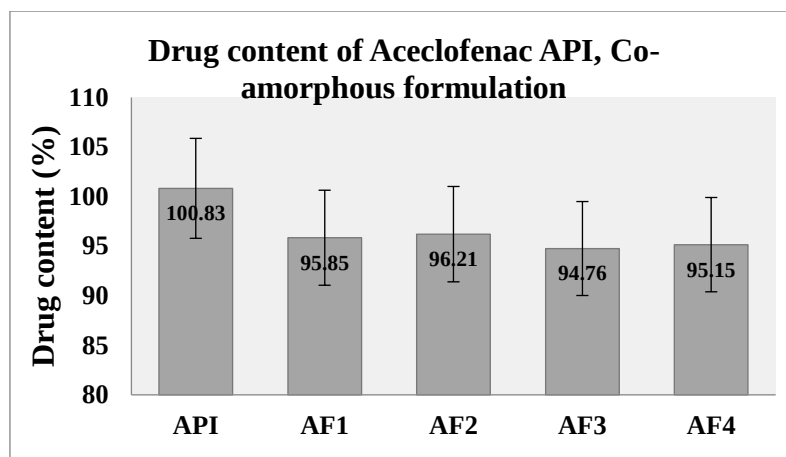


Figure 21: Estimation of drug content of aceclofenac API & co-amorphous formulation

DISCUSSION

The present study was carried out for the preparation, evaluation and characterization of co-amorphous drug formulation prepared by ball milling method. Co-amorphous formulations with molar ratio of drug conformer (1:1 and 1:3) were prepared with the selected conformer. All the prepared co-amorphous formulations were found to be fine and free-flowing powders [11]. The prepared optimized co-amorphous formulations were characterized by FTIR, DSC and DLS. The mixture of fluconazole with 0.1 N HCl was found to be 260 nm with UV spectral analysis. The correlation coefficient for the standard curve of fluconazole was found to be 0.996 in the concentration range of 2 to 10 µg/ml, with the regression equation $0.028x - 0.009$. The λ_{max} of aceclofenac with pH 7.5 phosphate buffer was found to be 274.65 with UV spectral analysis [12]. The correlation coefficient for the standard curve of aceclofenac was found to be 0.982 in the concentration range of 10–50 µg/ml, with the regression equation of $0.012x - 0.03$. The melting points of the drugs were determined using a standard method [13]. The observed melting point of fluconazole was found to be 138.8 °C, while the observed melting point of aceclofenac was found to be 151.34 °C, which therefore indicates the purity of the drug sample [14]. The FTIR spectra of pure fluconazole alone and fluconazole with maltose were recorded at a wavelength of 4000 to 400 cm^{-1} . The FTIR interpretation of fluconazole with maltose is shown. The spectra of pure fluconazole showed that the characteristic peaks in the spectrum of fluconazole are 3012 due to O-H stretching, 1252 due to C-O stretching, 1269 due to C-F stretching and 1617 due to C=N stretching and mixing with maltose at or around the required wavenumber of the pure drug. Therefore, it was concluded that fluconazole was calculable with maltose as a conformer [15]. The FTIR spectra of pure aceclofenac alone and aceclofenac with aspartame were recorded at a wavelength of 4000-400 cm^{-1} . The FTIR interpretation of aceclofenac with aspartame is presented. EnglishThe spectra of pure aceclofenac showed that the characteristic peaks of aceclofenac spectrum are 2835 due to O-H stretching, 1770 due to C=O stretching, 716.24 due to C-Cal and 3317.22 due to -NH stretching and mixing with aspartame at or around the required wavenumber of the pure drug. Therefore, it was concluded that aceclofenac was calculable with aspartame as a conformer. [16][17] An in vitro drug release study of pure drug fluconazole was carried out in 0.1 N HCl and the cumulative drug release percentage was calculated and summarized and the CDR% of fluconazole was found to be 67.52% at 180 min [18][19]. An in vitro drug release study of pure aceclofenac was carried out in phosphate buffer pH 7.5 and the cumulative drug release percentage was calculated and summarized and the CDR% of fluconazole was found to be 65.58% at 180 min [20].

4. CONCLUSIONS

Research studies were undertaken on the preparation, evaluation and characterization of co-amorphous solid dispersions of acidic and basic drugs for oral drug delivery using artificial sweeteners as conformer using dry grinding by ball mill technique. Therefore, from the experimental results, the following results were concluded. The optimized formulations revealed the desired particle size of the formulations, CDR% and drug content for both formulations. The optimized FFO formulation shows that it requires a particle size of 55.25 μm , a CDR of 82.39% and a drug content of 94.97%, while AFO shows that it requires a particle size of 49.52 μm , a CDR of 85.45% and a drug content of 95.19% respectively and found no statistical significance of the difference between the predicted value and the actual value. The characterization study of the optimized FFO and AFO formulation showed that the drug is calculable with the conformer and formulation processing. From the dissolution study of co-amorphous formulations of fluconazole, the results showed in vitro drug release in the range of 76.26% to 89.85%, while the results of co-amorphous formulations of aceclofenac showed in vitro drug release in the range of 74.64% to 92.75%. Therefore, from the above studies, the results were obtained for amorphous drugs that showed good in vitro drug release irrespective of the acidic and basic form of drugs. The problem of in vitro release of acidic and basic forms of drugs for oral delivery system can be solved by using co-amorphization technique by selecting a suitable conformer for stabilization of co-amorphous formulation. The current study has improved the physicochemical properties of drugs in the formulation for oral drug delivery systems. Therefore, the formulation requires a suitable conformer and processing through appropriate preparation methods providing maximum solubility and in vitro release of the drug at the site of absorption.

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