

Original Article

Preparation of Co-Amorphous System Formulation of Poorly Aqueous Soluble API's for Suitable Acidic & Basic Drug for Oral Drug Delivery

Roshan Gyawali ^{1*}, S. Rajarajan ², Yuvraj Regmi ³, Sachin Aryal ⁴

1. Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, India
2. Professor, Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, India
3. Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, India
4. Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, India.

* Correspondence: roshangyawali36@gmail.com

Abstract: The oral route of drug administration is one of the most preferred routes of administration because of higher patient compliance, less expensive manufacturing costs and ease of administration. Drug substances having low aqueous solubility are becoming extensively widespread. The limited aqueous solubility of drugs presents a major challenge during development of dosage form results in poor absorption after oral route administration, for a drug become orally bioavailable, it has to dissolve in GI fluids, especially for drugs belonging to BCS class II & IV. This study described the preparation of co-amorphous system formulation of poorly aqueous soluble API's for suitable acidic & basic drug for oral drug delivery. 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 for 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. The results determined that the production yields for co-amorphous formulations were found to be in the range of 88-92%. The production yields for co-amorphous formulations were found to be in between 88-92% and the production yield for the optimized formulation was found to be 92%. The result concludes that drug and coformer used in formulations were found compatible with each other. Co-amorphous formulations were prepared by ball milling technique at a constant speed for 60 min and 120 min by taking 1:1 M and 1:3 M drug coformer ratio was most suitable.

Keywords: co-amorphous system, acidic & basic drug, oral drug delivery

1. INTRODUCTION

The oral route of drug administration is one of the most preferred routes of administration because of higher patient compliance, less expensive manufacturing costs and ease of administration [1]. Furthermore, oral administration is used for both local and systemic delivery of a wide range of drug molecules, from small molecule drugs to large bio macro molecules. Despite the above mentioned advantageous features, oral delivery faces several limitations, such as poor solubility, poor permeability, fast degradation in the gastrointestinal tract, and an inability to penetrate the protective mucosal barrier

[2]. Delivery of drugs through the oral route is the most accepted route for the drug administration among the various route because of its advantages like noninvasive administration, painless and self administration and high patient complaisance [3]. Drug substances having low aqueous solubility are becoming extensively widespread in the research and development speculations of discovery oriented pharmaceutical companies [4]. The most recent decade has seen a substantial number of new chemical entities coming into poorly soluble drug category which commonly leads to poor oral bioavailability [5]. However, 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 [6]. For example, poorly soluble bioactive ingredients may lead to low absorption which definitely results in low bioavailability and a low therapeutic index [7]. In oral drug delivery systems, gastrointestinal absorption significantly depends on the solubility and dissolution rate of drug molecules [8]. However, at present, approximately 90% of new chemical entities and 40% of currently marketed drugs belong to the Biopharmaceutical Classification System (BCS) II and IV classes, which suffer from the problems of poor water solubility and low bioavailability [9]. It is well established that dissolution is frequently the rate-limiting step in the gastrointestinal absorption of a drug from solid dosage forms. Aqueous solubility is a key parameter influencing biological activity, formulation and in vitro and in vivo biopharmaceutical properties [10]. However, many drugs currently used and in development have poor water solubility and belong to Classes II and IV of the Biopharmaceutical Classification System (BSC), i.e., has low solubility. 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 [11]. 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 micellar solutions, complexation with cyclodextrins or the use of lipid based vehicles for the delivery of lipophilic drugs to name few [12]. 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 [13]. Compared to their crystalline counterparts, amorphous solids lack the long-range order of molecular packing and have higher internal energy [14]. 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 [15]. In the last years a new strategy, alternative to amorphous polymeric, is co-amorphous solid dispersions with solubility and stability improvements over the corresponding amorphous and crystalline drugs [16]. They combine two or more low molecular weight ingredients into a homogenous amorphous single-phase and have been used to stabilize amorphous forms of low solubility drugs [17]. Due to the low MW components, low amount of stabilizer (co-former) is required, and thus oversized dose units and hygroscopicity problems inherent to polymeric amorphous SDs are avoided [18]. Co-amorphous SDs provide high drug solubility due to the high energy of the amorphous state and because no energy is needed for the rearrangement of the crystal lattice during dissolution [19]. Additionally, they may exhibit high stability and improved dissolution not only compared to their crystalline homologues but also to the individual amorphous forms [20]. The main reason for these improvements is the strong solid-state interactions between the components [21]. In addition, the stability of co-amorphous mixtures is due to the increase of T_g and to the homogeneous molecular-level dispersions achieved by high energy mixing [22]. Impregnations with small molecules, e.g., amino acids, are considered critical for preventing recrystallization [23]. Until now, about 50 different combinations of drug-drug and drug-excipient co-

amorphous systems in different molecular proportions have been reported [24]. Based on the selection of co-formers, coamorphous systems can be categorized into drug-excipient and drug-drug coamorphous systems [25]. In drug-excipient coamorphous systems, the excipients can be urea, sugars, nicotinamide, amino acids and carboxylic acid, etc [26]. In particular, amino acids have been extensively used as co-formers in coamorphous system to enhance physical stability and dissolutions [27]. The study describe the preparation of co-amorphous system formulation of poorly aqueous soluble API's for suitable acidic & basic drug for oral drug delivery. It also verify the Pre-formulation studies with including screening of co-amorphous system.

2. MATERIALS & METHOD

Following are the materials used in the study, Aceclofenac, Fluconazole, Aspartame & Maltose. Similarly, followings are the equipments used i.e. Electronic analytical balance, Ball mill, FTIR, Dissolution Apparatus, UV-Visible Spectrophotometer, Electronic Analytical balance & Melting point apparatus. There are different method of preparation of Co-amorphous formulation, Ball milling, Milling methods like ball milling have demonstrated their potential in generation of stable co-amorphous and are most widely used methods due to ease of handling. Final product properties depend upon the milling temperature and thermal stability of the drug along with its T_g. Benefits of ball milling include low chemical degradation and high recovery compared to other preparation methods. Efficiency of the process increases if the milling temperature is below T_g of drug. The formation of co-amorphous mixtures was assessed by mechanical activation. The formulations were prepared by ball milling. A total mass of 5 gm of respective drug and respective cofomer at a molar ratio of 1:1M and 1:3M was placed in 165 ml ball milling stainless steel jar with ten 9.5 mm stainless steel balls and two 1.6 cm stainless steel balls. Subsequently, the mixtures were ball milled in a ball mill with rpm of 100. The ball milling process was performed in a room temperature for 60 to 120 min according to optimization protocol. The individual formulations were milled under the same conditions. After BM, the jars were placed in a dedicator in order to reach room temperature before opening to avoid moisture absorption. 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 cofomer 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. Coamorphous production yield was determined by formula mentioned below.

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

A weighed amount of blend was poured into a graduated cylinder and the volume (V_o) 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 (V_f) 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;

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

The prepared co-amorphous formulations were subjected to in vitro dissolution. Dissolution test was carried out using USP paddle method. The stirring rate was 50 rpm, Phosphate buffer pH 7.5 was used as dissolution medium and dissolution medium was maintained at 37 ± 0.5 °C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Aceclofenac at 274.65 nm by using UV-visible spectrophotometer. The prepared co-amorphous formulations were subjected to in vitro dissolution. Dissolution test was carried out using USP paddle method, the stirring rate was 50 rpm, 0.1 N HCl was used as dissolution medium and dissolution medium was maintained at 37 ± 0.5 °C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Fluconazole at 260 nm by using UV-visible spectrophotometer. From each batch of prepared Aceclofenac co-amorphous formulation, 50 mg of powder collect randomly and take equivalent to 10 mg was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in pH-6.8 phosphate buffer. For both the sample and standard solutions absorbance was measured at 274.65 nm in UV- Visible spectrophotometer. From each batch of prepared Fluconazole co-amorphous formulation, powder sample was collect randomly a quantity, which is equivalent to 100 mg of Fluconazole was accurately weighed and transferred into 100 ml volumetric flask. To this, 50 ml of 0.1M HCl solution was added and sonicated for 10 min with occasional shaking to disperse and dissolve the contents. The volume was made up to 100 ml with 0.1M HCl solution. Same concentration of standard solution was prepared by dissolving 100 mg of standard drug in 0.1 N HCl. For both the sample and standard solution absorbance was measured at 260 nm in UV-Visible spectrophotometer. Thermogram of both respective co-amorphous formulations was obtained using differential scanning calorimeter outfitted with an intercooler. Indium standard was implied for calibrating DSC enthalpy and temperature scale. Co-amorphous samples were kept in aluminum pan hermetically and heated at constant heat of 10°C/min over temperature range of 10-200°C. By purging nitrogen with flow rate of 10ml/min inert atmosphere was maintained. The size of nanoparticles was determined by dynamic light scattering (Nano ZS 3600, Malvern Instruments, Malvern, UK), with varying duration greater than 20 s. The dispersant used was water having RI (1.33), viscosity (0.8872 cP). Disposable sizing cuvette was used for determination, the stability study of prepared both co-amorphous formulations were carried out as per the guidelines provided by ICH Q1 AR2. According to ICH guidelines accelerated and long term testing are adopted for the stability testing. Due to time limitation only accelerated testing is adopted for only one month. The testing procedure covered those features susceptible to change during storage and likely to influence quality, safety and efficacy. The analytical procedure was fully validated and the assay method and drug release study was stability-indicating. The physical evaluations like physical appearance colour

and shape of formulation was carried out. The assay and drug release study was performed to justify the product stability.

3. RESULTS & DISCUSSION

3.1 Analytical methods

Different concentrations of Fluconazole solutions were prepared using 0.1 N HCl and absorption was measured at 260 nm. Graph was plotted using drug concentration at X- axis and absorbance at Y-axis.

Table 01: Standard calibration curve data for Fluconazole in 0.1N HCl

Standard calibration curve of Fluconazole		
Sl. No	Concentration ($\mu\text{g/ml}$)	Absorption (nm)
1	2 $\mu\text{g/ml}$	0.053
2	4 $\mu\text{g/ml}$	0.099
3	6 $\mu\text{g/ml}$	0.163
4	8 $\mu\text{g/ml}$	0.216
5	10 $\mu\text{g/ml}$	0.282

The melting point of Fluconazole was found to be 138.8°C (average) and according to IP 2007 the melting point of Fluconazole was within the range of 138-140°C.

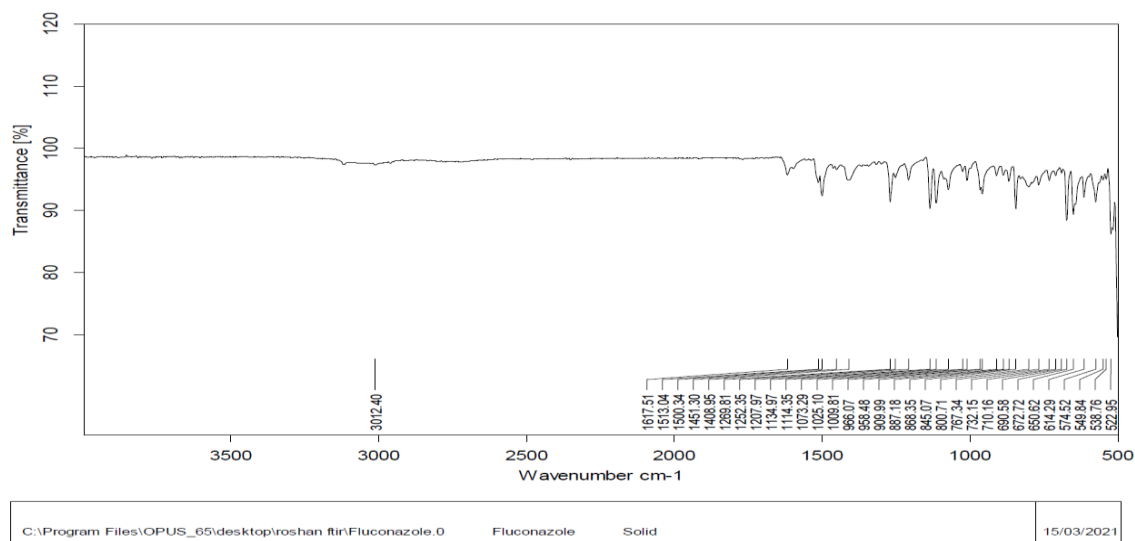


Figure 01: IR Spectra of Fluconazole

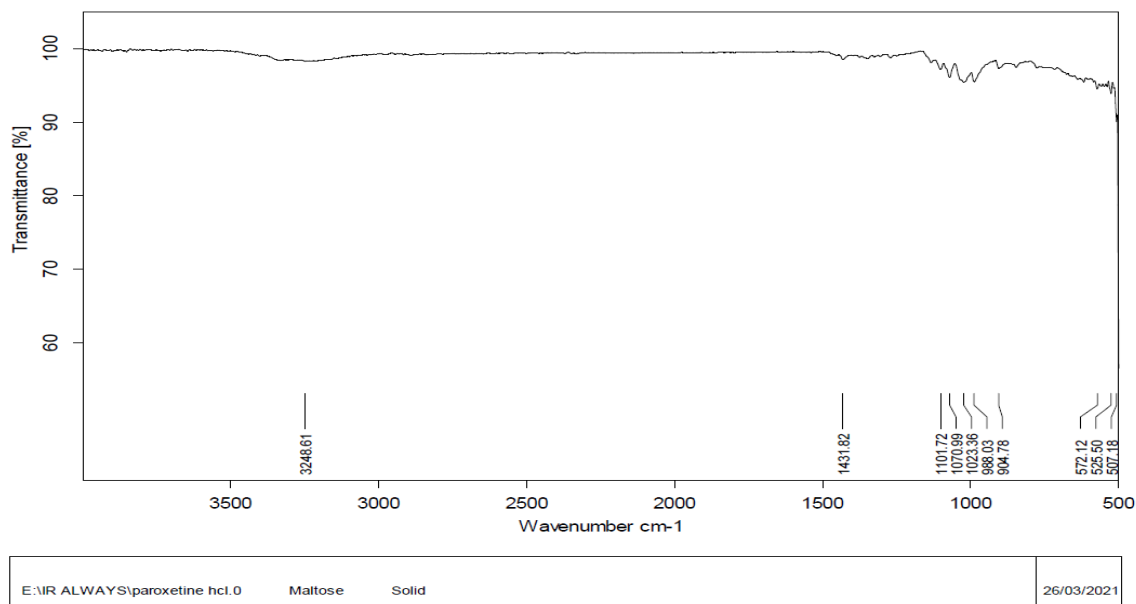


Figure 02: IR Spectra of Maltose

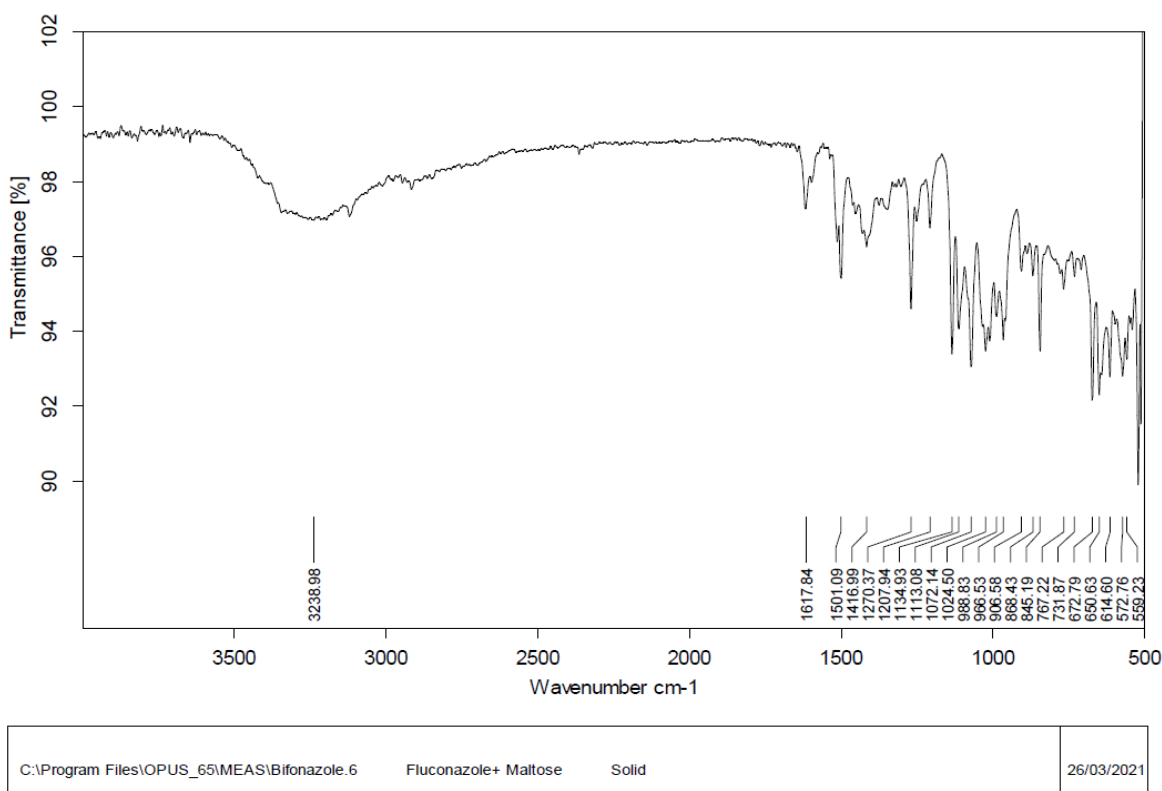
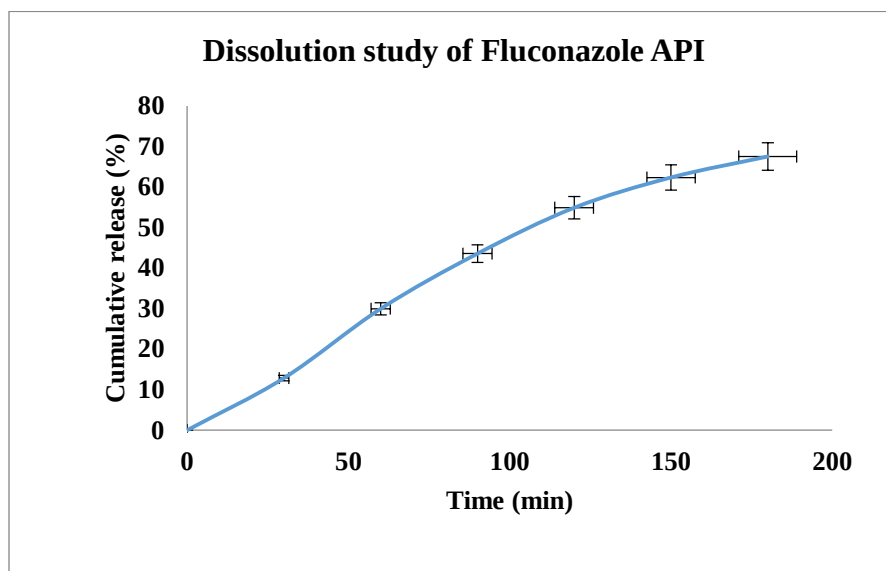


Figure 03: IR Spectrum of Fluconazole + Maltose

Table 02: IR interpretation of Fluconazole and Maltose

Functional group	Range (Cm ⁻¹)	Observed value in pure fluconazole (Cm ⁻¹)	Observed value in fluconazole maltose (Cm ⁻¹)
-O-H	3550 - 3000	3012.40	3015
-C-O	1382 -1036	1252	1250
-F	1400–1100	1269	1270
C=N	1500-1650	1617	1618

**Figure 04:** *In-vitro* drug release of Fluconazole API**Table 03:** Production yield of Fluconazole co-amorphous formulation

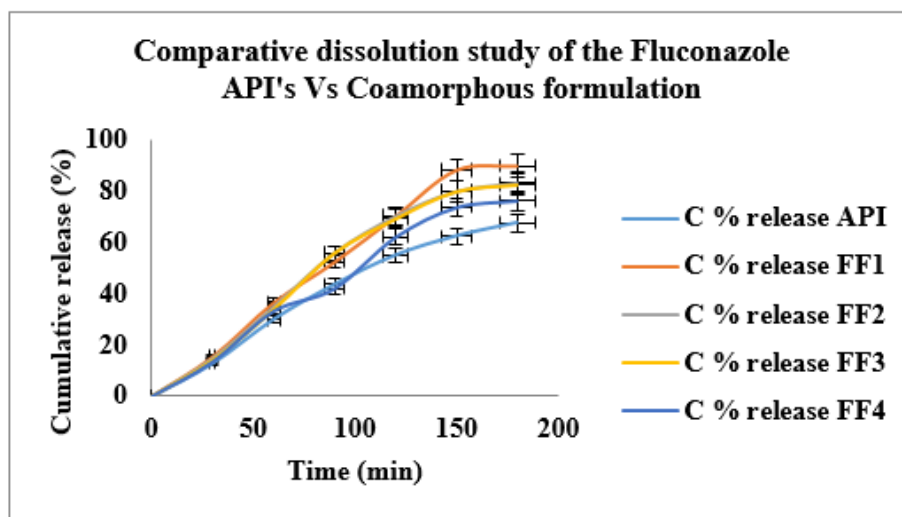
Sl. No.	Formulation	Yield (%)
1	FF1	90
2	FF2	92
3	FF3	88
4	FF4	90
5	FFO	90

Table 04: Micromeritic properties of Fluconazole co-amorphous formulation

Sl. No	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio
1	FF1	0.606	0.870	1.44
2	FF2	0.615	0.851	1.38
3	FF3	0.625	0.870	1.39
4	FF4	0.597	0.833	1.40
5	FFO	0.588	0.870	1.48

Table 05: Comparison of *In-vitro* drug release of pure fluconazole API's and Co-amorphous formulation

Time (min)	CDR % API	CDR % FF1	CDR % FF2	CDR % FF3	CDR % FF4
0	0	0	0	0	0
30	12.85	15.43	14.79	14.14	13.5
60	29.96	36.41	34.8	33.83	33.18
90	43.56	52.27	55.8	55.79	41.97
120	54.88	70.04	70.06	69.09	61.95
150	62.34	88.14	79.78	79.78	73.63
180	67.52	89.85	83.05	82.41	76.26

**Figure 05:** Comparative *In-vitro* drug release study of fluconazole API's and Co-amorphous formulation

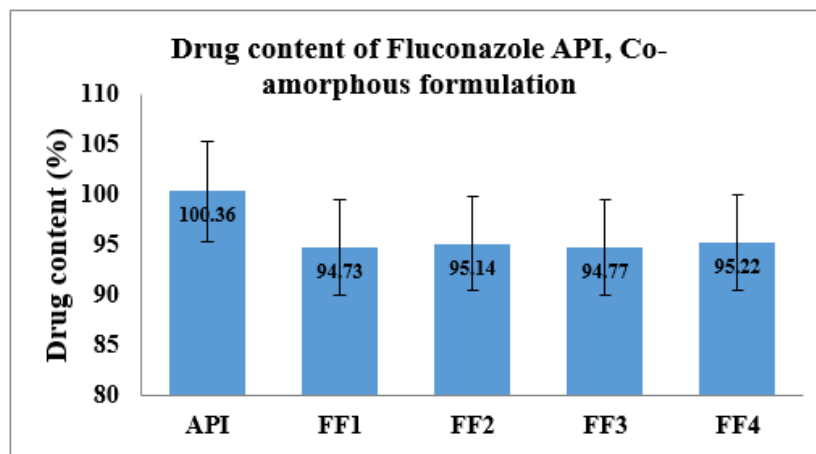


Figure 06: Estimation of drug content of fluconazole API & co-amorphous formulation

With selected coformer, co-amorphous formulations at 1:1 and 1:3 drug coformer molar ratios we made. All prepared co-amorphous powders were fine and free-flowing, this optimized co-amorphous formulation was characterized by FTIR, DSC, and DLS. The UV spectral study revealed a λ_{max} of 260 nm for fluconazole in 0.1N HCl. The standard curve correlation coefficient for fluconazole was 0.996 in the 2-10 $\mu\text{g/ml}$ concentration range, with a regression equation of $0.028x - 0.009$. The λ_{max} of aceclofenac in pH 7.5 phosphate buffer was 274.65 according to UV spectral analysis. Aceclofenac standard curve correlation coefficient was 0.982 (10-50 $\mu\text{g/ml}$), using a regression equation of $0.012x - 0.038$. Calculated co-amorphous formulation micromeritic characteristics. The flow characteristics of all formulations were unsatisfactory. The bulk density, tapped density, and Hausner ratio of fluconazole co-amorphous formulation were 0.597 to 0.625 gm/mL, 0.833 to 0.870, and 1.38 to 1.48, respectively. The optimized formulation had 0.588, 0.870, and 1.48. In 0.1N HCl for 3 hours, co-amorphous formulations released drugs in vitro. Fluconazole co-amorphous formulations had 76.26–89.85% CDR%. The fluconazole co-amorphous formulations greatly increased fluconazole CDR%, with FF1 having the highest at 89.85% and API and optimized formulation at 67.52% and 82.40%, respectively. In phosphate buffer pH 7.5 for 3 hours, co-amorphous formulations released drugs in vitro. We calculated CDR%. Aceclofenac from co-amorphous formulations had 74.64%–92.75% CDR. Af1 had the highest CDR% (92.75%), whereas API and optimized formulation had 65.58% and 83.70%, respectively.

3.2 Preformulation studies

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.

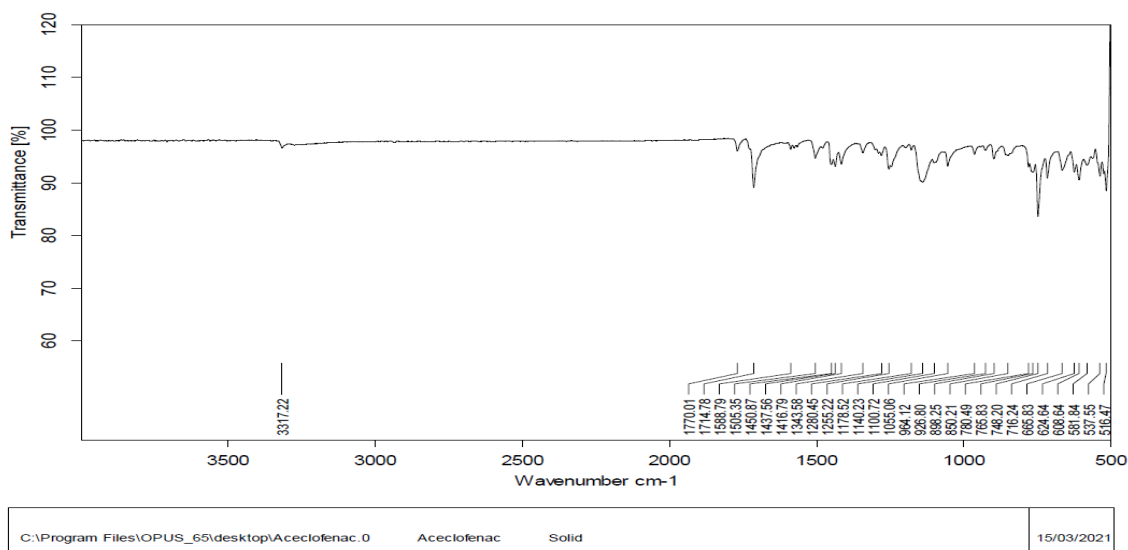


Figure 07: FTIR spectra of Aceclofenac

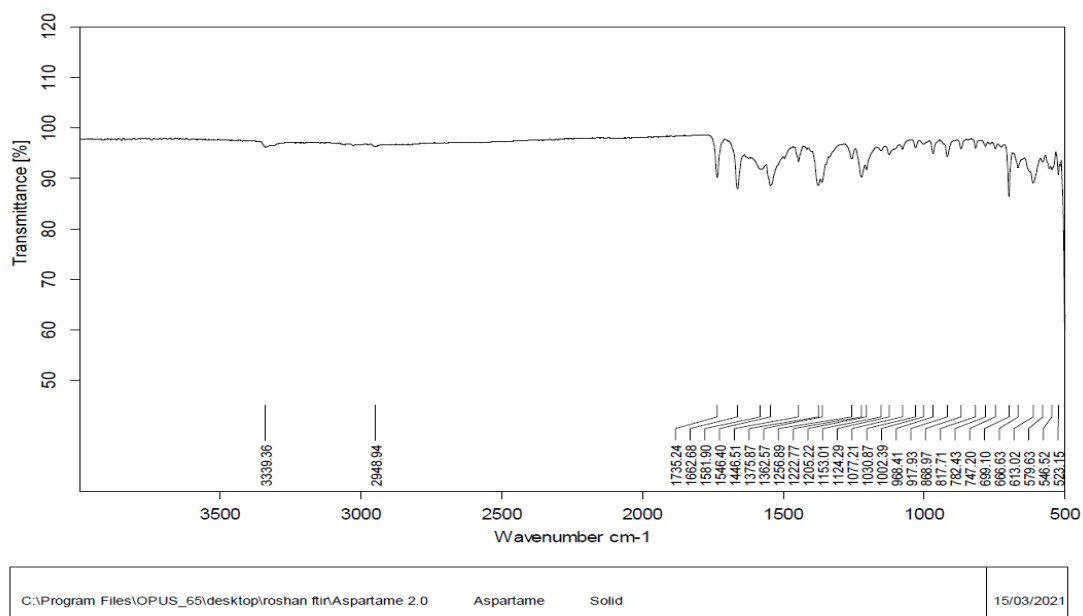


Figure 08: FTIR spectra of Aspartame

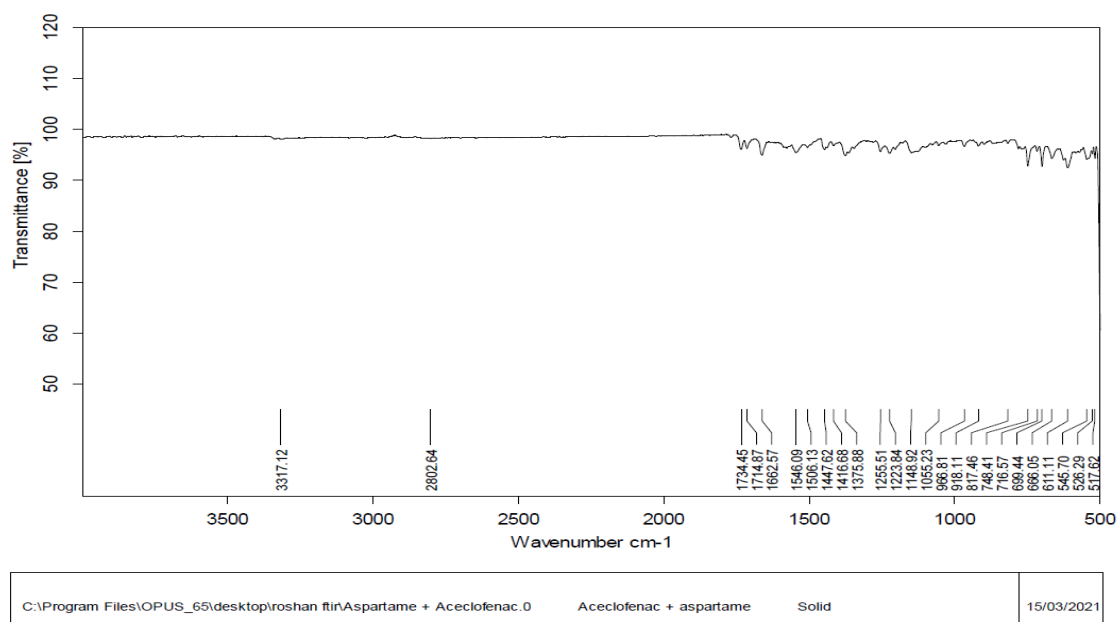


Figure 09: FTIR spectra of Aceclofenac + Aspartame

Table 06: IR interpretation of Aceclofenac

Functional group	Range (Cm ⁻¹)	Observed value in pure aceclofenac (Cm ⁻¹)	Observed value in aceclofenac with 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 07: *In-vitro* drug release profile of aceclofenac API

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

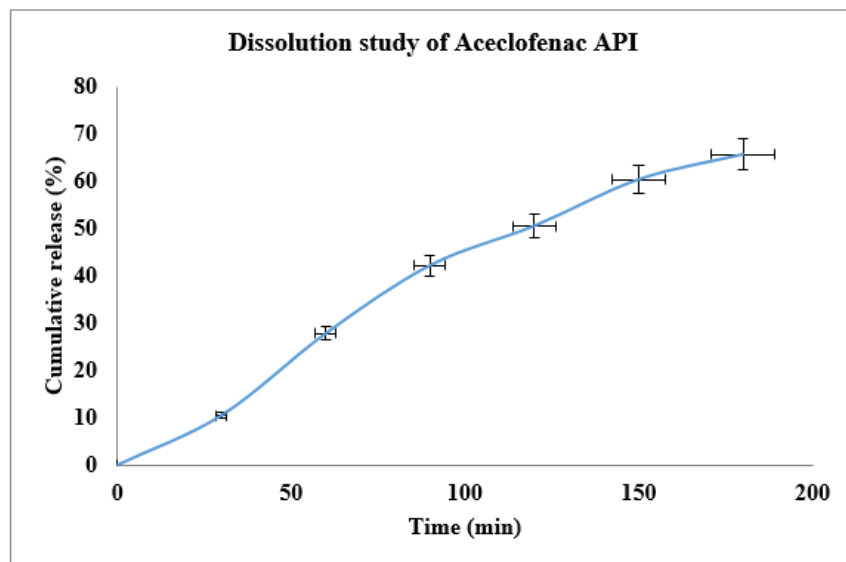


Figure 10: *In-vitro* drug release of Aceclofenac API

Table 08: 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 09: Micromeritic 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 10: 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

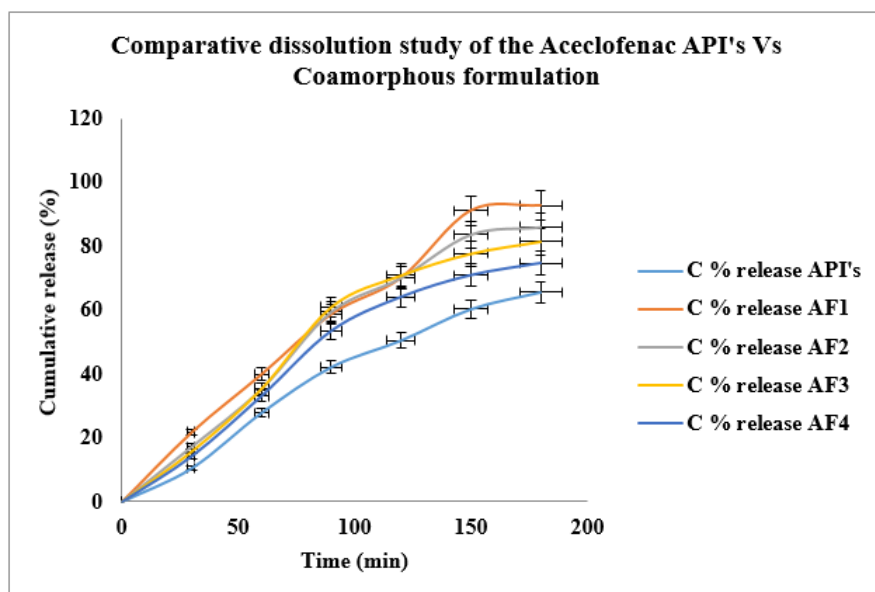


Figure 11: Comparative *In-vitro* drug release study of aceclofenac API's and Co-amorphous formulation.

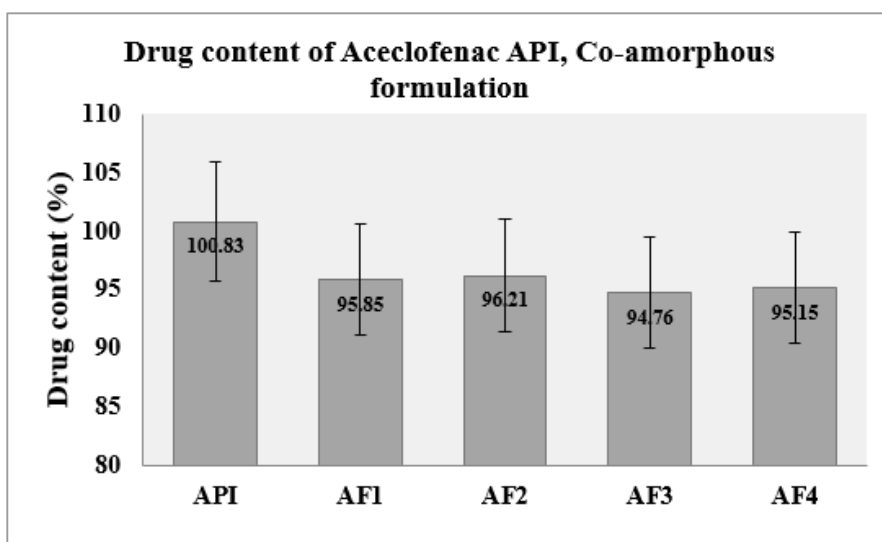


Figure 12: Estimation of drug content of aceclofenac API & co-amorphous formulation

This showed that aceclofenac co-amorphous formulations increased CDR%. Fluconazole co-amorphous formulations had 94.73-95.22% medication. FF4 had the maximum drug content with 95.22%, while API and optimized formulation had 100.36% and 93.57%, respectively, suggesting ball milling may have

decreased drug content. Aceclofenac co-amorphous formulations had 94.76-96.21% medication. AF2 had the maximum drug concentration with 96.21%, whereas API and optimized formulation had 100.83% and 93.33%, respectively, suggesting ball milling may have decreased drug content. We examined developed compositions' thermal properties. DSC measured melting point, peak onset, and peak appearance to verify drug integrity in improved fluconazole co-amorphous formulations. The DSC thermogram of fluconazole improved formulation showed an endothermic peak at 140.25°C, the typical melting point. To verify drug integrity in optimized aceclofenac co-amorphous formulations, DSC monitored melting point, peak onset, and peak appearance. The DSC thermogram of the improved aceclofenac formulation showed an endothermic peak at 150.67°C, the standard melting point. DLS examined optimal formulation shape and size distribution. The improved co-amorphous fluconazole formulation has a particle size distribution of 53.70µm, as shown from the peak intensity. DLS examined optimal formulation shape and size distribution. The optimum co-amorphous formulation for aceclofenac has a particle size distribution of 49.50µm, per the strength of the peak. Both optimized formulations underwent one-month accelerated stability testing. After stability testing, physical appearance, drug content %, and drug release did not alter. Thus, optimized formulations may meet ICH stability standards.

3.3 DISCUSSION

The present study was carried out for preparation, evaluation and characterization of the co-amorphous based drug formulation prepared by ball milling method. Co-amorphous formulations at drug cofomer molar ratio (1:1 and 1:3) were prepared with selected cofomer. All prepared co-amorphous formulations were found to be fine and free flowing powders. The prepared optimized co-amorphous formulations were characterized by FTIR, DSC and DLS. The λ_{max} of fluconazole with 0.1N HCl was found to be 260 nm with the UV spectral analysis. The correlation coefficient for standard curve of fluconazole was found to be 0.996 in the concentration range of 2-10 µg/ml, with the regression equation $0.028x - 0.009$. The λ_{max} of aceclofenac with phosphate buffer of pH 7.5 was found to be 274.65 with the UV spectral analysis. The correlation coefficient for standard curve of aceclofenac was found to be 0.982 in the concentration range of 10-50 µg/ml, with the regression equation was $0.012x - 0.038$. The Micromeritic properties for the prepared co-amorphous formulations were calculated. It was observed that the flow properties of all the formulations were found to be poor. The bulk density, tapped density and Hausner ratio of fluconazole co-amorphous formulation were found to be in between 0.597 to 0.625 gm/mL, 0.833 to 0.870 gm/mL and 1.38 to 1.48 respectively and bulk density, tapped density and Hausner ratio of optimized formulation was found to be 0.588 gm/mL, 0.870 gm/mL and 1.48 respectively. In-vitro drug release from the prepared co-amorphous formulations was studied in 0.1N HCl for 3 hours. The CDR% of the fluconazole from the co-amorphous formulations was found to be in between 76.26-89.85%. FF1 exhibited the highest CDR% with 89.85% while API and optimized formulation exhibited 67.52% and 82.40% respectively that indicated that there was significant increase in CDR% of fluconazole from the fluconazole co-amorphous formulations. In-vitro drug release from the prepared co-amorphous formulations was studied phosphate buffer pH 7.5 for 3 hours. The CDR% was calculated. The CDR% of the aceclofenac from the co-amorphous formulations was found to be in between 74.64%-92.75%. AF1 exhibited the highest CDR% with 92.75% while API and optimized formulation exhibited 65.58% and 83.70% respectively that indicated that there was significant increase in CDR% of aceclofenac from the aceclofenac co-amorphous formulations. The drug content of fluconazole co-amorphous formulations was found to be in between 94.73-95.22%. FF4 exhibited highest drug content with 95.22%, while API and optimized formulation exhibited 100.36% and 93.57% which indicated slight decrease in drug content that is may be due to physical processing by ball milling. The drug

content of aceclofenac co-amorphous formulations was found to be in between 94.76-96.21%. AF2 exhibited highest drug content with 96.21%, while API and optimized formulation exhibited 100.83% and 93.33% which indicated slight decrease in drug content that is may be due to physical processing by ball milling. The thermal behavior of prepared formulations were studied. The melting point, peak onset and appearance of any peak were noted using DSC to confirm the integrity of drugs within the optimized fluconazole co-amorphous formulations. The DSC thermogram of fluconazole optimized formulation exhibited an endothermic peak at 140.25°C corresponding to standard melting point of fluconazole was found. The thermal behavior of prepared formulations were studied, the melting point, peak onset and appearance of any peak were noted using DSC to confirm the integrity of drugs within the optimized aceclofenac co-amorphous formulations. The DSC thermogram of aceclofenac optimized formulation exhibited an endothermic peak at 150.67°C corresponding to standard melting point of aceclofenac was found. DLS was used to study morphology and size distribution of the prepared optimized formulations. Particle size distribution of optimized co-amorphous formulation for fluconazole was found to be 53.70µm which was confirmed from the intensity of particle size distribution peak. DLS was used to study morphology and size distribution of the prepared optimized formulations. Particle size distribution of optimized co-amorphous formulation for aceclofenac was found to be 49.50µm respectively which was confirmed from intensity of particle size distribution peak. One month accelerated stability studies were preformed for the both optimized formulation. From stability studies data, it was shown that there was no much change in the physical appearance, drug content percentage and drug release after stability test. Hence the optimized formulations was may found to possess stability compliances as per requirements of ICH guidelines.

4. CONCLUSIONS

Research studies were under taken on the preparation and evaluation and characterization of co-amorphous solid dispersions of acidic and basic drugs for oral drug delivery by using artificial sweeteners as a coformer utilizing dry milling by ball mill technique. Hence from the experimental results, following results have been concluded. From FTIR study, drug and coformer used in formulations were found compatible with each other. Co-amorphous formulations were prepared by ball milling technique at a constant speed for 60 min and 120 min by taking 1:1 M and 1:3 M drug coformer ratio was suitable. Results of dissolution studies of fluconazole API showed CDR of 67.52%, while aceclofenac API showed CDR of 65.58%. Drug content results of fluconazole API showed 100.36%, while aceclofenac API showed 100.83% of drug content. From the optimization study, optimized formulation of fluconazole FFO contains drug: coformer ratio 1:1M milling for 88.68 min were considered as optimal formulations with particle size 57.30 µm giving maximum CDR% at 82. 68%, and 94.96% drug content, while optimized formulation of aceclofenac AFO contains drug: coformer ratio 1:2.24 M milling for 117.78 min were considered as optimal formulations with particle size 49.50 µm giving maximum CDR% at 85.45 %, and 95.19 % drug content. The optimized formulations revealed the desired particle size of formulations, CDR% and drug content for both formulations. The optimized formulation FFO shows require particle size 55.25 µm, CDR 82.39% and drug content 94.97%, while AFO shows require particle size 49.52 µm, CDR 85.45% and drug content 95.19% respectively and found no statistical significance of the difference between predicted and actual value. Characterization study of both optimized formulation FFO and AFO showed that drug is comptable with coformer and formulation processing. From the dissolution study of fluconazole co-amorphous formulations results showed the in-vitro drug release from range of 76.26% to 89.85%, while aceclofenac co-amorphous formulations results showed the in-vitro drug release from range of 74.64% 92.75%. Hence

from the above studies, results were obtained for amorphous drugs exhibited good in-vitro drug release irrespective of acidic and basic form of drugs. The in-vitro drug release problem of the acidic and basic forms of drugs for oral delivery system can be overcome by using the co-amorphization technique by selecting suitable coformer for the stabilizing the co-amorphous formulation. The current study was feasible to be improving physicochemical properties of the drugs in formulation for oral drug delivery systems. Hence formulation required suitable coformer and processing via suitable preparation methods giving maximum solubility and in-vitro drug release in site of absorption.

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