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Dissolution methods to discriminate *in vitro* dissolution of poor water soluble weak base drug using three strategies: Acid modification, solvent evaporation and gastroretentive: Ciprofloxacin HCl case

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ABSTRACT: This study used dumping and transfer methods to examine the dissolution of a poorly water-soluble weak base, the ciprofloxacin HCl (Cipro). The objective is to investigate the impact of pH variations from the stomach to the intestine on drug dissolution and precipitation (ppt). Three strategies were utilized to enhance the solubility and reduce the ppt of Cipro. First, it employed the acid modification concept, combining Cipro with fumaric acids (FA). The second was solvent evaporation, which transformed the medication from crystalline to amorphous. Third, the gastroretntive dosage form releases the drug slowly and remains buoyant. The produced samples were examined using FTIR, FESEM, and DSC. The FESEM showed a decrease in particle sizes of prepared samples. The FTIR presented a change in the position of the peak associated with the carbonyl group from 1712 cm^{-1} to 1704 cm^{-1} in the Cipro-FA complex and a peak shift to 1730 cm^{-1} of Cipro when treated by solvent evaporation. Additionally, the thermogram of the Cipro-FA complex demonstrated a clear shift of peaks to 148.73 °C and 240.47 °C, revealing possible hydrogen bonding. The thermogram of Cipro by solvent evaporation presented a disappearance of the peak at 162.44 °C. The Cipro *in vitro* dissolution studies on the prepared samples revealed distinct differences in the dissolution profiles between dumping and the most mimicking body transfer method. To conclude, the samples exhibited improved dissolution profiles and a reduced ppt amount; specifically, the complexation of Cipro –FA was the optimal strategy for enhancing solubility and dissolution while reducing ppt.

KEYWORDS: Ciprofloxacin; floating system ; fumaric acids; gastroretentive dosage form; solvent evaporation.

1. INTRODUCTION

The solubility of medications with poor water solubility and weak base properties (PWWB) is generally influenced by the pH of the solution. In acidic pH conditions, the medication becomes ionized, leading to an increase in the solubility of the base drugs. Consequently, when the pH increases, the PWWB loses a proton and becomes uncharged, decreasing its ability to dissolve [1, 2]. To overcome this precipitation, this study primarily focused on three strategies, starting with acidic modification to enhance the solubility of PWWB. Acidic modification involves the addition of organic acids, which act as acidic excipients, to the formulations. This is a commonly employed approach to enhance the solubility of a weak base drug [2, 3]. The acids aid in maintaining a balanced pH level between the stomach and the intestinal media, ensuring the medication's solubility [4, 5]. The second strategy was solvent evaporation to induce amorphization, enhancing the transformation of the crystalline substance into an amorphous state [6]. The final one was the gastroretentive approach, precisely, the floating system. This method involves the administration of medication in a controlled release buoyant dosage form, which remains in the stomach for an extended period. This allows for the gradual movement of the medication to the intestinal environment, thereby decreasing the formation of drug precipitate [7]. These strategies were applied to ciprofloxacin (Cipro) as a weak base antibacterial drug, representing the aim of this study.

Ciprofloxacin (Cipro) is an orally administered antibiotic belonging to the fluoroquinolone class. It is frequently administered to treat a wide range of bacterial illnesses globally. The water solubility of Cipro is

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pH-dependent. Cipro's limited solubility at neutral pH restricts its bioavailability. It is categorised as a class IV medication according to the Biopharmaceutics Classification System (BCS) because of its low solubility and membrane permeability [8]. Not only the precipitation of antibacterials in the intestinal lumen decrease drug absorption to the systemic circulation, but it also affects the normal microbial flora [9].

To explore this study, the dissolution behavior of the formulation's observation was via two methods that demonstrated the gastric acidic and basic intestinal environments. The first dissolution method was the dumping in one compartment in addition to the second method, which is a multi-compartmental method (the transfer model). The last model mimics the *in vivo* state by considering two compartments, the stomach and intestine, as this method guarantees the constantly changing environment that the drug and formulation are exposed to during transit in the gastrointestinal system [10]. The transfer model has been employed to examine the supersaturation and precipitation properties of PWWB; however, to our knowledge, no study has been conducted on different strategies to enhance the dissolution by studying the dissolution behaviour of Cipro via the transfer method [11]. The purpose of this study was to evaluate the dissolution and precipitation of Cipro HCl using dumping and the transfer multicompartment methods for the three approaches (acid modification , amorphazation by solvent evaporation and gastroretentive - floating system) that were selected to enhance poor-water soluble weakly base drug solubility.

2. RESULTS AND DISCUSSION

2.1 Characterization of the prepared samples

All the prepared samples were investigated for possible changes the following studies might detect.

2.1.1. Fourier Transform Infrared Spectroscopy (FTIR)

This study aimed to detect the shifts in peaks of the Cipro formulations in their spectrograms, as depicted in Figure 1. The carbonyl group of Cipro showed a slight shift from 1712 cm-1 to 1704 cm-1 in the Cipro complexed with FA, while a noticeable carbonyl-associated peak shift to 1730 cm-1 of Cipro when treated by solvent evaporation with methanol. Also, the spectrograms of Cipro in both approaches showed a decrease in the intensity of the peaks related to the hydroxyl group. This intensity decrease in the related peaks of the hydroxyl group was found in the hydroxyl group of 12-hydroxyoctadecanoic acid due to their interactions [12]. These changes in Cipro via solvent evaporation might be attributed to the physical interaction of the hydrogen bonds between Cipro molecules, which might be an amorphous formation. The change in the Cipro's peak positions in the complex Cipro-FA might be due to the hydrogen bonding as was reported by Mohamed et al [13].

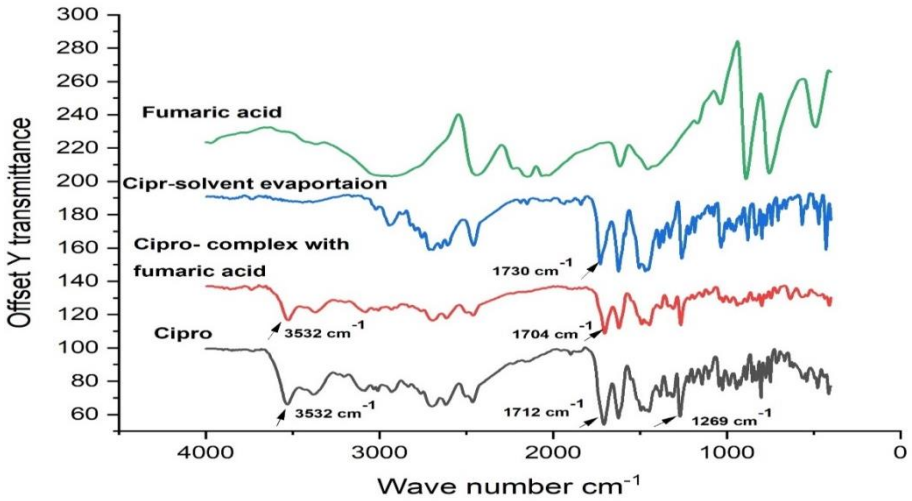

Figure 1. FTIR spectrograms of the Cipro, Cipro-FA complex, Cipro solvent evaporation and FA

2.1.2 Field emission scanning electron microscopy (FESEM)

This method was employed to ascertain the dimensions and surface morphology of Cipro particles. The photos in Figure 2 depict the before and after sample preparation in both procedures (acid

modification and solvent evaporation), demonstrating a size reduction. This reduction could potentially facilitate the alteration or improvement of Cipro's dissolution by increasing the exposed surface area available for dissolution. In previous studies, Cipro SEM images showed a decrease in particle size and a change in the particle's morphology after treating the drug with the solvent evaporation technique [14, 15].

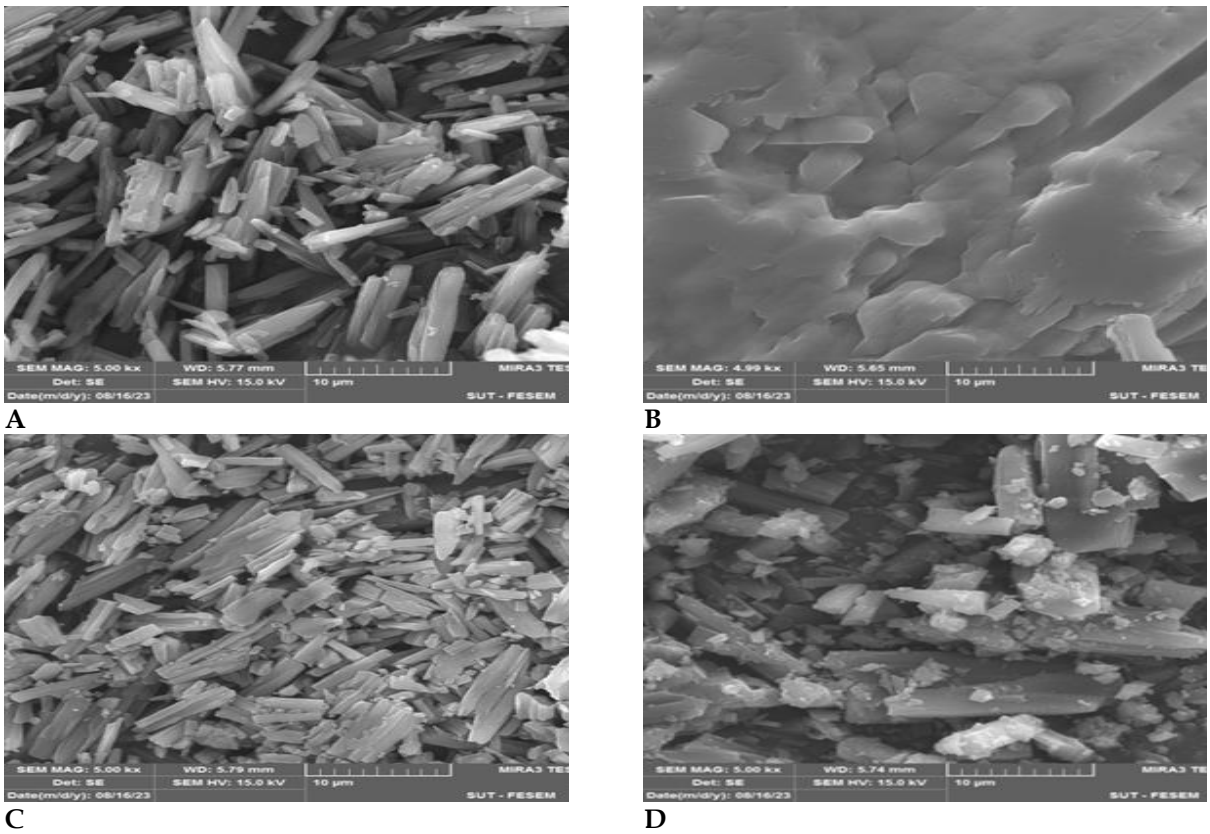

Figure 2. FESEM images A, B, C and D were scaled against 10 µm, as image A represents the control of the Cipro for both strategies. Images A and B represent the Cipro and FA before mixing and complexing, while image C represents the Cipro complex with FA after mixing. Image D represents Cipro after applying solvent evaporation.

2.1.3. Differential scanning calorimetry (DSC)

The DSC is an essential method for determining the possible changes for any formulation processed for amorphization or complex formation. The changes in the drug and selected formulations thermograms can be shown in Figure 3A, B, C and D of DSC. The Cipro thermogram was at 319.04 °C, showing a sharp peak referring to pure Cipro and close to the melting point reported at 318.82 °C by Indah Widyastuti *et al* [16]. Also, the thermogram of FA showed melting peaks at 66.03 °C and 264.33°C, where the former peak was similar to the one presented at 66 °C as mentioned previously [17]. However, at 279 °C, a peak presented a difference from the received FA that might refer to the FA polymorphism [18]. The thermogram of the Cipro-FA complex demonstrated a clear shift of peaks to 240.47 °C and 148.73°C, revealing a high possibility of hydrogen bonding between Cipro and FA. molecules The thermogram of Cipro by solvent evaporation presented a disappearance of the peak at 162.44 ℃ [8]. Both changes pointed to the amorphization formation.

In a nutshell, a shift of the characteristic peak in FTIR spectrograms and the Cipro with their formulations presented a change in melting point due to the high possibility of amorphization and hydrogen bonding formation.

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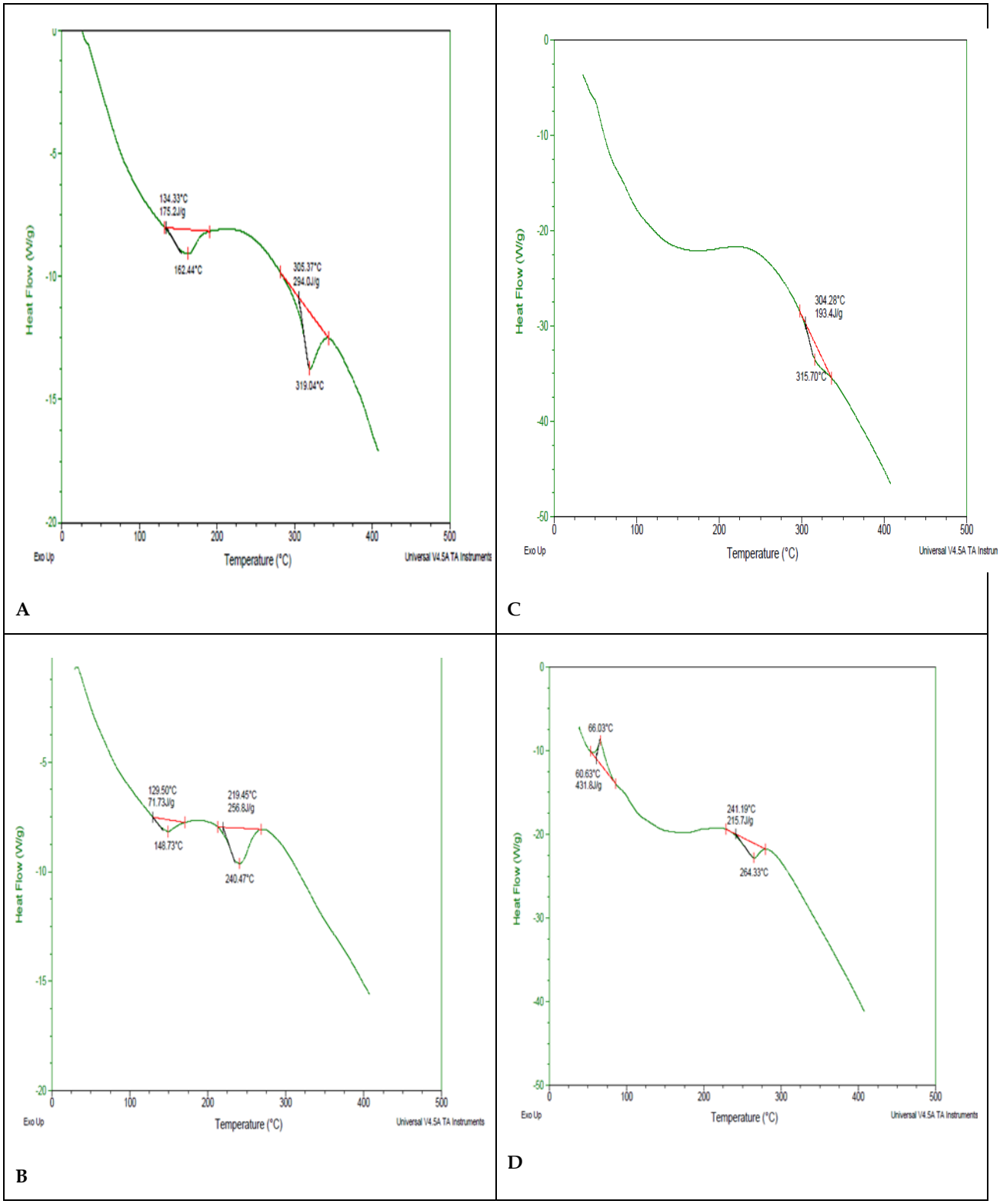

Figure 3. DSC thermogram of (A- Cipro B- Cipro-FAcomplex C- Cipro solvent evaporation and D- FA)

2.2. In vitro dissolution of Cipro in gastric and intestinal media

The purpose of this dissolution application using different methods was to assess the performance of Cipro in different media, as depicted in Figure 4. Cipro exhibited a quick dissolution in gastric media, reaching a maximum dissolution of around 99.36 % after 10 min. This finding differed from another study, which demonstrated that Cipro had a dissolving rate of up to 80 % within 120 min in HCl media without any precipitation. This was due to Cipro's high solubility in the stomach's acidic environment [19].

Conversely, the dissolution of Cipro in the intestinal medium exhibited a very reduced dissolution rate. The value reached approximately 50.04 %, 48, 98 %, 46.36 % and 41.95% after 1 hr, 2 hr, 3 hr and 4 hr, respectively. This profile exhibited a decrease in the dissolution with the time of the experiment, reflecting a continuous reduction in the Cipro dissolved amount. Thus, in turn, the amount of precipitation was 55.72 %. Gomez *et al* examined the *in vitro* dissolution of Cipro in phosphate buffer media and observed that Cipro dissolution was less than 15 % [19].

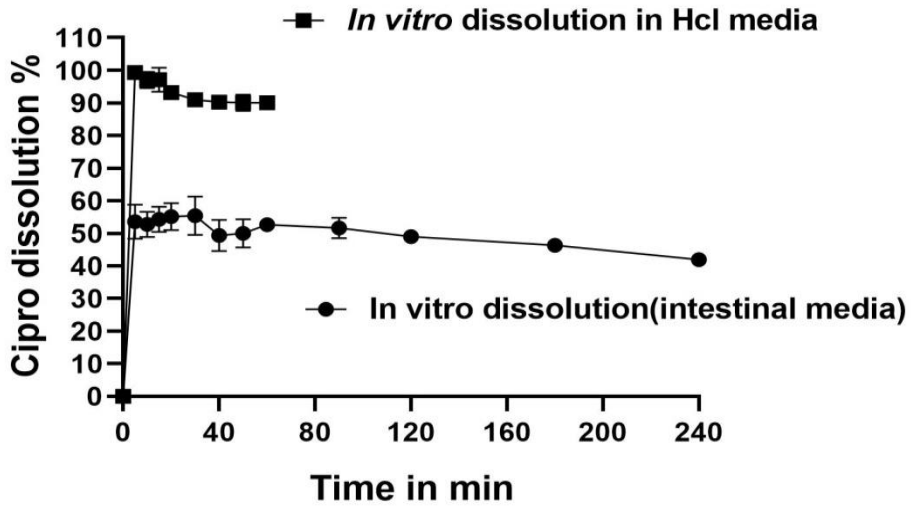

Figure 4. *In vitro* dissolution of Cipro in gastric and intestinal media

2.3 Dumping and transfer method of Cipro alone (control)

This experiment served as a control to investigate and evaluate the impact of the dissolution method on the isolation of different approaches that influenced drug dissolution and precipitation. The dumping and transfer procedures are illustrated in Figure 5A. The dissolution of Cipro in the dumping method resulted in a 93.73% initial dissolution rate, which then showed 93.02% after 2 hours, as shown in Table 1; then, the Cipro dissolution decreased to 87.34% after 4 hours. This is a noticeable dissolution profile of Cipro in intestinal media that departed the dissolved amount with the time of experiment showing more ppt.

The transfer process led to a gradual rise in Cipro amount, increasing from 28.13% to 54.14%, 67.54% to 76.61% after 1hr, 2hr, 3hr, and 4hr, respectively, as presented in Table 1. These values accurately represented and imitated the typical physiological behaviour of the stomach and intestines. The ppt obtained through the dumping method was 17.88% and formed rapidly within the first few min of dissolution. On the other hand, the ppt produced by the transfer method had a higher weight percentage of about 26.12% and appeared gradually, as shown in Table 2.

Previous reports harmonized with our findings, revealing Cipro's enhanced dissolution in acidic pH conditions and lower dissolution when it reaches the colon at pH 7.4 using the dumping method [20].

2.3.1. Dumping and transfer methods for Approach 1 (Acid modification)

The complexation of weak base drugs with the organic acid was utilized to enhance the solubility and reduce precipitation by introducing an acid, such as verapamil, to form a complex combined with the FA [21]. The acid in the intestine, which maintains the low pH, enhanced verapamil solubility from 50 mg/ml to 100 mg/ml. Consequently, the drug remains soluble in the formulation [22].

The dissolution profiles of the dumping and transfer method of the Cipro-FA complex is depicted in Figure 5 (B). The rate of Cipro dissolution using the dumping method was quick, reaching 96.95% after 1 hour (Table 1). The Cipro persistence values remained high at 97.26%, 94.83% and 93.2% after 2, 3and 4 hrs, respectively. By contrast, the transfer method showed a steady rise in the dissolution of Cipro, reaching 35.89%, 67.96%, 98.56%, and 97.61% after 1 hr, 2 hrs, 3 hrs, and 4 hrs, respectively. The precipitation of Cipro, as shown in Table 2, was lower when using the dumping method than the transfer method. However, there was a very significant difference ($p < 0.1$) and very highly significant ($p < 0.01$) in ppt between the control and the Cipro-FA complex in dumping and transfer methods, respectively. The release of Cipro in this

approach in both methods was greater than in control, as shown in Table 1. The obtained results were consistent with those observed by Surov *et al*, who reported a complexed Cipro with FA, but using a simple *in vitro* dissolution method in phosphate buffer pH 6.8, gaining an augmenting in the Cipro dissolution amount reaching 60% of Cipro after 3 hours [8].

2.3.2. Dumping and transfer methods for Approach 2 amorphization by solvent evaporation

Using methanol, an optimal solvent for dissolving Cipro, facilitates the conversion of its less soluble crystalline state into a more soluble amorphous state by utilising the solvent evaporation process [23]. The dissolution in both techniques exhibited dissimilar behaviour, as depicted in Figure 5(C). The dissolution of Cipro in the dumping method in this approach was less than the release of Cipro in both control and complexation of Cipro – FA at all times of the experiment, as shown in Table 1, while in the transfer method in this approach at 1st hr the release of Cipro was less than the control and complexation of Cipro – FA, after that the release of Cipro increased and became greater than control but remained less than Cipro –FA complex until the end of experiment as shown in Table 1. The ppt in this approach in the dumping method was very highly significant ($p < 0.01$) compared to the control, while in the transfer method, the ppt was significantly different ($p < 0.05$) compared with the control, as shown in Table 2. Bonthagarala *et al.* used simple *in vitro* dissolution in pH 7.2, applying the solvent evaporation technique, and found that the dissolution of Cipro reached an optimal or maximal level within 10 minutes [24].

2.3.3. Modified transfer of Approach 3 (Floating system)

The investigation of this strategy was limited to the transfer method, as seen in Figure 5 (D), due to the impracticality of complete solubilization of the gastroretentive system in the stomach. The release percent of Cipro after 1hr, 2hr and 3hr of the experiment were lower than the control and other approaches, since at 4hr, the release percent stayed less than solvent evaporation and complexation approaches; at the same time, it became greater than control, as shown in Table 1. The ppt of Cipro in this approach was lower than the control, and was a significant ($p < 0.5$) variation in ppt seen between the control group and the Cipro by the floating system.

The results obtained by another worker using simulated gastric fluid (pH 1.2) increased from 56.47% to 78.22%, similar to our release outcome [25].

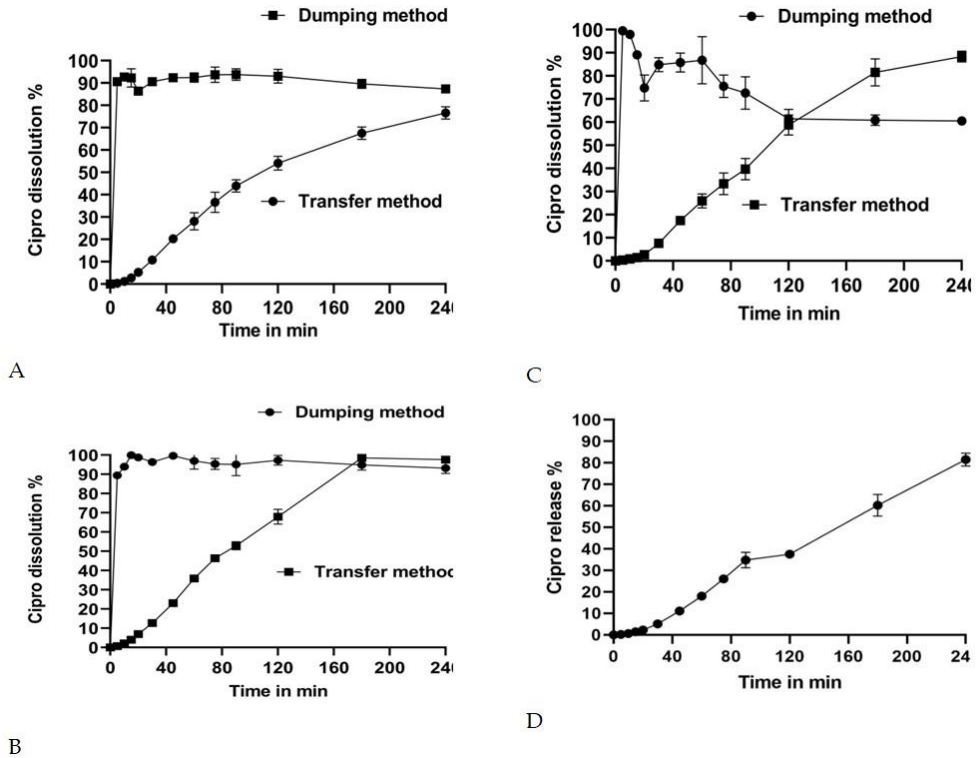

Figure 5. (A) The *in vitro* dissolution of Cipro alone as a control using the dumping and the transfer methods for 240 min. (B) The *in vitro* dissolution of the Cipro -FA complex using dumping and transfer methods for 240 min. (C) The *in vitro* dissolution of dumping and transfer method of Cipro by amorphization using solvent evaporation. (D) Cipro *in vitro* release by the modified transfer method using the floating system for 240 min.

Table 1. Summary of *in vitro* dissolution percentage of Cipro in dumping and transfer method after 1hr, 2 hr, 3hr and 4 hr.

Method	Release % (1hr) (±SD)	Release % (2 hr)(±SD)	Release % (3hr) (±SD)	Release % (4 hr)(±SD)
In vitro dissolution (intestinal media)	*50.04(±4.36)*	*48.98(±2.03)*	*46.36(±0.8)*	*41.95(±1.27)*
Dumping control	*93.73(±3.41)*	*93.02(±3.10)*	*89.60(±2.01)*	*87.34(±0.48)*
Transfer control	*28.13(±3.83)*	*54.14(±3.09)*	*67.54(±2.77)*	*76.61(±2.71)*
Dumping Cipro –FA complex	*96.95(±4.21)*	*97.26(±2.52)*	*94.83(±2.67)*	*93.2(±2.71)*
Transfer Cipro –FA complex	*35.89(±1.23)*	*67.96(±3.87)*	*98.56(±1.24)*	*97.61(±1.36)*
Dumping (solvent evaporation)	*86.78(±10.16)*	*61.43(±4.13)*	*60.85(±2.27)*	*60.56(±0.8)*
Transfer (solvent evaporation)	*25.93(±2.99)*	*58.79(±4.36)*	*81.55(±5.88)*	*88.37(±2.35)*
Transfer (floating)	*18.05(±0.45)*	*37.54(±1.72)*	*60.27(±5.01)*	*81.55(±2.99)*

Table 2. Summary of precipitate of Cipro in dumping and transfer method

Method	Dumping method % of ppt (± SD)	Transfer method % of ppt (±SD)
Cipro alone as a control	17.88 (±2.62)	26.12 (±1.53)
Cipro- FA complex	0.43 (±0.23)	1.50 (±1.05)
solvent evaporation	42.51 (±5.81)	12.39 (±2.062)
(Floating)	----------	14.49 (± 8.017)

----------, dumping was not applied for the floating system.

3. CONCLUSION

The dissolution profiles of different prepared formulations and precipitation of Cipro were different after applying dumping and transfer dissolution methods. Obviously, the outcome of the complexation of Cipro –FA promoted the increase in the dissolution of Cipro and decreasing the ppt, representing the best approach in both methods, dumping and transfer. Interestingly, the dumping generated a decreased Cipro dissolution attitude and a growing ppt with the time of dissolution method in contrast to the transfer method.

4. MATERIALS AND METHODS

4.1 Materials

Ciprofloxacin HCl (Cipro) was bought from Indian Co. Ltd, while fumaric acid was purchased from Triveni Interchem Pvt. Ltd /India). Also, sodium alginate and calcium carbonate were obtained from Meron Group /India and CALSPAR /India, respectively.

4.2. Methods

4.2.1 Samples preparation

The samples in this investigation were made using the selected approaches described below to be used in various dissolution processes.

Strategy I using the acid modification

The process involved mixing equal amounts of Cipro and fumaric acid (FA) by mortar and pestle [3]. The complexes were then dissolved in 100 ml of HCl pH 1.2 with stirring and controlled heating at 37 °C in the case of the dumping method or 250 ml of HCl in the case of the transfer method.

Strategy II using (Solvent evaporation)

Cipro was placed in a suitable container, and around 3-5 ml of methanol was added and shaken for a few minutes until Cipro was dissolved, followed by a methanol evaporation phase left in the hood for sufficient time; then, weighing 500 mg Cipro from the leftover powder to be utilized in the dissolution techniques [24, 26].

Strategy III using gastroretentive system (Floating system)

Gradually, 200 mg sodium alginate was added to a boiled 10 ml water while swirling continuously and heating at 37 °C. The solution was cooled before adding 500 mg of Cipro by heating it to 37 °C and stirring it at 100 rpm for 15 minutes (min). A 100 mg of calcium carbonate was added to the liquid and stirred until a homogeneous dispersion [27].

4.2.2. Characterization of prepared samples

Fourier transform infrared spectroscopy (FTIR)

The Cipro and prepared formulation samples in strategy I and II were combined with potassium bromide and compacted into a disc. The KBr discs were fabricated by crushing the particles using a hydraulic press. The spectral range spanned from 400 to 4000 cm-1 using Shimadzu FTIR spectroscopy [26].

Field emission scanning electron microscopy (FESEM)

The chosen prepared samples underwent investigation of their surface morphology using FESEM to take a picture of the sample surface that had been previously polished with argon ion beams in a highly vacuumed atmosphere [28].

Differential scanning calorimetry (DSC)

A quantity of Cipro samples, ranging from 6.5 to 10 mg, were heated in an aluminium pan in a nitrogen atmosphere. The heating rate was set at 10 °C per minute, and the temperature range was between 5 and 300 °C. Differential scanning calorimetry (DSC) analysis was conducted using a nitrogen gas flow rate of 20 pounds per square inch [29].

4.2.3. In vitro dissolution methods for evaluation of Cipro behavior in gastric media

None of the dissolution methods in this study used surfactants in the buffer solution, guaranteeing the Cipro sink condition. This assisted in discriminating the impact of the dissolution method technique and the chosen strategy.

The experiment involved adding 500 mg of Cipro to 100 ml of HCl (pH 1.2) while stirring at 100 rpm and a temperature of 37 ^{o}C using a dissolution apparatus. Samples of 5 ml were taken at specific time intervals (5, 10, 15, 20, 30, 45, and 60 min), and a 5 ml was continuously replaced. The absorbance values of the samples were then measured using a UV spectrophotometer. These absorbance values were substituted into the Cipro calibration curve equation (y= 0.1006x+0.0343) in gastric media, which had an R2 value of 0.9994. The dissolution process was performed three times.

4.2.4. In vitro dissolution of Cipro in intestinal media

The 500 mg of Cipro was directly added to 900 ml of intestinal media with a pH of 7.2. The media was prepared by mixing 450 ml of HCl solution with a pH of 1.2 and 450 ml of phosphate buffer with a pH of 8.4. The mixture was continuously stirred at 50 rpm, and a temperature of 37 ℃ was set in the dissolution apparatus. A sampling of 5 ml was at specific time intervals (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, and 240 min) and continuously replaced with an equal volume. The samples were then analysed using a UV spectrophotometer, following the equation (y = 0.0879 x+ 0.011 with R2 = 0.9986) of the Cipro calibration curve in pH 7.2. The Cipro dissolution in the intestinal medium was replicated 3 times. Next, the 900 ml solution was passed through Whitman filter paper to collect the precipitate (ppt). The collected ppt was then dissolved in HCl solution to be quantified using a UV spectrophotometer.

4.2.5. Dumping method

Cipro alone as a powder, subjected to the dumping dissolution procedure, was used as a control or a reference for the acid modification and solvent evaporation strategies. In this procedure, depicted in Figure 6(A), 100 ml of HCl solution pH of 1.2 was removed, representing a fraction of the overall intestinal buffer media. The 500 mg of Cipro was then dissolved in this 100 ml and then added to 800 ml of intestinal media composed of 350 ml of HCl solution and 450 ml of phosphate buffer. The entire process occurred in a container, with a controlled temperature of 37 ^{o}C and continuous stirring at 50 rpm. The sampling was conducted at certain time intervals of 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, and 240 min. Five ml samples

were taken and replenished with equal volumes as this dissolution process was replicated thrice [30]. Subsequently, the samples were analysed using UV spectroscopy to determine their concentrations. Next, the final dissolution media was filtered using a Whatman filter paper with a pore size of 0.45 µm to gather the ppt of the Cipro. The ppt was then dissolved in an HCl solution and quantified using the calibration curve of Cipro in the acidic medium (Figure 6).

4.2.6. Transfer method

The chosen samples to implement the transfer technique for Cipro were the Cipro alone as a control in addition to the Cipro-treated via acid modification and solvent evaporation strategies. The peristaltic pump, depicted in Figure 6(B), was employed to carry out this procedure. It facilitated fluid transport to compartments through tubes, as illustrated in Figure 1(B). The pump was outfitted with three tubes that regulated the fluid velocity through the tubes at a 5 ml/min rate. The first tube facilitated the transfer of the gastric media to the intestinal media. Simultaneously, the second one aided in transporting the fluids from the intestine compartment to the sink/supersaturation compartment. The 3rd one conveyed the fluid from the reservoir to the intestinal compartment. The gastric compartment was filled with a solution of 500 mg Cipro dissolved in 250 ml of HCl solution with a pH of 1.2. The solution was stirred at a speed of 100 rpm to reproduce the conditions of the empty stomach. Furthermore, the intestinal compartment was filled with 250 ml of intestinal media, which had a pH value of 7.2 [31]. The third compartment, the sink/supersaturation compartment, which was initially empty, received fluid from the second compartment through a tube. A filter paper was placed at the tip of the tube to remove any undissolved drug from the intestinal compartment. The sink/supersaturation compartment was subjected to a rotational speed of 50 rpm. The fourth compartment, the reservoir, initially held 250 ml of phosphate buffer pH 8.4 for 50 min of the experiment. It was then replaced with intestinal media pH 7.2, kept at a constant temperature of 37 °C, as all compartments were kept in the water bath for incubation at body temperature. This study was replicated three times.

The samples were collected from the sink/supersaturation compartment at specific intervals (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, and 240 min). These samples were then analysed using a UV spectrophotometer, applying the calibration curve equation of Cipro in pH 7.2. Continuous filtering of the intestinal media was accompanied the whole dissolution procedure to gather and dissolve the ppt in HCl pH 1.2 to estimate the quantity of Cipro precipitated (Figure 6) [31].

4.2.7. Modified transfer method (for gastroretentive strategy – floating system)

This is an altered transfer technique that was executed for the floating approach. It was derived from a prior study that employed the multicompartment method, with a minor adjustment involving the inclusion of a peristaltic pump [32]; Figure 6(C) illustrates a system that involved a stomach compartment containing 70 ml of HCl with a pH of 1.2, and an intestinal compartment filled with 400 ml of a solution with a pH of 7.2. Furthermore, two reservoirs were filled with an HCl media pH of 1.2 and an intestinal phosphate buffer pH of 8.4. Both reservoirs were placed in a water bath set at a temperature of 37°C. This was done to provide a constant supply of stomach and intestinal media to the gastric and intestinal compartments. The sink or supersaturation compartment began in an empty state. When the peristaltic pump was activated, the fluid moved from the gastric reservoir to the gastric compartment and, similarly, from the intestinal reservoir to the intestinal compartment. The transfer rate between the gastric and intestinal compartments was 2 ml/min. Simultaneously, the movement of substances from the intestinal compartment to the sink or supersaturation compartment was regulated using a filter membrane at a 4 ml/min flow rate. The samples were collected from the sink/supersaturation compartment at specific time intervals of 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, and 240 min. The samples were then analyzed using a UV spectrophotometer. Additionally, the intestinal media underwent filtration to collect the ppt, which was subsequently dissolved in HCl media and examined using a UV spectrophotometer (Figure 6).

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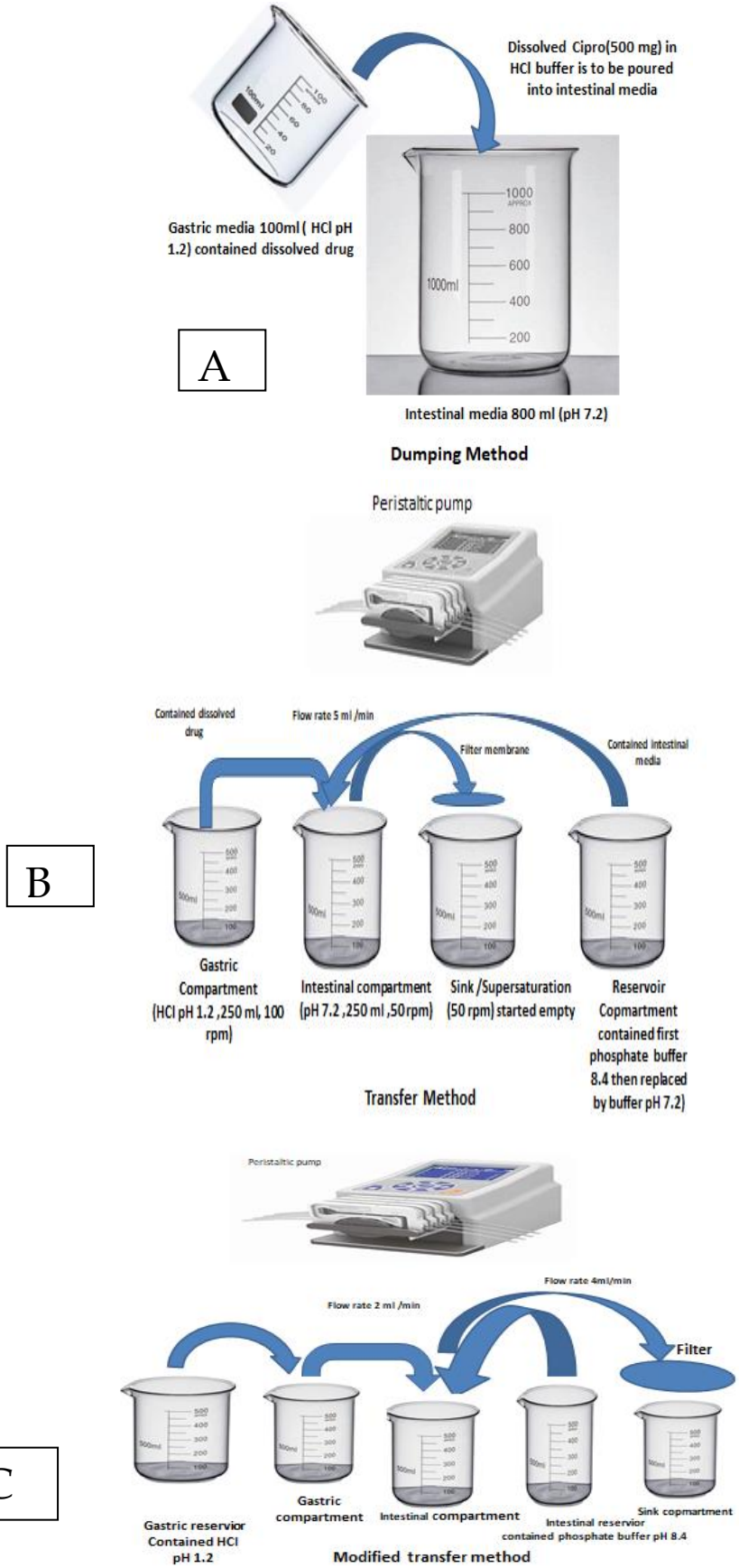

Figure 6. (A) Diagram depicts the dumping method (B) The diagram depicts the transfer system with a peristaltic pump showing all the compartments and the media volumes (C) Modified transfer method of multicompartment dissolution.

4.2.8. Statistical analysis

The ppt of all prepared formulations of different strategies were statistically analyzed using Prism software, specifically employing one-way ANOVA with post hoc analysis**, the significance level** ($P > 0.05$ - not significant, $P \leq 0.05$ - significant, $P \leq 0.01$ - very significant and $P \leq 0.001$- highly significant) [33,34].

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