EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 8
10-19
Year: 2019

PREPARATION AND EVALUATION OF CHEWABLE TABLETS OF NAFTOPIDIL

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Article Received on 24/05/2019 **Article Revised on 15/06/2019** **Article Accepted on 04/07/2019**

ABSTRACT
Naftopidil is a weak basic antihypertensive agent and is promising in treatment of benign prostatic hyperplasia. Unfortunately, it has low oral bioavailability due to poor dissolution and extensive pre-systemic metabolism. Accordingly, the objective of this work was to develop chewable tablets which liberate most of naftopidil in the oral cavity. This required dissolution enhancement which was achieved via co-grinding with citric and/or tartaric acid. The co-ground mixtures were evaluated using Fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction. Optimum mixtures were prepared chewable tablets. Co-grinding of naftopidil with tartaric acid developed amorphous naftopidil. Co-grinding with citric acid alone or in combination with tartaric acid developed co-crystalline product. These physical changes were associated with significant enhancement in naftopidil dissolution rate, even at pH6.8. Incorporation of the co-ground mixtures in SMEDDS was synergistic. The tablets liberated significant amounts of naftopidil at pH 6.8 after crushing. Repeating the dissolution on intact tablets, the results were the same for dry tablets, with liquisolid tablet liberating smaller amount of drug. In conclusion, dry co-grinding of naftopidil with citric and/or tartaric acid modified the crystalline structure with subsequent dissolution enhancement irrespective to the pH. The developed new co-crystalline product was successfully prepared as chewable tablets which underwent pH independent liberation of naftopidil from chewable tablets.

KEYWORDS: Co-grinding, Co-crystal, amorphous solid, dissolution rate, naftopidil, citric acid**.**

INTRODUCTION
Naftopidil is a novel antihypertensive which exerts its function by blocking the α-1-adrenergic receptor (α_1-AR). In addition to the antihypertensive activity, the drug is now employed for the treatment of benign prostatic hyperplasia (BPH).[1] This application is based on its antagonistic effect on α_1-AR which reduces the tone of prostatic smooth muscle with subsequent immediate effect on urine flow and subsequently reliefs the elevated urethral pressure.[2,3] Naftopidil can also induce apoptosis or G_1 cell-cycle arrest providing promising growth inhibitory effects on human prostate cancer cells.[4] Naftopidil is a weak basic drug with a pKa of 7.3 and is practically insoluble in water.[5] It has low oral bioavailability (17%) which is attributed to poor dissolution and first pass effect. The drug was classified in some literature reports as class IV drug.[6] This suggests that the drug suffers from poor permeability as well. Enhancing drug dissolution can play an important role in improving the oral bioavailability of the drug after oral administration. The benefit can be maximized if dissolution enhancement is to be achieved using membrane permeability enhancer with the developed dosage form being suitable for intraoral administration. Various formulation strategies have been developed to overcome poor dissolution of naftopidil. These include solid dispersions with cyclodextrin and development of rapidly disintegrating tablets.[7,8]

Considering the basic nature of the drug, the pH of the saliva (pH 6.8) was considered as a factor in testing the dissolution rate of the developed formulation. Accordingly, citric acid and tartaric acid were used as pH modifiers to enhance dissolution rate. For maximum benefit the organic acid will be subjected to dry co-grinding with naftopidil to allow for crystalline structure modification in addition to pH modulation.

MATERIALS AND METHODS
Materials
Naftopidil was purchased from GK sales, Baoji, China. Acetonitrile (HPLC grade) was obtained from BDH, Poole, England. Citric acid, tartaric acid, potassium dihydrogen phosphate (pharmaceutical grade), sodium hydroxide and hydrochloric acid (analytical grade) were obtained from El Nasr Chemical Company, Cairo, Egypt. AvicelPH 102, Aerosil 200, magnesium stearate and

sucralose were kindly provided by Sigma Pharmaceutical Industries, Quesna, Egypt.

Assay of naftopidil

Naftopidil was analyzed using UV spectroscopy. The Stock solution of naftopidil was prepared by dissolving naftopidil in acetonitrile to produce a concentration of (1mg/ml). Series of concentrations were prepared by dilution with acetonitrile, 0.1N HCl or phosphate buffer (pH 6.8). UV-visible spectrophotometer (JENWAY, Staffordshire, UK) was utilized to detect the absorbance values of the different prepared concentrations at 230nm. Calibration curves in acetonitrile, 0.1N HCl and phosphate buffer solution were constructed using the detected absorbance values. These calibration curves were utilized to detect the drug concentration in drug content test and drug dissolution test. This method was utilized by other investigators for naftopidil quantification.[9]

Preparation of co-ground mixtures

The drug was co-ground with citric acid to produce binary mixtures with ratios 1:2 and 1:3. Likewise, the drug was co-ground with tartaric acid producing binary mixtures with ratios 1:2 and 1:3. Finally drug, citric and tartaric acids were co-ground with each other with ratio 1:2:2 producing the ternary co-ground mixture as presented in Table 1. These mixtures were subjected to dry co-grinding using mortar and pestle for fixed grinding time (45 minutes).

Table 1: The compositions and dissolution parameters of the co-ground mixtures.

Formula	Drug	Citric acid	Tartaric acid	Q5 (%) in PH 6.8	DE (%) in PH 6.8
Pure drug	25 mg	-	-	1.2 (0.84)	2.3 (0.65)
F1	25 mg	50 mg	-	32.9 (0.9)	39.1 (0.21)
F2	25 mg	75 mg	-	46.5 (0.58)	47.3 (0.59)
F3	25 mg	-	50 mg	23.5 (0.19)	33.1 (0.29)
F4	25 mg	-	75 mg	32.8 (0.8)	36.7 (0.31)
F5	25 mg	50 mg	50 mg	57.69 (0.1)	62.9 (1.1)

-Q5 is the amount released after 5 min and DE is the dissolution efficiency
-Values between brackets are S.D (n = 3).

Preparation of physical mixture

This involved geometric mixing of selected formulation ingredients with the aid of mortar and pestle.

Physical characterization of the prepared formulation

Differential scanning calorimetry (DSC)

Differential scanning calorimeter DSC6 module, Perkin Elmer (Waltham, USA) was utilized to detect the thermal behavior of naftopidil, the excipients and the different prepared formulations. Samples equivalent to around 3 mg of the drug were loaded into aluminum pans and then crimped. The thermal behavior of each sample was detected using heating rate being adjusted at 10^{o}C/min in the temperature range of 25-350^{o} C under continuous flow of nitrogen gas.

Fourier transforms infrared spectroscopy

FTIR spectrophotometer (Bruker Tensor 27, Ettlingen, Germany) was used to detect the FTIR spectra of naftopidil, citric acid, tartaric acid and their co-ground mixtures utilizing potassium bromide (KBr) diffuse reflectance mode with detection by DLaTGS detector. Sample preparation was done by mixing the test powder with KBr then compressing the mixtures into disks by hydraulic press. The compressed samples were scanned in the range of 4000-400 cm^{-1}.

Powder X-ray diffraction (PXRD)

The X-Ray diffraction pattern of naftopidil was monitored using GNR APD 2000 pro-X-Ray diffractometer which employs Cu Ka radiation (1.54056 A^{o}) (Agrate Conturbia, Italy). This diffractometer is equipped with a primary Gobel mirror and a super-speed VA^{o} NTEC-1 position sensitive sensor. The samples were scanned from 3 to 65^{o} at step size of 0.03^{o} and the data were collected at ambient temperature.

Preparation of conventional and chewable tablets

The co-ground mixture showing optimum dissolution pattern and it was used to prepare chewable tablets (CG tab).To elucidate the effect of co-grounding technique, the ingredients of the optimum formulation was physically mixed and used to prepare tablets (PM tab). All tablets contained 25 mg of unprocessed naftopidil (control tablets) or its equivalent formulation according to the composition presented in Table 2.

Preparation of tablets involved mixing the tablet ingredients according to the formulation presented in Table 2. Mixing operation was achieved according to descending order strategy. The mixtures were compressed by 10 mm punch into tablets of suitable hardness (4-5 kp). This.

Table 2: Compositions of chewable tablets.

Ingredient	Cont tab	CG tab	PM tab
Drug	25 mg	25 mg	25 mg
Citric acid	-	50 mg	50 mg
Tartaric acid	-	50 mg	50 mg
Avicel pH 102	300 mg	300 mg	300 mg
Aerosil 200	30 mg	30 mg	30 mg
Sacralose	20 mg	20 mg	20 mg
Magnesium stearate	5.0 mg	5.0 mg	5.0 mg

-- Cont tab is control tablets, CG tab is tablets contain coground F5,
-PM tab is tablets contain physical mix.

was achieved using a single punch tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India).

Evaluation of chewable tablets

Uniformity of weight

This was conducted according to USP 30 (2007). The weight of each of randomly selected 20 tablets was recorded. The average weight was calculated and weight of individual tablet was compared with that average. The allowed percentage deviation is 5%. The tablets were considered acceptable if no more than two tablets deviate from the limit and no tablet deviates by more than twice the limit.

Tablet friability

This utilized Erweka friability tester (Heusenstamm, Germany). The weight of the selected tablets was recorded before being subjected to 100 revolutions before careful de-dusted and weighed again. The percentage loss was calculated and was taken as a measure for the friability with the tablets being acceptable if the friability does not exceed 1% [(10)].

Hardness test

This utilized Erweka hardness tester and was determined using 10 tablets which were selected randomly. The average of the hardness was calculated.

Drug content uniformity

This was done to confirm the uniformity of potency. The test involved random selection of 30 tablets for each formula. The content of each of 10 tablets was determined. This involved powdering of the tablet and dispersing the powder into acetonitrile with gentle heating to solubilize the drug. The mixture was filtered and suitably diluted with acetonitrile before determination of the drug content spectrophotometrically at 230 nm. Tablets pass the test if the content of each of at least 9 tablets was in the range of 85–115% of the labeled amount of naftopidil. The tenth tablet should not contain < 75% or >125% of the labeled content. If this was not the case, the drug content of each of the remaining 20 tablets would be determined. The tablets will be accepted if the contents of the 20 tablets were within the limit.[10]

Disintegration test

The disintegration time was determined for 6 tablets which were loaded in the disintegration units of Copley Scientific disintegration equipment (Model: NE4-COP, Nottingham, UK). The test employed distilled water maintained at 37 °C as disintegration medium.

Determination of in vitro drug dissolution

The dissolution studies utilized the USP type II dissolution equipment (paddle method) (Copley, NG 42JY, Nottingham, UK). The dissolution medium was 900 ml of 0.02 M potassium di-hydrogen phosphate with the pH adjusted to 6.8 using 1N sodium hydroxide solution to simulate the pH of the saliva. The dissolution medium was maintained at 37 ± 0.1 °C with the paddle rotating at a rate of 100 rpm. The drug (25 mg) was added in the form of unprocessed powder or equivalent amount of coground formulations. Samples (5ml) were collected periodically and were filtered immediately using 0.45 µm Millipore filter before quantification of the drug in the collected samples by UV spectrophotometry. The dissolution medium was replenished with 5 ml of fresh dissolution fluid to keep the media volume constant. The same conditions were applied for the powdered co-ground mixtures in the development stage.

For chewable tablets, the dissolution test was conducted for crushed tablets as well as intact tablets using the same dissolution conditions as above. Additionally, another dissolution protocol was conducted in which drug dissolution was tested in 900 ml buffer system of pH value 6.8 for 5 minutes at the end of which the pH was immediately adjusted to 1.2 by the addition of 35 ml of 5N HCl. This design was used in a trial to mimic the actual sequence of chewing then swallowing the tablet. The collected samples were treated as before. The study was conducted in triplicates. The cumulative amounts of drug dissolved (expressed as percentage of the dose) was plotted as a function of time to produce the dissolution profiles which were used to calculate the dissolution parameters. The dissolution parameters included the amount of drug liberated in the first 5min (Q5) and the dissolution efficiency (DE). The later was calculated according to Khan (1975).[11]

Statistical Analysis

All experiments were conducted at least in triplicates and statistical analysis employed Student *t*-test, with *P*-value less than 0.05 was quoted as significant.

RESULTS AND DISCUSSION

Differential scanning calorimetry

Figure 1shows representative thermograms of the unprocessed naftopidil, citric acid, tartaric acid and their co-ground mixtures. The calculated thermodynamic parameters are presented in Table 3.

The thermogram of pure unprocessed naftopidil was characterized by sharp endothermic peak at 127.6 ^{o}C. This endotherm corresponds to the melting transition of the drug. The degradation of the drug was reflected as broad exothermic peak which was recorded at 313^{o}C (Figure 1 and Table 3). This thermogram is similar to that recorded by other investigators who provided similar explanation to the thermal events of naftopidil.[7] The thermal behavior of the anhydrous citric acid was characterized by two endothermic peaks, the first one is sharp and was detected at 158.9^{o}C with the second being seen at 208.98^{o}C as very broad endotherm (Figure 1 and Table 3). These endotherms can be attributed to the melting transition and decomposition of citric acid, respectively. These findings correlate with the properties of citric acid and agree with the published thermal pattern for the same material.[12] The thermal pattern of tartaric acid was characterized with asymmetric endothermic peak with sharp apex which showed broadening towards higher temperature. The temperature corresponding to the apex (213.9^{o}C) was taken as a measure for Tm of tartaric acid (Figure 1). This behavior reflects the existence of tartaric acid in the form of DL, racemic form with the asymmetric peak representing the thermal events of the melting with decomposition behavior of the acid. This correlates well with the specification of the material and is supported by the published data on the same acid.[13] Dry co-grinding of naftopidil with citric acid at 1:3 weight ratio resulted in a mixture (F2) having thermal behavior different from that of unprocessed drug and citric acid. The co-ground mixture showed one broad symmetric endothermic peak at 183.1^{o}C with an onset of 160^{o}C and endset of 203^{o}C (Figure 1 and Table 3). Interestingly, the decomposition peaks of the unprocessed naftopidil and pure citric disappeared. This finding suggests the formation of new crystalline species. Co-grinding of naftopidil with tartaric acid at 1:3 weight ratio. (F4) showed significant changes in the thermal behavior of both the drug and tartaric acid. The endothermic peak corresponding to the melting transition of drug and the exothermic decomposition peak were abolished. This was associated with a change in the appearance of tartaric acid peak which underwent significant broadening and became more symmetric compared with that of the unprocessed tartaric acid. The Tm of this peak was recorded 191.8^{o}C with new small peak appearing at 215.33^{o}C (Figure 1and Table 3). This thermal pattern suggests possible transformation of the drug into amorphous form with modification of the crystalline structure of tartaric acid or development of completely new crystalline species which requires further confirmation with other instrumental techniques (see below). Co-grinding of naftopidil with both citric and tartaric acids at weight ratio of 1:2:2, produced a thermal event representing the combined thermograms of the co-ground binary mixtures of the drug with either citric acid or tartaric acid. This was revealed as a biphasic endothermic peak which showed two apexes at 164.3 and 194.52 ^{o}C with the first apex appearing as shoulder. This again suggests the development of new crystalline species (Figure 1). Similar change in the thermal behavior was recorded for piracetam after co-grinding with either citric acid or tartaric acid with the resulting species being identified as a new co-crystalline product.[14]

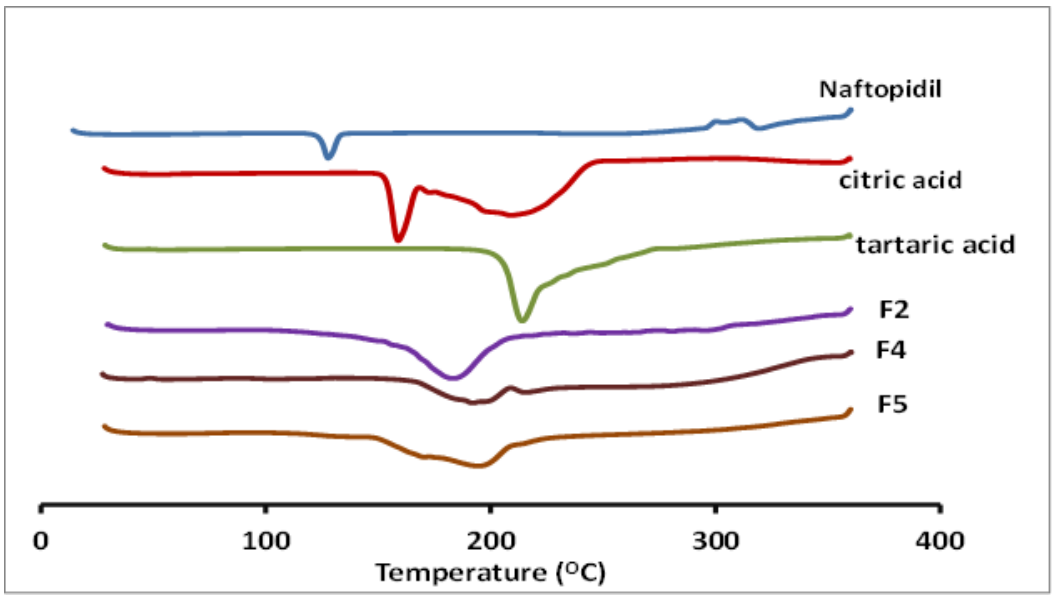

Figure 1: DSC thermograms of pure drug, citric acid, tartaric acid and different co-ground mixtures. Formulation details are in Table 1.

Table 3: The thermodynamic parameters of pure drug, citric acid, tartaric acid and different co-ground mixtures.

	Onset (^{o}c)	Endset (^{o}c)	Tm (^{o}c)	Enthalpy (J/g)
Pure drug	124.05 295.86	132.57 290.02	127.67 330.27	33.5 2.4
Citric acid	153.97 187.25	166.31 243.29	158.97 208.95	106 362
Tartaric acid	205.6	226.12	213.93	402
F2	160	203.6	183.19	307
F4	43.88 167.31 209.4	53.13 206.91 227	48.57 191.86 215.33	1.4 105 11.2
F5	150.8	210.86	194.52	282

- *For detailed formulation refer to Table 1*

Fourier transforms infrared spectroscopy

Figure 2 shows the FTIR spectra of pure naftopidil, citric acid, tartaric acids and their co-ground mixtures. The FTIR spectrum of pure unprocessed naftopidil showed the characteristic peaks of the drug which were noticed at 3443 cm^{-1} for OH-stretching, at 3049 cm^{-1} for aromatic CH stretching, at 2938 and 2924 cm^{-1} for the aliphatic CH stretching vibrations and at 1580, 1500, 1480 cm^{-1} for aromatic C=C group stretching vibration. The absorption band of CN and CO stretching vibrations were seen at 1268 and 1239 cm^{-1} with the C–O–C stretching peaks appearing at 1178, 1141 and 1102 cm^{-1}. The C–H bending was recorded as composite bands in the range of 1337-1305 cm^{-1} (Figure 2). Similar FTIR spectrum was recorded by other investigator with the recorded absorption bands being similarly assigned.[7] The FTIR spectra of citric acid (Figure 2) shows the characteristic peaks for its functional groups with the hydroxyl groups being seen as three absorption bands which were recorded at 3498, 3451, 3293 cm^{-1}. These bands can be assigned for the alcoholic OH, the central carboxylic OH and the terminal carboxylic OH, respectively. This assignment is acceptable taking into consideration the presence of resonance in case of carboxylic OH group allowing its detection at lower wave number compared with the alcoholic OH. The central carboxylic OH was of lower intensity and was noticed at higher wave number than the terminal ones due to intramolecular hydrogen bonding. The absorption bands of the carboxylic C=O were recorded at 1749 and 1702 cm^{-1}. The existence of six intense bands at 3498, 3291, 1756, 1708, 1174 and 1140 cm^{-1} in the FTIR spectrum is indicative for the presence of citric acid in dimeric form. Similar FTIR spectrum was recorded for citric acid with the absorption bands being similarly assigned.[15]

Co-grinding of naftopidil with citric acid resulted in a product with an FTIR spectrum different from that of the individual components. The difference was manifested as broadening and fusion of the peaks corresponding to the hydroxyl groups of the components. This was associated with the shift and fusion of the peaks corresponding to the C=O of citric acid to develop a new very intense absorption band at 1729 cm^{-1}. These changes indicate at least hydrogen bonding between the naftopidil and citric acid. This is further strengthened by disappearance of the C-N stretching absorption band of the drug (Figure 2). Similar changes have been recorded after co-grinding of citric acid with another nitrogen containing drug.[12]

The FTIR spectrum of tartaric acid showed the characteristic peaks that correlates with its function groups. The hydroxyl groups were shown as bi-forked peak with the apex being seen at 3413 cm^{-1}. Other major peaks were detected at 1743 cm^{-1} for C=O groups, at 1456,1401, 1328 cm^{-1} for C-O-C bending vibrations and at 1290,1239,1220 cm^{-1} for C-O stretching vibrations (Figure 2). The recorded spectrum simulates the published data for tartaric acid.[16] Co-grinding of naftopidil with tartaric acid resulted in a product with compromised FTIR spectrum compared with that of the individual components. The difference was manifested as a change in the appearance and position of the bi-forked peak of the hydroxyl groups of tartaric acid. This peak appeared with broad peak with two sharp apexes at 3411 and 3360 cm^{-1}. This change was accompanied by a shift in the peak corresponding to the C=O group to appear as very intense absorption band at 1741cm^{-1}. These changes suggest possible hydrogen bonding between the naftopidil and tartaric acid. This suggestion is further strengthened by disappearance of the peak corresponding to the C-N stretching vibration of the drug (Figure 2). Co-grinding the ternary mixture of naftopidil, tartaric acid and citric acid produced crystalline material having FTIR spectrum showing the sum of the spectra of the co-ground binary mixtures with peaks corresponding to the hydroxyl groups fusing to form very broad intense cluster of peak with an apex recorded as 3414 cm^{-1}. The peak corresponding to the C=O groups was seen as sharp intense peak at 1732 cm^{-1} which is in between the two values of the C=O peak of drug/tartaric and drug/citric co-ground mixture (Figure 2). Once again these changes can be considered as diagnostics for at least hydrogen bonding formation between naftopidil with the acids. As for the binary systems the peak corresponding to the C-N stretching vibrations was vanished which can further confirms the suggestion (Figure 2).

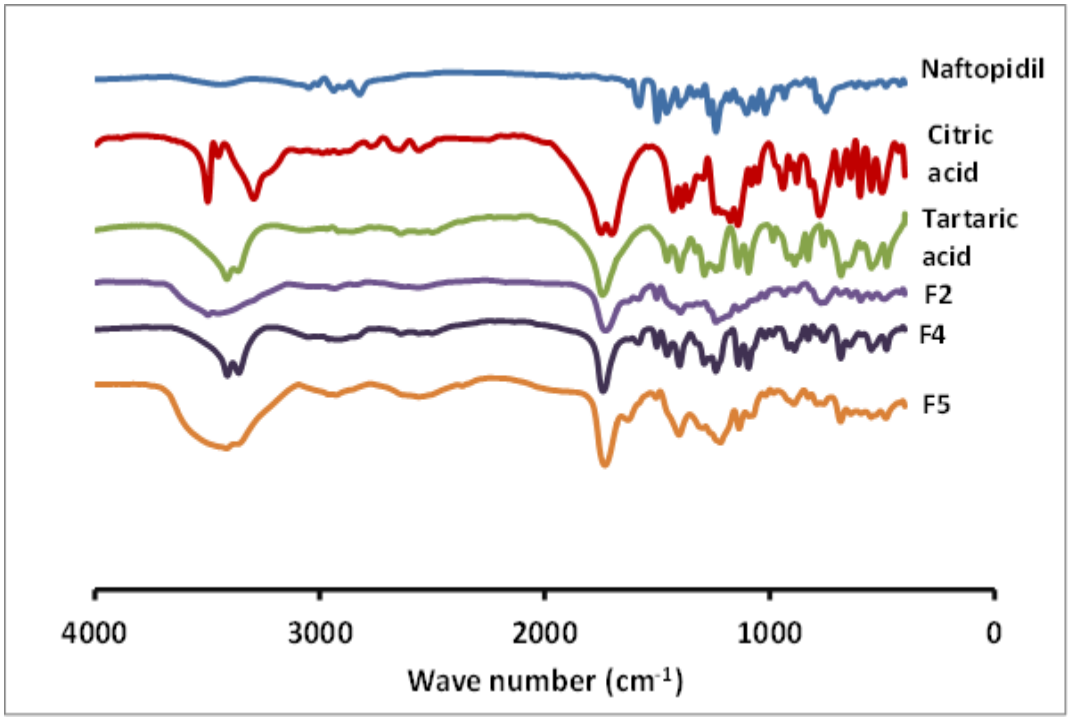

Figure 2: FTIR spectra of pure drug, citric acid, tartaric acid and different co-ground mixtures. Formulation details are in Table 1.

Powder X-ray diffraction (PXRD)

Figure 3 shows the recorded X-ray diffraction pattern of the unprocessed naftopidil, pure citric acid, pure tartaric acid and co-ground mixtures of naftopidil with citric and/or tartaric acids. The recorded diffraction peaks are presented in Table 4. The X-ray diffraction pattern of pure unprocessed naftopidil reflected the crystalline nature of the drug as indicated from the recorded sharp intense distinct diffraction peaks.[8] The crystalline nature of citric acid and tartaric acid was similarly revealed from the diffraction patterns of these materials (Figure 3 and Table 4).

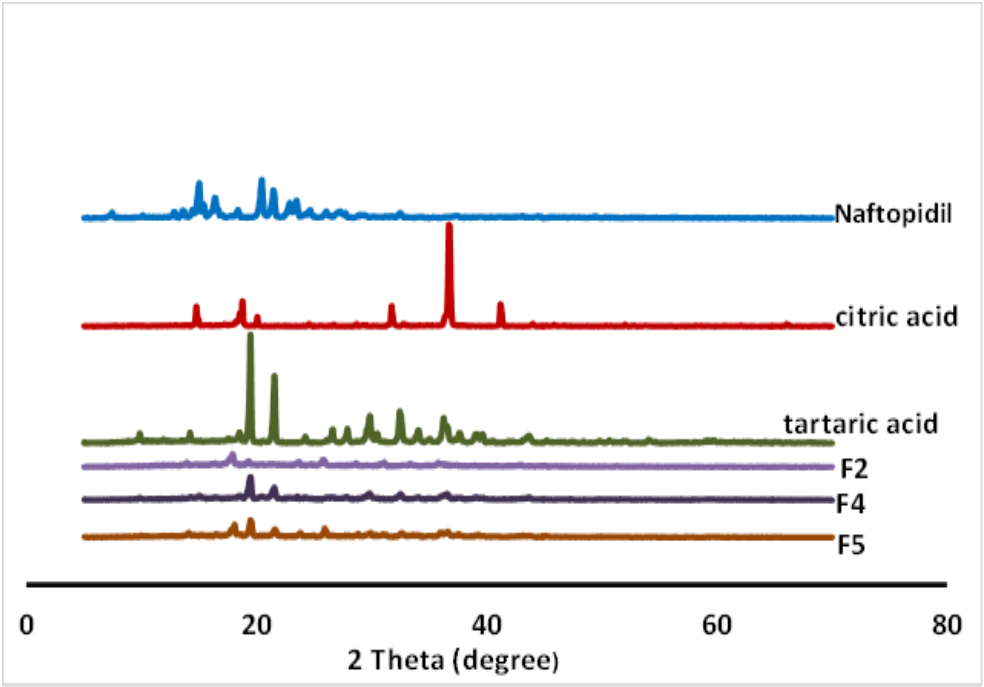

Figure 3: X-ray diffraction pattern of pure drug, citric acid, tartaric acid and different co-ground mixtures. Formulation details are in Table 1.

Co- grinding of naftopidil with citric acid and/or tartaric acid produced crystalline materials having compromised X-ray diffraction pattern compared with that of the individual components of the co-ground mixture. Generally, the recorded diffraction pattern showed peaks of low intensity which is expected due to particle size reduction. Detailed analysis of the diffractograms indicates the complete disappearance of most of the diffraction peaks of the drug. This was the case after co-grinding naftopidil with either citric acid or tartaric acid. The same was noticed after co-grinding with both acids (Figure 3 and Table 4). With respect to the diffraction peaks of the acids, some of the peaks were disappeared with others being detected. The new finding in these diffraction patterns was the detection of new peaks which were seen at 2Ɵ values of 13.82, 17.87, 19.16, 23.6, 25.73, 28.5, 30.8, 31.01, 34.04, 35.75, 39.02, 42.67 in case of naftopidil citric acid mixture with disappearance of the characteristic crystalline peaks of the drug and citric acid. This suggests the development of new crystalline structure probably new co-crystals. This is consistent with the published data for citric acid with efavirenz.[17]

For tartaric acid naftopidil mixture, most of the diffraction peaks of the drug were vanished with only two peaks being noticed at 2Ɵvalues of 14.93 and 20.27^{o} which appeared with lower intensity. The characteristic peaks of tartaric acid were preserved in this diffractogram with no new peak being shown. This pattern suggests possible amorphousization of the drug. For the ternary mixture, most of the characteristic peaks of naftopidil were absent except those peaks at 2Ɵvalues of 16.34, 25.9, 28.87, 43.07^{o} which were noticed as very short peak. Five new peaks appeared at 2Ɵ values of 17.96, 17.99, 23.75, 30.8 and 35.93 ^{o}. Other peaks of the diffractogram of the ternary mixture originated from tartaric acid and were of low intensity (Figure 3). This again suggests development of potentially new crystalline product. Overall, the X-ray diffraction pattern suggests development of co-crystalline product in co-ground mixtures. This supposition is supported by the DSC and FTIR data.

Table 4: The characteristic diffraction peaks of pure drug, citric acid, tartaric acid and different co-ground mixtures.

	2 Theta (degrees)
Pure drug	7.37, 12.7, 12.6, 13.52, 14.3, 14.93, 15.3, 16.34, 16.9, 18.29, 20.27, 21.45, 22.85, 23.45, 24.59, 25.9, 26.03, 27.23, 27.59, 28.87, 32.24, 43.07, 44.15.
Citric acid	14.75, 18.74, 20.03, 31.73, 36.71, 41.8.
Tartaric acid	9.77,14.18, 18.47, 19.37, 21.53, 24.02, 26.5, 27.68, 29.6, 30.44, 32.48, 34.01, 34.9, 36.41, 37.52, 39.02, 39.59, 43.58, 45.1, 49.7, 50.6, 51.94, 53.9
F2	13.82, 17.87, 19.16, 23.6, 25.73, 28.5, 30.8, 32.8, 34.04, 35.75, 39.02, 43.67.
F4	9.77, 14.93, 19.37, 20.27, 21.45, 27.68, 29.6, 32.48, 34.01, 36.41, 39.02, 43.58.
F5	9.77, 14.18, 16.34, 17.96,17.99, 19.37, 21.53, 23.75, 25.9, 28.87, 29.6, 30.38,32.48, 35.93, 36.41, 37.52,39.02,43.07, 43.58.

In vitro dissolution studies for co-ground mixtures

The recorded dissolution profiles of control unprocessed drug and co-ground mixtures in buffer solution (pH 6.8) are presented as cumulative percentage drug released versus time plots in Figure 4. Dissolution parameters, selected as the percentage drug released after 5 (Q5), and the dissolution efficiency (DE) were calculated and are shown in Table 1.

The unprocessed naftopidil showed very slow dissolution with only 1.2% of the labeled amount being released after 5 min, reaching a total of 5% at the end of dissolution time with dissolution efficiency of 2.3% (Table 1). This reflects the lipophilic nature of the drug with poor wettability.

For drug released from the co-ground mixtures, there was a dependence on the composition of each mixture. Naftopidil was co-ground with either citric or tartaric acid in weight ratios of 1:2 and 1:3. Co-grinding with citric acid showed significant increase ($P < 0.05$) in Q5, compared to control followed by gradual release with Q60 of 48% and 55% for F1 and F2, respectively. The dissolution efficiency was similarly improved (Table 1). This indicates the dependence of the dissolution enhancement on the citric acid concentration. This could be attributed to the newly formed co-crystalline, in addition to reduced drug particles as a result of grinding that provided large surface area. This proposition is supported by X-ray diffraction and DSC data. Additionally, creation of acidic microenvironment around the drug particle, due to citric acid, would enhance naftopidil (basic drug) dissociation and hence dissolution rate. Similar findings have been published after co-grinding of citric acid with other basic drugs such as verapimil and itraconazole.[18,19]

For tartaric acid co-ground mixtures, there was a significant increase in release rate from formulations F3 and F4 compared to pure drug (Figure 4 and Table 1). Such enhancement can be similarly explained as those for citric acid. Tartaric acid was previously reported to increase the dissolution of acyclovir through co-crystal formation.[20] It worth noting that tartaric acid improved dissolution rate of the drug to a lesser extent compared to acid (Table 1). This could be attributed to chemical structure of the two compounds with the tri-carboxylic group of citric acid providing more acidic environment

in the stagnant layer around drug particles compared to the di-carboxylic tartaric acid. It also provides more sites for hydrogen bonding as evidenced from FTIR data.

The ternary co-ground mixture, drug: citric acid: tartaric acid at weight ratio of 1:2:2 (formula F5), was more efficient in enhancing the rate of drug release compared to the corresponding binary systems with Q5 and Q60 of 57.7% and 70.5%, respectively. The calculated dissolution efficiency was 63% (Figure 4 and Table 1). These findings reflect the synergistic effect of both organic acids and verify the possible development of new crystalline form with physical changes in the drug crystals.

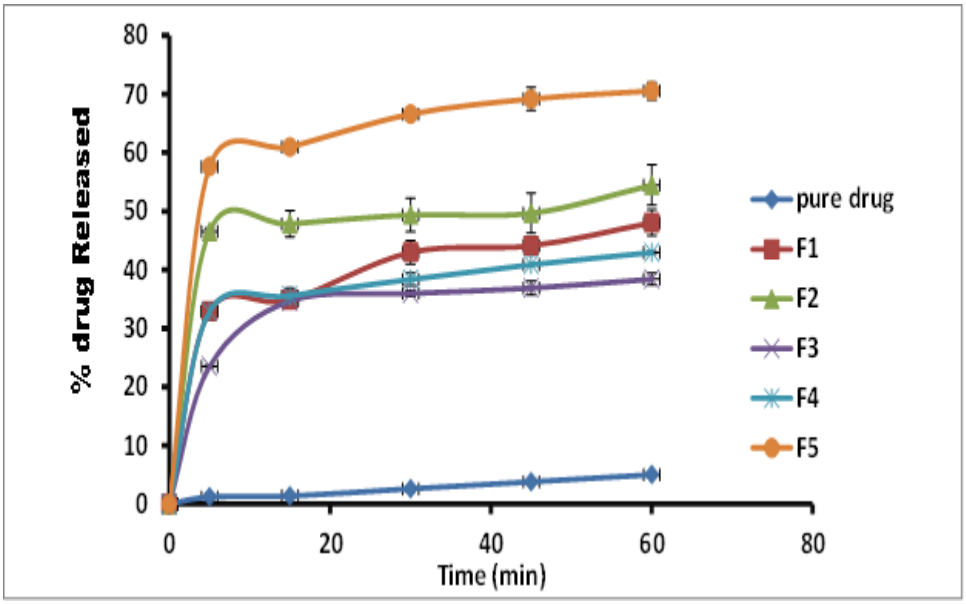

Figure 4: The dissolution profile of pure drug, co-ground mixtures in PH 6.8. Formulation details are in Table 1.

Characterization of chewable tablets

The tablets were prepared using pure drug, co-ground formula F5 or its physical mixture to obtain Control tab, CG tab and PM tab, respectively. All prepared tablets were accepted regarding weight variation test, with deviation from the mean weight being less than 2%. This reflects proper mixing and good flowability of the tested formulations. The drug content uniformity was in the range of 94.3 ±2.8 to 98.8% ±2.1%. Regarding tablet friability, values were in the range of 0.5 –0.8%.

Tablet hardness was measured to be 5.3 ±0.2, 5.1 ±0.2 and 5.22±0.27 kp for Cont tab, CG tab and PM tab, respectively. These results are satisfactory according to the acceptance criteria of the USP. Though not all pharmacopoeias call for disintegration test for chewable tablets, the International Pharmacopoeia recommend performing disintegration test to address concerns about the efficiency of chewable tablets that may be swallowed intact. The disintegration time in minutes was 0.33± 0.02, 0.8±0.1 and 1.6 ±0.1 for Cont, PM and CG tablets, respectively. The relative long time for CG tab may ascribe to the cohesiveness of the co-ground mixture under compression.

In vitro dissolution of chewable tablets

Drug dissolution was tested for all tablets with or without prior crushing to address concerns of possible variation in drug release if tablets were chewed or swallowed whole, respectively. The dissolution studies involved two protocols. The first protocol involved tablets dissolution in phosphate buffer system pH 6.8, simulating the salivary conditions. The second protocol was designed to mimic the normal in vivo pathway of chewable tablets after administration. This involved two phases representing buccal and gastric phases. First phase involves dissolution for 5 min in buffer pH 6.8, after which the pH was adjusted to 1.2 simulating the gastric phase. The dissolution profiles are presented as cumulative drug release versus time plots in Figure 5. The dissolution parameters were calculated and are presented in Table 5.

The results of the drug dissolution from pre-crushed tablets in alkaline media are shown in Figure 5A. For Cont tab (contains unprocessed naftopidil), the drug was liberated slowly with Q5 and % DE of 3.1 ±0.5 and 4.1±0.3, respectively. These results are higher than that of pure drug powder in the same dissolution conditions (Figure 5A and B, Table 5). This may be due to drug adsorption on the surface of other tablet excipients that introduced large surface area for drug dissolution.CG tab (co-ground F5) showed a marked increase in drug dissolution with initial release of 55% of the loaded dose and DE of about 60%. It worth noting that the recorded parameters for CG tablets are in good correlation with the corresponding co-ground particles. This indicates that the compression force, though increased tablet hardness, did not affect the dissolution behavior of naftopidil co-ground solid state. For comparative purpose, the components of F5 were physically mixed to produce PM tab that showed improved dissolution parameters

compared to control, but was still inferior to CG tab (P < 0.05). The components of CG tab and PM tab provide acidic micro-surroundings due to presence of citric and tartaric acids. However, the superiority of the co-ground mixture (CG tab) could be due to the recorded changes in drug crystalline nature which provided further enhancement in the drug release rate.

The overall result suggests the superiority of the co-ground mix (F5) in enhancing naftopidil dissolution with better release efficiency.

Noteworthy, the dissolution profiles for intact tablets were similar to the pre-crushed ones (Figure 5B), with similar dissolution parameters (P<0.05). This result eliminates the concern of swallowing the tablet whole either intentionally or by mistake.

For the biphasic protocol, the dissolution profiles for crushed and intact tablets are shown in Figure 5C and D, respectively. The extracted dissolution parameters are illustrated in Table 5. For the first 5 minutes in basic media, all tablets showed a Q5 similar to those obtained for the first protocol. Following pH change to acidic (pH 1.2), burst drug release was observed with Q5 (measured after 5 min after pH switching) approaching 100% release. This behavior was anticipated regarding the weak basic nature of the drug.[5] All tablets showed similar values concerning Q5 and dissolution efficiency (P <0.05).

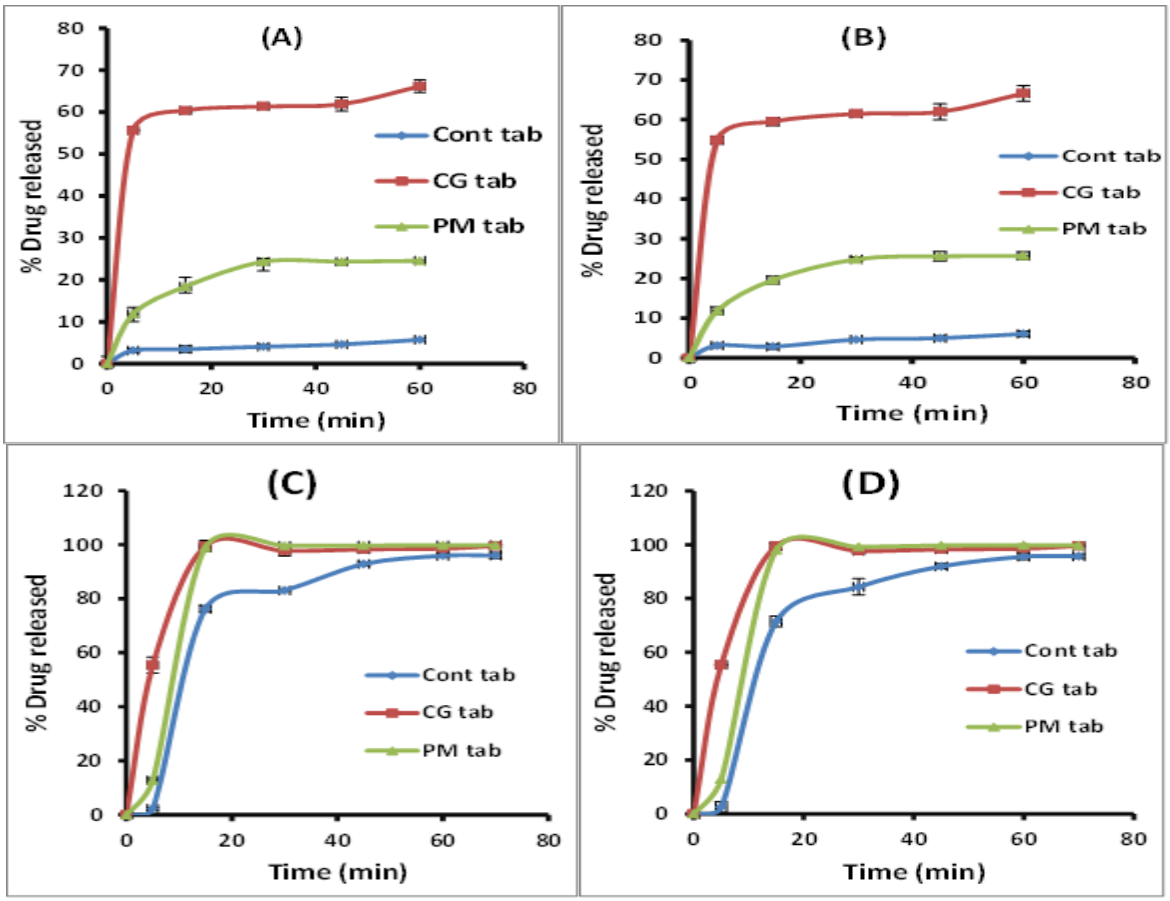

Fig 5: Dissolution profiles of crushed tablets (A and B) and intact tablets (C and D)using pH variation protocol. Formulation details are in Table 2.

Table 5: Dissolution parameters of crushed and intact tablets represented as the amount released after 5 min (Q5) and dissolution efficiency (DE) at different pH media.

Tablet type	Tablet condition	Q5 (%) in PH 6.8	Q5 (%) in PH 1.2	DE (%) in PH 6.8	DE (%)in PH 1.2
Cont tab	crushed	3.1 (0.452)	76.2 (1.77)	3.99 (0.29)	75.55 (0.6)
PM tab	crushed	11.8 (1.6)	98.9 (0.31)	20.4(1.01)	86.7 (1.9)
CG tab	crushed	55.64(0.73)	99.56 (0.11)	58.1 (0.4)	90.44 (0.7)
Cont tab	intact	3.3(0.658)	71.47 (4.1)	4.11(0.58)	74.7 (0.9)
PM tab	intact	11.98(0.455)	98.03(0.25)	21.05(0.56)	86.4 (0.2)
CG tab	intact	55.97(1.01)	99.56(0.11)	58.8(0.22)	90.44(0.1)

- Cont tab is control tablets, PM tab is tablets containing physical mix,, CG tab is tablets containing co-ground F5.
-Values between brackets are S.D (n = 3).

4. CONCLUSION

Co-grinding of naftopidil with citric acid and/or tartaric acid was able to develop a new crystalline product probably of co-crystal type. This new crystalline form showed faster dissolution with the drug undergoing a pH independent dissolution. The developed new co-crystalline product was successfully prepared as chewable tablets which underwent pH independent liberation of naftopidil.

Conflicts of interest: The authors declare that they have no competing interests.

REFERENCES

1. Kawabe K. Latest frontiers in pharmacotherapy for benign prostatic hyperplasia. Yakugaku Zasshi, 2006; 126: 199-206.
2. Masumori N. Naftopidil for the treatment of urinary symptoms in patients with benign prostatic hyperplasia, 2011; Ther Clin Risk Manag, 7: 227–238.
3. Roehrborn, CG, SCHWINN DA. α1-Adrenergic Receptors and Their Inhibitors in Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia. J. Urol, 2004; 171: 1029–1035.
4. Kanda H, Ishii K, Ogura Y, Imamura T, Kanai M, Arima, K, Sugimura Y. Naftopidil, a selective α-1 adrenoceptor antagonist, inhibits growth of human prostate cancer cells by G1 cell cycle arrest. Int. J. Cancer, 2008; 122: 444–451.
5. 5. Borbe, HO, Metzenauer P, Szelenyi I. 5-HT1A-agonistic properties of naftopidil, a novel antihypertensive drug. Eur J Pharmacol, 1991; 205: 105-107.
6. Farthing MJ, Alstead EM, Abrams SM, Haug G, Johnston A, Hermann R, Niebch G, Ruus P, Moltz KH, Turner P. Pharmacokinetics of naftopidil, a novel anti-hypertensive drug, in patients with hepatic dysfunction. Postgrad. Med. J, 1994; 70: 363–366.
7. Patil R, Nerkar P, Mahajan H, Ige P. Dissolution rate enhancement and physicochemical characterization of naftopidil in solid dispersions with B-CD and HP B-CD. IAJPR, 2015; 5: 988-994.
8. Khemchand G, Indrajee S. Formulation and evaluation of orally disintegrating tablets of antihypertensive drug naftopidil. AJPRD, 2015; 3: 1-7.
9. Adithya BP, Krishna, UV, Vijayalakshmi M, Kumar, AR. Spectrophotometric estimation of naftopidil in bulk and dosage form. Int. Res J Pharm, 2012; App Sci. 2: 26–30.
10. United States Pharmacopeia 30 National Formulary 25. Rockville (MD), United States Pharmacopial Convention, 2007.
11. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27: 48–49.
12. Lin HL, Hsu PC, Lin SY. Theophylline-citric acid co-crystals easily induced by DSC-FTIR microspectroscopy or different storage conditions. Asian J. Pharm, 2013; Sci., 8: 18–26.
13. Fukami T, Tahara S, Yasuda C, Nakasone K. Structural Refinements and Thermal Properties of L(+)-Tartaric, D(–)-Tartaric, and Monohydrate Racemic Tartaric Acid, 2016; Int. J. Chem., 8: 9–21.
14. Rehder S, Klukkert M, Löbmann KA, Strachan CJ, Sakmann A, Gordon K, Rades T, Leopold CS. Investigation of the formation process of two piracetam cocrystals during grinding. Pharmaceutics J, 2011; 3: 706–722.
15. Bichara LC, Brandán SA, Lans, HE, Ferrer EG, Gramajo, MB. Vibrational study and force field of the citric acid dimer based on the SQM methodology. Adv. Phys. Chem, 2011; 55: 53-62.
16. Sevukarajan M, Sodanapalli R, Thanuja B, Nair R. Preparation and Pharmaceutical Characterization of Supra molecular Complex of Isoniazid with L (+) Tartaric acid. J. Biomed. Sci, 2011; 3: 397–402.
17. Chadha R, Saini A, Arora P, Chanda S, Dharamvirsinghjain. Cocrystals of efavirenz with selected conformers: Preparation and characterization. Int. J. Pharm. Pharm. Sci, 2011; 4: 244–250.
18. Streubel A, Siepmann J, Dashevsky A, Bodmeier R. pH independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. J. Controlled Release, 2000; 67: 101-110.
19. Hamishehkar H, Emami S, Lamei B, Valizadeh H, Jouyban A. Evaluation of solubility and dissolution profile of itraconazole after cogrinding with various hydrophilic carriers. J. Drug Deliv. Sci. Technol, 2014; 24: 653–658.
20. Sarkar A, Rohani S. Cocrystals of acyclovir with promising physicochemical properties. J. Pharm. Sci, 2014; 104: 98–105.