RESEARCH ARTICLE

Utilization of Ultrasonication Technique for the Preparation of Apigenin Nanocrystals

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ABSTRACT

Background: Different techniques had been used to affect particle size and morphology. In this work, the ultrasonication technique was applied to prepare apigenin nanocrystals and study the potential of this technique on the particle size, crystallinity, solubility, and dissolution rate that might improve drug activity.

Method: Ultrasonication method was used to prepare apigenin nanocrystals suspension using two stabilizers, tween 80 and poloxamer 188 and optimizing the procedure by using different sonication time, power, and different concentration of stabilizers. The apigenin suspension was characterized by using differential scanning calorimetry (DSC), powder X-ray diffraction (P-XRD), fourier transforms infrared (FTIR), Particle size, polydispersity index (PDI), zeta potential, saturated solubility and drug dissolution.

Results: The prepared apigenin nanocrystals using tween 80 and poloxamer 188 as stabilizers showed high crystallinity than the pure drug powder with a particle size of 88.7 nm and 89 nm, for nanocrystals prepared by using polymeric and surfactant stabilizers and about 35 times increment in water solubility in room temperature at 37°C as well as about 31 times and about 41 times solubility increment in simulated gastric, and intestinal media and significantly higher dissolution rate (98% within 120 minutes) in comparison to the pure drug which showed only 20% release.

Conclusion: This study provides the successful utilization and optimization of ultrasonication technique to prepare nanosized stable apigenin nanocrystals using surfactant and polymeric stabilizers with fast dissolution rate and better physical properties compared to other reported methods. It suggests the potential of utilizing these nanocrystals to prepare an oral formulation with a fast onset of action and bioavailability improvement.

Keywords: Apigenin, Nanocrystals, Solubility, Ultrasonication.

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INTRODUCTION

Particle technology is a technique used to improve solubility and bioavailability of poorly aqeous soluble drugs through physical modification of drug products by several approaches from the conventional size reduction processes to the newer particle technologies.[1] Several drug delivery systems based on particle technology have been developed, for example, polymeric nanoparticles,[2] nanomicelles,[3] nanogel,[4] and nanocrystals.[5,6]

Nanocrystals can be defined as pure small particles having a crystalline structure with a size below 1-µm. Nanocrystals are characterized by pure (100%) APIs with no carriers and are stabilized by surfactant or polymer. The pharmaceutical benefits of nanocrystals include improvement in saturation solubility, dissolution rate, oral bioavailability, and reproducibility of oral absorption.[7]

Two basic approaches are involved in the production of nanocrystals, the top-down process (nanocrystals are formed by the application of mechanical pressure and attrition forces to reduce the particle size to the nanosize range) and bottom-up technique nanocrystals are formed from the molecular state.[8] Various production techniques have been developed based on these two basic approaches, including wet milling,[9] high-pressure homogenization,[10] microfluidization,[11] controlled precipitation,[12] hydrosols technique,[13] controlled crystallization during freeze-drying (CCDF),[14] supercritical fluid technologies[15] and precipitation-ultrasonication technique.[16]

Precipitation-ultrasonication technique is a popular way for improving micro scale-mixing and mass transfer. Ultrasonic waves breach the saturated solution by creating and disrupting of cavitation bubbles, which can cause extreme heating and cooling cycles. In the cavitation bubbles, high temperature and pressure are produced, which are responsible for promoting effective molecular collision. Primary nucleation is resulted

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due to excessively partial over-saturation after molecular collisions.[17] The high energy of ultrasonication improves the thermodynamic stability of nanosized crystals, and the added surface-active agent enhances crystal re-ordering, which will reduce the surface-free energy. This ultrasound energy is also reported to show an erosion effect on large crystals, causing the disruption of crystal agglomerates, and enhanced the rate of adsorption of the stabilizer on the crystal surface.[18]

The ultrasonication technique provides better control of the desired size and avoids final product contamination in comparison to other techniques such as the milling method.[17] Ultrasonication method is a very effective method used to produce nanocrystals to improve the solubility of poorly aqueous drugs such as preparation of esomeprazole nanosuspension using evaporative precipitation ultrasonication,[19] efavirenz nanosuspension using precipitation-ultrasonication method,[20] and the preparation of nitrendipine nanosuspension using precipitation-ultrasonication method to enhance nitrendipine solubility.[18]

Apigenin, 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one is a naturally occurring bioactive flavonoid that is obtained from several fruits and vegetables in the form of either O-glycosides or C-glycosides.[21] The most common sources for apigenin are parsley, celery, celeriac, and chamomile tea.[22]

Apigenin available commercially as light yellow crystals and has anti-inflammatory, anti-cancer, antibiotic, antiviral, antidiabetic, and antioxidant activities.[23] Its formulation development is difficult because it comes under biopharmaceutical classification system (BCS) class II (presents low solubility and high permeability). It has been reported as practically insoluble/poorly soluble in water (solubility: 0.001mg/L at ambient temperature).[24] The present study aims to prepare apigenin nanocrystals using ultrasonication technique and optimize the product to achieve maximum increment in drug solubility and faster dissolution rate that leads to improve its bioavailability and onset of activity.

MATERIALS

Apigenin purity > 99.0% by high performance liquid chromatography (HPLC) was provided by Hyperchem, china, tween 80 (polysorbate 80), poloxamer 188 were provided from Himedia laboratory, India, and deionized water provided from Sigma Chemical Co., Limited, USA used as dispersion media.

Preparation of AP Nanocrystal Suspension

A 500 mg of apigenin powder is dispersed in 10 ml deionized water in the presence of different percentages of tween 80 (1 and 2% w/w) and different percentages of poloxamer 188 (1% and 2% w/w).[25] The samples were placed in magnetic stirrer at 100 rpm and 25°C for 5 minutes. The ultrasonic system with probe diameter 6 mm immersed about 1 cm in the solution with frequency and maximum power 20 kHz and 900 w was used. The temperature of the samples in the ultrasonic system is controlled at room temperature firstly; afterward. it is cooled to -5°C. The sonication duration is designed as 2 seconds duration of sonication following 2 seconds silent duration. During cooling, the power ultrasonic is applied. Different sonication time (3 and 6 minutes) and sonication power (200, 400, 600 watt) were applied for all the prepared formulas (F1-F24). After sonocrystallization apigenin nanosuspension is centrifugated, filtered and the wet residue was dried at room temperature sieved to receive the final powder.

Table 1, Content and optimization conditions of the prepared formulas. Q1

Characterization of Apigenin Nanosuspension

Particle size, polydispersity index (PdI), and zeta potential:

The samples (F1-F24, and the pure drug) is dissolved in 10 mL of deionized water and agitated gently. Then, the particle size and PdI were measured using a zeta-sizer (Malvern Instruments, UK). The same device is used to measure the zeta potential using a unique cell provided with two electrodes(26).

X-ray powder Diffraction (XRPD)

The pure drug of apigenin and apigenin formulas (F1-F24) were examined by X-ray Diffractometry (Shimadzu 6000, Japan). The operating conditions were: voltage 40 kV; current 30 mA; scanning speed 1/min. Using a 0–50° (2θ) range, the Cu-target X-ray tube and Xe-filled detector documented the results.[27]

Differential Scanning Calorimetry (DSC)

The pure drug of apigenin and apigenin formulas (F1-F24) were examined by DSC 60 (Shimadzu, Japan). The sample was sealed in the aluminum pans (5–6 mg) and heated at the rate of 10°C/min, covering a temperature range of 50 to 500°C with purging of dry nitrogen at a constant rate. An empty aluminum pan was used as reference. Indium/zinc were used to calibrate the DSC temperature and enthalpy scale of instrument.[28]

Fourier Transforms Infrared Spectroscopy (FTIR)

Compatibility of the drug and the content prepared formulas (F1–F24) were carried out using Fourier transformed spectrophotometer (Shimadzu, Japan) in the range of 400-4000/cm by KBr disc method. A baseline correction was made using dried potassium bromide.[29]

Solubility Study

Determination of Saturated Solubility of Apigenin

Solubility of pure apigenin and the prepared formulas (F6, F20) in water, 0.1 N HCl solution, and phosphate buffer saline (pH 6.8) was studied by adding an excess amount of apigenin to 10 mL of a specific medium and shaking at 50 rpm for 48 hours at 25°C and 37°C and then sonicated for 10 minutes. Then filter the solution through 0.2 µm filter syringe and analyzed by UV-spectrophotometer at λ max 336 nm.[30]

In vitro Dissolution Studies

The dissolution study was carried out using USP type II (paddle type) dissolution test apparatus. The dissolution test was applied for the pure apigenin and all the prepared formulas (F1-F24). A 10 mL of powder was accurately weighed and put into the capsule. The capsule was kept in the rotary basket of dissolution apparatus at 50 rpm ± 1. The dissolution media was 900 mL

Table 1: Composition of the prepared apigenin formulas.

Formulation number	*Poloxamer 188*	*Tween 80*	*Sonication power (w)*	*Sonication power (w)*	*Sonication power (w)*	*Sonication time (m)*	*Sonication time (m)*
F1		1%	200			3	
F2		1%	200				6
F3		1%		400		3	
F4		1%		400			6
F5		1%			600	3	
F6		1%			600		6
F7		2%	200			3	
F8		2%	200				6
F9		2%		400		3	
F10		2%		400			6
F11		2%			600	3	
F12		2%			600		6
F13	1%		200			3	
F14	1%		200				6
F15	1%			400		3	
F16	1%			400			6
F17	1%				600	3	
F18	1%				600		6
F19	2%		200			3	
F20	2%		200				6
F21	2%			400		3	
F22	2%			400			6
F23	2%				600	3	
F24	2%				600		6

of 0.1 N HCl (pH 1.2) and 0.1 N phosphate buffer (pH 6.8) with 0.5% SLS at 37°C.

Samples of 5 mL were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45, 60, and 120) and filtered using a 0.22 µm millipore filter paper, then analyzed spectrophotometrically at 336 nm. The samples withdrawn were replaced by fresh dissolution medium to maintain sink condition and constant volume. Each preparation was tested in triplicate and the mean value was calculated.[31]

RESULTS AND DISCUSSION

In this work 24 formulas of apigenin were prepared using two types of stabilizers polymeric stabilizer (poloxamer 188) and surfactant stabilizer (Tween 80) in two different concentrations 1 and 2% for each one. The ultrasonication method was utilized and optimized by using different sonication power (200, 400 and 600 w) and different sonication time (3 and 6 minutes). The prepared formulas were evaluated as follows:

Particle size, polydispersity index (PdI), and Xeta Potential

The zeta potential is stability determining parameter where zeta potentials above the absolute value of 30 mV are required for storage stability of a charge-stabilized dispersion. The zeta potential of all formulas was comparably low,close to zero as shown in Table 2, which could be attributed to the absence of charge in nanosuspension ingredients due to nonionic stabilizers (tween 80 poloxamer 188). The nonionic copolymer (Polaxamer 188) and the nonionic surfactant (tween 80) acts by steric stabilization. Providing good steric stability for maintaining the stability of single layer nanodispersion.[32]

Particle sizes were determined as the intensity weighted mean diameter of the particle bulk population, and the polydispersity index (PdI) was determined as a measure for the width of the size distribution. The smaller the polydispersity index (PdI) value, the more monodisperse and uniform the particles, and the higher the PdI value, the wider the size distribution. The prepared formulas showed particle size ranging (88.7-381.4 nm) where F6 and F20 showed smaller particle size 89 and 88.7 nm, respectively. The polydispersity index (PdI) for all the prepared formulas (F1–F24) showed low PdI (0.056-0.7), indicating a uniform monodispersed state where the reported data suggest that PdI value > 0.7-1 is considered to have broad distribution of particle size.[33]

X-ray Powder Diffractometry (XRPD)

The XRPD analysis was performed to show any changes in the apigenin nanocrystals' inner structure compared to the apigenin powder. It can be observed that the characteristic peaks at 7.12, 10.21, 11.52, 14.34, 15.03, 16.58, and 17.86 θ

in the XRD pattern of the apigenin in the prepared formulas (F1–F24) were the same as that of the pure apigenin, indicating the crystalline structure.[34]

Figure 1 presents the XRD pattern of F6 and F20 as a representative of XRD patterns for the prepared formulas. The intensity of XRD pattern referred to the degree of crystallinity. All the prepared formulas and the pure drug showed high crystallinity; the results agreed with apigenin nanocrystals prepared by the supercritical antisolvent method.[35]

Differential Scanning Calorimetry DSC

DSC curves (Figure 2) of the apigenin powder and the prepared apigenin formulas (F1-F24) were studied to show any change in the crystalline state of apigenin after the sonocrystallization method. DSC curves for all the prepared formulas as well as pure drugs showed sharp peaks at range (367–370 °C) representing the melting point of the drug. Figure 2 showed the DSC for F6 and F20 as a representative of the prepared formulas.

The slight decrease in melting point of the prepared formulas (F6 and F20), where both show melting point (367°C) in comparison to the pure drug (370°C) after the ultrasonication process, could be attributed to the reduction of particle size to the nanometer range. Since the reduction of dimensions of particles from micron range or even bigger down to nano range, the surface-to-volume ratio increases significantly and the surface energy substantially affects the material's interior "bulk" properties. So the nanosized small particles have a higher proportion of surface molecules with fewer nearest neighbors than larger particles, and thus they are more weakly bound and less constrained in their thermal motion than molecules in the body of crystals, which is supposed to be responsible for the decrease of the melting point.[36] It was observed that there is a slight decrease in the melting point of apigenin nanocrystals prepared by a supercritical antisolvent method in comparison with pure drugs.[35]

Fourier-transform infrared spectroscopy (FTIR)

From FTIR spectra for the pure drug and the prepared apigenin formulas (F1–F24), It was observed that they had the same characteristic peaks indicating the compatibility of the additives used in the experimental conditions. Figure 3 shows the FTIR for F6 and F20 as representative of the formulas in comparison to a pure drug.[37]

Determination of Saturated Solubility of Apigenin

Table 3 shows the saturated solubility of apigenin from the supplied powder and the prepared formulas (F1- F24) in water, 0.1 N HCl solution, and phosphate buffer (pH 6.8) at 25 °C and 37 °C. It was observed that all the prepared apigenin formulas showed higher saturated solubility than pure apigenin, and this could be the decrease in particle size to nano size range leads to increased surface area of particles, reflecting the efficacy of the ultrasonication method and the optimized conditions applied in the preparation of apigenin formulas. Also, the presence of tween 80 and poloxamer 188 in the preparation of apigenin formulas decreased surface tension and increased the water solubility of drug nanocrystals.

It was observed that F6 has higher saturated solubility than other formulas (F1–F24) prepared using tween 80 in different

Table 2: The mean particle size, the polydispersity index (PdI), and zeta potential of the prepared apigenin formulas.

Formula code	*Mean particle size (nm)*	*PDI*	*Zeta-potential (nm)*
F1	318.4	0.783	0.313
F2	295.6	0.391	0.335
F3	244.6	0.337	0.529
F4	90.2	0.508	0.416
F5	125.2	0.59	0.265
F6	89.0	0.389	0.230
F7	110.8	0.604	0.325
F8	150.4	0.612	0.310
F9	108.5	0.056	0.318
F10	123.4	0.557	0.238
F11	111.5	0.515	0.245
F12	153.7	0.626	0.295
F13	116.4	0.399	0.142
F14	159.0	0.77	0.345
F15	183.4	0.576	0.252
F16	163.6	0.115	0.148
F17	171.2	0.523	0.145
F18	117.0	0.455	0.138
F19	154.0	0.759	0.246
F20	88.7	0.386	0.135
F21	146.8	0.62	0.141
F22	96.5	0.343	0.538
F23	125.2	0.599	0.343
F24	131.5	0.433	0.233

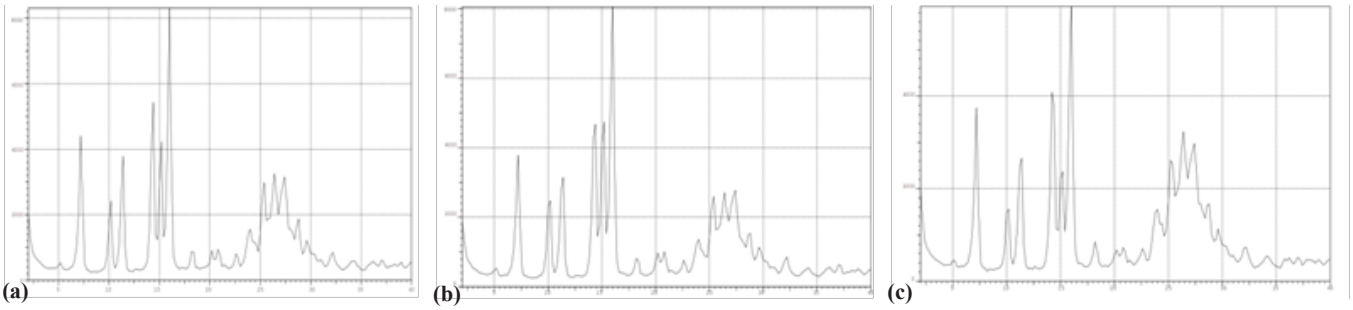


Figure 1: XRPD patterns of (a) apigenin pure powder, (b) apigenin nanocrystals (F6) and (c) apigenin nanocrystal (F20).

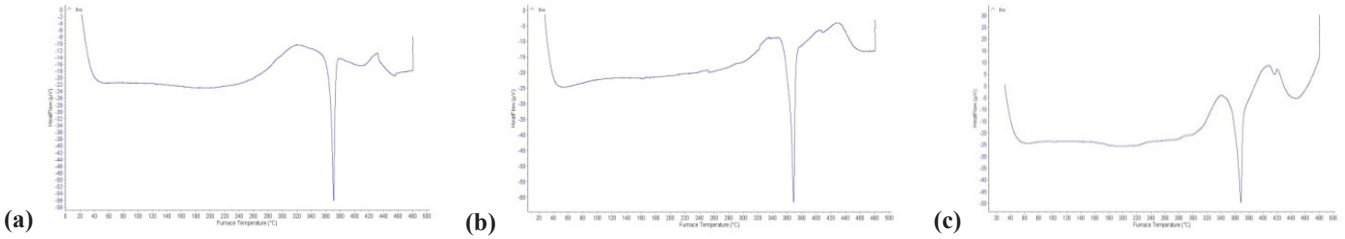


Figure 2: DSC curves of (a) apigenin pure powder, (b) prepared nanocrystals (F6) and (c) prepared nanocrystals (F20)

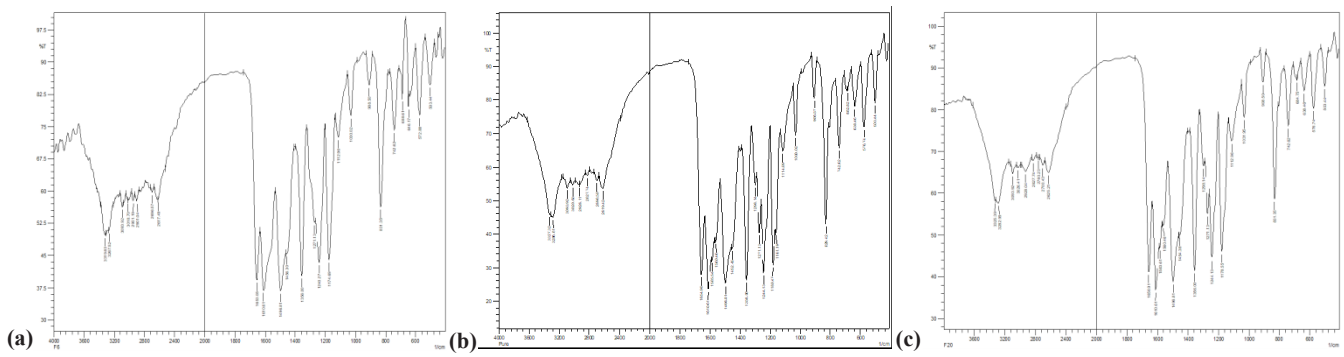


Figure 3: FT-IR spectra of (a) apigenin pure powder, (b) prepared nanocrystals (F6) and (c) prepared nanocrystals (F20)

concentration (1 and 2%) at different sonication condition, and this could be related to that F6 has a smaller particle size than other formulas (F1–F12), and according to Ostwald-Freundlich equation, the saturated solubility is increased with the decrease in particle size providing a larger surface area of drug particles to be in contact with the solvent.[38]

While F20 (containing poloxamer 188) showed higher solubility than all the prepared formulas indicating the efficiency of poloxamer 188 (polymeric stabilizer) in coating the drug particles with higher stabilization ability than surfactant and so inhibit crystals aggregation and improving drug solubility although that particle size of F20 nanocrystas is not significantly different from F6 nanocrystals.

In-vitro Dissolution Studies

Figure 4 shows the dissolution profile of the drug from all the prepared formulas in comparison to the pure drug in both 0.1 N HCl (pH 1.2) and 0.1 N phosphate buffer (pH 6.8). All the prepared formulas showed much higher dissolution profile than the pure drug indicating the efficiency of the applied method in reducing the particle size without affecting the crystallinity. Since the drug is weakly acidic compound therefore it showed higher dissolution profile in pH 6.8 than pH 1.2.

The pure drug gave 10% release in pH 1.2 and 20% release in pH 6.8 within 20 minutes and reached 20 and 40% release in pH 1.2 and pH 6.8 respectively within 120 minutes, due to its larger particle size in comparison to the prepared nanocrystals and this matches with Noyes-Whitney equation which presented that the surface area of particles increased as the particle size decreased and resulted in higher contact of drug particles with the dissolution medium.[39]

Formula F13 containing (1% poloxamer 188) gave 28 and 38 % drug release in pH 1.2 (after 20 and 120 min respectively) as well as 48 and 77% in pH 6.8 tween 80, keeping the same sonication conditions) which gave 17 and 25% drug release (after 20 and 120 min respectively) in pH 1.2, as well as 40% and 62% in pH 6.8. This indicating the efficacy of polymeric stabilizer (poloxamer 188) in producing smaller particle size (116.4 nm for F13) and higher saturated solubility in different

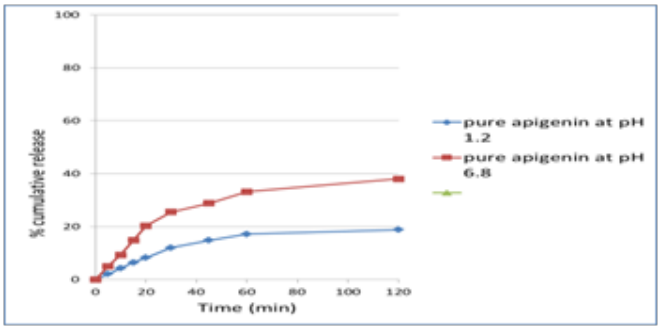
Table 2: The saturated solubility of apigenin from the supplied powder and the prepared formulas (F1-F24) in water and different pHs at 25 and 37 °C.
(A) at 25 °C

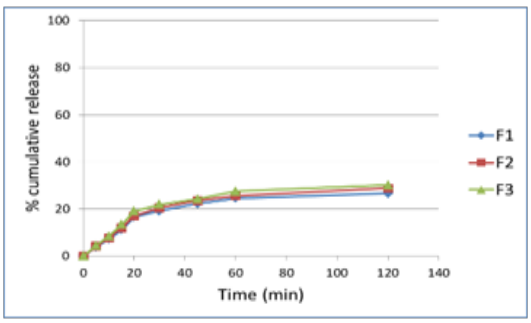
	Saturated solubility in water (µg/mL)	*Saturated solubility in pH 1.2 (µg/mL)*	*Saturated solubility in pH 6.8 (µg/mL)*
Pure apigenin	1.32	1.173	1.62
F1	19.6	16.4	22.2
F2	20.4	16.9	23.8
F3	21.9	17.8	25
F4	24.7	20.4	29.6
F5	23.6	19.5	28
F6	29.6	26.97	36.18
F7	24.8	20.2	29.8
F8	23.9	19.8	28.6
F9	25.1	21.1	31
F10	24.8	20.3	30.2
F11	25.1	21.8	31.1
F12	24	19.9	29
F13	25.7	22	31.7
F14	24.5	20.7	29.6
F15	24	20	28.9
F16	24.23	20.3	29.3
F17	23.9	19.9	28.7
F18	25.5	23.7	32
F19	25	23.9	32.7
F20	35.01	31.67	41.8
F21	26.2	24.8	33.4
F22	31.3	27	36.5
F23	27	25.2	35
F24	26.1	24.6	34.3

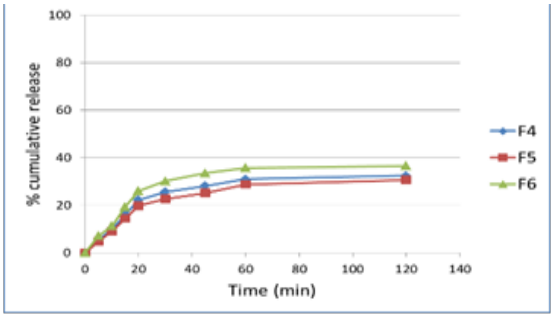
(B) at 37 °C.

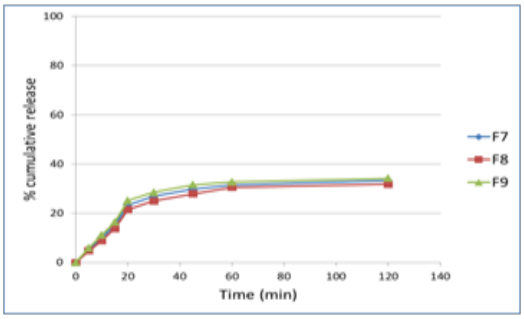
	Saturated solubility in water (µg/mL)	*Saturated solubility in pH 1.2 (µg/mL)*	*Saturated solubility in pH 6.8 (µg/mL)*
Pure apigenin	1.38	1.192	1.692
F1	19.75	16.5	22.29
F2	20.62	16.98	23.91
F3	22	17.91	25.13
F4	24.95	20.48	29.71
F5	23.9	19.6	28.095
F6	30.36	27.41	36.85
F7	24.98	20.32	29.91
F8	24.09	19.9	28.69
F9	25.19	22	31.14
F10	24.92	20.42	30.32
F11	25.17	21.91	31.23
F12	24.12	20	29.14
F13	25.79	22.12	31.82
F14	24.64	20.84	29.71
F15	24.13	20.09	29
F16	24.3	20.38	29.39
F17	24.1	20.1	28.82
F18	25.59	23.82	32.14
F19	25.23	23.99	32.83
F20	35.64	32.18	42.12
F21	26.29	24.91	33.51
F22	31.4	27.13	36.6
F23	27.12	25.29	35.2
F24	27.4	24.7	34.43

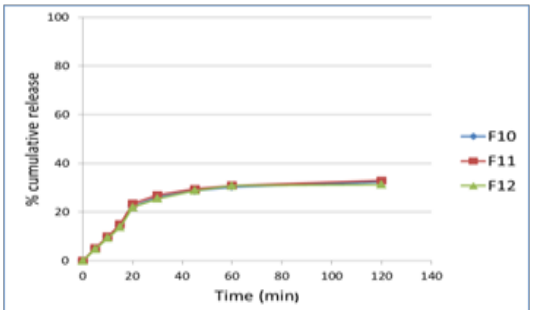
(A)

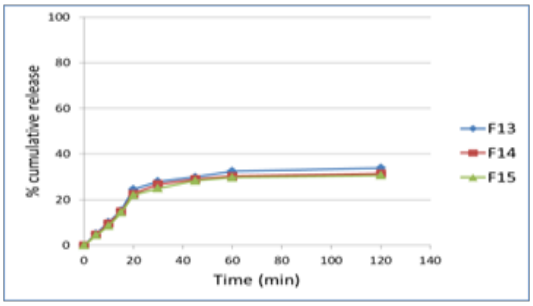


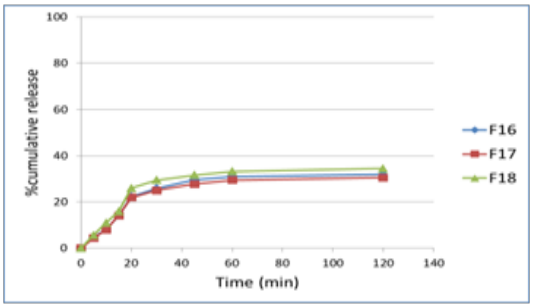


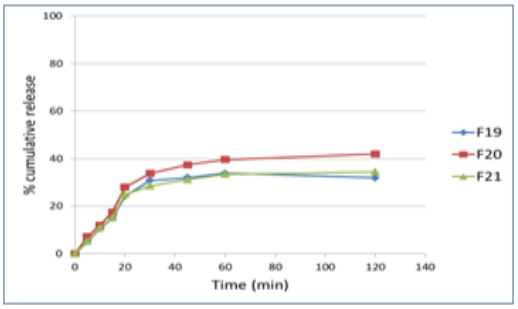












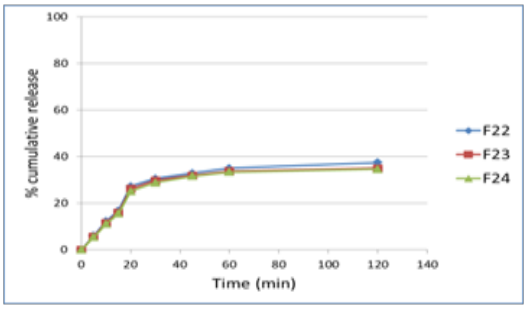


Figure 4(A): Dissolution results of pure apigenin and prepared apigenin formulas (F1-F24) at 0.1 N HCl pH 1.2.

(B)

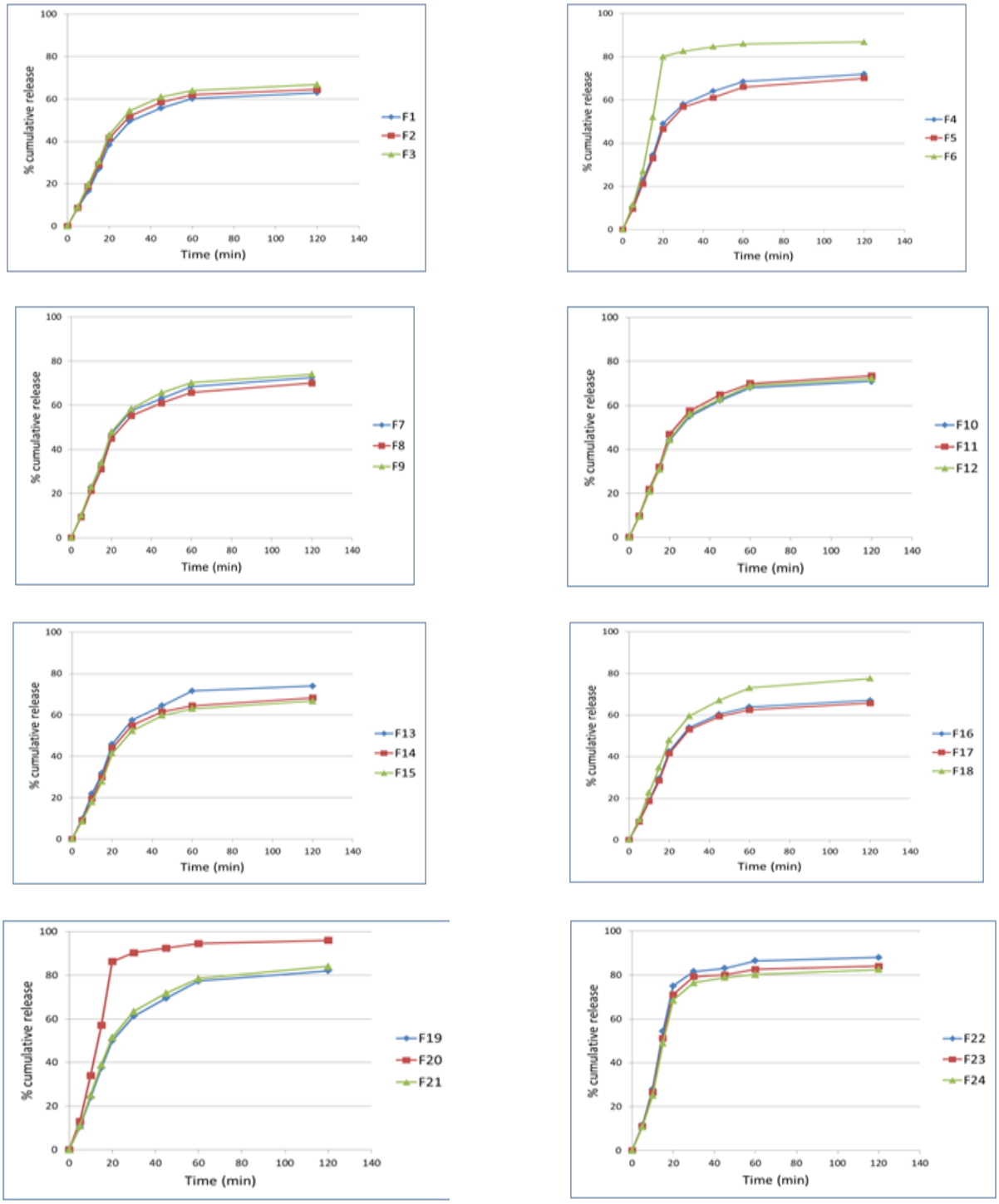


Figure 4(B): Dissolution results of pure apigenin and prepared apigenin formulas (F1-F24) at phosphate buffer pH 6.8.

media. Since it can be adsorbed on the surface of the prepared crystals, it lowers the surface tension, increasing the wettability of drug particles and inhibiting Ostwald ripening better than surfactant stabilizer (tween 80).[40] The results showed that the release of the drug from F7 (containing 2% tween 80) was significantly ($p < 0.05$) higher than the release of the drug from F1 (containing 1% tween 80, keeping the same sonication condition) in both pH 1.2 and pH 6.8, since increasing the amount of surfactant can enhance drug wettability and affecting drug solubility and dissolution.[21]

Formulas F2, F4, and F6 (containing 1% tween 80, and 6 minutes sonication time) were exposed to ultrasonication with

different powers 200, 400, and 600 w, respectively, and the results showed that there was a slight nonsignificant increase in drug release upon increasing sonication power from 200 w (F2) to 400 w (F4) while using 600 w (F6) showed significant ($p < 0.05$) high increase in drug release in both pH 1.2 and pH 6.8. This can be explained that increasing the sonication power led to more uniform distribution of the prepared crystals with small particle size associated with higher saturated solubility in 0.1 N HCl and phosphate buffer pH 6.8 (as well as in water).

While for poloxamer 188, the results showed that F22 and F24 (containing 2% poloxamer 188 and 6 minutes sonication time) prepared using 400 and 600 w sonication power led to a slight nonsignificant decrease in drug release while upon using 200 was sonication power (F20) there was significant ($p < 0.05$) increase in drug release accompanied with small particle size and higher saturated solubility in pH 1.2 and pH 6.8 (in addition to water). This can be explained by that low sonication power (200 w, F20) did not affect the polymer integrity and property. The polymer can be adsorbed and surrounded by the prepared nanocrystals better than higher sonication power energy produced and affecting the polymer.[41] Therefore, for polymeric stabilizers, low sonication power was enough to give the best results, while surfactant stabilizers required higher energy.

The sonication time also had effect on drug dissolution rate where F6 (1% tween 80, 6 minutes sonication time) showed significantly ($p < 0.05$) high drug release (80% within 20 minutes and 88% within 120 min in pH 6.8) in comparison to F5 (1% tween 80, 3 min sonication time), which gave 48% drug release within 20 minutes and 70% within 120 minutes in pH 6.8, knowing that both formulas prepared using 600 w sonication power. These results indicated that applying longer sonication time (6 minutes) resulted in more crystals distribution and prevented aggregation and caused further reduction in particle size (where the particle size of F6 crystals was 89 nm while F5 crystals had 125.2 nm particle size) that led to improving drug solubilization and dissolution. The same results were observed with the effect of the duration of ultrasonication for the preparation of efavirenz nanosuspension using the precipitation-ultrasonication method.[21] Same results were observed with polymeric stabilizer where F19 sonicated for 3 minutes, gave 50% drug release within 20 minutes and 82% within 120 minutes in pH 6.8. While F20 sonicated for 6 minutes gave 88 and 98% drug release within 20 and 120 minutes respectively in pH 6.8.

The overall results revealed that particle size, drug solubility, and dissolution profile were highly affected by ultrasonication conditions, and apigenin nanocrystals stabilized by a surfactant (1% tween 80) required high sonication power (600 w) and 6 min sonication time to get the best nanocrystals (F6) with small particle size, high solubility (in water, pH 1.2 and pH 6.8) and high drug release. While apigenin nanocrystals stabilized by polymeric stabilizer (2% poloxamer 188) required less sonication power (200 w) and 6 minutes sonication time to get best nanocrystals (F20) with small particle size (88.7 nm), higher solubility in water and other media and higher drug release (98%) in phosphate buffer pH 6.8 within 120 minutes). The applied ultrasonication method was efficient in getting apigenin nanocrystals using surfactant and polymeric stabilizers, so both F6 and F20 formulas can be used to prepare apigenin solid dosage form.

CONCLUSION:

This work proved the successful application of sonocrystallization using a probe ultrasonicator with optimized conditions to prepare apigenin nanocrystals by using both surfactant and polymeric stabilizers. The optimum formulas showed stable high crystallinity with particle size <100 nm, which exhibited a much more rapid dissolution rate and rapid initial burst effect than the pure supplied drug powder. The high improvement in dissolution rate and solubility of the nanocrystals might be the key factor responsible for oral absorption and bioavailability enhancement as well as the fast onset of action for such BCS II compound apigenin.

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