DOI: http://dx.doi.org/10.31351/vol27iss1pp39-52

Preparation and Characterization of Domperidone Nanoparticles for Dissolution Improvement

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Abstract

This study was carried out to prepare and characterize domperidone nanoparticles to enhance solubility and the release rate. Domperidone is practically insoluble in water and has low erratic bioavailability range from 13%-17%. The domperidone nanoparticles were prepared by solvent/antisolvent precipitation method at different polymer:drug ratios of 1:1 and 2:1 using different polymers and grades of poly vinyl pyrolidone, hydroxy propyl methyl cellulose and sodium carboxymethyl cellulose as stabilizers. The effect of polymer type, ratio of polymer:drug, solvent:antisolvent ratio, stirring rate and stirring time on the particle size, were investigated and found to have a significant ($p \leq 0.05$) effect on particle size. The best formula was obtained with lowest average particle size of 84.05nm, which composed from 2:1 of PVP-K15:drug and solvent/antisolvent volume ratio of 1:10. This formula was freeze dried and studied for compatibility by FTIR and DSC, surface morphology by Field Emission Scanning Electron Microscope (FESEM) and crystalline state by XRPD. Then domperidone nanoparticles were formulated into a simple capsule dosage form in order to study of the *in vitro* release of drug from nanoparticles in comparison pure drug and mixture of polymer:drug ratios of 2:1. The release of domperidone from best formula was highly improved with a significant ($p \leq 0.05$) increase. it can conclude that nanoparticles showed better *in vitro* dissolution profiles in comparison with pure drug

Keywords: Domperidone, Solvent/antisolvent precipitation, Polymers, Polyvinyl pyrrolidone, Nanoparticles, Dissolution rate, Release.

تحضير وتوصيف الجسيمات النانوية للدومبيريدون لتحسين التذوب

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الخلاصة

أجريت هذه الدراسة لتحضير وتوصيف الجسيمات النانوية للدومبيريدون لزيادة ذوبانيته وزيادة سرعة إطلاق الدواء. الدومبريدون هو معاكس للدوبامين ويستخدم مضاد للغثيان والقيء، الدومبريدون غير قابل للذوبان في الماء ويعاني نقص التوافر الحيوي من ١٣- ١٧٪. تم تحضير الجسيمات النانوية للدومبيريدون بواسطة طريقة ترسيب المذيب / مضاد المذيب باستخدام نسب مختلفه من البوليمر: نسب ١:٢ و ١:١ من البوليمر لدواء وباستخدام بوليميرات(HPMC-E50, HPMC-E15, CMC-30, PVP-K30, PVP-K15) كمثبتات.
تم دراسة تاثيرنوع البوليمر و تركيزه ونسبة المذيب الى مضاد المذيب وسرعة ووقت التحريك على حجم الجسيمات النانويه من خلال قياس حجم الجسيمات والمساحة السطحيه لها ومعامل التوزيع للجسيمات . F8 والتي تحتوي على نسبة بوليمرلدواء تساوي ١:٢ ونسبة حجم مذيب لمضاد مذيب تساوي ١:١٠ فقد تم اختيارها كأفضل الصيغ مع متوسط حجم للجسيمات ٨٤,٠٥ نانومتر و تم تجفيفها والتحقيق فيها لدراسات التوافق بين الدواء والبوليمرات من خلال(FTIR) ، شكل الجزيئات باستخدام (FESEM)، الحاله البلورية للجسيمات النانويه باستخدام-X RAY، والاستقرار لها. ثم تمت صياغة جزيئات دومبيريدون النانويه في كبسولة.اضهرت النتائج إلى ان حجم الجسيمات النانوية يتأثر حسب نوع وتركيز البوليمر، ونسبة الدواء الى البوليمر، نسبة المذيب: نسبة المضادة للمذيبات، سرعة ووقت تحريك الناتج. وجد ان تحرير الدواء من الجسيمات النانوية كان اسرع وبنسبه عاليه من الدواء الخام ومزيجها مع البوليمرات .

الكلمات المفتاحية: الدومبيريدون ، الترسيب بالمذيب ومضاد المذيب ، البوليمر ، بولي فينايل بايروليدون ، الجسيمات النانوية ، معدل الاذابة ، الاطلاق.

Introduction

The solubility, dissolution rate and bioavailability of drugs are important factors for achieving in vivo effectiveness. The bioavailability of orally administered medications depends on their capability to be absorbed via gastrointestinal tract. It appears that enhancement

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Received: 5/12/ 2017
Accepted: 3/2/2018

of the solubility of poorly water soluble APIs can translate to an increase in their bioavailability. Beside the coming of new technologies in drug detection, combinatorial chemistry, and computer helped drug design, there was growing in the progress of new chemical entities with perfect therapeutic potential. However due to of the complicated chemistry, nearly 40% of the drug applicants in the development pipeline and about 60% of new APIs produced by chemical synthesis are introduced with poor aqueous solubility causing in low and variable bioavailability [1,2]. At the present time nanotechnology offers various methods in the area of dissolution enhancement of low aqueous soluble drugs. nanoparticles formulation technology has achieved a considerable attention by the formulation scientists. Pharmaceutical nanoparticles are defined as solid, submicron-sized drug carrier that may or may not be biodegradable. The advantages of nanoparticles include lower drug toxicity, reduce the dose needed, improved bioavailability, increase drug targeting ability, decrease drug resistance ,increase patient compliance and reduced cost of treatment[3,4].The aim of this research to formulate domperidone as nanoparticles in capsule dosage form using precipitation method of solvent/antisolvent to improve dissolution rate. Domperidone is antiemetic drug has chemical structure is 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl) propyl] -4piperidinyl1] -1,3 dihydro -2H –benzimidazole -2-one) [5], domperidone is practically insoluble in water and slightly soluble in ethanol and methanol[6], and have low oral bioavailability (13-17%) is thought to be due to hepatic first-pass and intestinal metabolism and poor aqueous solubility [7].

Materials and method

Materials

Domperidone (Science Lab–INDIA), hydroxy propyl methyl cellulose of HPMC-E50LV and HPMC-E15LV (Gromax Chemicals–USA), polyvinyl pyrrolidone of PVP-K15, PVP-K30 (ALPHA Chemika-INDIA) Na-CMC-30 (Calbiochem–USA), DMF (Sinopharm Chemical Reagent–China), disodium hydrogen orthophosphate, sodium Chloride, and Hydrochloric acid 37% (BDH Laboratory-England), potassium dihydrogen orthophosphate (Fine Chem–India) and Lactose (Carlo Erba Reagent-Italy) were used as received in this study.

Methods

Preparation of domperidone nanoparticles

The domperidone nanoparticles were prepared using solvent/antisolvent of precipitation technique [8]. A certain amount of pure domperidone was completely dissolved in dimethyl formamide (DMF). The drug solution with specific concentration was injected at 1mL/min using ordinary syringe into water solution containing specific concentration of stabilizer of each (PVP-K15, PVP-K30, HPMC-E15, HPMC-E50, andCMC-30) with continuous stirring. Precipitation of nanoparticles in form of colloidal solution occurred gradually upon mixing. The nanoparticles were then lyophilized to obtain the nanoparticles powder. The composition and variable conditions of preparation of different formulas are listed in table (1).

Table 1. Composition of domperidone nanoparticles formulas

Formula	Polymer	polymer: drug ratio	Solvent: anti solvent ratio
F1	HPMC-E50	1:1	1:10
F2	HPMC-E15	1:1	1:10
F3	PVP-K15	1:1	1:10
F4	PVP-K30	1:1	1:10
F5	CMC-30	1:1	1:10
F6	HPMC-E50	2:1	1:10
F7	HPMC-E15	2:1	1:10
F8	PVP-K15	2:1	1:10
F9	PVP-K30	2:1	1:10
F10	CMC-30	2:1	1:10
F11	HPMC-E50	2:1	0.5:10
F12	HPMC-E15	2:1	0.5:10
F13	PVP-K15	2:1	0.5:10
F14	PVP-K30	2:1	0.5:10
F15	CMC-30	2:1	0.5:10
F16	HPMC-E50	2:1	2:10
F17	HPMC-E15	2:1	2:10
F18	PVP-K15	2:1	2:10
F19	PVP-K30	2:1	2:10
F20	CMC-30	2:1	2:10

Particle size and poly dispersity index measurement (PDI)

The ABT-9000 dynamic light scattering nano laser (Angstrom-USA particle size analyzer was used to measure the average particle size and poly dispersity index (PDI), as measures for the

width of the size distribution, and the specific surface area (SSA) for all prepared domperidone nanoparticles formulas.

Study of variables affecting on size of domperidone nanoparticles

Effect of type and concentration of stabilizer

Different stabilizer at two ratios of polymer to drug concentration of 1:1 and 2:1 were used in the preparation of domperidone nanoparticles. Formulas F1-F10, were prepared and used to illustrate the effect of polymer type and concentration on the size of domperidone nanoparticles.

Effect of time of stirring

The effect of time of stirring of 5 and 30min from finished addition of drug solution on size of formed nanoprticles was studied using polymers of PVP-K15, HPMC-E50, and CMC-30 at two ratios polymer to drug concentration of 1:1and 2:1.

Effect of rate of stirring

The effect of stirring rate was studied using 500, 700 and 1100rpm; this effect was examined in all formulas.

Effect of solvent /anti solvent ratio

The effect of the ratio of volume of solvent:antisolvent on the size of the formed nanoparticles was studied in three ratios of 0.5:10, 1:10 and 2:10 in all polymers at polymer**:**drug ratio of 2:1.

Characterization of lyophilized domperidone nanoparticles

Determination of drug content and loading efficiency.

Assay was carried out by taking 6mg powder of lyophilized nanoparticles and dissolved in 20mL DMF in dry volumetric flask and sonicated for 20min and then volume was completed to 60mL with same solvent and filtered on 0.45µm filter. The absorbance of filtrate was then determined using UV-visible spectrophotometer and the drug content was calculated accordingly. The loading efficiency of nanoparticles was determined from the theoretical and actual drug contents [9]. This experiment was done in triplicate.

$$\%\textbf{Loading Efficiency (LE)} = \frac{\textbf{Actual drug content}}{\textbf{Theoretical drug content}} \times 100$$

Determination of saturated solubility

Solubility of pure domperidone and domperidone nanoparticles was determined in each medium of 0.1N HCl of pH 1.2, phosphate buffer solution of pH 6.8, and distilled water using the shacking-flask method [10]. Plus, to ensure increase in saturated solubility of domperidone nanoparticles is due to reduction particle size, physical mixture of polymer of PVP-K15 and pure domperidone in ratio of 2:1 was used and studied. An excess amount of each powder was added in test tube containing 10mL medium, the tubes were sealed well and covered with aluminum foil then incubated in a shacking water bath at 37º C for 72h. Sample of solution was drawn, filtered and the concentration of domperidone was determined spectrophometrically at the measured λmax using corresponding calibration curve equation in each media. The experiment was performed in triplicate and the average value was calculated.

Field emission scanning electron microscope

Field emission scanning electron microscope (FESEM) (Zeiss-Germany) of pure domperidone powder, PVP-K15 powder were confirmed by direct dusting of powder on carbon tape, while FESEM for liquid formula (F8), sample was done by the droplet evaporation technique. A droplet of liquid was settled on carbon tape and dried at room temperature. Images were taken by secondary electrons using 1kV and different magnification powers.

X-ray powder diffraction (*XRPD)*

X-ray powder diffraction was used to study crystalline structure of drug, polymer and the prepared nanoparticles. The X-ray diffraction have the operating voltage and current were 60 (kV) and 80 (mA) respectively.

Fourier Transform Infrared Spectroscopy(FTIR)

FTIR spectra were obtained using FTIR spectroscope. Samples that studied were pure domperidone, PVP-K15, physical mixture of PVP-K15 and pure domperidone (at ratio of 2:1), and selected nanoparticles formula. Sample was milled, mixed with potassium bromide and pressed in a form of disc of 13mm in diameter. The disc was analyzed by FTIR spectroscopy at 4000-400cm^{-1}.

Differential scanning calorimetry (DSC)

DSC (-60, Shimadzu-Japan) was used to determine the crystalline state of drug particularly when converted to nanoparticles and thermal characteristics of samples were determined by an automatic thermal analyzer system. Exactly weighed samples of 5mg were placed in non-hermetically aluminum pan and heated at the rate of 20º C/min against an empty aluminum pan as a reference covering a temperature range of 50 to 300º C [11].

In vitro dissolution study of domperidone nanoparticles from capsule dosage form

Capsules prepared by simple manual filling of hard gelatin capsule with fixed quantity domperidone and lactose as filler. Then dissolution study for capsule containing domperidone nanoparticles were performed in a paddle type dissolution apparatus according to BP 2009 monograph [12]. Three types of capsule were prepared, containing lyophilized domperidone nanoparticles equivalent to 10mg of domperidone, 10mg of pure domperidone and physical mixture of polymer:pure domperidone using PVP-K15 in ratio of 2:1 equivalent to 10mg of domperidone. Each capsule was dispersed in 900 ml of 0.1NHCl of pH1.2 with aid of special sinker of butter fly to prevent floating at 37±0.5° C and rotated paddle 50rpm. A 5mL sample was draw at specific time intervals from 5-120min for analysis and replaced with same volume of fresh media to maintain sink condition at 37±0.5° C. Then sample was analyzed using UV-spectrophotometer at wave length 284nm. Afterward the accumulative percentage of release was calculated and draw against time. The experiment was performed in triplicate and the average value were calculated.

Statistical analysis

The results of the experiments are given as a mean samples ± standard deviation (SD) and were analyzed for differences using one-way analysis of variance (ANOVA) at $p \leq 0.05$ and the dissolution profiles data were fitted to f1 and f2 difference and similarity factor to determine the effect of nanoparticles formulation on the dissolution patterns of domperidone from the prepared dosage form [13].

Results and Discussion

Evaluations of prepared domperidone nanoparticle

Particle size and polydispersity index analysis

The particle size of all the prepared formulas were characterized and found within a range of nanometer sizes as shown in table (2). The most essential parameters for the produced suspended nanoparticles were the mean particle size and poly dispersity index that in turn determine and control the physicochemical properties like saturated solubility and dissolution profile [14]. ABT-9000 nano laser particle size analyzer is a particle size analyzer working on basis of dynamic light scattering theory (DLS), was used to measure the size of domperidone nanoparticles and PDI "The common range of PDI values are 0-0.05 (monodisperse standard), 0.05-0.08 (nearly monodisperse), 0.08-0.7 (mid-range polydispersity), and >0.7 (very polydisperse)" [15]. All formulas were showed monodisperse PDI except, F10 which showed a nearly monodisperse PDI while F7 and F9, showed medium range of PDI. The specific surface area (SSA) of the particles is the summation of the areas of the exposed surfaces of the particles per unit mass. Result of this study showed a reduction in particle size and consequently high surface area of domperidone nanoparticles when compare with pure drug [16]. Particle size of formulas F1-F5 of different polymer used at same polymer:drug ratio of 1:1 gave different particle size range of 334-667.5nm, this indicates that, polymers have different affinity to domperidone particle, even at same ratio. The lowest particle size was achieved with PVP-K15 polymer in F3, the measured particle size of formula F6-F10 at polymer:drug ratio of 2:1 was significantly ($p \leq 0.05$) decreased that are in range from 84.05-265.5nm, the smallest particle size was attained with PVP-K15 polymer (F8) at this ratio. The smallest size obtained in F8 as shown in figure (1) this might be due to high affinity of PVP-K15 to domperidone and low viscosity grade than other polymers of HPMC and CMC. Also that, it is found that the increase in the polymer concentration lead to a decrease in the prepared particle size of domperidone nanoparticles, as result of complete wrapping or covering and stabilize of drug particle in small size. Therefore, F8 was selected and subjected for further studies. The polymers used in this study were anionic and cationic, which might be play an important role in stabilizing of the system by steric effect, this is could be achieved by adsorbing of polymer onto the surface of particle through an anchor part that is strongly interacts with the dispersed particles, while the other solvated tail part extends into the bulk medium[17]. The effect of stirring time on domperidone nanoparticles as shown in figure (2), it is found that the increase in the time of stirring lead to increase size of domperidone nanoparticles. This finding agrees with that obtained by Chopra [18]. The higher stirring rate induces rapid nucleation toward smaller drug particles [19]. The effect of stirring rate on size of the prepared domperidone nanoparticles and was found that, the increase in stirring rate led to a significant ($p \leq 0.05$) decrease in the size of the prepared domperidone nanoparticles as shown in figure (3). The effect of ratio of volume of solution containing drug (solvent) to the solution containing polymer (antisolvent) on the size of the prepared domperidone nanoparticles was studied and

results are concise in figure (4), and it was found that the solvent: antisolvent volume ratio of 1:10 gave the significant ($p \leq 0.05$) lowest mean of particle size in comparison to other ratios, that is might be result of optimum molecular distribution of drug and polymer for stabilization. The same result has been observed by Dong and coworkers in the preparation of spironolactone nanoparticles using 1:10 ratio [20].

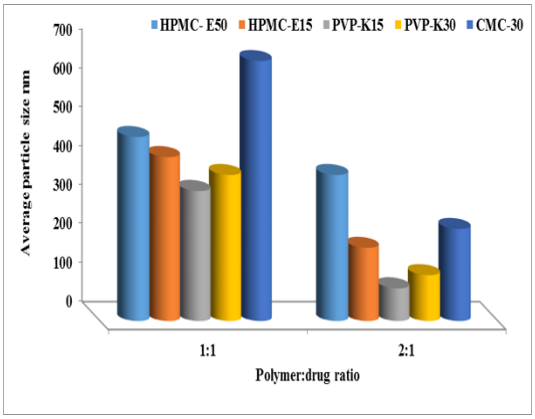

Figure 1. Effect of type and concentration of polymers in on average size (n=3) of domperidone nanoparticles

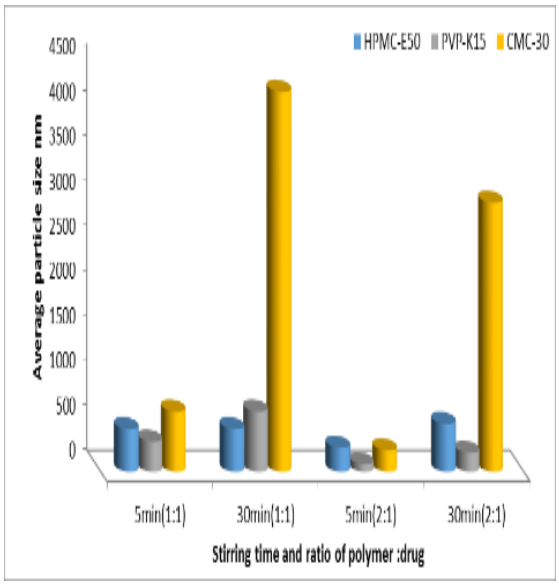

Figure 2. Effect of time of stirring on average size (n=3) of domperidone nanoparticles

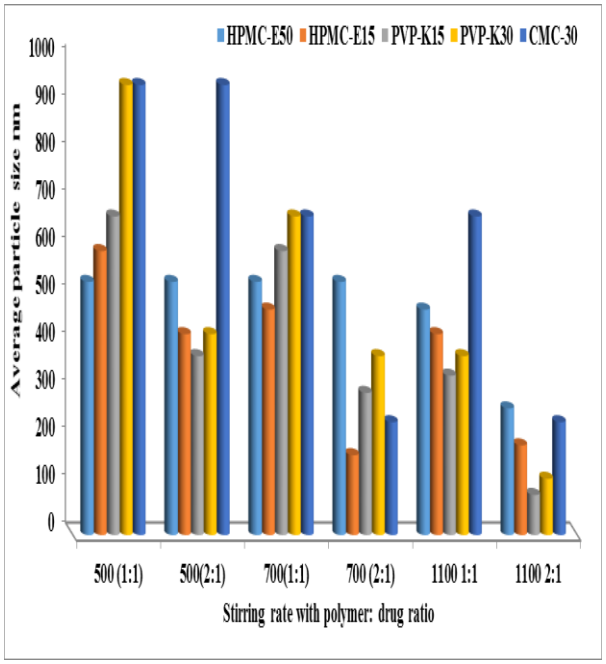

Figure 3. Effect of stirring rate on the average size (n=3) of domperidone nanoparticles

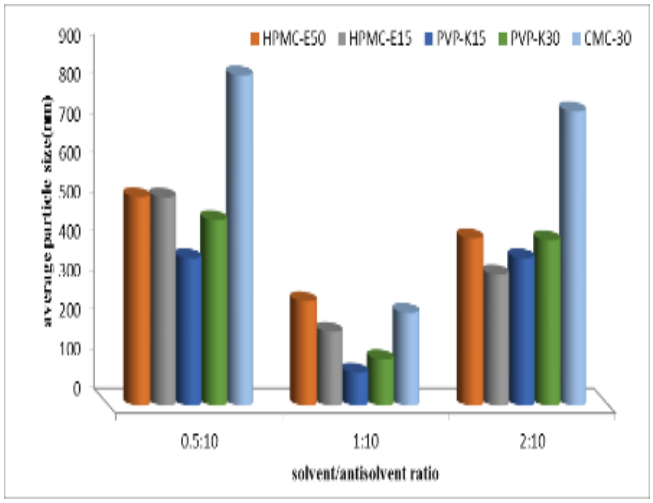

Figure 4. Effect of solvent:anti solvent ratio on the average size (n=3) of domperidone nanoparticles

Table 2. Average of particle size ranges (n=3), averages, poly dispersity index (PDI) and specific surface area (SSA) of prepared domperidone nanoparticles.

Formula	Particle size range	PDI	SSA m^2/g
F1	472.5	0.009	4.5
F2	421	0.009	5.01
F3	334	0.014	6.3
F4	375	0.012	6.01
F5	667.5	0.014	3.32
F6	188	0.05	11.34
F7	167.5	0.15	12.49
F8	84.05	0.011	28.07
F9	118	0.3	17.07
F10	236.5	0.064	9.22
F11	530.5	0.01	4.43
F12	530.5	0.009	4.38
F13	375	0.026	5.82
F14	472.5	0.018	4.8
F15	840.5	0.036	2.62
F16	426	0.009	5.06
F17	334	0.009	6.39
F18	375	0.009	6.2
F19	421	0.021	5.19
F20	749	0.045	2.89

Evaluation of selected formulas of domperidone nanoparticles

Drug content and loading efficiency

The measured drug content result from formula F8 was 1.94±0.01mg. The loading efficiency of F8 was 97.3±0.5%, so that the solvent:antisolvent method was effective in preparing domperidone nanoparticles.

Saturated solubility of pure domperidone and nanoparticles.

General statement of solubility increases when particle size decreases, is due to the increase of the surface area was considered. So on, the saturated solubility of domperidone nanoparticles of F8 was increased significantly ($p \leq 0.05$) in all solvent media of 0.1N HCl of pH 1.2, phosphate buffer of pH 6.8 and water as shown in table (3), and to ensure increase in saturated solubility of domperidone nanoparticles is due to reduction particle size, physical mixture of PVP-K15 and pure domperidone (at ratio of 2:1) was used and studied.

Table 3. The average (±SEM, n=3) of saturated solubility in mg/mL of domperidone nanoparticles and pure domperidone at 37±0.5° C.

	0.1N HCl of pH 1.2	Phosphate buffer of pH 6.8	Water
Pure domperidone	0. 98± 0.0033	0.02± 0.001	0.016± 0.0004
F8	2.769± 0.0003	0.08± 0.001	0.08± 0.002
Physical mixture of PVP-K15:pure domperidone (2:1)	1.4± 0.03	0.03± 0.001	0.035± 0.0005

Field emission scanning electron microscope(FESEM)

FESEM imaging of pure domperidone powder, PVP-K15 powder and dried liquids of F8 showed a reduction in particle size of domperidone particles to nano range. Pure domperidone particles were presented with irregular shape, rough surface and large particles as shown in figure (5). Polyvinyl pyrrolidone PVP-K15 showed spherical shape as in figure 6 (A and B). FESEM of F8 as in figure 7, explained uniform and small particles size and this result might be caused by adsorption or capping effect of the stabilizer on drug surface and reduce size of domperidone particle to nanometer size.

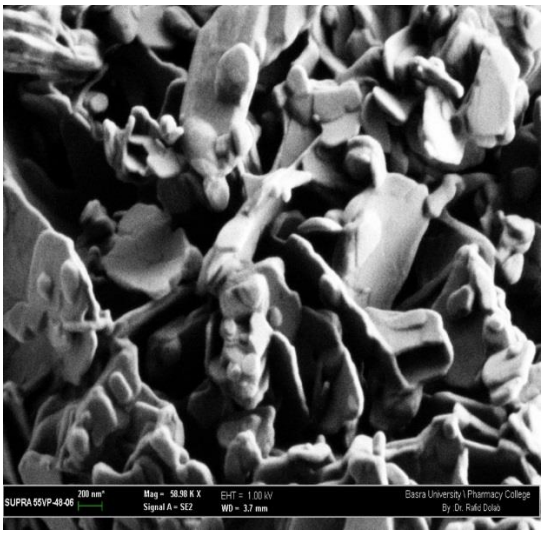

Figure 5. FESEM of pure domperidone withmagnification power of (58.98kX).

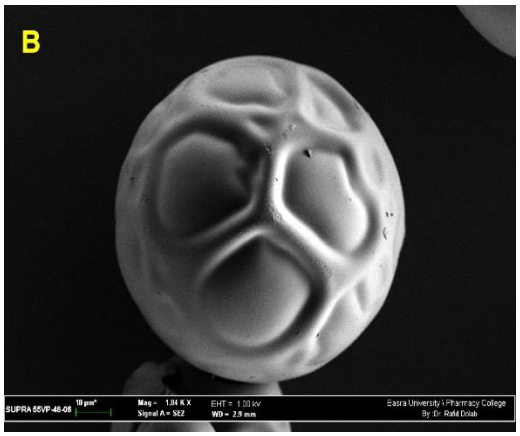

Figure 6. FESEM of PVP-K15 particle with magnification power of A-395X and B-1.84kX.

Figure 7. FESEM of F8 with magnificationpower of 180.35 kX.

X –ray powder diffraction analysis

The obtained spectrum of X-ray diffraction test of pure domperidone showed several strong characteristic peaks at 2θ = 9.28º, 14.94º, 15.58º, 19.80º, 24.80º, and 32º as shown in figure (8), which indicates the crystalline state of pure drug. XRPD of PVP-K15 showed low intense peaks due to the amorphous nature as shown in figure (9). Some domperidone peaks were still appeared with the physical mixture as in figure (10). Domperidone nanoparticles of F8 as shown in figure (11) showed less number and low intense of diffraction peaks in comparison to that of pure domperidone, which indicates that the crystalline structure of domperidone was reduced and part of it converted into amorphous state, similar result was also found in candisartan nanoparticles that prepared by Filipcsei's research group [21].

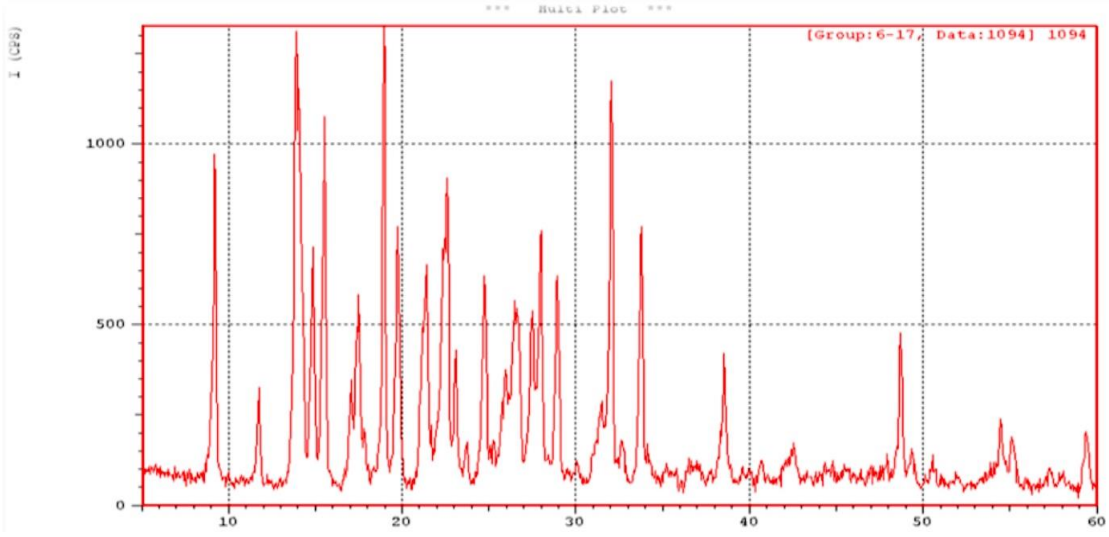

Figure 8. XRPD spectrum of pure domperidone

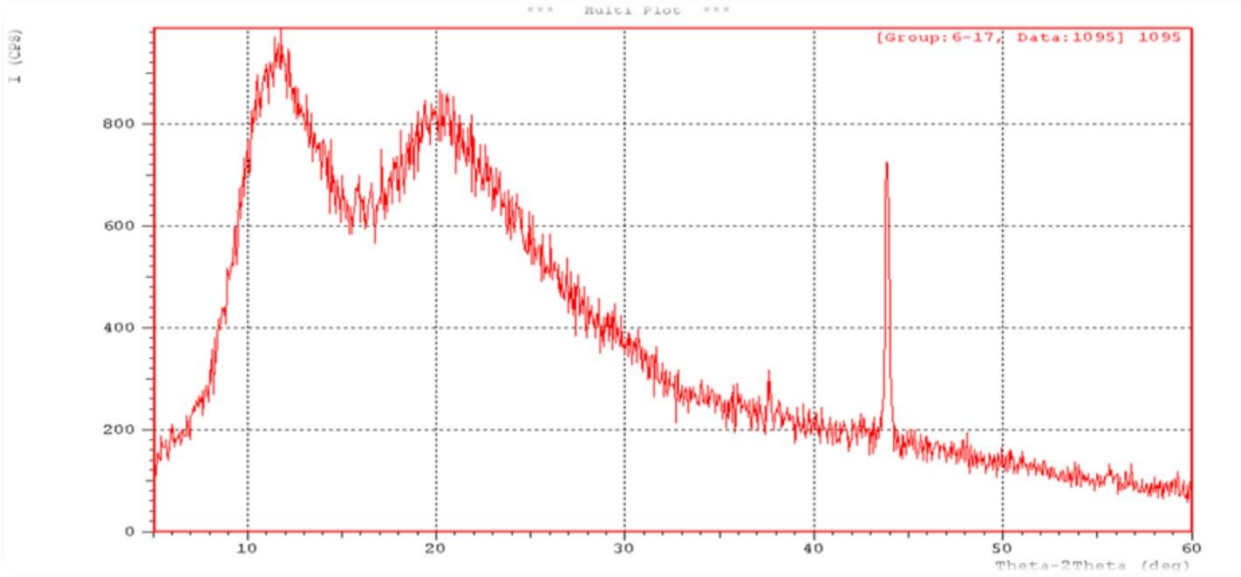

Figure 9. XRPD spectrum of polymer PVP-K15

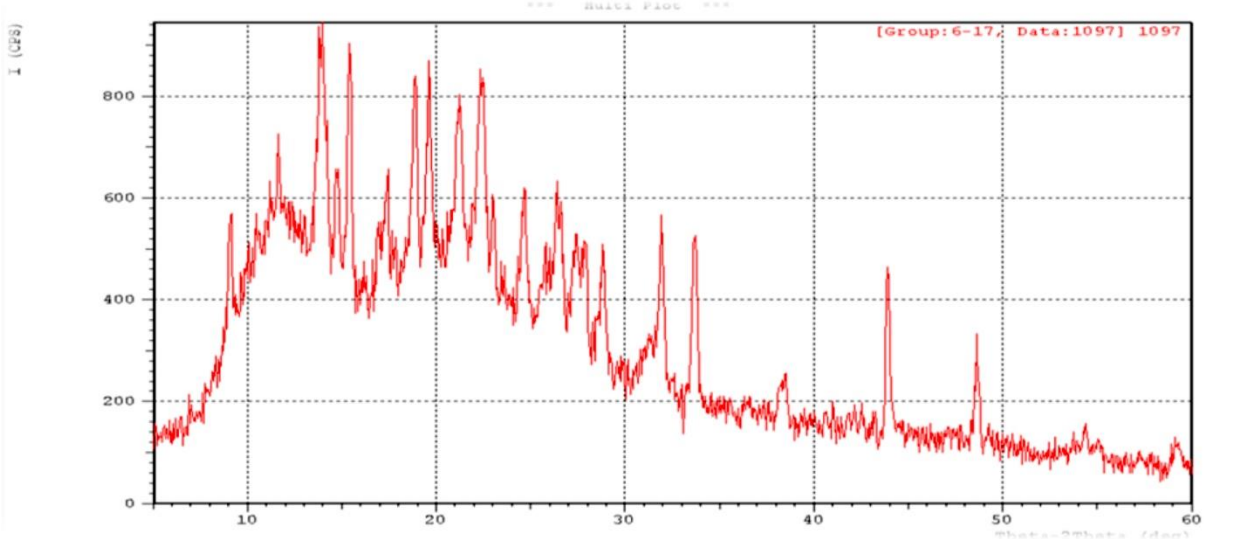

Figure 10. XRPD spectrum of physical mixture of PVP-K15 and pure domperidone (at ratio of 2:1)).

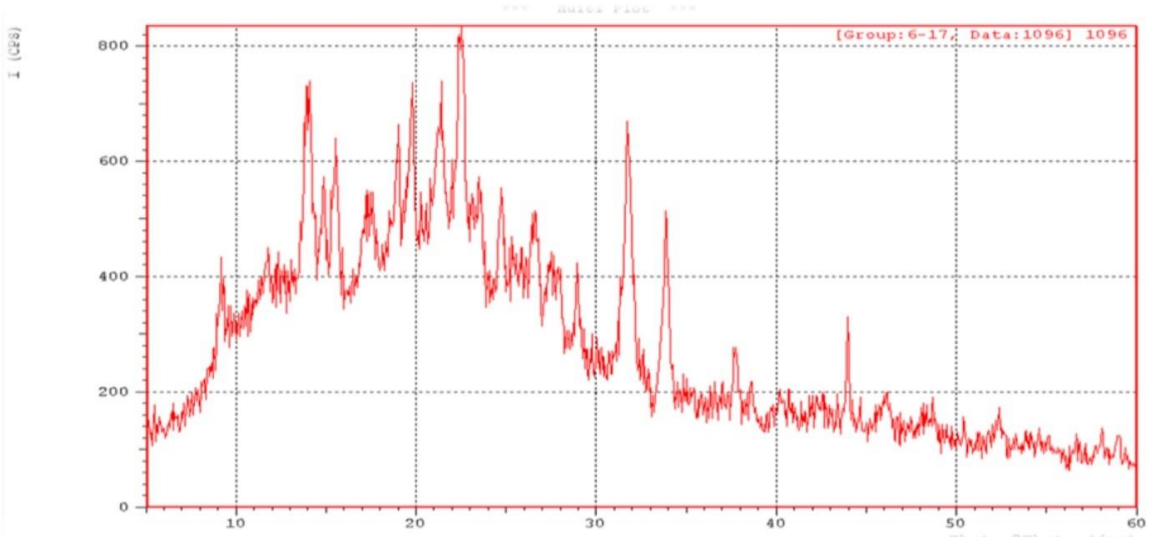

Figure 11. XRPD spectrum of F8

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR was carried out for domperidone and nanoparticles of F8. Domperidone exhibited a strong characteristic absorbance band at 1714 cm^{-1} due to C = O stretching vibrations of amide functional group CONHR, and N− H bending characteristic band at 1693 cm^{-1}, N−H stretching band of secondary amine appeared at 3126 cm^{-1} as a single band, symmetric and asymmetric C−H stretching bands appeared at 2810 and 2941 cm^{-1} respectively. As well as aromatic symmetric and asymmetric C− H stretching bands appeared at 3024 and 3074 cm^{-1} respectively, and the aromatic C = C stretching band appeared at 1624 cm^{-1}[22] as shown in figure (12). The resulted FTIR of PVP-K15, the physical mixtures of PVP-K15:pure domperidone (2:1) and F8 as in figures (13, 14 and 15) showed the presence of main peaks of domperidone which indicates there is no interaction or complexation between drug and polymer during preparation of nanoparticles.

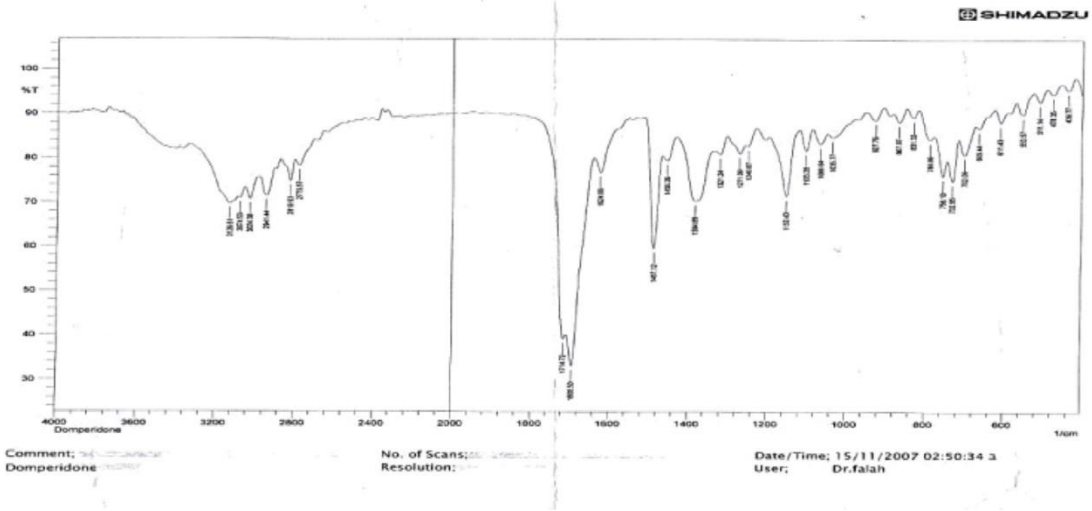

Figure 12. FTIR spectrum of pure domperidone

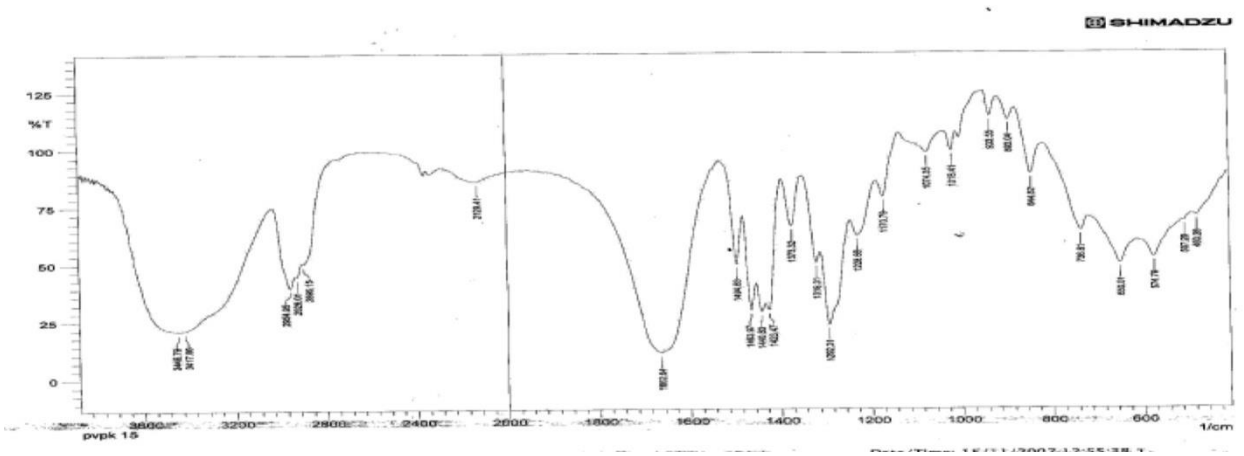

Figure 13. FTIR spectrum of PVP-K15

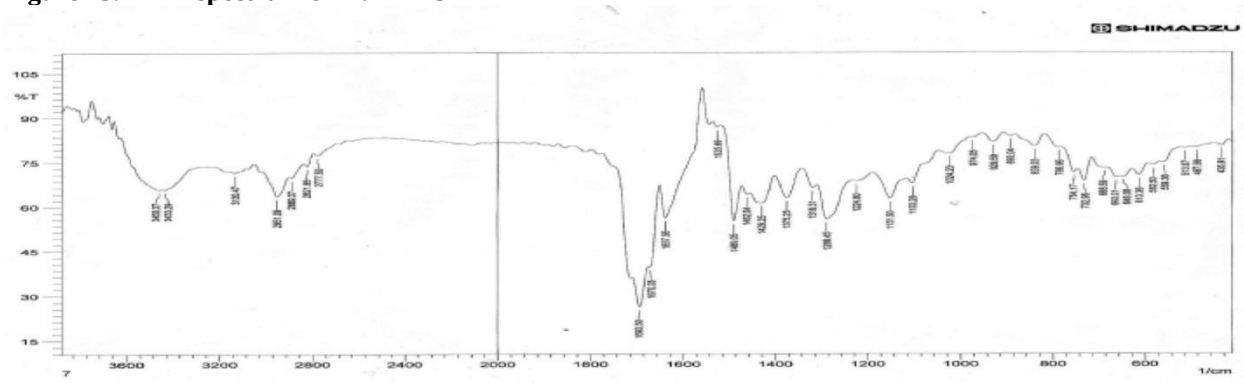

Figure 14. FTIR spectrum of physical mixture of PVP-K15:pure domperidone (2:1)

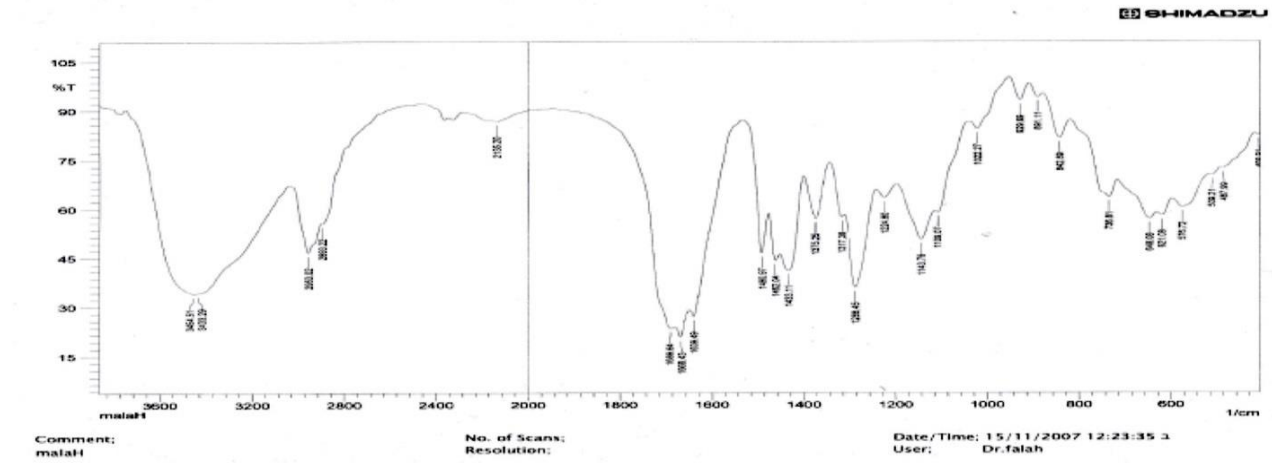

Figure 15 . FTIR spectrum of F8

Differential scanning calorimetry (DSC)

DSC thermogram of domperidone as in figure (16) showed a sharp endothermic peak at 249ºC, this melting point of pure domperidone as referenced [23] and revealed that the drug has crystalline nature with high purity. DSC of PVP-K15 as in figure (17) showed broad peak of water evaporation at 107º C this indicate amorphous nature of this polymer. Physical mixture of PVP-K15:pure domperidone (2:1) showed broad and low intensity peak of domperidone which is nearly at same position within the range of melting point in figure (18). This indicates no chemical reaction or complexation between drug and polymer, DSC of F8 in figure (19) showed remarkable reduction in peak intensity in

comparison with pure domperidone, that indicates a reduction of crystalline state of domperidone and conversion of part of it to amorphous state, this result with that obtained X-ray diffraction analysis of formula (F8) agrees with Younis finding [24].

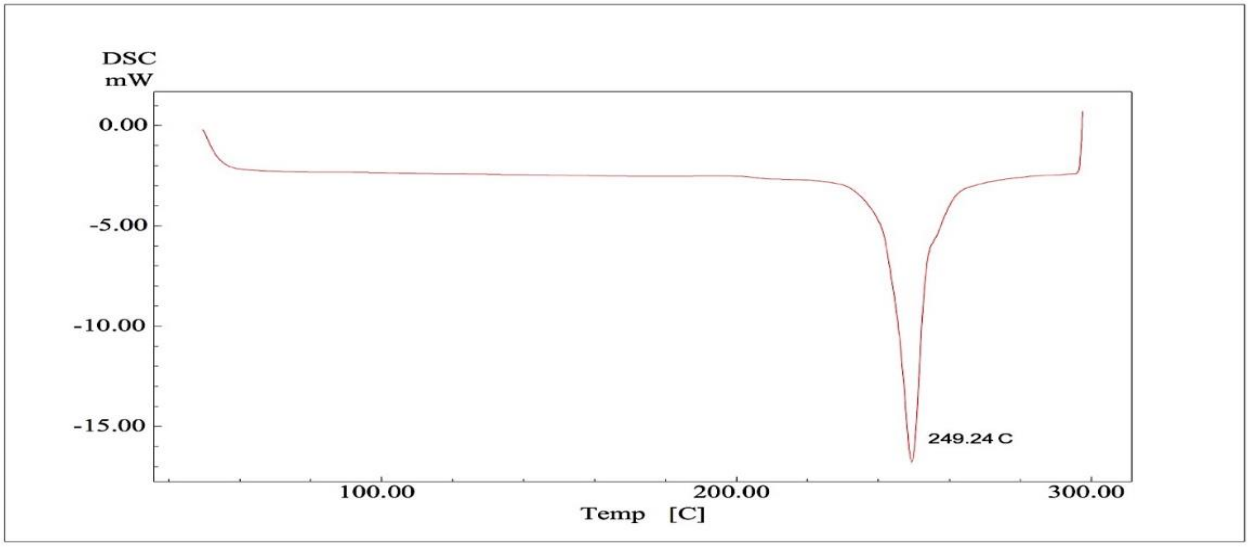

Figure 16. DSC thermogram of pure domperidone.

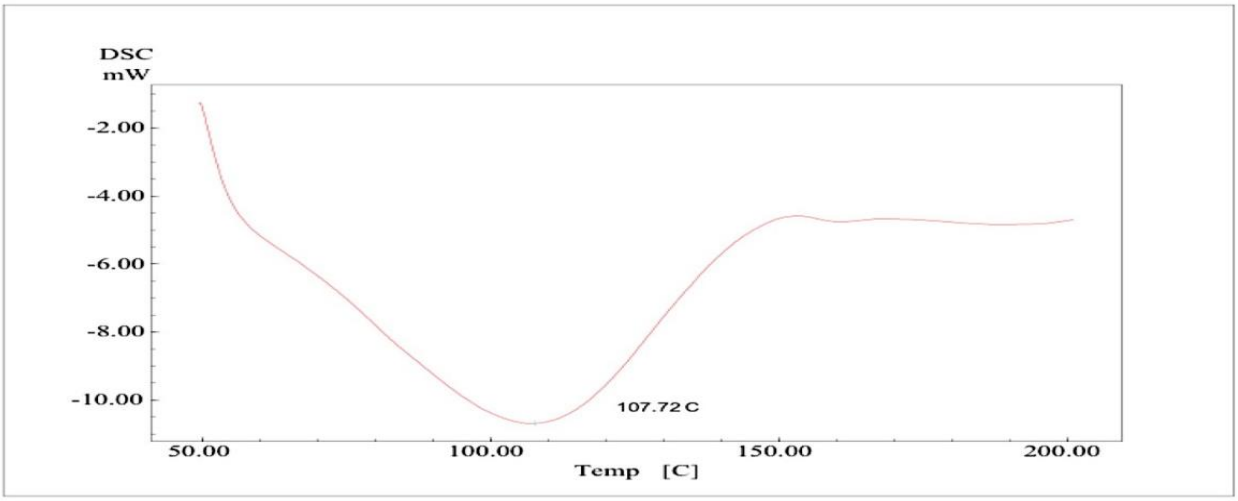

Figure 17. DSC thermogram of PVP-K15

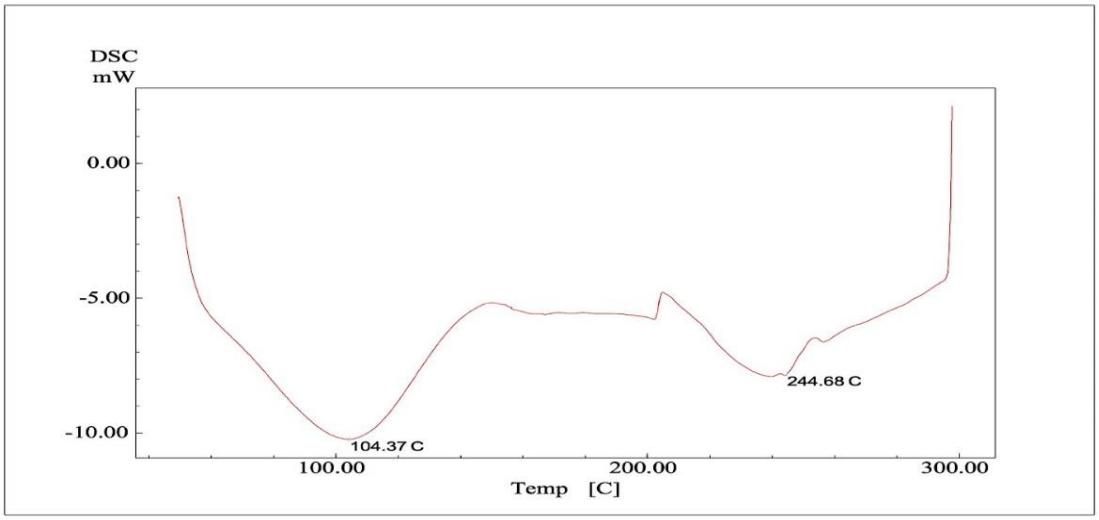

Figure 18. DSC thermogram of physical mixture of PVP-K15:pure domperidone (2:1)

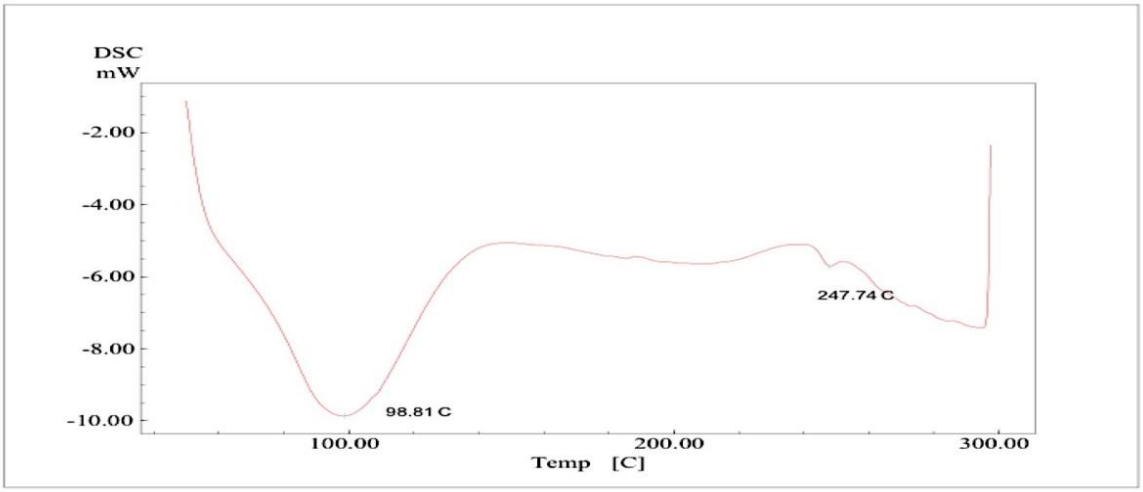

Figure 19. DSC thermogram of domperidone nanoparticles (F8)

In-vitro dissolution study of domperidone nanoparticles form capsule dosage form

The percentage of drug release at15min and the time required for released 100% of drug were considered for the comparison of the dissolution results between pure and nanoparticles of domperidone. The release of domperidone from F8 was faster in comparison with pure domperidone, and reached to100% of accumulative % of drug release at 15min., whereas the pure domperidone reached to 58% and 90% at 15min at the end of the study, respectively, as shown in figure (20). In addition, physical mixture of PVP-K15:pure domperidone (2:1) reached 60% and 90.9% at15 and 75min, respectively. These results indicate that, the increase in percentage of release of domperidone from nanoparticles was due to the increase in the surface area of these particles [25] and to the reduction in crystalline state of domperidone. These findings support that, the use of precipitation method was efficient and effective in preparing nanoparticles.

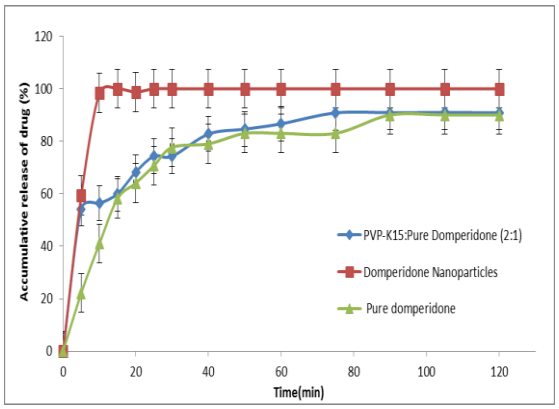

Figure 20. The *In-vitro* release of the pure domperidone, F8, physical mixture of PVP-K15:pure domperidone (2:1) in 0.1N HCl of pH 1.2 at 50rpm and 37° C (±SEM, n=3).

The comparison between the dissolution profiles was done using difference and similarity test of f1 and f2 respectively. The data of accumulative percentages of release of drug from selected formula was fitted using a Microsoft Excel program to calculate f1 and f2 and the obtained results as illustrated in table (4). It was noticed that the dissolution profiles of domperidone from nanoparticles was not similar in comparison with the pure drug as a reference, F8were not similar as f1 values was higher than 15, whereas their f2 values were lower than 50[26]. From these results, it can conclude that nanoparticles showed better in vitro dissolution profiles in comparison with pure drug.

Table 4. Difference and similarity test (f1 and f2) of selected formula and physical mixture of PVP-K15:pure domperidone (2:1) compared versus pure domperidone

	f1	f2
F8	37.6	29.46
Physical mixture of PVP-K15:pure domperidone (2:1)	9.02	50.5

Conclusions

Depending on obtained results, one can concludes that, PVP-K15 gave best formula (F8), the variables of type, concentration of stabilizer, volume ratio of solvent: anti solvent, time and rate of stirring showed considerable effect on decreasing of the size of domperidone nanoparticles. on increase of polymer: drug ratio, the size of produced domperidone nanoparticles was decreased, and 1:10 volume ratio of solvent: antisolvent was best than the other ratios. Analysis by DSC, FESEM and XRPD of nanoparticles of F8 indicated a reduction in crystalline state of domperidone nanoparticles. The dissolution of domperidone was highly improved against pure drug, which give 100% accumulative release at 15min.

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