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Preparation and Characterization of Nimesulide Nanoparticles For Dissolution Improvement

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Abstract:

Nimesulide is one of the types of non-steroidal anti-inflammatory drugs, widely used as analgesic and antipyretic. It is classified as class II drugs according to BCS guidance because of low solubility in water that leads to decrease in dissolution rate. So, the objective of this study was to decrease particle size, increase solubility and dissolution rate of nimesulide by preparation of nimesulide nanoparticles using solvent/antisolvent precipitation method by addition of organic solution of drug onto the solution of stabilizer. The size of nimesulide nanoparticles were studied and considered by particle size analyzer, drug content and loading efficiency. The freeze-dried nanoparticles were characterized by field emission electron microscope, X-Ray powder diffraction, differential scanning calorimetry and saturated solubility measurement. Tablet was manufactured by direct compression. The tablets were evaluated for drug release to measure the effect of nanoparticles on the dissolution improvement of drug.

Key words: Nimsulide; solvent/antisolvent; nanoparticles: dissolution rate; release.

تحضير وتوصيف الجسيمات النانوية للنميسولايد لتحسين التذويب

الخلاصة:

النميسولايد هو أحد انواع ادوية مضادات الالتهابات غير الاستيرويدية ويستعمل بصورة واسعة كمهدئ للالم وخافض للحرارة. هو يتبع التصنيف الثاني للأدوية تبعا لنظام التصنيف للصيدلانيات البيولوجية بسبب قلة ذوبانيته في الماء التي تؤدي الى قلة معدل الاذابة. الهدف من الدراسة كان لتحضير الجسيمات النانوية من النميسولايد بتطبيق طريقة المذيب\مضاد المذيب. الجزيئات النانوية حضرت بإذابة كمية محددة من الدواء بالأسيتون. عند حقن المحلول الدوائي بالماء الحاوي على مثبت يحصل ترسيب للجزيئات النانوية للنميسولايد وقد تم تقيم الجسيمات بقياس حجم الجسيمات و المحتوى الدوائي و كفاءة انحباس الدواء. شكل الجزيئات والذي حدد بواسطة المجهر الإلكتروني الباعث الحقلي للإلكترونات و مقياس حيود الاشعة السينية للباودرو المسعر الماسح التبايني. الباودر المجفف بالتبريد تم ضغطه الى اقراص بواسطة طريقة الضغط المباشر. وتم تقيم الحبوب لاطلاق الدواء لقياس تأثير الجسيمات النانوية على تحسين التذويب للدواء.

الكلمات الرئيسية: النمسولايد ، المذيب ومضاد المذيب ، الجسيمات نانوية ، معدل الاذابة ، الاطلاق.

Introduction:

The solubility, dissolution and gastric permeability are important parameters that regulate the rate and level of drug absorption [1]. The solubility of a drug in water is essential property that have a main role in the drug absorption after oral administration [2]. Around 40% of drugs are belonged to class II in Biopharmaceutics Classification System (BCS) Guidance, which represents low solubility–high permeability feature. Drugs that fall under this class have inadequate bioavailability because of their low solubility and dissolution rate [3]. There are many methods that can be used to increase drug solubility which are classified as chemical and physical modifications. The chemical modifications include salt formation and prodrug synthesis while the physical modification can be applied by micronization and nanonization to decrease the particle size, complexation and creation of polymorph [4]. In drug delivery, the production of drug in nanosize and serial

applications of nanonization had been applied to drug delivery like nanocapsules [5], nanotubes [6] and nanocrystals [7]. The reduction in particle size to nano-diameter falls under nanotechnology.

There are many recent studies and researches in the field of manufacturing nanoparticles for many medication, especially those of low water solubility. Sun *et al.,* prepared 5-flurouracil loaded chitosan nanoparticles for treatment of cancer by ionic gelation [8]. Indifferent study Swath *et al.,* worked on the formulation of ibuprofen nanoparticles loaded with ethyl cellulose [9].

Nime-sulide, is N-(4-Nitro-2-phenoxy-phenyl) methane sulfonamide which belong to nonsteroidal anti-inflammatory drugs, can be used in medical practice widely as analgesic and antipyretic, it is poorly soluble in water belong to class II in BCS guidance as a low solubility and high permeability [10], therefore we aimed to prepare nimesulide nanoparticles to increase surface area and dissolution of nimsulide in tablet dosage form.

Material and Method

Material

Nimesulide(Nutraplus,India),polyvinylpyr-rolidone (PVP-15) (Alpha chemika, India), carboxy methyl cellulose (CMC) (EMD chemicals, Germany), hydroxy propyl methylcellulose (HPMC) grades of A4C, E15, and K15 (Gromax Enterprises Corporation, USA), acetone (Romil, UK), hydrochloric acid (BDH laboratory, England), lactose (Carloerba, Italy), methanol (Gainland chemical company, UK), tween 80 (Atlas chemie, Algieria), sodium chloride (Sigma, USA) and microcrystalline cellulose (Avicel) PH102 (FMC corporation, USA) were used as received in this study.

Methods

Preparation of nimesulide nanoparticles

A nimesulide nanoparticles formulation were prepared by solvent/antisolvent precipitation method [11]. Drug solutions were prepared by dissolving 50mg of drug in 5mL acetone as a solvent and then each solution was injected into 50mL of water containing 50 mg of stabilizer of different grade of HPMC, CMC and PVP as shown in table (1) at 1mL/min using hotplate magnetic stirrer at 200rpm. Upon injection, nimesulide nanoparticles were produced immediately.

Table -1: Types of stabilizer used in different nimesulide nanoparticles formulations

Formulation	Type of stabilizer
F1	MC-A4C
F2	HPMC-E50
F3	HPMC-K15
F4	CMC-30
F5	PVP-15

Freeze drying of nanosuspension

In order to save nanoparticles in dried-powder state from the nanosuspensions, water-removal was occurred via vacuum freeze-dryer, so that the selected formulation was lyophilized using vacuum freeze dryer at a controlled temperature of (- 50) ˚C and the pump operating at a pressure lower than 0.055mmHg over a period of 48–72 hour.

Evaluation of nimesulide nanoparticles

Particle size determination of prepared nanoparticles

After precipitation of nanoparticles in anti-solvent solution, liquid sample before dried was taken and put in 4mL quartz cell of ABT-9000 Nano Laser particle size analyzer.

Determination of nimesulide content in nanoparticles

The drug content was measured by triturating 100mg of freeze dried nanoparticles with methanol in mortar and then transferred to volumetric flask and completed the volume with methanol to 10mL. After that, sample was sonicated for 15min by sonicater to ensure complete dissolution. Then, filtered by ordinary filter paper and read spectrophotometrically to calulated the amount of drug from corresponding calibration curve [12].

Loading efficiency and percent yield of prepared nanoparticles

The percentage of yield of nanoparticles was calculated after drying the formulation by lyophilization. The dried powder representing the actual weight of nanoparticles weight divided by the sum of drug and stabilizer weight used in preparation (theoretical weight) as show in the equation:

%Yield = (actual weight/theoretical weight) x100%

The loading efficiency calculated by dividing the actual drug content on the theoretical drug content and multiply the result by100(13).

Field emission electric scanning microscope (FESEM)

The FESEM is a kind of electron microscope that image formulation surface by scanning with low energy beam of electron. It was used to give specific characterization for nanoparticles without necessity to contrast discoloration to sample [14]. Thus, it was used to scan the selected formulation and pure drug by dusting of small amount of powder onto the carbon tape that fixed on the stab.

X-ray powder diffraction analysis

The atomic and molecular structure of nanoparticle were studied by X-ray powder diffraction (XRPD) which can be used to approve crystalline state of materials. This method was used to confirm whether the nanoparticles are in crystalline or in amorphous form. The study was established by XRD-6000 at continuous scan range of 2θ = 5 - 50̊, as the working voltage and current were 60kV and 80mA, respectively [15].

Differential scanning calorimetry (DSC)

DSC was used to evaluate compatibility of drug with polymer and the crystallinity of the sample. A 10mg of solid sample was analyzed using non-hermetically aluminum pans and heated at a rate of 20 ˚C/min against a vacant aluminum pan as a reference wrapper at temperature range was from 50 to 300 ˚C (13).

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of drug, polymer and selected formulation of nanoparticles were determined by grounded solid sample with potassium bromide and compressed in special disc then measured under infrared spectroscopy [16].

Preparation of tablet dosage form

Direct compression method was followed to prepare three formulations of nimesulide tablets containing pure, physical mixture and nanoparticle of a selected formulations. Each tablet contained anhydrous lactose as diluent and microcrystalline cellulose PH102 (Avecil)® at percent of 10% as disintegrating agent as shown in table (2). This tablet was prepared in order to analyze the effect of nanonization on the dissolution behavior of nimsulide.

Table-2: Composition of nimesulide tablets.

Material	Tablets		
	F5	Pure drug	Physical Mixture
Lyophilized powder	200mg	0	0
Nimsulide	0	50	50
PVP-15	0	0	150
MCC (Avicel)® PH 102	40mg	40mg	40mg
Lactose	160mg	310mg	160mg
Tablet weight	400mg	400mg	400mg

In vitro release study

The dissolution study was carried out by using dissolution apparatus type II (paddle method). Each tablet was dispersed in 900mL of dissolution medium. Different dissolution media of 0.1N HCl, water and phosphate buffer of pH7.4 prepared with 2% w/v tween 80 were incubated at 37 ºC ±0.5 and rotator of paddle at 75 per minute [17]. A 5mL was withdrawn at several time intervals and replaced by the same fresh media, the withdrawing samples was filtered by 0.45µm filter syringe and diluted on need and measured spectrophotometrically at λ max. The concentration of nimesulide released was calculated using calibration curve equation. The test was done in triplicate and the mean was calculated and the percentages of accumulative of nimesulide released were plotted against time to obtain dissolution profiles.

Statistical analysis

The results of study were given as an average of triplicate ± SEM (stander error of mean) and analyzed by ANOVA for analysis of variance at level ($p<0.05$). In addition, the difference and similarity of dissolution curves were analyzed using f1 and f2 analysis, respectively. The difference factor (f1) evaluating the percent error between two curves concluded all time points, and is given by:

$$f_1 = \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \times 100$$

Where I is the dissolution sample number, n is the number of dissolution times, and Ri and Ti are the amounts of the reference drug and the test drug dissolved at each time point i. The percent error is zero when the test drug and reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

The similarity factor (f2) is a logarithmic transformation of the sum-squared error of differences between the test Ti and reference Ri over all time points, and is given by:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{i=1}^{n} |R_i - T_i|^2\right]^{-0.5} \times 100\right\}$$

The standards for similarity factor and difference factor are 50- 100 and 0-15 for all, respectively [18].

Results and discussion

Evaluation of nimesulide nanoparticles

Particle size determination of prepared nanoparticles

Numerous experiments and modifications have been made to the surrounding conditions to gain the best nanoparticles with good physical properties that achieve the desired target of the formulation of pharmaceutical compounds of nimesulide in various forms. Table -3 includes the

sizes obtained from all the prepared nanoparticles. The F5 in which the PVP was used as stabilizer in the preparation of nanoparticle, showed the smallest size, and this effect could attribute to the increase in the affinity to drug molecules and decrease in viscosity of PVP polymer. Thus, the F5 formulation was used for further investigation.

Table -3: The mean ± SEM of particles size of nanoparticle formulation, (n=3).

Formulation number	Particle size mean (nm)
F1	477.5±22.5
F2	1058±61
F3	1677.5±106.5
F4	1187±68
F5	66.5±4.1

Loading efficiency and percent yield of nimesulide nanoparticles

Loading efficiency of selected formulation of F5 was 94.1% and the percentage of yield was 86%.

Nanoparticle drug content

The result demonstrates that each 100mg of lyophilized of F5 nanoparticles was contained 94.1 ± 0.3mg of pure nimesulide.

Nanoparticle shape determination

Field emission electrical scanning microscope (FESEM)

The particles shape and topography of pure drug and nanoparticles were determined using FESEM as shown in figures (1 and 2), respectively. The image 2 shows good surface morphology and smaller particle size of F5 formulation in comparison to image 1 of pure drug powder. This work is similar to that recorded by Thadkala's group studies of ezetimibe nanosuspension [19].

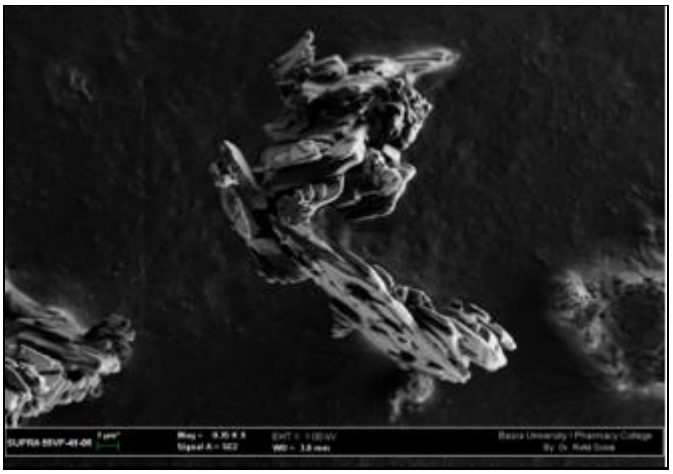

Figure -1: FESEM image of pure nimesulide

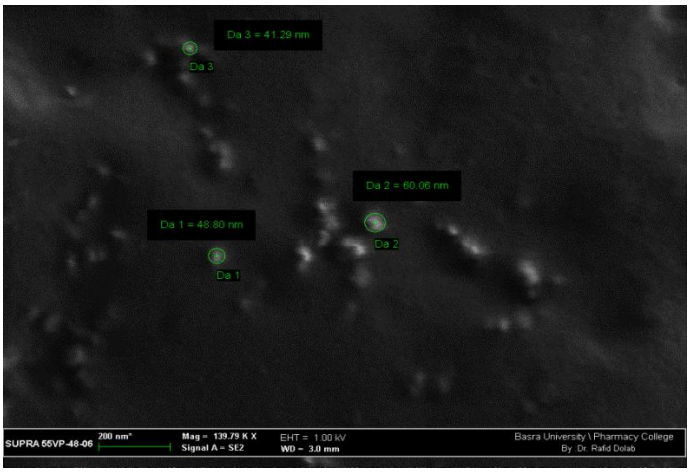

Figure -2: FESEM image of F5 nanoparticles.

X-Ray powder diffraction (XDR)

The X-Ray powder diffraction profile of pure nimesulide as shown in figure (3) exhibited sharp peaks with high intensity for 2θ value of 19.4° and 21.5° that referred to the crystalline structure of the drug and the X-Ray profile of physical mixture that showed the characteristic crystalline peaks as in figure (4) [20]. On the other hand, the less intense and large diffraction peaks that showed in X-ray figure (5) of F5 indicated that the drug loss of some of its crystalline identity or might be converted to amorphous form. This result likewise the work of Semalty et al to improve nimesulide dissolution by preparation of nimesulide-phosphatidylcholine complex [21].

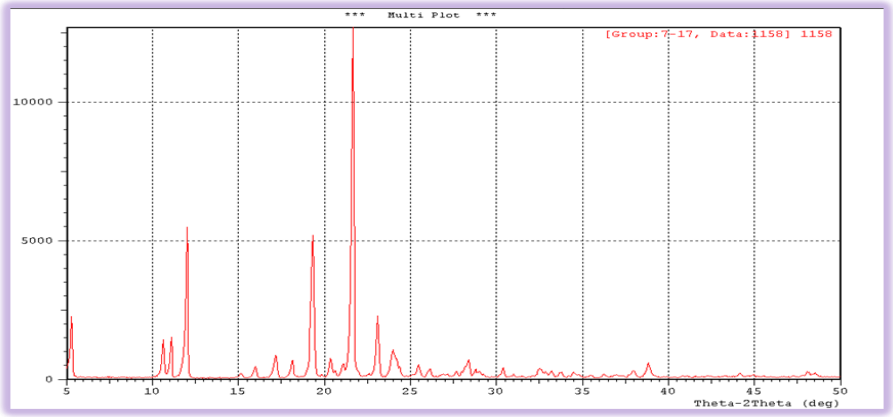

Figure-3: X-Ray powder diffraction profile of pure nimesulide

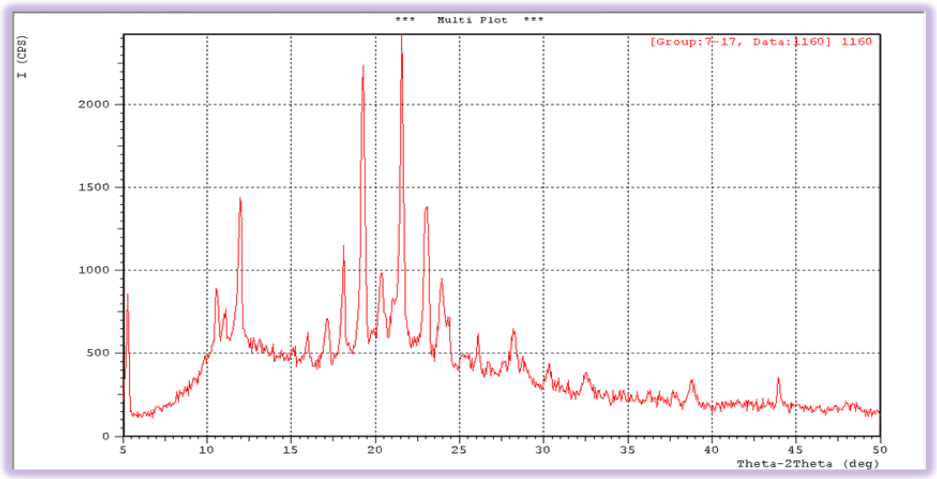

Figure -4: X-Ray powder diffraction profile of physical mixture

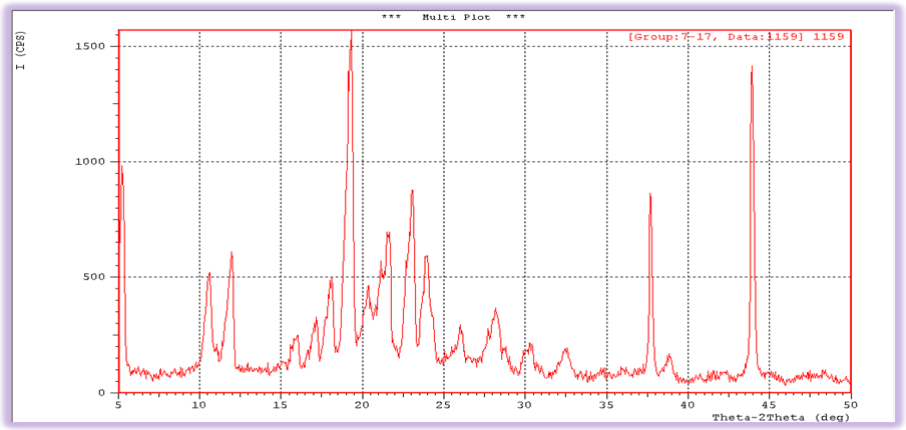

Figure -5: X-Ray powder diffraction profile of F5.

Fourier transform infrared spectroscopy (FTIR)

The results of the of FTIR tests transmittance bands of pure nimesulide powder were demonistared in table -4 and figure -6.

Table -4: FTIR characteristic peaks of pure nimesulide

Peak	Type
3284cm^{-1}	Stretching vibration of secondary amine
1153cm^{-1} and 1342 cm^{-1}	Stretching vibration of SO2
Weak bands 3128cm^{-1}	Stretching of alkane CH3
1593cm^{-1}	Stretching of nitro group NO2

While, figures (7) and (8) represent the FTIR of polymer and F5 formulation respectively. The result of the prepared nanoparticles formulation showed no shifting to the characteristic peaks that reveals no interaction between drug and PVP polymer. Also, The FTIR of physical mixture showed the characteristic peaks at same positions which means no interaction between the drug and polymer as shown in figure (9) [22].

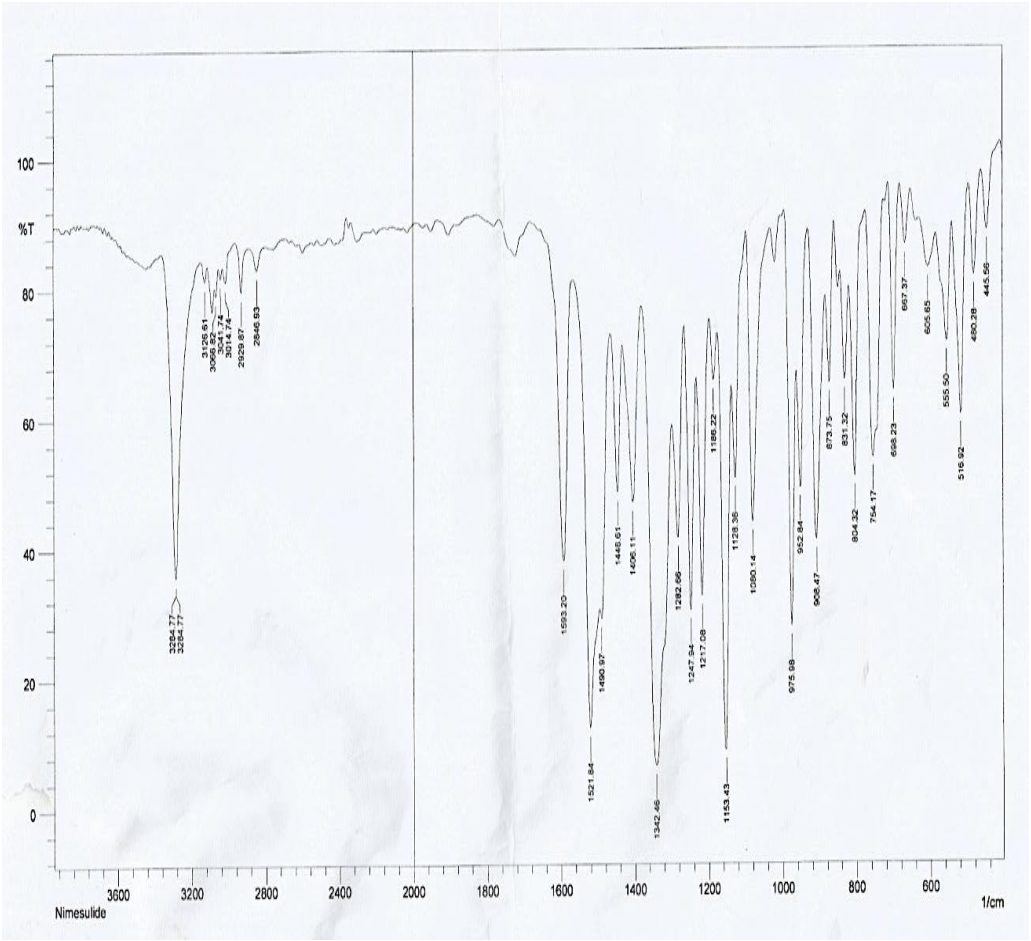

Figure -6: FTIR spectrum of pure nimesulide.

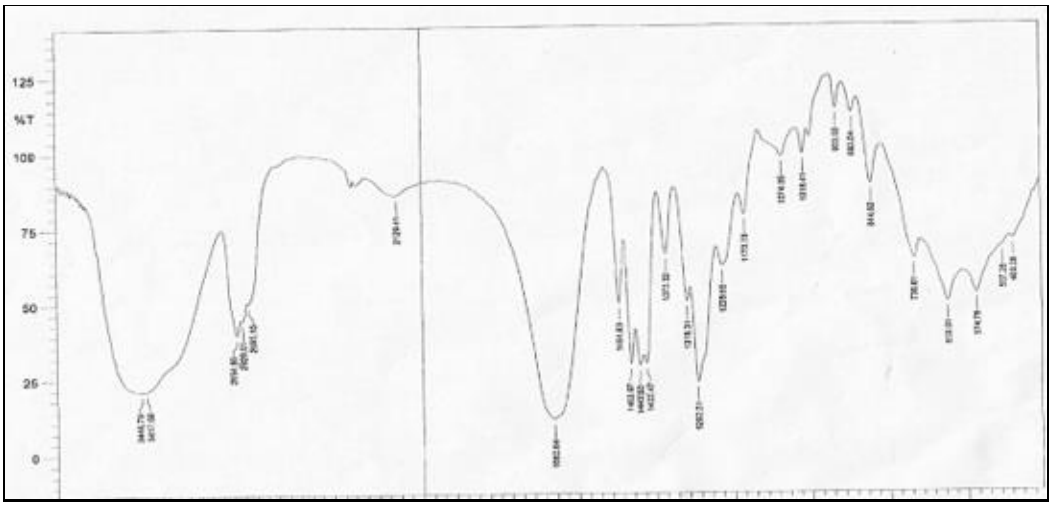

Figure -7: FTIR spectrum of PVP polymer

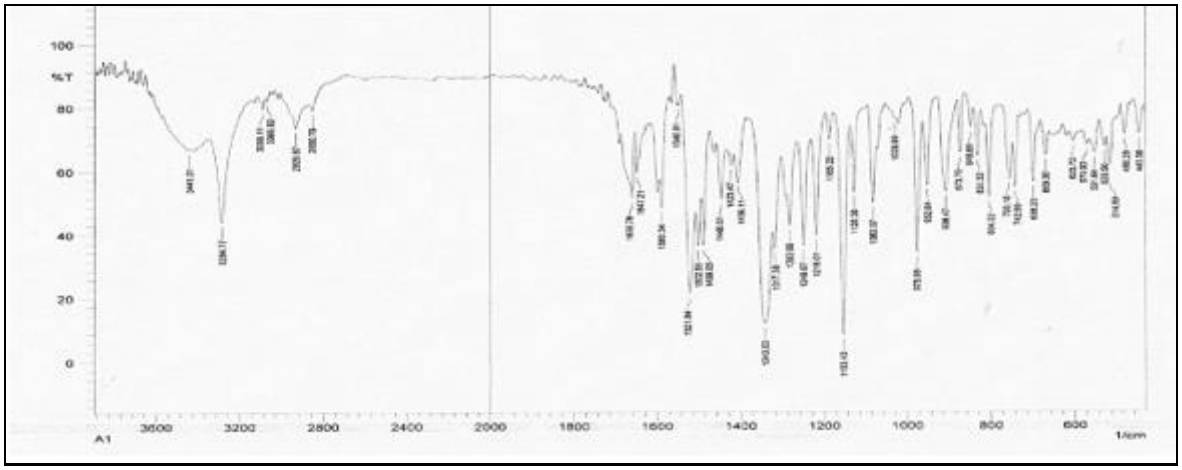

Figure -8: FTIR spectrum of F5 nanoparticles.

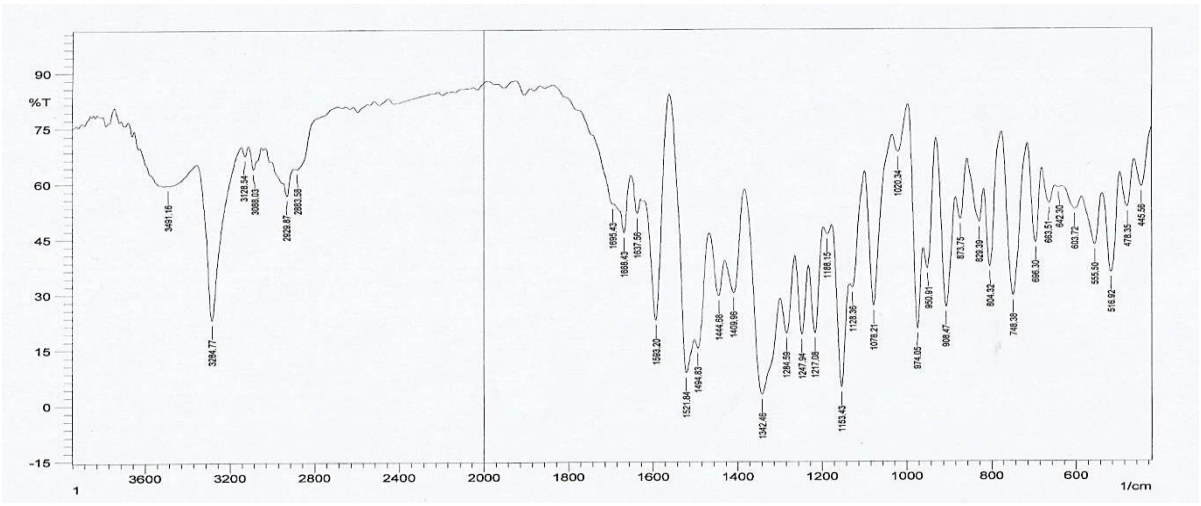

Figure -9: FTIR spectrum of physical mixture.

Differential scanning calorimetry (DSC)

The DSC test of nimesulide showed a sharp endothermic peak at 154̊ C which is closed to the melting point of the pure crystalline state of drug as represented in figure (10) and a broad peak of PVP at 120.73 ºC as shown in figure (11) [23]. The result of DSC of F5 showed a suppression and a broad melting endothermic peak of both PVP and drug to 92º and 144ºC respectively with reduced intensity. Also, the suppression of melting endothermic peaks of both PVP and drug in the physical mixture were 98º and 148ºC respectively, as screened in figure (13). These changes possibly participate in solubility enhancement result and the obtained results are in agreement with investigation by Cheow's work [24].

The DSC pattern of physical mixture of pure nimesulide drug with PVP polymer is shown in figure (13) revealed no change in the endothermic peak of drug which implies there was no interaction between drug and polymer this is supports the results of FTIR study.

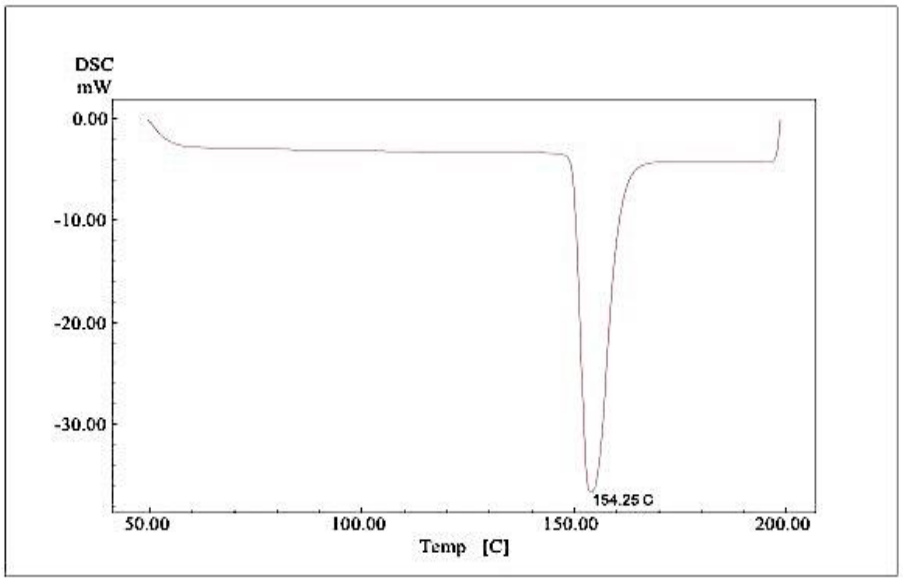

Figure -10: DSC spectrum of pure nimesulide

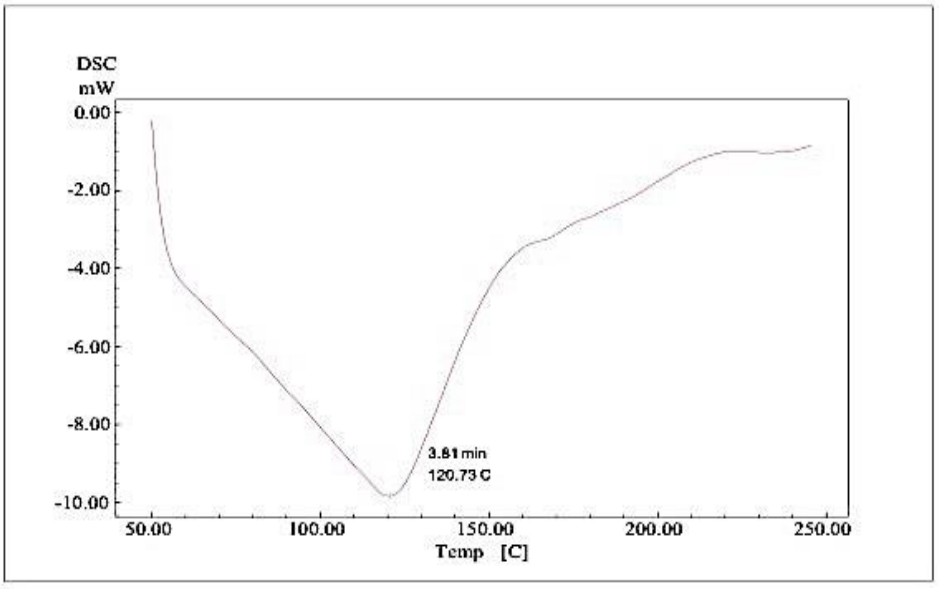

Figure -11: DSC spectrum of PVP polymer.

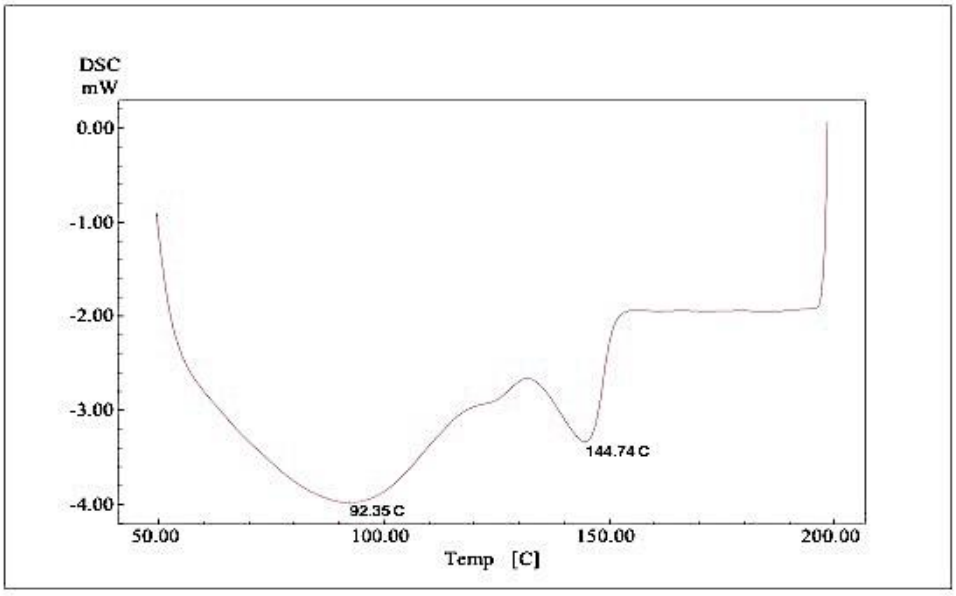

Figure -12: DSC spectrum of F5 nanoparticles.

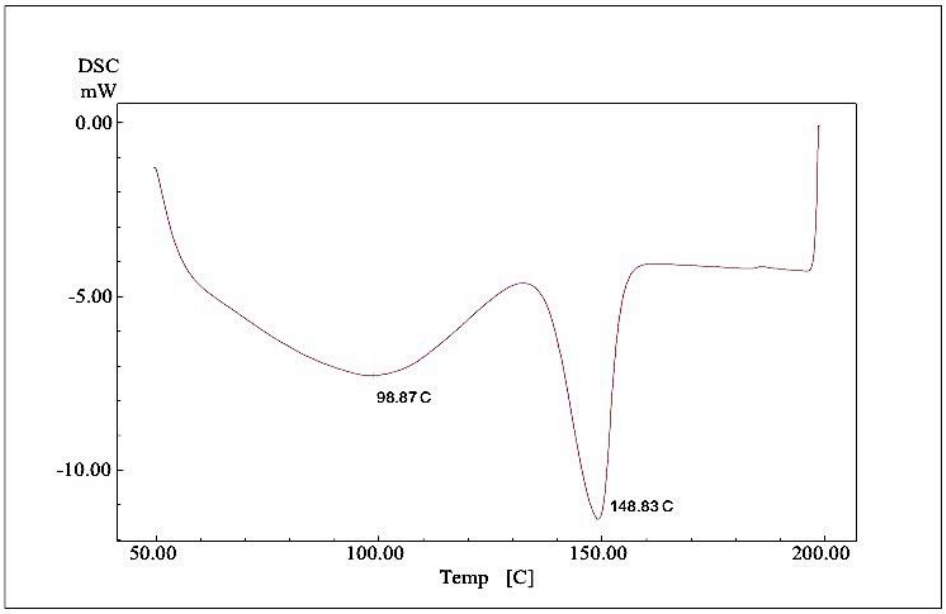

Figure -13: DSC spectrum of physical mixture

***In vitro* release of nimsulide study**

The release studies of nimesulide from tablet of nanoparticles (F5), physical mixture of drug with polymer mcompressed tablet and pure drug tablet as a reference were tested firstly in water and then in 0.1N HCl (pH 1.2) as shown in figures (14) and (15), respectively.

The result showed a very low release percentage of three tested tablets reached to 4% and 10% in water and 0.1N HCl respectively. These results might be

attributed to the low solubility of drug in acidic condition, as nimsulide is weak acid and practically insoluble in water. On the other hand, an experiments were done for the release of the drug in phosphate buffer at pH 7.4 and 2% w/v tween 80 to maintain the sink condition of the release study as shown in figure (16) [17].

The release profile of drug from tablets containing nanoparticles (F5) showed a significant increase and rapid dissolution rate ($p<0.05$) compared to that from tablet containing pure drug. The release was completed within 60min, which is in contrast to the pure drug which showed a low release rate. Therefore, the formulation of nimesulide tablets containing nanoparticles of the drug remarkably enhance the dissolution rate in tablet dosage form. Also, this effect has been found in many works like that obtained by Mansouri and co-researchers, as in the preparation of ibuprofen formulation as nanoparticles using solvent: anti solvent method [25].

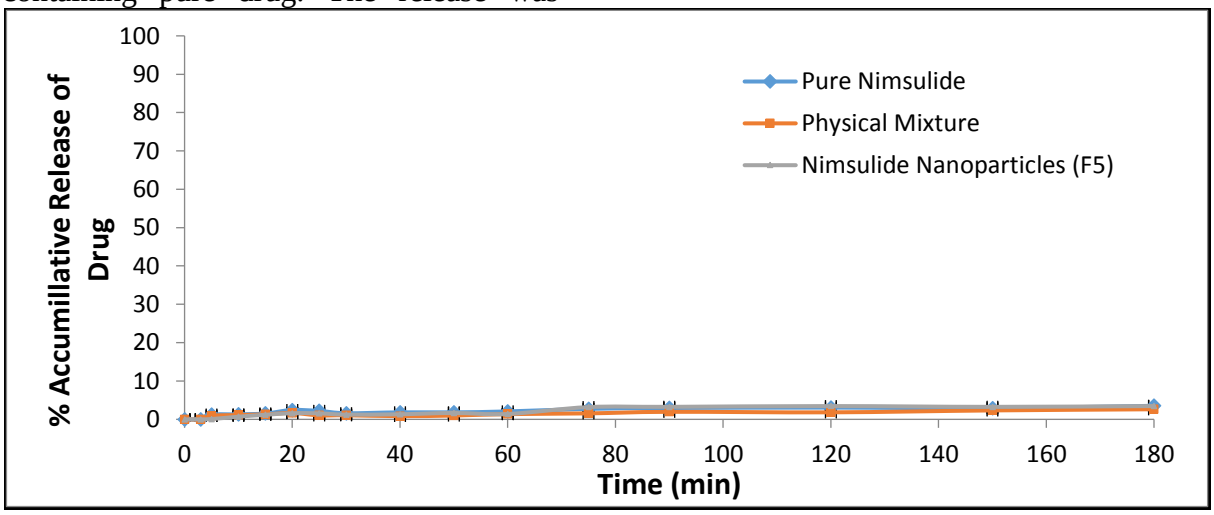

Figure -14: In vitro release profiles of pure nimesulide, drug polymer physical mixture and F5 formulation tablet in phosphate buffer (pH7.4) and 2%w/v tween 80 (Mean±SEM).

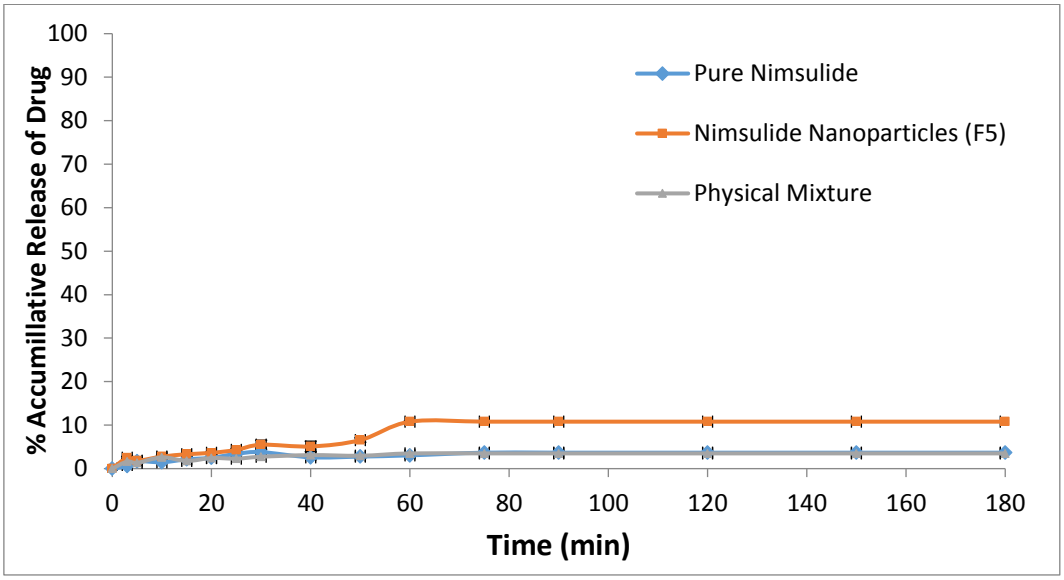

Figure -15: *In vitro* release profiles of pure nimesulide, drug polymer physical mixture and F5 tablet formulation in water (Mean±SEM).

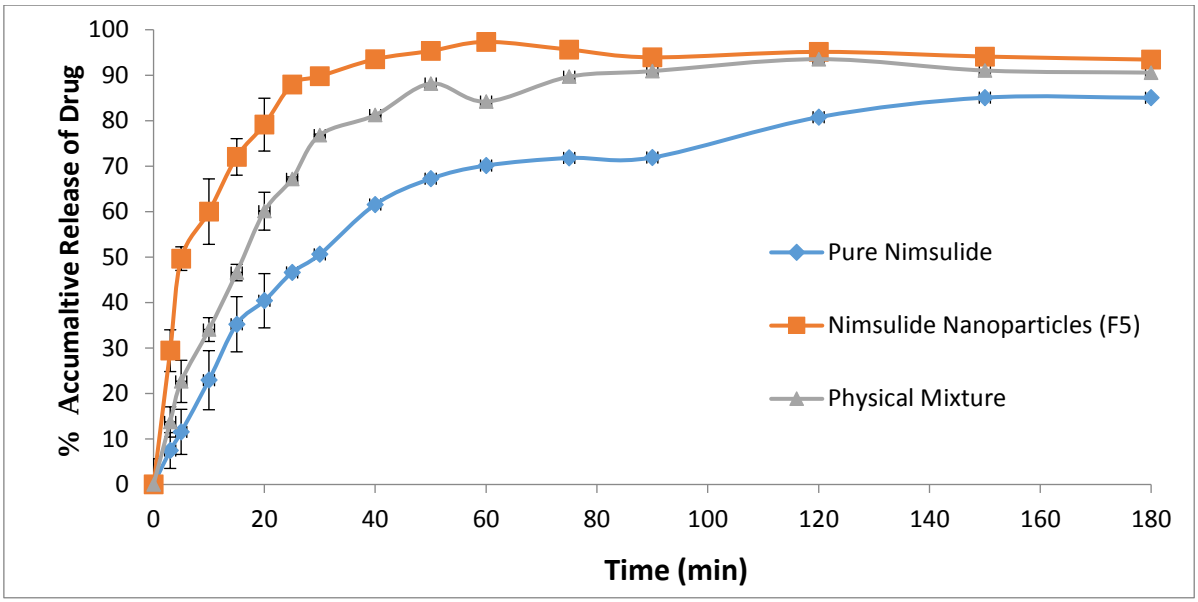

Figure -16: *In vitro* release profiles of pure nimesulide, drug polymer physical mixture and F5 tablet formulation in 0.1N HCl (pH1.2) (Mean±SEM).

The difference factor of f1 and similarity factor of f2 have been widely used for dissolution profile comparison [26, 27, 28]. They were calculated to compare the dissolution profiles of pure, physical mixture, nano incorporated tablet in each media as shown in table (5). The results showed that the dissolution profile for nimsulide from F5 was not similar to pure and physical mixture containing tablets as f1 values were higher than 15. Plus, it was differing since f2 values were lower than 50 [29].

Table -5: Values of calculated difference factor (f1) and similarity factor (f2) of dissolutions data of pure, physical mixture and nanoparticles (f5).

Media	Pure & F5		Pure & physical mixture		Physical mixture & F5	
	f1	f2	f1	f2	f1	f2
Phosphate buffer (pH7.4) & 2% tween 80	51.6	26.9	27.4	40.4	18.9	40.9

Conclusions

Based on the results, the study gives the following conclusions:

•The solvent/antisolvent technique is a good way to formulate drug nanoparticles due to simple handling.

•PVP polymer can be used to prepare nimesulide nanoparticles successfully than other polymer.

•Polymer: drug ratio 1:1 was more effective to decrease particle size.

•Acetone solvent was efficient to prepare nanoparticle.

•FTIR profiles confirm the compatibility of drug and excipient.

•The dissolution of nimesulide from tablet was pH dependent and does not depend on the particle size in water and 0.1N HCl dissolution media.

•The dissolution of nimsulide was significantly improved by nanoparticles formulation in phosphate buffer (pH7.4) and 2%w/v tween 80 dissolution media.

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