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RESEARCH PAPER

Preparation and Evaluation of Nimesulide Nanosuspension as Hydrogel Dosage Form

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ABSTRACT

Topical drug administration is a technique of applying different dosage forms, including ointments, creams, hydrogels, to the skin and different sections of the body, it has systemic or local effect. Nimesulide is a non-steroidal anti-inflammatory medication with strong analgesic, and anti-inflammatory properties, it was used in this research and prepared as nanoparticles, which was then incorporated into hydrogel for topical application, to increase solubility of Nimesulide, which is class II in BSC, and reduce their systemic side effects. Nimesulide nanosuspension were prepared by solvent/antisovent method at different polymer: drug ratios (1:1, 2:1, and 3:1) using polymers as polyvinyl pyrrolidone (PVP-K15, PVP-K30), hydroxypropyl methylcellulose (HPMC-E5) and poloxamer-188. The effect of polymer type and concentration on the particle size, poly dispersity index, specific surface area was studied. Among twelve prepared formulas, F2 was selected as best formulas with an average particle size of 59. 5 nm. It was lyophilized and investigated for surface morphology by FESEM, drug–excipients compatibility studies by DSC, crystalline state by XRPD and then Nimesulide nanosuspension of F2(1%w/w Carbopol) was formulated into hydrogel dosage forms and subjected for further evaluation. The results indicated that particle size of nanosuspension was found to be affected by type and concentration of polymer and when increase polymer: drug more than 1:1 led to increase particle size. In addition, the release profile of F2 hydrogel formula was better than plain Nimesulide hydrogel. From this, it is concluded that the dissolution rate of Nimesulide nanosuspension was increased through particle size reduction to nanometer size.

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INTRODUCTION

Creating medications with low water solubility that have a good bioavailability has become a significant scientific, industrial, and medical challenge. Researchers began searching for novel size reduction technologies because they could not reduce particle size as much using traditional methods. This was made possible by advances in nanotechnology, which included the use of nanosuspension, nanoemulsion, and number of other approved particles in the nano size range (below 1 millimeter particle diameter) [1]

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To achieve targeted and sustained drug release, nanoparticles and microparticles are being studied more and more [2]. These systems have been thoroughly investigated for topical application to the skin as well as oral and intravenous administrations. One of the human body's easiest organs to access for topical drug delivery of many kinds is the skin. Conventional topical medications are primarily administered to the skin for localized effects; however, modern technology and the inclusion of penetration enhancers in the preparations can reach systemic benefits as well [3]. Topical drug delivery systems are intended to distribute drug molecules via the skin, ocular, vaginal, and rectal routes. A wide range of pharmacological dosage forms are included in it, such as lotion, powder, solution, suspension, emulsion, and semisolid (including cream, hydrogel, ointment, and paste). The majority of semisolids are made of hydrogel [4]. Hydrogel is a hydrophilic three-dimensional network of materials that have been chemically or physically cross-linked. These materials have well-defined structures and are absorbent; they can hold high quantities of water up to hundreds of times their dry weight [5]. In general, nanoparticle–hydrogel hybrid systems combine two distinct components into a single preparation, providing favorable biological and physicochemical characteristics that neither of the two components could achieve on its own [6]. Since it improves medication release and diffusion across biological membranes, the nanoparticle-hydrogel combination can increase drug bioavailability and patient compliance [7]. Nimesulide is a favored COX-2 inhibitor that has been efficiently used for the treatment of a diversity of inflammatory and painful disorders, including osteoarthritis. it is poorly soluble in water belong to class II in BCS guidance as a low solubility and high permeability [8]. Nimesulide had a half-life of two to five hours and was 99 percent plasma protein bound, when used orally, its distribution volume ranges from 12 to 27 L. As a result, it is not widely dispersed and mostly stays in the systemic circulation, which could contribute to liver failure [9]. In addition to that, the oral use of Nimesulide

Table 1. composition formula of Nimesulide nanosuspension.

Number of formulas	Nimesulide (mg)	HPMC-E5 (mg)	PVP-K15 (mg)	PVP-K30 (mg)	Poloxamer 188 (mg)
F1	50	50			
F2	50		50		
F3	50			50	
F4	50				50
F5	50	100			
F6	50		100		
F7	50			100	
F8	50				100
F9	50	150			
F10	50		150		
F11	50			150	
F12	50				150

shows several side effects like gastrointestinal disturbances, vomiting, diarrhea, epigastric pain, and heartburn [10], so it was necessary to switch from an oral to a topical delivery method by the drug loaded nanoparticles can be applied topically as hydrogel for inflammation area.

MATERIALS AND METHODS

Nimesulide (Nutraplus,India),polyvinylpyrrolidone (PVP-K15 and PVP- K30) (Alpha chemika, India), hydroxy propyl methylcellulose (HPMC-E5) (Gromax Enterprises Corporation, USA), Poloxamer -188 (Shanghai Send Pharmaceutical Technology Co.Ltd, china), acetone (Romil, UK), carpobol 940 (Alpha chemika, India), sodium chloride (Sigma, USA) , disodium hydrogen orthophosphate BDH Laboratory supplies, England, Potassium dihydrogen phosphate from(Sd Fine-Chem Limited, India) and dialysis membrane (Shanghai Dianrui Biotechnology Co.,Ltd).

Preparation of Nimesulide nanosuspension

As indicated in Table 1, twelve formulations for Nimesulide nanoparticles were created using the solvent/antisolvent precipitation method. Nimesulide nanoparticles were generated instantly after drug solutions were made using 5 mL of acetone as solvents and 50mg of drug (10 mg/ml) and then injected into 50 mL of water containing different ratio of stabilizer (HPMC-E5, PVP-K15, PVP-K30 and poloxamer188) at a rate of 1 mL/min, and polymer: drug ratio was 1:1,2:1 and 3:1 [11].

Evaluation of particle size, surface area and poly dispersity index

For all twelve formulas, particle size determination was carried out using the ABT-9000 nano laser particle size analyzer. This dynamic light scattering method measures the intensity of light scattered by the molecules in the sample as a function of time, at a constant temperature of 25 °C, and at a scattering angle of 90 °C, for every formula, the samples' average diameters, surface areas, and polydispersity index were measured and recorded.

Evaluation of variables effect on the properties of prepared Nimesulide nanosuspension

Effect of type of polymer on Nimesulide nanosuspension

Four formulas (F1, F2, F3 and F4) were prepared containing different polymers of HPMC-E5, PVP-K15, PVP-K30 and poloxamer-188. The ratio of 1:1 of polymer: drug was used for all these formulations to show the effect of polymer on physical characterization of Nimesulide nanosuspension.

Effect of concentration of polymer on Nimesulide nanosuspension

Twelve formulas (F1-F12) were prepared containing different concentration at polymer: drug ratio of 1:1, 2:1, and 3:1 and the results recorded.

Characterization of lyophilized powder

Field emission scanning electron microscope FESEM

The FESEM is a type of electron microscope that uses an electron beam with high energy to scan and photograph formula surfaces. The test done by directly dusting the powder on double-sided carbon tape, the FESEM of raw Nimesulide powder and lyophilized powder of a selected formula were verified and the secondary electrons used 1kV and various magnification powers to obtain images**.**

Differential scanning calorimetry (DSC)

DSC was used to evaluate sample crystallinity and drug and polymer compatibility. The raw

Nimesulide and powder of selected formula was placed in tight aluminum pans and heated at a rate of 20˚C per minute, with a reference wrapper of an empty aluminum pan, the temperature range was 50˚C to 300˚C.

X-ray powder diffraction analysis

The crystalline structure of raw Nimesulide and the chosen formula of lyophilized Nimesulide powder were investigated using X-ray powder diffraction. The working voltage and current for the X-ray diffraction were 60 kV and 80 mA, respectively.

Preparation of Hydrogel

The selected formulas of Nimesulide nanosuspension were incorporated separately within hydrogel formulation using carbopol 940 (1% w/w and 2% w/w). The weighted amount of Carbopol 940 was dispersed in 40 ml distilled water and stirring at 1100 rpm for 90 minutes, by using magnetic stirrer until get a uniform dispersion. The pH was adjusted to 6.8 by adding

approximately 3ml of sodium hydroxide 10% (w/v), and then the mixture was left for swelling for one day to obtain a high viscous solution. The freshly prepared formulas of Nimesulide nanosuspension were gradually added to viscous solution of carbopole 940 with stirring using magnetic stirrer. Then spatulation for 60 minute to ensure uniform dispersion of hydrogel mixture. Furthermore, a solution of propyl paraben 0.01% (w/v) and methyl paraben 0.1% (w/v) in water was added to this blend of hydrogel [12]. The final weight of hydrogel was completed to 100 gm using water and pH adjusted using 1ml of NaOH 10% (w/v) solution with continuous stirring for 60 min; The prepared hydrogels formulas were packed in wide mouth plastic container covered with screw capped plastic lid, containers were kept at room temperature for one day for more assessment. Moreover, a plain hydrogel was prepared using raw Nimesulide powder for comparative study using Carbopol 940 (1% w/w).

Evaluation of the prepared hydrogels

Physical appearance of hydrogel formulations

Hydrogel were visually examined for color, homogeneity, and clarity**.**

Measurement of pH

The pH of hydrogel was tested at room temperature using a digital pH meter by submerged pH meter electrode in hydrogel formula, this test was established to find out the possibility of in vivo any side effect [13]. The experiments were conducted in triplicate.

Spreadability Test

Finding the spreadability is crucial when assessing topical formulations, after 2 days of

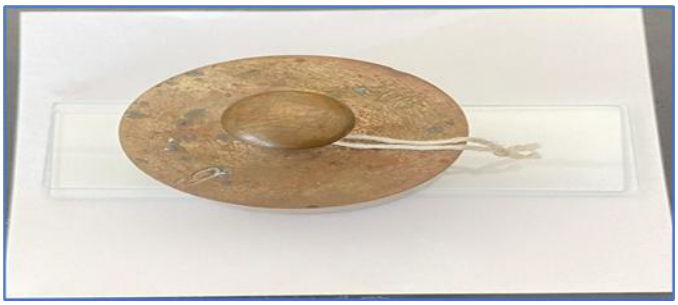

Fig. 1. Assembly for spreadability test.

Fig. 2. Fungilab viscometer (cup and pop method).

preparation, the diameter of Nimesulide hydrogel between two glass slides was measured to assess its spreadibility. A 500 mg weight sample of the hydrogel was put on a glass slide's circular region. The sample was sandwiched between two glass slides and squeezed for one minute using a 200 g weight as shown in Fig. 1. After removing the 200 g weight, the spread area's circumference (in centimeters) was measured. The spread area's diameter was used as a spreadability comparison value [14]. The experiments were conducted in triplicate.

Determination of Drug Content

Nimesulide content in hydrogel formulations was determined by dispersing 600 mg from hydrogel formulation in 50 ml phosphate buffer pH (7.4) and shaking for 20 minutes on magnetic stirrer and then sonication for 60minute, after that filtered by 0.45µm cellulose membrane. Nimesulide content in sample was calculated after dilution with appropriate volume of phosphate buffer pH 7.4 in UV-spectrophotometric Shimadzu 1800 at 397.6 nm [15]. The experiments were conducted in triplicate.

Rheological analysis (Viscosity of Nimesulide hydrogel)

Rheology describes the deformation of a body under the influence of stress. The rheological studies.

In Vitro Drug Release

In vitro release of Nimesulide from plain

Table 2. Averages particle size, poly dispersity index PDI and specific surface area (SSA) of prepared Nimesulide nanosuspension.

Number of formulas	Average particle size (nm)	Poly dispersity index PDI	Specific surface area SSA(m^2/gm)
F1	530.5	0.011	4.15
F2	59.5	0.01	35.14
F3	334	0.04	6.3
F4	943	0.01	2.28
F5	676.5	0.008	3.12
F6	188	0.05	10.5
F7	477.5	0.005	4.5
F8	1058	0.01	2.12
F9	1187	0.007	1.9
F10	298	0.009	7.6
F11	667.5	0.01	3.3
F12	1332	0.009	1.16

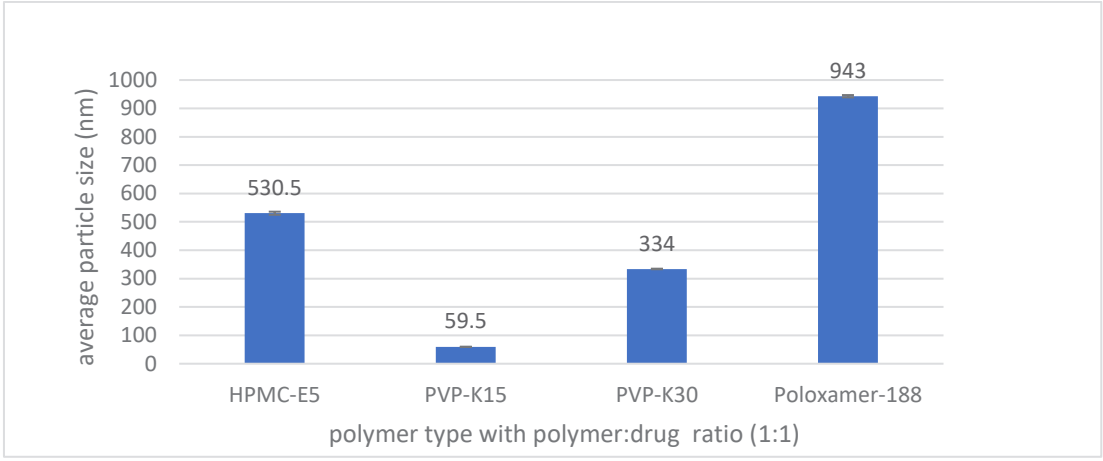

Fig. 3. The effect of polymer type on size of Nimesulide nanosuspension (mean± SEM n=3)).

hydrogel (contain raw Nimesulide with carpobole 940 1%w/w), and hydrogel of the selected formula (contain Nimesulide nanosuspension with carpobole 940 1%w/w and 2%w/w) were evaluated using modified Franze diffusion cell which consists of receptor and donor compartments separated by membrane. Dialysis tubing method was used to study In vitro release rate in which a synthetic dialysis membrane (cut off 14000 Dalton) was used. It was soaked overnight in phosphate buffer (pH 7.4), one end of glass tube was covered by a dialysis membrane which was securely mounted on the tube by a robber band. A specific amount of hydrogel (1000 mg) equivalent to 10 mg Nimesulide was spread on specific surface area (3.4 cm^2) of membrane. The tube containing hydrogel was partially immersed in beaker containing 200ml of phosphate buffer (pH 7.4) with constant shaking at 100 rpm at 37 ºC. At various time intervals (0.5 ,1,2,3,4,5,6,8,10 and 12 hr.), samples were withdrawn and replaced with phosphate buffer (pH 7.4) to maintain sink condition, the withdrawn samples were filtered through 0.45 µm and measured at 397.6 nm using UV- spectrophotometric [18]. The experiments were conducted in triplicate.

Statistical analysis

The experiments' findings are shown as mean sample ± standard deviation (SD) for n = 3.In addition the one-way analysis of variance (ANOVA) was used to check for differences in the experiment outcomes at p≤0.05.

RESULTS AND DISCUSSION

Evaluations of prepared Nimesulide nanosuspension

Particle size, specific surface area (SSA) and polydispersity index analysis (PDI)

The average particle size of all the prepared formulas was characterized using ABT-9000 nano laser particle size analyzer. The prepared Nimesulide nanoparticles formulas showed an average particle size values within nano range except F8, F9 and F12 formulas, the average particle size of Nimesulide nanoparticles formulas was shown in Table 2. The smallest size 59. 5 nm for F2 contain PVP-K15 in ratio polymer: drug (1:1) and the largest size 1332 nm for F12 which contain poloxamer-188 in ratio polymer: drug (3:1), this result due the fact that Nimesulide has a high affinity to PVP-K15 than to other polymers used in this research as well as because the PVP-K15 has low viscosity grade [19]. The specific surface area (SSA) of the particles is the summation of the areas of the exposed surfaces of the particles per unit mass. As shown in Table 2, an inverse relationship between particle size and surface area [20], and the prepared formulas SSA values range between 35.14 and 1.16 m2/gm; F2 had the biggest surface area and F12 had the least. Furthermore, the particle analyzer's polydispersity index was used as a parameter to describe the distribution of nanoparticle sizes. The PDI of all nanoparticles shown in Table 2, which have the monodispersed standard range (0-0.05) and that, indicates good uniformity of nanoparticles [21].

Variable effect on size of Nimesulide nanosuspension

Effect of type of polymer

Formulas F1–F4 prepared in the same polymer: drug ratio (1:1) as shown in Fig. 3, the impact of polymer type on mean particle size was investigated. The findings demonstrated that PVP-k15 produced a notable reduction in nanoparticle size, while poloxamer 188 produced the largest nanoparticles, due to low viscosity grade and the high affinity of PVP-K15 polymer to Nimesulide than other polymers. According to results the sequence of polymer's effect in reducing particle size of Nimesulide was as the following: PVP-K15 > PVP-K30 > HPMC-E5> Poloxamer-188.

Impact of polymer concentration

Formulas F1–F12 examined varying the polymer concentration under all polymer: drug percentages of 1:1, 2:1, and 3:1. According to the results, as seen in Fig. 4, a significant increase in mean particle size was induced by a polymer concentration increase more than a 1:1 ratio for all polymers. This could be because the polymer layer surrounding each particle is thicker, causing the particles to aggregate [22], and the large number of polymer chains that join together during the diffusion process, which increases the contact between polymers.

Characterization of Nimesulide nanoparticles

Field emission scanning electron microscope (FESEM)

Fig. 5-A shows the FESEM image with 9.45 Kx magnification power, it was illustrated the presence

of raw Nimesulide particles with irregular form, rough surface, and big particles. While FESEM image of F2 formula showed a reduction in particle size of Nimesulide particles to nanometer range, in which the uniformity of particle sizes was clarified by the FESEM of F2 formula, as shown in Fig. 5-B image at a magnification power of 180.35Kx. It's possible that the stabilizer's adsorption or capping action on the drug surface produced this outcome, which reduced the size of the Nimesulide particle to nanoscale size and the similar result was obtain in preparation of Ezetimibe nanosuspension by solvent antisolvent method [23].

Differential scanning calorimetry (DSC)

Raw Nimesulide's differential scanning

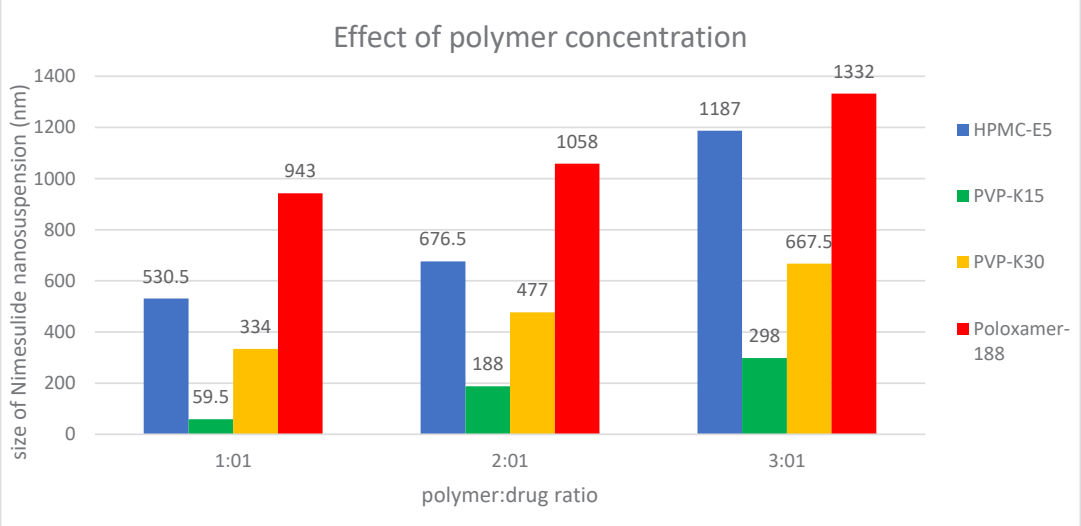

Fig. 4. The effect of polymer concentration on size of Nimesulide nanosuspension mean± SEM (n=3).

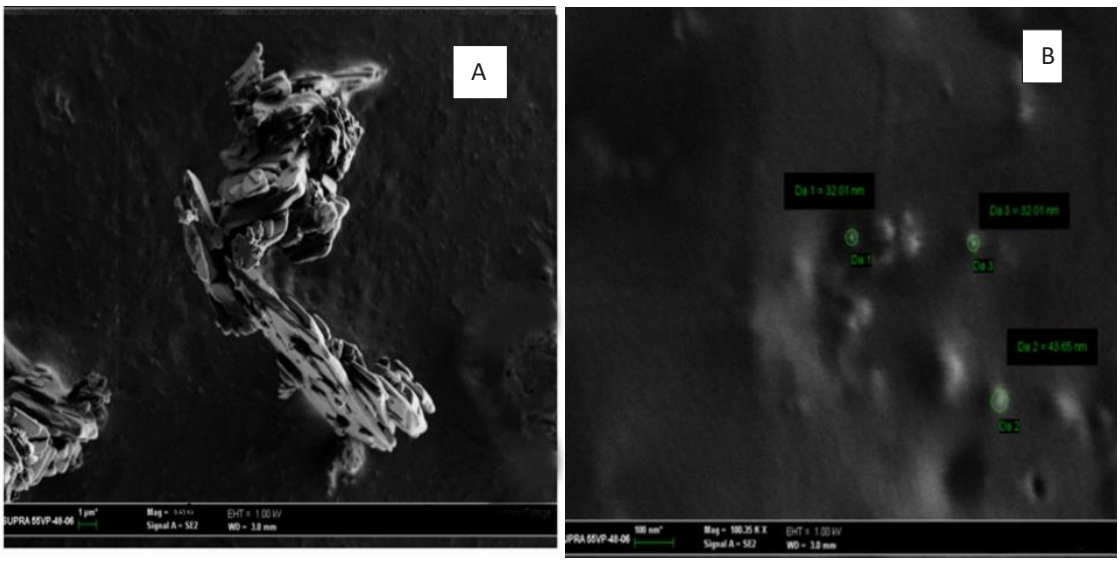

Fig. 5. (A) FESEM of raw Nimesulide and(B) Nimesulide nanoparticles (F2)

calorimetry revealed a distinct endothermic peak at 154 C, which indicates the drug's melting point and represents the drug's pure crystalline state as shown Fig. 6-A. However, the DSC of F2 formula in Fig. 6-B showed a lower intensity of peak and enthalpy when compared to the raw drug. This finding indicates that the drug's crystallinity has decreased, which may have improved its solubility [24].

X-ray powder diffraction (XRD)

The crystalline structure of Nimesulide was demonstrated by the strong, highly intense peaks in the X-ray powder diffraction profile of raw Nimesulide as exhibited in Fig. 7-A for 2θ values of 12º, 19.5º, and 21.8º. Conversely, the x-ray of F2 formula displays as big diffraction peaks and less intense as shown in Fig. 7-B. This indicates that the drug's crystalline state has diminished and that some of it has turned to amorphous form [25].

Characterization of Nimesulide hydrogel

Physical Appearance of Hydrogel

Fig. 8 shows the physical characteristics of Nimesulide nanosuspension (F2) in hydrogel form. The hydrogel formulation produced a white, translucent, and uniform texture.

pH determination

Nimesulide nanosuspension hydrogel (F2 formula) pH was measured to look into any potential negative effects, and the results showed that it was 5.7 and 5.9 for F2 hydrogel with Carbopol 940 1%w/w and 2% w/w respectively. Furthermore, the pH of the plain hydrogel of Nimesulide particles was measured and it was 5.5 as illustrated in Table 3. Since the pH of the skin typically ranges from 4 to 6, the pH of these hydrogels falls within the range of standards topical preparation [26]. The pH values of the hydrogels were comparable to the normal pH of the skin, based on the results, indicating that the application was suitable for the skin.

Spread ability measurement

Spreadibility test shows the size of the area that gel spreads easily on the skin or affected area. In this research the hydrogel forms of F2 (1%) had the maximum spreadability (12.2 g.cm/sec), followed by the plain hydrogel of raw Nimesulide (10.4 g.cm/sec) then the result of spreading F2 (2%) was equal (8.5 g.cm/sec) as shown in Table 3. One of the most crucial characteristics of a hydrogel to achieve the best results when applied topically its spreadability, which also affects the gels' therapeutic effectiveness, as a result, the gel should spread easily across the applied surface [27].

Determination Nimesulide content in hydrogel formulation

Drug content of Nimesulide hydrogels were calculated for F2 (1%) and F2 (2%) formulas and for plain hydrogel contain raw Nimesulide, and it was found 96.1 %, 94.5% and 94% respectively, as shown in Table 3. The drug content of the formulations exhibited that the drug particles

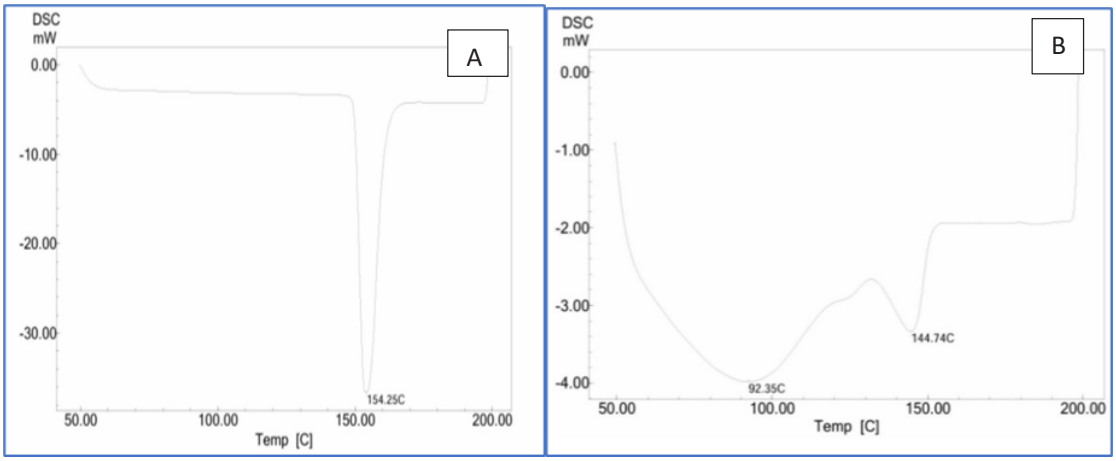

Fig. 6. (A) DSC of raw Nimesulide and(B) DSC of F2 formula.

were uniformly distributed within the hydrogel's forms.

Determination viscosity of hydrogel

Viscosity holds a main contribution in determining the drug content and its release from the prepared hydrogel formulation. To assess the influence of gelling agent on gel viscosity, viscosity research was conducted, for F2 (1%) and F2 (2%) hydrogel formulas and the viscosity was varied between 9500 cps to 99160 for F2 (1%) and 28630 cps to 296755 cps for F2 (2%), these results indicate that hydrogel viscosity increase with increasing gelling agent (carbopol 940) concentration. Hydrogel viscosity was generally measured at different shear rates. It was discovered that the hydrogel's viscosity decreased as the shear rate increased, resulting in non-Newtonian flow behavior [28], as seen in Fig. 9. The outcomes demonstrated that carbopol 940 was an effective as gelling agent for hydrogel formulation preparation.

In vitro Nimesulide release study

The in vitro release study was done in phosphate buffer solution (pH 7.4). Fig. 10 explain the release of drug through synthetic dialysis membrane (cut off 14000 Dalton) for F2 hydrogel (1%w/w and 2%w/w) and plain hydrogel of raw Nimesulide(1%). At 4hr. the cumulative percentages of drug release from F2 hydrogel (contain 1% w/w Carbopol) was found to be 74.2%, the release reached to 100%

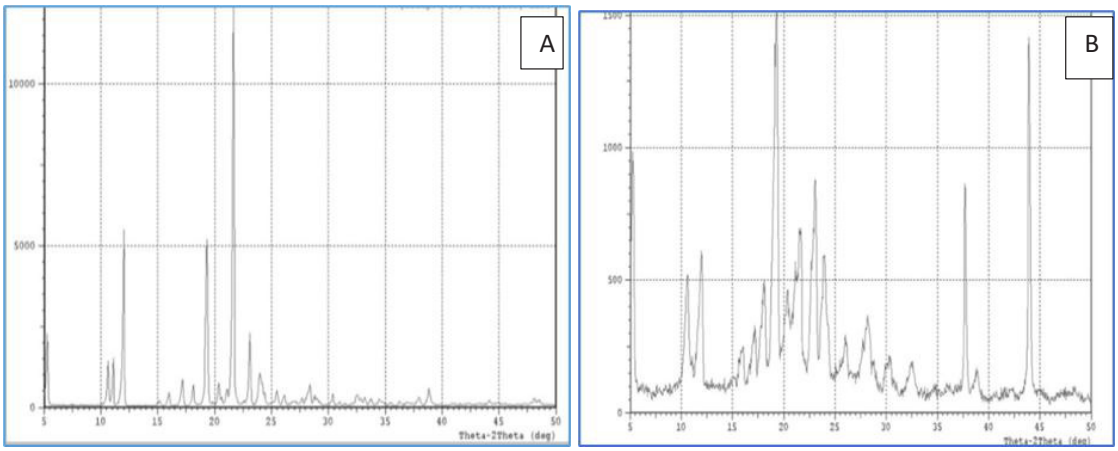

Fig. 7. (A)x-ray of raw Nimesulide and(B) x-ray of F2 formula.

Fig. 8. Photograph of prepared Nimesulide hydrogel F2 formula.

at 8 hours, while F2 hydrogel (contain 2% w/w Carbopol) was reached to 35% at 4 hr. and to 68% at 8 hr. At the same time, plain hydrogel of raw Nimesulide gave the lowest release percentage, where at 4hr the percent of cumulative drug release was 20.3%, and at 12hr the percent of release reached to 68.6. As seen from the results there is a significant difference ($p<0.05$) between the F2 hydrogel contain 1% w/w Carbopol and F2 hydrogel contain 2% w/w Carbopol as well as the hydrogel contain raw Nimesulide. This indicates that Nimesulide nanosuspension enhances medication release and dissolution from hydrogel formulation. Walaa A. Saihood showed similar profile of release in the preparation of prednisolone hydrogel [29] In addition, it was found, as the viscosity of hydrogel layer increased as in F2 hydrogel (contain 2% w/w Carbopol) the diffusional path length increased with hindrance of drug release [30].

CONCLUSION

According to the results attained, Nimesulide nanosuspension was successfully prepared by solvent antisolvent precipitation technique and it was an effective method, the PVP-K15 is the best polymer used to prepare Nimesulide nanosuspension. The prepared formulation of Nimesulide nanosuspension-hydrogel showed a best drug release profile compered to raw Nimesulide hydrogel and good spreadability and viscosity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this

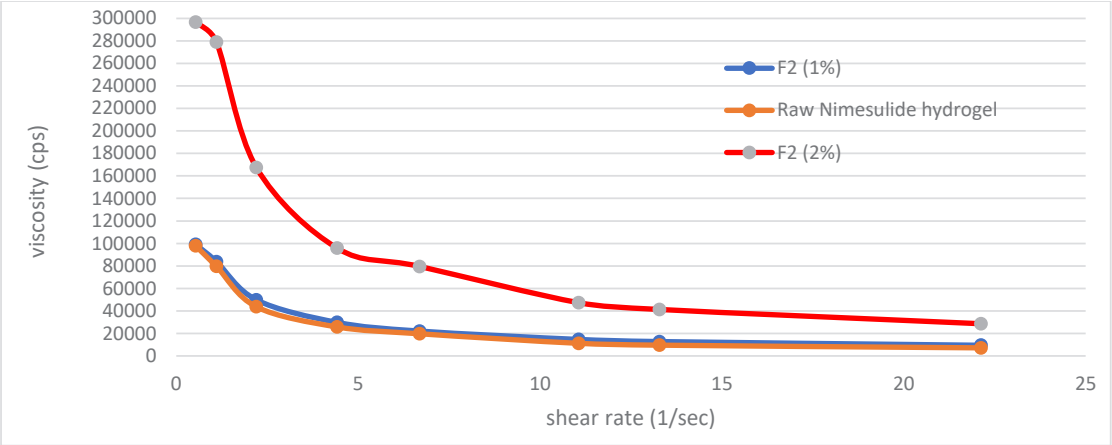

Fig. 9. Viscosity profile for plain hydrogel of Nimesulide and for F2 hydrogel.

Table 3. Drug Content, pH, and Spreadibility of Nimesulide Hydrogel.

Formula	pH	Spreadibility g.cm/sec	Drug content
F2 hydrogel 1%w/w	5.7	12.2	96.1%
F2 hydrogel 2% w/w	5.9	8.5	94.5 %
Raw Nimesulide hydrogel	5.5	10.4	94 %

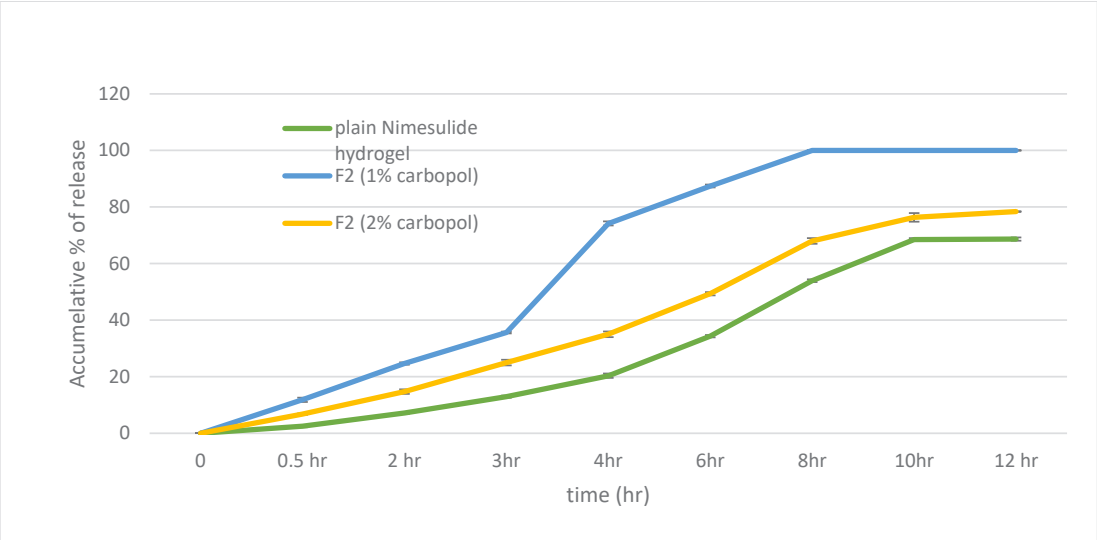

Fig. 10. in vitro release profile of Nimesulide nanosuspension hydrogel F2 (1%w/w and 2% w/w) and plain Nimesulide hydrogel (mean± SEM (n=3)).

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