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Formulation and Characterization of Ketoprofen Nanoparticles as Hydrogel Dosage Form

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ABSTRACT

Nanoparticle technology is currently widely employed to accelerate drug dissolving and greatly improve bioavailability. Nanoparticles were mixed with hydrogel to create a nanoparticle-hydrogel hybrid system as an alternative to traditional dosage forms. The purpose of this work is to create an effective hydrogel form containing ketoprofen nanoparticles for topical application, ketoprofen a potent non-steroidal anti-inflammatory drug. Eleven nanoparticle formulations of ketoprofen were prepared and characterized for particle size, specific surface area SSA and PDI, by use different polymers (PVP-K15,HPMC-E15 and HPMC-E50) in three different polymer: drug ratio (1:1,2:1 and 3:1).The results indicate increasing in the concentration of PVP K15 generally reduces significantly ($p \leq 0.05$) ketoprofen particle size, so select the smallest size formula F3 contain PVP-K15 in ratio polymer :drug (3:1) was 74.9 nm for further characterization which are SEM, X-ray and DSC ,then use this F3 formula to prepare hydrogel and assessment the physical appearance, pH, drug content, spreadability test, viscosity, and in-vitro drug release. The results showed the drug content of ketoprofen nanoparticles F3 in hydrogel was 96.4%, spreadipility was 11.2 $gm.cm^2/sec$, hydrogel viscosity was (6500cps to 75400cps), and drug release from F3 hydrogel was 96.13% at 10hr. there was a significant enhancement in drug release from this nanoparticle hydrogel than plain ketoprofen hydrogel.

Keywords: Ketoprofen, Nanoparticles, Hydrogel, and Improve Dissolution.

I. INTRODUCTION

The drug molecule's solubility could play a significant role in finding out how much dissolves and can be absorbed. A compound with low water solubility could have a slow rate of dissolution and insufficient absorption during the gastrointestinal residence period. The number of medication applicants who classified it as having low water solubility has increased in the field of drug innovation, and in the new year, 70% of new drug candidates demonstrated poor water solubility. Currently, over 40% of oral medications with quick release that are sold are classified as nearly insoluble in water.[1] Nanotechnology is the study of materials and technologies at the nanoscale, as demonstrated by the creation, processing, and use of materials and devices with nanosized particles ranging from a few to several hundred nanometers.[2] The development of novel drug dosage forms through nanotechnology concepts is producing promising nanotechnology tools for disease treatment[3], medication-loaded nanoparticulate systems, often known as nanomedicines or nanodrugs, have started to produce surprising findings related to medication efficacy and the lack of side effects. Actually, by optimizing drug concentration at the site of action, these nanocarriers can create a deeper and longer bond between the active agent and the unhealthy tissue or cells.[4] IN this research ketoprofen prepared as nanoparticles and incorporate to hydrogel dosage form. Ketoprofen chemical name is 3-Benzoyl-α methyl benzene acetic

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acid. It has a molecular weight of 254.3g/mol and a dissociation constant (pKa) value of (4.5). Ketoprofen a potent non-steroidal anti-inflammatory drug (NSAID) that is often used for the treatment of acute and chronic arthritic disease. Ketoprofen has pharmacological effects that are believed to be related to the suppression of prostaglandin production.[5] When patient has arthritis in joints, you may not need to subject yourself to the risks of oral nonsteroidal anti-inflammatory medication, such stomach upset or heart problems to achieve some relief. To reduce pain in aching joints, apply a topical NSAID to the affected area. When it comes to pain treatment, topical NSAIDs are just as effective as oral NSAIDs, but they come with a lower risk: benefit-to-cost ratio.[6] So, to reduce the side effect of ketoprofen and increase it is solubility prepared as nanoparticles and then as hydrogel dosage form similar study done by Rai Muhammad and Sarfraz.[7,8] Hydrogels are known as smart drug delivery systems.[9] Because of the physical or chemical cross-linking of hydrophilic polymer chains, hydrogels are three-dimensional network systems that have the ability to absorb more water.[10] Because of chemical or physical cross-linking, these complexes are not dissolved by the suitable media.[11] Physical and chemical crosslinking processes are used in the development of hydrogel compositions.[12] The current problem for existing pharmaceuticals is improving their safety efficacy ratio, which needs to be addressed rather than developing novel drugs that incur large cost and time constraints.[13] From this conclude that nanoparticles and hydrogels are therefore a good option for improvement solubility and reduced side effect associated with use ketoprofen.

II. METHODS AND MATERIAL

Materials

Ketoprofen from (Lishuinanming Chemical CO., LTD china), poly vinyl pyrrolidone PVP-K15 from (ALPHA Chemika-INDIA), Hydroxypropyl methyl cellulose HPMC-E15 and HPMC-E50 from (Gromax Chemicals - USA), carpobol 940 (Alpha chemika, India), Ethanol (Hayman Ltd. UK), disodium hydrogen orthophosphate (BDH Laboratory supplies, England), Potassium dihydrogen phosphate from(Sd Fine-Chem Limited, India), sodium chloride (Sigma, USA) , and dialysis membrane from (Shanghai Dianrui Biotechnology Co.,Ltd).

Method

Preparation of Ketoprofen nanoparticles

Different formulas of ketoprofen nanosuspensions were prepared by the solvent: antisolvent technique.[14] Ketoprofen 25 mg, was dissolved in ethanol (5 ml) and this organic solution of drug injected by using syringe at rate 1 ml /min into 50 ml of water containing different types of polymers (PVP-K15, HPMC-E15 and HPMC-E50), these polymers used in three different ratios (polymer :drug ratio 1:1,2:1 and 3:1) at 1000 rpm for 30 min, Ketoprofen is particularly insoluble in water, therefore, it precipitates with stabilizer as fine particles. The nanosuspension were then lyophilized to obtain the nanoparticles powder. The constituents and several conditions of preparation of different formulas of nanoparticles are listed in Table (1) below.

TABLE I: Composition of ketoprofen nanoparticles formulas

No. of formula	Ketoprofen (mg)	PVP-K15 (mg)	HPMC-E15(mg)	HPMC-E50 (mg)	Solvent: anti solvent ratio
F1	25	25			1:10
F2	25	50			1:10
F3	25	75			1:10
F4	25		25		1:10
F5	25		50		1:10
F6	25		75		1:10
F7	25			25	1:10
F8	25			50	1:10
F9	25			50	1:10
F10	25	75			0.5:10
F11	25	75			2:10

Evaluation of the prepared ketoprofen nanoparticles

Measurement of Particle size, poly dispersity index (PDI) and SSA

The average particle size, specific surface area (SSA), and PDI a measurement for the range of the size distribution were determined for each generated ketoprofen nanoparticle formula using the ABT-9000 dynamic light scattering nano laser particle size analyzer (Angstrom Advanced Inc.-USA), when samples are uniformly distributed within a cell and exposed to laser light, the light will scatter with varying energy due to the Brownian motion of the nanoparticles. After the photons are

counted using a photon counter, they are converted into signals using auto-arithmetic correlation. In order to obtain the size distributed curve, correlation curves are finally analyzed by specialized particle sizing software.

Formulation variables effect on the properties of prepared ketoprofen nanoparticles

Impact of stabilizer type

F1, F4 and F7 formulas were prepared containing different polymers (PVP-K15, HPMC-E15 and HPMC-E50 respectively) in the same polymer: drug ratio (1:1) and used to study the effect type of polymer on size of ketoprofen nanoparticles as show in table (1)

Impact of stabilizer concentration

Ketoprofen nanoparticles prepared formulas from F1 to F9 by use three polymers (PVP-K15, HPMC-E15 and HPMC-50) in three different polymers: drug ratio 1:1 ,2:1 and 3:1 to show effect of polymer concentration on size of ketoprofen nanoparticles as shown in table (1).

Impact of solvent/antisolvent ratio

The effect of the ratio of volume of solvent: antisolvent (ethanol: water) on the size of the formed ketoprofen nanoparticles was studied in three ratios of 1:10, 0.5:10 and 2:10 respectively at 1000 rpm for 30 min in F3, F10, and F11 at Polymer: drug ratio of 3:1 (PVP-K15) as shown in table (1).

Characterization of Lyophilized Powder scanning electron microscopy (SEM)

The surface morphology of the particles for raw ketoprofen and lyophilized powder of smallest size formula were distinguished using a scanning electron microscope (INSPECT S50). Direct powder deposition on double-sided carbon tape and coating with gold served as confirmation of the process(Dixit et al., 013)

X-ray diffraction

The crystalline structure of raw ketoprofen and a selected formula of produced nanoparticles were investigated using X-ray diffraction. The operational voltage and current for the X-ray diffraction were 30 kV and 40 mA, respectively.

Differential scanning calorimetry (DSC)

The crystalline nature of raw ketoprofen and the lyophilized nanoparticles powder of a chosen formula were evaluated using DSC, which also helped to explain the drug's compatibility with polymers and the thermal characteristics of the samples that were examined using an automatic thermal analyzer system. In this test used an empty aluminum pan as a reference, precisely weighed samples of 5 mg were placed in a non-hermetically aluminum pan and heated at a rate of 20ºC/min. Range of temperatures: 50°C to 300°C.[15]

Preparation of ketoprofen Hydrogel

The smallest size formula of Ketoprofen nanosuspension was added individually to the hydrogel formulation using carbomer 940 concentrations (1% w/w). The calculated amount of carbomer 940 was dissolved in 40 milliliters of distilled water and stirred with a magnetic stirrer for one hour at 700 rpm to achieve a uniform dispersion. The pH was then adjusted to 6.8 by adding roughly 5 milliliters of 10% (w/v) sodium hydroxide, and the mixture was allowed to swell for twenty-four hours to produce a high viscosity solution. Then on magnetic stirrer was added gently the freshly made ketoprofen nanosuspension formulation to the viscous solution of carbomer 940. Next, spastulation for one hour to ensure that the hydrogel mixture is evenly distributed. Furthermore, this hydrogel combination was supplemented with a 0.1% (w/v) methyl paraben and a 0.01% (w/v) propyl paraben solution in water. The hydrogel's final weight was reached at 100 grams using water.[16] The manufactured hydrogel formulations were placed in screw-capped plastic jars with a wide mouth. The jars were additionally covered with aluminum foil and left in a dark area at room temperature for 24 hours in order to do additional testing. And plain ketoprofen hydrogel prepared by same procedure for comparative study.

Evaluation of the prepared ketoprofen nanoparticles hydrogels

Physical appearance of hydrogel formulations

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

Measurement of pH

A digital pH meter was used to test hydrogel formulations at room temperature by submerging the electrode in the hydrogel formulation to determine the pH of the gel form.[17]

Spreadability Test

After two days of formulation ketoprofen hydrogels' spreadability was determined by measuring their diameter between two glass slides 0.5 g of prepared hydrogel put between two glass plate. Then put 0.2kg weight on these glasses for five minutes. Where no more spreading was expected the increase in the diameter due to spreading of the gels was recorded.[19]

Determination of Drug Content

The amount of ketoprofen in hydrogel formulations was measured by dispersing 300 mg of the formulation in 30 ml of phosphate buffer (pH 7.4), stirring the mixture for 30 minutes on a magnetic stirrer, sonicating it for an hour, and then filtering it through a 0.45 µm cellulose membrane. The amount of ketoprofen in the sample was determined using a UV-spectrophotometric Shimadzu 1800 at 260 nm after it had been diluted with the proper volume of phosphate buffer pH 7.4.[20] The experiment conducted triplicate and average was recorded.

Viscosity study

The viscosity ketoprofen hydrogels was measured using viscometer (Fungi-Lab rotational viscometer- Spain). The spindle number R6 was used, this method called cub and bob method. Spindle was immersed in cup containing sample of hydrogel form, the rheological study has been performed with increase the rotation speed from (10) to (100) rpm and decreasing rotation speed from (100) to (10) rpm.[21] The time interval between the determinations and the duration of each measurement have been ten seconds, viscosities of the different formulations were determined at 25°C following the guideline of the manufacturer and average of triplicate was recorded.

In vitro drug release

Drug release from ketoprofen nanoparticles hydrogel (used selected formula) and from plain ketoprofen hydrogel were assessed using dialysis membrane (cut off 14000 Dalton). The experiment was tested in a dissolution apparatus (paddle method) with a 100-rpm rotation speed at 37± 0.5 ºC and contain phosphate buffer with pH 7.4 was used as a dissolution media and it was used to soak the dialysis bag. Each dialysis bag contained (600mg hydrogel of selected formula equivalent to 15 mg of ketoprofen then the bag was sealed at both ends, and it placed in 200ml phosphate buffer pH (7.4).[22] Five ml were removed and substituted by the same volume at the time interval (0,5 ,1 ,2 ,4, 6, 8,10, and 12hr.). The sample media was measured using UV spectrophotometry. The drug release studies were conducted in triplicate.

Statistical analysis

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

III. RESULTS AND DISCUSSION

Evaluation of the prepared ketoprofen nanoparticles

Measurement of Particle size, poly dispersity index (PDI) and specific surface area SSA

The size and uniformity (polydispersity index) of suspended nanoparticles are crucial, as they dictate properties like solubility and dissolution.[23] In this study found all ketoprofen nanoparticle formulations to be in the nanometer range as shown in table (2). The smallest particles (74.9 nm) were achieved with formula F3 contain PVP-K15 (3:1 polymer: drug ratio) which is significantly decreased ($p \leq 0.05$), while the largest (667.5 nm) were seen in formula F9 contain HPMC-E50, also at a 3:1 ratio. The specific surface area (SSA), the total surface area of particles per unit mass, largest surface area is achieved by decreasing particle size.[24] This study found that the formulation with the smallest particles (F3) had the largest SSA (33.14 m^2/g), while the formulation with the largest particles (F9) exhibited the smallest SSA (3.3 m^2/g) were($p \leq 0.05$). The polydispersity index (PDI) measures how uniform particle sizes are in a sample, a critical factor for stable nanosuspensions. A lower PDI indicates a more uniform (monodisperse) sample(Yang et al., 2014). Table 2 shows that F1-F6 were monodisperse, F7-F9 were nearly monodisperse, and F10 and F11 had mid- range polydispersity.

TABLE II: Average particle size of prepared ketoprofen nanoparticles, SSA and PDI

Number of formulas	Average particle size (nm)	SSA m^2/g	PDI
F1	**334**	**6.3**	**0.012**
F2	**125.5**	**14.2**	**0.009**
F3	**74.9**	**33.14**	**0.008**
F4	**236.5**	**9.22**	**0.014**
F5	**317**	**6.39**	**0.05**
F6	**530.5**	**4.2**	**0.014**
F7	**375**	**5.65**	**0.06**
F8	**530.5**	**4.43**	**0.05**
F9	**667.5**	**3.3**	**0.08**
F10	**375**	**9.22**	**0.1**
F11	**236.5**	**5.65**	**0.3**

Formulation variables effect on the properties of prepared ketoprofen nanoparticles

Impact of type and concentration of stabilizer on size of ketoprofen nanoparticles

Different polymers used to stabilize ketoprofen nanosuspensions at a 1:1 polymer-drug ratio resulted in varying particle sizes (334 nm, 236.5 nm, and 375 nm for formulas F1, F4, and F7, respectively) as shown in figure (1). This demonstrates that polymer type significantly influences the final particle size, likely due to differing affinities between the polymers and the ketoprofen particles. Common stabilizers like PVP-K15 create a steric barrier to prevent particle aggregation, while amphiphilic stabilizers enhance this effect through a "wetting" mechanism.[25] HPMC, another frequently used stabilizer, is thought to interact strongly with the hydrophobic surface of drug nanoparticles due to its alkyl substituents.[26] Formula F1-F9 show the effect of polymer concentration on size of ketoprofen nanoparticles as in figure (1) below, F1-F3 in these formula use PVP-K15 in ratio 1:1, 2:1 and 3:1 respectively to prepare ketoprofen nanoparticles. The smallest particle size was achieved with pvp-k15 in F3 (74.9 nm) in polymer: drug ratio 3:1 then F2 (125.5 nm) with ratio 2:1 and F1 (334nm) in ratio 1:1. The size of ketoprofen nanoparticles is significantly influenced by the concentration of the polymers used for stabilization. Increasing the concentration of PVP K15 generally reduces significantly ($p \leq 0.05$) particle size, likely due to improved particle coating and stabilization. However, insufficient PVP K15 leads to aggregation. While with use HPMC (E15 and E50), increasing the polymer: drug ratio (from 1:1 to 3:1) increases particle size significantly($p \leq 0.05$). This is probably because, after all drug particles are coated, additional polymer either thickens the coating on each particle or causes the coated particles to clump together. Therefore, finding the optimal polymer concentration is essential for controlling nanoparticle size.[27]

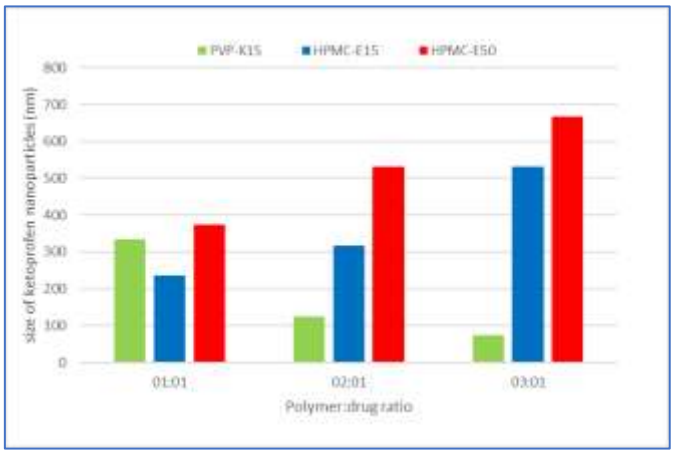

Fig1: Impact of stabilizer type and concentration on ketoprofen nanoparticles.

Impact of solvent/antisolvent ratio

Figure 2 shows the effect of the solvent-to-antisolvent volume ratio on ketoprofen nanoparticle size. A 1:10 ratio yielded the smallest average particle size, a statistically significant result ($p \leq 0.05$) compared to other ratios. This agrees with Dong et al.'s findings[28] for spironolactone nanoparticles, where a 1:10 ratio also produced the smallest particles.

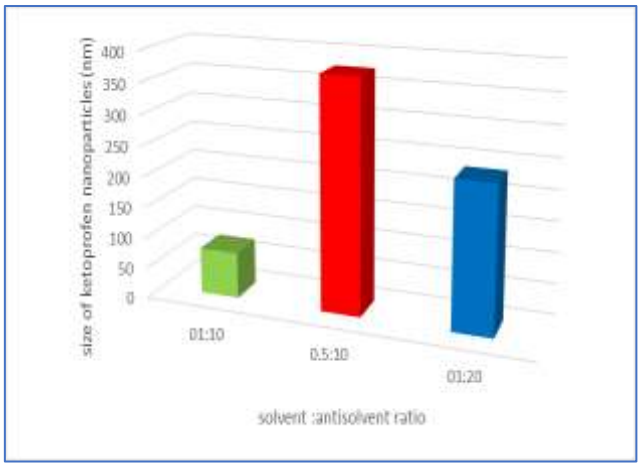

Fig 2: Impact of solvent: antisolvent ratio on size of ketoprofen nanoparticles

Characterization of Lyophilized Powder

Scanning Electron Microscope SEM of lyophilized ketoprofen nanoparticles

The morphology of the particles was examined using a scanning electron microscope. SEM pictures of raw ketoprofen particles are displayed in Figure (3-A). They revealed that the drug particles had the appearance of big crystal-shaped particles. Figure (3-B) showed the morphology of the lyophilized drug nanoparticles for F3 at a magnification power of 86.5 kx. There is no indication of agglomerations, and the particles in these formulations are discrete with a modest and homogeneous distribution.

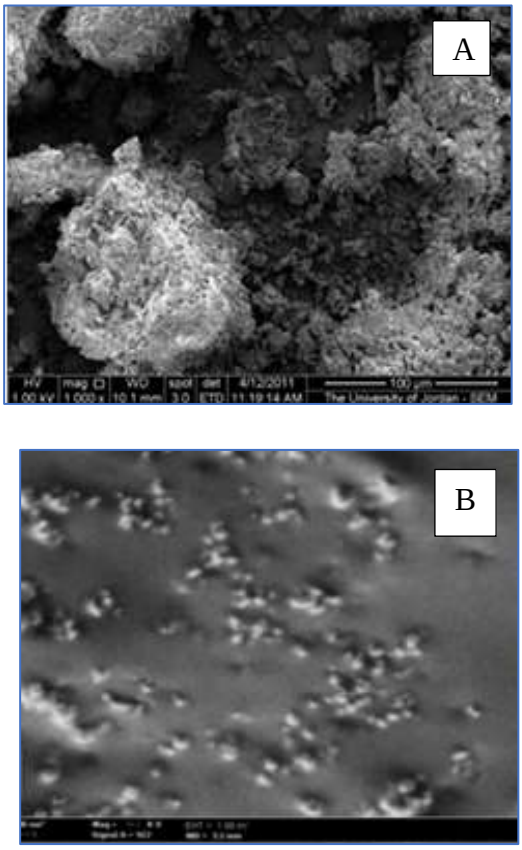

Fig 3: SEM image of raw ketoprofen (A) and F3 (B)

X-ray diffraction

The X-ray diffraction technique was used to ascertain the physical characteristics of drug particles. The crystalline forms of raw ketoprofen and particles of drug in the selected formula (F3) were evaluated to prove the effect of nanoprecipitation technique as an approach of particles reduction on the crystallinity of drug particles. The sharp and strong peaks for raw Ketoprofen particles at specific 2θ value (14. 6º, 18.5º, 23. 6º, and 24.9º) in X-ray diffraction graphs were observed in figure (4-A) below. Also, the X-ray pattern of Ketoprofen powder showed the presence of several separated peaks which indicated the crystallinity of drug particles. The results of the X-ray diffraction for F3 showed that the X-ray diffraction graphs of Ketoprofen nanoparticles in these formulas were changed. several peaks were missing; in addition to that the parameters of peaks were also changed such as position of peaks and the intensity of peaks, as illustrated in figures (4-B). It could be concluded that the X-ray diffraction confirmed the changing in drug crystal structure and some of powder particles converted to amorphous state.

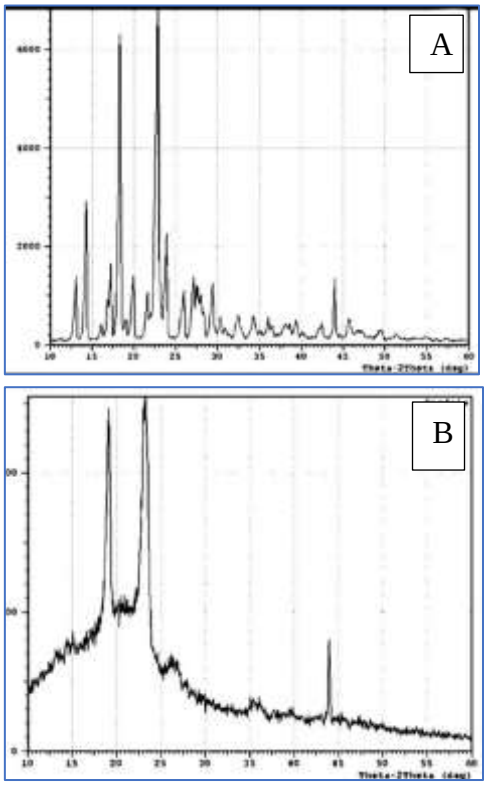

Fig 4: X-ray of raw ketoprofen (A) and F3 (B)

Differential scanning calorimetry DSC

To confirm the physical state of materials in formulation, DSC was performed for raw Ketoprofen powder and lyophilized powder of best formulas (F3). DSC scan of Ketoprofen showed a single sharp endothermic peak at 97.28ºC corresponding to the melting point of drug, which indicated the crystalline state of drug[29], as shown in figure (5-A). While the selected formulas, the crystalline structure had been reduced significantly and the melting endothermic peak was shifted from to 90.15ºC as show in figures (5-B). DSC study proved that

crystallinity of Ketoprofen was reduced in nanoparticles formulations and this result match the above X-ray result of ketoprofen nanoparticles formula F3.

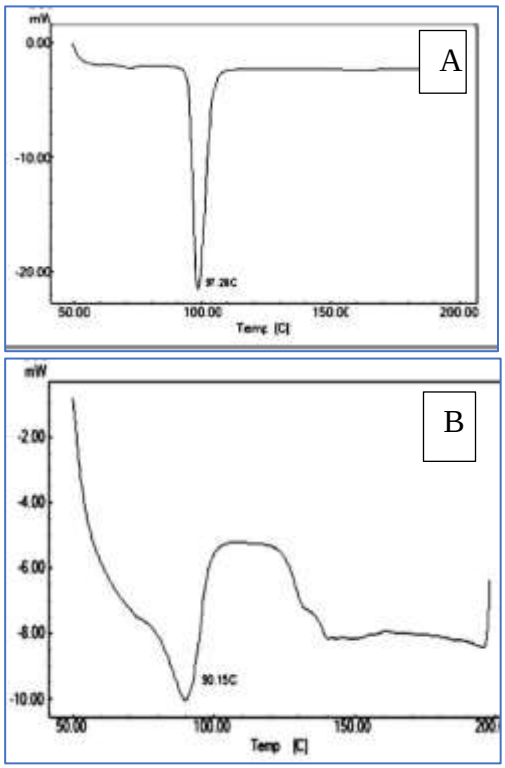

Fig 5: DSC of raw ketoprofen (A) and F3 (B)

Evaluation of the prepared ketoprofen nanoparticles hydrogels

Physical appearance of ketoprofen hydrogel

The color and physical appearance of F3 in hydrogel formulation gave a translucent and homogenous consistency as show in figure (6).

Fig 6: physical appearance of F3 hydrogel

pH measurement of hydrogel

The pH of hydrogel containing F3 ketoprofen nanoparticles and PH of plain hydrogel of ketoprofen are (5 and 5.5) respectively. This result with normal range of skin PH (4 to 6)[30], and this implies the appropriateness of the application on the skin.

Spreadability test for hydrogel

Spreadability of F3 hydrogel and plain hydrogel of ketoprofen were (11.2 gm.cm^2/sec and 7.4 gm.cm^2/sec) respectively. Spreadability parameter is an important factor in enhancing the patient compliance. Uniform application of gel on the skin is dependent on the spreadability of gel, where a good gel takes less period to spread.[31]

Determination drug content in hydrogel formulation

When the drug content of ketoprofen was measured, it was found to be 96.4% ±0.03 for the hydrogel made with the F3 formulation and 94.33% ±0.02 for the plain ketoprofen gel. The formulations' drug content test revealed that the drug particles were evenly dispersed throughout the gels.

Viscosity study

The viscosity of the ketoprofen nanoparticles F3 hydrogel found in range (6500cps to 75400cps) and (5400cps to 65700cps) for plain ketoprofen hydrogel as shown figure (7), generally the viscosity of hydrogels was determined at various shear rates, it was found that decrease in the viscosity of hydrogel as the rpm was increased.

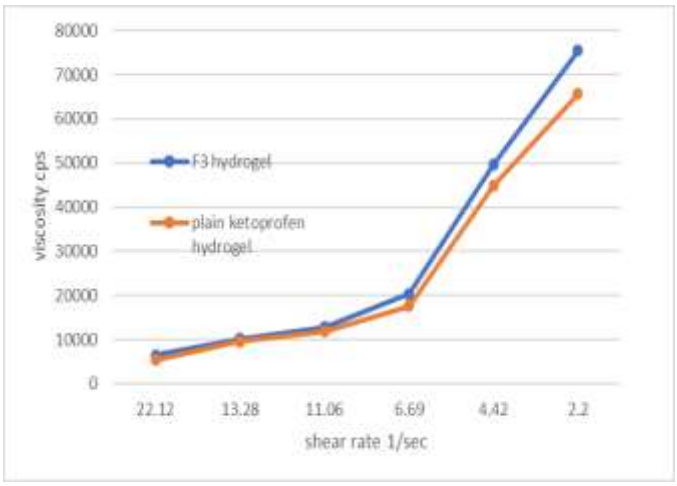

Fig 7: Viscosity profile of F3 and plain ketoprofen hydrogel mean±SEM (n=3).

Invitro release of ketoprofen hydrogel

The in vitro drug release studies were carried out in phosphate buffer solution PH 7.4 for 12 hr. using dialysis membrane and used dissolution apparatus (paddle method) with a 100-rpm rotation speed at 37± 0.5 ºC. Figure 8 shows the in vitro drug release study of F3 hydrogel and plain ketoprofen hydrogel. The percentage of cumulative drug released from these two formulations were 96.13% and 53.3% respectively at 10 hr., from this result show plain hydrogel of Ketoprofen gave the lowest release percentage, in comparative to hydrogel contain ketoprofen nanoparticles F3. So, there is a significant difference ($p<0.05$) between them. These findings suggest that the increased percentage of ketoprofen release from F3 hydrogel was due to an increase in the surface area of these nanoparticles, this result corresponds with the Noyes-Whitney equation, which establishes that an decrease particle size lead to an increase in dissolving rate and hence bioavailability[32], as well as a reduction in crystalline state of ketoprofen , as validated by X-ray analysis. These data support the hypothesis that the precipitation process was an efficient and successful way for preparing nanoparticles.

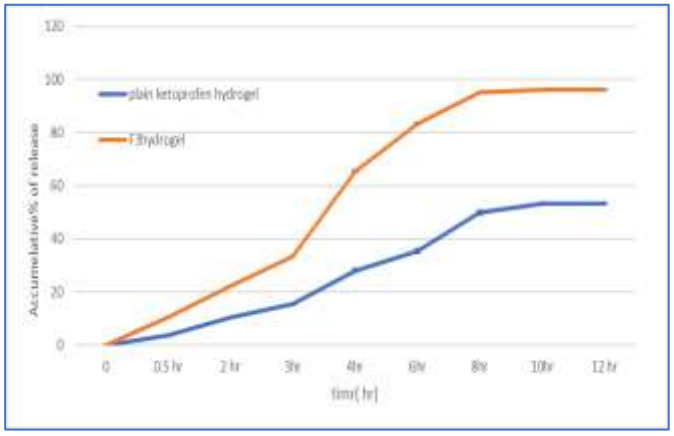

Fig 8: Release profile for plain ketoprofen hydrogel and F3 hydrogel mean±SEM (n=3).

IV.CONCLUSION

According to the data, the solvent antisolvent approach was a successful and efficient way for manufacturing ketoprofen nanoparticles. Among three polymers, PVP-K15 give best formulas (F3) with polymer: drug ratio 3:1, increase ratio of polymer: drug give best result on size of ketoprofen nanoparticles. While when use HPMC (E15 and E50) for prepare ketoprofen nanoparticles,was found increasing the polymer :drug ratio above 1:1 increases particle size. The nanoparticle-hydrogel F3 formulation demonstrated good spreadability, viscosity, and drug release profiles than plain ketoprofen hydrogel.

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