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Fabrication and Characterization of Nanoparticles Based Matrix Tablets of Flurbiprofen for Sustained Drug Delivery System.

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Abstract
The objective of existing work was development by keeping two objectives in mind, firstly to prepare and evaluate flurbiprofen (FBL) loaded nanoparticles and secondly, fabrication of nanoparticles loaded matrix tablets through wet-granulation.Using particle-size, zeta-potential, and entrapment effectiveness as determinants, physiochemical characteristics of FBL-loaded nanoparticles were determined. Spectroscopy techniques like X-ray powder diffraction and differential scanning calorimetry as well as infrared spectroscopy were used to investigate the nanoparticles (PXRD). All batches of nanoparticles were subjected to in vitro dissolving investigations using modified USP dissolution equipment, and the data was evaluated using zero & first order, Higuchi, Korsmeyer, and Hixson-Crowell equations.The resulting FBL nanoparticles were physically stable and had particles that ranged in size from 150 to 350 nm. Overall drug-release of FBL through matrix tablets was found sustain up to 16 hrs. The drug release kinetics profiles revealed that all the formulations follow non-Fickianmechanism.

1. Introduction

The large number of active pharmaceutical compounds with poor water solubility that come as a result of the drug research process limits oral bioavailability and dissolution rate [1-2]. Drugs having low water solubility are associated with large molecular weight and greater log-P value [2]. The rate-limiting factors for oral absorption are the medication's solubility, dissolution, and permeability. Bio-availability of the medicine may be influenced by a variety of physiological, physicochemical, and environmental factors. Drug size reduction promotes oral bioavailability by increasing the drug's effective surface area, which improves the drug's solubility and rate of dissolution [3–4].

Nanomaterials are used as diagnostics or deliverymeans for therapeutics to specific targeted regions in predeterminedway in nanosystems, two relatively young but quickly emerging fields of study.

Nanoparticles may be used to address issues with oral bioavailability and slow degradation [5-8]. In order to achieve the formulation, one can either use a top-down approach (wherein larger particles are broken down into smaller ones) or a bottom-up approach (wherein the smallest particles are first) (such as creating smaller particles by precipitation

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at the molecular level) [9–13]. One of the most efficient ways to produce therapeutic chemical nanoparticles that are not easily soluble in water is through nanoprecipitation [14]. On the other hand, the presence of a stabilizer can prevent crystal-growth and particles agglomeration caused by Van der Waals forces or Ostwald ripening [15]. Steric stabilizers such HPMC K4M (Hydroxypropyl methylcellulose K4M) and poloxamer 407 provide stable dispersion via steric hindrance [13]. Due to its practical insolubility non water, the drug flurbiprofen (FLB) is classified as class-II BCS molecule. Although there are many drug delivery systems that have been successfully used recently, there are still some issues that need to be resolved and cutting-edge technology needs to be developed in order to successfully transport medications to their target sites. In promotion of an advanced system of drug delivery, nano-systems are presently explored to a large extent [16-21].

Recently, many researchers focused on polymer matrix system for controlled drug delivery system. Matrix technologies have repeatedly proven to be popular among oral-controlled formulations due to their low complexity, simple manufacturing, high repeatability, stable raw materials and dose form, ease of scale-up, and simplicity of process validation [22-30].

Alginates are among the most adaptable biopolymers and are utilized in a variety of applications [31-32]. Alginate's traditional uses as adjuvant in dosage forms often rely on its thickening [33], gel-forming [34], and stabilizing properties [35]. The needs for custom-made polymers have increased as a result of the need for improved and longer-lasting medication administration management. A controlled-release product's design may benefit greatly from the use of hydrocolloids like alginate [36]. When alginic acid is hydrated at low pH, a "acid gel" with a high viscosity is produced. A divalent cation acting as the calcium ion makes alginate gel more quickly as well. The medication is homogeneously disseminated in controllable polymeric matrices in oral solid dose forms such polymer matrix systems. It appears that one might potentially control the release of pharmaceuticals from polymer matrix systems by altering the substance that the medications are encapsulated in. For the purpose of developing controlled release formulations such as tablets with a two- or three-layer matrix [37], HPMC polymer is being employed as a tablet matrix forming material.The aims of the current study were development and assessmentof flurbiprofen-loaded matrix tablets based on nanoparticles as a sustained drug delivery technology.

2. Materials And Methods

2.1. Materials

Flurbiprofen (FBF), hydroxypropyl methylcellulose K4M (HPMC K4M), and Poloxamer 407 were gently donated by Sun Pharma Pvt. Ltd. Ahmednagar.The analytical purity standard was adhered to for each and every one of the reagents and other compounds that were utilized. Throughout the entirety of the experiment, water that had been distilled twice was utilized.

2.2. Methods

2.2.1. Experimental Design for fabrication of FBF loaded nanoparticles

In preliminary screening investigations, it was examined how process and formulation factors affected FBF nanoparticles as well as its stability. It was determined that drug-polymer ratios were crucial formulation parameters,as well as the fact that the speed at which the stirrer was operating was a critical determinant of the success of the mixing procedure. Thus, the drug-polymer ratios and the mixing speed are both free parameters. The 3^2 factorial design was used to examine and optimize the effects of three different levels (-1, 0 and +1) of specified process and formulation parameters. The drug concentration, ratio of drug to surfactant, and stirring time were all kept at 0.1 percent w/v during the entire experiment.

2.2.2. Preparation of physical-mixture of FLB, HPMC K4M and Poloxamer 407

A physical mixture was made for comparison with the optimized formulation by combining FLB, HPMC K4M, and poloxamer 407 in the same ratios. After thoroughly combining the components in a mortar until they achieved a consistent consistency, the mixture was strained through a

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screen with a 40-mesh opening and placed in a desiccator.

2.2.3. Preparation of FLB loaded nanoparticles

Table 4 details the nanoprecipitation method used to create FLB nanoparticles. FLB and HPMC K4M exactly balanced thendissolved in 10 ml of ethanol using a sonicator. The synthesized organic phase of the drug was injected into hundred ml of distilled-water that contained poloxamer 407 at various ratios using a syringe (26 G) operating constantly (0.5 ml/min). The mixture was stirred for an hour at various speeds with a mechanical stirrer. The excess ethanol was removed by air drying. The nanoparticles were next subjected to a 15-minute sonication. Lyophilization was done on the optimized FB8 formulation. Testing was done on the resulting nanoparticles. A container that was airtight was used to preserve the freeze-dried product until further characterization.

2.3. Evaluation of optimized FBF nanoparticles

2.3.1. Particle size distribution and zeta potential
The Nanoparticles Analyzer SZ-100 Zetasizer was used to determine the average particle-size and PDI of nanoparticles in suspension (Horiba Scientific, Japan). Laser Doppler Anemometer and Nanoparticles Analyzer SZ-100 zeta potential (Horiba Scientific, Japan). For accurate testing, deionized water was used to dilute the samples to the correct consistency. Each sample went through a battery of three tests [18].

2.3.2. Fourier transforms infrared spectroscopy (FTIR)

Spectra were recorded using an infrared spectrophotometer (Alpha T Bruker). Scanning was performed at 4000-400 cm^{-1} with a sample weight of roughly 2-3 mg after dry KBr was added to the mix.

2.3.3. Differential scanning calorimetry (DSC)

Thermogram obtained by differential scanning calorimetry (DSC; Mettler Toledo, Staresw 920) at a flow rate of 40 ml/min in a nitrogen atmosphere and a temperature range of 25 to 200 ° C.

2.3.3. Powder X-ray diffraction (PXRD)

PXRD patterns on a diffractometer were captured (Miniflex 600 X-ray diffractometer, Rigaku Corporation, Japan). Sample scanned from 5-80° at a rate of 2°/min.

2.4. Solubility study

Phosphate buffer was used to measure saturation-solubility of in sealed glass vials at 370.5°C (pH 7.2). All vials were shaken for 72 hours at 100 rpm in a rotary shaker. The resultant dispersions underwent a 10-minute centrifugation at 40,000 rpm at 4°C. A UV/Visible spectrophotometer was used to analyze the supernatant after filtering it at 247 nm. There were three runs of each experiment.

2.5. In vitro dissolution testing

The USP Type II disso-apparatus and phosphate buffer were utilized in this study to investigate the in vitro dissolution of pure FLB, as well as a physical combination and an enhanced nanoparticles of FB8 (pH 7.2). A total of 100 mg of FLB was added to 900 ml of dissolving media, which was kept at 37±0.5°C throughout the process. The paddle rotated at a rate of 75 revolutions per minute. In order to keep track of the sink's status, five milliliter samples were obtained every five, ten, twenty, thirty, forty-five, and sixty minutes. After that, they were promptly switched out for brand new dissolving medium. All of the chemicals were passed through a Whatmann filter while being analyzed using a UV spectrophotometer set at 247 nm. There were three separate runs of each experiment.

2.6. Physical stability

Over the course of six months at 4°C and 25°C, the improved FB 8 physical stability was examined. Small aliquots of the nanosuspension were taken for particle-size & PDI determination after three and six months of storage. Three times each sample was analyzed.

2.7. Preparation of FLB nanoparticles loaded matrix tablets by direct-compression

Microcrystalline cellulose was used as the directly compressible vehicle, and magnesium stearate was used as the lubricant, in the process of formulating nanoparticles-based matrix tablets by employing

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the direct compression technique. All of the materials were screened with a mesh 40 screen before being combined with one another, and the powder mixture was then compressed on a multiple punch rotary tablet machine employing round, flat, and plain punches of 5 millimetres in diameter. In total, three formulations with varying amounts of sodium-alginate were created (F1, F2, and F3), and their respective formulae can be seen in Table 1.

2.9. Evaluation of Tablets

2.9.1. Physical evaluation of granulates

For the granules that had been formed, angles of repose, bulk and tapped densities, and Carr's index were all measured.

2.9.2. Physical evaluation of Tablets

All aspects of the physical properties of tablets, including weight variation (n = 20), thickness (n = 10), hardness (n = 10), and friability (n = 10), were evaluated.

2.9.3. Fourier transforms infrared spectroscopy

Utilizing an IR Spectrophotometer, FTIR analyses of pure drugs, sodium alginate, physical mixtures, and optimized formulations of matrix tablets were conducted, and spectra were collected (Alpha T Bruker). Dry KBras well as samples weighing two to three milligrams were mixed, and the scan speed was 400 to 400 cm^{-1}.

2.10. Swelling behavior studies

In a phosphate buffer solution with a pH of 6.8, the ability of each batch of tablets to swell in vitro was evaluated. After that, the chosen matrix tablets were weighed, and then they were placed in metal baskets that had a tarnished appearance. After that, these baskets were submerged in a phosphate buffer solution of 6.8 at 37±0.5°Cand 100 revolutions per minute.The basket containing the matrix tablets was taken out at predetermined intervals, casually stained using tissue-paper for removal of extra water, and weighed again. Then, as soon as possible, they were returned to the disintegration vessel.

The following formula was used to get the percentage of swelling:

Percentage degree of swelling = [(Ws – WD) / WD] × 100

2.11. *In vitro* Drug Release

The in-vitro release research of FLB nanoparticles packed matrix tablets (F1 to F3) was carried out with the help of the USP apparatus II (paddle method). As the dissolution media, phosphate-buffer with a pH of 6.8 was used, and it was maintained at 37°C(5°C) and 100 revolutions per minute in 900 milliliters of 0.1 percent hydrochloric acid. It took 2 hours in a pH 6.8 phosphate-buffer and 22 hours in 0.1 N HCl to test the overall release of FLB tablets. 5 ml samples of the total dissolving media were taken at predetermined intervals of 0, 1, 1, 2, 4, 8, 12, 16, 20 and 24 hours, and the same amount of fresh media was substituted in their place. By measuring the absorbance of each drug's release, the percent cumulative drug release was calculated.

2.12. Drug release kinetics

Following investigations on drug release in vitro, its kinetics profile analysis was carried out by taking into account various release kinetics, such as zero-order, first-order, and Higuchi kinetics. The release mechanism was established by assuming the Hixson-Crowell and Korsmeyer-Peppas model.

2.13. Stability study

Formulations were stored for stability testing in accordance with the International Conference on Harmonization (ICH) at accelerated temperatures (400°C 200°C / 75°RH 5°RH for 90 days). Following each month, the physical traits and drug release profile were identified for examination.

3. Results And Discussion

3.1. Experimental Design

Data from the experimental runs were subjected to regression analysis, which produced the equations shown in Table 2 with statistically significant F ratios (p 0.05), Adj-R2 values between 0.8-1, and statistically non-significant lack of fit values (p > 0.05). The data were well-fit by these model equations. A synergistic impact is shown by a

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positive sign, whereas an antagonistic effect showed with a negative sign [1, 32–33].

Entrapment efficiency = +83.93 (Surface mean model)……. (1)

Particle size = $271.8 – 9.45 \times X_1 – 28.02 \times X_2 + 18.1 \times X_1.X_2 + 20.25 \times X_1^2 + 16.75 \times X_2^2$ (Quadratic model)……. (2)

Zeta potential = $– 11.65 + 2.69 \times X_1 + 1.11 \times X_2 – 0.4 \times X_1.X_2 – 0.098 \times X_1^2 + 0.23 \times X_2^2$ (Quadratic model)……. (3)

FBF: HPMC K4M: Poloxamer 407 ratio and stirring speed (RPM) are represented by X1 and X2, respectively.

According to equations (2) and (3), increasing stirring duration reduces particle size while increasing surfactant concentration up to a certain level improves entrapment efficiency. Zeta-potential reduced by increased surfactant content.

3.2. A. Impact of formulation parameter (FBF: HPMCK4M: Poloxamer 407 ratio) on entrapment efficiency, particle-size and zeta-potential

The proportion 1:1:2 of drug, polymer, and surfactant, as shown in Figs. 1A and 1C, demonstrated better entrapment effectiveness. Higher surfactant concentrations than what is advised resulted in poorer entrapment efficiency, which was probably brought on by drug surface adsorption. With increased surfactant content, a little drop in zeta potential was seen. The existence of micelle production and higher drug surface adsorption may be the cause of this.

3.2. B. Effect of a process parameter, namely stirring speed, on the entrapment efficiency, particle size, and zeta-potential of the mixture

As can be observed in Figure 1B, the stirring speed has a direct influence on the rate at which the particle size decreases.It might be brought on by enhanced particle counter diffusion and attrition during nanoprecipitation. The attraction between nanocrystals is induced by additional mechanical energy.

3.3. A. Model Validation

To create the optimum FBF nanoparticles, Design-Expert software analyzed the desirability function. Table 3 shows the model verification results, which contrast actual and anticipated values for entrapment effectiveness, particle size, and zeta potential using model equations.

3.4. Evaluation of optimized FBF nanoparticles

3.4.1. Particle-size and zeta-potential analysis

The statistics for mean particle size, percent entrapment efficiency, and zeta potential for all formulations are shown in Table 3, FBF powder was found to have average particle-size of 16.41 x 2.41 mm, whereas optimized nanoparticles (FB8) had average particle-size of 263.3 x 2.73 nm, a considerable (2-fold) reduction in particle size. The monodispersity of nanoparticles is shown by the fact that the PDI of all batches of nanoparticles was determined to be in between 0.258 0.01 to 0.411 0.02. The optimized nanoparticles' (FB8) PDI value was 0.266 0.02. The nanoparticles stability index is called the zeta potential [37–39]. When there is an enough amount of stability, sterically stabilized systems have lower zeta potential value values [41-42]. It was revealed that the zeta potentials of every batch of nanoparticles ranged from -15.91 0.08 mV to -7.91 0.37 mV. The batch of improved nanoparticles with the number FB8 has a zeta potential of -10.2 0.42 mV.

3.5. Drug entrapment efficiency (%) analysis

The entrapment effectiveness of a polymeric carrier is measured as the amount of drug actually entrapped in relation to the amount of drug initially loaded [20, 43]. As can be seen in Figure 4, the formulation FB8 with an FBF:HPMC K4M:poloxamer 407 ratio of (1:1:2) resulted in a polymeric matrix with the optimal viscosity, allowing for more efficient drug entrapment. The right ratio of the three ingredients allowed us to reach our goal. One-way analysis of variance followed by Dunnett's test showed that the drug entrapment efficacy of formulation (FB8) was significantly different from FB6 (p 0.05).

3.6. Fourier transform infrared spectroscopy analysis

Spectra of FBF and its nanoparticles showed that the typical broad peak of FBF, generated by

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hydrogen bonding in the molecule, was expanded in the lyophilized formulation (Fig.5). Stretching of the C-F bond is represented by a prominent peak at 1404 cm-1 in the IR spectrum of flurbiprofen, whereas stretching of the carbonyl group (C=O) is represented by a peak at 1687 cm-1. Carboxylic acid group O-H stretching is represented by the 3072 cm-1 peak, whereas C-H stretching is represented by the 2945 cm-1 and 2981 cm-1 peaks. In the case of HPMC K4M, the distinctive peaks peaked at Hydrogen bonding has strengthened in lyophilized FB8 nanoparticles, as seen by a minor shift in the peaks from 2976 cm-1 to 2981 cm-1 and from 3072 cm-1 to 3074 cm-1.Physical mixture and lyophilized nanoparticles spectra both displayed the identical signal.The findings also demonstrated that any chemical interactions between FBF and polymers did not increase the pace at which FBF dissolved [44].

3.7. Differential scanning calorimetry (DSC) analysis

Figure 6 displays thermograms of lyophilized nanoparticles, physical mixture, lyophilized drug, lyophilized poloxamer 407, and lyophilized poloxamer 407.Due to the FBF's crystalline structure, it showed an abrupt endothermic at 117.88°. The physical mixing of drug& HPMC (K4M) and poloxamer 407 did not alter the peak of FBF, which clearly shows that there was no physical interaction between the excipients and the medication (117.54°). A pointed endothermic peak at 117.08° was seen in lyophilized nanoparticles, which may indicate that the drug and excipient miscibility or decreased particle size is the cause. The aforementioned findings demonstrate that crystallinity didn't change considerably throughout the formation of FBF. By analyzing the XRD data, the DSC results were confirmed [1-2, 39-40].

3.8. *Powder X-ray diffraction analysis*

To find out how excipients and the formulation process affected the crystallinity of FBF, an X-ray diffraction research (Fig. 7) was done on crude FBF, HPMC K4M, Poloxamer 407, physical mixture, and lyophilized nanoparticles FB8. Indicating its crystalline nature, FBF showed clear and distinct peaks at 2 values of 12.1, 18.0, 19.8, 19.9, 22.7, and 24.1°, HPMC K4M and poloxamer 407 XRD pattern demonstrated their amorphous nature. The unique FBF peaks were still visible in the lyophilized nanoparticles and physical mixture, but their intensities were slightly diminished. The tiny interactions between the added excipients and the medicine at particular angles may be the cause of the slight change in crystallinity [6, 9, 41–42].

3.9. Surface morphology by TEM study

Fig.8 shows the findings of the TEM analysis, together with TEM graphs of the completed nanoparticles, which demonstrate the shape of the flurbiprofen nanoparticles suspended in the nanoparticles.The photos show spherical forms with improved particle agglomeration and dispersion.

3.10. Saturation solubility study

Fig. 9 displays the saturation solubility data of FBF, mixture, and freeze dried powder in 0.1 N HCl (pH 1.2), in phosphate buffer (pH 4.5), and in phosphate buffer (pH 7.2).When lyophilized powder was compared to pure FBF, Saturation solubility increased by a factor of over 77 in 0.1N HCl (799.7 10.3 g/ml versus 10.3 2.1 g/ml), by over 14 in phosphate buffer pH 4.5 (981.3 3.2 g/ml versus 67.33 3.7 g/ml), and by over 10 in 0.1N HCl (1023.7).FBF showed that its solubility rose when pH rose because it is an acidic substance by nature. In 0.1 N HCl, a substantial increase in solubility was seen. With a pKa value, FBF is acidic by nature.

3.11. Dissolution study

Biphasic drug release was depicted (Fig. 10) for FBF-loaded nanoparticles. Due to the existence of free drug that was not confined in the polymer system, rapid drug release was seen in the first phase. Due to the sluggish diffusion of FBF through the polymer matrix, a second phase of slow drug release was noticed. An early rapid release and the drug's maximal release profile were taken into consideration when optimizing each batch. Batches that had smaller particle sizes and less drug entrapment displayed a strong burst effect. In comparison to the physical combination and pure FBF, the dissolving profile of optimized FBF nanoparticles in all three media showed a notable improvement in dissolution rate. Compared to 38.21 percent and 34.41 percent, the drug release

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from the nanoparticles FB8 was 96.33%, 84.31 percent, and 72.09%.This significant rise in dissolving rate may be brought about by the polymers' increased wettability and decreased particle size. Noyes-Whitney equation states that a relative increase in effective surface area leads to a relative increase in dissolution rate. Steric stabilizers like HPMC K4M and poloxamer 407 keep particles from aggregating and increase wettability for better medication solubility.

According to the regression coefficient values (R^2 = 0.998 and R^2 = 0.993, respectively), the *in vitro* drug release profile of the enhanced FBF nanoparticles (FB8) was best fitted with zero order kinetics for dissolution in 0.1N HCl& phosphate buffer (pH 4.5). (Table5). Korsmeyer-Peppas model predicted that it will dissolve with highest efficiency (R2= 0.995) in phosphate buffer at pH 7.2.According to Korsmeyer Peppas model, all of the FBF nanoparticles had release exponent (n) values that were lower than 0.45, which showed that Fickian diffusion was the drug release mechanism. Difference (f1) & similarity (f2) factorsafter comparing the FB8 dissolving pattern in 0.1N HCl to the phosphate buffer (pH 7.2) werefound as 14 and 64, respectively.

3.12. Physical stability study

Due to nanoparticles aggregation and Ostwald-ripening progression, physical stability is a major issue in the creation of nanoparticles. Ostwald ripening, which causes larger particles to develop from smaller ones and adds to the instability of nanosuspension, over the course of three months, a physical stability analysis of improved FBF nanoparticles was conducted at 4° and 25°. Particle size and particle distribution index (PDI) both marginally increased after 3 months in both storage settings (Table 6). Therefore, there was only a slight increase in particle size. For the full three months, the absolute zeta potential of the nanoparticles ranged from -11.160.45 mV to -10.20.42 mV, demonstrating their physical stability. The presence of HPMC K4M and Poloxamer 407, which are known crystal agglomeration inhibitors [12–13, 26], may be to blame.

3.13. Evaluation of FLB nanoparticles loaded matrix tablets and granules

3.13.1. Characterization of granular properties

The flow characteristics of granules made for compressing matrix tablets were assessed; the findings are displayed in Table 7. Angle of repose values ranged from 23.20° to 26.20°, indicating excellent particle flow for all formulations. The powder formulation's bulk density ranged from 0.47±0.00 to 0.49±0.02 (gm/cm^3), but its tapped density ranged from 0.52±0.005 to 0.53±0.03 (gm/cm^3), indicating that it was not a bulky powder. The compressibility (percent) was found between 8.16±0.39 to 10.26±0.81; this shows that the tablet blend has good compressibility. These numbers show that the produced granules had satisfactory flow characteristics.

3.14. Physicochemical evaluation of FLB nanoparticles loaded matrix tablets

Table 8 presents mean tablet weightwas 250mg, the diameter of 6mm were obtained. The tablets hardness, friability, and active ingredients were all evaluated. The relative standard deviations were less than 2.0%, showing that the contents of the formulations were mixed uniformly; the amount of the active component for each of the 10 units tested was determined to be between 98.70±1.23% – 99.78±1.00 %. Mean values for hardness ranged from 5.30±0.34 to 5.33±0.035 kg/cm^2. Thickness of the tablets observed in between 2.41± 0.03 to 2.45 ± 0.08mm.

3.15. FTIR Study

When determining how well medication and excipients interact, FTIR characterisation studies are crucial. As can be seen in Fig. 11, flurbiprofen exhibits characteristic peaks at 1698 $cm^{-1}$and 2920 cm^{-1}which were related to carbonyl and hydroxyl stretching.Pointed
peak at 1404 cm^{-1} indicates the stretching of C-F, whereas the peak at 1687 cm^{-1} shows the stretching of the carbonyl group (C=O). The peak at 3072 cm^{-1} represents the O-H stretching of the carboxylic acid group, whereas the peaks at 2945 cm^{-1} and 2981 cm^{-1} indicate the C-H stretch. The medium bands at 1621, 1581, 1563, 1513 and1482 cm^{-1}can be categorized as biphenyl ring stretching modes.

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The C-H stretching vibration is attributed to the bands seen in the 3120–3030 cm^{-1}region.Sodium alginate peaks showed different functional group. O–H stretch vibration found in between 3000–3600 cm^{-1}. C–H stretch found in between 2920–2850 cm^{-1}. In the physical mixture, all the characteristics peaks of drug and sodium alginate were observed in FTIR spectra. Finally, there were no changes in the FTIR bands of FLB influrbiprofen nanoparticles based matrix tablets (F2) and pure flurbiprofen, which indicate no chemical interaction between the drug and excipients used.

3.16. *In vitro* Drug Release Study

As shown in Fig. 12, sodium alginate 25 mg (formulation F1) a sustained release polymer, released 90.23 ±1.23 % of the medication after 16 hours, indicating sodium alginate prolonged action. As a natural polymer, sodium alginate has the ability to regulate both the flow of the drug out of the tablet and the influx of the dissolution medium into it. The polymer sodium alginate also may help to enhance compressibility and build more homogenous matrices with uniform channels for water to diffuse through and dissolve the medicine in a regulated manner. The 50 mg sodium alginate in Formulation F-2 releases 93.56 percent of the medication after 20 hours. The release rates have been found to be increased when sodium alginate utilized in the right amounts as a channeling agent. Sodium alginate based F-3 formulated tablets was released 99.41 % of drug after 24 h.

Above discussed results suggested that, due to intermolecular interaction, hydration of alginic acid results into highly viscous "acid gel." Water molecules are physically imprisoned inside the alginate matrix following gelation, yet they are still free to move about. This is crucial when making matrix tablets, which act as an oral controlled and sustained drug delivery method.The results also provide an explanation for why alginate immediately hydrate to form a hydrocolloidal layer with a high viscosity. This creates a diffusion barrier that slows the movement of tiny molecules, such as medicines.

3.17. Drug Release Kinetics study

In vitro drug dissolution profiles included zero, first, Higuchi kinetics, Hixon-Crowell model and release mechanism was understand by treating by Korsmeyer–Peppas equation. Table 9 revealed that Higuchi's equation best characterized the drug release of nanoparticles because the plots had the highest linearity (R^2 = 0.9922), then zero order (R^2 = 0.9788). This explains why, according to square root kinetics (also known as Higuchi's kinetics), the medication diffuses at a noticeably slower pace due to diffusion rises. According to KorsmeyerPeppas model, all of the FBF nanoparticles loaded matrix tablets had release exponent (n) values that were higher than 0.45, which showed that Fickian diffusion was the drug release mechanism. However, it was also discovered that drug release was almost zero-order kinetic, proving release was unaffected by sodium alginate concentration. The Hixson-Crowell cube root law was also used to illustrate the *in vitro* dissolution data. The outcome likewise showed a shift.

4. Conclusions

This study successfully generated matrix tablets based on flurbiprofen nanoparticles via a wet granulation technique. The solubility, dissolving rate, and stability of nanoparticles in water were all impressive. The resulting flurbiprofen nanoparticles had a mean particle size of 200-400 nm and were physically stable. The presence of excipients slightly diminished the drug's crystalline quality in the formulation. As a result, stable nanoparticles of flurbiprofen could be developed thanks to the steric stabilization provided by the polymeric system of HPMC K4M and poloxamer 407. Moreover, Flurbiprofen nanoparticles loaded matrix tablets are able to prove sustain drug release through matrix tablets followed non-Fickian release kinetics.

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References

[1] S. Suresh, B.K. Ahuja, S.K. Jena, S.K. Paidi, S. Bagri, Formulation, optimization and *in vitro–in vivo* evaluation of febuxostat nanosuspension, Int.J.Pharm. 478 (2015)540–552.

[2] S. Verma, R. Gokhale, D.J. Burgess, A comparative study of top-down and bottom-up approaches for the preparation of micro/nanosuspensions. Int.J. Pharma. 380 (2009)216–222.

[3] Shrivastava, S. Sakthivel, B. Pitchumani, A.S. Rathore, A statistical approach for estimation of significant variables in wet attrition milling: Powder Technol. 211 (2011)46–53.

[4] R.M. Khalil, M.A. Kassem, A.A. Abdel Rahman, M.M. Ghorab, M.B. Ahmed, Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs. Int. J. Pharm. 340 (2007)126–133.

[5] Ghosh, S. Bose, R. Vippagunta,F. Harmon, Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. Int. J. Pharm. 409 (2011)260–268.

[6] Y. Wang, X. Hu, X. Chen, X. Lin, L. Zhang, X. Tang,et al. A combined bottom-up/top-down approach to prepare a sterile injectable nanosuspension. Int. J. Pharm. 472 (2014)130–139.

[7] R.H. Muller, C.M. Keck, Twenty years of drug nanocrystals: where are we and where do we go? Eur. J. Pharm. Biopharm. 80 (2012) 1-3.

[8] X. Zhang, J. Guan, R. Ni, L.C. Li, S. Mao,Preparation and Solidification of redispersiblenanosuspensions. J. Pharm. Sci. 103 (2014)2166–2176.

[9] P.P. Ige, R.K. Baria, S.G. Gattani, Fabrication of fenofibratenanocrystals by probe sonication method for enhancement of dissolution rate and oral bioavailability, Colloids Surf. B. Bio-interfaces 108 (2013**)** 366– 373.

[10] F. Cui, D. Xia, P. Quan, H. Piao, S. Sun, Y. Yin, et al. lPreparation of stable nitrendipinenanosuspensions using the precipitation–utrasonication method for enhancement of dissolution and oral bioavailability. Eur. J. Pharm. Sci. 40 (2010) 325–334.

[11] T. Niwa, S. Miura, K. Danjo,Universal wet-milling technique to prepare oral nanosuspension focused on discovery and preclinical animal studies development of particle design method. Int. J. Pharm. 405 (2011) 218–227.

[12] Z. Bujanakova, E. Dutkova,M. Balaz,E. Turianicova,P. Balaz, Stability studies of As_4S_4nanosuspension prepared by wet milling in poloxamer 407. Int. J. Pharm. 478 (2011) 187–192.

[13] X. Tang,H. Yang,F. Teng,P. Wang,B. Tian,X. Lin,et al. Investigation of nanosuspension stabilized by Soluplus to improve bioavailability. Int. J. Pharm. 477 (2014) 88-95.

[14] C.M. Patel, M. Chakraborty, Z.V. Murthy,Preparation of fenofibrate nanoparticles by combined stirred media milling and ultrasonication method. Ultrason. Sonochem. 21 (2014) 1100-1107.

[15] X. Ying, Y. Xu,Y. Lu,X. Liu,Z. Yin,W. Wu,et al. Enhanced dissolution and oral bioavailability of aripiprazolenanosuspensions prepared by nanoprecipitation/homogenization based on acid–base neutralization. Int. J. Pharm. 438 (2014) 287– 295.

[16] Y. Xie, C. Hong,Y. Dang, G. Lin,Y. Yao, G. Li,et al. Effects of stabilizing agents on the development of myricetin nanosuspension and its characterization: An in- vitro and in-vivo evaluation. Int. J. Pharm. 47 (2014) 251–260.

[17] P.M. Kearney, C. Baigent, J. Godwin, H. Halls, J.R. Emberson, C. Patrono,Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. Br. Med. J. 332 (2006) 1302-1305.

[18] B. Yadav, Y.S. Tanwar, Development, characterization and in-vitro evaluation of flurbiprofen solid dispersions using

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

polyethylene glycols as carrier. J.Appl. Pharm. Sci. 6(4) 2006 60-66.

[19] G. Zhai, M. Sun, Y. Gao, Y. Pei, C. Guo, F. Cao,et al. Development of nanosuspension formulation for oral delivery of quercetin. J.Biomed.Nanotechn. 6 (2010) 325–332.

[20] B.P. Sahu, M.K. Das,Nanosuspension for enhancement of oral bioavailability of felodipine. Appl. Nanosci. 4 (2014) 189–197.

[21] Z. Attari, S. Kalvakuntla, M.S. Reddy, M. Deshpande, C.M. Rao, K.B. Koteshwara,Formulation and characterization of nanosuspensions of BCS class II and IV drugs by combinative method. J. Exp. Nanosci. 11(4) 2014) 276-288.

[22] T. Higuchi, K.A. Connors, Phase-solubility techniques. Adv. Anal. Chem. Instrumen. 4 (1965) 117-212.

[23] A.M. Cerdeira, M. Mazzotti, B. Gander,Formulation and drying of miconazole and itraconazolenanosuspensions. Int. J. Pharm. 443 (2013) 209– 220.

[24] S.K. Singh,K.K. Srinivasan,K. Gowthamarajan,D.S. Singare,D. Prakash, N.B. Gaikwad, Investigation of preparation parameters of nanosuspension by top-down media milling to improve the dissolution of poorly water-soluble glyburide. Eur. J. Pharm. Biopharm. 78 (2011) 441–446.

[25] J.Y. Choi, J.Y. Yoo, H.S. Kwak, B.U. Nam, J. Lee, Role of polymeric stabilizers for drug nanocrystal dispersions. Curr. Appl. Phys. 5 (2005) 472–474.

[26] M. Kakran, N.G. Sahoo, L. Li, Z. Judeh, Y. Wang, K. Chong, et al. Fabrication of drug nanoparticles by evaporative precipitation of nanosuspension. Int. J. Pharm. 383(1-2) (2010)285–292.

[27] S. Das, P.K. Suresh, Nanosuspension: a new vehicle for the improvement of the delivery of drugs to the ocular surface: Application to amphotericin B, Nanomedicine: Nanotech. Bio. Med. 7(2) (2011) 242–247.

[28] S. Chandran, A. Roy, R.N. Saha, Effect of pH and formulation variables on in-vitrotranscorneal permeability of flurbiprofen: a technical note. AAPS Pharm. Sci. Tech. 9 (2008) 1031-1037.

[29] A.A. Date, V.B. Patravale, Current Strategies for engineering drug nanoparticles. Curr. Opin. Colloid Interface Sci. 9 (2004) 222–235.

[30] Y. Lu, N. Tang, J.P. Qi, W. Wu, Phase solubility behavior of hydrophilic polymer/cyclodextrin/lansoprazole ternary system studied at high polymer concentration and by response surface methodology. Pharm. Dev. Technol. 17 (2012) 236–241.

[31] R. Shegokar, R.H. Muller,Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int. J. Pharm. 399 (2010) 129–139.

[32] R. Mauludin, J. Moschwitzer, R.H. Muller, Fast dissolving ibuprofen nanocrystal loaded solid dosage forms. Int. J. Pharm. Pharm. Sci. 4(3) (2012)543-549.

[33] B. Sinha, R.H. Muller, J.P. Moschwitzer, Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. Int. J. pharm., 453 (2013) 126–141.

[34] R. Ravichandran, Development of an Oral CurcuminNanocrystal Formulation. J. Nanotechnol. Eng. Med. 3(4) (2003) 041007.

[35] G.D. Wang, F.P. Mallet, F. Ricard, P.P. Heng Jerry, Pharmaceutical nanocrystals. Curr. Opin. Chem. Engg. 1(2) (2012) 102-107.

[36] M. Nakarani, A.K. Misra, J.K. Patel, S.S. Vaghani, Itraconazole nanosuspension for oral delivery: Formulation,characterization and in vitrocomparison with marketed formulation. DARU, 18(2) (2010)84-90.

[37] R.H. Muller, K. Peters, Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size-reduction technique. Int. J. Pharm. 160 (1998) 229–237.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[38] B.E. Rabinow, Nanosuspensions in drug delivery. Nature Rev. Drug. Disc. 3 (2004) 785–796.
[39] J.U. Junghanns, R.H. Muller,Nanocrystal technology, drug delivery and clinical applications. Int. J. Nanomed. 3 (2008) 295–309.
[40] S. Onoue, H. Takahashi, Y. Kawabata, Y. Seto, J. Hatanaka, B. Timmermann, et al. Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. J. Pharm. Sci. 99 (2010) 1871.
[41] M.P. Kumar, Y.M. Rao, S. Apte, Formulation of nanosuspensions of albendazole for oral administration. Curr. Nanosci. 4 (2008) 53-58.
[42] R. Kumar, P.F. Siril, Preparation and characterization of polyvinyl alcohol stabilized griseofulvin nanoparticles. Mater Today: Proc. 3 (2016)2261–2267.
[43] D. Sharma, M. Soni, S. Kumar, G.D. Gupta, Solubility enhancementeminent role in poorly soluble drugs. Res. J. Pharm. Tech. 2(2) (2009)220–224.
[44] H. DeWaard, W. Hinrichs, H. Frijlink, A novel bottom–up process to produce drug nanocrystals: controlled crystallization during freeze drying. J. Control Release 128 (2008)179–83.

Table 1. Composition of FLB nanoparticles loaded matrix tablets

Ingredients	Formulation-1	Formulation-2	Formulation-3
Optimized nanosuspension (mg)	100	100	100
Sodium alginate (mg)	25	50	75
Lactose Monohydrate (mg)	29.94	24.94	19.94
Talc (%)	3.00	3.00	3.00
Magnesium Stearate (%)	1.5	1.5	1.5
Total Weight	159.44	179.44	199.44

Table 2. Profile of statistical analysis for the experimental plan.

Responses	Sources		
	Model *p* value	Adj-R^2	Lack of fit test *p* value
Entrapment efficiency	-	-	0.2371
Particle size	0.0488	0.8415	0.9727
Zeta potential	0.0081	0.952	0.5359

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Table 3. A Compared assessment profile of observed and predicted values of responses of optimized FBF nanoparticles.

Factors		Predicted value			Observed value*		
FBF: HPMC K4M: Poloxamer 407	Stirring Speed (rpm)	Entrapment Efficiency (%)	Mean Particle Size (nm)	Zeta Potential (mV)	Entrapment Efficiency (%)	Mean Particle Size (nm)	Zeta Potential (mV)
1:1:2	1500	83.92	271.8	-11.65	85.14 ± 0.93	263.3 ± 2.73	-10.2 ± 0.42

* All values are mean ± SD (n=3).

Table 4. Preparation of FBF nanoparticles using 3^2 factorial design.

Formulation Code	Independent Variables				Dependent Variables		
	Formulation Variable		Process Variable		Y_1	Y_2	Y_3
	X_1	FBF:HPMC K4M: Poloxamer 407	X_2	Stirring Speed (rpm)	Entrapment Efficiency (%)	Mean Particle Size (nm)	Zeta Potential (mV)
FB1	− 1	1:1:1	− 1	500	83.47 ± 1.12	371.2 ± 2.08	-15.91 ± 0.08
FB2	0	1:1:2	− 1	500	83.61 ± 1.07	315.6 ± 2.28	-12.7 ± 0.13
FB3	+1	1:1:3	− 1	500	81.37 ± 0.77	303.4 ± 0.93	-9.18 ± 0.88
FB4	− 1	1:1:1	0	1000	85.19 ± 0.94	289.7 ± 1.59	-13.93 ± 0.94
FB5	0	1:1:2	0	1000	84.29 ± 1.08	270.0 ± 3.11	-11.6 ± 0.18
FB6	+1	1:1:3	0	1000	80.54 ± 0.87	296.2 ± 2.21	-9.63 ± 0.18
FB7	− 1	1:1:1	+1	1500	84.74 ± 0.82	277.1 ± 1.16	-13.03 ± 0.17
FB8	0	1:1:2	+1	1500	89.83 ± 0.93	263.3 ± 2.73	-10.2 ± 0.42
FB9	+1	1:1:3	+1	1500	82.31 ± 1.13	281.7 ± 0.73	-7.91 ± 0.37

Where +1 is higher level, -1 is lower level and 0 is mid level for the independent variable and all values are expressed as mean ± SD (n = 3).

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Table 5. Release Kinetic profiles of *in vitro* drug release of optimized FBF nanoparticles FB8.

Dissolution Medium	Zero Order	First Order	Higuchi Model	Hixon-Crowell	Korsmeyer – Peppas		Diffusion Mechanism
	R^2				R^2	Release Exponent (n)	
0.1 N HCl	0.998	0.992	0.985	0.967	0.970	0.225	Fickian diffusion
Phosphate Buffer pH 4.5	0.993	0.989	0.988	0.991	0.993	0.240	Fickian diffusion
Phosphate Buffer pH 7.2	0.990	0.863	0.979	0.975	0.995	0.239	Fickian diffusion

Table 6. Particle size, PDI and zeta potential values of optimized FBF nanoparticles (FB8) during three months of storage at 4°and 25°.

Parameter	At 4 °		At 25 °	
	Initial	After 3 months	Initial	After 3 months
Particle size (nm)	263.3 ± 2.73	271.12 ± 0.93	263.3 ± 2.73	293.12 ± 1.09
PDI	0.266 ± 0.02	0.272 ± 0.01	0.266 ± 0.02	0.274 ± 0.01
Zeta potential (mV)	-10.2 ± 0.42	-10.41 ± 0.77	-10.2 ± 0.42	-11.16 ± 0.45

Table 7. Micrometrics profile of FLB nanoparticles loaded matrix granules

Parameters	Formulations		
	F1	F2	F3
Bulk density (gm/cm^3)	0.47±0.00	0.49±0.02	0.47±0.03
Tap density (gm/cm^3)	0.53±0.03	0.52±0.05	0.52±0.07
Compressibility (%)	9.66±0.33	8.16±0.39	10.26±0.81
Angle of Repose (°)	26.20±1.40	25.20±1.56	23.20±1.36

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Table 8. Physical Properties of Flurbiprofen nanoparticles loaded matrix tablet.

Parameters	Formulations		
	F1	F2	F3
Weight Variation (mg)	256.9	259.8	257.8
Hardness	5.32±0.37	5.33±0.35	5.30±0.34
Thickness (mm)	2.41±0.03	2.45±0.08	2.44±0.06
Friability (%)	0.36±0.41	0.33±0.42	0.35±0.43
Drug Content (%)	98.70±1.23	98.22±1.08	99.78±1.00

Table 9. The drug release kinetics profiles of Flurbiprofen nanoparticles loaded matrix tablets.

Formulation	Zero order	First order	Higuchi Model	Hixon-Crowell model	Korsmeyer – Peppas		Diffusion Mechanism
	R^2	R^2	R^2	R^2	R^2	Release Exponent (n)	
F1	0.983	0.944	0.966	0.966	0.983	0.493	Non-Fickian
F2	0.955	0.952	0.884	0.972	0.987	0.487	Non-Fickian
F3	0.983	0.944	0.965	0.958	0.993	0.489	Non-Fickian

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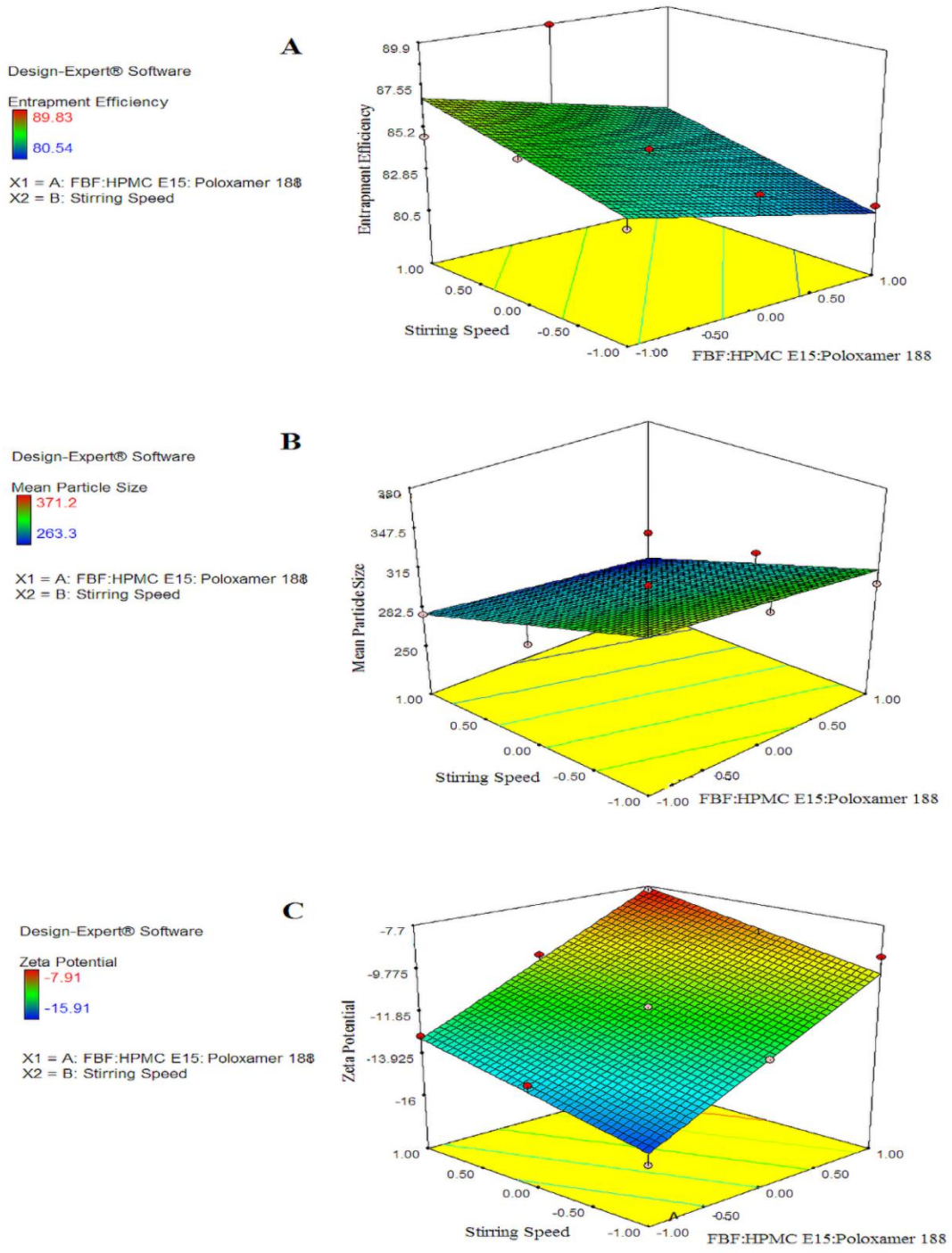

Figure 1. Response surface plots illuminating the FBF effect HPMC K4M: Effects of poloxamer 407 concentrations and stirring rates on entrapment effectiveness, mean particle size, and zeta potential (A), (B), and (C), respectively.

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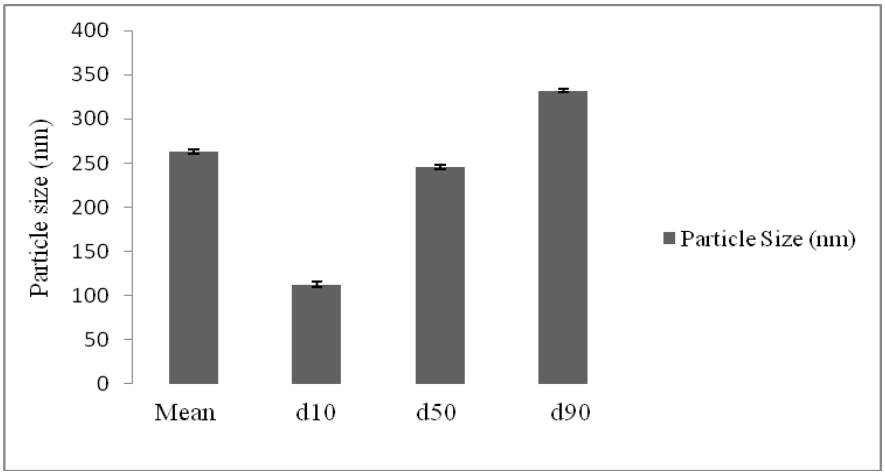

Figure 2. Histogram representing the data of Mean particle size, d10, d50 and d90.

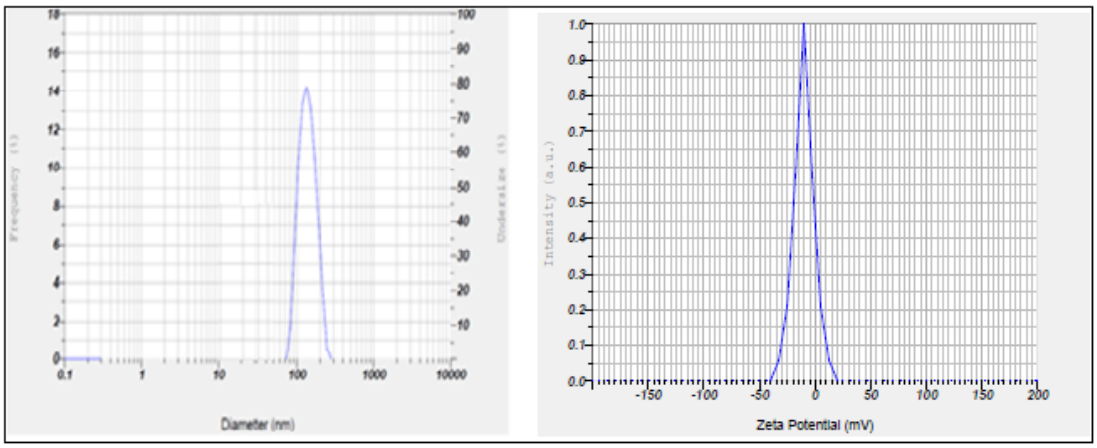

Figure 3. The particle size and zeta potential distribution pattern of optimized batch of nanoparticles (FB8).

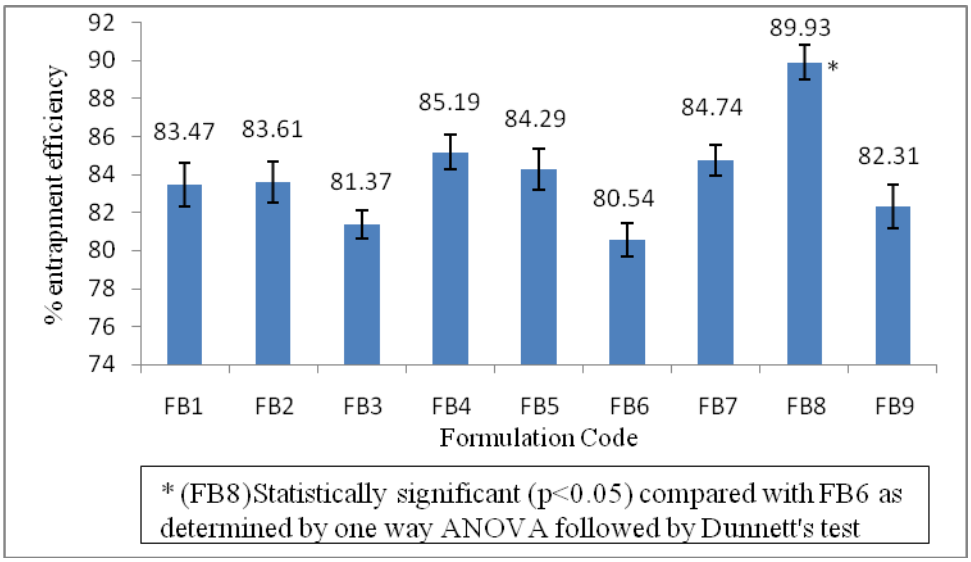

Figure 4. Graphical representation of entrapment efficiency (%) of FBF nanoparticles.

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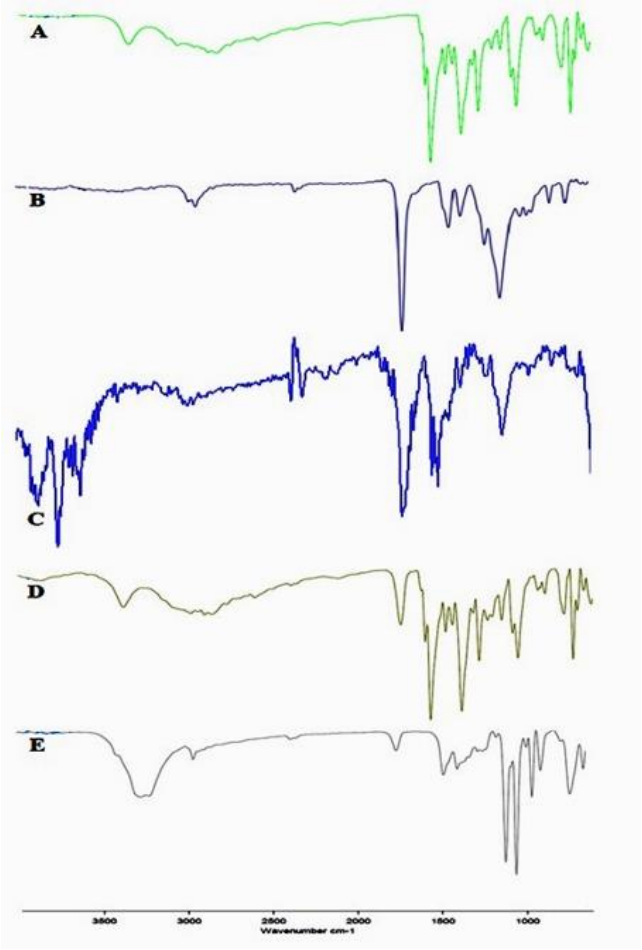

Figure 5. FTIR spectra of pure FBF (A), HPMC K4M (B), Poloxamer 407 (C), Physical mixture of Pure drug and HPMC K4M (D) and Lyophilized nanoparticles FB8 (E)

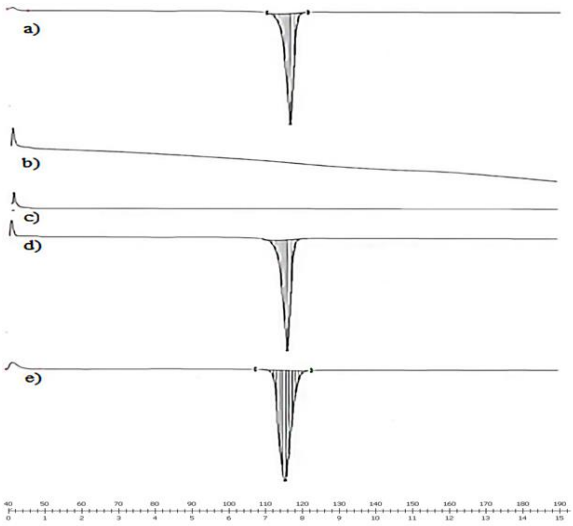

Figure 6. DSC curves of crude FBF (A), HPMC K4M (B), Poloxamer 407 (C), physical mixture (D) and lyophilized nanoparticles FB8 (E).

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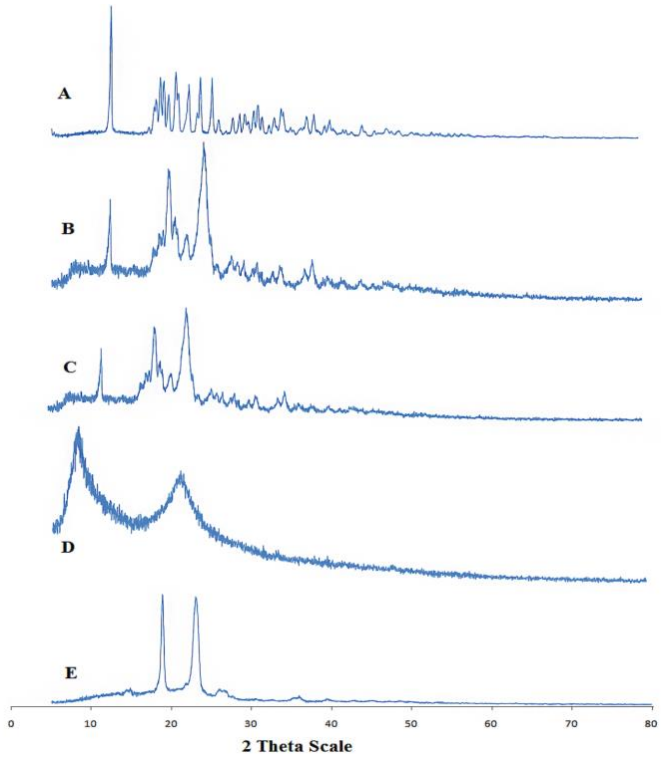

Figure 7. PXRD spectra of crude FBF (A), physical mixture (B), lyophilized nanoparticles FB8 (C), HPMC K4M (D) and poloxamer 407 (E).

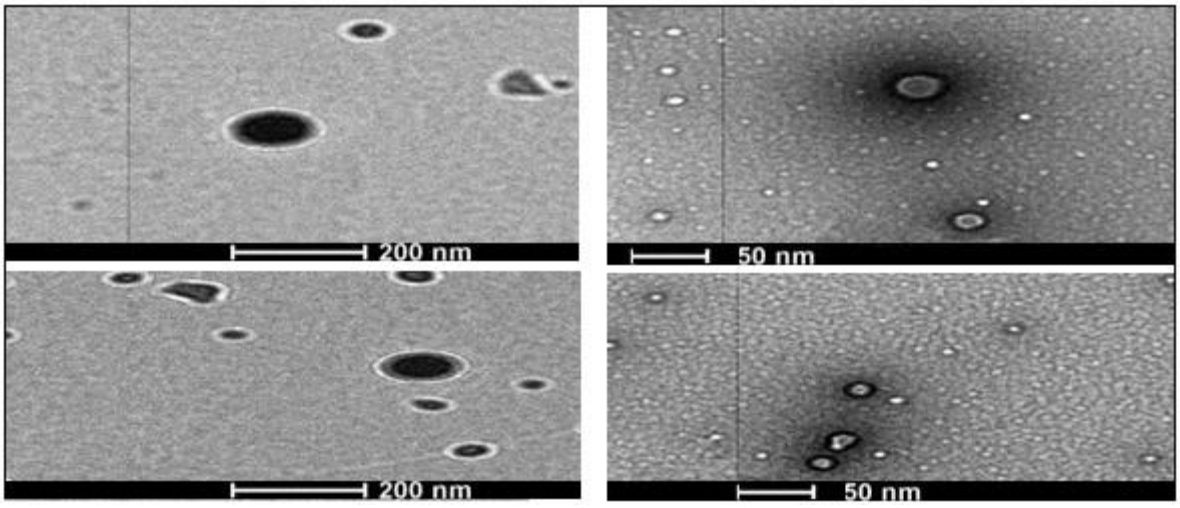

Figure 8. TEM images of optimized formulation of nanoparticles FB8.

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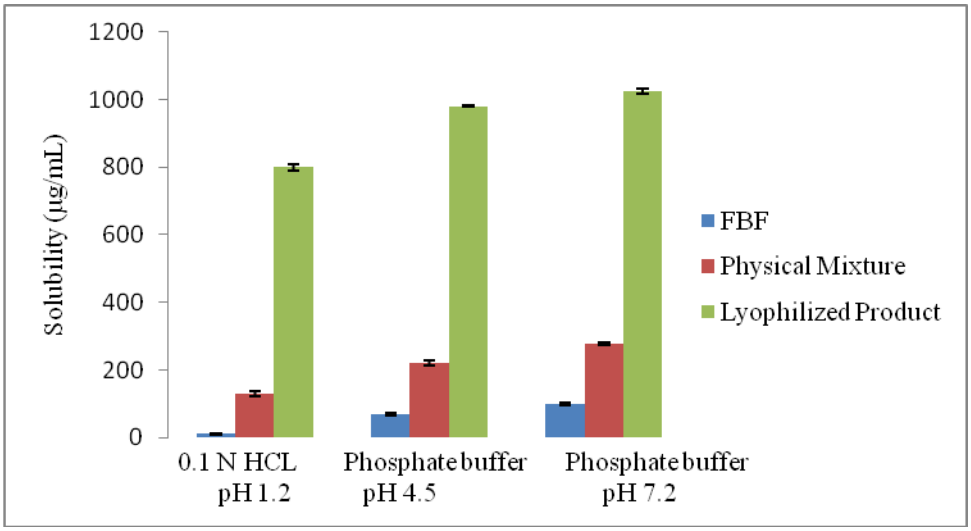

Figure 9. Saturation solubility of FBF, Physical mixture and Lyophilized product in 0.1 N HCl (pH 1.2), phosphate buffer (pH 4.5) and phosphate buffer (pH 7.2). All values are mean ± SD (n = 3).

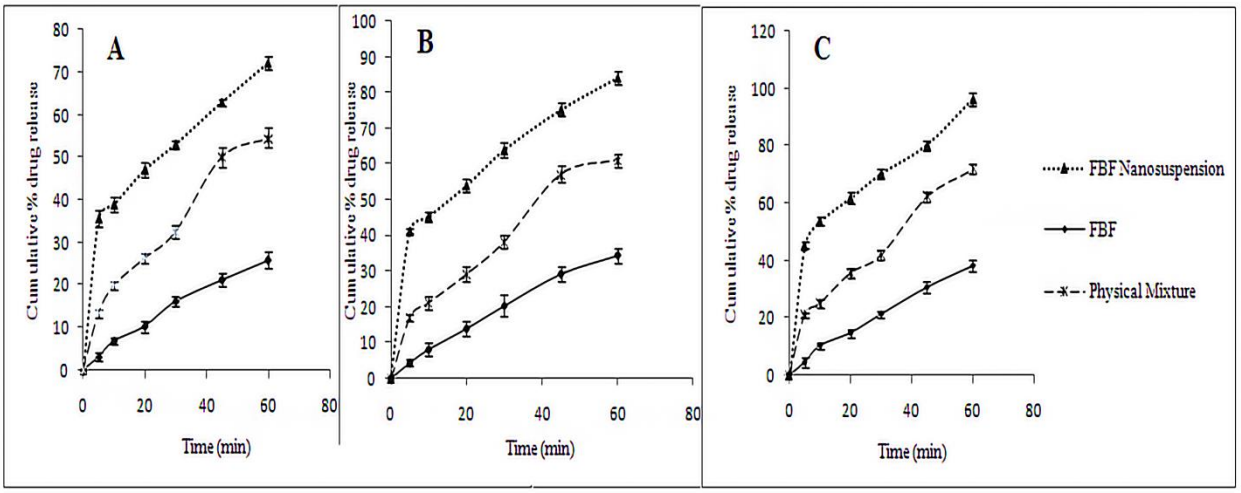

Figure 10.*In Vitro* drug release profile of pure FBF, physical mixture and optimized FBF nanoparticles (FB8) in 0.1 N HCl pH 1.2 (A), in phosphate buffer pH 4.5 (B) and in phosphate buffer pH 7.2 (C).

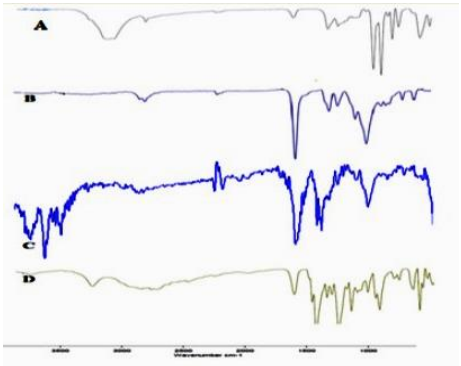

Figure 11. FTIR spectra of Flurbiprofen nanoparticles (a), Sodium alginate (b), Physical mixture of nanoparticles and sodium alginate (c) and powdered tablets (d)

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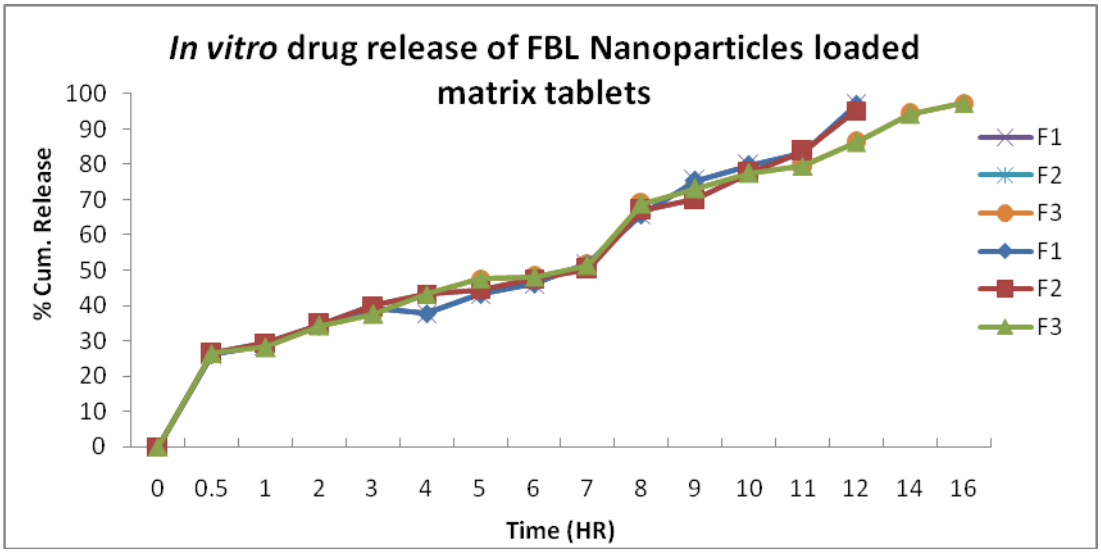

Figure 12: Comparative Drug release profile of flurbiprofen nanoparticles loaded matrix tablets.