J Nanostruct 14(4): 1327-1339, Autumn 2024

RESEARCH PAPER

Design and Characterization of Prednisolone Nanoparticles for Potential Therapeutic Applications

Walaa A. Saihood [1]*, *Hayder K. Abbas* [2]

[1] *College of Pharmacy, Department of Pharmaceutics, Mustansiriyah University, Baghdad, Iraq*

[2] *Department of Pharmaceutics, College of Pharmacy, University of Alkafeel, Iraq*

ARTICLE INFO

Article History:
Received 11 July 2024
Accepted 15 September 2024
Published 01 October 2024

Keywords:
Nanoscale
Prednisolone nanoparticles
SEM
Therapeutic

ABSTRACT

Prednisolone is a corticosteroid medicine used to treat a variety of conditions, including allergies, inflammation, autoimmune disorders, and certain types of cancer. This drug has poor solubility and high permeability. The purpose of this study was to improve the solubility and rate of dissolution of prednisolone by fabricating nanoparticles using various stabilizers through the solvent-antisolvent precipitation technique. A total of eighteen different formulas were developed and tested for the size of particle, polydispersity index (PDI), entrapment efficiency (EE), and in-vitro dissolution .The best formulas were further evaluated after lyophilization and converted to nanoparticle powder by assessing their solubility. Furthermore the best formulation also were characterized by Powder X-Ray Diffraction (PXR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscope (SEM) and Fourier Transforms Infrared Spectroscopy (FTIR). The results of the study revealed that the particle size of the drug particles in all the formulations was nanosized, ranging from 50 .8 nm to 364.7 nm. The dissolution rate of the chosen lyophilized formulas was superior to that of the free drug in phosphate buffer at pH 7.4. The FT-IR spectroscopy results indicated that the combination of prednisolone with different stabilizers did not have an effect on the peak positions or trends. This research determined that prednisolone nanoparticles could be successfully created by the application of precipitation technique, with the use of various stabilizers.

How to cite this article
Saihood W., Abbas H. Design and Characterization of Prednisolone Nanoparticles for Potential Therapeutic Applications. J Nanostruct, 2024; 14(4):1327-1339. DOI: 10.22052/JNS.2024.04.032

INTRODUCTION

The ability of a drug to dissolve is essential for achieving the desired level of concentration in the bloodstream for optimal therapeutic effect.

The Biopharmaceutical Classification System categorizes compounds with low solubility and high permeability as Class II [1]. These substances dissolve slowly and in an unpredictable manner. The delivery of drugs can be difficult due to incomplete release from the dosage form, leading to issues such as low bioavailability and high variability between individuals. One of the most common ways to improve solubility and speed up the dissolution rate is to reduce the particle size of the substance. Various techniques have been developed to achieve this goal. Nanotechnology has been employed to reduce the size of drug particles in order to improve solubility [2]. This has been achieved through a variety of techniques, such as particle size reduction and nanostructuring. These approaches have been shown to be effective in increasing the solubility

* *Corresponding Author Email: walaaabed1993@gmail.com*

of drugs, thus improving their bioavailability. A Nanoparticle suspensions can be produced using a variety of methods, with precipitation being a popular choice for drugs with low solubility. This technique is used to create particles that are smaller than one micron in size.

Mixing of drug solution with anti-solvent can lead to a rapid increase in the concentration of the drug present. resulting in the formation of ultrafine crystalline or amorphous drug solids. [3].

The addition of pharmaceutical stabilizers when preparing medication nanoparticles by the precipitation method is essential in order to counteract the extra non-bound energy of newly exposed surfaces.

They are used in nanosuspensions to act as wetting agents for drug particles, preventing Ostwald ripening and the aggregation of the particulate. [4] Stabilization strategies often involve the use of steric and/or electrostatic stabilization. Electrostatic stabilization can be achieved through the use of ionic surfactants and charged polymers, while steric stabilization can be achieved through the use of non-ionic surfactants. [5].

Prednisolone is a synthetic corticosteroid that is similar to its natural counterpart prednisone in structure, with the exception of two less hydrogens near C_{11} [6].

Prednisolone is a medication used to treat a variety of conditions, including certain types of cancer, autoimmune disorders, inflammatory diseases, and allergies.

It is a type of steroid drug. [7],it is a glucocorticoid and due to its lipophilic composition, it may easily pass through cell membranes to reach the glucocorticoid receptor (GCR) in the cytoplasm and play an essential role in synthesis of anti-inflammatory proteins [8]. The purpose of this study was to create prednisolone nanoparticles using the solvent-antisolvent technique in order to increase the solubility and dissolution rate of prednisolone (Fig. 1).

MATERIALS AND METHODS

Materials

Prednisolone was supplied from pioneer drug manufacturing company, Iraq. HPMC of E5, E15 and E50 grades were obtained from Baoji Guokang Biotechnology co.,Ltd. Poloxamer 188 and PVPk30 were supplied by Xi'an sonwu Biotech co.,Ltd. China. PEG4000 was supplied from HiMedia Laboratories Pvt.Ltd, India. Disodium Hydrogen Phosphate (Na_2HPO_4), Sodium Dihydrogen Phosphate (NaH_2PO_4),HCL and Sodium Hydroxide were supplied from Thomas Barker(chemicals) Pvt. Ltd, India and Ethanol was from Sasma, Netherlands.

Methods

Characterization of prednisolone

Solubility of drug

Drug solubility was assessed by mixing an excess amount of the pure drug with 25 mL of phosphate buffer (pH 7.4) and, then a magnetic stirrer at temperature of 37°C was used for stirring for 24 hours.

The sample was filtered through filter membrane of 0.45 µm as well as analyzed using a UV-spectrophotometer at the wavelength of

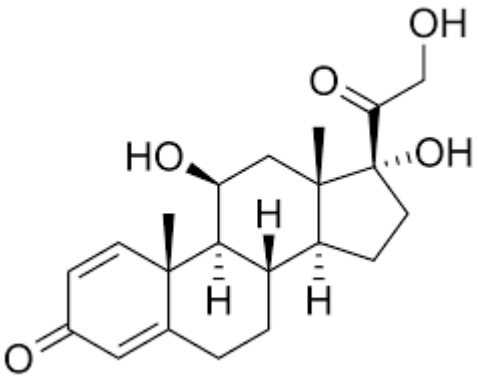

Fig. 1. Prednisolone structure [6].

maximum absorbance for prednisolone. [10,11].

Prednisolone nanosuspension

Table 1 shows the eighteen Prednisolone nanoparticles formulas that were prepared using the solvent-anti-solvent precipitation method. Prednisolone was dissolved in ethanol, which is an organic solvent to prepare an organic phase of drug in ethanol (32mg/ml). A syringe was used to slowly inject 50 ml of an aqueous solution of water containing various stabilizers in ratios of 1:1, 1:2, and 1:3 with an organic solution of drug in ethanol.

The two solutions were mixed and kept under mechanical agitation at a speed of 500 rpm with the help of a magnetic stirrer at 50°C for 1 hour in order to evaporate the organic solvent and obtain the desired nanosuspension. [12,13].

Characterization of nanoparticles size and polydispersity index

Brookhaven ZetaPlus particle size analyzer was used to determine the size and PDI of nanoparticles by measuring the intensity of light scattered by the particles in the nanosuspension at a scattering angle of 90º and at a temperature of 25 ºC as a function of time. Small volume of nanosuspension was used in these measurements [14].

Entrapment efficiency

The efficiency of entrapment was performed by using a cooling ultracentrifuge (at 4°C and 14000rpm for 40 minutes) in which centrifugation was done on varying ratios of nanosuspension.

The amount of free drug present in the supernatant solution was determined by measuring the absorbance of sample solution of the supernatant layer using a UV spectrophotometer [15].

The centrifugation was recurrent three times for each formula and the mean was taken.

Dissolution study of prednisolone nanosuspension

An in vitro dissolution study of the successful prednisolone nanosuspension was conducted using USP dissolution test apparatus-II. The dissolution media was 900 ml of phosphate buffer (pH) at 37 ± 0.5ºC, and the stirring speed was set at 50 rpm.

Five-milliliter samples were taken at predetermined intervals, and then filtered and determined the content of drug by UV spectrophotometric analysis [16,17].

Freeze drying of nanosuspension

Freeze drying is the most commonly used method to obtain dried nanoparticles of drug from nanosuspension. This technique works by removing water from the sample through sublimation and desorption under vacuum.

The selected formulas were transferred to a cell of a lyophilizer and frozen using liquid nitrogen. The frozen samples were then placed in an ALPHA

Table 1. Composition of Prednisolone nanosuspension using different stabilizers.

No. of Formula	Drug (mg)	Poloxmer 188 (mg)	PVP K30 (mg)	E5 of HPMC (mg)	E15 of HPMC (mg)	E50 of HPMC (mg)	PEG 4000 (mg)
1	40	40					
2	40	80					
3	40	120					
4	40		40				
5	40		80				
6	40		120				
7	40			40			
8	40			80			
9	40			120			
10	40				40		
11	40				80		
12	40				120		
13	40					40	
14	40					80	
15	40					120	
16	40						40
17	40						80
18	40						120

1-2 LD plus lyophilizer for 24 hours at a specified condenser temperature (-40) and pressure (0.9 mbr).

The powders obtained were placed in a cup and sealed tightly with a parafilm, then stored at room temperature for further investigation [18].

Characterization studies of lyophilized formulas
Determination of drug solubility

An excessive amount of the lyophilized formula was placed in phosphate buffer pH 7.4. The aqueous dispersion of lyophilized formula in phosphate buffer was then stirred in a magnetic stirrer at 25°C for 24 hours to determine the saturated solubility of the powder. The sample was then filtered through 0.45 µm filter and analyzed by UV-spectrophotometer at *λ max* for prednisolone [10,11].

Determination of drug content of lyophilized powder

An accurately weighed amount of 10 mg of prednisolone was dissolved separately in 10 ml of ethanol using a volumetric flask to estimate the drug content. Samples were sonicated for 30 minutes using a sonicator, then filtered through a 0.45µm filter and diluted with the appropriate volume of diluent.

The amount of drug in a lyophilized powder sample was determined using UV/visible spectrophotometric analysis at a specific λ max, based on a standard curve [19].

Visualization by scanning electron microscopy (SEM)

The morphology and surface topography of particles for both pure drug and lyophilized powder of selected formulas were studied using a Tescan Vega2 Scanning Electron Microscope. The procedure was confirmed by direct deposition of powder on double-sided carbon tape and coated with gold [20].

Differential Scanning Calorimetry (DSC)

Shimadzu DSC was used to assess the physical compatibility between prednisolone drug and the polymers used in the preparations by determining the thermal behavior of pure prednisolone powder and the formulated samples.

A Differential Scanning Calorimetry experiment was conducted on 5mg samples placed in aluminum pans. The temperature was increased from 30 to 250ºC at a rate of 10ºC/min while the samples were exposed to a nitrogen gas stream [21].

Fourier transforms infrared spectroscopy (FTIR)

Several FTIR spectra were obtained using Shimadzu8400s FTIR spectrophotometer for determining of chemical compatibility. Samples

Table 2. Nanoparticle size, PDI, Entrapment efficiency (EE) and Similarity factor (*f2*).

Formulas number	Particle size (nm)	PDI	Percentage of Entrapment Efficiency ± SD	Similarity factor (*f2*)
F1	*260*	*0.005*	78.4 ± 0.21	28.18
F2	*196.7*	*0.494*	80.9 ± 0.20	20.91
F3	*71*	*0.005*	89.7 ± 0.20	17.49
F4	*286*	*0.387*	71.5 ± 0.54	25.60
F5	*202*	*0.005*	75.8 ± 0.21	25.28
F6	*105.1*	*0.005*	87.6 ± 0.30	19.18
F7	*87*	*0.499*	76.5 ± 0.50	20.25
F8	*95*	*0.303*	79.7 ± 0.51	21.39
F9	*177*	*0.220*	86.9 ± 0.51	23.91
F10	*50.8*	*0.005*	91.2 ± 0.25	17.07
F11	*61*	*0.448*	85.6 ± 0.51	17.79
F12	*126*	*0.447*	82.6 ± 0.52	18.32
F13	*111*	*0.466*	83.6 ± 0.50	19.03
F14	*120*	*0.197*	85.8 ± 0.32	23.20
F15	*124*	*0.411*	86.5 ± 0.20	23.38
F16	*364.7*	*0.540*	79.2 ± 0.21	21.66
F17	*144.9*	*0.639*	83.5 ± 0.32	18.27
F18	*67.8*	*0.552*	86.3 ± 0.51	22.77

of pure drug, polymer and selected formulas, samples were separately mixed with infrared grade KBr and then pellets were obtained by use a hydraulic press. The pellets were scanned at wave number range of 4000- 400 cm^{-1} [22].

Powder x-ray diffraction (XRD)

Powder X-ray diffraction was employed to analyze the molecular structure of prednisolone nanoparticles. The XRD-6000 Shimadzu powder X-ray diffractometer was used in this test, with an operating voltage of 40 kV and current of 30 mA, and a continuous scan range of 2ɵ from 5 to 50º [23].

RESULTS AND DISCUSSION

Determination of prednisolone saturation solubility

The saturation solubility of prednisolone was found to be 0.235 ± 0.006. The solubility of ionic compounds containing anions with negelchable basicity (such as the conjugate bases of strong acids) is not affected by changes in pH. The chemical structure of prednisolone, as seen in Fig. 2, does not possess any acidic or basic properties [25].

Nanoparticle size and PDI

Table 2 shows that the estimated average particle size was between 50.8 nm and 364.7

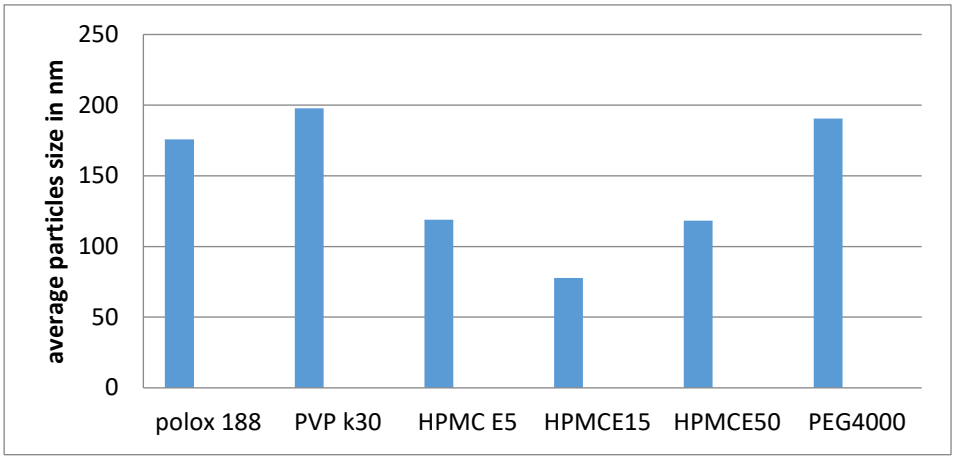

Fig. 2. Nanometre size of prednisolone nanoparticles.

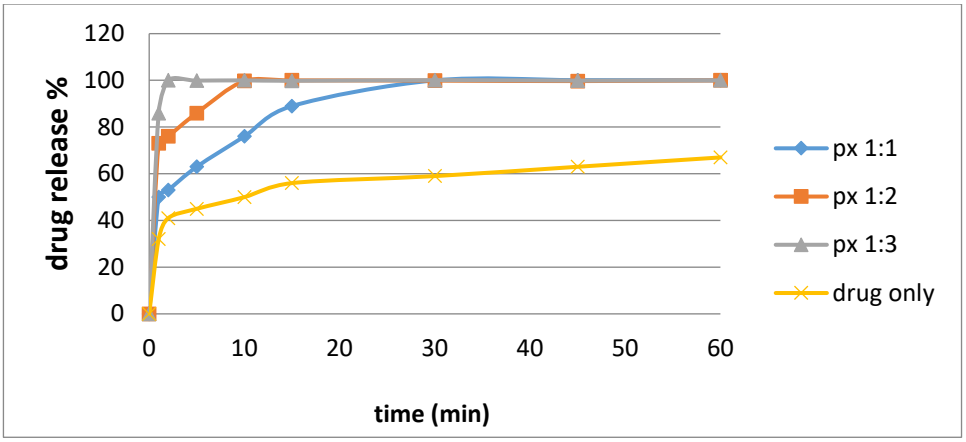

Fig. 3. Dissolution profiles of Poloxamer 188 formulas.

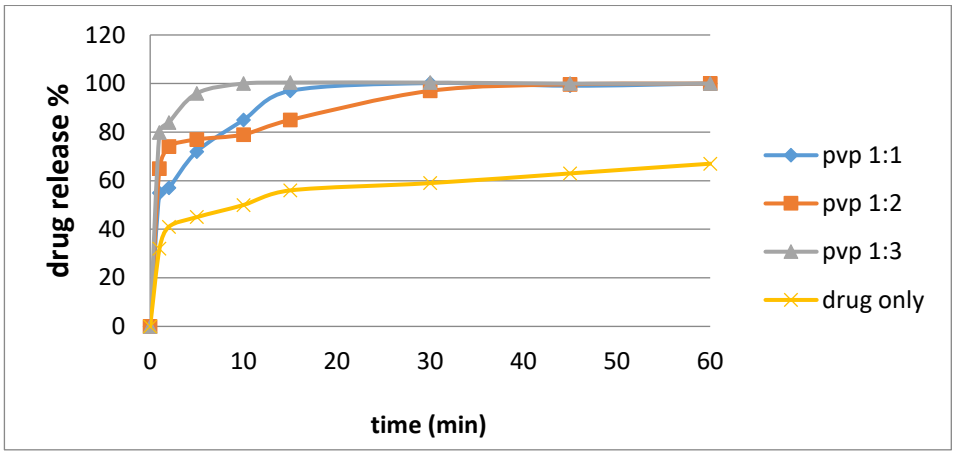

Fig. 4. Dissolution profiles of PVP K30 formulas.

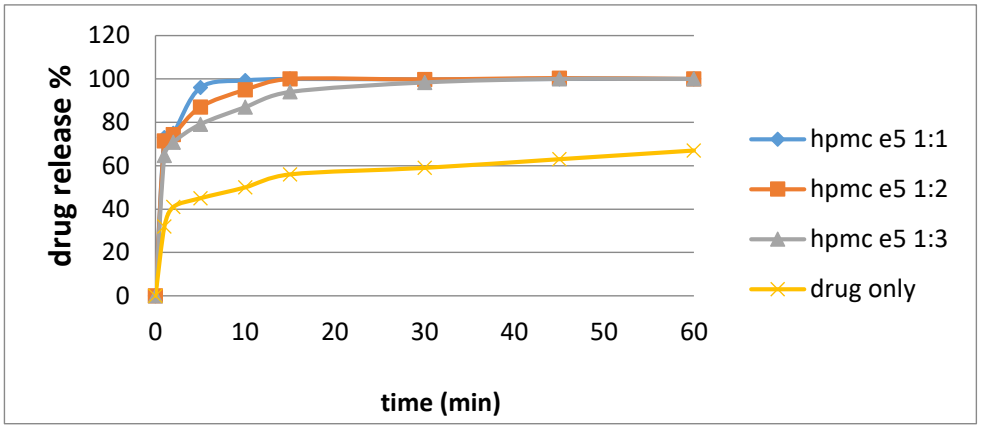

Fig. 5. Dissolution profiles of HPMC E5 formulas

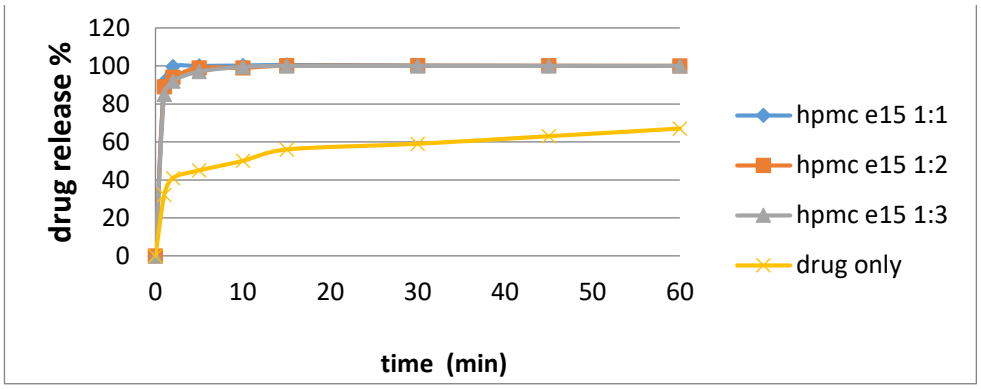

Fig. 6. Dissolution profiles of HPMC E15 formulas

nm and the PDI was varied from 0.005 to 0.639 depending on the formulation variables. The particle size distribution of nanoparticles was found to be good and uniform, since the PDI values ranging from 0 to 0.08, indicating a monodisperse system, while the values between 0.08 and 0.7 indicate a mid-range polydispersity [26].

Effect of drug/stabilizer ratio and type of polymer

As seen in Table 2 the entrapment efficiency increases with an increase in the amount of polymer until a 1:3 drug: polymer ratio is reached, except formulas containing HPMC E15 as polymer. This could be attributed to the increased polymer coating around the drug [27].

The size of particles decreases in the following: F1 > F2 > F3, which corresponds to a 1:1, 1:2 and 1:3 ratios of prednisolone to poloxamer188, respectively. These outcomes explained that the size of particles decreased in a consistent pattern as the ratio of Poloxamer188 increased. The similar consequence was detected with PVPK30 and PEG4000. The primary coverage of the new surfaces that were produced competing with the agglomeration of uncovered particles may be the cause of these consequences. As a result, a rise in the stabilizer concentration in the main dispersion may cause the newly formed particle surfaces to be quickly covered, or it may cause the high number of polymer chains associated with the diffusion process to cause an increase in polymer-polymer contact [28].

Conversely, as the ratio of hydroxyl propyl methylcellulose increases, the particle size increases in all ratios used. The size of particles was increased in the order of F7 < F8 < F9,

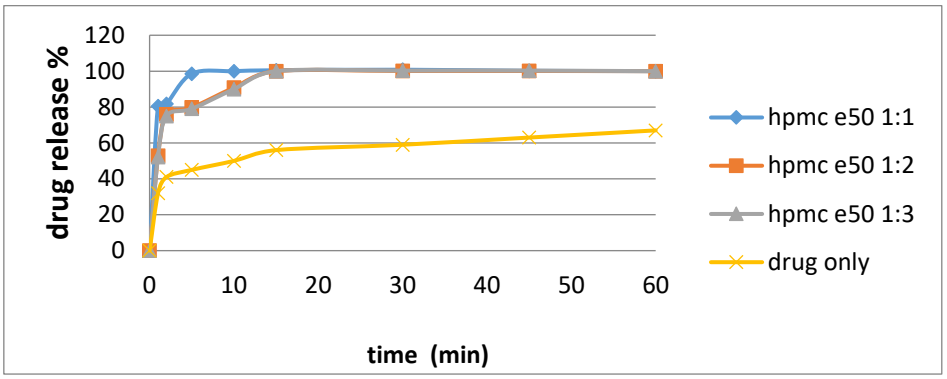

Fig. 7. Dissolution profiles of HPMC E50 formulas

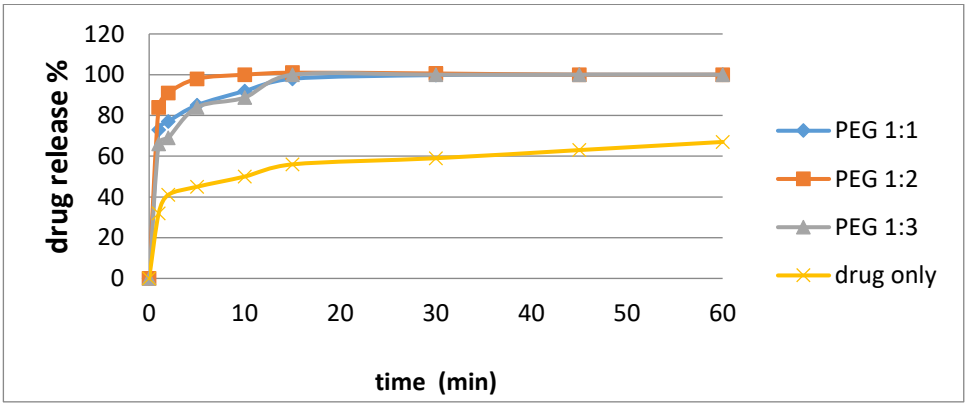

Fig. 8. Dissolution profiles of PEG 4000 formulas

corresponding to a drug: stabilizer (E5 of HPMC) ratio of 1:1, 1:2 and 1:3, respectively.

Similar results were seen when comparing the particle sizes of grades E15 and E50.

Since the increasing in the concentration of polymer would result in a thicker polymer coating

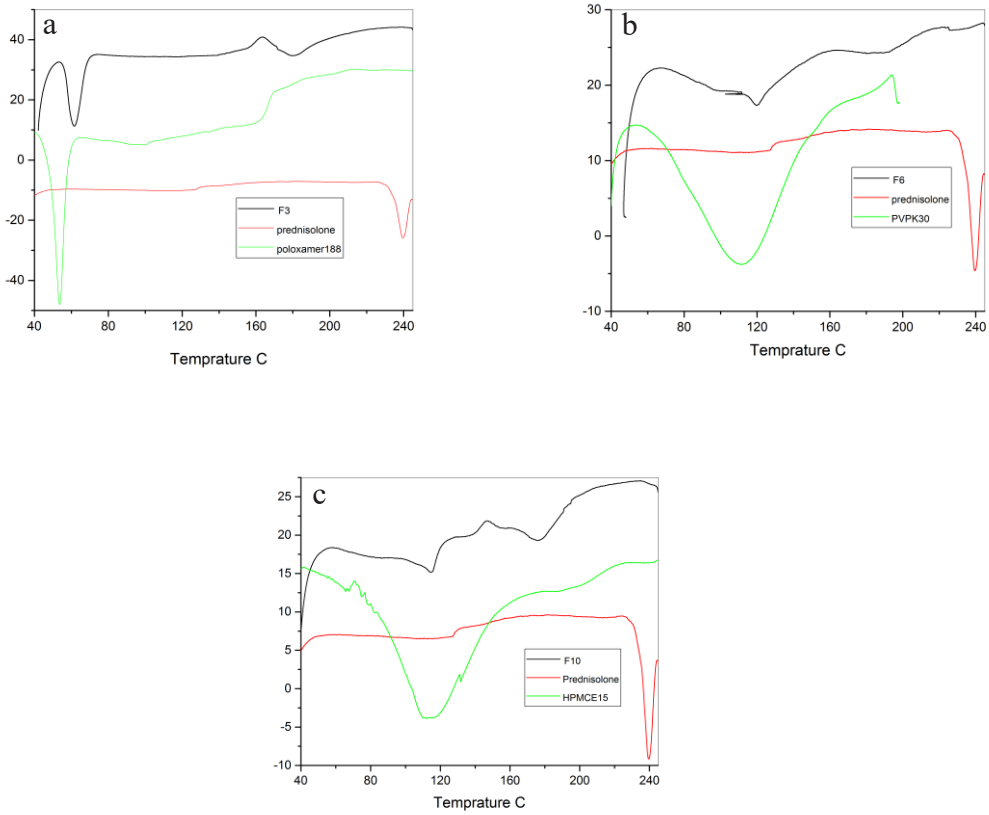

Fig. 9. DSC thermogram of lyophilized prednisolone formulas. A: F3, Poloxamer188 F6, B: PVPK30 C: F10, HPMCE15.

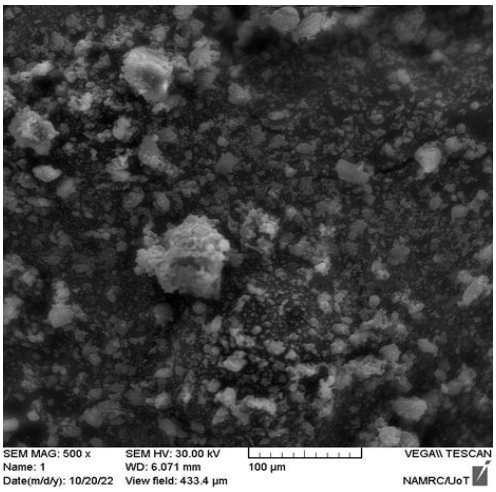

Fig. 10. SEM micrographs for pure prednisolone powder at 500 x magnification.

around each particle, or may lead to the formation of an aggregate of multiple particles [29].

HPMC has been demonstrated to produce the smallest particle sizes due to its hydrophobic component, which has a strong attraction to drug particles and can thus efficiently performance as a steric barrier to avoid growth of large particles.

HPMC was found to be the most effective stabilizer, producing the smallest particle size, due to its strong adsorption on the drug particle surface and high rate of diffusion [30].

Figs. 3-8 illustrate the results of dissolution studies.

Results specify that there is a statistically significant improvement ($p<0.05$) in the release of drug from prepared formulas when compared to the release of the pure drug.

The dissolution parameters of all formulations were calculated using the DDSolver tool, including similarity (f2) factors. The Food and Drug Administration recommends that f2 values greater than 50 (50-100) indicate similar dissolving characteristics [31]. When compared to the pure drug as a reference, the dissolution profiles of prednisolone nanosuspensions were found to be significantly different, as indicated by f2values below50.

Selection of the best formulas

Depending on the results of the particle size analysis, PID, EE and drug release, it can be concluded that F3, F6 and F10 nanosuspension formulas were the best, and will be further characterized after lyophilization by assessing their solubility, drug content, powder x-ray properties, DSC, SEM and FTIR.

Drug loading

The loading of drug in the optimized formulas F3, F6 and F10 was detected, with the percentages of drug content in each formula being 99.34% ± 0.155, 99.07% ± 0.236 and 98.1% ± 0.214, respectively. It appears that the precipitation method is an effective way to reduce the average particle size.

Saturation solubility of lyophilized powder

The results showed that the saturation solubility of prednisolone was 1.592mg/ml ±0·089 for F3, 1.671mg/ml ± 0.055 for F6, and 1.646mg/ml ±0·102 for F10. The average particle size of the drug has been reduced, resulting in a dramatic increase in its saturation solubility in certain formulations up to seven times greater than its solubility in phosphate buffer pH 7.4 (0.235 mg/ml) [32].

Differential scanning calorimetry (DSC)

The DSC spectrum of pure prednisolone showed an intense, sharp endothermic peak at 240 ºC, which is consistent with its melting point, indicating the purity and crystallinity of the drug

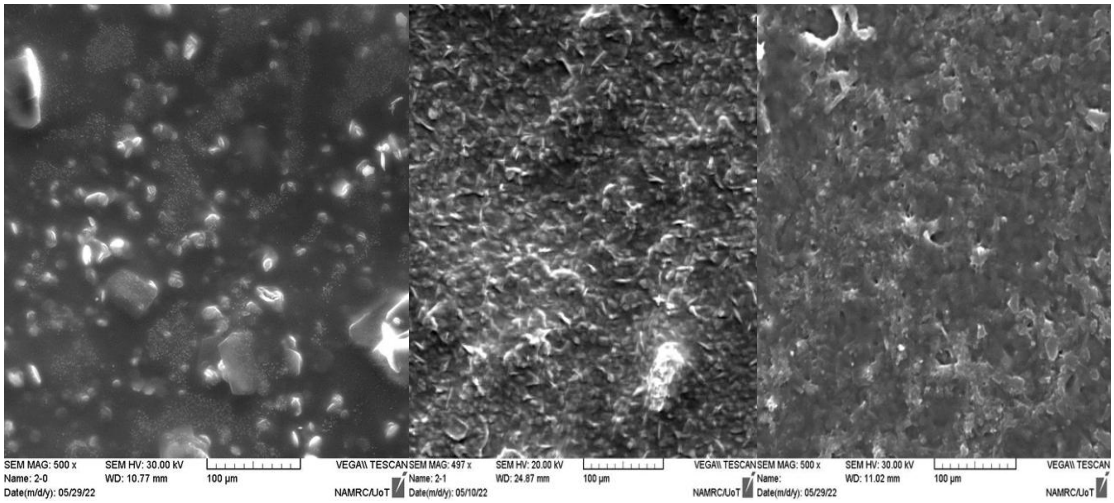

Fig. 11. SEM micrographs for Prednisolone formulas: A) F3, B) F6, C) F10 at 500 x magnification.

particles [24].

The DSC of F3, F6 and F10 showed shifting of the peaks and loss of the melting endotherm as seen in Fig. 9. The lack of a distinct melting peak in the DSC thermogram of prednisolone after its preparation as nanoparticles could be attributed to a change in the lattice property of the drug from crystalline to semi-crystalline or amorphous form.

Scanning Electron Microscopy

Fig. 10 displays SEM images of pure prednisolone particles at 500X magnification. The particles are seen to be aggregated into large crystals. On the other hand, the morphology of precipitated drug nanoparticles in lyophilized powder of F3, F6 and F10 formulas was also examined and illustrated in Fig. 11.

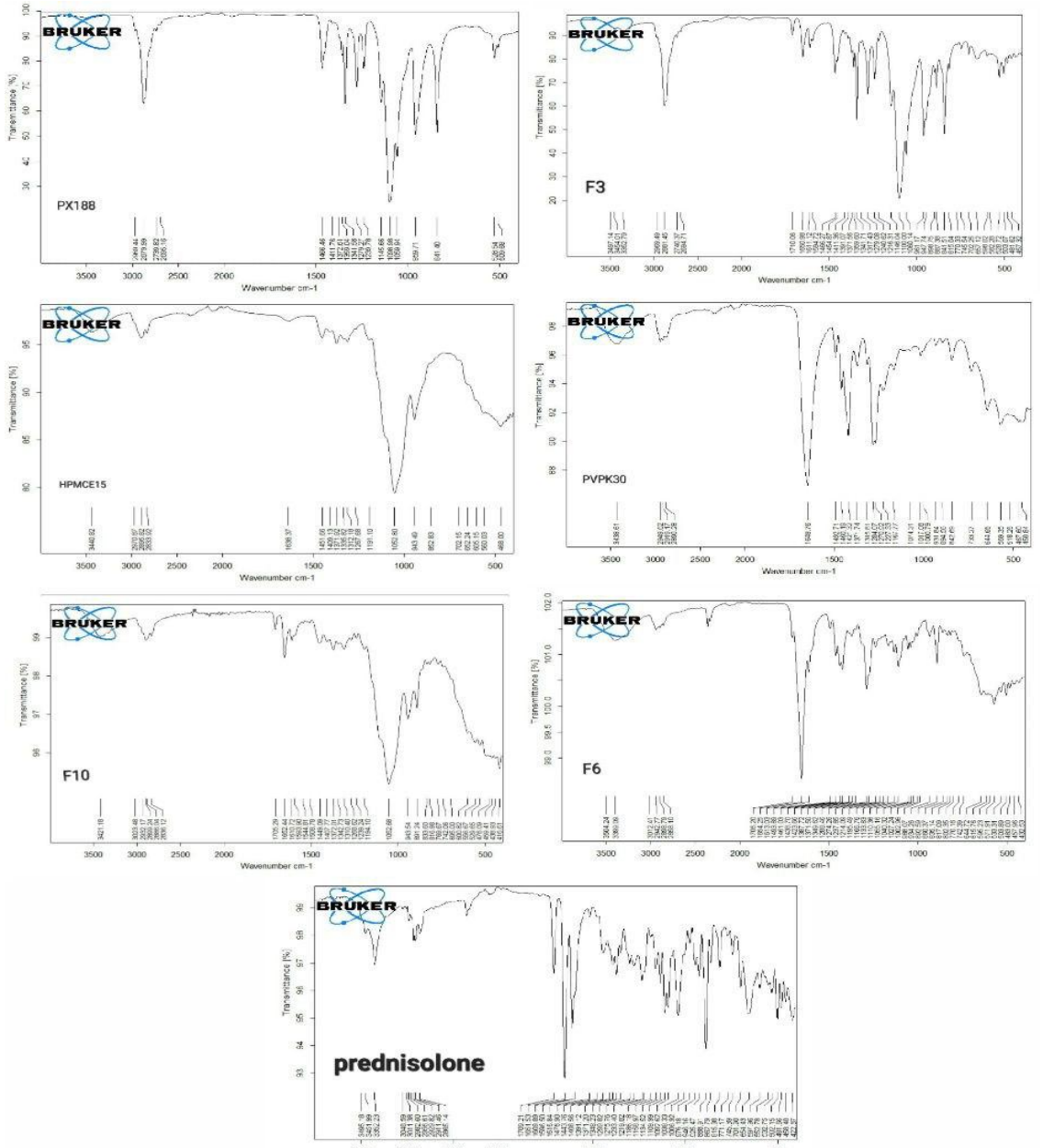

Fig. 12. FTIR spectra for Poloxamer188, PVPK30, HPMCE15, formulas (F3, F6, F10) and pure prednisolone powder.

Scanning electron microscopy (SEM) images of the formulas indicated that the particles were discrete with a uniform distribution, with no indication of agglomeration. Furthermore, the drug crystals were not present [33].

Fourier Transform Infrared Spectroscopy (FTIR)

The spectroscopy of FT-IR was employed to analyze the potential interaction between prednisolone and polymer in the prepared formulas.

It is possible that interactions will happen between the carbonyl groups and/or hydroxyl of prednisolone and the OH groups of poloxamer 188, PVPK30, and HPMCE15.

Any indication of interaction between molecules would be evidenced by a shift in the location of the C=O vibration and a decrease in the intensity of the O-H stretching, based on the strength of the reaction.

The FT-IR spectroscopy outcomes indicated that the addition of prednisolone to poloxamer 188, PVPK30 and HPMCE15 did not alter the peak positions or patterns of the spectra. A characteristic bands of the OH groups in the spectrum of prednisolone at 3500-3200 cm^{-1} as well as there are two strong bands at 1709 cm^{-1} and 1651 cm^{-1} for carbonyl stretching, the spectrums of poloxamer, PVPK30 and HPMC E15, respectively. The spectrum of poloxamer exhibited main bands at 2879 cm^{-1} (C–H stretching) and 1198 cm^{-1} (C–O stretching). Major vibrations detected in the spectrum of PVPK30, which were found at 2950-2890 cm^{-1} (C–H stretching) and at 1648 cm^{-1} (C=O stretching). The spectrum of HPMC E15 exhibited essential bands at 3300-3500 cm^{-1} (O-H stretching), at 2970-2830 cm^{-1} (C–H stretching) and at 1052 cm^{-1} (C-O stretching).

When comparing the spectra of each polymer individually and the solid dispersions of prednisolone with poloxamer 188, PVPK30 and HPMCE15, no major changes were observed in the location of the absorption bands. The results of the study showed that there is no

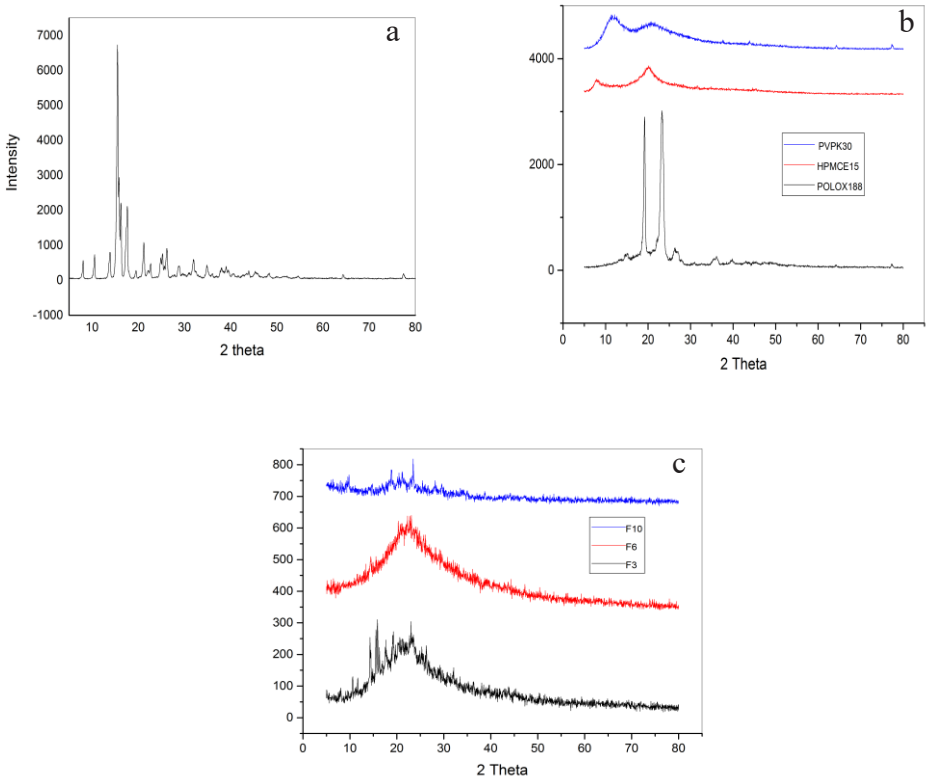

Fig. 13. XRD for A) pure prednisolone powder B) Polymers poloxamer188, PVPK30, HPMCE15 and C) formulas (F3, F6, and F10).

Table 3. Important FTIR Bands of Prednisolone in F3, F6 and F10 formulas.

Formula	O-H stretching of prednisolone cm^{-1}	C=O stretching of prednisolone cm^{-1}	
F3	3500-3200	1710	1650
F6	3500-3200	1706	1654
F10	3500-3200	1705	1652

interaction between the drug molecules and the stabilizers used in all formulations. The spectra can be seen as the combination of the spectra of prednisolone and the polymers, as shown in Fig. 12. Table 3 illustrated the important FTIR bands of prednisolone in F3, F6 and F10.

Powder x-ray diffraction (PXRD)

X-ray diffraction was used to analyze the crystalline forms of pure drug and particles of drug in the selected formulations (F3, F6 and F10) in order to verify the effectiveness of antisolvent precipitation as an appropriate method for reduction the crystallinity of drug particles. Furthermore to describe the physical nature of prednisolone nanoparticles. The X-ray patterns of pure prednisolone drug particles showed specific, sharp, narrow and high intensity diffraction peaks, as illustrated in Fig. 13.The X-ray outline of Analysis of the crystalline structure of prednisolone drug revealed a number of distinct peaks [34].

The diffractogram of PVP K-30 and HPME15 show low intense peaks, indicating that they are mainly amorphous in nature. Moreover, Poloxamer 188 has two characteristic peaks, indicating that it is crystalline in nature, as seen in Fig. 13 [35,36].

On the other hand, the XRD results of the prepared formulas (F3, F6 and F10) indicated a change in the X-ray diffraction pattern of the prednisolone particles in these formulations. Several peaks were disappeared, additionally to that the position and intensity of peaks were also changed as explained in Fig. 13. The X-ray diffraction graph can be used to detect changes in diffraction peaks that may indicate the formation of a blend of two forms, such as crystalline and amorphous forms.

CONCLUSION

The anti-solvent precipitation method has been demonstrated to be a promising technique for the production of prednisolone nanoparticles. Different stabilizers were used in the preparation of these nanoparticles at drug-to-stabilizer ratios of 1:1, 1:2, and 1:3. .These ratios were effective to stabilize prednisolone nanoparticles.

The nanosuspension of the drug had a smaller particle size, which resulted in higher dissolution rate than the raw drug in phosphate buffer 7.4. The results of FTIR analysis indicate that there is no interaction between the drug and the polymers.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES

1. Ku MS, Dulin W. A biopharmaceutical classification-based Right-First-Time formulation approach to reduce human pharmacokinetic variability and project cycle time from First-In-Human to clinical Proof-Of-Concept. Pharmaceutical Development and Technology. 2010;17(3):285-302.
2. Douroumis D. Nanosuspensions with Enhanced Drug Dissolution Rates of Poorly Water-Soluble Drugs. Drug Delivery Strategies for Poorly Water-Soluble Drugs: Wiley; 2013. p. 265-286.
3. Mathew M, Krishnakumar K, Dineshkumar B, Nair SK. Antibiotics Nanosuspension: A Review. Journal of Drug Delivery and Therapeutics. 2017;7(2).
4. Ke AT. Transungual (nail) a promising drug Delivery system: a review. International Journal of Pharma and Bio Sciences. 2017;8(3).
5. Choi J-Y, Yoo JY, Kwak H-S, Uk Nam B, Lee J. Role of polymeric stabilizers for drug nanocrystal dispersions. Current Applied Physics. 2005;5(5):472-474.
6. Jack DB. Dictionary of drugs: Chemical data, structures and bibliographies, edited by J. Elks and C. R. Ganellin. Chapman and Hall, 1990, ISBN 0412273004. Biopharmaceutics and Drug Disposition. 1991;12(6):480-480.
7. Bashar T, Apu MNH, Mostaid MS, Islam MS, Hasnat A. Pharmacokinetics and Bioavailability Study of a Prednisolone Tablet as a Single Oral Dose in Bangladeshi Healthy Volunteers. Dose-response: a publication of International Hormesis Society. 2018;16(3):1559325818783932-1559325818783932.
8. Stahn C, Löwenberg M, Hommes DW, Buttgereit F. Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. Molecular and Cellular Endocrinology. 2007;275(1-2):71-78.
9. Anjali T, Prasanna Kumar PS, Srinivas N, Shivaji K. Formulation and evaluation of aceclofenac fast disintegrating tablets using sida acuta powder. International Journal of Pharmaceutical Chemistry and Analysis. 2024;11(1):77-84.
10. Patel V, Patel S. Delivering drug-polymer complex via quick dissolving film: A step towards the development of

an appropriate pediatric formulation. Asian Journal of Pharmaceutics. 2013;7(1):21.
11. Seedher N, Sharma P. Solubility and Stability Enhancement of Poorly-Soluble Drugs Clarithromycin and Prednisolone by Combination with Other Drugs. International Journal of Biological Chemistry. 2007;1(4):229-236.
12. Yadav PS, Kumar V, Singh UP, Bhat HR, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and d-mannitol. Saudi pharmaceutical journal: SPJ : the official publication of the Saudi Pharmaceutical Society. 2013;21(1):77-84.
13. Moorthi C, Kathiresan K. Fabrication of highly stable sonication assisted curcumin nanocrystals by nanoprecipitation method. Drug Invention Today. 2013;5(1):66-69.
14. Kim BS, Won M, Yang, Lee KM, Kim CS. In Vitro Permeation Studies of Nanoemulsions Containing Ketoprofen as a Model Drug. Drug Deliv. 2008;15(7):465-469.
15. Iftikhar SY, Iqbal FM, Hassan W, Nasir B, Sarwar AR. Desirability combined response surface methodology approach for optimization of prednisolone acetate loaded chitosan nanoparticles and in-vitro assessment. Materials Research Express. 2020;7(11):115004.
16. Abd-Elrahman AA, El Nabarawi MA, Hassan DH, Taha AA. Ketoprofen mesoporous silica nanoparticles SBA-15 hard gelatin capsules: preparation and in vitro in vivo characterization. Drug Deliv. 2016;23(9):3387-3398.
17. Nguyen KT, Vo AT-N, Truong PA, Vo KA, Vo Van T, Tran PH-L, et al. Enhance the Dissolution Rate of Prednisolone by Sonoprecipitation Method. IFMBE Proceedings: Springer Singapore; 2017. p. 519-522.
18. Malamatari M, Somavarapu S, Taylor KMG, Buckton G. Solidification of nanosuspensions for the production of solid oral dosage forms and inhalable dry powders. Expert Opinion on Drug Delivery. 2016;13(3):435-450.
19. Kushare SS, Gattani SG. Microwave-generated bionanocomposites for solubility and dissolution enhancement of poorly water-soluble drug glipizide: in-vitro and in-vivo studies. Journal of Pharmacy and Pharmacology. 2013;65(1):79-93.
20. Dixit M, Kini AG, Kulkarni PK. Enhancing the aqueous solubility and dissolution of olanzapine using freeze-drying. Brazilian Journal of Pharmaceutical Sciences. 2011;47(4):743-749.
21. Sahu BP, Das MK. Nanosuspension for enhancement of oral bioavailability of felodipine. Applied Nanoscience. 2013;4(2):189-197.
22. Patnaik S, Chunduri LAA, Akilesh MS, Bhagavatham SS, Kamisetti V. Enhanced dissolution characteristics of piroxicam–Soluplus® nanosuspensions. J Exp Nanosci. 2016;11(12):916-929.
23. Dixit M, Kulkarni PK, Vaghela RS. Effect of Different Crystallization Techniques on the Dissolution Behavior of Ketoprofen. Tropical Journal of Pharmaceutical Research. 2013;12(3).
24. 2007 Annual Report on Pesticide Residues according to Article 32 of Regulation (EC) No 396/2005. EFSA Journal. 2009;7(7):305r.
25. Vogt M, Derendorf H, Krämer J, Junginger HE, Midha KK, Shah VP, et al. Biowaiver Monographs for Immediate Release Solid OralDosage Forms: Prednisolone. J Pharm Sci. 2007;96(1):27-37.
26. Gadad AP, P SC, P M D, Mastiholimath VS. Moxifloxacin Loaded Polymeric Nanoparticles for Sustained Ocular Drug Delivery. International Journal of Pharmaceutical Sciences and Nanotechnology. 2012;5(2):1727-1734.
27. Shid L R, Dhole SN, Kulkarni N, Shid L SL. Formulation and Evaluation of Nanosuspension Delivery System for Simvastatin. International Journal of Pharmaceutical Sciences and Nanotechnology. 2014;7(2):2459-2475.
28. Lebouille JGJL, Stepanyan R, Slot JJM, Cohen Stuart MA, Tuinier R. Nanoprecipitation of polymers in a bad solvent. Colloids Surf Physicochem Eng Aspects. 2014;460:225-235.
29. Dong Y, Ng WK, Shen S, Kim S, Tan RBH. Preparation and characterization of spironolactone nanoparticles by antisolvent precipitation. Int J Pharm. 2009;375(1-2):84-88.
30. El-Badry M, Fetih G, Salem-Bekhit MM, Shakeel F. Formulation and Evaluation of Nanosuspension of Albendazole for Dissolution Enhancement. Nanoscience and Nanotechnology Letters. 2013;5(9):1024-1029.
31. Spagnoli S, Maso MD. A Comparison of USP Paddle With CrescentShaped Spindle Dissolution Profiles. Dissolution Technologies. 2006;13(3):20-25.
32. Li W, Yang Y, Tian Y, Xu X, Chen Y, Mu L, et al. Preparation and in vitro/in vivo evaluation of revaprazan hydrochloride nanosuspension. Int J Pharm. 2011;408(1-2):157-162.
33. Lai F, Pireddu R, Corrias F, Fadda AM, Valenti D, Pini E, et al. Nanosuspension improves tretinoin photostability and delivery to the skin. Int J Pharm. 2013;458(1):104-109.
34. Palanisamy M, Khanam J. Solid dispersion of prednisolone: solid state characterization and improvement of dissolution profile. Drug Development and Industrial Pharmacy. 2010;37(4):373-386.
35. Xie Y, Li G, Yuan X, Cai Z, Rong R. Preparation and in vitro evaluation of solid dispersions of total flavones of Hippophae rhamnoides L. AAPS PharmSciTech. 2009;10(2):631-640.
36. LaFountaine JS, Prasad LK, Brough C, Miller DA, McGinity JW, Williams RO, 3rd. Thermal Processing of PVP- and HPMC-Based Amorphous Solid Dispersions. AAPS PharmSciTech. 2016;17(1):120-132.