Preparation and Evaluation of Hydrogel Containing Prednisolone Nanoparticles

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Abstract:

Currently, nanoparticles technology is well known and it used to augment the rate of drug dissolution and considerably increased bioavailability. Nanoparticles have been combined with hydrogel to form nanoparticle-hydrogel hybrid system as a substitute to conventional dosage forms.

The goal of this study is to prepare an effective hydrogel form containing prednisolone nanoparticles as a hybrid biomaterial system for transdermal application. Six hydrogel formulations containing prednisolone nanoparticles were prepared and characterized for particle size, entrapment efficiency, physical appearance, pH, drug content, spreadability test, viscosity, in-vitro drug release and ex-vivo diffusion. The results showed that the all preparations in the nanometer size and the drug content of prednisolone in hydrogel was ranged from 96.24% to 99.15% and there was a significant enhancement ($p<0.05$) in drug release and permeation from the prepared nanoparticles -hydrogel formulas when compared with plain hydrogel of prednisolone. From this study, it can be concluded that nanoparticle-hydrogel system could be a possible drug delivery technology for transdermal application of prednisolone drug.

Key words: nanoparticle, prednisolone, nanosuspension, particle size, hydrogel.

تحضير وتقييم هيدروجيل يحتوي على الجزيئات النانوية لبريدنزولون

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الخلاصة

حاليًا، تقنية الجسيمات النانوية معروفة جيدًا وتستخدم لتحسين معدل اذابة الأدوية التي لا تذوب بالماء وزيادة التوافر البيولوجي بشكل كبير. تم دمج الجسيمات النانوية مع الهيدروجيل لتكوين نظام هجين جسيمات نانوية هيدروجيل كبديل لأشكال الجرعات التقليدية. الهدف من هذا العمل هو إعداد شكل هيدروجيل فعال يحتوي على جسيمات نانوية لعقار البريدنيزولون كنظام هجين للمواد الحيوية لتطبيق عبر الجلد. تم تحضير ستة تركيبات هيدروجيل تحتوي على جسيمات نانوية من عقار البريدنيزولون وتم تقييم حجم الجسيمات، كفاءة التحميل، المظهر الفيزيائي ، درجة الحموضة ، محتوى الدواء ، اختبار القابلية للانتشار ، اللزوجة ، تحرر الدواء ، والنفاذية خارج الجسم الحي. أظهرت النتائج أن جميع المستحضرات هي في حجم النانومتر ونسب محتوى الدواء من عقار بريدنيزولون في الهيدروجيل تراوحت من ٩٦,٢٤٪ تحرر الدواء ونفاذية الجسيمات النانوية المحضرة بصيغ هيدروجيل بالمقارنة إلى ٩٩,١٥٪ وكان هناك تحسن ملحوظ في مع الهيدروجيل العادي من البريدنيزولون. من هذه الدراسة، يمكن استنتاج أن نظام الجسيمات النانوية مع الهيدروجيل يمكن أن يكون تقنية توصيل دواء قابلة للاستعمال عبر الجلد لعقار البريدنيزولون.

الكلمات الأساسية: الجسيمات النانوية، بريدنيزولون ، معلق نانوي ، حجم الجسيمات ، هيدروجي

Introduction

Nanocarriers can be used to produce a high drug concentration at the sites of absorption and action, making a long connection between the active ingredient and biological tissue/ membrane and improving effectiveness with low side effects [1,2]. Drug nanoparticles provide many properties such as increased saturation solubility, enhance dissolution rate and increase the adhesion to site of action or absorption [3]. Prednisolone is an adrenocortical steroid used for several illnesses for example, endocrine disorders, rheumatic disorders, collagen diseases, skin diseases and allergies [4]. Commercially, oral dosage forms prednisolone of are available in the market, yet topical formulations are not created conventional. Prednisolone is class II according to Biopharmaceutics Classification System [5].

The topical administration has been used for systemic medication effects as well as for local effects for treating skin disorders. Nowadays, gel forms are more popular among the other types of semisolid preparations in both cosmetic and medicinal applications [6]**.** In comparison to creams and ointments, gels in general provide a quicker release of the drug component, irrespective of the water solubility of drug. Hydrogel is hydrophilic with a three-dimensional network of physically or chemically cross-linked materials. These materials are absorbent and maintain well-defined structures (capable of holding big quantities of water up to thousands of times their dry weight)[7]. Nanoparticles can be loaded inside the hydrogel matrix by way of blending of theses nanometer particles with polymer dispersion [9]. Otherwise, the nanometer particles can be prepared by fusion with gel network after gelation of polymer[10].

Nanoparticle–hydrogel hybrid systems generally mix two different constituents in one preparation, which give good biological and physicochemical properties for this combination that no one of the two components be able to attain separately [11]. Nanoparticle-hydrogel composite can improve drug bioavailability and patient compliance, since it enhances drug release and diffusion across biological membranes [12] . So that, the purpose of the current research is to prepare prednisolone nanoparticles, then load these nanoparticles into a hydrogel matrix to form nanoparticle-hydrogel hybrid system for transdermal application.

Materials

Prednisolone is from Pioneer manufacturing co., Carpobol 934 is from HiMedia Laboratories Pvt.Ltd, India, Poloxamer 188 and PVPk30 are from Xi'an sonwu Biotech co.,Ltd.china, HPMC E15 is from Baoji Guokang Bio-technology co.,Ltd. China, Disodium Hydrogen Phosphate (Na2HPO4), Sodium Dihydrogen Phosphate (NaH2PO4) and Sodium Hydroxide are from Thomas Barker (chemicals)Pvt. Ltd, India. Ethanol is from Sasma ,Netherlands and the Cellulose membrane is from Special lap. Products, USA.

Methods

Preparation of prednisolone nanosuspensions

Different formulas of nanosuspensions were formulated using antisolvent precipitation method. Prednisolone was dissolved in ethanol at room temperature to prepare an organic phase of drug in ethanol. The organic solution of drug in ethanol was poured into an aqueous solution of water containing different types of stabilizers. The mixture of two solutions (organic solution of drug and aqueous solution of stabilizers) was agitated using magnetic stirrer for 60 min at 500 rpm in which, the temperature was kept at 50°C in order to get rid of organic solvent by

evaporation . Addition of organic solution by means of a syringe drop wise positioned with the needle directly into aqueous phase containing stabilizer[13]. Prednisolone is insoluble in water; therefore, it precipitates with stabilizer as fine particles. The procedure was repeated using different types of stabilizers. Various ratios of drug to stabilizer were investigated in these preparations as presented in table (1).

Table (1): Prednisolone Nanosuspensions Formulas

Code of formula	Prednisolone ratio	Poloxamer 188 ratio	PVPk30 ratio	HPMC E15 ratio
F1	1	1		
F2	1	3		
F3	1		1	
F4	1		3	
F5	1			1
F6	1			3

(1ofprednisolone refer to 40 mg prednisolone , 1 of stabilizer refer to 40 mg of stabilizer and 3 of stabilizer refer to 120 mg of stabilizer)

Particle size determination

Brookhaven zetaplus laser particle size analyzer was used in determination of the size of particles. It is a dynamic light scattering, that determining the light intensity which scattered by the particles as a function of time. The average diameters and polydispersity index of samples (without dilution of samples) were measured for each formula at scattering angle 90º and constant temperature of 25ºC[14].

Freeze drying of nanosuspension

Freeze drying method was used for drying of the best formulas of prednisolone nanosuspesions, which is the most prevalent method for drying of drug nanoparticles from nanosuspension. At a condenser temperature of -40 ºC and pressure of 0.9 mbar.The resultant powders were placed in suitable containers, which firmly closed and covered with parafilm at room temperature for additional investigation.

Preparation of Hydrogel

The selected formulations of prednisolone nanosuspension were incorporated separately within hydrogel formulation using 0.4% and 0.8% concentration of carbomer 934 ,as seen in Table (2) The calculated amount of carbomer 934 was dispersed in 40 ml distilled water and stirring at 1000 rpm for 30-90 minutes, by using magnetic stirrer until get a uniform dispersion. The pH of mixture was adjusted to 7 by adding approximately 4 ml of 10% (w/v) sodium hydroxide [15], after that the mixture was left for swelling for 24 hr. to obtain a high viscous dispersion. The freshly prepared formulas of prednisolone nanosuspension (50ml) were slowly added to viscous dispersion of carbomer 934 with stirring using magnetic stirrer. Then spatulation for 1 hr. to confirm the formation of uniform dispersion of hydrogel mixture. Furthermore, a solution of methyl paraben 0.1% (w/v) and propyl paraben 0.01% (w/v) in water was added to this mixture of hydrogel to act as preservatives [16]. The finishing weight of hydrogel was completed to 100 gm using water. The prepared hydrogels formulas were sealed and kept at room temperature in dark place for 24 hr. for further testing. Moreover, hydrogel containing one of the best-lyophilized formula was prepared

(hydrogel contain lyophilized powder of optimum formula rather than nanosuspension) as well as the gel of pure drug also was prepared as plain gel by dispersing the prednisolone in gel base for comparative studies.

Table (2): Compositions of Hydrogels (0.5 % prednisolone)

Ingredients	Plain Hydrogel	F5 0.4%	F5 0.8%	F4 0.4%	F4 0.8%	F2 0.4%	F2 0.8%	F2 lyophilized
Prednisolone (mg)	500	500	500	500	500	500	500	500
Carbopol 934	0.4%	0.4%	0.8%	0.4%	0.8%	0.4%	0.8%	0.4%
PVP K30 (mg)	-	-	-	1500	1500	-	-	-
HPMC E15 (mg)	-	500	500	-	-	-	-	-
Poloxamer 188(mg)	-	-	-	-	-	1500	1500	1500
Methyl paraben (%)w/v	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben (%)w/v	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH 20%	4ml	4ml	4ml	4ml	4ml	4ml	4 ml	4ml
DW qs ad	100ml	100ml	100ml	100ml	100 ml	100 ml	100 ml	100ml

Hydrogel assessment

Physical inspection of hydrogel formulations

Hydrogel formulas were observed visually for homogeneity, color and clarity**.**

pH measurement

Hydrogel formulas were tested at room temperature with a digital pH meter by immersing the electrode in hydrogel formulation in order to assess the pH of gel form [17,42].

Spreadability Test

After 48 hours of preparation, the hydrogels' spreadability was assessed by measuring their diameter between two glass slides. A glass plate with a circle of 1 cm diameter was marked with 0.5 g of gel, and a second glass plate was placed on top. Five minutes were given for a weight of 0.2 kg to rest on the upper glass plate. Where no more spreading was expected the increase in the diameter due to spreading of the gels was noted [18].

Determination of Drug Content

Determination of the content of drug in gel form was done by dispersing 0.4 g from the hydrogel formulation in 50 ml of phosphate buffer pH 7.4, stirring for 15 minutes on a magnetic stirrer, then sonicating for 60 mins, and finally filtering through a 0.45 µm cellulose membrane. The quantity of prednisolone in the hydrogel formulations was estimated by UV-spectrophotometry at the determined wavelength [19].

Viscosity measurement

The rheology of semisolid products gives critical information about the stability of semisolid dosage forms. The rheological studies were carried out using rotational viscometer by a technique called cup and bob. The rheological study was performed by using Myr viscometer with increase the spindle rotation speed from (6) to (100) rpm [20] .All measurements were done at room temperature and the average of triplicate was taken.

In vitro drug release

Drug release from hydrogel was assessed using dialysis approach (Molecular cut off 8000-12000 Dalton "Da") (commonly used for drug release studies in dermal dosage forms and suitability of pore size for removal of small drug particles). Phosphate buffer with pH 7.4 was used as a dissolution solvent and it was used to soak the dialysis bag. Each dialysis bag contained (400mg hydrogel) hydrogel formulation of prednisolone [21], then the bag was sealed at both ends, and it placed in phosphate buffer pH (200ml) (7.4)[22]. The experiment was tested in a dissolution apparatus (paddle method) with a 100 rpm rotation speed at 37± 0.5 ºC. Five millilitres were removed and substituted by the same volume at the specified times. The sample media was measured using UV-VIS spectrophotometry [23,24]. The in-vitro release of prednisolone was also done for the prepared plain hydrogel and hydrogel of the best-lyophilized formula (contain lyophilized powder and the other formula contain nanosuspension). The drug release studies were conducted in triplicate [41].

Ex-vivo permeation

Preparation of skin

Adult male rat was obtained from Iraqi Center for Cancer Research and Medical Genetics, Al-Mustansiriyah University for the permeation studies. Skin was excised from the abdominal region of rat after removing hair carefully with a razor taking care to prevent any damage to the surface of the skin, and then the subcutaneous fat and connective tissue were trimmed, Figure (1). The excised skin was washed and examined for integrity and then kept in a refrigerator at 4 ºC overnight for future usage [25]

Figure (1): Rat skin preparation for Ex-vivo permeation study after removal of hair and connective tissues.

Ex-vivo permeation studies:

Franz diffusion cells with water bath system (Franz diffusion cell apparatus Copley scientific ,UK in Bagdad university/college of pharmacy) was used for ex-vivo skin permeation test containing from six cells and each one composed from two parts a lower receptor and upper donor compartment Rat skin membrane that, removed previously was mounted and fixed firmly with an O-ring (to fix the skin on the cell) onto receptor compartment of Franz cells in which, the medium of receptor (each cell has 12 ml volume capacity) part consisting from phosphate buffer solution (pH 7.4) [26]. Then, prednisolone hydrogel sample was placed on skin surface in the donor champer part at 600 rpm and at temperature 37 ± 0.5ºC to mimic in-vivo circumstances [27,28]. Periodically Samples (0.1 ml) were withdrawn at scheduled time intervals for 8 hr. The removed samples were replaced and the withdrawn samples

were then inspected spectrophotometrically at λmax of prednisolone.

Stability study

The stability study was done for the optimum hydrogel formulas. These best formulas filled in collapse tubes and stored at room temperature for 3 months. Samples were withdrawn from formulas at the end of each month and examined for various physical tests such as appearance, colour change, drug content and pH[17,18].

Statistical Examination

The outcomes of testing were presented as an average of samples ±standard deviation (SD) where n=3.The experiments data were evaluated using a one-way analysis of variance (ANOVA) in Excel; the outcomes are significant if $p < 0.05$ and insignificant if $p > 0.05$.

Results and Discussion

Size range

All preparations were found to be in the nanometer size as listed in table (3). The smallest particle size of nanoparticles was found to be 50.8 nm for formula F5 as shown in figure (2) and table (3), on the other hand, the entrapment efficiency was assessed, it was ranged from 71.5% ± 0.54 to 91.2% ± 0.25. According to the PDI values obtained from this study, it can concluded that all formulations are monodisperse systems[29].

The Effect of Polymer type on the size of prednisolone nanoparticles

As shown in figure (2). The results indicated that a substantial increase in particle size obtained with PVPk30>Poloxamer188>HPMCE15.

These results may possibly due to the different attraction of these stabilizers towards the particles of drug and to the viscosity differences that produced by these polymers. HPMC polymer commonly used as a stabilizer due to the presence of alkyl substituent. HPMC has been shown to produce the lowest particle sizes since its hydrophobic component has a higher affinity for drug particles and can thus well performance as a steric barrier to avoid growth of large particles. Additionally, HPMC produced the smallest particle size when utilized as a stabilizer due to it had a significant adsorption on the surface of drug particle and satisfactory rate of diffusion to the surface of drug particles [30].

The effect of polymer concentration on the size of prednisolone nanoparticles

The size distribution of particles was increased in the order of F2 (71nm) < F1 (260nm) that conform to 1:3 and 1:1 of drug: polymer (poloxamer188 formulations) ratio, respectively, this is seen in table (3) .These results showed that the average size of particles was decreased when the quantity of Poloxamer188 was increased. Similar results were noticed with PVPK30. The range of particle size was also increased in the order of F4 (105nm)<F3 (286nm) that correspondent to 1:3 and 1:1 of drug: stabilizer (PVPk30 formulations) ratio, respectively. These results may be due to that the new formed particle surfaces were rapidly covered, as result of the increased stabilizer concentration in the dispersion may be the cause of these consequences. The hydrophilic property of polymers chains provide steric hindrance counter to aggregation of particles or it may cause the large number of polymer chains and an increase in polymer-polymer contact [30]. On the contrary, the size of a particle is determined by the ratios of HPMC present. As the amount of HPMC increases, the size of particles increases as detected for HPMCE15 F6 (126 nm) > F5 (50.8 nm) .Generally, the increasing in particle size can be attributed to the supersaturating of mixture and faster nucleation rate since the addition of polymer leading to an increase in the concentration of polymer molecules and may result in the construction of polymer coating around the drug particles up to a certain point when the polymer molecules covered all particles of drug. At

that time, an increasing in the concentration of polymer would increase the width of the stabilizer coating around drug particles. Moreover, this may be due to the formation of an aggregation of suspended particles [31,32].

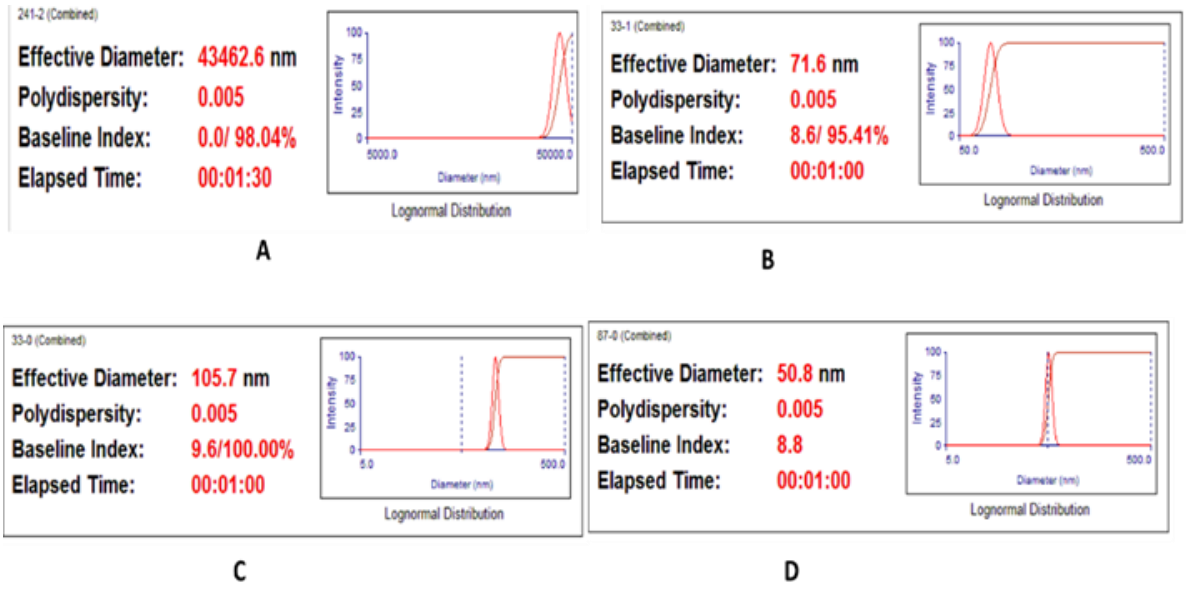

Figure (2): Graphs from dynamic light scattering showing particle size and PDI A: Raw material of prednisolone; B: F2 Nanoparticle; C: F4 Nanoparticles; D: F5 Nanoparticles

Table (3): Particle Size, PDI and Entrapment Efficiency.

Formula	Particle size average (nm)	Polydispersity index PDI	Percentage of Entrapment Efficiency ± SD
raw drug	43462.6	0.005	-
F1	260	0.005	78.4 ± 0.21
F2	71.6	0.005	89.7 ± 0.2
F3	286	0.387	71.5 ± 0.54
F4	105.1	0.005	87.6 ± 0.3
F5	50.8	0.005	91.2 ± 0.25
F6	126	0.447	82.6 ± 0.52

Drug content in lyophilized formulas

Drug content for optimized formulas (lyophilized powder) was evaluated in F2, F4 and F5; the percentages of drug in formulas were 99.34% ± 0.155, 99.07±0. 236 and 98.1% ± 0.214, respectively. The results of this study demonstrate that the method used to prepare the hydrogel formulations was successful in providing formulations with a consistent drug content and minimal variability, since prednisolone drug particles were dispersed uniformly throughout the hydrogel**.**

Physical inspection of hydrogel formulations

All hydrogel formulations showed a white colour with a homogenous texture and no signs of separation or precipitation, as shown in Figure (3).

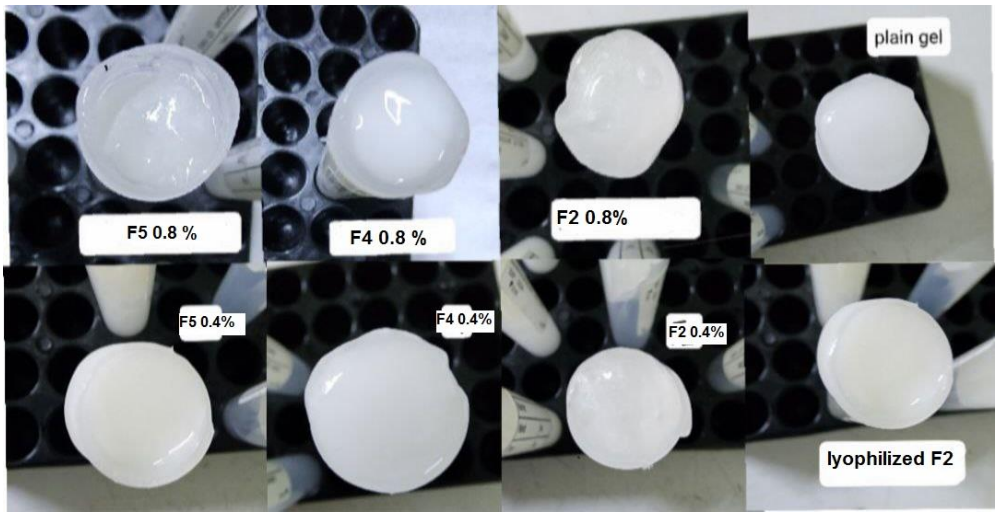

Figure (3): Physical appearance of different hydrogel formulation

pH measurement

The pH value of the hydrogels was shown in table (4). The pH of the formulations decreased when the active ingredients added to the base of gel. The pH of the skin normally ranges from 4 to 6 [33]. According to the results values, the gels' pH values were similar to the skin's normal pH value as listed in table (3), which indicates the suitability of the formulations for application on the skin.

Spreadability test

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[34]. Spreadability of different hydrogels was shown in table (4). The results showed that there is inverse relationship between polymer concentration and spreadability, since prednisolone hydrogels spreadability decreased by increasing the polymer ratio [35] as illustrated by the spreaded circle diameter. These results agree with the results obtained from measuring the spreadability of hydrogel containing carbopol 934 as a polymer in Honey-based hydrogel by Reham F. El-Kased [36] .

Drug Content in hydrogel

Drug content of prednisolone in hydrogel was determined, and it was ranged from 96.24% to 99.15%, as shown in table (4). The drug content of the formulations showed that the drug particles were uniformly distributed within the gels forms.

Table (4) Spreadibility, pH and drug content for the prepared prednisolone hydrogels.

Formula	pH	Drug content %	Spreadability (cm)
F2 (0.4%)	5.91 ± 0.20	98.82 ± 0.05	6.7 ±0.1
F2 (0.8%)	5.95 ± 0.21	97.54 ± 0.04	4.3 ±0.2
F4 (0.4%)	5.78 ± 0.18	99.15 ± 0.05	6.0 ±0.2
F4 (0.8%)	5.85 ± 0.21	96.89 ± 0.05	3.9 ±0.1
F5 (0.4%)	6.08 ± 0.17	98.55 ± 0.06	6.6 ±0.1
F5 (0.8%)	6.15 ± 0.15	97.23 ± 0.03	4.2 ±0.2
F2 lyophilized 0.4%)(	5.56 ± 0.09	97.68 ± 0.05	7.0 ±0.2
Plain hydrogel (0.4%)	5.22 ± 0.15	96.24 ± 0.04	6.7 ±0.2

Viscosity measurement

Viscosity plays a significant role in determining the drug permeation. Generally, the viscosity of preparations reveals to the consistency and usually gel form show non-Newtonian pseudoplastic rheology because the slope of the line decrease with increasing the magnitude of velocity or in essence the viscosity decreases, as seen in Figure (4) [37]. Upon increasing the polymer ratio, the viscosity of the hydrogel formulas was increased. The highest viscosity was detected in F4 hydrogel 0.8% formula and the lowest with 0.4% hydrogel containing lyophilized powder (F2).

In vitro drug release

The release profile of prednisolone from hydrogel formulas was described in figure (5). According to outcomes, the release of the drug could be categorized in the resulting order: F2 (0.4%) > F2 lyophilized (0.4%) > F4 0.4% > F5 (0.4%) > F2 (0.8%) > F4 (0.8%) > F5 (0.8%) > plain hydrogel, where the percentages of the drug released after 4 hours were 90.46 %, 86%, 85.33%, 84.64 %, 77.33%, 74.77%, 71.71 % and 48.92% respectively. The results showed a significant difference ($p<0.05$) between all the prepared nanoparticles -hydrogel formulas and the plain prednisolone hydrogel, the enhancement of drug release can be due to the incorporation of nanoparticles into hydrogel . It was observed with increasing carbopol 934 ratio there is consequent delay in drug release. Universally, an increase in the medium viscosity as result of increasing polymer concentration would lead to further firm construction and a subsequent decreasing in the rate of release [38]. Moreover, the drug release was influenced by the nature of polymer as well as the network structure of polymer used. There is no significant difference ($p> 0.05$) was observed between the drug release of F2 formula containing nanosuspension and F2 formula containing lyophilized nanoparticles of the same ratio of drug to polymer (due to the effect drug particles size). Similar pattern of release was observed by Ondansetron HCl Nanoparticles for Transdermal Delivery by Amjed H. Noor however prednisolone showed faster rate of release which can be due to the different type and nature of the drug and polymers used [39].

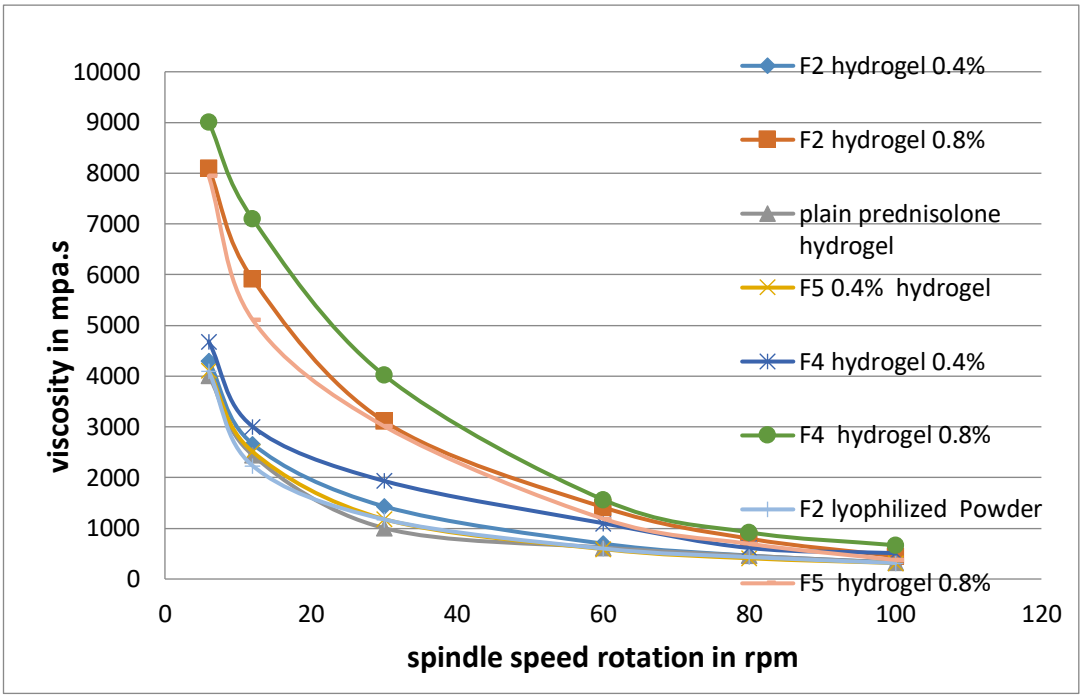

Figure (4): Viscosity versus velocity for different formulations of prednisolone hydrogels

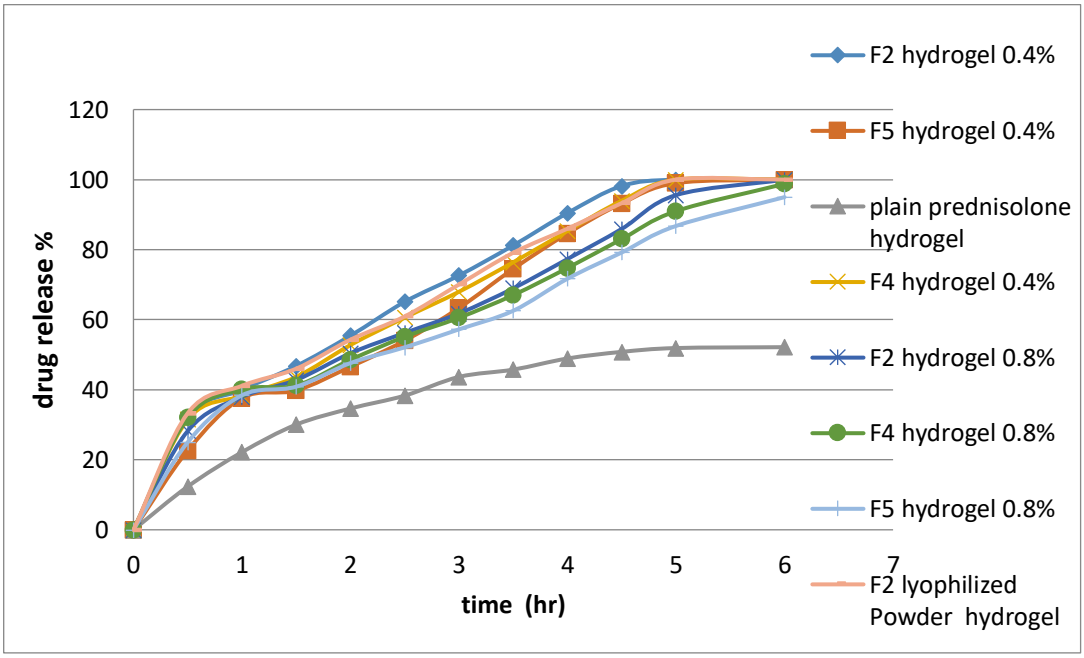

Figure (5): The cumulative percentage release of drug from different formulations of prednisolone hydrogels compared with plain prednisolone hydrogel.

Ex-vivo permeation

The permeation study was done in phosphate buffer (pH 7.4). Figure (6) illustrated the permeation of drug through rat skin. The amount of cumulative permeation of prednisolone from hydrogel formulations of F2 (0.4%), F4 (0.4%), F2 (0.4%) lyophilized, F5 (0.4%) , and plain hydrogel at 8 hr. were found to be 2 mg, 2 mg, 1.95 mg, 1.93 mg , and 0.80 mg per

1.77 cm^2 surface area respectively. The results showed that, there is a significant difference ($p<0.05$) between plain hydrogel and other nanoparticles- hydrogel formulations. F2 (0.4%) hydrogel showed the highest permeation percentages than others. At the same period, the plain gel of prednisolone exhibited the lowest release.
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The small size of the drug particles in the hydrogels may lead to lager surface area and higher contact between the drug particles and the skin's surface, resulting in improved permeation as well as to the concentration gradient across the skin membrane that acts as a driving force for drug permeation [40]

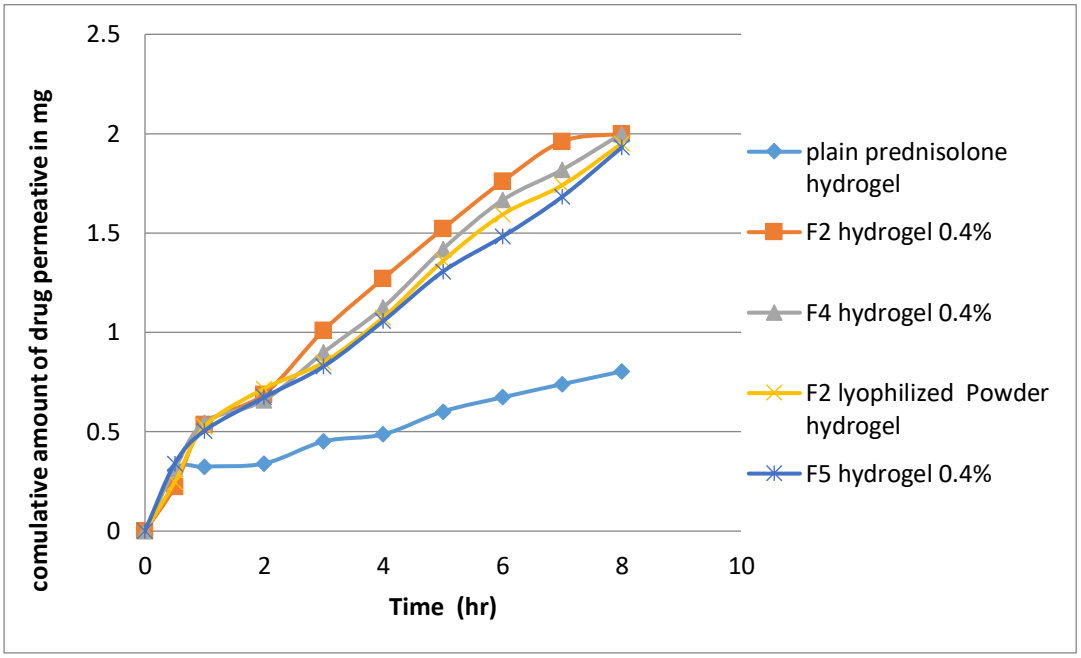

Figure (6) Ex-vivo permeation of prednisolone from different hydrogel formulations compared to plain prednisolone hydrogel at pH 7.4 through 1.77 cm^2 rat skin at 37°C.

Stability study

The prepared prednisolone hydrogel formulas were found to be stable upon storage at room temperature for 12 weeks, where no significant changes were observed in the evaluated parameters such as color, homogeneity, pH and drug content, as listed in table (5).

Table (5): Stability Study Data of Prednisolone Nanoparticles- Hydrogel Formulations after Three Months .

parameter	F2 0.4% hydrogel at Room temperature	F4 0.4% hydrogel at Room temperature	F5 0.4% hydrogel at Room temperature
appearance	homogenous	homogenous	homogenous
pH	5.77	5.71	6.05
colour	white	white	white
Drug content	98.65	99.02	98.19

Conclusion

According to the results obtained, prednisolone nanoparticles was successfully prepared by solvent evaporation technique and it was an efficient method. All the prepared formulations of nanoparticle-hydrogel showed a good spreadability, viscosity, drug release and permeation across rat skin.

References

1- Kumar A, Chen F, Mozhi A, Zhang X, Zhao Y, Xue X, Hao Y, Zhang X, Wang PC, Liang XJ. Innovative pharmaceutical development based on unique properties of nanoscale delivery formulation. Nanoscale. 2013;5(18):8307-25.

2- Ehmann F, Sakai-Kato K, Duncan R, Pérez de la Ossa DH, Pita R, Vidal JM, Kohli A, Tothfalusi L, Sanh A, Tinton S, Robert JL. Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines. Nanomedicine. 2013 May;8(5):849-56.

3- Müller RH, Gohla S, Keck CM. State of the art of nanocrystals–special features, production, nanotoxicology aspects and intracellular delivery. European journal of pharmaceutics and biopharmaceutics. 2011 May 1;78(1):1-9.

4- Palanisamy M, Khanam J. Solid dispersion of prednisolone: solid state characterization and improvement of dissolution profile. Drug development and industrial pharmacy. 2011 Apr 1;37(4):373-86.

5- Zakeri-Milani P, Nezhadi SH, Barzegar-Jalali M, Mohammadi L, Nokhodchi A, Valizadeh H. Studies on dissolution enhancement of prednisolone, a poorly water-soluble drug by solid dispersion technique. Advanced Pharmaceutical Bulletin. 2011 Jun;1(1):48.

6- Basha BN, Prakasam K, Goli D. Formulation and evaluation of gel containing fluconazole-antifungal agent. International Journal of Drug Development and Research. 2011;3(4):109-112.

7- McKenzie M, Betts D, Suh A, Bui K, Kim LD, Cho H. Hydrogel-based drug delivery systems for poorly water-soluble drugs. Molecules. 2015 Nov 13;20(11):20397-408.

8- Gao W, Vecchio D, Li J, Zhu J, Zhang Q, Fu V, Li J, Thamphiwatana S, Lu D, Zhang L. Hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery. Acs Nano. 2014 Mar 25;8(3):2900-7.

9- Thomas V, Yallapu MM, Sreedhar B, Bajpai SK. Breathing-in/breathing-out approach to preparing nanosilver-loaded hydrogels: Highly efficient antibacterial nanocomposites. Journal of Applied Polymer Science. 2009 Jan 15;111(2):934-44.

10- Merino S, Martin C, Kostarelos K, Prato M, Vázquez E. Nanocomposite hydrogels: 3D polymer–nanoparticle synergies for on-demand drug delivery. ACS nano. 2015 May 26;9(5):4686-97.

11- 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. 2013 Jan 1;21(1):77-84.

12- Nunes D, Andrade S, Ramalho MJ, Loureiro JA, Pereira MC. Polymeric nanoparticles-loaded hydrogels for biomedical applications: a systematic review on in vivo findings. Polymers. 2022 Mar 2;14(5):1010.

13- Moorthi C, Kathiresan K. Fabrication of highly stable sonication assisted curcumin nanocrystals by nanoprecipitation method. Drug Invention Today. 2013 Mar 1;5(1):66-9.

14- Kim BS, Won M, Yang, Lee KM, Kim CS. In vitro permeation studies of nanoemulsions containing ketoprofen as a model drug. Drug Delivery. 2008 Jan 1;15(7):465-9.

15- Speedy L. The effects of shear on neutralized carbomers in aqueous conditions. Monash University, Australia, semanticscholar. org. 2014

16- Kim BS, Won M, Yang, Lee KM, Kim CS. In vitro permeation studies of nanoemulsions containing ketoprofen as a model drug. Drug Delivery. 2008 Jan 1;15(7):465-9.
17- Arora R, Aggarwal G, Harikumar SL, Kaur K. Nanoemulsion based hydrogel for enhanced transdermal delivery of ketoprofen. Advances in Pharmaceutics. 2014 Dec 16;2014.
18- Helal DA, El-Rhman DA, Abdel-Halim SA, El-Nabarawi MA. Formulation and evaluation of fluconazole topical gel. Int J Pharm Pharm Sci. 2012;4(5):176-83.
19- Suksaeree J, Monton C, Sakunpak A, Charoonratana T. Formulation and in vitro study of ketoprofen pseudolatex gel for transdermal drug delivery systems. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;6(2):248-53.
20- Mowafaq M. Ghareeb. Formulation and characterization of rizatriptan benzoate as intranasal nanoemulgel. Int. J. Drug Deliv. Technol. 2022;12, 546-552.
21- Ueda CT, Shah VP, Derdzinski K, Ewing G, Flynn G, Maibach H, Marques M, Rytting H, Shaw S, Thakker K, Yacobi A. Topical and transdermal drug products. InPharmacopeial forum 2009 May (Vol. 35, No. 3, pp. 750-764).
22- Hayder K. Abbas, Inas F. AbdulRazzaq, Yasmien A. Salal, Dhurgham Q. Shaheed. Preparation and evaluation of proniosomal form containing diphenhydramine HCl. Drug Invention Today.2020 May13(2):313-323.
23- Samia O, Hanan R, Kamal ET. Carbamazepine mucoadhesive nanoemulgel (MNEG) as brain targeting delivery system via the olfactory mucosa. Drug delivery. 2012 Jan 1;19(1):58-67.
24- Bayanati M, Khosroshahi AG, Alvandi M, Mahboobian MM. Fabrication of a thermosensitive in situ gel nanoemulsion for nose to brain delivery of temozolomide. Journal of Nanomaterials. 2021 Mar 13;2021.
25- Zhao X, Liu JP, Zhang X, Li Y. Enhancement of transdermal delivery of theophylline using microemulsion vehicle. International journal of pharmaceutics. 2006 Dec 11;327(1-2):58-64.
26- Mostafa DM, Abd El-Alim SH, Asfour MH, Al-Okbi SY, Mohamed DA, Hamed TE, Awad G. Transdermal fennel essential oil nanoemulsions with promising hepatic dysfunction healing effect: in vitro and in vivo study. Pharmaceutical development and technology. 2019 Jul 3;24(6):729-38.
27- Kaur R, Ajitha M. Transdermal delivery of fluvastatin loaded nanoemulsion gel: Preparation, characterization and in vivo anti-osteoporosis activity. European journal of pharmaceutical sciences. 2019 Aug 1;136:104956.
28- Laothaweerungsawat N, Neimkhum W, Anuchapreeda S, Sirithunyalug J, Chaiyana W. Transdermal delivery enhancement of carvacrol from Origanum vulgare L. essential oil by microemulsion. International Journal of Pharmaceutics. 2020 Apr 15;579:119052.
29- Abbas HK, Bader QA, Hussein AH, Shaheed DQ. Preparation and in vitro evaluation of clove oil microemulsion. Int. J. Pharm. Res. 2020 Apr;12:422-30.
30- El-Badry12 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):1024-9.
31- Dong Y, Ng WK, Shen S, Kim S, Tan RB. Preparation and characterization of spironolactone nanoparticles by antisolvent precipitation. International journal of pharmaceutics. 2009 Jun 22;375(1-2):84-8.
32- Shekunov BY, Baldyga J, York P. Particle formation by mixing with supercritical antisolvent at high Reynolds numbers. Chemical Engineering Science. 2001 Apr 1;56(7):2421-33.
33- Lukić M, Pantelić I, Savić SD. Towards optimal ph of the skin and topical formulations: From the current state of the art to tailored products. Cosmetics. 2021 Aug 4;8(3):69.

34- Kumar L, Verma R. In vitro evaluation of topical gel prepared using natural polymer. International journal of drug delivery. 2010 Jan 1;2(1).
35- Jelvehgari M, Montazam H. Evaluation of mechanical and rheological properties of metronidazole gel as local delivery system. Archives of pharmacal research. 2011 Jun;34(6):931-40.
36- El-Kased RF, Amer RI, Attia D, Elmazar MM. Honey-based hydrogel: In vitro and comparative In vivo evaluation for burn wound healing. Scientific reports. 2017 Aug 29;7(1):9692.
37- Baby DK. Rheology of hydrogels. InRheology of Polymer Blends and Nanocomposites 2020 Jan 1 (pp. 193-204). Elsevier.
38- Zakaria AS, Afifi SA, Elkhodairy KA. Newly developed topical cefotaxime sodium hydrogels: antibacterial activity and in vivo evaluation. BioMed research international. 2016 Jan 1;2016.
39- Noor AH, Ghareeb MM. Formulation and evaluation of ondansetron HCl nanoparticles for transdermal delivery. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2020 Dec 27;29(2):70-9.
40- El Maghraby GM. Transdermal delivery of hydrocortisone from eucalyptus oil microemulsion: effects of cosurfactants. International Journal of Pharmaceutics. 2008 May 1;355(1-2):285-92.
41- AlEbadi NN, Al-Lami MS. Formulation and in-vitro Evaluation of Ethosomes using Anastrozole as a Modeling Drug. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2022;22(4):90-105.
42- Ali MH, Ali WK. Preparation and Evaluation of Emulgel as Topical Drug Delivery for Nimesulide by Using Conventional Emulsion. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2019 Dec 1;19(4):16-26.