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Role of Nanoparticulate System in Improving the Cutaneous Targeting of Drugs

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ABSTRACT— Mometasone furoate (Mome) is a topically applied glucocorticoid with very potent anti-inflammatory effect. Although it is a water insoluble drug, systemic absorption might take place if used to large areas causing moderate side effects. The aim of this study is to formulate a nanosuspension based-gel formulas of this drug to reduce the tendency for systemic absorption. These formulas were prepared by solvent-antisolvent precipitation method using probe sonicator instrument and four stabilizers (PVA, PVP, Poloxamer188 and Tween 80). The stabilizer type, drug:stabilizer ratio, addition of co-stabilizer, sonication power and sonication time. The nanosuspensions particle size, polydispersity index and zeta potential were evaluated to select the most stable formulas. Mome optimized formulas were freeze-dried and further characterized using FTIR, DSC, PXRD and SEM. Then they were incorporated in Carbopol 940 gel base to prepare Mome nanosuspension gels (GF1-GF4) at a concentration of 0.1% w/w to be evaluated for pH, viscosity, drug content, in vitro drug release and ex vivo skin permeation test. FTIR revealed the absence of interactions between drug and polymers used. DSC and PXRD demonstrate the reduction of powder crystallinity with some amorphization. Drug release study showed appropriate drug release from the gel base (more than 90% within 3 hrs). Ex vivo permeation study highlighted the ability of nanosuspension based-gel formulation GF2 to increase permeation and localization of mome in comparison with Elica cream (marketed product). This research declares the ability of nanosuspensions to increase localization of (Mome) within skin with minimum systemic absorption.

KEYWORDS: Carbopol 940 gel base, Elica cream, Mometasone furoate, polydispersity index.

1. INTRODUCTION

More than 40% of medications have trouble being formulated into standard dose forms because they are not water soluble [1]. The Biopharmaceutics Classification System reflects that Class II and IV drugs have poor solubility in both aqueous and organic environments, poor dissolution, and low bioavailability [2]. Although many ways (like micronization, cosolvency, oily solution, salt creation, solid dispersion and ß-cyclodextrin inclusion complex) were dealt with these problems, but they did not work with all medications equally [3]. Accordingly, the drugs that are poorly soluble or insoluble in both water and oils and the substances that have a high log P value, high melting point, and high dosage can be treated by using nanosuspension technology. It is a biphasic system made up of nanoscale drug particles stabilized by surfactants for parenteral and pulmonary delivery as well as oral and topical application. The solid particles in nanosuspensions typically have a particle size distribution that is smaller than one micron, with an average particle size between 200 and 600 nm [4]. Precipitation technique, media milling, high-pressure homogenization in water, high-pressure homogenization in non-aqueous medium, and a combination of Precipitation and high-Pressure homogenization are some of the different techniques used to prepare nanosuspensions [5]. However, this technology has disadvantages [6] including; poorly soluble drug in aqueous and organic media were difficult to be formulated. The non-aqueous solvent to be miscible with

antisolvent (usually water) in the presence of surfactant were potentially toxic. Besides, the particle characters were difficult to preserve such as the particle size and the amorphous fraction [7]. The gels are semisolid systems formed of a dispersion of either big organic molecules or small inorganic molecules that are encased and interpenetrated by liquid.

Large organic particles are dissolved in the continuous phase, randomly coiling in the flexible chains, while inorganic particles are not dissolved but rather scattered throughout the continuous phase in gels [8]. The aim of this study was to investigate the potential of mometasone furoate formulated as a nanosuspension based gel to enhance the cutaneous delivery of the drug into the skin.

2. MATERIALS AND METHODS

Regarding Mome; we detected melting point using the capillary tube method [9], λ max using UV- visible spectrophotometer from 200-400 nm wavelength to have the maximum absorption [10] and the saturated solubility in deionized water as well as in water/ethanol mixture (75:25) by adding an excess amount of pure powder to 5 ml at 25 ºC. All these solutions were kept at a magnetic stirrer for 72 hours [11]. Mome nanosuspension (Mome NS) was prepared using solvent-antisolvent precipitation method with probe sonicator instrument to prevent the elevated temperature during working and continued until the formation of a nanosuspension liquid formulas which converted to dry power by subjecting them to lyophilization process so as to remove water from liquid preparation without excessive damage, enhancing stability on storage and reconstitutable by adding water, or another suitable aqueous diluent [12]. Different polymers and a surfactant were used to prepare Mome NS including PVA, PVP, PX-188 and Tween 80. Also, the effect of concentrations (1%, 2% and 3%) of each polymer and a surfactant was studied to be evaluated on P.S and PDI and zeta potential in three different ratios (drug: stabilizer ratio 1:1, 1:2, and 1:3) [13]. Three formulas were prepared to evaluate the effect of increasing sonication power (up to 70 rpm) on the P.S and PDI. While another three formulas were prepared to evaluate the effect of increasing sonication time (6-12 minutes) on the P.S and PDI. Concerning liquid Mome NS; P.S and PDI of all formulas for color, homogeneity (presence or absence of any aggregation) were estimated by visual inspection and were measured by dynamic light scattering technique (DLS) under temperature 25°C, time 100 second and each sample were read three times without dilution. Therefore, all reads represent the mean ± S.D. Zeta potential was also assessed by measuring the velocity of electrophoretic mobility of the particle in the sample of the selected formula during applying an electric field which was then converted into ZP [14]. Four Mome NS based gel formulas containing Mome at a concentration of 0.1% w/w were prepared using Carbopol 934 polymer at a concentration of 1.5% w/w as gelling agent.

Statistical analysis was carried out using either t-test or one-way ANOVA followed by the Tukey test to determine the presence of any significant difference between or among the data. All data is presented as the mean ± SD with P values of ≤ 0.05 being regarded as statistically significant.

3. RESULTS

Three types of stabilizers (PVA, PVP & PX188) were used in all NS formulas, The P.S reduction was noticed as 162.5nm, 517nm and 434.7 nm for the formulas that stabilized by PVP, PVA and Poloxamer (PX)188 respectively. These results are shown in Table- 1

Table 1: Average P.S, PDI and Z-potential for the liquid Mome NS formulas

F. No.	Polymer conc.	D:P ratio	Processing variables S.P., S.T	Particle size nm	PDI	Z-potential
F5	PVA 3%	1:3	50%, 6 min	517.2	0.005	27.90

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F10	PVP 3%	1:3	50%, 6 min	162.5	0.005	35.79
F15	PX-188 3%	1:3	50%, 6 min	434.7	0.005	38.12

The effect of different polymers concentrations (1%, 2% or 3%) on the particle size and PDI of Mome NS were shown in Figure 1

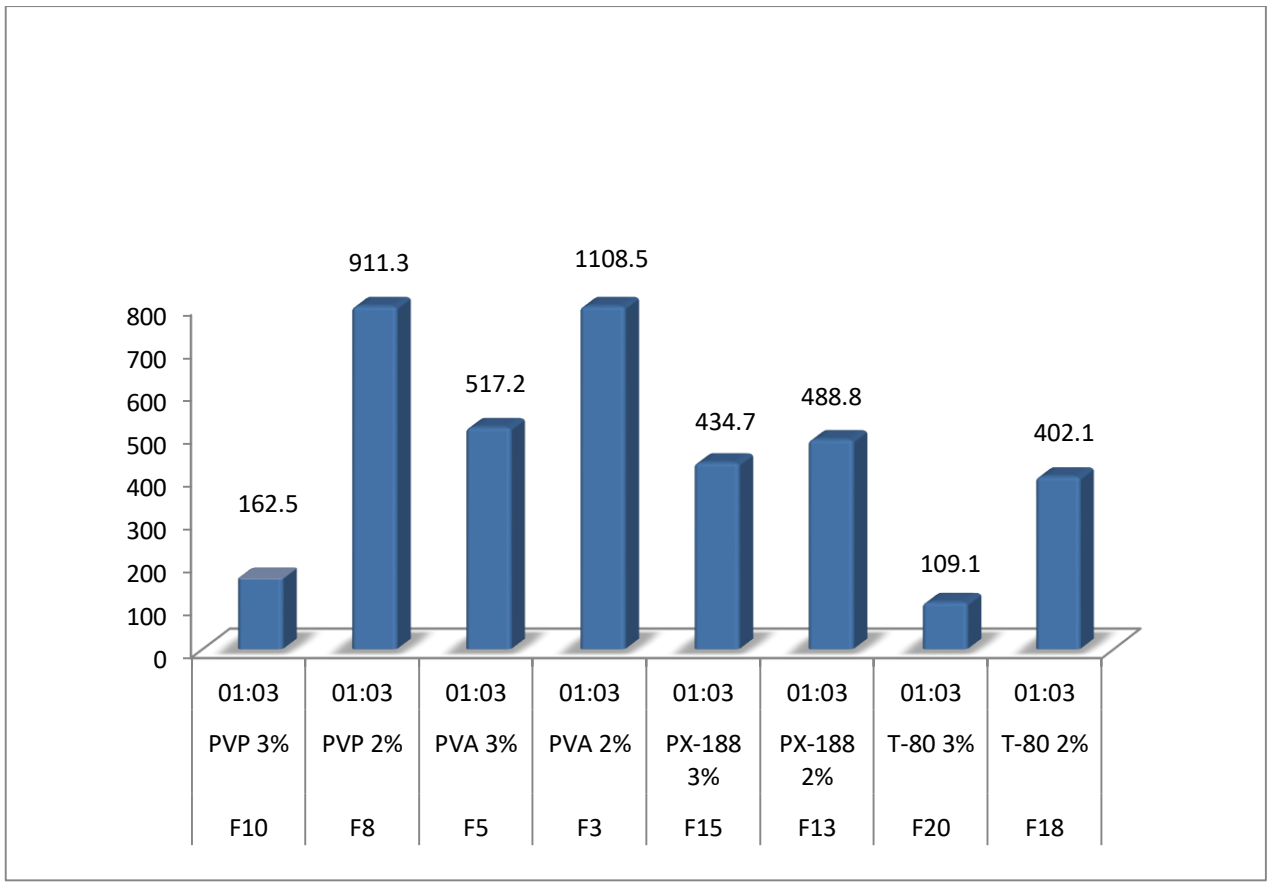

Figure 1. Effect of the polymers concentrations on the particle size of Mome NS

The effect of drug: polymer ratio (1:1, 1:2 or 1:3) at sonication power (50%) and active sonication time of 6 min showed that as the stabilizer ratio increased, the particle size was decreased [Table 2].

Table 2: Effect of Stabilizer Ratio on the PDI of Mome

Stab. Ratio	Tween 80	PVA	PVP	PX 180	
(1% / 1:3)	0.23	0.452	0.005	0.347	
(2% / 1:3)	0.2	1.040	1.040	0.282	
(3% / 1:3)	0.005	0.005	0.005	0.005	0.3

The effect of adding Tween 80 (a nonionic stabilizer with significant wettability) on particle size and polydispersity index showed a significant reduction in particle size. For examples formulas (F5, F10, F15) which had a particle size 517nm, 162.5 nm, 434.7nm respectively.

When Tween 80 was added a significant decrease in the particle size appeared as in F21, F22, and F23

which the particle size became 68.1, 65.3 and 57.3 respectively [Table 3].

Table 3: Effect of addition of Tween 80 on the particle size of Mom

Formula. No.	Polymer conc. (3%+3%)	D:P ratio	Processing variables S.P., S.T	Particle size nm	PDI	Z-potential
F21	**PVA+T-80**	**1:3**	**50%, 6 min**	**68.1**	**0.411**	**24.82**
F22	**PVP+T-80**	**1:3**	**50%, 6 min**	**65.3**	**0.201**	**35.14**
F23	**PX-188+T-80**	**1:3**	**50%, 6 min**	**57.3**	**0.19**	**43.49**

Regarding the effect of sonication power on the formulations of Mome NS, no significance was raised when using sonication power 50% For examples formulas (F11, F12, F13 and F14) did not showed any reduction in particle size (1079.3nm, 830.7 nm, 488.8 nm and 705.6 nm respectively. When using sonication power 70%, still significant reduction in particle size was not obtained as in formulas F24, F25 and F26) which had a particle size (512.3 nm, 161.7 nm and 428.4 nm respectively [Table 4].

Table 4: Effect of sonication power on the different formulas of Mome NS

Formula. No.	Polymer conc. (3%+3%)	D:P ratio	Processing variables S.P., S.T	Particle size nm	PDI	Z-potential
F11	PX-188 2%	1:1	50%, 6 min	1079.3	0.252	28.55
F12	PX-188 2%	1:2	50%, 6 min	830.7	0.281	24.47
F13	PX-188 2%	1:3	50%, 6 min	488.8	0.252	22.05
F14	PX-188 3%	1:2	50%, 6 min	705.6	0.09	29.12
F24	PVA 3%	1:3	70%, 6 min	512.3	0.731	22.56
F25	PVP 3%	1:3	70%, 6 min	161.7	0.45	31.07
F26	PX-188 3%	1:3	70%, 6 min	428.4	0.5	32.94

Regarding the effect of sonication time on the formulations of Mome NS, no significance was found when increasing the time from six minutes to twelve minutes because the nanosuspension system reaches to the smallest size with six minutes. For example, F5, F10 and F15 were with sonication time 6 minutes did not show any changes in the particle size and when the procedure was shift to twelve minutes, still no significance was obtained as F27, F28 and F29 [Table 5].

Table 5: Effect of sonication time on the different formulas of Mome NS

Formula. No.	Polymer conc.	D:P ratio	Processing variables S.P., S.T	Particle size nm	PDI	Z-potential
F5	PVA 3%	1:3	50%, 6 min	517.2	0.005	27.90
F10	PVP 3%	1:3	50%, 6 min	162.5	0.005	35.79
F15	PX-188 3%	1:3	50%, 6 min	434.7	0.005	38.12
F27	PVA 3%	1:3	50%, 12 min	505.1	0.326	25.15
F28	PVP 3%	1:3	50%, 12 min	113.1	0.5	28.17
F29	PX-188 3%	1:3	50%, 12 min	403.2	0.42	34.06

4. Discussions

There are some drugs topically used on skin to treat certain dermatological conditions without fear of developing unwanted effects. But when they were used on large cutaneous area, potentially side effects started. In the present study, we try to find out that using of nanosuspensions of these drugs e.g. Mometasone furoate (a very potent anti-inflammatory skin drug) may help in increasing the drug permeation and minimizing its systemic unwanted effects. It was cleared that the cumulative permeated amount of Mome in µg/cm2 from different NS gel formulas showed insignificant difference. However, the permeated amount from gel F23 was higher than other formulas. This may be due to the smaller particle size of 57 nm in comparison to others. When comparison made with Elica® cream (a marketed product), NS gel formulas showed greater permeation than the cream (650-680 µg/cm2, 490 µg/cm2 respectively. This can be attributed to the smaller particle size that provides greater chance for these particles to adhere and penetrate the skin. Also NS gel formulas provide higher saturated solubility and concentration. In our study, the NS gel formulas enhanced the skin deposition of Mome but also increased its permeation across the skin and these results indicate that the sonication time with a power of (50%) is sufficient to produce the smallest particle size and this was agreed with Chung, D.D. [15].

5. Conclusion

According to the findings of this study, the NS gel base formula showed higher drug permeation and localization within skin particularly when the drug: stabilizer ratio is of 1:3

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