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Original article

Evaluation of the bioavailability of hydrocortisone when prepared as solid dispersion

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ABSTRACT

This study was conducted to formulate, characterize, and investigate the bioavailability of hydrocortisone (HCT) when prepared as solid dispersions. HCT was mixed in an organic solvent with polyethylene glycol 4000 (PEG 4000) and Kolliphor® P 407. Spray drying technique was employed to form a solid dispersion formulation at a specific ratio. Physical and chemical characterization of the formed particles were achieved using differential scanning calorimetry, scanning electron microscopy, Fourier transform infrared spectroscopy, and powder X-ray diffractometry. Furthermore, comparative *in vitro* and *in vivo* studies were conducted between the formulated particles against neat HCT. The formulated solid dispersion showed elongated particles with leaf-like structure. Formation of new chemical bonds in the formed particle was suggested due to the change in the vibrational wave numbers and the significant improvement in the bioavailability of the dispersed particles proved the importance of this technique.

1. Introduction

Glucocorticoids were firstly utilized at around 1950 to treat rheumatoid arthritis. Steroids are polycyclic hydrocarbons and are vital compounds in different biological processes. In particular, hydrocortisone, which is the pharmaceutical form of cortisol, is a common hormone drug used for conditions like asthma and dermatitis. It is in class VII, low potency drug and has only around 100 min of plasma $t_{1/2}$ (Cevc and Blume, 2004; He et al., 2017; Moodley et al., 2017).

PEG 4000 and Kolliphor® P 407 share close chemical structure (Liu et al., 2015). PEG 4000 is a hydrophilic compound and used largely in pharmaceutical applications. Kolliphor® P 407 (also known as poloxamer 407), consists of hydrophobic and hydrophilic parts. It is amphiphilic in nature and can form micelles upon reaching specific critical micelle concentration (CMC) (Liu et al., 2015; Cespi et al., 2012). Both polymers have been used extensively to enhance active pharmaceutical ingredients (APIs) overall bioavailability (Park et al., 2009; Betageri and Makarla, 1995; Moneghini et al., 2001; Dumortier et al., 2006; Wong et al., 2006).

Compounds that lack the necessary aqueous solubility are subject to different formulation approaches such as; reducing particle size, complexation, and solid dispersion with a hydrophilic polymer (Chiou and Riegelman, 1971; Ruiz-Rubio et al., 2018). Recently, solid dispersion formulations are achieved using techniques like spray drying and hot melt extrusion (Jung et al., 1999; Altamimi et al., 2018; Yin et al., 2005; Crowley et al., 2007; Follonier et al., 1994). The aim of the formulator is merely to increase the dissolution rate that later will improve the overall bioavailability if the dissolution was the rate limiting step. However, if, during formulation, active pharmaceutical ingredients APIs become amorphous an increase in the equilibrium solubility exists. The formulator must carefully select the carrier polymer to prevent high free energy amorphous state from recrystallization.

APIs and other drugs or carriers are dissolved in a mutual organic solvent. Thereafter, the spraying process started by spraying the formed solution through a specifically selected size nozzle. Later, continuously forming droplets will instantaneously face a dry air to evaporate the organic solvent. The dry particles are

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collected after going through a cyclone to separate heavy particles from lighter ones. During the spray drying process, one should carefully consider factors such as; feeding rate, the viscosity of the solution, the glass transition temperature of the formed materials, selected temperature in drying camper, and the amount of residual solvent.

Hydrocortisone has been formulated as freeze-dried formulation, complexed with β-cyclodextrin, and extruded as glassy ribbon using hot melt extrusion (HME) methods to enhance the *in vitro* characteristics (Cavalli et al., 1999; Frank and Kavaliunas, 1983; Corrigan and Crean, 2002; DiNunzio et al., 2010). In the present study, HCT: polymer dispersions were formulated through a spray drying technique to investigate not only the *in vitro*, but also, *in vivo* characteristics of the spray-dried hydrocortisone.

2. Materials

Hydrocortisone was purchased from "AVONCHEM Ltd., (Cheshire, UK)". PEG 4000 was purchased from "BDH laboratory Supplies (Poole, UK)". Kolliphor® P 407 was purchased from "BASF (Ludwigshafen, Germany)". High performance liquid chromatography (HPLC) grade organic solvents were purchased from "Sigma Aldrich (St. Louis, MO, USA)".

3. Methods

3.1. Solid dispersion formation

Hydrocortisone with Kolliphor® P 407 or PEG 4000 were mixed in a mass ratio of 1:4 and dissolved in 500 mL of ethanol. The clear solution was spray-dried using a "Mini Spray-Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland)". The aspiration, inlet air temperature, and the flow rate were 100%, 65 °C, and 25%, respectively (Altamimi et al., 2018).

3.2. Differential scanning calorimetry (DSC)

The thermal study was conducted using a "DSC 8000, Perkin Elmer Instruments (Shelton, CT, USA)" at a heating rate of 10 deg/min. Aluminum pan and lid was used to hermetically seal samples of ~3 mg (Altamimi and Neau, 2016a). Pure indium was used for calibration (T_m 156.60 °C, enthalpy of fusion 28.45 kJ/g). Nitrogen gas (N_2) at a rate of 20 mL/min was used to purge both sample and reference cells and "PYRIS software" was used to analyze generated data.

3.3. Fourier transform infrared spectroscopy (FTIR)

The IR fingerprint of hydrocortisone, PEG 4000, Kolliphor® P 407 mixtures were obtained using an Alpha Bruker Platinum -ATR. Briefly, the lens was cleaned using distilled water and Kimwipe before testing. After the internal calibration of the instrument indicated a pass signal, the sample was placed and the spectrum was acquired. The spectra were collected at 24 scans and across 4000–400 cm^{-1} wavenumber (Chittur, 1998; Belfer et al., 2000).

3.4. Powder X-ray diffraction (PXRD)

X-ray data generated using "Ultima IV diffractometer (Rigaku, Tokyo, Japan)". The 2θ range was over the 3–60° and at a scan speed of 0.5 deg/min. Cu with Ka = 0.1540562 nm monochromatized as graphite crystal for the tube anode. The peak patterns were collected for each sample under the following conditions; the voltage of 40 kV, tube current of 40 mA, step size of 0.02°, counting time 1 s/step (Tantishaiyakul et al., 1999; Yamashita et al., 2003).

3.5. Scanning electron microscopy (SEM)

Sample's morphology was taken using "SEM, Zeiss EVO LS10 (Cambridge, UK)". Double-sided adhesive carbon tape was used to mount the samples on the stubs "SPI Supplies (West Chester, USA)". Gold was used to coat the mounted samples under vacuum in "Q150R sputter coater unit from Quorum Technologies Ltd. (East Sussex, UK)" at 20 mA for 1 min under an argon atmosphere. The voltage of 15 kV was used to capture the data (Zidan et al., 2012).

3.6. Liquid chromatography method

HPLC analysis was conducted using "Waters HPLC system (Waters, USA)" attached to an isocratic/gradient HPLC pump, Autosampler, and a programmable dual absorbance UV–visible detector. A column of 150 mm × 4.6 mm RP C8 was used with methanol:water (CH_3OH:H_2O) (80:20% v/v). The flow rate was set at 1.0 mL/min and at a detection wavelength at 254 nm. For each sample, a volume of 20 μl was injected into the HPLC system using the Autosampler.

3.7. In vitro drug dissolution

An automated "USP Type II dissolution apparatus (UDT-804, LOGAN Inst. Corp., USA)" was used with 900 mL of distilled water as a dissolution medium and maintained at 37 ± 0.5 °C. A suitable amount of each formulation (equivalent to 10 mg hydrocortisone) was filled in a hard gelatin capsule. Each body of the hard gelatin capsule was carefully separated from its cap and was placed on a suitable base holder on a balance. The required amount was carefully situated in the capsule body with the help of a mini spatula. Then, the cap was tightly fitted in the capsule body. Later, the filled capsules were inserted into stainless steel sinkers and placed at the bottom of the vessels.

Samples were withdrawn at predetermined time intervals 5, 15, 30, 45, 60, 90, and 120 min through 10-μm filter tips (LOGAN Instruments Corp., USA). Then freshly prepared dissolution medium was replaced immediately. Samples were analyzed using the developed HPLC® method.

3.8. In vivo study

Male Wister Albino rats (weight 200–220 g) were obtained from "College of Pharmacy experimental animal care center, King Saud University, Riyadh, Saudi Arabia". Access to food was prohibited overnight before dosing of different drug formulations. HCT neat powder and the formulated PEG 4000 or Kolliphor® P 407 solid dispersions were dispersed homogeneously in 0.3% carboxymethylcellulose to form suspensions at 5 mg hydrocortisone/10 mL. Rats were divided into three groups for each of the formulation administration. The drug and its formulations (equivalent to 5 mg hydrocortisone/kg b.wt.) were orally introduced to the rats through a gavage. 500 μl of blood samples were drawn at following time intervals of 30 min, and 1, 2, 4, 6, 9, 12, 24 h into heparinized tubes through the retro-orbital plexus vein. Later, centrifugation was conducted for each sample at 5000 rpm and for 10 min, to collect the plasma. Finally, plasma samples were kept at −80 °C refrigerator for analysis. Access to food was allowed after 3 h of drug administration. All procedures were done according to international guidelines for using the animals.

3.9. Plasma sample preparation:

Protein precipitation method was used to processes the extracted samples. Briefly, 200 μl of plasma and 750 μl methanol are mixed in 1.5 mL Eppendorf tube. 50 μl IS (Prednisolone

100 μg/mL) was added to the tube and vortexed for 1 min. The mixture was subjected to centrifugation at 15,000 rpm (15,000*g*) for 10 min. Exactly 750 μl of the supernatant was transferred to different tubes and 5 μl was injected into the LC/MS/MS for analysis.

3.10. UPLC-MS/MS method

Here, a validated "UPLC-MS/MS (UPLC: Waters Acquity, Milford, MA, USA)" was performed to determine HCT concentration-time profile. Conditions for analysis include the use of a BEH C_{18} column (50 mm × 2.1 mm, 1.7 μm) and acetonitrile plus 0.1% formic acid (40:60, v/v) at a 0.25 mL/min as a flow rate. HCT and IS compounds were detected by "TQ detector (Waters Corp., Milford, MA, USA)". Electrospray ionization (ESI) was the ion source under positive ionization mode and multiple reactions monitoring (MRM) mode. Identification of the ionized pairs (*m*/*z*) was as follows: Hydrocortisone: 363.24 → 121.03 (cone voltage 32 V, collision energy 24 V), Prednisolone: 403.172 → 385.224 (cone voltage 42 V, collision energy 13 V).

4. Results and discussions

4.1. Solid dispersion formation and hydrocortisone content

Water is a suitable solvent for spray drying technique due to its high surface tension. In addition, organic solvents and surfactants can be used when faced with low soluble drugs. When formed droplets interact with hot air, drying process started inducing transport of heat and mass. Factors such as; drying energy, droplet density, droplet size, and liquid surface tension are important for any spray drying processes (Vehring, 2008; Paudel et al., 2013). Here, ethanol was selected due to the high solubility of hydrocortisone ~14.70 mg/mL and its high permissible daily exposure (PDE) limit for the residual content (Fig. 1a) (Paudel et al., 2013; Ali et al., 2009). Hydrocortisone was formulated with PEG 4000 (Fig. 1b) and poloxamer 407 (Fig. 1c) to yield dispersed mixtures. For all formulations, HCT content was found to be ≥95% and such small deviation was adjusted during the dissolution study.

4.2. Differential scanning calorimetry (DSC)

Performing thermal analysis is crucial to determine the physical reaction patterns in response to temperature changes. Sharp melting peak for HCT of 226 °C and enthalpy of fusion (ΔH_{fus}) of ~115 J/g as shown in Fig. 2 (Cavalli et al., 1999; Velaga et al., 2002; Ali et al., 2011). One melting peak was found for poloxamer 407 at a peak temperature of 58 °C and enthalpy of fusion (ΔH_{fus}) of 134 J/g. PEG 4000 showed a single endothermic melting peak at a temperature around 61 °C (Altamimi and Neau, 2016a). For spray dried mixtures, however, melting peak of HCT was not detected indicating a complete transformation of the crystal form to the amorphous counterpart.

It is known that chemicals are either glass formers or non-glass formers. Furthermore, such glassy state could be stable or non-stable. If an exothermic peak is found during the cooling stage, the compound is considered non-glass-former. However, glass formers present T_g followed by a crystallization peak that precedes the melting stage of the compound. In other cases, T_g only is exhibited and no crystallization peak is detected. In the latter state, the molecules are considered stable amorphous. Generally, chemicals with an $M_W \leq 300$ g/mole are considered non-glass formers and proved difficult to practically predict their glass transition temperature (Mahlin and Bergström, 2013; Baird et al., 2010).

To determine HCT glass forming ability, the drug was under heating and cooling cycle and rate of 20 °C/min (see Fig. 3). Clearly, a glass transition temperature was detected at ~95 °C, indicating HCT is a stable glass-former.

4.3. Fourier transform infrared spectroscopy (FTIR):

The energy in the infrared IR region induces vibrational frequencies in the bonds between atoms and such vibrations are detected by IR spectra. Therefore, different active pharmaceutical ingredients are identified through their fingerprints. In addition, IR can detect any newly formed bonds (Huang et al., 2008; Altamimi and Neau, 2017; Watson, 2005).

The IR spectra for Hydrocortisone, Kolliphor® P 407, PEG 4000 and drug:polymer mixtures are shown in Fig. 4. The neat HCT has characteristic peaks at 3411 and 2918 cm^{-1} for O—H and C—H groups, respectively. C=O groups two prominent peaks at around 1709 and 1638 cm^{-1} (Raghavan et al., 2001; Katas et al., 2012).

Kolliphor® P 407 has characteristic peaks at 3414, 2876, and 1099 cm^{-1}, representing O—H, C—H, C—O, respectively (Eloy and Marchetti, 2014). Vibrational stretching of PEG 4000 is clear at 2876 cm^{-1}, representing C—H stretching. The ether characteristic peak is found at 1096 cm^{-1} (Patel and Patel, 2008).

HCT shows a tendency for hydrogen bonding in the hydroxyl and the carbonyl groups. For the spray-dried formulation between HCT and Kolliphor® P 407, no significant differences in the entire assigned peaks were found. Nevertheless, a hydrogen bonding with O—H is suggested due to the ether vibrational shifted to lower wave number of 1097 cm^{-1}. No significant shifts in the vibrational bands were found in the HCT with PEG 4000.

4.4. Powder X-ray diffraction (PXRD)

The diffraction pattern for HCT, PEG 4000, Kolliphor® P 407, and the formulated particles are shown in Fig. 5. The X-ray spectra for crystalline HCT exhibited distinct peaks at diffraction angles (2θ) equal to 14.500°, 16.200°, and 17.500° (Corrigan and Crean, 2002; Thakur and Gupta, 2006). The PEG 4000 and Kolliphor® P 407 showed two main peaks at diffraction angles (2θ) equal to 19.350° and 23.300°. However, the intensity of the peaks in Kolliphor® P 407 proved to be twice as much as PEG 4000 peaks. Due to the fact that polyethylene glycol (PEG) represents the crystalline domain of poloxamer 407, such an agreement between the

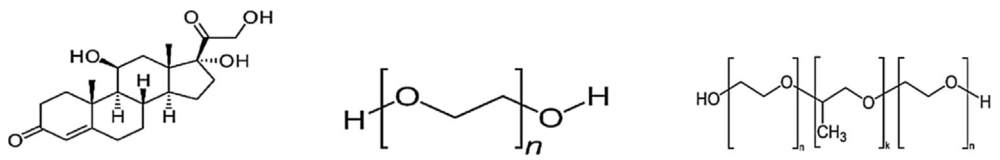

Fig. 1. Chemical structure for (a) Hydrocortisone, (b) PEG 4000, and (c) Kolliphor® P 407. The subscript n and k denotes the number of monomers.

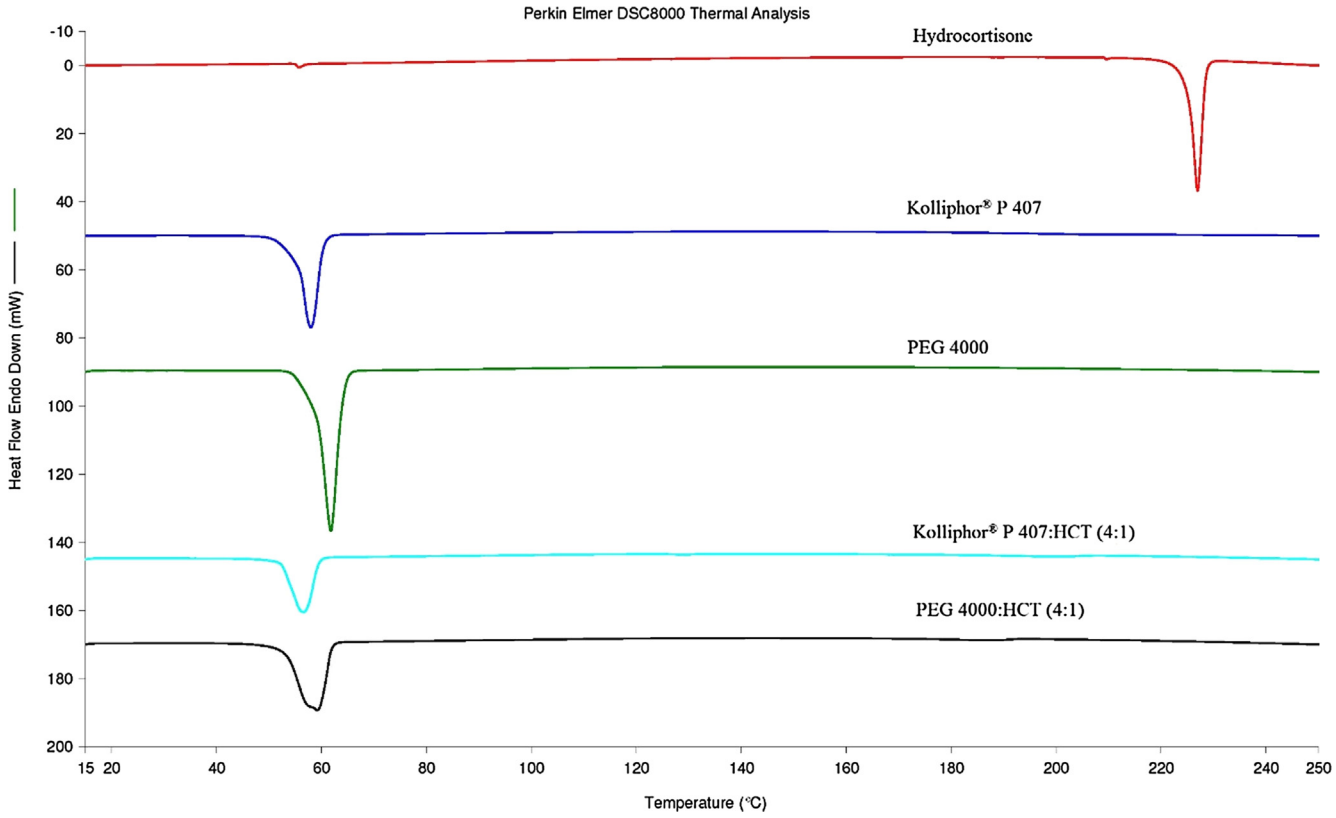

Fig. 2. Thermograms for Hydrocortisone, Kolliphor® P 407, PEG 4000 and polymer:drug mixtures at 4:1 ratio.

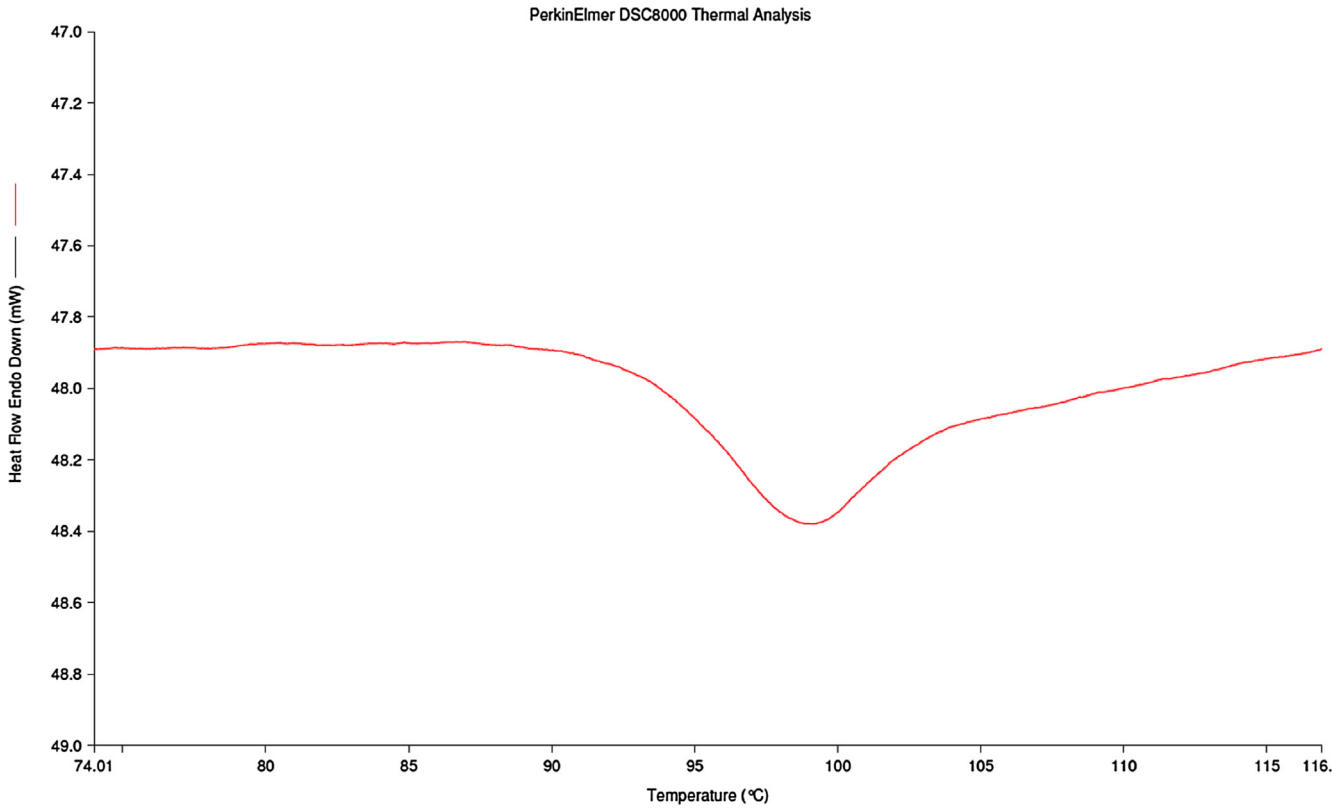

Fig. 3. Thermogram for HCT showing the second heating cycle and proving the existence of T_g.

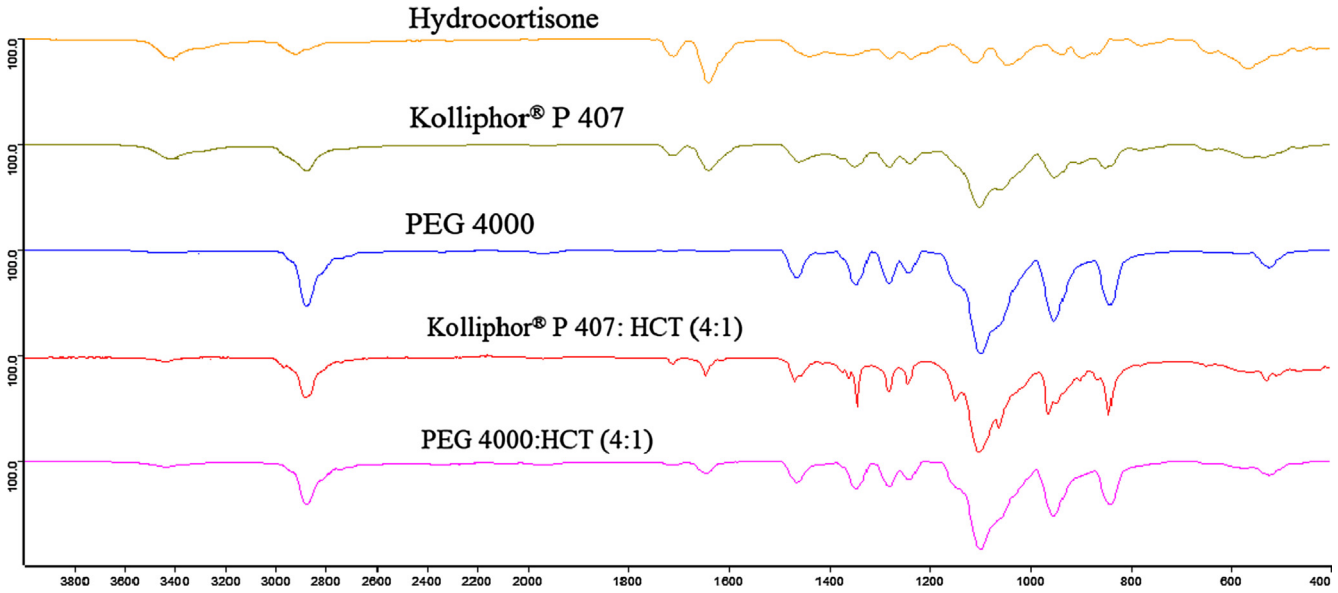

Fig. 4. FTIR analysis for hydrocortisone, Kolliphor® P 407, PEG 4000 and spray dried mixtures at (4:1) ratio.

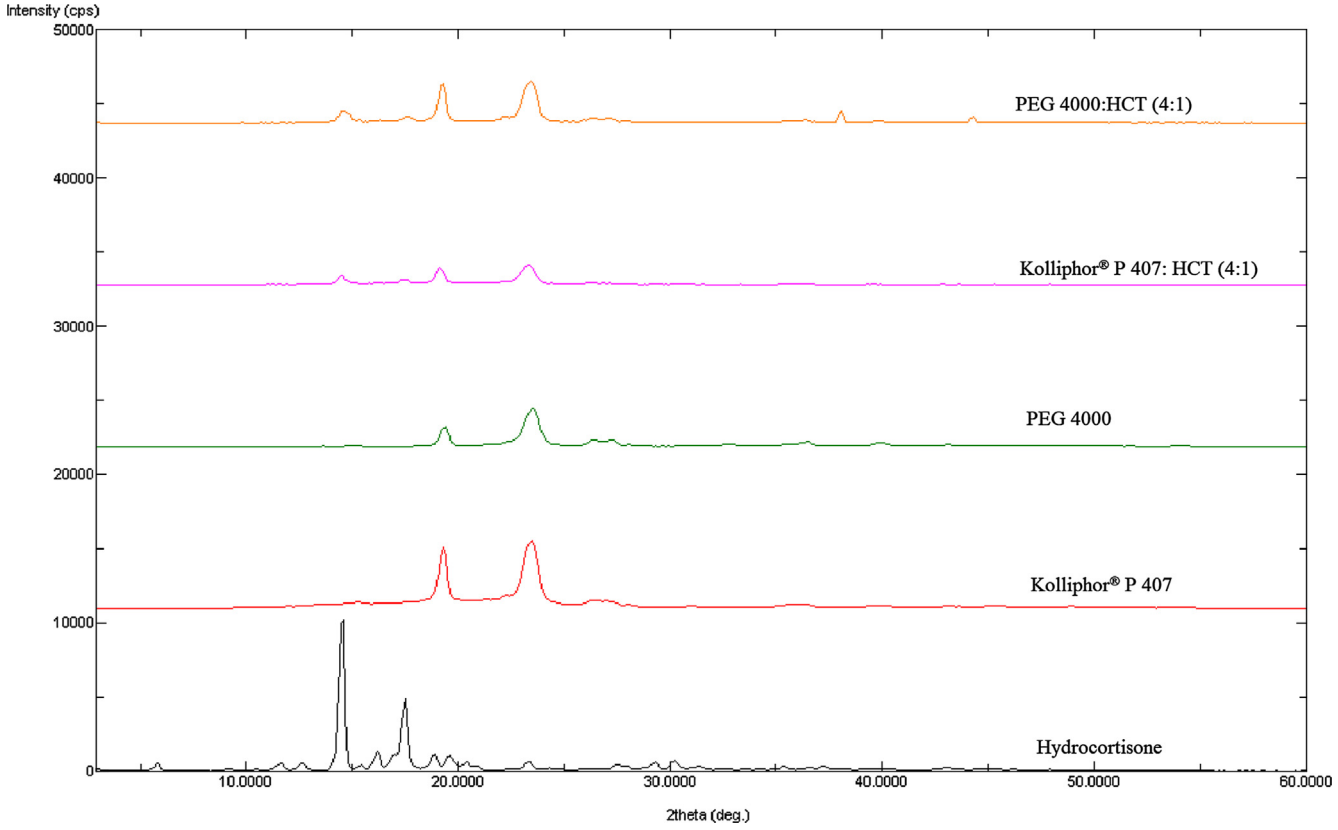

Fig. 5. PXRD patterns for HCT, Kolliphor® P 407, PEG 4000 and spray dried mixtures at 4:1 ratio.

X-ray pattern is expected (Biswal et al., 2008; Eloy and Marchetti, 2014; Bley et al., 2010; Ali et al., 2010).

The spray dried HCT pattern showed a significant decrease in the intensity in comparison to neat crystalline peaks. In the selected ratio formulation with either polymer, the peaks for the crystalline HCT showed nearly a halo pattern. HCT peaks intensity decreased by ~20 fold indicating nearly complete alteration of HCT crystalline form.

4.5. Scanning electron microscopy (SEM)

The surface analysis of the HCT and spray dried formulations is shown in Fig. 6. The crystalline form of HCT is clear due to the presence of sharp edges. Droplets produced by spray drying techniques are expected to render spherical particles after drying. However, elongated leave like structure was found for Kolliphor® P 407 (Mackellar et al., 1994). The tendency to elongate the particles also

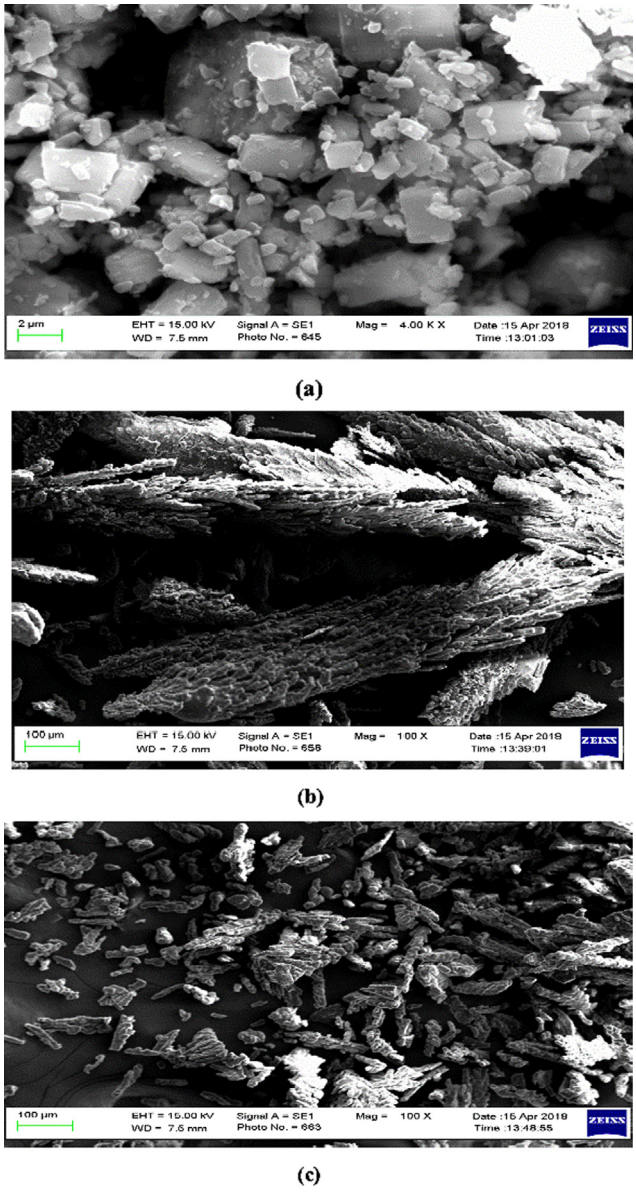

Fig. 6. SEM images showing the surface morphology for (a) HCT, (b) Kolliphor® P 407:HCT, and (c) PEG 4000:HCT spray dried solid dispersion.

exists for PEG 4000 dispersion with less detected length. The elongated shape was attributed to the gelling effect of Polyethylene glycol domain when solubilized with ethanol (Cespi et al., 2012).

4.6. In vitro drug dissolution

The dissolution profiles for HCT, physical mixtures and spray dried formulations are shown in Fig. 7. The solubility of HCT in water at 37 °C has been reported to be ~360 µg/mL (Loftsson, 1998; Loftsson et al., 2003). In fact, the experimental solubility in water was determined in our lab and found to be 314 ± 8.7 µg/mL. Such finding was in agreement with literature data (Ali et al., 2009). Tested materials showed near plateau in their dissolution profile at 30 min compared with neat HCT. Kolliphor® P 407 physical mixtures were around 80% release at the end of the experiment timeline and higher than 96% for the spray dried formulation. This finding ascertains the effect of not only the selected polymer but also the utilized technique and their ability to enhance the physicochemical properties (Altamimi and Neau, 2016b).

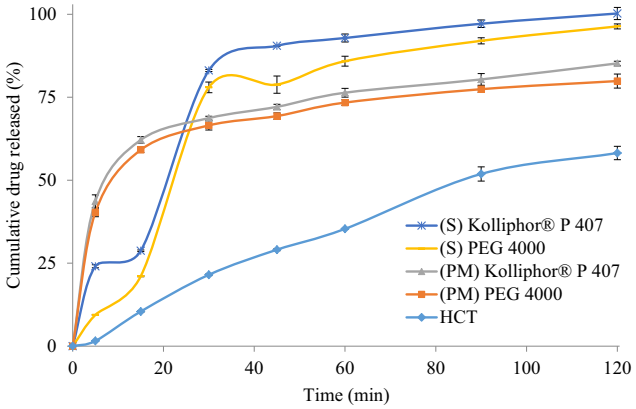

Fig. 7. Dissolution profiles for HCT, physical mixtures and spray dried dispersion in the ratio of 1:4.

4.7. Pharmacokinetics (PK) study in rats

Non-compartmental pharmacokinetic (PK) analysis was done in plasma from different administration groups (Fig. 8). To compare the PK of hydrocortisone formulations, Kolliphor® P 407 and PEG 4000, neat hydrocortisone was used as a reference and administered to a separate group of rats. The dose was set at 5 mg hydrocortisone/kg b.wt. of rats in all the administrations. This dose is equivalent to 50 mg hydrocortisone for an adult 60 kg human. Table 1 shows the comparison of different PK parameters of the formulations with neat hydrocortisone. Both the formulations appear to significantly increase ($p < 0.01$) plasma half-life ($t_{1/2}$) of hydrocortisone after oral administration. Kolliphor® P 407 did exhibit an increase in C_{max}, area under the curve of concentration * time versus time or the first-moment curve (AUMC), area under the plasma concentration-time curve (AUC) and mean residence time (MRT); however, it was found to be insignificant when compared with the hydrocortisone reference group.

Very few studies appeared in database search reporting hydrocortisone or cortisol pharmacokinetics in rats, when compared the results of the present investigation it appears to be in agreement with a similar study involving cortisone and cortisol pharmacokinetic profile (Lin et al., 2012). PEG 4000 formulation did not have any significant effect on C_{max} of the hydrocortisone; however, it significantly increased the overall drug exposure in terms of AUC and MRT. The data indicate a moderately delaying effect of PEG 4000 on the bioavailability of hydrocortisone. It is not correlated with the findings in the in-vitro drug dissolution experiment and indicates a significant involvement of biological factors associated

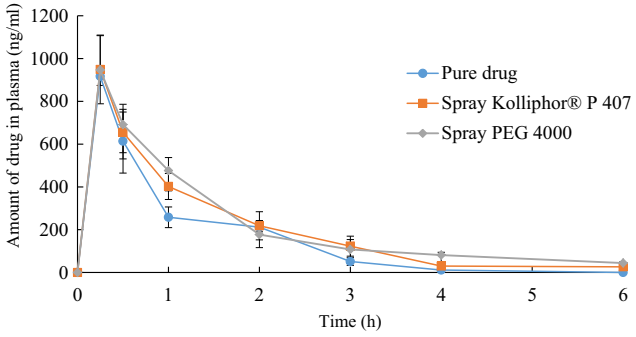

Fig. 8. HCT concentration-time profile resulting from an oral administration of neat HCT and spray dried mixtures at the equivalent dose of (5 mg/kg). (Mean ± standard error).

Table 1
Non-compartmental pharmacokinetics of coarse hydrocortisone, PEG 4000 and Kolliphor® P 407 formulations in rats after oral administration (equivalent to 5 mg hydrocortisone/kg b.wt.).

Drug/Formulation	$t_{1/2}$ (h)	C_{max} (ng/ml)	AUMC (ng h^2/ml)	AUC (ng h/ml)	MRT (h)
Hydrocortisone	0.471 ± 0.028	921.57 ± 72.18	1002.90 ± 161.27	929.55 ± 139.80	1.08 ± 0.08
Kolliphor® P 407	1.061 ± 0.12**	1004.9 ± 183.89^{NS}	1862.90 ± 671.37^{NS}	1218.41 ± 235.55^{NS}	1.50 ± 0.28^{NS}
PEG 4000	1.219 ± 0.19**	972.2 ± 139.45^{NS}	2653.40 ± 655.72*	1389.34 ± 54.13**	1.90 ± 0.39*

NS = not significant (Compared with hydrocortisone administration group).
* $p < 0.05$.
** $p < 0.01$.

with oral administration of drugs. These factors may include gastric and intestinal pH that significantly influences the absorption of orally administered drugs (Mitra and Kesisoglou, 2013; Taniguchi et al., 2014). In the past, modified release formulations of hydrocortisone have been proposed and studied targeting hydrocortisone hormone replacement therapy (Ceccato et al., 2018; Whitaker et al., 2014). The PEG 4000 appears to be controlling the release of hydrocortisone in-vivo in a way that restricts the quick absorption of all the hydrocortisone after oral administration. In the case of PEG 4000, further in-vivo studies are needed to see if this PK profile of PEG 4000 is more suitable for a particular disease condition.

5. Conclusion

Such work showed the improvement when drugs formulated using spray drying technique. Formulations with complete HCT amorphous form were successfully obtained. Successful solid dispersion formation is based on careful selection of the mixture ratio. Better dissolution rate was found for the selected drug:polymer ratio. Particularly, the spray dried mixture showed nearly complete drug release during the experimental time. Improvement in the bioavailability is expected when dissolution rate improved. Significant improvement of spray dried formulation over the neat HCT was exhibited in the *In vivo* study. Twofold higher at AUC and MRT were observed for spray dried HCT:PEG 4000 compared to other formulations.

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