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Polymeric nanoparticles based topical gel of poorly soluble drug: Formulation, *ex-vivo* and *in vivo* evaluation

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ABSTRACT

The study was conducted to evaluate the potential application of nanocapsules and nanospheres as topical drug delivery systems for indomethacin (as model drug). Both were prepared by nanoprecipitation using poly (ε-caprolactone) and hydroxypropyl β-cyclodextrin polymers and evaluated for morphology, particle size, zeta potential, EE% and *in vitro* drug release then incorporated in methylcellulose and Carbopol 940 gel bases and evaluated for *in vitro* release. The selected formulations and market product were evaluated for *ex vivo* human skin permeation and anti-inflammatory and analgesic activities by paw edema and hot plate methods respectively. Results showed that nanocapsules had slight higher EE% and larger particle sizes than nanospheres. *In vitro* release and zeta potential were nearly similar. Methylcellulose exhibited higher *in vitro* release than Carbopol 940 after 3 h (except NS2). *Ex vivo* skin permeation studies showed significant higher cumulative amount of IND (and flux) from NC1/MC and NS1/MC (1573.06 ± 14.23 μg/cm^2 and 1452.24 ± 23.18 μg/cm^2 respectively) than market product. They also showed enhancement ratio and permeability coefficient rate of ~1.5 and ~2 respectively. NC1/MC proved to be significantly higher pharmacodynamic effects than market product. All results showed that NC1/MC could provide a promising formula as a topical delivery of indomethacin.

1. Introduction

Transdermal drug delivery has been useful in developing new applications for existing drugs and for reducing first-pass drug degradation effects. Sometimes, it can also decrease the drug-associated side effects such as in case of nitroglycerin and fentanyl patches which exhibited fewer side effects than conventional oral dosage forms (Prausnitz et al., 2004). However, transdermal drug administration should overcome obstacles basically the barrier function introduced by the horny layer of skin. This may be the reason why only a limited number of drugs have been presented for dermal or transdermal use. So the emphasis in transdermal delivery has been increasingly focusing on overcoming resistance associated with skin barrier property. In the past years, different strategies have been proposed to facilitate drug permeation (Bonina et al., 2001). Commonly, there are basic ways in enhancing permeability as following: the principal is to disrupt skin barrier physically (Subedi et al., 2010), e. g. micro scratches, electroporation, ultrasound or removal of the *stratum corneum*. Surfactants or solvents are considered effective chemical enhancers acting by modifying bilayer construction of intracellular lipids (Williams and Barry, 2012). Another way, and also the most promising one, is to apply drug delivery systems that enable enhance drug solubility and achieve target-specific delivery and controlled release (Yingjie et al., 2014).

One of the most promising drug delivery system across the skin is the use of nanocarriers (Bouwstra and Honeywell-Nguyen, 2002). Nanocarriers or nanoparticles include many systems such as polymeric nanoparticles (such as nanocapsules and nanospheres), lipid nanoparticles (such as solid lipid nanoparticles, nanostructured lipid carrier and nanoemulsion), liposomes and others. The small size of the nanoparticulate carriers have been suggested as the basis why such vehicles can enhance the skin permeation of the pharmaceutical active ingredients they entrap,

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while at the same time protecting the pharmaceutical active ingredients from degradation (Guterres et al., 2007; Jenning et al., 2000). In addition to their small size, other physical properties of the nanoparticles, such as their charge and lipophilicity, have been proposed as being important in determining the skin permeation profile of the compounds they contain (Hoet et al., 2004).

Polymeric nanoparticles can be classified as nanospheres (matrix system) or nanocapsules (reservoir system). Nanocapsules (NC) are nanoparticles containing either an oily or aqueous core surrounded by a polymeric shell, typically in combination with a mixture of lipophilic and hydrophilic surfactants whereas nanospheres (NS) are polymer-only matrix systems. One of the main advantages of NC over NS is a higher drug loading (Guterres et al., 2007; Rübe et al., 2005). The polymers used to prepare NC and NS are typically biodegradable and biocompatible (Kumari et al., 2010). In addition, NC contain a combination of hydrophilic and lipophilic surfactants (generally in the concentration range from 0.2 to 2 wt%), necessary to increase their stability (Legrand et al., 1991). Non-steroidal anti-inflammatory drug (NSAID), indomethacin (IND), was chosen as a model substance for our study. It is widely used as analgesic and for the treatment of local and systemic inflammatory pathologies and rheumatoid arthritis as well. IND is classified as BCS class II (low solubility/high permeability).

Therefore, a comparative study between NC and NS was conducted for testing the effect of polymeric nanocarrier type on skin permeation. NC and NS were prepared by nanoprecipitation method using two polymers; poly (ε-caprolactone) (PCL) and hydroxypropyl β-cyclodextrin (HP β-CD). The prepared formulation was then characterized for morphology, pH, particle size, zeta potential, EE%, and *in vitro* drug release. Formulations were then incorporate into different gel bases and tested for *in vitro* drug release. *Ex-vivo* permeation and *in vivo* pharmacodynamic studies were carried out for selected formulations and then compared with available commercial market product (Indotopic® gel).

2. Materials and methods

2.1. Materials

PCL, HP β-CD, span 60, methylcellulose powder (MC) and carrageenan were purchased from Sigma Aldrich (Germany). Miglyol 812 (capriylic/capric triglycerides) was gifted from Caelo, Hilden (Germany). IND was kindly supplied by Memphis Company for pharmaceuticals (Cairo, Egypt). Tween 80 was purchased from ADWIC Pharm (Cairo, Egypt). Carbopol 940 was gifted from Goodrich Chemical Company (England). Triethanolamine (TEA) was purchased from Sigma Chemical Company (USA). Acetone were purchased from Morgan Pharm. Company (Cairo, Egypt). All other chemicals and solvents were of analytical grade.

2.2. Methods

2.2.1. Preparation of NC and NS

Drug-free and IND-loaded NS and NC were prepared by the nanoprecipitation-solvent evaporation technique reported by Fessi and coworkers (Fessi et al., 1989). Briefly, the organic phase was composed of polymer (PCL or HP β-CD), IND, Span 60 (lipophilic surfactant) and Miglyol 812 (in case of NC only) all dissolved in acetone. Organic phase was injected drop wise with stirring (Magnetic stirrer, thermolyne Corporation, USA) into the aqueous phase containing Tween 80. After 10 min, acetone was removed by evaporation in water bath (40 °C) and the final formulation was adjusted to 30 ml with 1% IND content. The formulations are outlined in Table 1.

2.2.2. Morphology and pH

The morphology of NC and NS was studied by transmission electron microscopy (TEM) (JEOL JEM-1010S Tokyo, Japan). Formulations were diluted with distilled water and dropped on a carbon-coated copper grid, forming a thin liquid film. The films on the grid were allowed to dry at room temperature, and then observed by TEM.

For pH determination, definite quantity (10 ml) was taken the electrode of the pH meter (Jenway temperature, pH and millivolt meter, model 5310, England) was immersed inside.

2.2.3. Particle size and zeta potential determination

Determination of mean particle size and zeta potential of the IND loaded NC and NS formulations were performed using dynamic light scattering (Zetasizer, Malvern Instruments, UK). The measurements were performed after dilution by 200 folds with bi-distilled water at room temperature (25 °C).

2.2.4. Drug encapsulation efficiency percentage (EE%)

Determination of total IND concentration was basically depending on dissolution of polymers. Aliquot of 1 ml of NC and NS separately diluted with 25 ml acetonitrile. To determine non-encapsulated IND concentration, 1 ml of each dispersion was centrifuged (Biofuge primo centrifuge, England) at 17,000 rpm for 15 min followed by filtration. Next the filtrate was analyzed for IND content by UV visible spectrophotometer (Shimadzu, Japan) at 320 nm. The entrapment efficiency of IND was then calculated according to the following Eq. (1):

$$EE\% = (Td - Fd/Td) \times 100, \quad (1)$$

where %EE = the encapsulation efficiency in percentage, Td is the total drug concentration during preparation and Fd is the amount of free (non-encapsulated) drug in the filtrate after centrifugation.

2.2.5. Preparation of NC and NS gel formulations

The gel formulations of NC and NS were prepared using Carbopol 940 (2% w/w) and MC (3% w/w) as gelling bases. Carbopol 940 has hydrophilic nature with cross-linked structure and insoluble in water whereas MC is a semi synthetic polymer and well-known for the thermo-reversibility that form hydrogels in water upon heating and subsequently dissolves upon cooling (Bain et al., 2013). Both polymers are used as topical carrier for controlled release drug delivery system. NC and NS suspensions were added to Carbopol 940 and the suspension gently stirred (magnetic stirrer, thermolyne Corporation, USA) till the gel swelled. Then triethanolamine was added to neutralize acidic nature of Carbopol 940 molecule which led to gelatinization (Zhao et al., 2014). In case of MC, the weighed amount was added to distilled boiled water

Table 1
Compositions of different formulations (n = 3, ±SD).

Code	Drug	Oil	Lipophilic SAA	Acetone	Polymer	Water	Hydrophilic SAA
NC1	300 mg	1.5 ml Miglyol oil	0.225 g Span 80	75 ml	0.375 g PCL	150 ml	0.45 g Tween 80
NC2	300 mg	1.5 ml Miglyol oil	0.225 g Span 80	75 ml	0.375 g HPβ-CD	150 ml	0.45 m Tween 80
NS1	300 mg	___	0.225 g Span 80	75 ml	0.375 g PCL	150 ml	0.225 g Tween 80
NS2	300 mg	___	0.225 g Span 80	75 ml	0.375 g HPβ-CD	150 ml	0.225 g Tween 80

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