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Preparation and evaluation of plga nanocarriers gel for topical delivery

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ABSTRACT

In last decades, the study of inorganic and colloidal particles such as nanocapsules, nanospheres, nanostructured lipid carrier, etc. has been focused as dermal/transdermal drug delivery carriers. If compared with the traditional oral administration route, transdermal delivery shows additional advantages: it minimizes the first-pass metabolism, it avoids drug degradation under the extreme acidity of the stomach, it prevents erratic delivery due to food interactions, and it provides more controlled delivery. In the present study topical gel of carbopol containing biodegradable nanocarriers was prepared and evaluate on the basis of drug content, effect of neutralizing agents, pH, viscosity and in-vivo permeation study. The result shows that electrostatic repulsion plays a critical role in forming a gel, its viscosity and gel strength depending on pH. The amount and type of neutralizing agent used affects the viscosity of the formulation significantly.

Key words: Transdermal, controlled delivery, nanocarriers, gel.

INTRODUCTION

During the last years, developments in transdermal drug delivery have been incremented focusing mainly on overcoming problems associated with the skin barrier properties. If compared with the traditional oral administration route, transdermal delivery shows additional advantages: it minimizes the first-pass metabolism, it avoids drug degradation under the extreme acidity of the stomach, it prevents erratic delivery due to food interactions, and it provides more controlled delivery [1,2].

In last decades, the study of inorganic and colloidal particles such as nanocapsules, nanospheres, nanostructured lipid carrier, etc. has been focused as dermal/transdermal drug delivery carriers. In general, solid colloidal nano-carriers systems have been extensively studied as drug delivery systems (DDS), mostly for oral and parenteral applications, and have shown to be one of the most promising strategies to achieve site-specific drug delivery [3]. To be considered as potential human drug delivery systems requires that the material has to be biocompatible, preferentially biodegradable, or at least should be able to be excreted [4]. This may be the reason why only a limited number of biodegradable polymeric nanoparticles [5,6,7], solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)[8,9,10] have been studied with respect to their potential for drug systemic and topical administration. Nanoparticles can be used to deliver a wide variety of substances as hydrophilic or hydrophobic drugs, proteins, vaccines, biological macromolecules, etc., and they can be formulated for targeted delivery, e.g. to the brain[11,12], lungs[13,14,15], lymphatic system[16], or made for long term systemic circulation.

The mechanism of interaction of the nanoparticulated carrier systems and the skin and also the transport pathways within the membrane of the drug and/or the carrier, are required to establish the possibility of using such systems to optimize the drug transport process[17]. It has been described that SLN, due to its particle size, are able to ensure a high adhesion to the SC enhancing the amount of drug which penetrates into the viable skin. Furthermore, for nanocarriers between 200 and 400 nm an occlusive effect has been described on artificial membranes[18], and reducing the trans-epidermal water loss and increasing the penetration of a occlusion sensitive drug into the skin layers[19].

Epilepsy is operationally defined as a group of neurologic disorders characterized by recurrent episodes of convulsive seizures, sensory disturbances, abnormal behavior, loss of consciousness or all of these[20]. The word 'epilepsy' stems from the Greek *epilambanein*, meaning 'to be seized', or 'to be overwhelmed by surprise'[21].

Oxcarbazepine (OXZ) or (10, 11-dihydro-10-oxo-carbzepine) is a newer aromatic antiepileptic agent, approved in the United States on January 14, 2000. (As defined by recent American Academy of Neurology- American Epilepsy Society guidelines, a newer antiepileptic drug is one approved by the U.S. Food and Drug Administration since 1990)[22] which was developed as a second-generation and follow-up compound to Carbamazepine (CBZ). OXZ has a similar therapeutic profile to CBZ but produces much less side effects on patients. Clinically it has been used to treat several types of epilepsy[23,24,25,26]. The chemical structures of OXZ, and metabolites are shown in Fig. 1.

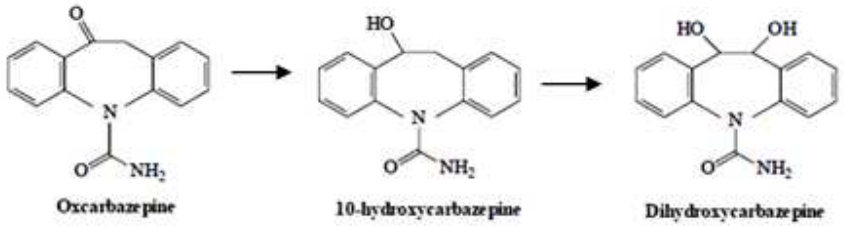

Fig.1: The chemical structure of OXZ and metabolite

After oral administration OXZ is rapidly and almost completely absorbed from the gastrointestinal tract with peak concentrations obtained after about 1 h. The parent compound is eliminated mainly by hepatic metabolism with plasma half-life of 3-5 h[27]. After shorter half-life of the OXZ suspension formulation, due to poor water solubility, for oral delivery was approved on May 25, 2001. Tablet and suspension formulations were approved on August 7, 2003, for use as monotherapy in the treatment of partial seizures in children aged 4-16[28].

The present study was focused on the preparation and evaluation of PLGA nanocarriers gel associated with OXZ. The long-term goal of our study is to develop new Oxcarbazepine formulations for the treatment of diseases.

MATERIALS AND METHODS

Oxcarbazepine was generous gift from Sun Pharmaceutical, Ahmedabad, India. PLGA, Carbopol, Acetonitrile (analytical grade) Acetic acid, Acetone, Dichloromethane, PVA, Ethyl acetate were produced from New Era Chemicals, Meerut Cant, Meerut, India. All reagents used were analytical grade and ultra pure water was used throughout.

Formulation of Nanoparticles

PLGA nanoparticles loaded with Oxcarbazepine (OXZ NP) were prepared using a solvent extraction method. Oxcarbazepine were dissolved in a solution of PLGA in ethyl acetate. This organic phase was added drop wise into an aqueous phase, containing 1% of PVA as a quasi-emulsifier, under stirring with a magnetic stirring bar. The resulting O/W emulsion was homogenized with a high-speed homogenizer at 13500 rpm for 10 minutes. To complete the precipitation, water was added up to 200 ml under stirring with a magnetic bar. Organic solvent was then removed using a rotating evaporator. The resulting nanoparticles suspension was freeze-dried and stored until use.

Preparation of gel of OXZ NP using carbopol

Carbopol polymers are very high molecular weight poly acrylic acids. They are having pKa 6.5 and their aqueous dispersions are mildly acidic in nature. OXZ NP was used for development of transdermal gel formulation. OXZ NP

complex equivalent to 5mg /gm of Oxcarbazepine was dissolved in the optimized vehicle (water and NMP 5%v/v). Then required quantity (0.5 and 1% w/w) of carbopol was added to above solution and the dispersion was mixed with mechanical stirrer for 6 h, so that carbopol swelled completely. The resultant viscous dispersion was neutralized by adding neutralizing agents. Triethanolamine (TEA) and sodium hydroxide (NaOH) in 0.5 and 1.0 % w/w concentrations were tried as neutralizing agents. Addition of neutralizing agent causes spontaneous gel formation. The dispersion was further stirred continuously for 15 min to obtained smooth and clear gel formulation.

Evaluation of carbopol gel of OXZ NP

Drug content

Gel formulations containing 1 mg Oxcarbazepine was taken in 10 ml volumetric flask, dissolved in methanol and volume made up to 10 ml with methanol. Then the solutions were filtered through the membrane filter (0.22 µm). The samples were analyzed spectrophotometrically after suitable dilutions at 230 nm. The drug content of all the formulations was found to in the range of 98-100%

Effect of neutralizing agent

Carbopol polymers must be neutralized in order to convert in to the gel formulation. Commonly used neutralizing agents are the metal hydroxides like sodium hydroxide or amines like triethanolamine.

In the present study for neutralization triethanolamine and sodium hydroxide were tried in 0.5% and 1% w/w of gel formulation.

pH of the gel formulations

The formulations were diluted in the ratio of 1:25 using distilled water. The pH was determined using silver/ silver chloride pH glass electrode and 500 digital pH meter, which was previously, calibrated using standard buffer solutions. All the gels were tested in triplicate to obtained mean pH value. The diluted gels were in contact with the electrode to allow the pH value to stabilize.

Viscosity

The viscosities of gels were measured using Brookfield Viscometer CAP 2000. The measurements were performed at 25˚C with spindle no. 4. at different rpm. The studies were conducted at 20 rpm at which maximum torque (87-97%) was observed. Each data point is a mean of triplicate analysis (Table 1).

Table 1. Formulation and evaluation of OXZNP gel formulations with polymer (Carbopol)

Formulation code	Carbopol (w/w)	Neutralizing agents (w/w)	pH	Viscosity	Drug content
OXZNPCG-1	0.5	Sodium Hydroxide (0.5%)	7.8	11632 cp	0.987 mg
OXZNPCG-2	0.5	Sodium Hydroxide (1.0%)	9.2	11985 cp	0.992 mg
OXZNPCG-3	1.0	Sodium Hydroxide (0.5%)	7.4	21455 cp	1.01 mg
OXZNPCG-4	1.0	Sodium Hydroxide (1.0%)	8.9	23419 cp	0.991 mg
OXZNPCG-5	0.5	Triethanolamine (0.5%)	5.4	10960 cp	0.988 mg
OXZNPCG-6	0.5	Triethanolamine (1.0%)	6.5	11214 cp	0.982 mg
OXZNPCG-7	1.0	Triethanolamine (0.5%)	5.2	20765 cp	1.02 mg
OXZNPCG-8	1.0	Triethanolamine (1.0%)	5.7	22890 cp	1.01 mg

The gel formulations of OXZ NP with 1% w/w of Carbopol, neutralized with NaOH and TEA were found to have good consistency and thus the formulations OXZNPCG-3, OXZNPCG-4, OXZNPCG-7, and OXZNPCG-8 were further subjected to *in-vitro* permeation studies.

***In-vitro* permeation studies**

The *in-vitro* permeation studies of the Oxcarbazepine from the gel formulations were carried out using guinea pig skin. The carbopol gel formulations OXZNPCG-3, OXZNPCG-4, OXZNPCG-7, and OXZNPCG-8 containing 5 mg /gm of Oxcarbazepine were subjected to permeation studies.

The steady state flux values obtained with different OXZNP gel formulations were compared by means of the one way ANOVA followed by Turkey-Kramer test for multiple comparison of different reservoir gel formulations.

RESULTS AND DISCUSSION

Literature reveals that NPs are having potential to act as penetration enhancer for transdermal administration of the drug. The solid complexes of OXZ NP were prepared by using solvent extraction method. The carring efficiency of the method was found to be 98.2 to 100.2 %.

Neutralization expands the long chains of carbopol by charge repulsion to produce an entangled gel structure. This electrostatic repulsion plays a critical role in forming a gel, its viscosity and gel strength depending on pH. Gels with good consistency can be formed on neutralization between pH 5 and 10 with metal hydroxides or amines

Addition of sodium hydroxide cause sharp increase in pH of gel formulations. Carbopol 0.5 % w/w and 1% w/w with 1% w/w NaOH as neutralizing agent produces gel with pH 9.2 and 8.9 respectively. The pH of gel after addition of NaOH increased up to 9.2, which may cause the irritation to the skin after application.

TEA produces the gel with the pH up to 6.5. Trails with TEA as the neutralizing agent in the concentrations 0.5 and 1% w/w, revealed that it forms the gel at all the concentrations. The pH values of gels formed with TEA as neutralizing agent were in the range of 5.2 to 6.5. The consistency and pH of the gel formulations was increased with TEA concentration.

From the results (Table 1.), it was observed that amount and type of neutralizing agent used affects the viscosity of the formulation significantly. At 0.5% w/w concentration of carbopol the viscosity was found to be lower than the required, with both the neutralizing agent. The viscosities of the formulations neutralized with NaOH were comparatively more than the formulations with TEA. This may be because of higher pH with NaOH than TEA as a neutralizing agent. This higher pH is not suitable for skin formulations, since it may cause irritation to the skin.

Table 2: Permeation study parameters of the developed OXZNP gel formulations

Formulations code	Flux ($\mu g/cm^2/h$)	Kp $cm/h \times 10^3$	D.R. µg/mg
OXZNPCG-3	16.5 ± 2.1	3.3	1.9± 0.2
OXZNPCG-4	14.2 ± 1.9	2.84	1.4 ± 0.4
OXZNPCG-7	23.1 ± 1.6	4.62	2.3 ± 0.3
OXZNPCG-8	17.2 ± 1.4	3.44	1.8 ± 0.2

The *in-vitro* permeation studies showed (Table 2) the highest flux of Oxcarbazepine from the OXZNPCG-7 formulation amongst all the carbopol formulations, which may be attributed to its pH and viscosity. As the pH of formulations increases the steady state flux was found to be decreased. Formulation OXZNPCG-7 with lowest pH of 5.2 shows maximum flux as compare to other formulations.

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