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Original Article

Gelatin Microspheres for the Controlled Release of All-trans-Retinoic Acid Topical Formulation and Drug Delivery Evaluation

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Abstract

A topical o/w cream containing tretinoin microspheres was prepared. Gelatin microspheres of tretinoin were prepared using coacervation method. These microspheres contained about 50% w/w tretinoin. The particle size range of microspheres was between 90-150 μm. In vitro drug release from microspheres and a cream formulation was studied. It was shown that drug release from microspheres followed Higuchi kinetics of release. However, drug release from the cream formulation followed zero order release profile.

Keywords: All-trans-retinoic acid; Tretinoin; Microencapsulation; Gelatin Microspheres; Coacervation; Zero order release; Topical cream.

Introduction

Tretinoin (All-trans-retinoic Acid, Vitamin A acid) is a widely used drug in the topical treatment of acne, photo-aged skin, psoriasis and other skin disorders. The main effect of tretinoin in the treatment of acne is to reduce the size and the number of comedones. Tretinoin is commonly used in a concentration of 0.05% w/w, incorporated in a lotion or/and an o/w cream (1). A long period of topical administration of the drug for 7-12 weeks is needed to have therapeutic effects (2). However, there are some side effects often appearing in the form of scaling, erythema, burning and stinging (1, 2). Tretinoin microsphere may minimize irritation effects. This delivery system works by entrapping the drug in Microspheres, which brings the medication more directly to the follicle and serves as a reservoir for the medication. It has been shown that 0.1% tretinoin microsphere gel is less irritating than 0.1% tretinoin cream (3). Different microencapsulation techniques have been used to control drug release form topical delivery systems (4-9). Meybeck has shown that maximum comedolytic activity of drug is reached at a concentration 5-10 times lower than when tretinoin is used as liposomes, compared to the conventional forms (10). This shows that, using particulate delivery systems, the amount of drug needed will decrease, hence reduce the side effects of the drug (11). More over the same study reveals that the percutaneus penetration to the blood vessels, which due to systemic side effect is not desired, decreaseds remarkably.

Tretinoin is also very unstable to radiation. In this regard the use of liposomes and other microencapsulation techniques in topical formulation is considered very useful (12). Therefore incorporation of tretinoin microspheres can protect drug against photo-degradation (13).

In this study tretinoin was micro-encapsulated using gelatin, which is a natural and biocompatible polymer. Particle size distribution and drug release from tretinoin microspheres were evaluated and drug release from topical microspheres cream formulations

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was compared with a non microencapsulated topical cream.

Experimental

Materials

Tretinoin (Laboratory MAG, Germany), food grade gelatin, glutaraldehyde 25%, toluene, isopropyl alcohol, sodium dihydrogen phosphate, potassium dihydrogen phosphate, sodium chloride, stearyl alcohol, cetyl alcohol, isopropyl myristate, tochopherol, propylene glycol, sodium lauryl sulfate, liquid paraffin and glycerin were purchased from Merck, Germany. Sesame oil (United Food Company, UAE), olive oil (kristal, Turkey), soft paraffin (Emad Darman Pars, Iran).

Methods

Microenapsulation method

A 5 ml solution (5% w/v) of gelatin in distilled water was prepared. 250 mg tretinoin was added to the gelatin solution. The suspension of tretinoin in gelatin solution was homogenized using a magnetic stirrer (Bibby HB502, England). The suspension was then added gradually to 50 ml sesame oil while stirred at 1000 rpm using an overhead stirrer (Stuart Scientific, UK). Then 30 ml of glutaraldehyde saturated toluene was added to the suspension/emulsion system. Stirring was continued for 4 h to allow the crosslinking of gelatin microspheres to be completed (14, 15). Microspheres were then filtered and washed with 30 ml of cold isopropyl alcohol at 5°C overnight. Microspheres were then dried at 37°C and stored in colored glass containers.

Micospheres characterisation

Particle size analysis of microspheres was carried out using standard mesh sieves (Endecotts Ltd, England). Surface morphology of microspheres was studied using light microscopy and scanning electron microscopy.

Drug content and release measurements

A known amount of microspheres was milled and immersed in HCl/isopropyl alcohol (1/1000 v/w) and stirred for 4 h and then left at room temperature overnight. Tretinoin is soluble in this medium. The remaining gelatin particles were separated. Drug Content of this solution was determined using UV spectrophotometer (Milton Roy Spectonic) at 352 nm. Drug release from microspheres was determined in phosphate buffer/isopropyl alcohol (80:20 v/v) (pH 7.4). 5 g of microspheres were placed in 900 ml release medium, stirring at 60 rpm. 5 ml samples were removed at different time intervals and analyzed spectrophotometrically at 352 nm.

Preparation of o/w cream formulation

Oil phase of the topical cream consisted of stearyl alcohol (12.5% w/v), soft paraffin (10.5% v/v) and propyl paraben (0.02% w/v). Water phase consisted of glycerin (10% v/v), propylene glycol (10% v/v), methyl paraben (0.18% w/w), sodium lauryl sulphate (1% w/w) and distilled water making the solution up to 100 ml. Both phases were heated at 75ºC and mixed. Then about 10 mg of gelatin microspheres were added to 15 g o/w cream resulting in a 0.025% tretinoin cream, homogenized using an overhead homogeniser (Silverson, England).

In vitro drug release from cream formulation

Drug release from microsphere cream formulation and a commercial non-microsphere tretinoin cream was measured using Frantz cell containing 50 ml of release medium [(HCl/isopropyl alcohol (1/1000 v/v)]. About 1 g of topical cream formulation was spread on the dialysis membrane present within the Frantz cell. The release medium was maintained at 37±0.2ºC. 4 ml Samples of release medium were removed at different time intervals and replaced with the same amount of fresh medium each time.

Results and Discussion

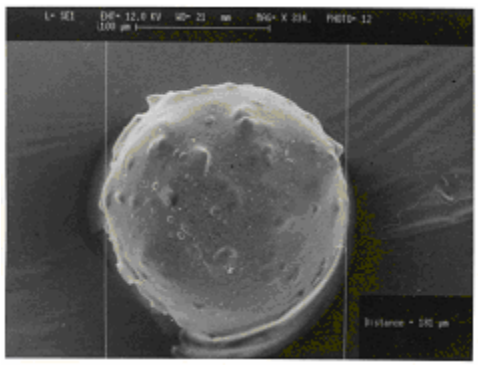

Figure 1. Scanning electron micrograph of gelatin microspheres containing tention.

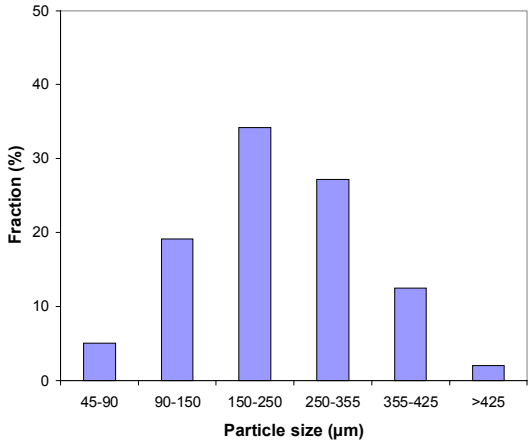

Figure 2. Particle size distribution analysis of tretinoin Microspheres.

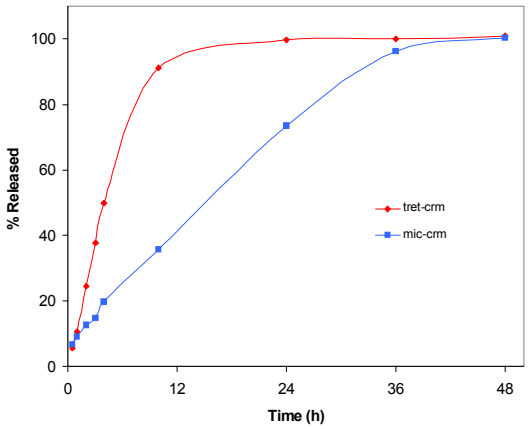

Figure 4. *In vitro* tretinoin release from microsphere cream prepared in this study compared to a non particulate commercial cream.

Gelatin microspheres of tretinoin prepared in this study were nearly spherical (Figure.1). The mean particle size of gelatin microspheres was 90-150 mm (Figure.2), which is suitable enough for topical cream formulations (3).

Drug Content of microspheres was approximately 50% (w/w). Figure 3 shows the profile of drug release from gelatin microspheres. As can be seen in this figure, nearly 70% of the drug content of microspheres was released in 12 h. The kinetics of drug release from gelatin microspheres was Fickian and followed first order model of kinetics (r^2=0.979). Figure 4 shows the profile of drug release from the o/w cream prepared using microspheres. In this figure drug release from the microsphere cream (containing 0.025% w/w tretinoin) and the non-commercial cream (containing 0.05% tretinoin) is compared. It can be seen that drug release from the microsphere cream and the commercial cream formulations are not the same. Drug release from the microsphere cream follows zero order kinetics

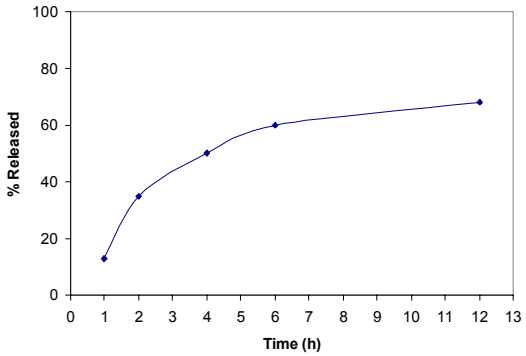

Figure 3. In vitro tretinoin release from gelatin microspheres in pH=7.4 phosphate buffer/Isopropyl alcohol (80/20 v/v).

while drug release from commercial cream follows Higuchi model of release kinetics. At the first 30 min, drug release from both formulations is the same (15%). However, after 10 h, only less than 40% of drug content of microsphere cream is released compared to the 90% drug release obtained from the commercial cream. After 24 h more than 70% of tretinoin content of microsphere cream is released. Zero order release from a topical semi solid dosage form is very much favored, as drug is released slowly and linearly. In this formulation tretinoin reaches the skin at molecular level rather than the crystalline form of tretinoin, which may cause irritation and other skin disorders. Side effects of tretinoin are reduced dramatically when it is microencapsulated (1, 3, 10, 11). Microencapsulation also protects tretinoin against photo-degradation (13). However, in-vivo release studies are needed to evaluate the efficiency and usefulness of topical formulations based on microencapsulation of tretinoin. This study confirms that zero order in vitro drug release from topical cream formulations containing microencapsulated tretinoin can be achieved.

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