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Original Article

Formulation and In Vitro Evaluation of Silver Sulfadiazine Spray

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Abstract

In order to improve local therapeutic techniques for the massively burnt patients and to minimize the pain associated with dressing change, the concept of topical film was utilized to formulate a topical antimicrobial spray. The commonly used topical antimicrobial silver sulfadiazine spray was formulated as a new drug delivery system. The release of therapeutic agents in vitro from medicated spray formulation was compared with that of the corresponding cream bases, utilizing a modified agar diffusion method. When using Pseudomonas aeroginosa as the test bacteria, silver sulfadiazine was found to produce a significantly larger zones of inhibition when used as the spray formulation instead of the cream form. Silver sulfadiazine spray, left in place for up to one day, appears to be as effective as the twice-daily cleansing and application of silver sulfadiazine cream. Also the periodic stability study of silver sulfadiazine in spray form, which was carried out using TLC, HPLC and particle size analyser methods, showed no significant degradation and crystal growth of active ingredient in the spray formulation after one year.

Keywords: Silver sulfadiazine; Formulation; Spray; Topical.

Introduction

Burning is one of the common and important injuries. If pretreatment is not initiated in time, serious damage may result because of much susceptibility of the burned surface. Infection due to Pseudomonas aeroginosa is one of the most common causes of mortality in burn cases. Although oral and parenteral antibiotic drugs are prescribed to treat the microbial infection, topical antibiotic therapy is essential for treatment of burn in most cases. Silver sulfadiazine is a topical antibiotic which is widely used in the form of cream (1, 2). Due to practical shortcomings of the medicated cream, such as: (I)- the necessity of wearing sterile gloves for its application. (II)- the necessity of applying at least a 1.6mm layer of cream (3). (III)- maceration after long usage and (IV)- soaking to clothing, bandage and so on (4, 5) in this study silver sulfadiazine spray has been designed and formulated for compensating these defects.

Because local drug action is dependent upon the rate of drug release from its vehicle (6), in vitro studies were performed to compare the release of medicaments from spray film with that of the cream.

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Experimental

Materials

Polyvinyl pyrrolidone K29 was purchased from BASF (Mannheim, Germany). Propylene glycol (Art No: 7478) and acetone (Art No: 100013) were supplied by Merck (Darmstadt, Germany). Isopropyl myristate was obtained from Henkel (Dusseldorf, Germany). Silver sulfadiazine was supplied by Boots (Milan,

Italy). Silicone emulsion (37%) was obtained from Penn White (Bukingham, UK). HPLC-grade acetonitrile, methanol and other chemicals were obtained from Merck (Darmstadt, Germany).

Methods

Formulation of silver sulfadiazine spray

Polyvinyl pyrrolidone was dissolved in 5ml of double distilled water. To this solution were added 3ml of propylene glycol and 1ml of isopropyl myristate. Then silver sulfadiazine (3g) was added to this solution while the solution being stirred. Then the silicone emulsion in acetone (2g/20ml) was added to this suspension. The entire suspension was whipped for 10 min using an electric mixer and poured into a 75ml canister. Finally, 40ml of butane/propane (70/30) was injected into the sealed spray canister.

Assay and stability of silver sulfadiazine spray

The silver sulfadiazine present in the spray formulation was tested according to the Pharmacopeia (7) and other references to determine the drug concentration and to evaluate the drug stability in the spray dosage form periodically.

Thin layer chromatographic method

Test solution: Equivalent of 50mg silver sulfadiazine was weighed and dissolved in 3ml of ammonium hydroxide (25%) solution and the solution was diluted to 10ml with methanol (0.05mg/ml).

Standard solution: 50mg of RS silver sulfadiazine was accurately weighed and dissolved in 3ml of an ammonium hydroxide (25%) solution. Then it was diluted to 10ml with methanol (0.05mg/ml).

The separation was performed on silica gel F254 plates with a diameter of 0.25mm using the following mobile phase: chloroform-methanol-25% ammonia (70:40:10); Rf 0.3. Spots appeared under UV detection at 254nm and iodine vapor (8).

High performance liquid chromatographic method

A stability indicating HPLC method, using a C_{18} column (novapac 3.9mm x 30 cm, 4 um, waters) was used. The mobile phase consisted of water, acetonitrile and phosphoric acid (900:99:1). The flow rate was about 2ml per minute. The detection wavelength was set at 254 nm. O-cresol was used as the internal standard and the sample and standard were prepared and chromatographed as directed under silver sulfadiazine monograph (8).

Analysis of particle size

Crystal growth is one of the major problems in suspension formulations. With this regard, measurement of particle-size for detection of crystal growth in silver sulfadiazine spray was done by Fritsch particle sizer (Analysette 22). The size of particles was measured by lazer based on the sedimentation rate of sprayed particles in ethyl alcohol (as the liquid vehicle).

In vitro antimicrobial effectiveness

Because pseudomonas aeroginosa has been frequently implicated as the invasive bacteria in burn wound sepsis, a microbiological agar diffusion method was utilized to compare the effectiveness of the spray with the cream. After autoclaving sufficient quantities of Bacto Antibiotic Medium 29 at 121 ºC and 15psi for 25 min, approximately 20 ml was poured into 100x20-mm sterile, disposable petri dishes. Upon congealing, 0.1 ml of Bacto Antibiotic Medium 5x10 /ml containing an overnight inoculum of Ps. aerogonosa (ATCC 1074) was

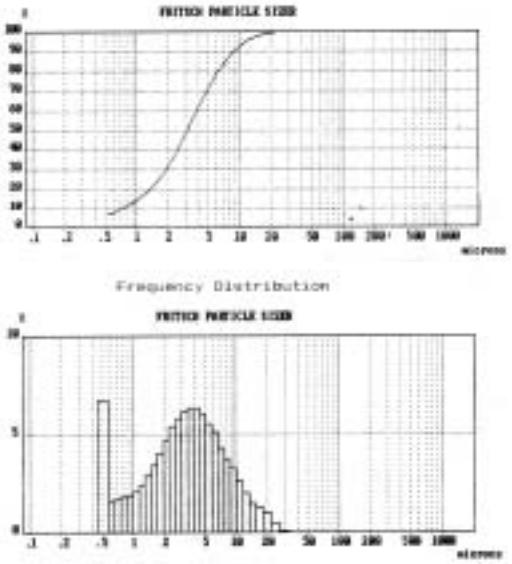

Figure 1. Particle size analyzing data of silver sulfadiazine spray one year after formulation.

Table 1. Invitro antimicrobial effectiveness of silver sulfadiazine spray formulation in comparison with medicated cream

Formulation	Mean Diameter Zone of Inhibition	SD	Student t Test
Silver sulfadiazine spray	24	12.8	1.6
Silver sulfadiazine cream	20	9.3	1.2

a- Results listed are mean values for 15 determinations

spread onto the agar medium with the aid of a sterile, L-shaped glass rod. Each plate was punched with a sterile stainless still punch with the following dimensions (each dimension having a tolerance of + 0.1mm); outside diameter 8mm, inside diameter 6mm and length 10mm. There were six holes with six diameter in each sterile plate. Each of 3 holes in a plate was filled with 0.004ml of the spray solution and the other three holes were filled with 30mg of the cream formulation and then incubated overnight at 37 ºC. Holes filled with the non-medicated spray solution and cream served as the control. Zones of inhibition were measured after 24h with an antibiotic zone reader.

Results and Discussion

Assay and stability of silver sulfadiazine spray

The particle size analyzing data (Figure 1) shows that more than 75 percent of particles are less than 5.52 microns in diameter. The results confirm that there has not been any significant crystal growth in the spray formulation after one year.

According to periodic tests performed on silver sulfadiazine spray after 6 and 12 months by TLC and HPLC, it was found that there has not been any residual spots or significant degradation of active ingredient in the spray formulation.

Antimicrobial effectiveness of silver sulfadiazine spray

To determine the effectiveness of the spray formulation as a dosage form, a modified 1 agar diffusion test was performed using Ps. aeroginosa as the test bacteria. The diameter of the zones of inhibition observed with the spray formulation was compared with those of the corresponding medicated cream and are shown in Table 1.

With respect to the spray formulation, statistical significance, as determined by the student t test, could be assigned to the data obtained. That is, the mean diameter zone of the zones of inhibition was significantly larger for the spray formulation than for the corresponding cream ($p<0.001$).

The results obtained in this study showed that silver sulfadiazine spray could be used because of its advantages such as providing rapid and more effective topical antimicrobial application, eliminating potential contamination and greatly reducing pain associated with dressing changes, preserving a good physical and chemical stability, avoiding the need for rubbing the product on the skin, and guaranteeing content sterility through application, over the cream form.

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