A STUDY ON DISSOLUTION RATES OF SILVER SULPHADIAZINE MICROCAPSULES USING DIFFERENT POLYMERS

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Abstract: Microencapsulation is a novel method of drug delivery system that enables topically applied drugs to dissolve more efficiently when applied locally. The technique consists of encapsulating drugs in micron-sized capsules of barrier polymers. The function of polymer is to enhance the rate of drug dissolution. The objective of this research is to design microcapsules carrying silver sulphadiazine (AgSD) with two different polymers and to study their morphology and dissolution pattern. The method employed is a spray drying technique with polymer sodium carboxymethylcellulose (SCMC) or hyaluronan (HA) as the polymer encapsulating material for the drug. The concentration of AgSD used was 1% w/v while the concentration used for the polymer was 2.5% w/v for SCMC and 0.75% w/v for HA. The morphology of the microcapsules obtained was determined under scanning electron microscope. The dissolution rates of the two different microcapsules were studied in deionised water at a fixed temperature of 37^0C over 72 h with the unprocessed AgSD as a control. The results showed that microcapsules were formed for the two different polymers with a typical 'dimple' like characteristics. The dissolution rate was increased by 60 percent for microcapsules with SCMC as polymer and 115 percent increased were determined for microcapsules with HA as polymer compared to their respective controls. The study suggests that microcapsules of HA containing AgSD are more likely to give a better therapeutic effect when applied locally because of its higher dissolution rate.

Keywords: Microcapsules, Spray drying, hyaluronan, sodium carboxymethylcellulose, dissolution

INTRODUCTION

Since last decade, a noticeable progress has been made in pharmacotherapeutic and pharmaceutics as many important new drugs have been introduced to clinical medicine [9]. The progress is not limited only to drug discovery but also in precise control of delivering the drug to the body as well as numerous advances in sophisticated delivery systems. These lead to the invention of the transdermal and other novel drug delivering systems. In the case of delivering drug through the transdermal route, it is crucial that the drug could penetrate past the surface and into the skin before it can actually provides favourable therapeutic impact. The formulation of drugs to be delivered via transdermal route can be achieved by using the rational approach. The potential benefits of transdermal delivery includes avoidance of drug degradation or drug absorption difficulties in the gastrointestinal tract and first pass effect by the liver; substitute for oral therapy when the oral drug delivery route is unsuitable because of underlying condition such as vomiting and diarrhea and avoidance of injections which in turn improves patient compliance and provides ease of rapid identification of the medication in emergencies.

There are three different routes of penetration for a drug molecule into the viable skin tissue namely hair follicles, sweat ducts and stratum corneum. When the skin is damaged, it needs to be treated immediately as further exposure to the environment will develop and introduce the 'open area' to medical complications. Application of the transdermal preparation to the damaged area will give clinical results when the drug is released from the vehicle, penetrated through the skin barriers and elicited pharmacological response. The main limitation for drug penetration through the skin is the molecular property of the drug. Ideally, drugs with low molecular weight, preferably less than 600 Dalton with adequate solubility in oil and water and have low melting point are ideal candidates for transdermal drug delivery system.

Microencapsulation is an important processing technology for design of drug delivery systems. During the process of microencapsulation, drugs are encapsulated in micron-sized capsules of barrier polymers. These polymers serve to control the rate of drug release. AgSD is an antibacterial drug effective against *Staphylococcus aureus*, haemolytic streptococci and generally against *Pseudomonas*

aeruginosa and *E. coli*. Jostkleigrewe, Brandt *et al* [4] found that the usage of dressing with 1% silver sulphadiazine cream in treating partial thickness burns of the hand completely eradicated the complications of infection. Nevertheless, the cream preparation has its limitation in terms of absorption to the skin as the dissolution rate of AgSD is very slow thus promotes infection due to opportunist microorganisms.

A previous worker has incorporated AgSD in sodium carboxymethylcellulose and reported that the dissolution rate of the drug in microencapsulation form was increased compared to the unprocessed drug. This study proposed to investigate whether the reported enhanced dissolution rate of AgSD was unique for that particular drug and the entrapment properties of SCMC only or whether it would be effective for different hydrophilic polymer.

MATERIALS AND METHODS

Materials

AgSD, 98% (Sigma-Aldrich Chemist, Steinheim, Germany), HA (Skye Pharma, Switzerland) and SCMC, (Honeywill and Stein Limited, Surrey, UK) were used.

Methods

Production of AgSD microspheres by spray drying for SCMC: The required weights of SCMC at 5% and 2.5% w/w concentrations for 600 ml suspensions were accurately weighed and transferred into a 1000 ml plastic beaker. Distilled deionised water was added and SCMC was allowed to stand for hydration for 24 h with occasional stirring. The required weights of drug (AgSD) to produce 1% w/v was weighed and added to the beaker. The suspension was then mixed at room temperature using a mini homogeniser (500 rpm) for 1 hour. These suspensions were then spray dried using the Buchi Spray Dryer operated using a pump flow (2 ml min^{-1}), inlet temperature (150 ^{0}C) and flow indicator set at 600 L h^{-1}. The suspension was fed to the nozzle with a peristaltic pump and was atomised by compressed air producing small droplets.

Production of AgSD microspheres by spray drying for HA: The required weights of HA at 0.75% w/v concentrations for 500 ml suspensions were accurately weighed and transferred into a 1000 ml plastic beaker. Distilled deionised water was added and HA was allowed to stand for hydration for 24 h with occasional stirring. The required weights of drug (AgSD) to produce 1% w/v was weighed and added to the beaker. The suspension was then mixed at room temperature using a mini homogeniser (500 rpm) for 1 hour. These suspensions were then spray dried using the Buchi Spray Dryer using a pump flow (3 ml min^{-1}), inlet temperature (170 ^{0}C) and flow indicator set at 600 L h^{-1}.

Scanning electron microscopy (SEM): Small amounts of microspheres were dispersed and mounted on the scanning electron microscopy stubs before sputter coating using an electrical potential of 20 kV, a current of 20 mA and high vacuum for 2 min. The conditions produced a film of gold approximately 15 to 20 nm in thickness. The stubs were examined using a scanning electron microscope and the photomicrographs were produced from randomly selected fields of view.

Assay for AgSD: A sample of microcapsules (10 mg) was dissolved in 5 ml of ammonia and the volume made up to 100 ml with distilled deionised water in a volumetric flask. The solutions were sonicated in a sonic bath for 20 minutes to ensure that all microcapsules dissolved. The UV absorbance of this solution was measured at 254 nm and the corresponding drug concentration was determined by reference to the calibration curve obtained. This was repeated three times for the unprocessed and AgSD incorporated in microcapsules, one containing SCMC and the other HA.

Drug Content:
The percentage drug content was calculated using the following equation (13)
Encapsulation efficiency (%) =[Actual drug content (mg)/Total mass of microcapsules (mg)] x 100

Dissolution Testing: Unprocessed drug (100 mg) was weighed into a square of muslin cloth, placing a weighing boat beneath the cloth to catch any loose powder. A magnetic stirrer rod was placed with the drug and the muslin was tied up to create a close system containing the drug powder. The BP 2001 paddle dissolution method was employed to carry out the dissolution studies. The vessels were filled with 1 L of deionised distilled water that had been sonicated for an hour. The system was allowed to equilibrate at 37 ^{0}C for an hour before the muslin bags were introduced into the medium. 10 ml of samples were removed and filtered through 0.20 µm filters, at intervals over 72 hours. The removed medium was replaced with fresh deionised distilled water to maintain a constant volume of 1 L. The UV absorbances of the samples were measured at 254 nm for AgSD. The concentration in solution after each sample time was determined by reference to the calibration curve. The weight of microcapsules employed in each study was calculated on the basis of the average drug content for each batch so as to ensure that 100 mg of the drug was present in each samples at the start of each dissolution study.

RESULTS AND DISCUSSIONS

Scanning electron microscopy

The micronised AgSD was more uniformed in shapes as it has been refined but comprised as an aggregate mass of crystals (Figure 1). These particles when spray dried with 2.5% SCMC, produced loose spherical microcapsules, however, the surface was not smooth and contained many hollow dimples (Figure 2).

The surface of the microcapsules, which were produced using HA as the polymer showed some differences, since there were no hollow dimples on the surface although an uneven surface did exhibit 'pimple' like characteristics (Figure 3).

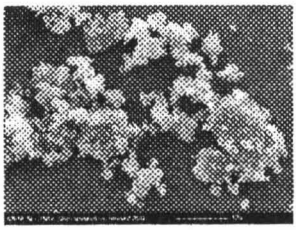

Figure1 The SEM of unprocessed (bar indicates 10µm)

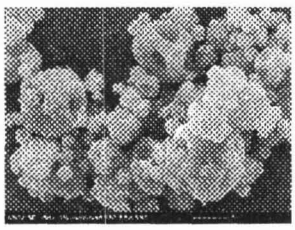

Figure 2 The SEM of micronised AgSD in 2.5% SCMC(bar indicates 3 µm)

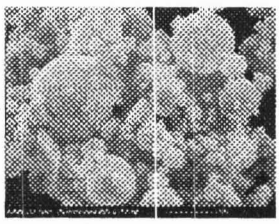

Figure 3 The SEM of micronised AgSD AgSD in 0.75% HA (bar indicates 10 µm)

Drug content in microcapsules formulations

Table 1 represents the content of drug in all microcapsules formulations. All formulations appeared to produce high drug content (more than 87%)

Table 1: Drug content in microcapsules formulations

Microcapsule formulations	% theoretical drug content	% actual drug content (mean ± sd)	% encapsulation efficiency (mean ± sd)
Micronised AgSD:SCMC (1:2.5)	28.57	27.25 ± 0.41	95.38 ± 1.44
Micronised AgSD:HA (1:0.75)	57.14	55.86 ± 0.19	97.75 ± 0.35

Dissolution testing

The mean percentage released for micronised AgSD was measured against time, the profile obtained is shown in Figure 3.4. The plateau region was obtained after 24 h and the total mean percentage released for micronised AgSD was approximately 2.00 percent compared to the microcapsules that employed 2.5% SCMC as the polymer shows the maximum percentage released at approximately 3.2 percent (Figure 3.5) whereas the final percentage of drug released was 4.3 percent for microcapsules with HA as the polymer barrier.

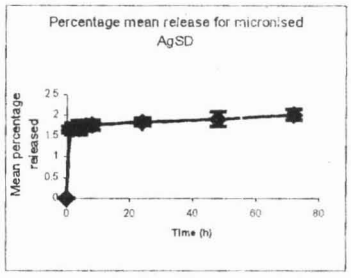

Figure 3.4 The dissolution of unprocessed unmicronised AgSD in distilled deionised water over 72 h at 37°C determined by UV spectroscopy (n=6; mean ± sd

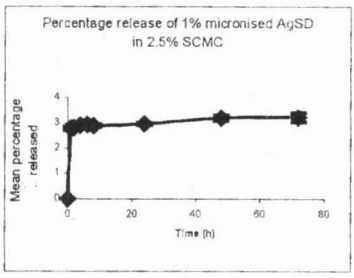

Figure 3.5 The dissolution of 1% micronised AgSD spray dried (2.5% SCMC) in distilled deionised water over 72 hour at 37°C determined by UV spectroscopy (n=6; mean ± sd)

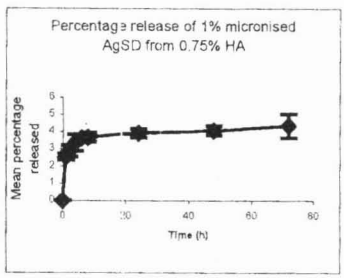

Figure 3.6 The dissolution of 1% micronised AgSD spray dried (0.75% HA) in distilled water over 72 hours at 37°C determined by UV spectroscopy (n=6; mean ± sd)

The microcapsules obtained for micronised batches of spray-dried products of AgSD observed under scanning electron microscope were spherical but also contained small hollow dimples on the surface. However, there were major differences in micronised AgSD spray-dried with 2.5% w/v SCMC and the one spray-dried with 0.75% HA as the earlier one exhibited dimple-like surfaces but the latter were more even. The sizes for both were also different as the latter particles were larger in diameter. Both two batches contained small dimples on the surface, a typical characteristic for spray-dried materials. The drying process of the droplets leads to this phenomena as the droplets entered the hot air stream and dries on the outside to form an outer crust with liquid still inside in the center. The liquid promotes a hole in the sphere for its vaporisation [10]. When compared to the unprocessed particles for all batches, the spray-dried products occurred in a more loose powder with minimal aggregation. Scanning electron microscopy has also been used to investigate the morphological changes of the matrix structure of the spray dried *chlorella* powder as well as the number of cells contained in it [6]. The influence of wall thickness and the smoothness of both internal and external surface of living cells microcapsules that had been developed to protect transplanted cell from immuno rejection were examined [11]. Therefore, this technique is very useful for assessing and evaluating the surface of microcapsules

The incorporation of drug in microcapsules could offer advantages including improved stability against oxidation, ease of handling, improved solubility, controlled release, and extended shelf-life [11] and also for masking the taste of unpleasant drug [7]. Microcapsules have the drug located centrally within an inner core encased in a unique polymeric membrane. To achieve delivery, the drug has to be extracted from the polymer. The polymer encapsulating has to be removed in order to determine the amount of drug incorporation [10]. The extraction method that is employed has to avoid destroying the core drug.

The dissolution of microcapsules product has been carried out by employing several types of dissolution apparatus as in the Pharmacopoeias. The most commonly used are basket or paddle method apparatuses. However, dealing with very fine particles such as microcapsules, the possibilities for the particles to escape from the mesh of the basket is high and this will definitely affect the dissolution process. In this study, the paddle method was employed. The same method has also been used by theophylline microcapsules incorporated in Eudragit-type film coating polymer prepared by a freeze-drying technique [1], tenoxicam microcapsules by a solvent evaporation technique [2] and with diclofenac sodium microcapsules prepared using a solvent evaporation technique [8]. Pallomo and the coworkers also reported that diclofenac microcapsules tended to float when the paddle method was used and it escaped from the mesh of the basket as well as floating. Thus in this study, muslin cloth

was used to 'encase' the sample of microcapsules and the buoyancy of the microcapsules was minimised by placing a magnetic stirrer rod in the muslin bag to prevent the microcapsules from floating.

The percentage of drug released was found to be higher when using 0.75% HA as polymer compared to that when using 2.5% SCMC. A high drug-to-polymer ratio has been found previously to increase viscosity of the internal phase and increase microcapsules size and drug release rate. The viscosity effect in the enhancement of the dissolution rate also reported by Shiralizadeh [10] as the microcapsules containing 10% w/w of SCMC produced the higher dissolution rate of the drug compared to the lower concentration drug. The higher release of drug when HA was employed as the polymer, might suggest that 0.75% HA had a higher viscosity then 2.5% SCMC. Hyaluronan, has the properties of amphiphilic molecules in aqueous solutions that is it is not only hydrophilic as the structure implies but also hydrophobic in its secondary structure. Hyaluronan had been proved to enhance the topical activity of the drug through depot formulation [3]. Studies on the effect of HA in partitioning diclofenac and ibuprofen when compared with other glycosamines; chondroitin sulphate and heparin and SCMC showed that HA promoted a greater partitioning effect compared to another glycosamines even though there was no significant difference. However, the partitioning of drug showed a significantly different result when HA was compared to SCMC. The advantage of using hyaluronan resides in its inherent biocompatibility, its unique rheological properties and its chemical versatility [5].

This study supports the evidence that incorporation of hydrophobic drug in a hydrophilic polymer serves as a promising technique for advanced transdermal drug delivery. There was an enhanced in dissolution rate of AgSD by incorporating it with SCMC but a similar increase was also obtained when HA was employed. However, the dissolution profiles for the two batches produced could only be used as a prediction for the enhancement of drug released. The dissolution profiles for all the batches used increased in the order; unprocessed micronised AgSD < micronised AgSD spray-dried with SCMC < micronised AgSD spray-dried with HA. Further study is to investigate the release of spray-dried products of micronised AgSD with HA in different cream and ointment base.

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