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DESIGN AND EVALUATION OF AZELAIC ACID MICROSPHERES BASED CREAM FOR TOPICAL TREATMENT OF ACNE

Husna N. K.[1], Nishad K. M.[2]*, Jaseena P.[3], Shahana[4], Sirajudheen M. K.[5] and Shijikumar P. S.[6]

[1-4]Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Malappuram, Kerala.
[5]Department of Pharmacy Practice, Jamia Salafiya Pharmacy College, Malappuram, Kerala.
[6]Department of Pharmaceutical Analysis, Jamia Salafiya Pharmacy College, Malappuram, Kerala.

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***Corresponding Author**
Nishad K. M.
Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Malappuram, Kerala.

ABSTRACT

Acne is a common inflammatory skin condition. It is characterized by scaly red skin, blackheads and white heads, pimples, pustules and nodules. Azelaic acid is a better treatment option for acne. Azelaic acid in a novel carrier system can give better patient compliance than any other conventional methods. The purpose of this study is to design and evaluate Azelaic acid microspheres-based cream for topical treatment of acne. Microspheres were prepared by ionotropic gelation method using sodium alginate as polymer and calcium chloride as cross-linking agent. The microsphere formulations (M1-M3) were evaluated for its particle size and entrapment efficiency. The optimized microsphere formulation (M3) was then incorporated into different cream formulations and further evaluated for its physical appearance, pH, spreadability, drug content and *in-vitro* drug release study. The results of the evaluation studies shows that the optimized microsphere (M3) is of spherical shape with average particle size range and of having better entrapment efficiency. The optimized microsphere incorporated cream of F5 formulation is better than other formulations. The formulation shows acceptable physical properties with good spreadability, pH and drug content. The *in-vitro* release study of optimized formulation shows that the drug release is in a controlled manner. The conclusion obtained from this study is that azelaic acid microsphere-based cream is effective controlled release treatment for acne.

KEYWORDS: Azelaic acid, microspheres, acne, cream, controlled release, polymer, skin.

INTRODUCTION

Acne is a common skin problem and estimated that around 80% people of age 11 to 30 are affected at least with mild acne and most people at some cases in their lives. Acne is that the pores of the skin blocked by sebum, hair, dead skin cells and bacteria, which leads to formation of blackheads, whiteheads, pimples and nodules. Acne might have found mostly on face, chest, shoulders and back, where the oil glands found most. Acne can be of different types based on its severity such as mild (few papules and pustues), moderate (multiples papules and pustules) and severe (inflamed pustules and nodules).[1]

The treatment of acne depends upon its severity, age, acne type. It has been reported for decades in various literatures that the topical therapy for acne is always better than that of systemic therapy.[2] Various topical treatment for acne include Azelaic acid, benzoyl peroxide, topical retinoids, topical antibiotics and other combination therapies.

Azelaic acid, a naturally occurring dicarboxylic acid which is present in whole grains. Topical azelaic acid is effective for the treatment of acne and against inflammatory rosacea.[3] Also it has been reported that azelaic acid causes fewer side effects compared to other drugs. Various limitations of conventional formulations include burning, rashes, itching etc. can be reduced by formulating a novel drug delivery form which will gradually distribute the medicament, avoid the frequent application and thereby reduce the irritation due it.

Microspheres are a novel drug delivery system which are spherical solid substances of having size range of 1 – 1000 µm.[4] It contain dispersed drug and polymers which are biodegradable in nature. The utilisation of microsphere technology reduces the adverse effects and release the drug in controlled manner. The microspheres can be dispersed into cream which is a semisolid system with suitable bases to form a homogenous form, which can be easily applied all over the skin.

The present study is to design and evaluation of Azelaic acid microsphere-based cream for topical treatment of

acne for reducing the frequency of application and to improve patient compliance.

MATERIALS AND METHODS

Materials

Azelaic acid was used as the drug which was purchased from Uprising Science Pvt Ltd, Jaipur, India. Sodium alginate used as polymer, Calcium chloride used as crosslinking agent for preparation of microspheres. All the other chemicals and reagents used in this study were of analytical grade.

Methodology

Preparation of Azelaic acid microspheres

Microspheres were prepared by ionotropic gelation method using sodium alginate as polymer and calcium chloride as cross-linking agent. Aqueous solution of Sodium alginate (2% w/v) was prepared. Required quantity of Azelaic acid was added to the prepared 100 ml solution of sodium alginate and mixed by magnetic stirrer. With help of a syringe and needle the obtained solution was extruded drop wise into 100 ml of aqueous calcium chloride solution (10% w/v) while stirring using a magnetic stirrer. After stirring for 20 minutes, the obtained microspheres were washed with water and air dried.

Table 1: Various formulations of Azelaic acid microspheres.

Ingredients	M1	M2	M3
Azelaic acid(g)	4	4	4
Sodium alginate (%)	1	1.5	2
Calcium chloride (%)	10	10	10

Preparation of Azelaic acid microsphere loaded cream:

The cream prepared by taking oil phase which contain liquid paraffin and bees wax and the aqueous phase containing borax and water were weighed and taken in separate beakers. Both heated in a water bath to 70°C. Aqueous phase was then added to oil phase and stirred continuously to form a homogeneous mixture.[5] The mixture was then cooled at room temperature to get smooth white cream. Formulated microspheres were uniformly dispersed into it.

Table 2: Various formulation of Azelaic acid microsphere loaded creams.

Ingredients	Formulations				
	F1	F2	F3	F4	F5
Azelaic acid loaded microsphere (g)	5	5	5	5	5
Beeswax (g)	3	3.5	4.5	5	4
Liquid paraffin (g)	11	11	11.5	12	12.5
Wool fat (g)	1.25	1	-	-	-
Borax (g)	0.2	0.2	0.2	0.2	0.2
Cetyl alcohol (g)	-	1.2	1	-	-
Glycerol (g)	-	-	1	1	-
Methyl paraben (g)	0.03	0.04	0.045	0.045	0.045
Propyl paraben (g)	0.004	0.004	0.005	0.005	0.005
Rose water	q.s.	q.s	q.s	q.s	q.s
Purified water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation Tests

Evaluation of Azelaic acid microspheres

Particle size analysis

Optical microscopy was used for the determination of average particle size of microspheres. Small quantity of microspheres were spread on a clean glass slide and average size of 50 microspheres was determined in each batch.[6]

Entrapment efficiency

50 mg of microspheres were accurately weighed and crushed using glass mortar and pestle and then transferred to 100 ml of phosphate buffer pH 6.8 taken in a beaker. It was mixed by magnetic stirrer for few minutes. 1 ml of sample was withdrawn and make up to 10 ml using phosphate buffer pH 6.8. Absorbance was taken at 210 nm and the concentration was calculated.[7]

Drug entrapment efficiency of the prepared microspheres in each batch was calculated in terms of percentage drug entrapment by using the formula,

$$\% \text{ entrapment efficiency} = \frac{\text{practical drug content}}{\text{theoretical drug content}} \times 100$$

Evaluation of microsphere loaded cream

Organoleptic evaluation

The cream thus obtained was evaluated for its organoleptic properties like odour, colour, and state.

Determination of pH:

pH of different formulated creams was measured by using pH meter. The pH meter was calibrated before use.[8]

Spreadability test

Required quantity of cream sample was placed between two glass slides and a 500 g of weight placed above the

slide for few minutes to compress and spread the cream uniformly between the slides. A specific weight of about 10 mg was placed on the pan and slowly increase till the slide start to slide.[9] The time which is required to separate the two slides was taken and the spreadability was calculated by the formula,

$$S = \frac{M \times L}{T}$$

S is spreadability (g.cm/s), L is Length of the glass slide (cm), T is time (s) and M is weight tied to the upper slide (g).

Test for microbial growth

Agar media was prepared and the formulated cream was inoculated on to plate with media by preparing well and same is done for standard preparation. The plates were placed in the incubator and are incubated in 37ºC for 24 hours. After the incubation period, the plates were taken out and the microbial growth were checked.

Drug content

About 1 g of formulated cream was dissolved in 100 mL phosphate buffer at pH 6.8 by constant stirring. It was then filtered and suitable dilutions were made using same buffer solution. Then analysed by UV spectrophotometer at 210 nm.[10]

***In-vitro* drug release study**

A modified apparatus consist of cellophane membrane was used to study the *in vitro* release of microspheres loaded cream formulation. The cellophane membrane should be soaked in a dissolution medium before its use and then tied to one end of a glass cylinder which is open in both ends. Phosphate buffer (pH 6.8) was used as the dissolution medium. 0.5 g of drug containing microsphere loaded cream was placed in to this assembly. The glass cylinder was connected to a stand and suspended in dissolution medium which was kept at room temperature and stirred by magnetic stirrer. About 2 ml of sample was collected at different time intervals of 5, 10, 15, 30, 60, 90, 120 minutes and sink condition was maintained by replacing with 2 ml of new buffer solution. The samples were collected, diluted and analysed by using UV spectrophotometer at 210 nm.[11]

RESULTS AND DISCUSSIONS

Particle size analysis

The results shows that the size of microspheres were varied from 210 to 240 µm. as shown in the table 3. From this, as the polymer concentration increases particle size also increases.

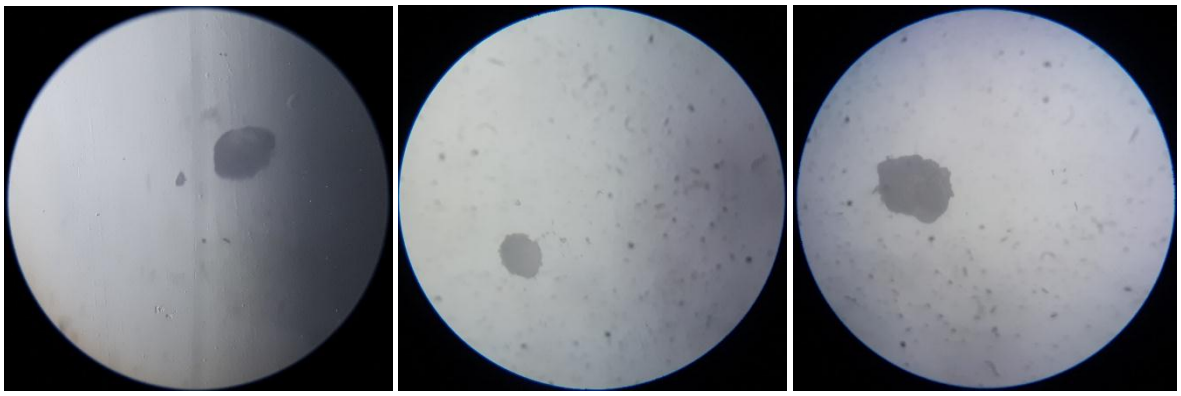

Figure 1: Microscopic view of microspheres (M3).

Entrapment efficiency

The percentage entrapment efficiency of the microsphere formulations is shown in table 3 and was found to be in the range of 38-55%. From the result, maximum entrapment efficiency was found for M3. As the amount of polymer increases entrapment of drug within the microsphere also increases.

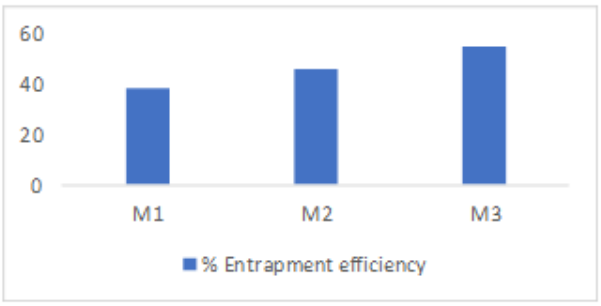

Figure 2: Entrapment efficiency.

Table 3: Particle size and Entrapment efficiency of Azelaic acid microspheres.

Formulations	Average particle size (µm)	% Entrapment efficiency
M1	210	38%
M2	225	46%
M3	240	55%

Thus, the microsphere formulation M3 was selected as the best microsphere formulation and was incorporated in to the cream.

Evaluation of microsphere loaded cream

Physical properties

The cream was of white in colour, soft and having pleasant odour.

Determination of pH

The pH of the creams was found to be in range of 5.1 to 6.0, which is good for skin pH. The formulations was shown pH nearer to skin required.

Spreadability test

The spreadability of different formulations of cream given in the table 4 and was found to be within the range of 5.62 to 10.24 gcm/s. Among this the best spreadable property was found to be for F5.

Figure 3: Spreadability test.

Irritability test

The formulated cream shows no redness, edema, irritation and inflammation during studies.

Test for microbial growth

There was no signs of microbial growth after 24 hours of incubation at 37ºC. Warm and humid climatic condition will support the growth of microorganisms. In such situations the products may severely contaminated, rapid growth would be expected. This will lead to biodegradation of product and increase risk of infection for consumers.

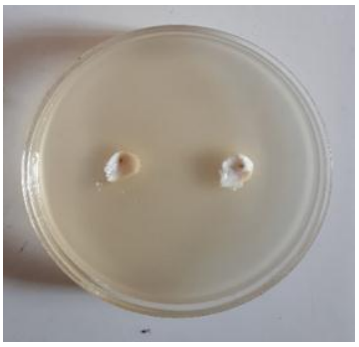

Figure 4: Before incubation.

Figure 5: After incubation

Drug content

The percentage drug content of different formulations was found to be within the range of 75.42-85.51%. The result is shown in table 4. Compared to all formulations F5 formulation found to have good drug content.

Table 4: pH, spreadability and drug content of microsphere loaded cream.

Formulations	pH	Spreadability	Drug content
F1	5.1	5.62	77.68%
F2	5.0	5.98	75.42%
F3	5.7	6.13	75.66%
F4	5.4	7.33	81.23%
F5	6.0	10.24	85.51%

***In-vitro* drug release study**

The in vitro drug release study were done by using cellophane membrane and phosphate buffer of pH 6.8 for 6 hours. The % drug release of optimized formulation is given in the table 5. From the result, it was found to be that the drug release from the formulation was in controlled manner.

Table 5: in-vitro drug release study.

Time (min)	% cumulative drug release
0	0
5	1.39%
10	3.45%
15	6.15%
30	9.67%
60	14.40%
90	20.81%
120	28.49%
180	38.12%
240	49.53%
300	59.44%
360	68.81%

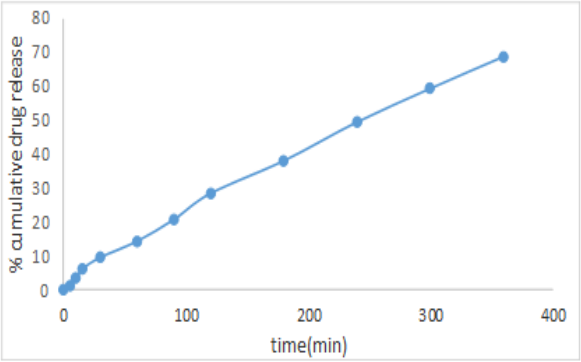

Figure 6: in-vitro drug release study

CONCLUSION

Azelaic acid microsphere based cream was prepared and evaluated. From this study, it can be concluded that the formulation of Azelaic acid microsphere loaded cream is of with controlled release of drug for prolonged period as it fulfils all requirement of controlled release dosage forms and study encourage further clinical trials and long term stability study on this formulation.

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CONFLICT OF INTEREST: Nil.

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