IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2020 Vol.:18, Issue:4

Formulating of Azithromycin, Mometasone Furoate Containing Cream and Its Evaluating for Anti-Infective Activity

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Shreya Durgule, Vrushali Sonar, Puja Patil, Sachin Pishawikar*

Department of Pharmaceutical Quality Assurance, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.

Submission: 26 June 2020
Accepted: 02 July 2020
Published: 30 July 2020

Keywords: mometasone furoate, azithromycin, pre-formulation, factorial design

ABSTRACT

Skin is exposed to various external traumas like wounds, burns, blisters, irritation as well as topical diseases *like psoriasis, vitiligo, cancer, and herpes*. The semisolid topical formulations like cream containing antibiotics are effective in treating infected traumatic skin lesions and nonbullous impetigo. One of the major advantages of such formulations is the adverse effect due to the systemic use of antibiotics can be eliminated or reduced. In present work, a successful attempt has been done in the design and development of cream consisting of mometasone furoate and azithromycin. Mometasone furoate is a medium-strength corticosteroid while azithromycin is a broad-spectrum antibiotic. A novel combination of steroid and broad-spectrum antibiotics should synergistically help in treating skin diseases or conditions such as eczema, psoriasis, allergies, and rash in a better way. Two-phase cream base consisting of stearic acid; lanoline and mineral oil as oil phase and water with triethanolamine as aqueous has been used for the development of cream. By applying factorial design B1 to B9 batches of cream were prepared and evaluated. B4 batch was found to be an optimized batch. The anti-infective activity results of optimizing batch B4showed promising results compared to marketed azithromycin gel formulation. For anti-bacterial activity, an optimized batch showed zone of inhibition 40.60, 40.00, and 32.08 mm against *E.coli, B. Ssubstillus*, and *S. aureus* compared to marketed azithromycin gel showing zone of inhibition 40.00, 40.40 and 30.01. For anti-fungal activity tested against *A.niger* the optimized batch has shown a 20.00 mm zone of inhibition compared to 30.00 mm shown by standard fluconazole. Results are promising and the presence of steroids should help in faster recovery in skin diseases and infections.

INTRODUCTION:

Over the last decades, the treatment of illness has been accomplished by administrating drugs to the human body via various routes of administration like oral, sublingual, rectal, parental, topical, inhalation, etc. A semi-solid formulation like ointment, creams are dominant formulations related to topical drug delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are also used to treat various skin diseases and conditions. The intention is to treat the disease directly as the drug or medicine will show its pharmacological effect on the surface of the skin or within the skin. [1-4]

Design of topical formulation containing drug

Dermatological products applied to skin ranges from liquids, semisolids to solid formulations like powders. The most popular products are semisolid preparations like cream, ointments, or gels. Some of these may be non-medicated, in the sense that these may be devoid of any therapeutically active ingredients. Such preparations may be categorized as cosmetics. Nevertheless, these products can provide desired physical outcomes through their protective, moisturizing, or emollient effects on the skin. Traditional ointment bases are oleaginous and consist of hydrocarbons like petrolatum, beeswax with doesn't allow the inclusion of water. Another category contains vegetable oils like cholesterol, lanolin, wool alcohol, or stearyl alcohol, which allow limited inclusion of water. The type of base used in formulating a topical dermatologic product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances provide an emollient effect to dry, irritated skin. More importantly, bases made up of non-volatile oleaginous substances (e.g., hydrocarbon bases) can form an occlusive barrier on the skin that prevents the escape of moisture from the skin into the environment. As a result, moisture accumulates between the skin and the ointment layer that causes hydration of the stratum corneum. Hydration of stratum corneum allows opening up of intra- and inter-cellular channels and pathways for easier passage of drug molecules. Additionally, the moisture layer provides a medium for dissolution of the drug that is otherwise dispersed as fine particles in the ointment base.[1-4] Systematic studies of cortisone uptake by the skin have shown that drug penetration is poor through dry skin, but is remarkably enhanced when stratum corneum is moist. Creams have good emollient properties, especially the w/o types, which maintain some degree of occlusion. However, the less hydrophobic films formed with o/w creams and water-soluble bases and gels do not provide an occlusive barrier to the skin and, thus, allow moisture to escape from its surface.

Some well-formulated gels have been successful in facilitating greater drug permeation into the skin when compared with ointments and creams, in which the drug may be dispersed as fine particles, but dissolution is inadequate because of their limited water content. Gels have a higher aqueous component that permits the greater dissolution of drugs, and also permit easier migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream bases. Also, many gels contain penetration enhancers, such as alcohol, in the formulation. Topical dermatologic products that require drugs to penetrate and localize enviable epidermal or dermal sites (such as local anesthetics or anti-inflammatory agents) may also occasionally include a vasoconstrictor, such as epinephrine, in the formulation to retard systemic uptake of the drugs and, thereby, prolong its local effect. [1-5]

MATERIALS AND METHODS:

Azithromycin dehydrate and Mometasone furoate were obtained as a gift sample from Unichem Laboratories Ltd Goa. Stearic acid; lanoline, mineral oil, triethanolamine, Potassium sorbate, citric acid were procured from Loba Chemie Pvt. Ltd., Mumbai.

Preformulation Study:

Pre-formulation studies were performed by determining the melting point, thin layer chromatography and spectral analysis of drugs azithromycin dehydrate, mometasone furoate as well as components of the cream base to confirm no interaction.

Drug Excipients Interaction Study:

Pure drug azithromycin dihydrate and mometasone furoate and individual excipients were mixed separately with IR grade KBr in the ratio of 100:1 and dispersed uniformly. The infrared spectra of these physical mixtures were determined over a wavenumber range of 4000-650 cm-1 by using Fourier Transform Infrared Spectrophotometer (FTIR-4100). The base-line corrected by using dried potassium bromide. FTIR spectra of mometasone furoate and azithromycin and optimized batch are shown in Figure 1(a) and 1(b).

Preparation of Cream:

A cream containing an oil phase consisting of stearic acid, lanoline, and mineral oil while the aqueous phase contains water and triethanolamine was used as two phases. They were separately heated on a water bath at 70^0c while preparing the cream. Potassium sorbate was used as a preservative and citric acid for pH adjustment of the cream. The aqueous phase was added to the oil phase in a dropwise manner with constant stirring along with the addition of both drugs from its low to high value.

Factorial Design:

A 3^2 factorial design was used in this study and 2 factors were evaluated, each at 3 levels; experimental batches were prepared at all 9 possible combinations. The amount of stearic acid and lanoline were selected as independent variables. The % drug content, spreadability, in-vitro drug release were selected as the dependent variable. The data obtained were subjected to 3-D response surface methodology to determine variables. The full factorial experimental design layout is shown in Table 1. The values of variables in a 3^2 factorial design are given in Table 2.

A statistical method incorporating interactive and polynomial terms was used to calculate the responses.

$$Y= b_0+b_1X_1+b_2X_2+b_12X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 trials, and bi (b1, b2, b12, b11, and b22) is the estimated coefficient for the corresponding factor Xi (X_1, X_2, X_1X_2, $X_{12,}$ and X_{22}), which represent the average result of changing one factor at a time.[5-8]

Table No. 1: Full factorial experimental design layout

Trials	Variables Level in Coded Form	
	X1	X2
1	-1	-1
2	-1	0
3	-1	+1
4	0	-1
5	0	0
6	0	+ 1
7	+ 1	-1
8	+ 1	0
9	+ 1	+ 1

Table No. 2: Amount of variables in 3^2 factorial design

Independent variables	Low (-1)	Medium (0)	High (1)
Stearic acid (X_1) (w/v)	1.50	1.85	2.40
Lanoline (X_2) (w/v)	1.00	1.25	1.50

EVALUATION OF CREAM

Physical Appearance and pH:

The prepared cream was inspected visually for clarity, color, and presence of any particulate matter. The pH was determined by dispersing accurately weighed 5 g of cream in 45 ml of water. Results for pH evaluation of various formulations are given in Table 3.

Spreadability determination:

For determination of spreadability, 3g of cream was applied between two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 minutes. Thereafter weight (50g) was added to the pan and the top plate was subjected to pull with the help of string attached to the hook. The time in which the upper glass slide moves over the lower plate to cover a distance of 10 cm was noted. A shorter interval indicates better spreadability. The spreadability (S) was calculated using the formula S = mL. /t, Where, S– spreadability, m-weight tied to the upper glass slide. L-length moved on glass slide t- time. [4-6] Spreadability of the different cream formulation is given in Table 4.

Drug content determination:

A quantity of cream equivalent to 10 mg of Azithromycin (0.1 g of cream) was transferred to a 100mL volumetric flask. The volume was made up with Phosphate buffer pH 7.4. From this 1, 2, 3, 4, 5, and 6mL were taken into a 10mL volumetric flask. In each flask 1mL of 0.001 M, $FeSO_4.7H_2O$ in methanol was added and volume was made with phosphate buffer pH7.4. Solutions were placed in orbital shaking at 25ºC for 1h. The dilutions prepared were in the range of 10-60µg/mL. Absorbance was recorded at 281nm against the solvent blank. The same procedure was applied for an equivalent quantity of cream containing 100 mg of mometasone furoate (0.1 g of cream). 10 ml of this solution was taken in another 100 ml volumetric flask to get a stock solution of 100 µg/mL of Mometasone furoate. From this stock solution, 1, 2, 4, 6, 8, 10 ml were withdrawn and diluted with phosphate buffer to obtain the different solutions of different concentrations of 10, 20, 40, 60, 80, 100 µg/mL. Absorbance was measured at λmax 209 nm using a UV-visible double beam spectrophotometer (Jasco V-530) against phosphate buffer as blank. The drug content of all formulation was calculated. [7-8] The obtained values of the drug content of different formulations are given in table 5 and 6.

Tube Extrudability:

The formulation understudy was filled in a clean, lacquered aluminum collapsible 5 tubes with a nasal tip of 5 mm opening and applied the pressure on the tube with the help of a finger. Tube extrudability was then determined by measuring the amount of cream extruded through the tip when pressure was applied on a tube. Shown in Table 7.

Viscosity:

The viscosity of formulated creams was measured by Brook field Viscometer (LVDV-III ultra-programmable Rheometer) using spindle CP-52 at varying speed and shear rates. The measurements were done over the range of speed setting from 0.10, 0.20, 0.30, 0.40 and 0.50 rpm in 60 s between two successive speeds as equilibration with a shear rate ranging from0.20 s-1 to 1.0 s-1. Results of viscosity are mentioned in table no.8.

COMPATIBILITY STUDIES

FT-IR studies:

FTIR studies were done to assess whether any possible interaction among drug, the polymer is done by FTIR spectrophotometer (Jasco-4100). Infrared spectrums of pure drug, physical mixture of ingredients of the formulation, and batches were recorded.

Differential scanning calorimetry (DSC):

DSC of the optimized cream batch was recorded using DSC (DSC 60 Shimadzu) equipped with an intra-cooler shown in Figures 2, 3, and 4.

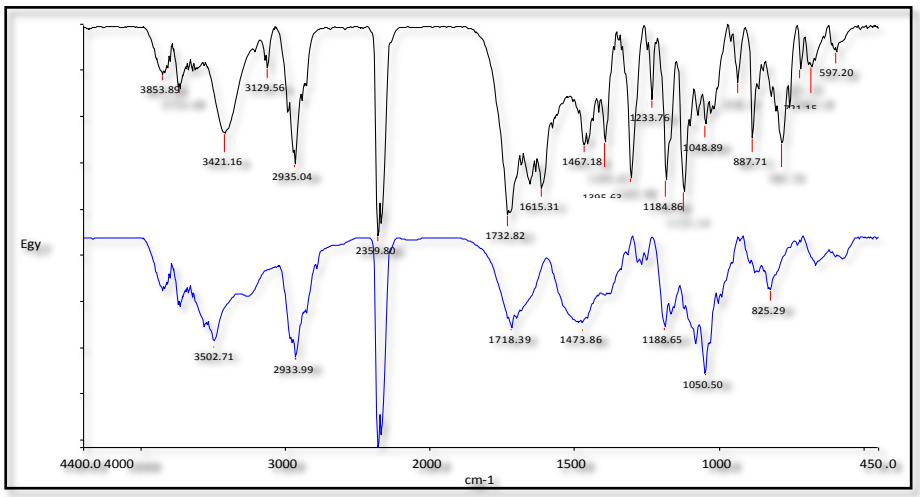
RESULT AND DISCUSSION:

A. Prefomulations Studies:

The melting point of drugs azithromycin dehydrate and Mometasone furoate were found to be between114-117 and >209°C (dec.) respectively.

B. Drug and Excipient Interaction Study:

FTIR study was carried out to study whether there is any interaction between drug and excipients. The IR spectrum of plain drugs and the IR spectrum of the optimized batch was compared. FTIR spectra of azithromycin, mometasone furoate, and the optimized batch are shown in Figure 1(a) and 1 (b).



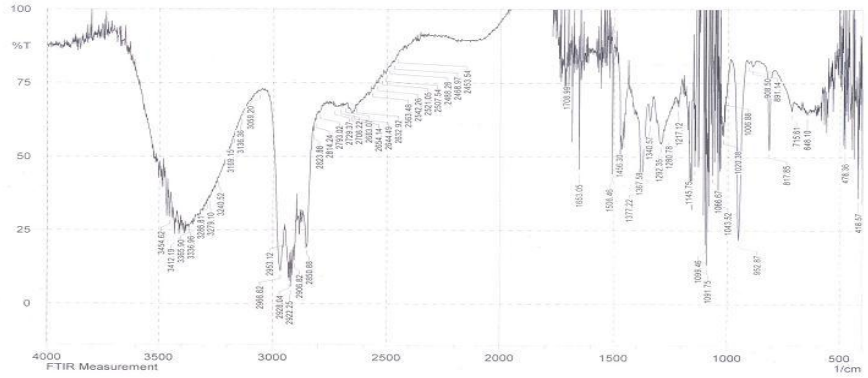


Figure No. 1: IR spectra of the optimized batch cream sample

Thus from the above IR spectrum, it is clear that there is no change in peak positions of mometasone furoate and azithromycin in a cream formulation. Hence it can be concluded that there is no interaction between mometasone furoate, azithromycin, and excipients. [6-9]

C. EVALUATION OF CREAM :[7-9]

In this study,

- **Physical appearance** - The cream was found to be white to off-white, with the absence of particulate matter.
- **Homogeneity:** The cream appeared homogeneous.
- **pH**: pH was optimized for different batches.

Table No. 3: pH values of different formulations determined at RT

Batch	pH
B1	7.2
B2	7.3
B3	7.4
B4	**7.3**
B5	7.3
B6	7.6
B7	7.5
B8	7.3
B9	7.4

➢ **Spreadability Test:** The values of the spreadability of all trial batches found to be between 12.32 to 14.16 g.cm/sec which indicates its easy spreading on the skin after application.

Table No. 4: Spreadability of the different cream formulations

Batch	Spreadability (g.cm/sec)
B1	13.35
B2	13.72
B3	14.16
B4	**13.37**
B5	13.22
B6	13.12
B7	13.61
B8	12.85
B9	12.32

➢ Drug content determination- The drug content of all trial batches is given in Tables 5 and 6.

Table No. 5: Drug content of AZI in the different cream formulations

Batch	% Drug Content
B1	98.35
B2	98.72
B3	99.16
B4	**99.22**
B5	99.11
B6	98.61
B7	99.26
B8	99.32
B9	98.35

Table No. 6: Drug content of mometasone furoate in the different cream formulations

Batch	% Drug Content
B1	99.72
B2	98.24
B3	99.87
B4	**98.27**
B5	99.55
B6	99.33
B7	97.15
B8	99.32
B9	99.82

The drug content for both medicaments was found to be well within the range 98.35 to 99.32 % w/v. As can be seen, it is much closer to 100% indicating no loss of drug during the cream formulations. Thus it complies with the standard for uniformity of drug content and suitability of methods adopted for formulating cream.

➢ **Tube extrudability Test:** The values of the extrudability of all trial batches were found to be between 96.18 to 97.18 % which indicates easy removal of the cream collapsible tube.

Table No. 7: Tube extrudability values of different formulations

Batch	Extrudability %
B1	96.84
B2	97.15
B3	97.04
B4	**97.08**
B5	97.13
B6	97.16
B7	96.18
B8	97.16
B9	97.18

➢ **Viscosity of creams**: The viscosity of all trial batches was found to be between 96.18 to 97.18 % which indicates ease of flow of cream from the collapsible tube. Results for the viscosity of different formulation are shown in Table 8.

Table No. 8: Viscosity values of different formulations

Batch	Viscosity in cps
B1	29930
B2	32598
B3	32727
B4	**30475**
B5	28080
B6	30727
B7	27825
B8	32568
B9	32287

Form the evaluation study of various batches it was found that **batch B4** can be considered as an optimized batch and was used for further evaluation.

D. COMPATIBILITY STUDY:

Differential scanning calorimetry (DSC)

Differential scanning calorimetric analysis covers a group of techniques that measure the physical properties of a substance as a function of temperature which is easily quantified on the DSC curve. DSC spectra of pure drug and optimized cream batch were obtained.

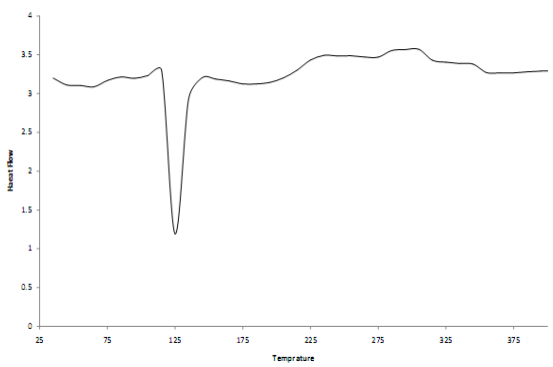


Figure No. 2: DSC of pure drug AZI

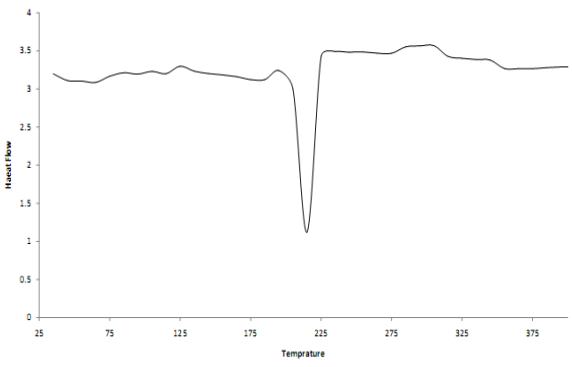


Figure No. 3: DSC of pure drug mometasone

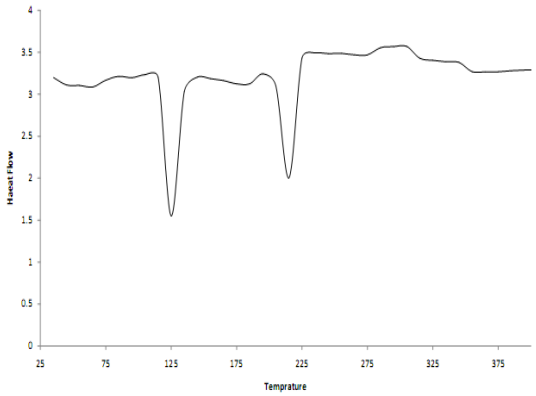


Figure No. 4: DSC Spectra of cream

DSC of AZI has shown an endothermic peak at 1250C, which corresponds to its melting point whereas in the case of mometasone furoate DSC spectra have shown an endothermic peak at 220°C which corresponds to its melting point. Formulation Cream showed little shift in an endothermic peak at 124.6°C in the case of AZI and 218°C in the case of mometasone furoate. The spectral evaluation indicates that there is no interaction between drugs and the ingredients of the cream base.

ACCELERATED STABILITY STUDY OF CREAM:

The stability study was carried out for optimized B4 batch at 40 ± 0.5 °C and 75 ± 5 % RH for 3 months using a programmable environmental test chamber (Remi, India). The samples were evaluated for physicochemical parameters like appearance, pH, spreadability, drug content. The results of accelerated stability study are mentioned in table no.9.

Table No. 9: Result of Stability Testing

Sr. No.	Test parameters	Results
1	Appearance	Good
2	pH	6.5
3	Spreadability (g cm./sec)	13.37
4	Tube extrudability	97.13
5	Drug content of AZI mometasone furoate	99.22% 98.27%

E. Anti- Infective Activity:

Antimicrobial study of cream[6-8]

Antimicrobial activity of optimized batch of cream B4 was carried out by the cup plate method. Test solution, control, and standard were prepared by using the only base and were pouredonplates. Marketed azithromycin gel was used as a standard.

The plates were placed incubated at 37ºC for bacteria and 27ºC for fungi. After incubation for 24Hr. for bacteria and 48Hr. for fungi, the diameter of the zone of inhibition (including the diameter disc) was measured and recorded in mm. The results for antibacterial activity are given in figure 5 and table 10 while for antifungal activity are mentioned in figure 6 and table 11 respectively.

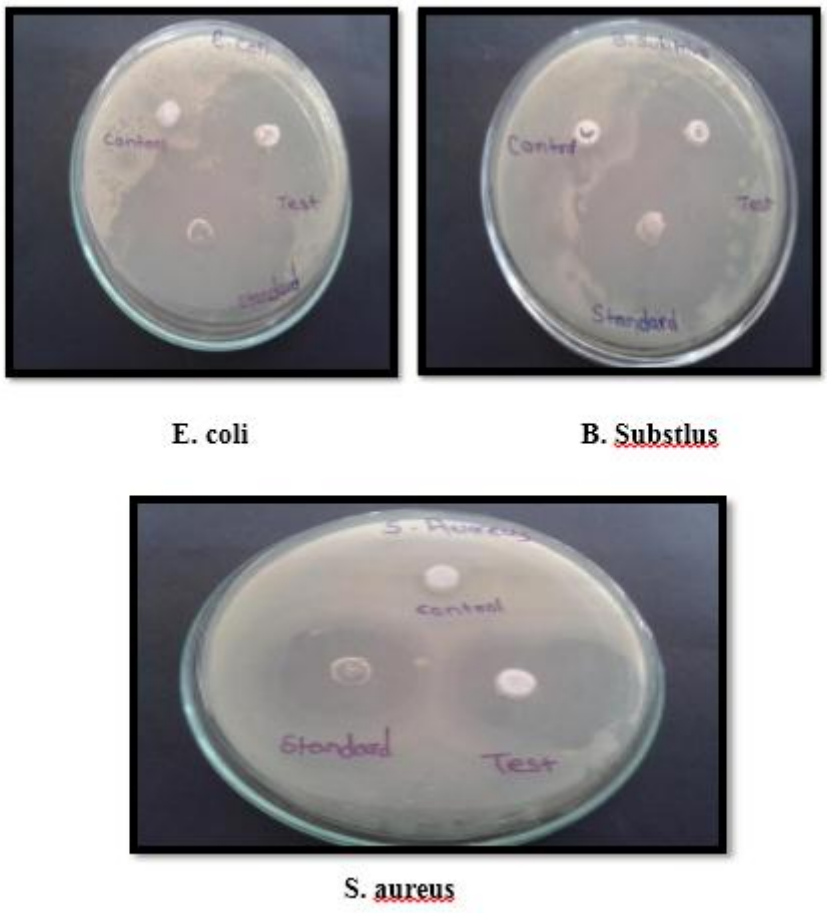
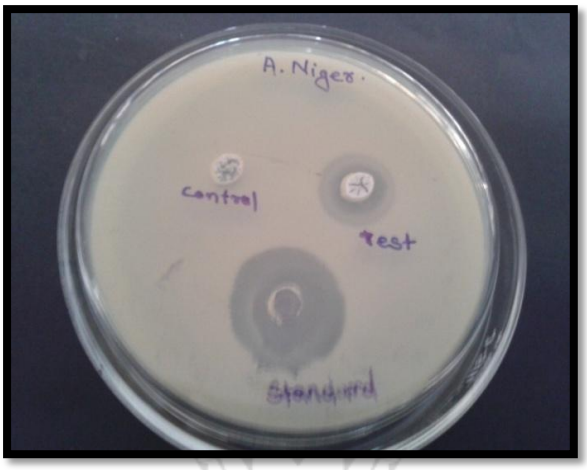


Figure No. 5: Antibacterial activity of Standard (azithromycin cream), control, and test samples

Table No. 10: Antibacterial activity of Standard (azithromycin cream), control, and test samples

Organisms	Zone of Inhibition*(mm)		
	Standard	Test	Control
E. coli	40.00	40.60	00.00
B. substillus	40.40	40.00	00.00
S. aureus	30.01	32.08	00.00



A. niger

Figure No. 6: Anti-fungal activity of cream against a standard (fluconazole), control and test samples

Table No. 11: Anti-fungal activity of cream against a standard (fluconazole), control, and test

Samples

Organisms	Zone of Inhibition*(mm)		
	Standard	Test	Control
A. niger	30	20	00.00

CONCLUSION:

From the results, it can be concluded that a successful attempt has been made in the design and development of cream containing AZI and Mometasone furoate combination which has

shown comparative anti-infective activity when with standard marketed azithromycin gel. The presence of steroids should help in better and faster recovery from infection.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENT:

The authors are thankful to Dr. H. N. More Principal for providing the workplace and facilities to carry out research work.

REFERENCES:

1. Ansel H.C., Allen L.V., Pharmaceutical Dosage Forms, and Drug Delivery System, Lippincott Williams and Wilkens, Baltimore, 2000, 244-246,249-251, 253-255,264-265.
2. Akash S, Mali Karekar P, DR. Yadav AV, Formulation and Evaluation of Multipurpose Herbal Cream, International Journal of Science and Research (IJSR), ijsr.net. 2015; 4(11):1495-1498
3. Bora A., Deshmukh S., Swain K. Recent advances in semisolid dosage forms. Int J Pharm Sci Res. 2014. 5(9):3594–3608.
4. Baravkar1 A. A., Kale R. N., Patil R.N., Sawant S.D., Pharmaceutical and Biological Evaluation of Formulated Cream of Methanolic Extract of Acacia Nilotica Leaves, Research J. Pharm. and Tech, 2008, 1(4), 480-483.
5. Kavitha K., Sivaramakrishnan R., Formulation and Evaluation of Topical Drug Delivery Systems of Fluconazole, Indian drugs, 2003, 40(12), 720-723.
6. Patel N.A., Patel N.J., Patel R.P., Comparative development and evaluation of topical gel and cream formulations of psoralen, Drug Discov Ther, 2009,3(5),234-242.
7. Suhagia B.N., Shah S.A., Rathod I.S., Patel H.M., Doshi K.R., Determination of Azithromycin in pharmaceutical dosage forms by Spectrophotometric method, 2006, 68 (2), 242-245.
8. Hsu S., Quan L., Topical antibacterial agents, Comprehensive dermatologic drug therapy, 2001, 472-96.
9. Patel R.P., Kamani R., Formulation Optimization and Evaluation of Mometasone Furoate Cream, Journal of Pharmacy, 2009
10. Rajalakshmi G., Damodharan N., Chaudhary V. V., Pogal J.R., Formulation and evaluation of clotrimazole and ichthammol ointment, International Journal of Pharma and Bio Sciences,2010,1(4), 975-6299.