International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

FORMULATION AND EVALUATION OF MICROSPONGE FOR TOPICAL DELIVERY OF OXAPROZIN

Sajal Kumar Chowdhury, Ankita Shukla, Dharmendra Singh Rajput, Naveen Gupta, Neeraj K Sharma

***School of Pharmacy, Madhyanchal Professional University, Bhopal, M.P**

Abstract

Ozaprozin Microsponges using EC and ERS 100 polymers for Preformulation, Preliminary selection of formulation and process variable, CQAs, QbD approach, DoE, Characterization of MS, Check Point Analysis and MS loaded Gel. Further, this chapter describes preparation of Ozaprozin microsponges and evaluation for % yield, % Entrapment efficiency, % drug content, SEM, FTIR spectral studies, and *% CDR*. Preparation of optimized microsponges gels was evaluated for *In vitro* diffusion studies, Anti- Fungal Study and primary skin irritation studies. It also describes the results and discussion of the thesis. Production yield and loading efficiency were calculated for all the microsponge formulations average of three determinations was considered and was found to be reproducible. The loading efficiency of the microsponge formulations were from 80%-90%. The FTIR spectrum of microsponge formulations shows the characteristic bands and all other peaks observed with individual compound have remained unaffected in microsponges formulations indicates microsponges formed were not a chemical reaction product, hence, the drug exists in original form and available for the biological action. SEM suggests the optimized microsponges were finely spherical, uniform in shape, no intact drug crystals are seen visually and inner structure was consisted of porous in nature with void spaces. The comparative dissolution profiles and regression coefficient values were also discussed.

Keyword: Microsponge, In Vitro Release, Preformulation and Oxaprozin

Corresponding Author:

Sajal Kumar Chowdhury

School of Pharmacy

Madhyanchal Professional University

Email id: researcharticle78@gmail.com

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

1. Introduction :

THE SKIN:

Topical formulations are intended to be applied to a certain area of skin for local action. They conveniently delivery drugs across the localize area of skin. Thus, they are product design to deliver drugs into the skin as a targeted organ for treating dermal disorders. For effective treatment of skin disorders the drug should penetrate and at the same time should depot in the skin for a required period of time. To elect such condition perfectly it requires drug diffusion outside the dosage form to the skin surface followed by its permeation to the barrier layer of skin (stratum corneum) both steps are highly prejudiced.

Skin is a vital structure that shelters the entire surface of body, forming a protective barrier against pathogens and injuries from the environment. It is one of the largest organs, with a surface area of approximately 1.8 m^2. It shields the body against heat, light, injury and infection. The skin plays a vital role in the immune system and protects the body from disease. (Tortora G et al., 2000)

INTRODUCTION TO MICROSPONGE DRUG DELIVERY SYSTEM:

Microsponge can be easily assimilated into the TDS which may retain dosage form on skin and has been used as oral delivery using bioerodible polymers particularly for colon precise delivery which may improve patient passivity due to its site specificity and extending dosage intermissions. (Won R., 1987, Newton D et al., 1991 and Kydonieus A et al., 1987)

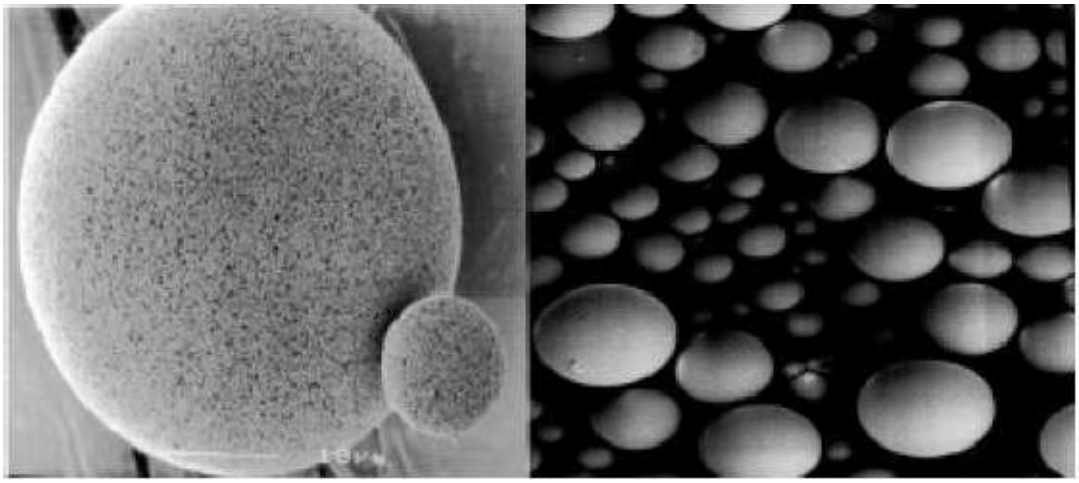


Figure 1.7: Photographs of highly porous nature of a microsponge Microsponge is defined as porous, inert units which is made up of synthetic polymers and act as a shield to the ensnared drug from degradation which can be easily entrapped in th form of creams, lotions, and powders. **(**Won R., 1987 and Delattre L et al., 1995) In case of Cosmetics and dermatological products, work only at outsided of skin. The active component in conventional marketed dosage form may extant in a moderately high concentration and absorbed rapidly on application upon skin. MDS may proposed to permit a modified rate of drug release of, thus posing prospective lessening in the side effects and maintain the therapeutic effect. (Cooke C., 1993 and Nacht S et al., 1992)

Formulation Aids: (Aritomi H et al., 1996)

The polymers which have been used to prepare microsponges are Ethyl cellulose, Eudragit RS 100, etc. which can form 'cage'

like structure. Sometimes plasticizers may be used to stabilize structure of microsponges.

2. Material and Methods

Methodology

Preformulation of Drug (Nevine S et al., 2012, Saboji J et al., 2011 and Dash A et al., 2001)

The preformulation study is mostly generate data useful to develope stable dosage forms that can be mass-produced for manufacturer.

Organoleptic Characteristics of Oxaprozin

Physical examine was done to check Organoleptic Characteristics of Oxaprozin like color and odor.

Determination of Melting Point of Oxaprozin

Melting point of Oxaprozin had been evaluated by the capillary method.

Identification and Determination of Wavelength Max (λ_{max}) of Oxaprozin

Stock solution (1000µg/mL) of **Oxaprozin** in methanol was prepared. This solution was a diluted to obtain the 100µg / mL solution. 5 mL of solution of Oxaprozin was diluted to prepare 50µg/mL of Oxaprozin which was scanned between 200 - 400 nm against blank solution methanol.

Solubility study of Oxaprozin

Preformulation solubility analysis was done, which included to dissolve the drug with an excess quantity in glass vials containing 20mL suitable solvent system and supernatant solution was filtered using 0.45 µm pore size filter after 24 hrs at room temperature. The first 10 mL of the filtrate was discarded and last portion of the filtrate was suitably diluted with water and assayed spectroscopically at 260nm. The procedure was followed by using different solvents like water, acetone, ethanol, chloroform, ether and pH 6.8 Phosphate buffer.

Preparation of Calibration Curve for Oxaprozin

Sample Preparation of stock and standard solutions for Oxaprozin

Oxaprozin was weighed accurately 100 mg and dissolved in 100 mL of methanol to get a 1000µg / mL solution was used as a standard stock solution. From Standard Stock solution 10 mL was withdrawn and volume was made with methanol in order to get a standard stock solution containing 100µg/mL and was used to prepare further dilutions. From this Working standard solution, dilution with methanol was made to get 10, 20, 30, 40, 50 µg/mL and measured absorbance at 260 nm for Oxaprozin

Identification of Drug- Oxaprozin by FT-IR Spectroscopy

Potassium bromide IR disc was prepared using 1mg of Oxaprozin on Hydraulic Pellet press which was scanned of 4000-400 cm^{-1} re in FTIR and obtained IR Spectrum was compared with a reference spectrum of Oxaprozin.

Drug- Excipients Compatibility Studies by FT-IR

Potassium bromide IR disc was prepared using Oxaprozin, Ethyl cellulose, Eudragit RS100, PVA, Carbopol 934 and mixture on Hydraulic Pellet press was scanned 4000-400 cm^{-1} region in FTIR and obtained IR Spectrum was

compared with a reference spectrum of Oxaprozin

Drug-Excipients Compatibility Studies by DSC

Thermal analysis of Drug Oxaprozin and polymers was studied employing differential scanning calorimetry which was done to ckeck compatability for Microsponges formulations

Formulation and Development of Oxaprozin Oxaprozin Microsponges by using QbD Approach

Method of Preparation of Oxaprozin Microsponges (Parikh B et al., 2010)

FLZ microsponges were prepared using Quasi- emulsion solvent diffusion methods. Two phases were prepared viz the inner phase and outer phase.The drug and polymer were dissolved in a Acetone. Later, inner phase was poured into outer phase which was containing PVA and Liquid paraffin as emulsifying agent and kept for 60 min with constant stirring. The obtained liquid had clarified to distinct the Microsponges and dried at 40 º C in an oven.

Selection of Formulation and Process Variables of Preliminary Trial Batches of Oxaprozin Microsponges

Preliminary trials were undertaken to establish effect of various Drug: Polymer ratio, Surfactant Concentration, Stirring rate, stirring time, a type of internal phase, Internal phase volume, External phase volume and evaluated for % yield, Entrapment efficiency and size of particles for CQAs selection to develop QbD Approach as per Table 4.20.

Selection of Concentration of Retardant Material (Polymer) in Internal Phase

The different ratio of drug: polymer (1:1, 1:2 and 1:3) were used to prepare microsponges to evaluate effect for their entrapped drug, loading efficiency and particle size.

Selection of Drug: Polymer Ratio

Blank microsponges were prepared using 20 mL internal phases (Acetone) and 50 mL of an external phase (Liquid Paraffin) with Polyvinyl alcohol with a ratio of Drug: polymer 7:1, 9:1, 11:1, 13:1 and 15:1 in the internal phase to check and select Drug: Polymer Concentration.

Selection of Internal Phase Type

For the selection of the internal and the external phases, various investigations were carried out using different internal phases viz. Acetone and Ethanol, with the constant external phases at 1500 RPM stirring speed. Various combinations of internal (Acetone and Ethanol) phase were investigated.

Selection of Internal Phase Volume

The varying volume of internal phase, i.e. Acetone was evaluated using 5mL, 10mL, 15mL and 20mL of the internal phase, with constant drug to polymer concentration at 9:1 in 50mL of Liquid paraffin as external phase, stirring speed of 1500 RPM with surfactant concentration of 0.75% w/v of the external phase to evaluate effect.

Selection of External Phase Volume

In order to evaluate the effect of external phase concentration i.e. Liquid paraffin, was evaluated using 40mL, 50mL and 60mL of the external phase. The formed particles were evaluated.

Selection of Surfactant Concentration

PVA as surfactant was used at diferent concentration ranging from 0.5 %, 0.75%, 1.0% and 1.25% w/v of the external phase and were observed for their physical characteristics to optimize and check the effect on microsponges.

Selection of Stirring Speed

The microsponge was formulated with varying speed of 1000, 1500, 2000 and 2500 RPM while all other variables continual and the formed microsponges were evaluated for free drug content and particle size to check stirring speed effect.

Selection of Stirring Time

The microsponges had produced at different time intervals i.e. 60 Min, 75 Min and 90 Min of stirring time while others are keeping all the other variables constant and the formed microsponges were evaluated.

Risk Assessment of Critical Quality Attributes from Preliminary trial Batches to Develop QbD Approach

Risk assesement has been done to select formulation and process variable which may affect product quality for CQAs by process characterization that define satisfactory changes in material and process parameters. Finally, This can result in quality assurance by Process Design Space to understand and develop control strategy. The critical quality attributes are categorized into high, medium and low risk parameters based on knowledge space. Usually high risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges. (Delasko J et al., 2005)

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

Formulation and Development of Oxaprozin Microsponges by DoE Using QbD Approach

A design space can signify formulation and process understanding viz. attributes which are related to drug substance, materials, equipment, IP and finished product quality. (Sandipan R et al., 2012) For this purpose, risk assessment had done based on the understanding process and formulation related parameters on microsponges quality. Preliminary studies and later Design of Experimentation (DoE) was carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, we proposed design space for obtaining robust formulation. Characterization of microsponges was done for various parameters viz. Particle size analysis, shape, micromeritics properties, encapsulation efficiency, percentage yield, *in vitro* drug releases shape and surface topography (SEM).

Characterization of Oxaprozin Microsponges (Nokhodchi A et al., 2007, Maiti S et al., 2006, Costa P et al., 2009 and Lokhandwala H et al 2013)

Preformulation Study for Oxaprozin

Oxaprozin is a synthetic triazole antifungal drug. It is a completely synthetic compound. It is BCS class-2 drug. The pure drug Oxaprozin and various other excipients such as Eudragit RS 100, Ethyl cellulose, PVA, Carbopol 934, etc. were subjected to various Preformulation parameters such as Organoleptic characteristic study, Melting Point Determination, solubility study Wavelength$_{max}$ (λ_{max}) Determination, Calibration curve, Identification of Drug by Oxaprozin, DSC study and FT-IR study. This includes the various Preformulation studies for the present research work and the result discusses below every parameter.

Organoleptic Characteristics of Oxaprozin

Table 4.7:Organoleptic Characteristics

PARAMETER	OBSERVED RESULT
Color	White powder
Odor	Odorless or with a faint characteristic odor
Appearance	White crystalline powder

The color of the Oxaprozin was visualized white with odorless or with a faint characteristic odor having a white crystalline powder appearance as shown in table 4.7.

Determination of Melting Point of Oxaprozin

The melting point results is shown in table 4.8.

Table 4.8: Melting point of Oxaprozin

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

Drug Name	Standard Value	Observed Value (Mean ± S.D.) (n = 3)
Oxaprozin	140℃	139 ± 1.38℃

Identification and Determination of Wavelength $_{Max}$ (λ_{max}) of Oxaprozin

Stock solution (1000µg/mL) of Oxaprozin in methanol was prepared. This solution was a diluted to obtain 100µg/mL solution. 5 mL of solution of Oxaprozin and volume was diluted to prepare 50µg/mL of Oxaprozin. This solution was scanned 200 - 400 nm against methanol.

The U.V spectrum of Oxaprozin was shown in figure 4.1. The resultant solution was scanned in the range of 200 to 400nm. The maximum absorbance was occurring at the 260 nm which

indicate the $\lambda_{max}$of Oxaprozin as shown in Table 4.9, which is partially similar to Oxaprozin λ_{max}as per I.P (260 nm).

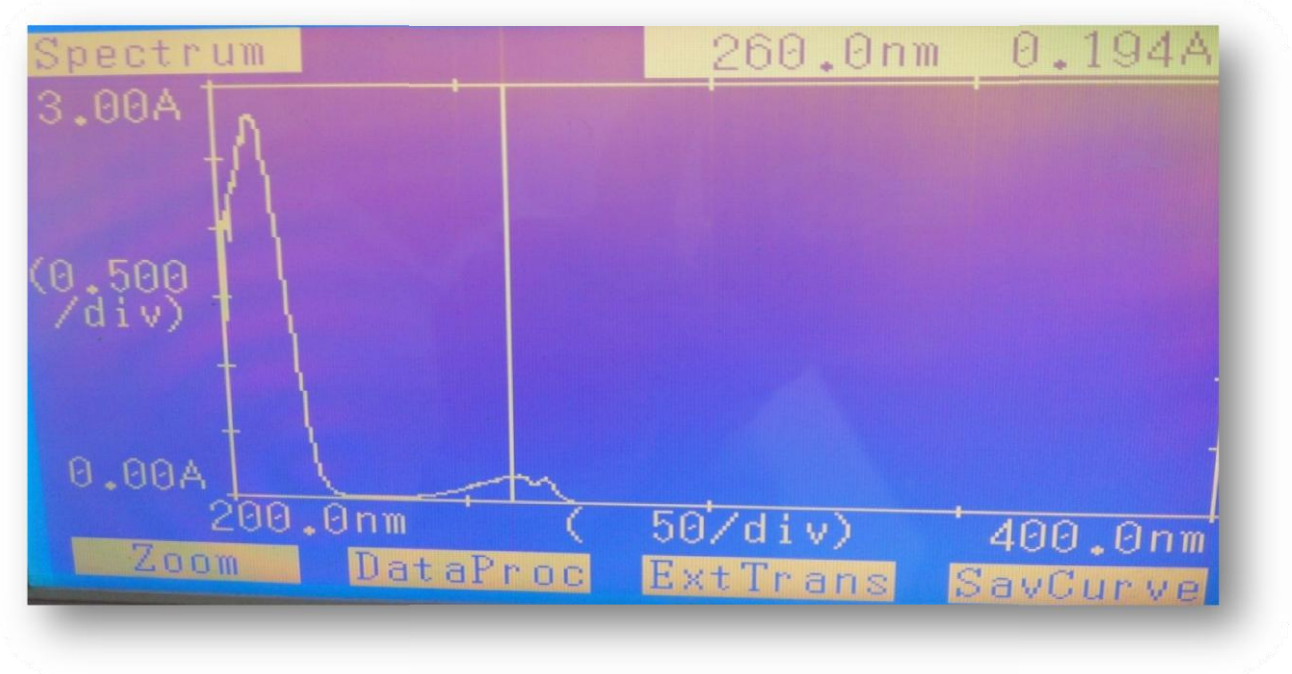


Figure 4.1: λmax Spectrum for Oxaprozin

Table 4.9: Wavelength$_{max}$ (λ_{max}) of Oxaprozin

Drug Name	Actual λ_{max}	Observed λ_{max}
Oxaprozin	260nm	261nm

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

Solubility study of Oxaprozin

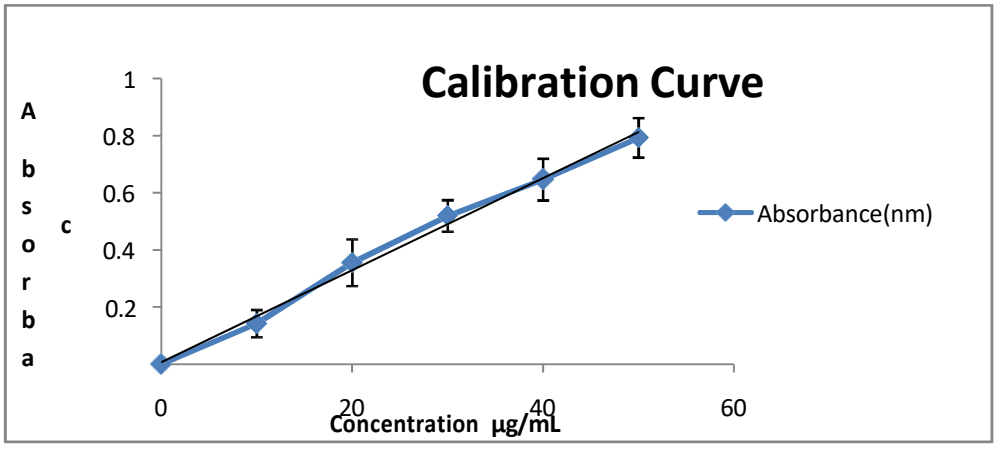
Table 4.10: Solubility of Oxaprozin

Solvent	Solubility
Water	Very Slightly soluble
Acetone	Freely Soluble
Methanol	Freely Soluble
Ethanol (95 %)	Freely Soluble
Chloroform	Slightly Soluble
MeOH (15%) + Phosphate buffer pH 7	Freely Soluble
0.1N HCl	Slightly soluble

Preparation of Calibration Curve for Oxaprozin

Table 4.11: Calibration curve of Oxaprozin

Sl. No.	Concentration (mcg/mL)	Absorbance(nm) (Mean ± S.D.) (n = 3)
1	0	0
2	10	0.142±0.48
3	20	0.355±0.82
4	30	0.519±0.55
5	40	0.646±0.73
6	50	0.792±0.69



International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

Figure 4.2: Oxaprozin Calibration curve

Table 4.12: Summery Report of calibration curve for Oxaprozin

Sl. No.	Parameters	Oxaprozin
1	**Wavelength (λmax)**	260
2	**Beer's limit (µg/mL)**	0-50
3	**Corrélation coefficient (R^2)**	0.994
4	**Slope**	0.016

The calibration curve for Oxaprozin was obtained by using the 0-50 µg/mL solution of Oxaprozin in methanol. The absorbance was measured at 260 nm. The calibration curve for Oxaprozin was shown in figure 4.2. The absorbance obtained for the given concentrations was shown in table 4.11. The calibration curve (Table 4.12) shows a regression equation Y= 0.0163x and R^2value 0.9940. The result revealed that the drug concentration between 0 – 50 µg/ml follows Beer Lambert's law as the regression coefficient was 0.9940.

Identification of Drug- Oxaprozin by FT-IR Spectroscopy

Potassium bromide IR disc was prepared using 1mg of Oxaprozin on Hydraulic Pellet press and scanned in region of 4000-400 cm^{-1} and obtained IR Spectrum was compared with a reference spectrum of Oxaprozin.

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

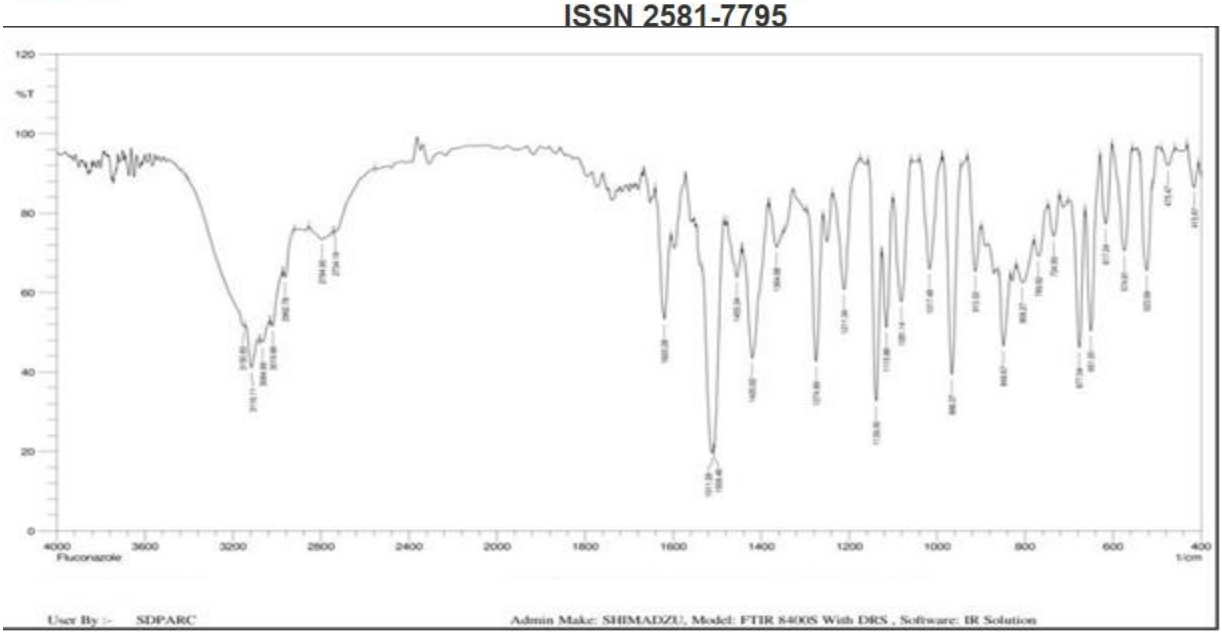


Figure 4.3:Identification of Oxaprozin by IR Spectrum Table 4.13:

Identification IR

Oxaprozin

Type of Vibration	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3116.11

Drug- Excipients Compatibility Studies by FT-IR

Drug- Oxaprozin IR Spectrum:

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

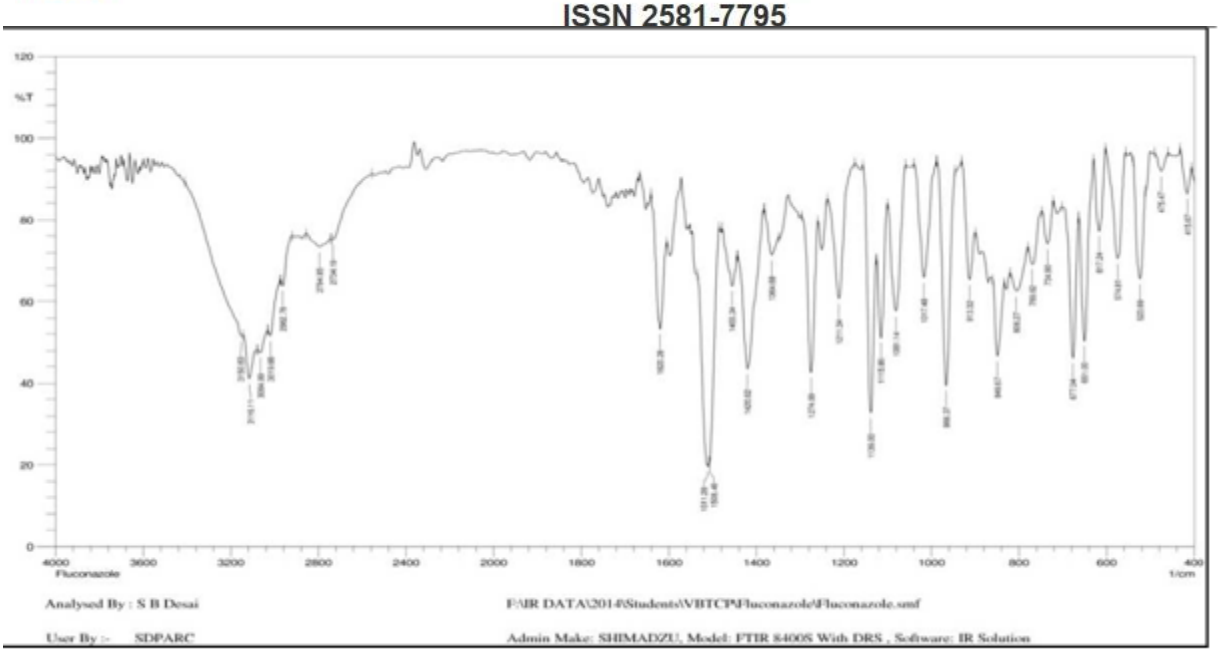


Figure 4.4: sample Drug Oxaprozin IR

Spectrum Table

4.14: Oxaprozin observed IR peaks

Type of Vibration	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3116.11

International Research Journal of Education and Technology
Peer Reviewed Journal
ISSN 2581-7795

Oxaprozin + Eudragit RS 100 IR Spectrum

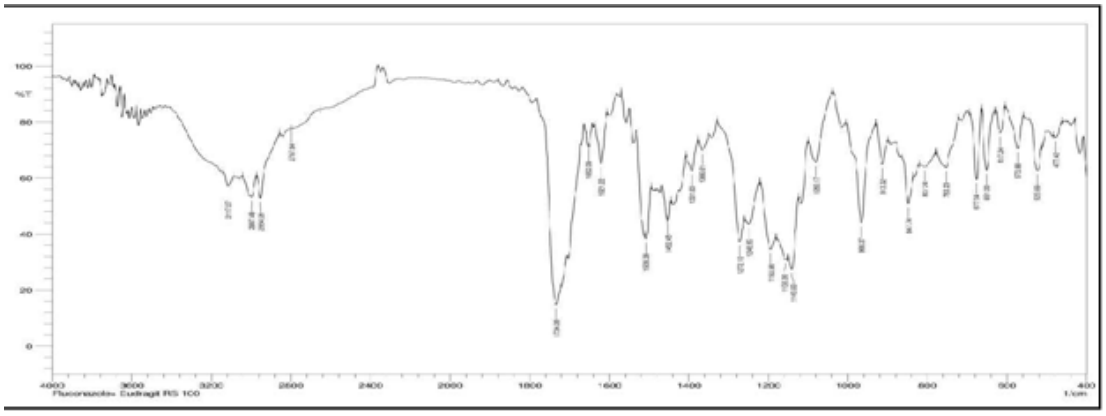


Figure 4.5: Oxaprozin and Eudragit RS 100 IR Spectrum

Table 4.15: FT-IR peaks of Oxaprozin and Eudragit RS 100 (mixture)

Type of Vibration	Observed Wave number (cm^{-1})	Peak obtained in mixture (cm^{-1})
C=N Stretching	1600-1700	1621.22
C-F Stretching	1000-1400	1140.93
C-H Stretching	3000-3100	3117.07
C=O Stretching	1690-1760	1734

Oxaprozin + Ethyl Cellulose IR Spectrum

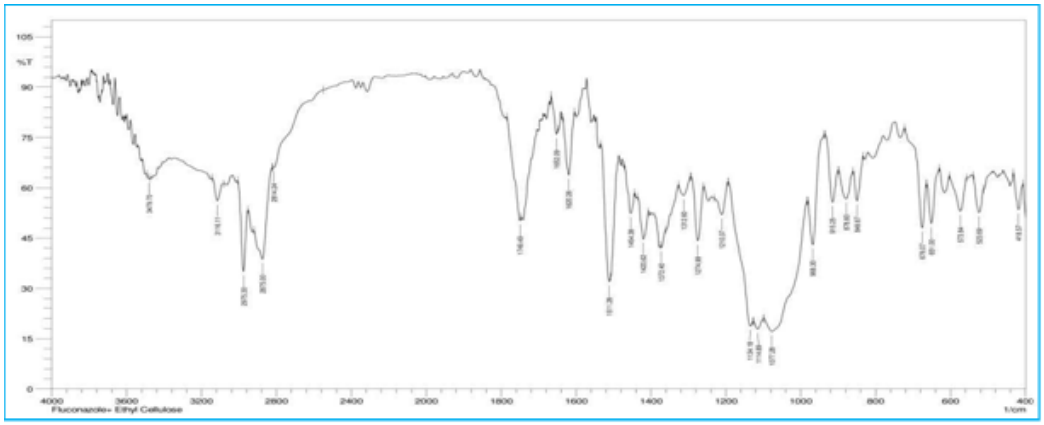


Figure 4.6: FT-IR Spectrum of Oxaprozin +Ethyl cellulose

BIBLIOGRAPHY :

1. B. Vijaya Kumar, Development and Evaluation of Guaifenesin Bilayer Tablet; International Journal of Pharmaceutical Sciences and Nanotechnology,oct-dec(2019) 3(3) 1122-1128.
2. Sonia Pandey, Formulation and In-vitro Evaluation of Bilayered Buccal Tablets of Carvedilol, Indian J.Pharm. Educ. Res. (2018) 44(3).
3. P. Dinesh Kumar, Formulation and characterizatioin of bilayer floating tablets of Ranitidine, Rasayan J.Chem., (2018) vol.3, no.2, 368-374.
4. R. Nagaraju, Formulation and Evaluation of Bilayer Sustained Release Tablets of Salbutamol and Theophylline International Journal of Pharmaceutical Sciences & Nanotechnology, (2018) Vol. 2 , 3.,638-646
5. Atram S.C., Formulation of bilayer tablet containing metoprolol succinate and amlodipine besylate as a model drug for antihypertensive therapy, Journal of Pharmacy Research (2018) 2(8), 1335-1347.
6. Ajit Kulkarni, Development and evaluation of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile, Iranian Journal of Pharmaceutical Research (2018) 8 (1): 15-25.
7. Bhavesh Shiyani, Formulation and Evaluation of Bi-layer Tablet of Metoclopramide Hydrochloride and IbuprofenAAPS PharmSciTech, (2017) Vol. 9, No. 3.818-827.
8. Chinam Niranjan Patra, design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, Acta Pharm. (2017) 57, 479–489
9. Vishnu M. Patel, Mucoadhesive Bilayer Tablets of Propranolol Hydrochloride, AAPS PharmSciTech (2016) 8 (3), 77.E1-E6.
10. Ziyaur Rahman, design and evaluation of bilayer floating tablets of captopril, acta pharm. (2016) 56, 49–57.
11. C. Narendra, Optimization of Bilayer Floating Tablet Containing Metoprolol Tartrate as a Model Drug for Gastric Retention, AAPS PharmSciTech. (2015) 7(2), 34.E1-E7.
12. F. Podczeck; The strength of bilayered tablets; European Journal of Pharmaceutical Sciences (2015) 29, 361–366.
13. Subas C. Dinda, Design and Evaluation of a Fixed Dose Combination Formulation of

Valsartan and Metformin Hcl for Biphasic Drug Release: a Novel approach to increase therapeutic efficacy; int j pharm sci tech (2014) vol-6, issue-1, 44-63.

14. Chuan-Yu Wu, A comparative study of compaction properties of binary and bilayer tablets, Powder Technology 189 (2014) 285–294.
15. Anil Chaudhary, Microporous bilayer osmotic tablet for colon-specific delivery; European Journal of Pharmaceutics and Biopharmaceutics (2011) 78,134–140.
16. Fridrun Podczeck, The tensile strength of bilayered tablets made from different grades of microcrystalline cellulose; European Journal of Pharmaceutical Sciences (2010) 41, 483– 488.
17. Girish S. Sonar, Preparation and in vitro evaluation of bilayer and fl oating-bioadhesive tablets of rosiglitazone maleateAsian Journal of Pharmaceutical Sciences (2007) 2 (4): 161-169.
18. Mukesh C. Gohel, Fabrication of Triple-Layer Matrix Tablets of Venlafaxine Hydrochloride Using Xanthan Gum, AAPS PharmSciTech, june (2011) Vol. 10, No. 2, 624-630.
19. MA Naeem, Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen; Tropical Journal of Pharmaceutical Research August (2011) 9 (4): 347-354.
20. B. Mallikarjuna Reddy, Determination of acetaminophen and methocarbamol in bilayered tablets using RP – HPLC, J Pharm Educ Res June (2010) Vol. 1, Issue No. 1, 71-74.
21. Dhruvita patel ,formulation & evaluation of bilayer tablet by using melt granulation techniques for treatment of Diabetes mellitus; journal of pharmacy & Bioallied sciences march (2012) supplement; S37-39.
22. Eduardo Pimenta, Fixed combinations in the management of hypertension: patient perspectives and rationale for development and utility of the olmesartan – amlodipine combination, Vascular Health and Risk Management (2008) 4(3) 653–664. Lawes, C. M. Hoorn, S. V., & Rodgers, A.Global burden of blood-pressurerelated disease, Lancet, (2008)371(9623). 1513-15.
23. Nahid Sharmin, Preparation and Characterization of Lidocaine Double Layer Buccal Tablet Using Mucoadhesive Carbopol Polymers, Dhaka Univ. J. Pharm. Sci. (2011) (June) ; 10(1): 29-34.
24. R. Natarajan, Formulation and Evaluation of Immediate Release Bilayer Tablets of Telmisartan and Hydrochlorothiazide;international journal of pharmaceutical sciences & nanaotechnology,.oct. (2011) (4) 3.455-464.
25. Sabahuddin Siddique, Development of Sustained Release Capsules Containing “Coated Matrix Granules of Metoprolol Tartrate, AAPS PharmSciTech, September (2010) Vol. 11, No. 3, 1306-1314.

26. Sathis Kumar Dinakaran, Formulation and evaluation of bi-layer floating tablets of ziprasidone HCl and trihexyphenidyl HCl; Brazilian Journal of Pharmaceutical Sciences jul./sep., (2011).vol. 47, n. 3, 21-29.
27. Sathis Kumar Dinakaran, Formulation and evaluation of bi-layer floating tablets of ziprasidone HCl and trihexyphenidyl HCl, Brazilian Journal of Pharmaceutical Sciences
    a. , July./sep., (2011) vol. 47(3) 545-555.
    b. Shiva Kumar Yellanki; Hydrodynamically balanced bilayer tablets of glycerol monooleate coated amoxicillin trihydrate: a novel approach to prolong the local action by gastric Retention, IntRJPharmSci. (2010) 01(01); 0038-0041