ECMC-P 2025 Conference
The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics
01–30 November 2025 | Online
Chaired by Prof. Dr. Maria Emília Sousa, Prof. Dr. Patrick J. Sinko and Dr. Alfredo Berzal-Herranz
pharmaceuticals pharmaceutics MDPI

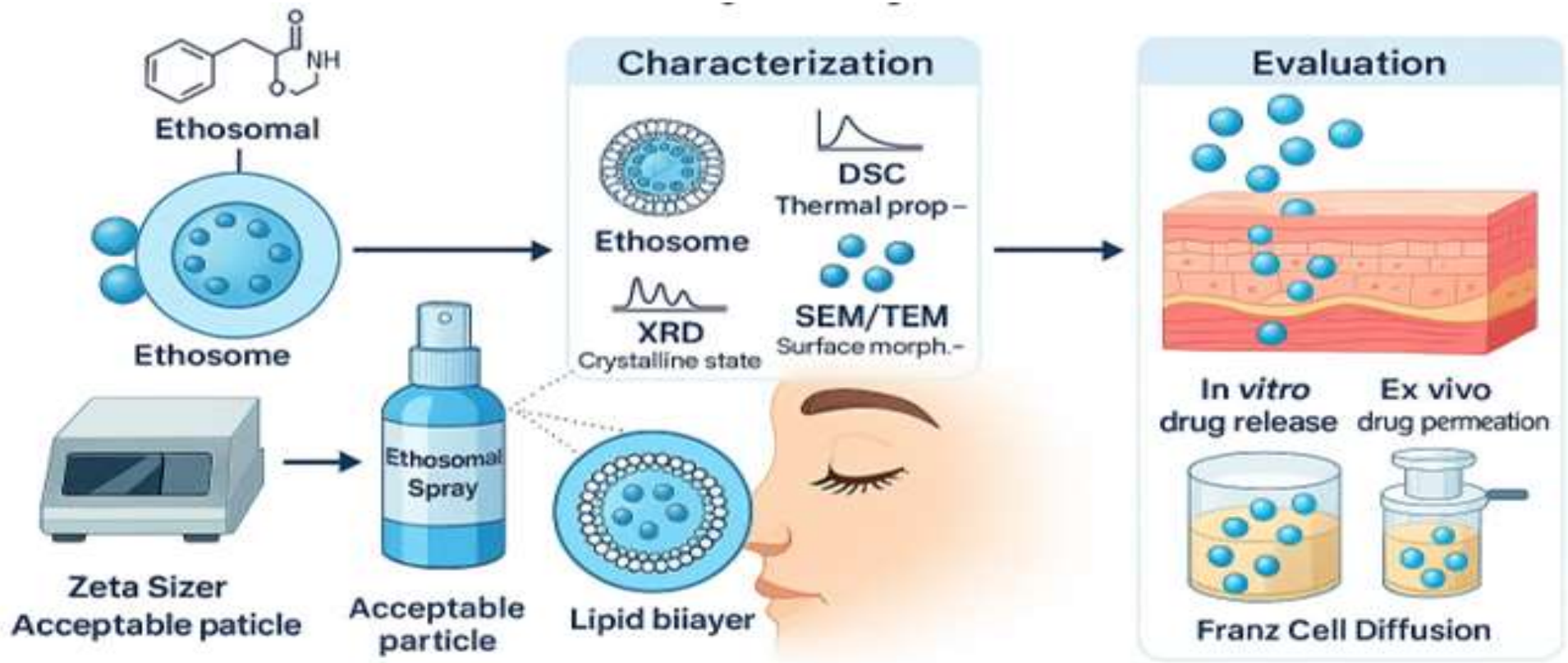
Rebamipide Loaded Ethosomes as a Potential Trans-Eyelid Delivery

Dina Kako[1,*], Mowafaq Ghareeb[2], and Mohammed Al-Iami[3]

[1] Lecturer of Pharmaceutics, University of Duhok, Kurdistan,Iraq.
[2] Department of pharmacy, College of pharmacy, University of Baghdad, Baghdad, Iraq.
[3] University of Basra, College of pharmacy, Basra, Iraq.

* Corresponding author: dina.kako@uod.ac

Rebamipide Loaded Ethosomes as a Potential Trans-Eyelid Delivery



ECMC-P 2025 Conference
The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics
01–30 November 2025 | Online
MDPI

Abstract: This study focused on developing a novel ethosome-based formulation of rebamipide for the trans-eyelid treatment of Dry Eye Disease (DED), a condition marked by tear film instability and ocular discomfort. Conventional eye drops often fail due to low bioavailability and frequent dosing. The optimized ethosomal system (E6) demonstrated favorable physicochemical properties, including a particle size of 242 ± 11.8 nm, PDI 0.221 ± 0.003, and high entrapment efficiency (94.5 ± 0.6%). Characterization by FTIR, DSC, and XRD confirmed the stability of rebamipide and its amorphous transformation, enhancing solubility. SEM and TEM analyses revealed smooth, spherical vesicles with uniform size distribution. The formulation remained stable for 180 days under refrigerated and ambient conditions. In vitro release showed a sustained, zero-order kinetic profile over 12 hours, while ex vivo permeation across eyelid skin achieved a flux of 0.4285 $mg \cdot cm^{-2} \cdot h^{-1}$ and a permeability coefficient of 0.1071 $cm \cdot h^{-1}$—approximately three times higher than the control. These results indicate superior penetration, controlled release, and prolonged drug retention compared with conventional topical delivery. The study concludes that ethosome-based trans-eyelid delivery of rebamipide offers a promising, patient-friendly strategy for DED management, potentially improving therapeutic outcomes and adherence. Further in vivo and clinical investigations are recommended to confirm its efficacy and safety.

Keywords: Rebamipide, Ethosomes, Transe-eyelids, Dry Eye Diseases, *Ex vivo*.

Introduction

Ocular drug delivery

- Focuses on administering medications to treat eye diseases
- It faces significant challenges

Dry Eye Diseases

- A multifactorial disease characterized by an unstable tear film.
- Categorized into evaporative dry eye and aqueous tear deficiency (ATD)

Tear Film

- The tear film comprises three layers: aqueous, lipid, and mucin layer.
- The lacrimal glands produce the aqueous component, Lipids from the meibomian glands, and mucins from conjunctival goblet cells

Nanocarriers

- Nanocarriers are classified diversely and show promise in pharmaceutical sciences
- Including micelles, nanosuspensions, nanoemulsions, nanoparticles, dendrimers, cubosomes, and nanowafers,

Vesicular system

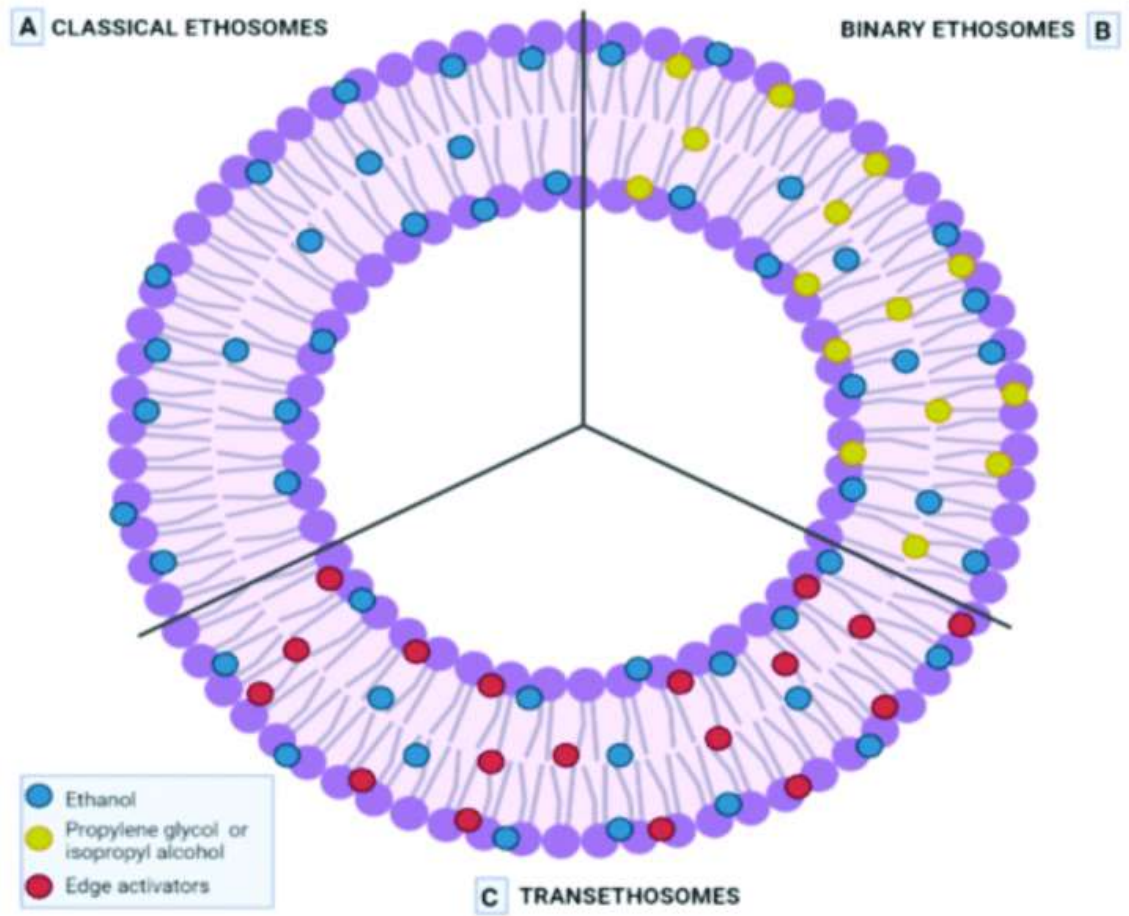
- Categorized based on their composition into non-lipid-based vesicular systems (niosomes) and lipid based vesicular systems (liposomes, ethosomes)

Ethosomes

- Ethosomes are a novel type of lipid-based drug delivery system that consists of either single-layered or multiple-layered vesicles made up mostly of phospholipids, polar lipids, and a significant amount of ethanol (20-45%)

Ethosomes

- Ethosomes are a novel type of lipid-based drug delivery system that consists of either single-layered or multiple-layered vesicles made up mostly of phospholipids, polar lipids, and a significant amount of ethanol (20-45%)



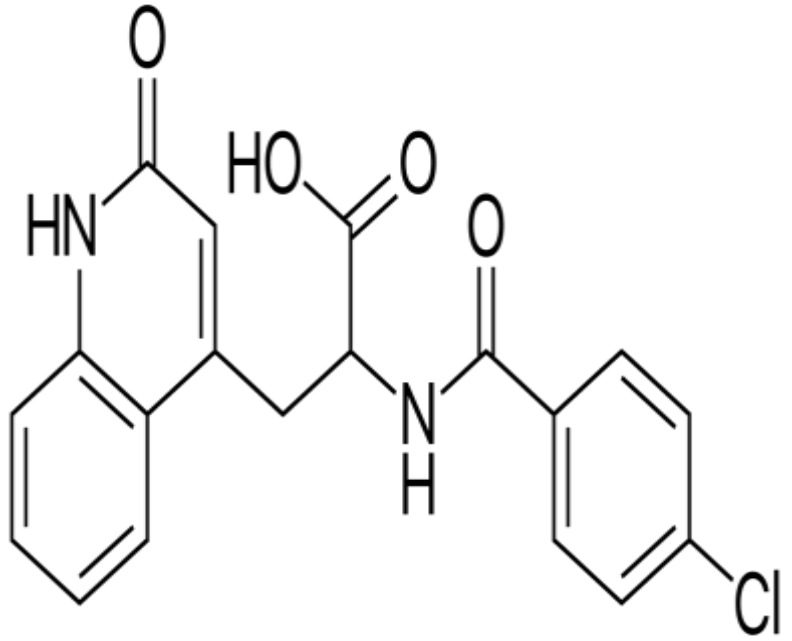
Classical, Binary, Transethosomes

Rebamipide

- Rebamipide, is an amino acid derivative, is used in the treatment of dry eye disease (DED), present in the market as eye drop suspension.

- It is classified as a class IV compound in the BCS.

- It is a pH dependent soluble drug.



Aim of the study

Development and evaluation of nanocarrier as a novel drug delivery system such as (ethosomes) for the ophthalmic delivery of rebamipide across the eyelid (trans-eyelid).

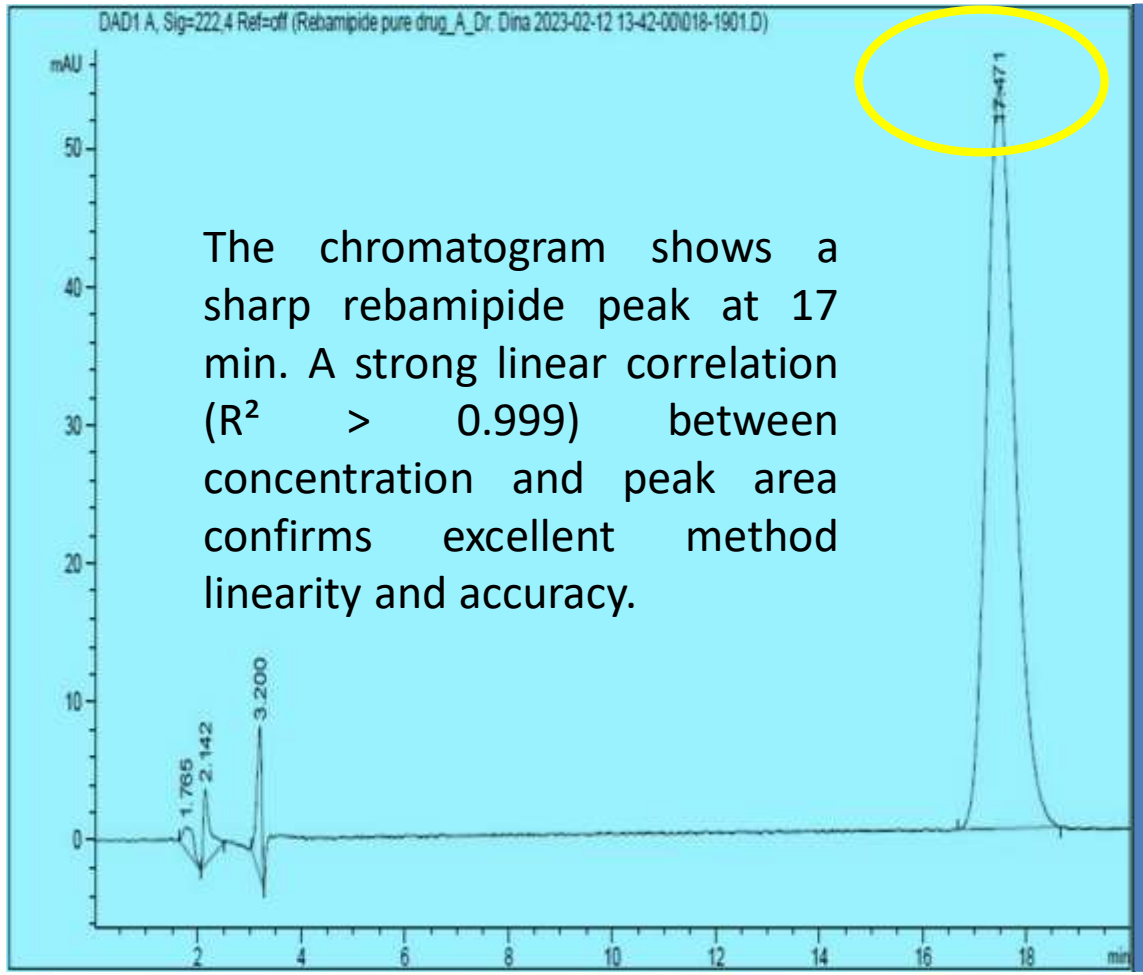
Improving the stability, encapsulation efficiency, drug release profile, and trans-eyelids permeation of rebamipide, for enhanced therapeutic efficacy in the treatment of the dry eye.

Improve patient compliance from conventional dosage form.

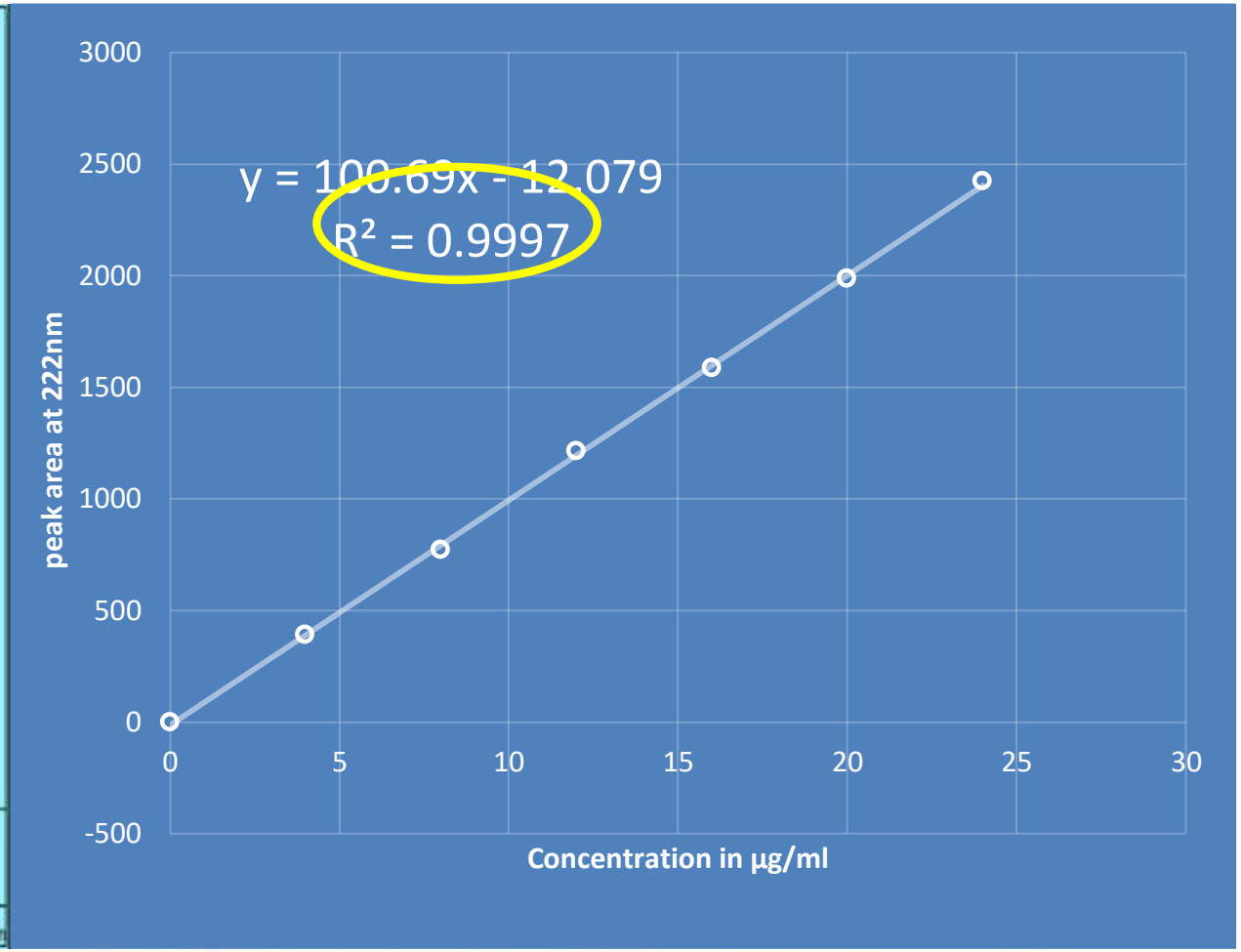
Results and Discussion

Characterization of rebamipide

Calibration curve of rebamipide



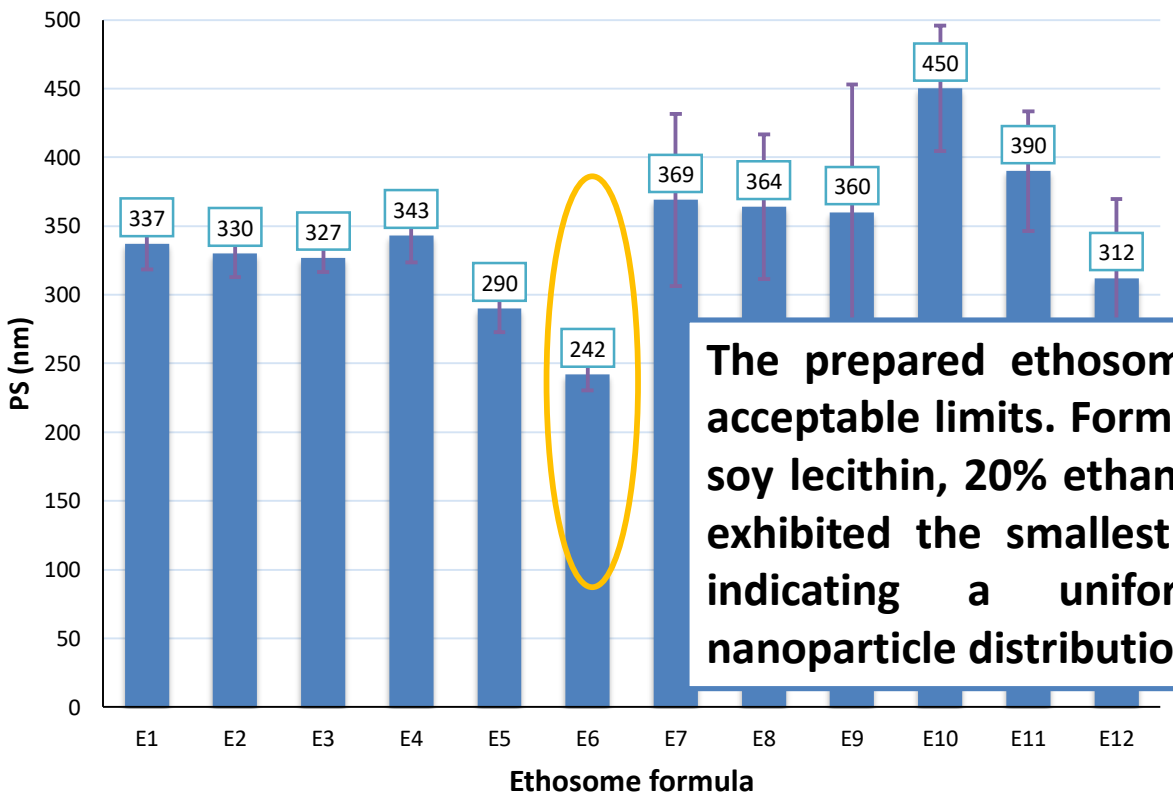
The chromatogram shows a sharp rebamipide peak at 17 min. A strong linear correlation (R^2 > 0.999) between concentration and peak area confirms excellent method linearity and accuracy.

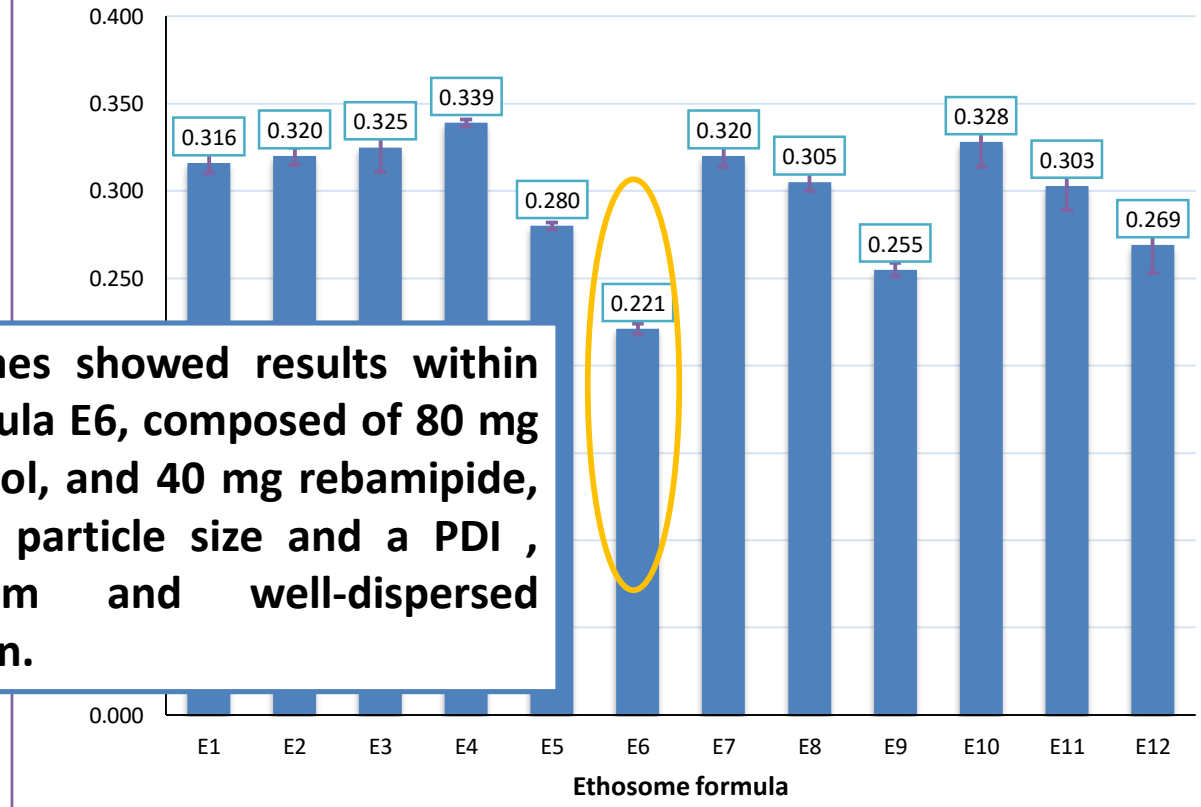


Results and Discussions

Selection of best formula

Particle size and PDI of ethosomes



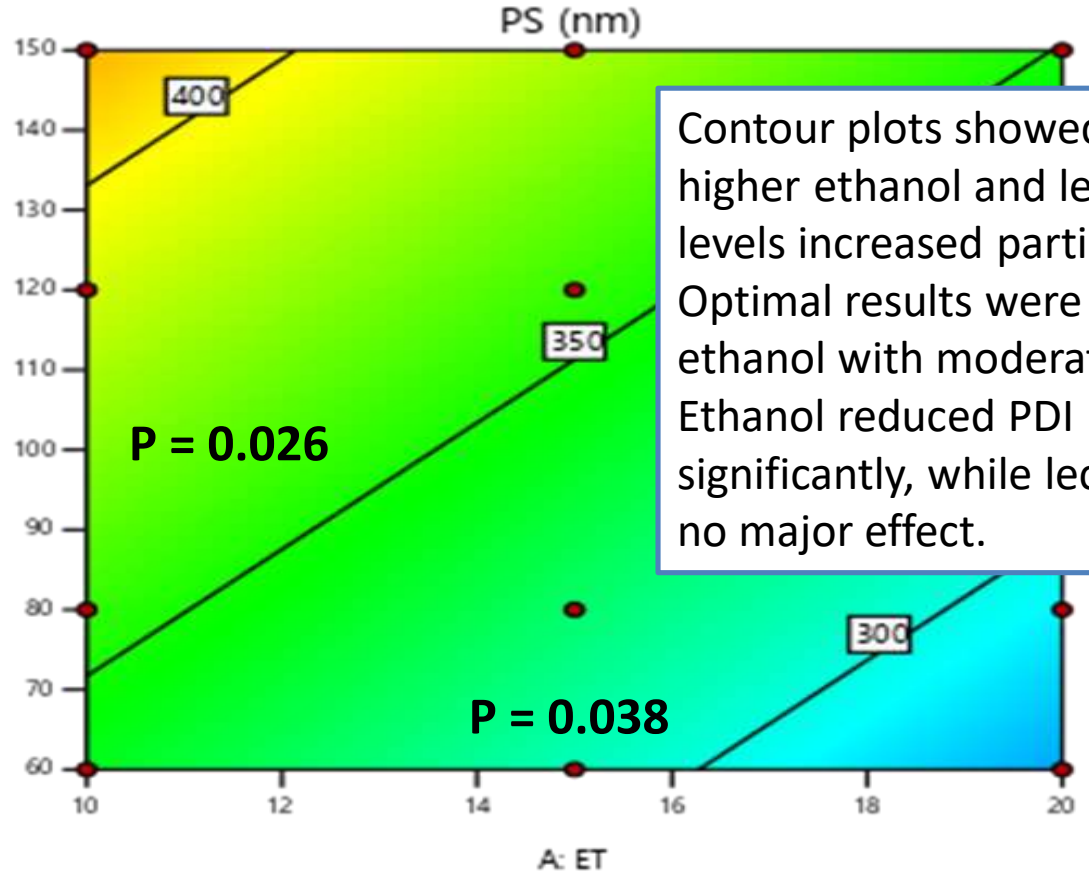


The prepared ethosomes showed results within acceptable limits. Formula E6, composed of 80 mg soy lecithin, 20% ethanol, and 40 mg rebamipide, exhibited the smallest particle size and a PDI , indicating a uniform and well-dispersed nanoparticle distribution.

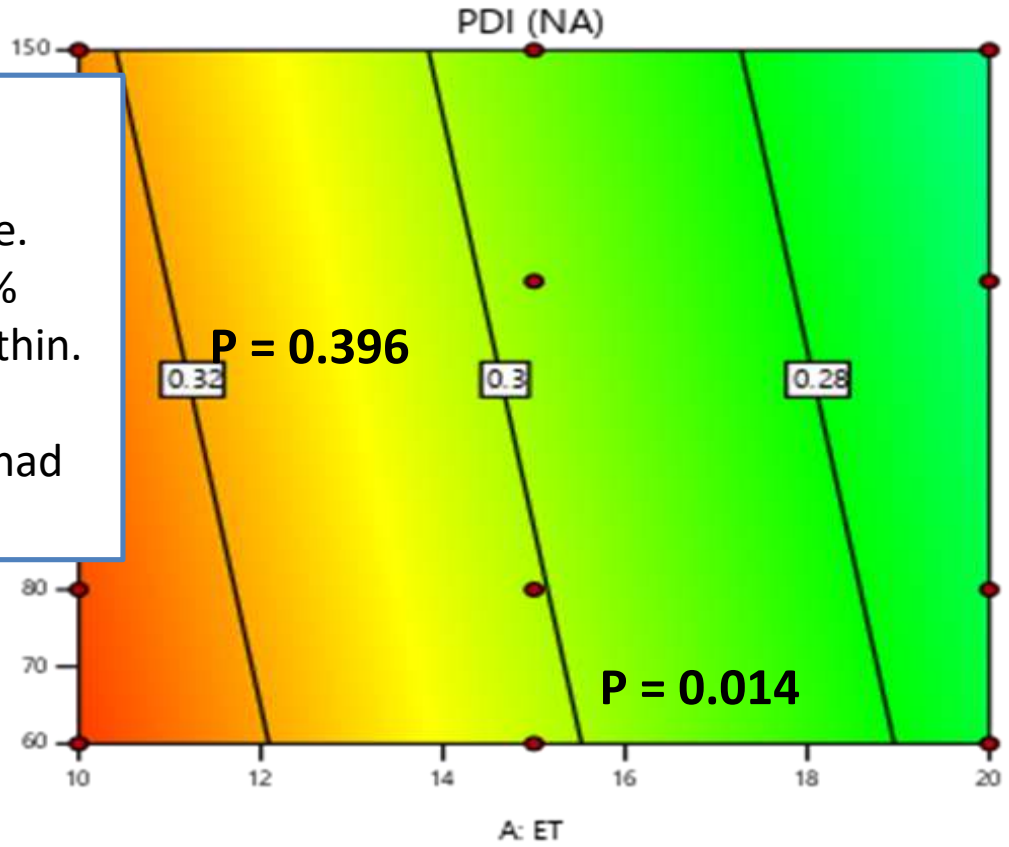
Results and Discussions

Selection of best formula

Contour plot of particle size and PDI of 12 formula of ethosomes



Contour plots showed that higher ethanol and lecithin levels increased particle size. Optimal results were at 20% ethanol with moderate lecithin. Ethanol reduced PDI significantly, while lecithin had no major effect.

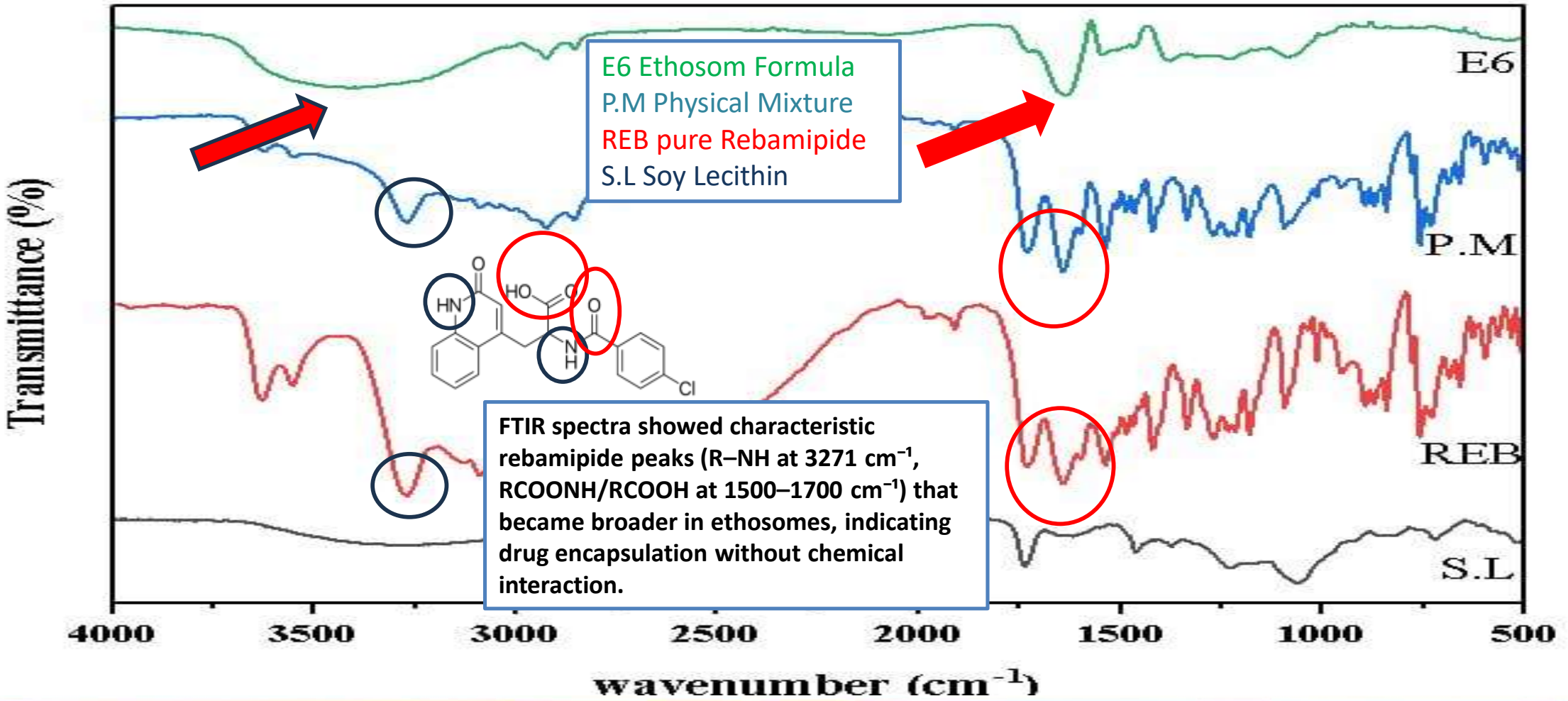


Results and Discussions

Selection of best formula

Formula No.	Ethanol %	Soy Lecithin mg	Rebamipide mg
E1	10	60	40
E2	15	60	40
E3	20	60	40
E4	10	80	40
E5	15	80	40
E6	20	80	40
E7	10	120	40
E8	15	120	40
E9	20	120	40
E10	10	150	40
E11	15	150	40
E12	20	150	40

Characterization of optimum formula and its biocompatibility

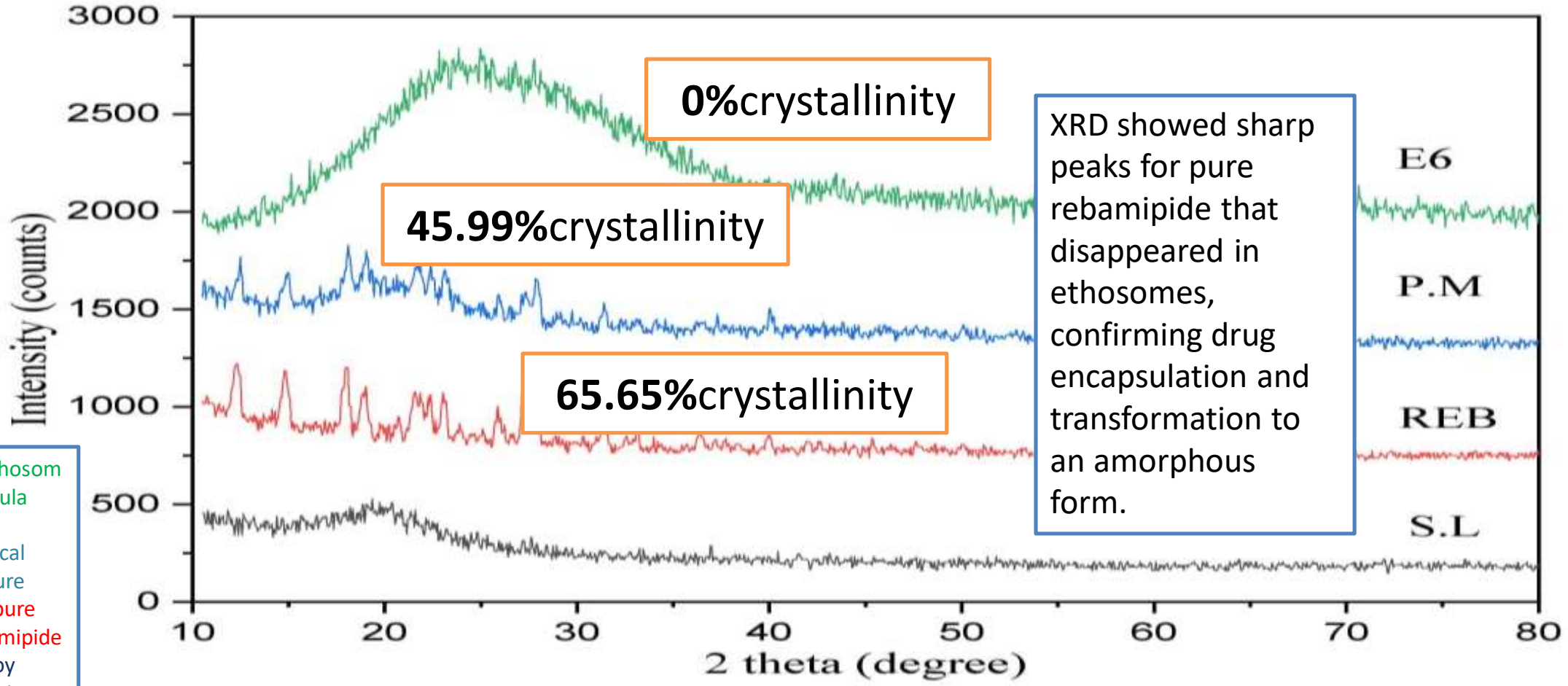


FTIR spectra showed characteristic rebamipide peaks (R–NH at 3271 cm^{-1}, RCOONH/RCOOH at 1500–1700 cm^{-1}) that became broader in ethosomes, indicating drug encapsulation without chemical interaction.

Results and Discussions

Fourier transform infrared spectroscopy FTIR

Characterization of optimum formula and its biocompatibility



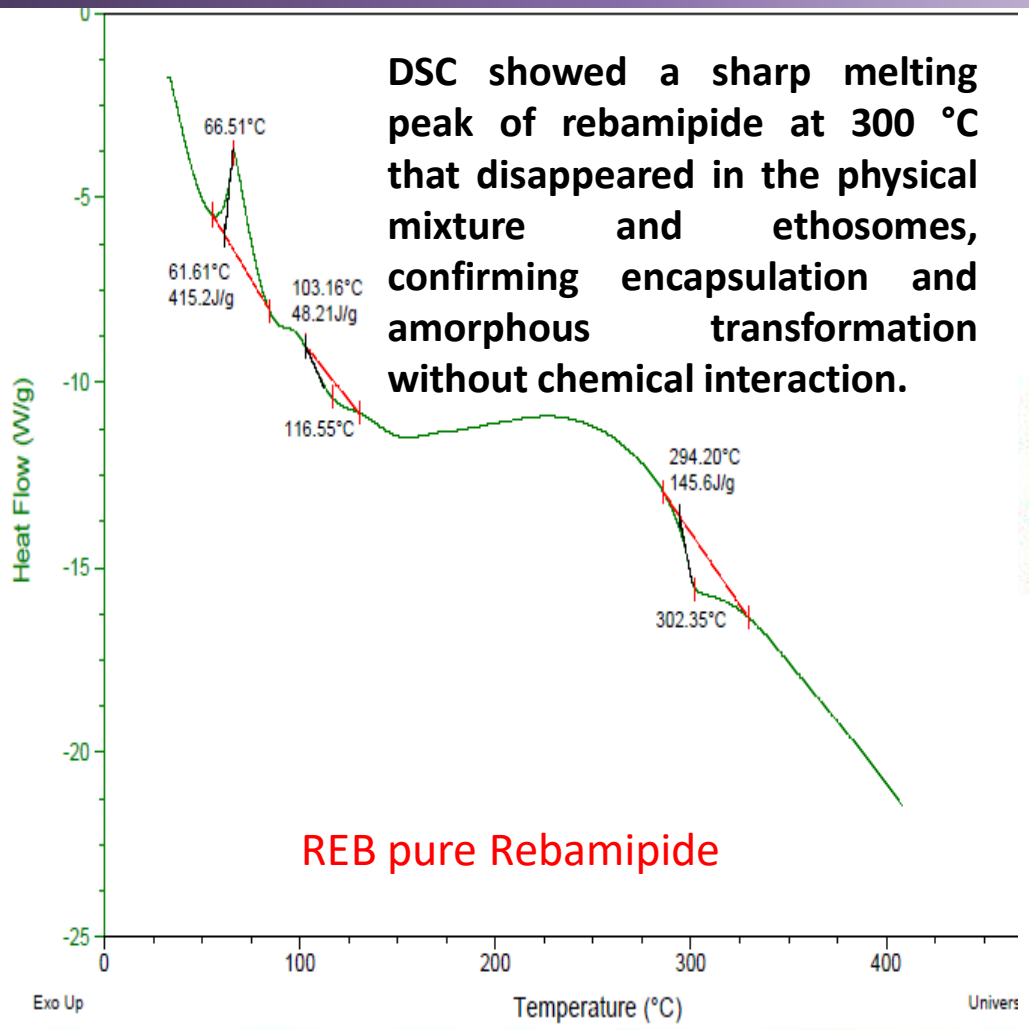
XRD showed sharp peaks for pure rebamipide that disappeared in ethosomes, confirming drug encapsulation and transformation to an amorphous form.

Results and Discussions

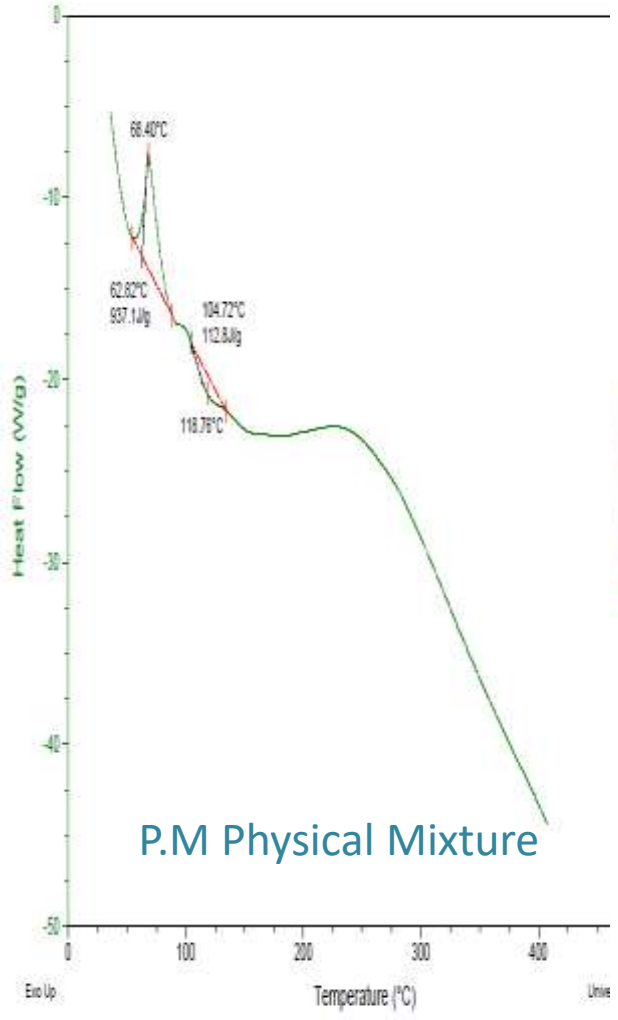
X-Ray diffraction study XRD

Characterization of optimum formula and its biocompatibility

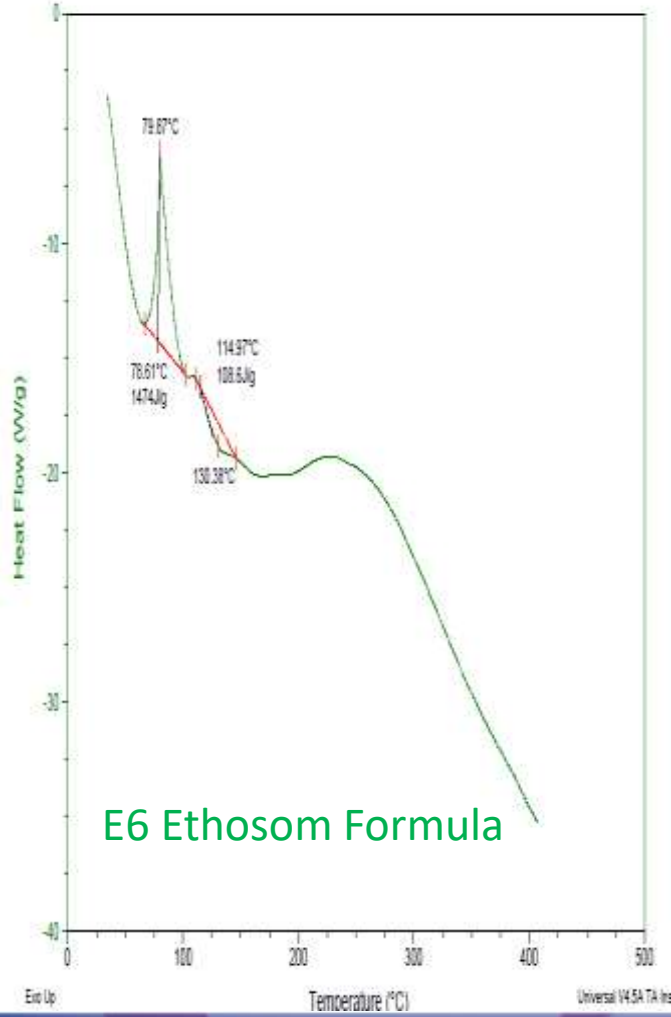
DSC showed a sharp melting peak of rebamipide at 300 °C that disappeared in the physical mixture and ethosomes, confirming encapsulation and amorphous transformation without chemical interaction.



REB pure Rebamipide



P.M Physical Mixture



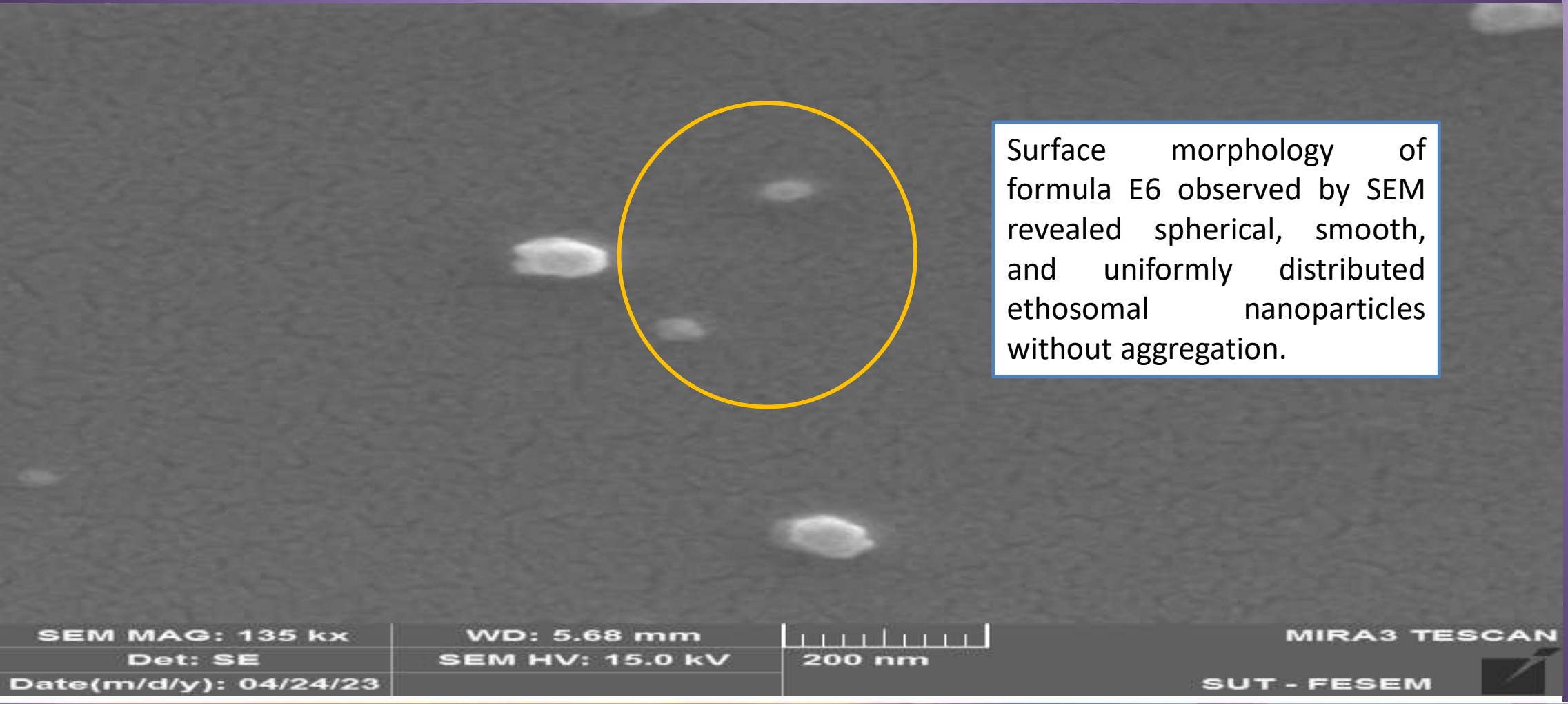
E6 Ethosom Formula

Results and Discussions

Differential scanning calorimetry

DSC

Vesicle morphology

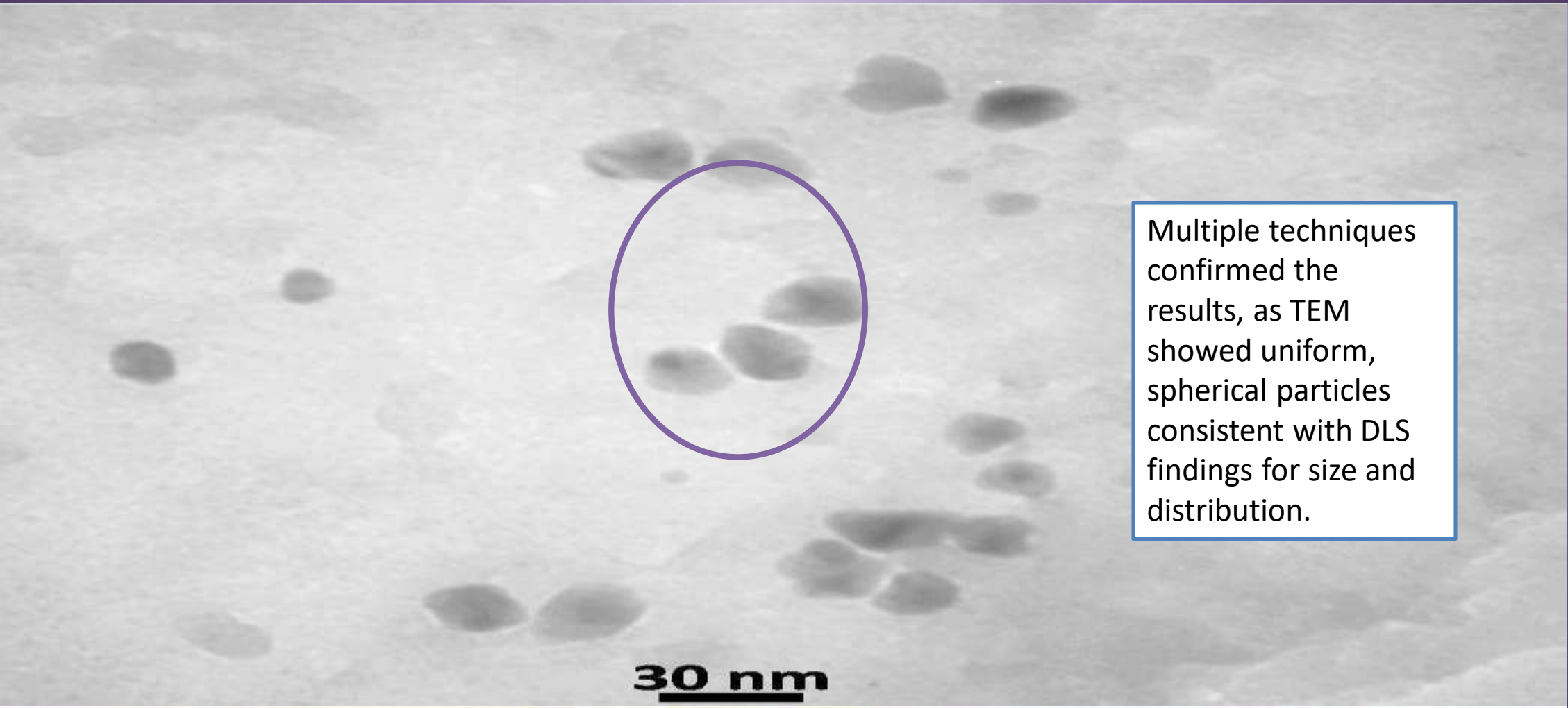


Surface morphology of formula E6 observed by SEM revealed spherical, smooth, and uniformly distributed ethosomal nanoparticles without aggregation.

Scanning electron microscope study SEM

Results and Discussions

Vesicle morphology



Multiple techniques confirmed the results, as TEM showed uniform, spherical particles consistent with DLS findings for size and distribution.

Transmission electron microscope study
TEM

Results and Discussions

Results and Discussions

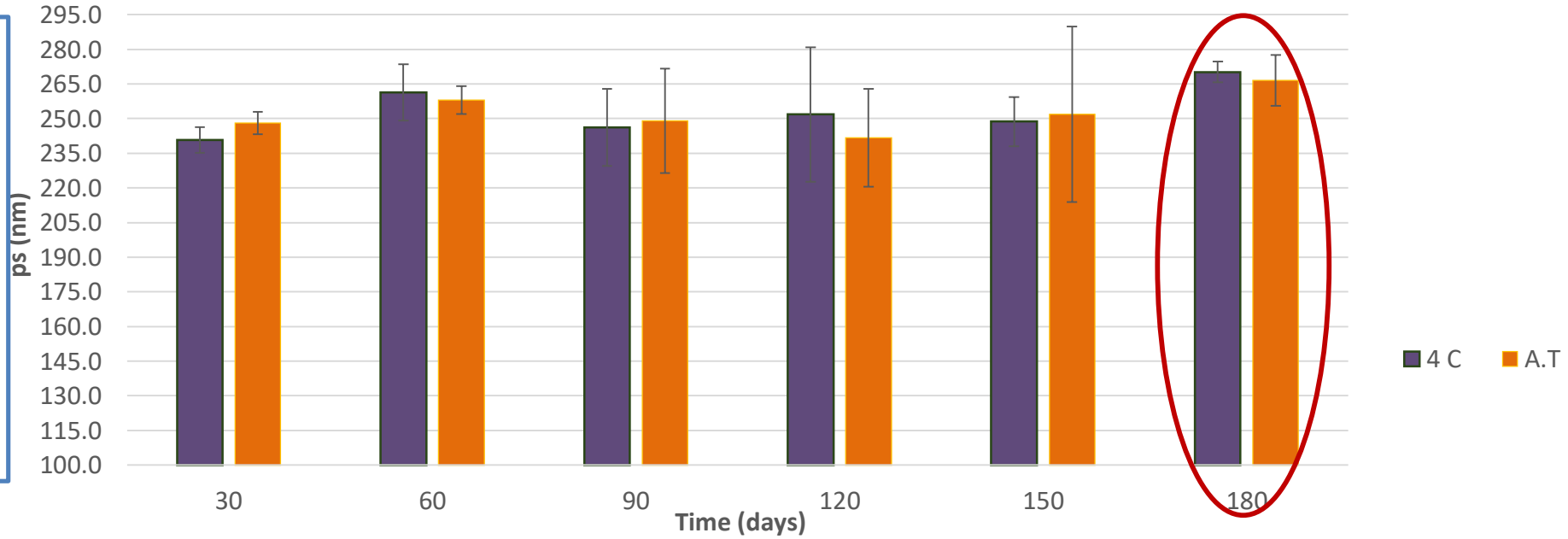
Drug content and Entrapment Efficiency

Formula	Entrapment efficiency %EE ± SD	Drug content % ± SD
Rebamipide ethosomes (E6) (n=6)	94.5 ± 0.6	90.5 ± 8

Stability study

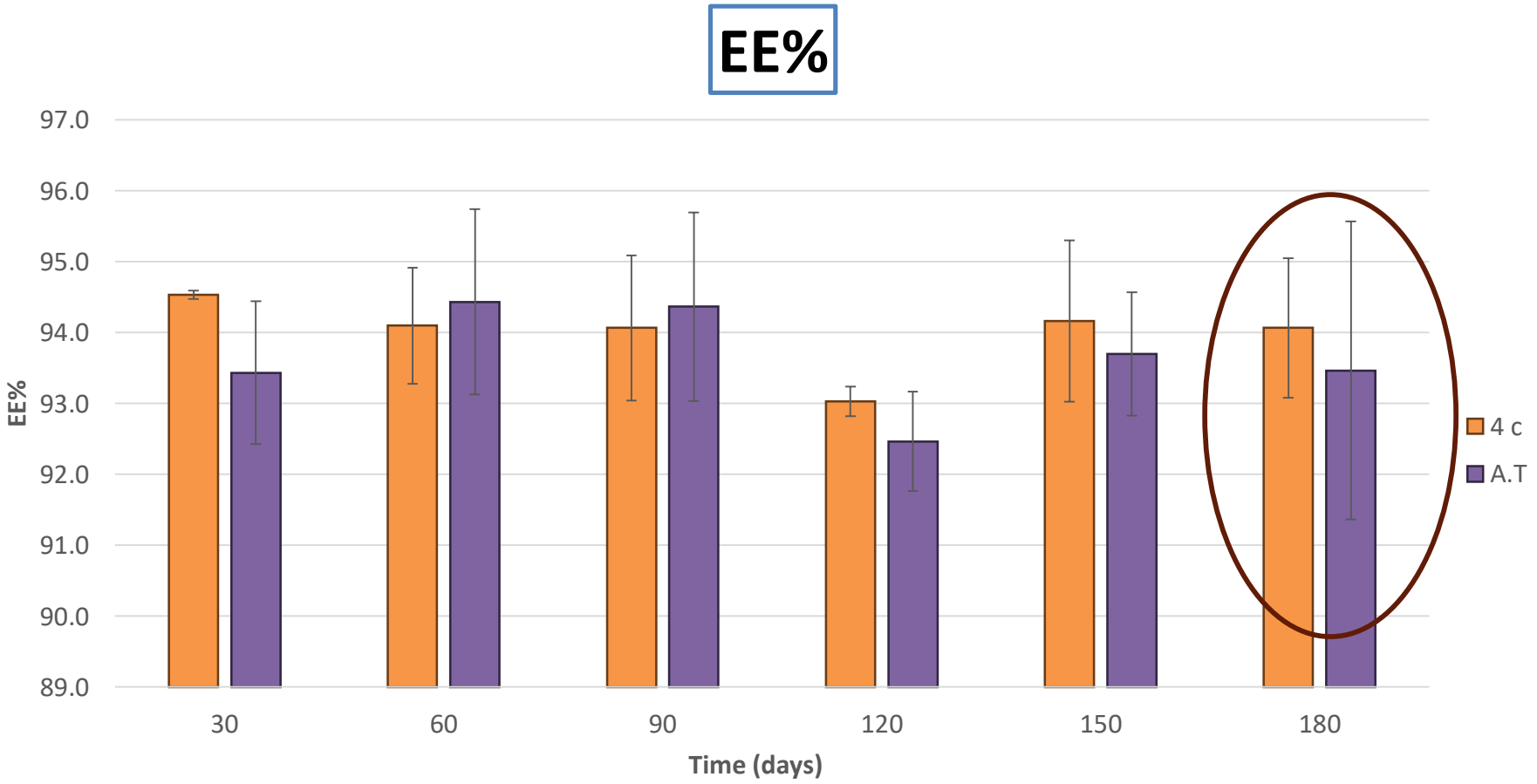
Particle size

After 180 days of storage at 4°C and ambient temperature, particle size, EE, and drug content remained stable with no significant physical changes.



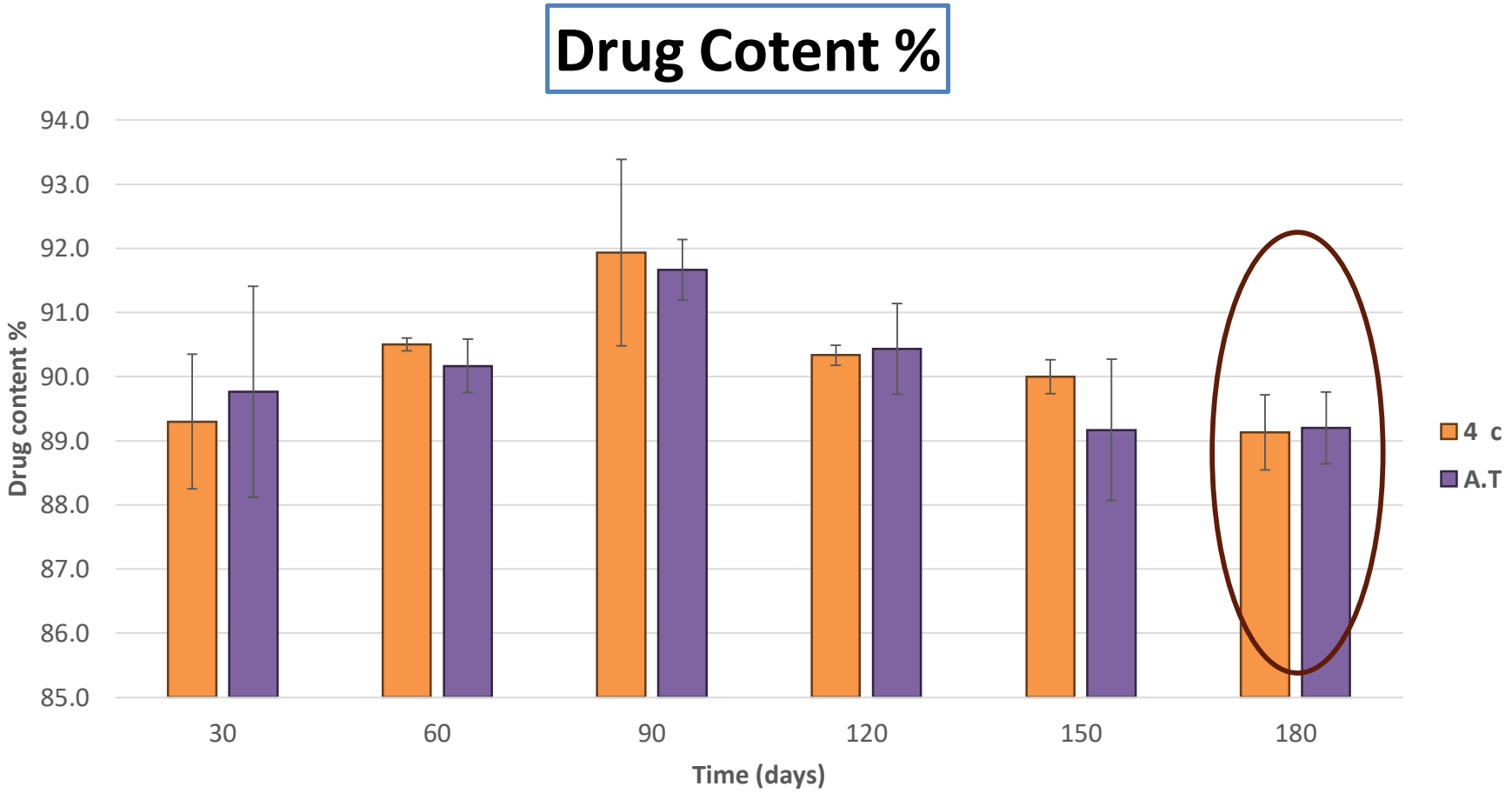
Stability study

Similarly, the entrapment efficiency (EE%) remained above 90% throughout the 6-month storage period, indicating excellent formulation stability and minimal drug leakage over time.



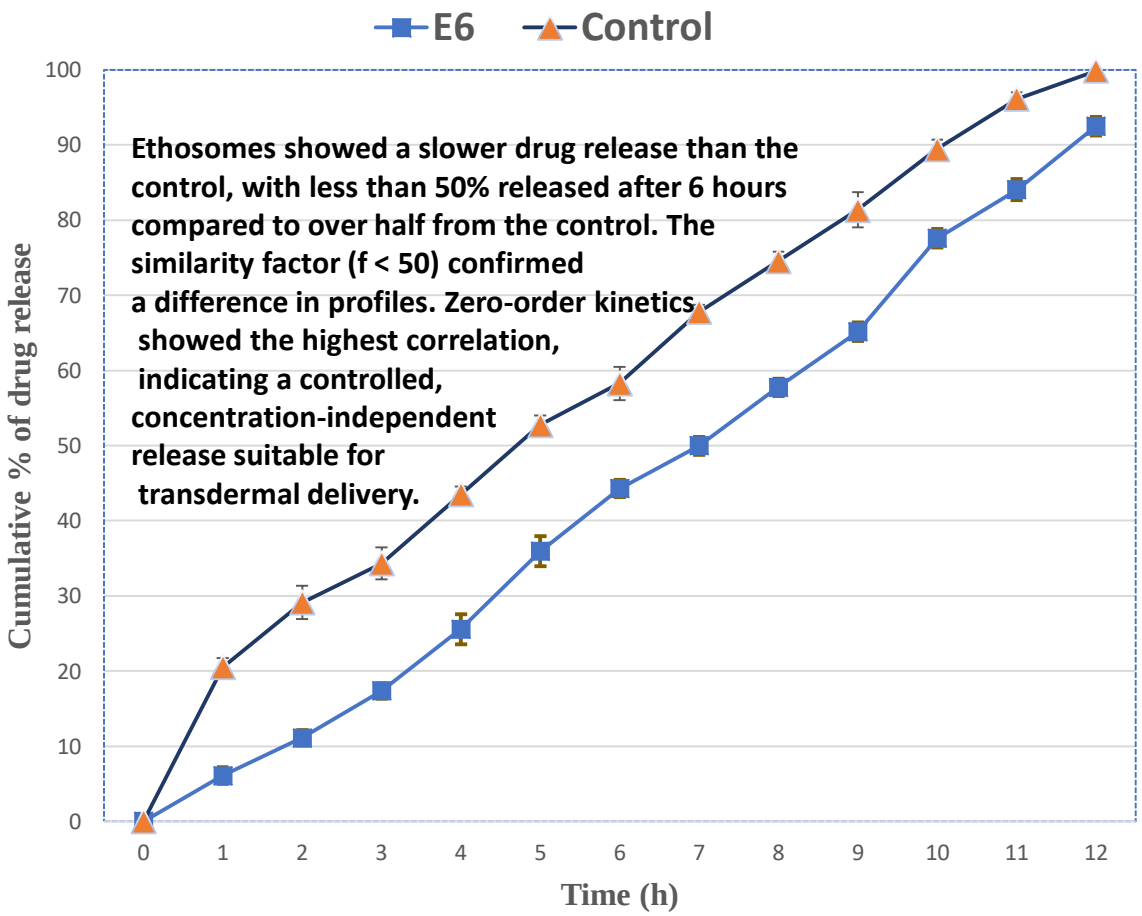
Stability study

The drug content remained consistent with the initial value, confirming the formula's stability for 6 months (180 days).



Results and Discussions

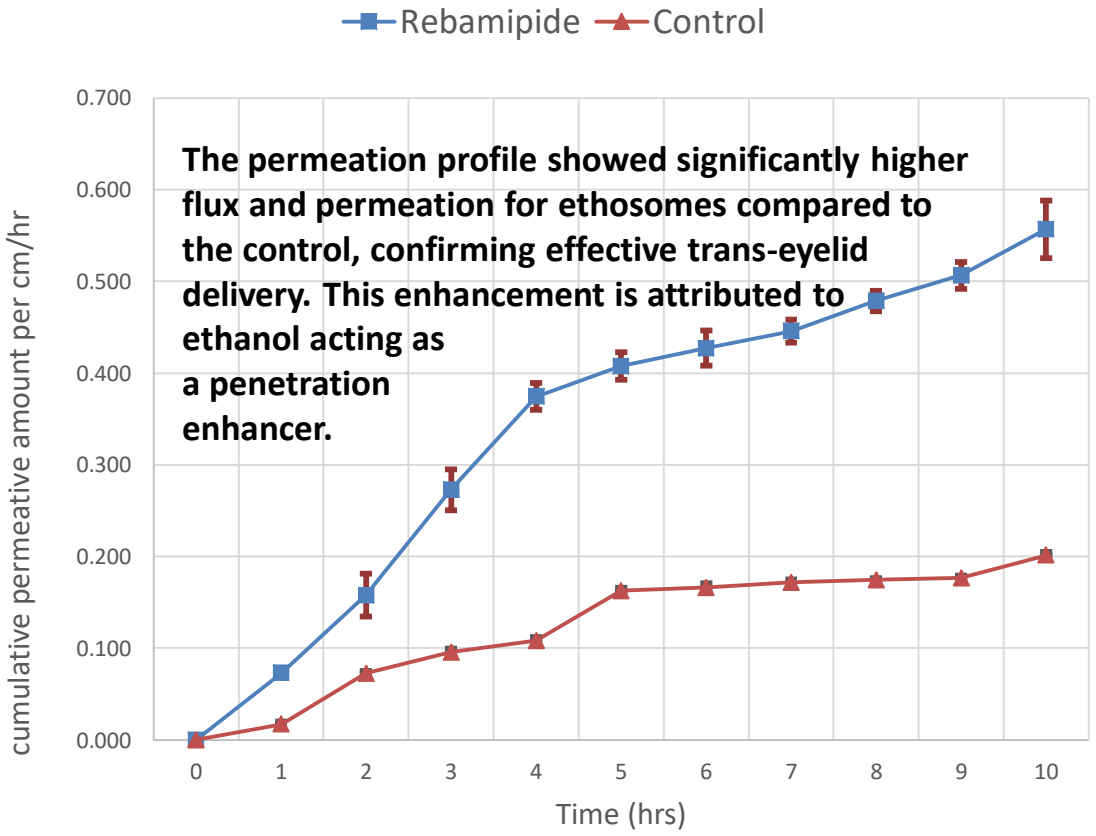
In vitro drug release and Release Kinetics



Formula	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixon - Crowell
E6	0.9966	0.8748	0.9623	0.9956	0.9941
Control	0.9969	0.6599	0.9818	0.9871	0.9847

(n=3) and results expressed as mean ± SD.

Ex vivo permeation study and it is parameters



The permeation profile showed significantly higher flux and permeation for ethosomes compared to the control, confirming effective trans-eyelid delivery. This enhancement is attributed to ethanol acting as a penetration enhancer.

Formula	J ($mg.cm^{-1}.h^{-1}$)	P ($cm.h^{-1}$)	% Permeation of drug after 10h
E6	0.4285 ± 0.0104	0. 1071 ± 0.0026	68,09 ± 3.1
Control	0.1610 ± 0.0088	0.0403 ± 0.0022	23,18 ± 0.22

(n=3) and results expressed as mean ± SD.

Conclusions

- Developed rebamipide-loaded ethosomes for ophthalmic drug delivery.
- High entrapment efficiency: 94.5 ± 0.6%.
- Stable drug content over 180 days under various storage conditions.
- Exhibited controlled, sustained drug release in vitro.
- Ex vivo permeation study showed 3x improved skin permeation compared to control.
- Ethosomes penetrate deeper skin layers, supporting sustained drug delivery.
- Promising delivery system for optimizing ocular drug delivery and treating dry eye syndrome.

Acknowledgments

I gratefully acknowledge the University of Duhok, College of Pharmacy, for research support