RESEARCH ARTICLE

Preformulation Studies of Bergenin: A Primary Step in Future Designing of Novel Drug Delivery System

Urvashi Sharma*, Sanjay Jain

Faculty of Pharmacy, Medi-Caps University, Rau, Indore, Madhya Pradesh, 453331, India

Received: 16th Jan, 2025; Revised: 2nd Feb, 2025; Accepted: 30th Apr, 2025; Available Online: 25th Jun, 2025

ABSTRACT

Preformulation studies are an essential stage in drug development, focused on elucidating the physicochemical and pharmacokinetic characteristics of a drug candidate to inform formulation design. Bergenin, a naturally occurring C-glucoside derivative of gallic acid, demonstrates a diverse array of pharmacological properties, encompassing anti-inflammatory, hepatoprotective, antiviral, and antidiabetic effects. Nonetheless, the effective incorporation of bergenin into an appropriate drug delivery system requires an extensive preformulation analysis. This research work was done with an objective to investigate the preformulation assessment of bergenin to evaluate its solubility in different solvents, compatibility, and crystallinity. The structural elucidation was done using FTIR spectroscopy and the X-ray diffraction (XRD) analysis validated the crystalline characteristics of bergenin, indicating a possible requirement for amorphization or particle size reduction methods to improve dissolving rates. Compatibility studies of drugs and excipients utilizing Fourier-transform infrared spectroscopy (FTIR) determined appropriate excipients for stable formulation. The results underscore significant problems, including inadequate solubility and crystallinity, that necessitate resolution via sophisticated formulation techniques such as solid dispersions or nanoencapsulation.

Keywords: Preformulation, Bergenin, Solubility, Crystallinity

How to cite this article: Urvashi Sharma, Sanjay Jain. Preformulation Studies of Bergenin: A Primary Step in Future Designing of Novel Drug Delivery System. International Journal of Drug Delivery Technology. 2025;15(2): 439-43. doi:10.25258/ijddt.15.2.9

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The primary approach towards the successful development of any dosage form is preformulation studies. Preformulation serves as the interface between a novel drug entity and the creation of its formulation, therefore it is an exclusive study offering a comprehensive roadmap for successful drug formulation development. It involves the physicochemical characterization of drug alone or by combining it with excipients, so as to ensure the compatibility, safety, efficacy and stability of formulated dosage form.[1] The preformulation studies generates critical data regarding the physical, chemical, biological, and mechanical characteristics of pharmaceuticals and excipients of any formulated dosage form, as well as their impact on the manufacturing process, packaging and storage. It also has a huge impact on formulation process and pharmacokinetic profiling of the resultant dosage form. Hence is a crucial step of drug developmental process from where one can easily derive the stability, storage conditions, half and shelf life of all marketed goods.[2]

Preformulation investigations commences subsequent to the completion of pre-clinical and clinical research. The early phase drug product development involves the characterization of the drug and provides insight about the properties and behavior of lead molecules. It represents the effective tool for research and development team which conducts the tests for gathering all the necessary information of active pharmaceutical ingredients (API). These collected physicochemical factors and biopharmaceutical principles are further employed for design and development of suitable drug delivery systems. The validation of the interaction between drug molecules and excipients is thoroughly examined at the preformulation stage, providing insights about their interactions and adduct formulation, facilitating the wise selection of drug molecules and excipients before formulation.[3]

Bergenin, a naturally occurring isocoumarin, is a secondary metabolite primarily derived from multiple species of the *Bergenia* genus and other medicinal flora. This bioactive molecule has garnered significant interest owing to its various pharmacological properties, such as anti-inflammatory, antiproliferative, hepatoprotective, antioxidant, antidiabetic, and antibacterial activity.[4] Its diverse therapeutic potential has established it as a promising candidate for drug formulation development. But despite the numerous pharmacological characteristics, the clinical advancement of bergenin is impeded by its limited bioavailability and solubility. Addressing these problems necessitates comprehensive investigations into its molecular mechanisms of action and the formulating the novel delivery technologies to improve its therapeutic efficacy. This study seeks to investigate the anticancer properties of bergenin, focusing on its cellular and molecular mechanisms, and to assess its potential for drug development.[5]

**Author for Correspondence: urvashi.ekta12@gmail.com*

Table 1: Organoleptic Characteristics of Bergenin

S.No.	Organoleptic Characteristics	Inference
1.	Color	White
2.	Odor	Odorless
3.	Physical state	Crystalline Solid
4.	Appearance	White colored powder

Table 2: Organoleptic Characteristics of Bergenin

S.No.	Melting Point	Average
1.	238.4°C	238.4°C
2.	238.4°C	
3.	238.3°C	

The present research focuses on preformulation studies of bergenin to address the solubility issues and to offer insights for its prospective pharmaceutical applications. Focus is directed towards examining the compound's compatibility with diverse excipients, its crystalline characteristics, and solubility profile, all of which are critical for the successful formulation of an effective dosage form.

MATERIAL AND METHODS

For this study, the phytocompound bergenin was chosen as drug, which was procured from Yucca Enterprises, Mumbai, India. All other ingredients and solvents, were obtained from Sigma-Aldrich and Research lab Fine Chem Industries.

Organoleptic Characterization

The organoleptic properties of Bergenin such as physical state, color, odor and appearance were examined visually.[6]

Melting Point

The melting point was determined using capillary method for which little amount of drug sample was filled in capillary tubes sealed from one end. The drug filled capillary was placed in melting point apparatus, and the heater was activated. The temperature was recorded from where the melting started upto its liquification.[7]

UV Spectroscopic Method Development

Determination of λmax

λmax determination was done using UV-visible spectrophotometer Model 1901. 1mg/ml of stock solution was prepared by dissolving 10 mg of drug in 10 ml of DMSO. From the stock solution,10 µg/mL dilution was made and sample was scanned between 200 to 400 nm for wavelength determination in respective mediums.[8]

Preparation of Calibration Curve

The calibration curves were prepared in different solvents including methanol, DMSO and phosphate buffer pH 7.4. Stock solution of 1mg/ml was developed by taking 50mg of bergenin and dissolving in 50ml of solvent. From this stock solution, 10 mL was aliquoted and diluted to 100 mL with the appropriate medium to achieve a concentration of 100 µg/mL followed by preparing further dilutions between 2 to 20 µg/mL. To make the calibration curve in a pH 7.4 phosphate buffer, bergenin was initially dissolved in DMSO and the volume was made up with phosphate buffer. Different dilutions between 2 to18 µg/mL were also made with respective buffer and absorbance was spectrophotometrically determined. The standard curve was constructed by plotting absorbances on the y-axis against concentration on the x-axis, utilizing linear regression analysis to generate the optimal straight line fit.[9]

Table 3: Calibration Curve of Bergenin at 275nm

Parameters	Methanol	DMSO	Phosphate Buffer 7.4
Beer's Law Range	2-20 µg/ml	2-20 µg/ml	2-18 µg/ml
Regression Equation	0.0468x + 0.0281	0.0718x - 0.0064	0.0289x + 0.0278
Correlation coefficient	0.9932	0.9904	0.9904

Determination of Solubility

Qualitative Solubility

Solubility of bergenin was assessed in different solvents including water, ethanol, methanol, acetone, DMSO and PBS (pH 7.4). Ten milligrams of drug was precisely weighed and subsequently suspended in 10 mL of various liquids in screw capped bottles. The tightly sealed bottles were agitated for 72 hours on a wrist action shaker (Yorco, New Delhi, India), followed by equilibration for 6 hours, after which the supernatant was taken, filtered and visually assessed to observe the qualitative solubility in the various solvents.[10]

Equilibrium Solubility

The shake flask method has been utilized to determine solubility. 10ml of phosphate buffer, pH 7.4, distilled water, ethanol, methanol, acetone and DMSO were placed separately in conical flasks and an excess quantity of drug sample was introduced into each flask and examined for the presence of undissolved solid at the bottom; the sample should be added until residual solid persists in the flask. The flask, after being appropriately covered, was stirred continuously for 24 to 48 hours using a magnetic stirrer set at 50 rpm to achieve equilibrium at 37 ± 1 ºC. Saturation was verified by the presence of undissolved excess solid at the bottom; the samples were filtered to eliminate undissolved API and to separate the supernatant from the samples, utilizing Whatman filter paper 0.45 µm size was used. Subsequently, samples were examined to determine absorbance using a UV-Visible Spectrophotometer at determined λmax in the respective medium following necessary dilutions with the same medium. The solubility was calculated as saturated equilibrium drug solubility in each respective medium.[11]

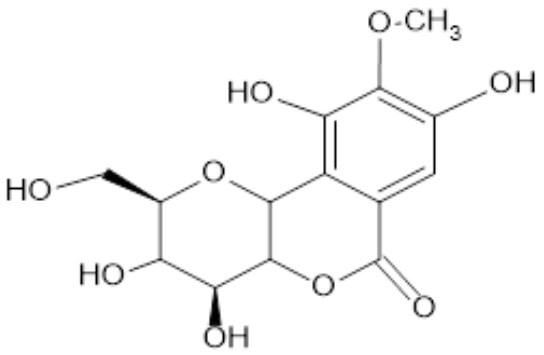

Figure 1: Structure of Bergenin

Partition Coefficient

N-octanol and a phosphate buffer solution was used for determining the partition coefficient of a drug. Both non aqueous and aqueous phases were taken in equal quantities and 10 mg of the drug was introduced into the solvent system, remaining undisturbed after shaking for 30 minutes in a separating funnel. The phases were separated followed by subsequent filtration using Whatman filter paper and analysed spectrophotometrically to ascertain the quantity of drug contained in each phase.[12]

FTIR Spectroscopy

FTIR analysis serves as essential evidence offering structural elucidation of compound. This technique offers a spectrum that encompasses an absorption band from which structural information about the chemical can be inferred. Bruker FTIR spectrometer (Tensor27, Bruker) with KBr pellet Model M-15 (Techno-Instruments) was used to get Fourier transform infrared (FTIR) spectra. Dried powdered potassium bromide thoroughly mixed with the powdered sample was subsequently compacted into a disc with a hydraulic pellet press. The produced disc was placed in a sample holder within an IR spectrophotometer, and the spectra was recorded after scanning from 4000 to 400 cm^{-1}.[13]

Table 4: Solubility of Bergenin in Various Solvents

S.No.	Solvents	Qualitative Solubility	Solubility
1.	Distilled water	----	0.059 mg/ml
2.	PBS 7.4	---	0.68 mg/ml
3.	Ethanol	----	1.08 mg/ml
4.	Methanol	++	95.34 mg/ml
5.	DMSO	++	62.73mg/ml
6.	Acetone	----	0.85 mg/ml

----Insoluble, --- Very Slightly Soluble, ++ Soluble

Drug Excipient Compatibility Studies

The drug excipient compatibility study helps to identify the chances of occurring interaction if any between drug molecules and formulation excipients. Physical observation such as color change, lump formation will be employed to identify the interaction by analyzing the peaks corresponding to their functional groups. For this, bergenin and excipients was combined in a ratio of 1:1 physical

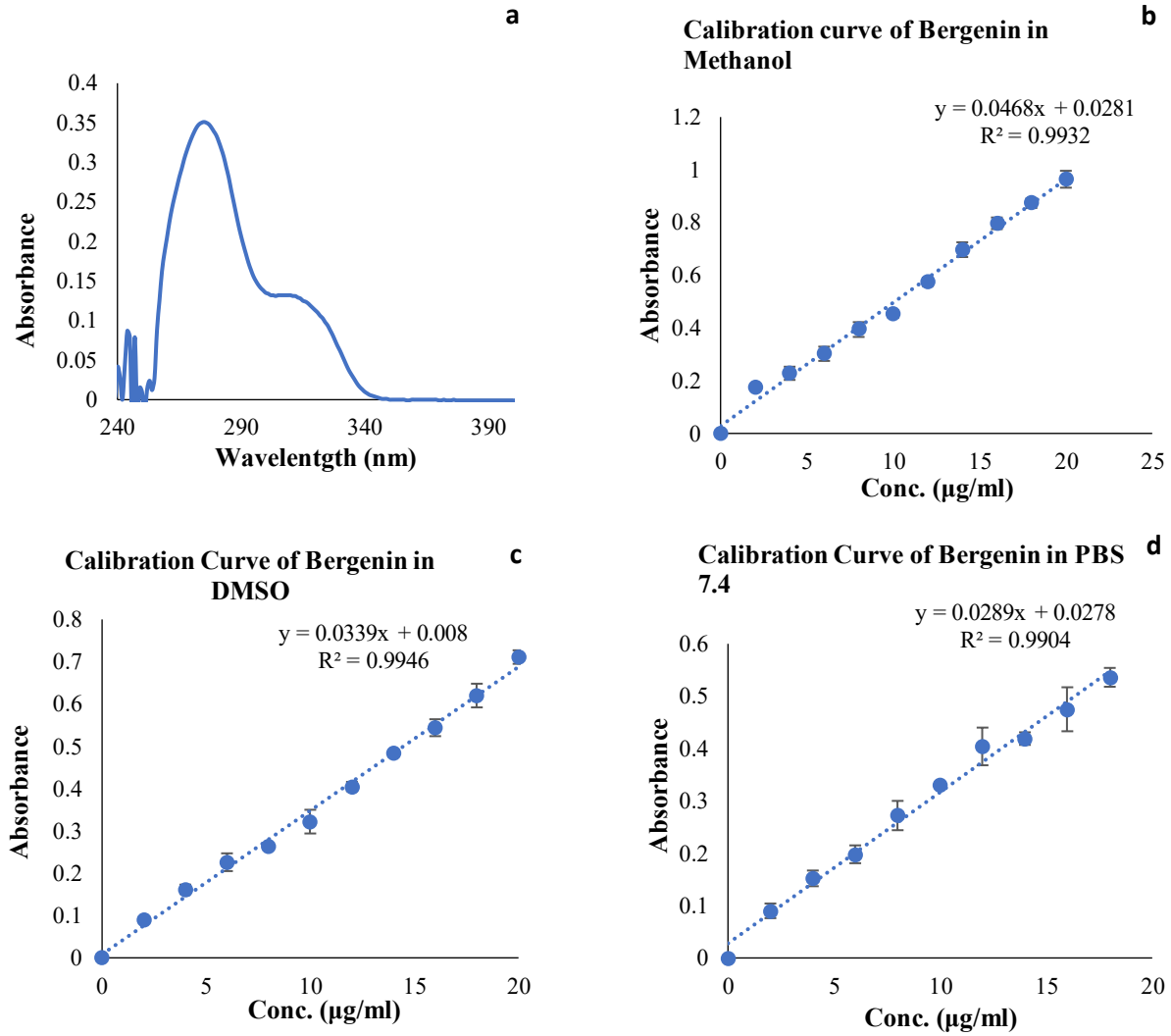

Figure 2: (a). UV Spectrum of Bergenin; (b). Calibration curve of Bergenin in Methanol; (c). Calibration curve of Bergenin in DMSO; (d). Calibration curve of Bergenin in PBS 7.4

mixture, and the mixture was observed for physical modifications.[14]

Powder X-ray Diffraction

X-ray powder diffraction is an approach commonly employed to assess the crystallinity of a substance. The X-ray diffractometer (Rigaku, Japan) utilized copper as the anode material and generated x-rays with generator settings of 100 mA and 40 kV, targeting the K-α1 wavelength type. The API was analyzed within a range of 0 to 50° at an angle of 2θ with a maximum scanning speed of 10°/min.[15]

RESULTS AND DISCUSSION

Organoleptic Characterization

The organoleptic properties like color, odor, physical state was inspected visually for bergenin and was found to be of white colored crystalline powder. All the results are specified in the Table 1.

Melting Point

The melting point estimation of Bergenin was done. The results computed the melting range of drug between 238.2-238.7°C. The obtained melting point 238.4°C was compared with standards which confirmed the purity of obtained substance All the results were taken in triplicate for accuracy and results are depicted in Table 2.

Determination of λmax and Calibration Curve

The λmax of Bergenin was ascertained using a UV-Vis spectrophotometer for which a standard solution of bergenin having a concentration of 10µg/mL in different solvents was scanned between 200 to 400nm. The maximum absorbance was recorded at a wavelength of 275nm, shown in Figure 2, which closely aligns with the standard given in literatures.

The calibration curves of Bergenin were made in three different solvents viz. methanol, DMSO and phosphate buffer pH 7.4 at a wavelength of 275nm using UV-Visible-spectrophotometer. The curves followed Lambert's Beer Law and exhibited linearity as shown in figure 2b. The corresponding data is also depicted in Table 3.

Determination of Solubility

Qualitative Solubility

Solubility studies were performed to identify the solvents that can be later used for formulation development. The quantitative study assesses the capability of solvent to dissolve the API. Results of the study are displayed in Table 4.

Partition Coefficient

Log P is generally correlated with ability of drugs to cross cell membrane because of its lipophilic characteristic. The partition coefficient of bergenin was evaluated and found to be -1.17, which demonstrated the poor lipophilicity of compound.

FTIR Spectroscopy

FTIR study of bergenin was carried out and confirmed the presence of different characteristic groups (Figure 3). In Bergenin, the broad peak at 3390 cm^{-1} correspond to the presence of OH stretch. The peaks at 3248 cm^{-1} confirmed the presence of aromatic C-H stretching. The peaks at 2952 cm^{-1}, 2891 cm^{-1} are attributed to C-H stretching of alkyl group, while the one at 1704 cm^{-1} indicated the C=O stretching. The peaks at 1611 cm^{-1}, 1529 cm^{-1}, 1463 cm^{-1} are due the presence of aromatic C=C stretching, 1374 cm^{-1} is attributed to CH bending while that of 1234 cm^{-1} and 1045 cm^{-1} are because of C−O−C stretching of aromatic group and the peak at 1133 cm^{-1} showed C-O stretching band of alcohol and at 859 cm^{-1} and 764 cm^{-1} are because of C-H Bending (out of plane).

Drug Excipient Compatibility Studies

The drug excipient compatibility was studied using physical mixture which was observed for physical changes. Results showed no change in change in color with appearance and no lump formation or sign of deterioration was observed, confirming the compatibility between drug and excipients.

Powder X-ray Diffraction

The results of XRD analysis confirmed the crystalline nature of Bergenin, which were shown by sharp peaks. The API samples was scanned for a 2θ range of up to 50°, result is illustrated in Figure 4. The recorded 2θ values were 6.61, 5.98, 5.15, 4.80, 4.48, 4.13, 3.92, 3.47 etc., which correspond with the literature of bergenin within a ±0.2

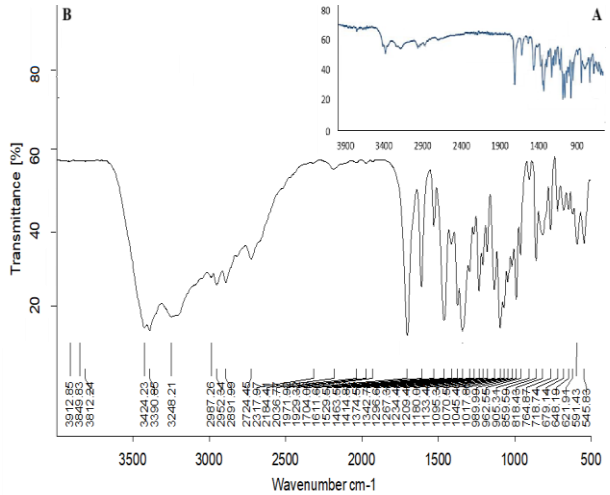

Figure 3: FTIR Spectrum of Bergenin

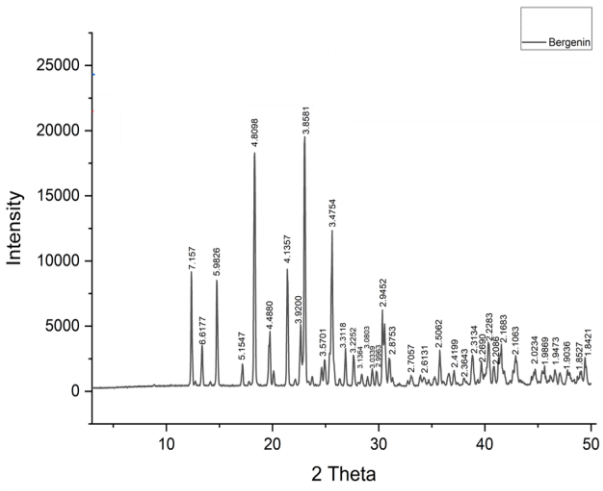

Figure 4: XRD Spectrum of Bergenin

deviation, hence confirming the purity and authenticity of given sample.

CONCLUSION

Preformulation analysis is considered as the crucial step before converting any lead molecule into a suitable formulation as it aids investigating the physical-chemical characteristics, thereby building a block for product development. The findings from the preformulation study contribute to the advancement of efficient, safe, and stable dosage formulations. The current research involved the preformulation analysis of Bergenin. The drug was confirmed as Bergenin using melting point determination and characteristic peaks found in infrared spectroscopy. The data obtained from solubility and partition coefficient analysis also proved the drug belonging to BCS Class IV. These results and crystalline characteristics suggest that effective solubility enhancement is necessary for successful formulation development to augment solubility and modify crystallinity. This research demonstrates a positive outcome for all characterization investigations and indicates that bergenin as an appropriate moiety for further formulation development.

REFERENCES

1. Desu, P.K., Vaishnavi, G., Divya, K., Lakshmi, U. An overview on Preformulation studies. Indo American Journal of Pharmaceutical Sciences. 2015; 2(10): 1399-1407.
2. Kengar, M., Howal, R., Aundhakar, D., Nikam, A., Hasabe, P. Physico-chemical Properties of Solid Drugs: A Review. Asian Journal of Pharmacy and Technology. 2019; 9(1): 53-9.
3. Ahirwar, K., Shukla, R. Preformulation Studies: A Versatile Tool in Formulation Design. Drug Formulation Design. 2023; Publisher: IntechOpen, In book: Drug Formulation Design
4. Bajpai, V. K., Shukla, S., Kang, S. C. Bergenin: A review of its pharmacological properties and therapeutic potential. Journal of Pharmacognosy and Phytochemistry. 2021; 10(2), 101-113.
5. Singh, R., Kumar, A., & Chauhan, S. Recent advances and applications of bergenin in drug discovery. Phytomedicine Reviews, 2020; 24(5), 150-160.
6. Deepika, Kaur, B., Gupta, M. HPLC Method Development and Validation for the Simultaneous Estimation of Pitavastatin and Telmisartan. Journal of Pharmaceutical Research and Reports. 2023; (4)140.
7. Anusha, V., Umashankar, M.S., Kumar, Y.G. Preformulation Studies of Pitavastatin Calcium– A Primary, Step in Further Design of Chronotherapeutic Formulation Synchronized with Circadian Rhythm. International Journal of Drug Delivery Technology. 2024;14(3):1578-1585.
8. Sharma, U., Agrawa, S., Chhajed, M., & Dwived, S. Improved dissolution and solubility characteristics of clopidogrel bisulphate using gelucire 44/14. European Journal of Parenteral and Pharmaceutical Sciences. 2024; 291.
9. Resmi DS. Formulation and Evaluation of Topical Econazole Nitrate Microsponge Loaded Hydrogel. Ijppr. 2018; 12 (1): 27-64.
10. Yadav PK, Swami H. Preformulation: Development of Solubility, UV and FTIR estimation of Phytobioactive Antifungal Compounds Allicin. International Journal of Pharmaceutical Quality Assurance. 2023;14(4):1055-1057
11. Ganesh BSP, Darna B. Development and In vivo Evaluation of Pitavastatin Self-Emulsifying Drug Delivery Systems. International Journal of Pharmaceutical Sciences and Drug Research. 2021; 13(3):295-302.
12. Chauhan S, Dwivedi A. Preformulation Studies, UV Spectral and FTIR Analysis of Allicin. International Journal of Pharmaceutical Quality Assurance. 2024;15(3):1168-1170.
13. Sharma, U., Joshi, A., Vyas, N., Malviya, S., & Kharia, A. Solubility Enhancement of Clopidogrel Bisulfate by Solid Dispersion Technique using Carboxymethylcellulose Sodium and Xanthan Gum. Journal of Drug Delivery and Therapeutics. 2017; 7(7), 35-37.
14. Sivapriya, S., Prabhakaran, L., Venkatesan, P. Evaluation of Drug-Excipient Compatibility for Paroxetine Nanoformulations using DSC and FTIR Analysis. YMER. 2024. 23(12): 858-865.
15. Akhter, M. H., Al-Keridis, L. A., Saeed, M., Khalilullah, H., Rab, S. O., Aljadaan, A. M., Rahman, M. A., Jaremko, M., Emwas, A.-H., Ahmad, S., Alam, N., Ali, M. S., Khan, G., & Afzal, O. (2023). Enhanced drug delivery and wound healing potential of berberine-loaded chitosan–alginate nanocomposite gel: Characterization and in vivo assessment. Frontiers in Public Health, 11, 1238961.