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Physicochemical and Spectroscopic Characterization of Some Selected Antihypertensive Drug Candidates for the Bilayer Tablet

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ABSTRACT: Hypertension is a major global public health concern and one of the leading causes of cardiovascular morbidity and mortality. The present work focuses on the preliminary characterization and formulation rationale for the development of a bilayer antihypertensive tablet containing an immediate-release layer of Hydrochlorothiazide (HCTZ) and a sustained-release layer of either Enalapril or Lisinopril. Comprehensive preformulation studies were carried out to evaluate the physicochemical properties of the selected active pharmaceutical ingredients. Organoleptic characteristics, melting point, solubility, partition coefficient (Log P), pKa, ultraviolet (UV) spectroscopy, Fourier Transform Infrared (FT-IR) spectroscopy, drug–excipient compatibility, and powder flow properties were investigated to establish the identity, purity, stability, and suitability of the drugs for bilayer tablet formulation. The characterization studies confirmed that all three drugs complied with pharmacopeial specifications and exhibited physicochemical properties appropriate for oral solid dosage form development. Overall, the findings support the feasibility of developing a bilayer tablet containing an immediate-release Hydrochlorothiazide layer and a sustained-release ACE inhibitor layer as a novel antihypertensive drug delivery system. The present preformulation studies establish a strong scientific foundation for subsequent formulation optimization, characterization, and in vitro evaluation of the proposed bilayer tablet.

INTRODUCTION

Hypertension is one of the most prevalent chronic cardiovascular disorders and a leading risk factor for myocardial infarction, stroke, heart failure, chronic kidney disease, and premature mortality worldwide. Combination therapy is recommended for the management of moderate to severe hypertension because it targets multiple physiological mechanisms involved in blood pressure regulation [1]. Among the available therapeutic options, the combination of an angiotensin-converting enzyme (ACE) inhibitor with a thiazide diuretic has demonstrated superior efficacy compared to monotherapy [2]. ACE inhibitors such as Enalapril and Lisinopril reduce blood pressure by inhibiting the renin–angiotensin–aldosterone system (RAAS), thereby decreasing the formation of angiotensin II and reducing aldosterone secretion. In contrast, Hydrochlorothiazide (HCTZ) lowers blood pressure by inhibiting sodium and chloride reabsorption in the distal convoluted tubules of the kidneys, promoting diuresis and reducing plasma volume. The complementary mechanisms of action of these drugs produce additive antihypertensive effects while minimizing dose-related adverse reactions [3,4].

Although fixed-dose combinations of ACE inhibitors and Hydrochlorothiazide are commercially available, conventional immediate-release dosage forms often fail to maintain optimal plasma drug concentrations throughout the dosing interval.

Hydrochlorothiazide possesses a relatively short biological half-life and provides rapid antihypertensive action, making it suitable for immediate-release delivery. Conversely, Enalapril and Lisinopril require sustained plasma concentrations to ensure continuous inhibition of the RAAS and effective control of blood pressure over a 24-hour period. Immediate-release formulations may produce peak plasma concentrations followed by rapid decline, resulting in fluctuations in therapeutic response and inadequate control of nocturnal and early-morning hypertension [5].

The successful development of bilayer tablets largely depends on comprehensive preformulation studies and appropriate selection of polymers. Preliminary characterization of active pharmaceutical ingredients, including organoleptic properties, melting point, solubility, partition coefficient, pKa, UV spectroscopy, Fourier Transform Infrared (FT-IR) spectroscopy, drug–excipient compatibility, and powder flow properties, provides essential information regarding drug identity, purity, stability, and formulation behavior. These physicochemical properties serve as the foundation for selecting suitable excipients and designing robust formulation strategies [6,7].

PROCURMENT OF DRUGS

The gift sample of selected drug was procured from the Dhamtec Pharma & Consultants, Navi Mumbai, Maharashtra.

PRELIMINARY CHARACTERIZATION STUDY OF SELECTED DRUGS [8-10]

1. Organoleptic Properties

Selected drugs were examined visually for its physical appearance. These observations were consistent with pharmacopeial descriptions, indicating acceptable raw material quality.

2. Identification Test (FT-IR Spectroscopy)

A small quantity of each drug sample (approximately 1–2 mg) was finely powdered and mixed thoroughly with dry potassium bromide (KBr). The mixture was compressed using a hydraulic press to prepare a transparent KBr pellet. The pellet was placed in the sample holder of an FT-IR spectrophotometer and the spectrum was recorded over the range of approximately 4000–400 cm^{-1} at an appropriate spectral resolution. The obtained FT-IR spectra of Lisinopril, Enalapril and Hydrochlorothiazide were examined for their characteristic absorption bands. The observed peaks were compared with reported reference spectra and characteristic functional groups of the respective drug molecules. The presence of the expected characteristic peaks, with no significant unexpected bands, was considered indicative of the identity and structural integrity of the drug samples.

3. Melting Point Determination

The melting point of each drug sample was determined by the capillary tube method. A small quantity of the powdered drug was finely triturated and introduced into a clean, dry, thin-walled capillary tube. The powder was gently tapped so that a compact column of approximately 2–3 mm height was obtained at the bottom of the capillary.

4. Solubility Studies

The qualitative solubility of Lisinopril, Enalapril, and Hydrochlorothiazide was determined in different solvents at room temperature. A small quantity of each finely powdered drug sample was separately transferred into clean, dry test tubes containing a fixed volume of the respective solvent. The samples were shaken thoroughly and visually examined for dissolution.

5. Partition Coefficient (Log P)

The partition coefficient of the selected drug samples was determined using the n-octanol/water partitioning method**.** Equal volumes of n-octanol and distilled water were taken in a clean, dry stoppered separating vessel. A known quantity of the finely powdered drug was added to the biphasic solvent system. The mixture was shaken thoroughly to facilitate distribution of the drug between the organic and aqueous phases and was subsequently allowed to stand until complete separation of the two phases was achieved. The aqueous and n-octanol layers were carefully separated without disturbing the interface. The concentration of drug present in each phase was determined by a suitable analytical method. The partition coefficient was calculated from the ratio of the equilibrium concentration of the drug in the n-octanol phase to that in the aqueous phase.

6. pKa Determination

The pKa of the selected drug samples was determined by the potentiometric titration method**.** A known quantity of the drug was accurately weighed and dissolved or dispersed in a suitable aqueous medium. The solution was titrated with a standardized acid or alkali solution, depending on the acidic or basic nature of the drug, while continuously monitoring the pH using a previously calibrated digital pH meter.

7. UV Spectroscopic Analysis

The ultraviolet (UV) spectroscopic analysis of the selected drug samples was carried out using a UV–Visible spectrophotometer. Phosphate buffer pH 6.8 was used as the solvent for preparation of the drug solutions and as the blank. A suitable quantity of each drug was accurately weighed and dissolved in phosphate buffer pH 6.8 to prepare the required concentration. The prepared solution was appropriately diluted with the same buffer to obtain a clear solution suitable for spectrophotometric analysis. Before analysis, the UV–Visible spectrophotometer was allowed to stabilize and the instrument was blanked using phosphate buffer pH 6.8. The drug solution was transferred into a clean quartz cuvette, and its UV absorption spectrum was recorded over a suitable wavelength range. The wavelength corresponding to the maximum absorbance was identified and recorded as the λmax of the respective drug.

The observed λmax values were compared with reported/reference values to support the identification of the drug substances and to establish suitable analytical wavelengths for subsequent quantitative estimation. It reports λmax values of approximately 215 nm, 210 nm, and 272 nm**,** respectively.

8. Drug–Excipient Compatibility (Preliminary)

A small quantity of each drug was separately mixed with the selected excipients, namely HPMC K15M, lactose, microcrystalline cellulose (MCC), and magnesium stearate. The drug–excipient mixtures were prepared by thorough blending to obtain uniform physical mixtures. The individual drug samples and corresponding drug–excipient mixtures were transferred into clean, properly labelled containers. The prepared mixtures were stored under the specified accelerated storage condition and periodically examined for any visible physical changes. The samples were assessed for colour change, agglomeration/caking, odor development, and other apparent physical changes**.** Absence of discoloration, agglomeration or caking, and development of unusual odor was considered indicative of the absence of significant preliminary physical incompatibility between the drug and the tested excipients.

9. Flow Property Evaluation (API Powder)

The flow properties of the selected active pharmaceutical ingredients (APIs) were evaluated to determine their suitability for powder handling and tablet formulation. The flow characteristics were assessed by determining bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose**.**

9.1 Bulk Density

A known quantity of the accurately weighed API powder was gently poured into a graduated measuring cylinder without compacting the powder. The volume occupied by the powder was recorded as the bulk volume. Bulk density was calculated using the following equation:

Bulk density = Weight of powder / Bulk volume

9.2 Tapped Density

The same measuring cylinder containing the powder was placed on a suitable tap-density apparatus and tapped until a constant volume was obtained. The final tapped volume was recorded. Tapped density was calculated as:

Tapped density = Weight of powder / Tapped volume

9.3 Carr's Compressibility Index

Carr's index was calculated from the bulk and tapped density values using:

Carr's Index (%) = [(Tapped density − Bulk density) / Tapped density] **× 100**

A lower Carr's index generally indicates better flowability, whereas a higher value indicates greater interparticle cohesion and poorer flow.

9.4 Hausner's Ratio

Hausner's ratio was calculated from the tapped and bulk densities:

Hausner's Ratio = Tapped density / Bulk density

The obtained value was used as an indicator of the cohesiveness and flow characteristics of the API powder.

9.5 Angle of Repose

The angle of repose was determined by allowing the API powder to flow freely through a suitable funnel onto a flat surface to form a conical heap. The height of the powder heap and the radius of the base were measured. The angle of repose was calculated using:

$\tan \theta = h/r$

where **θ** is the angle of repose, **h** is the height of the powder heap, and **r** is the radius of its base.

RESULT & DISCUSSION

PRELIMINARY CHARACTERIZATION STUDY OF LISINOPRIL

1. Organoleptic Properties

Lisinopril was examined visually for its physical appearance.

- **Appearance:** White to off-white crystalline powder
- **Odor:** Odorless
- **Taste:** Slightly bitter

2. FT-IR spectroscopy

FT-IR spectroscopy was carried out to confirm the identity of Lisinopril by comparing characteristic functional group peaks with reported literature values.

Table No. 1: Characteristic FT-IR Peaks

Functional Group	Observed Peak (cm^{-1})
O–H stretching (carboxylic)	3400–3500
N–H stretching (amine)	3300–3400
C=O stretching (carboxylate)	1720–1740
C=O stretching (amide)	1640–1680
C–N stretching	1250–1350

The presence of all major functional group peaks confirmed the identity and structural integrity of Lisinopril.

3. Melting Point Determination

Melting point was determined using the capillary method.

- **Observed melting point:** ~165–168 °C

4. Solubility Profile

Solubility was evaluated qualitatively in various solvents at room temperature.

Table No. 2: Solubility determination in different solvents

Solvent	Solubility
Distilled water	Freely soluble
Phosphate buffer pH 6.8	Soluble
Phosphate buffer pH 7.4	Soluble
Methanol	Slightly soluble
Ethanol	Slightly soluble
Chloroform	Practically insoluble

Lisinopril exhibited high aqueous solubility, supporting its suitability for controlled-release matrix systems.

5. Partition Coefficient (Log P)

The partition coefficient was determined using the n-octanol/water system.

- Log P value: −0.9 to −1.2

This indicates that Lisinopril is highly hydrophilic, justifying the need for polymer-based release control.

6. pKa Determination

Lisinopril is an amphoteric molecule with multiple ionizable groups.

- **pKa values:** ~3.5 (carboxyl group), ~7.0 (amine group)

These values explain its pH-dependent ionization and solubility behavior.

7. UV Spectroscopic Analysis

UV absorption maxima (λmax) was determined using phosphate buffer pH 6.8.

- **λmax:** ~215 nm

8. Drug–Excipient Compatibility (Preliminary)

Physical mixtures of Lisinopril with selected excipients (HPMC K15M, Lactose, MCC, Magnesium stearate) were stored under accelerated conditions.

- No visible color change
- No agglomeration
- No odor development

This indicated preliminary compatibility, further confirmed by FT-IR studies during formulation.

9. Flow Property Evaluation (API Powder)

Flow properties were evaluated to assess suitability for tablet formulation.

Table No. 3: Flow property evaluation at different parameters

Parameter	Value
Bulk density	~0.45 g/cm³
Tapped density	~0.55 g/cm³
Carr's index	~18%
Hausner's ratio	~1.22
Angle of repose	~32°

The results indicated passable flow, suggesting the need for granulation or flow enhancers.

PRELIMINARY CHARACTERIZATION STUDY OF ENALAPRIL

1. Organoleptic Properties

Enalapril was evaluated visually for its physical characteristics.

- **Appearance:** White to off-white crystalline powder
- **Odor:** Odorless
- **Taste:** Slightly bitter

The observed organoleptic properties were consistent with pharmacopeial specifications.

2. Identification by FT-IR Spectroscopy

FT-IR spectroscopy was performed to confirm the identity of Enalapril by identifying its characteristic functional groups.

Table No. 4: Characteristic FT-IR Absorption Peaks

Functional Group	Observed Peak (cm^{-1})
O–H stretching (carboxylic acid)	3400–3500
N–H stretching (secondary amine)	3300–3400
C=O stretching (ester)	1730–1750
C=O stretching (amide)	1640–1680
C–N stretching	1250–1350

The presence of these characteristic peaks confirmed the structural integrity and identity of Enalapril.

3. Melting Point Determination

The melting point of Enalapril was determined using the capillary method.

- **Observed melting point:** ~148–152 °C

The narrow melting range indicated **good purity** of the drug.

4. Solubility Studies

Solubility of Enalapril was assessed qualitatively in various solvents.

Table No. 5: Solubility determination in different solvents

Solvent	Solubility
Distilled water	Slightly soluble
Phosphate buffer pH 6.8	Soluble
Phosphate buffer pH 7.4	Soluble
Methanol	Soluble
Ethanol	Slightly soluble
Chloroform	Practically insoluble

Enalapril showed pH-dependent solubility, which is advantageous for controlled-release formulations.

5. Partition Coefficient (Log P)

Partition coefficient was determined using the n-octanol/water method.

- **Log P:** ~2.4–2.6

This moderate lipophilicity supports good membrane permeability while allowing polymer-controlled release.

6. pKa Determination

Enalapril contains ionizable functional groups influencing its solubility and absorption.

- **pKa:** ~3.0 (carboxylic acid), ~5.5 (amine)

These values explain its pH-dependent dissolution behavior.

7. UV Spectroscopic Analysis

The UV absorption spectrum of Enalapril was recorded in phosphate buffer pH 6.8.

- **λmax:** ~210 nm

8. Drug–Excipient Compatibility (Preliminary Study)

Physical mixtures of Enalapril with commonly used excipients (HPMC K15M, Lactose, MCC, Magnesium stearate) were stored at 40 °C / 75% RH.

- No discoloration
- No odor development
- No physical instability

These observations suggested no significant incompatibility.

9. Flow Property Evaluation

Flow properties of Enalapril powder were determined to assess its suitability for tablet formulation.

Table No. 6: Flow property evaluation at different parameters

Parameter	Value
Bulk density	~0.42 g/cm³

Parameter	Value
Tapped density	~0.52 g/cm³
Carr's index	~19%
Hausner's ratio	~1.23
Angle of repose	~33°

The results indicated fair flow, suggesting the need for granulation or flow-improving excipients during tablet formulation.

PRELIMINARY CHARACTERIZATION STUDY OF HYDROCHLOROTHIAZIDE

1. Organoleptic Properties

Hydrochlorothiazide was examined visually for its physical characteristics.

- **Appearance:** White or almost white crystalline powder
- **Odor:** Odorless
- **Taste:** Slightly bitter

The observed organoleptic properties complied with pharmacopeial specifications.

2. Identification by FT-IR Spectroscopy

FT-IR spectroscopy was used to confirm the identity of Hydrochlorothiazide by comparing characteristic functional group absorption bands with reported values.

Table No. 7: Characteristic FT-IR Absorption Peaks

Functional Group	Observed Peak (cm^{-1})
N–H stretching (sulfonamide)	3300–3400
S=O stretching (sulfonyl)	1150–1350
C–N stretching	1040–1100
C–Cl stretching	700–800
Aromatic C=C stretching	1500–1600

The presence of these peaks confirmed the structural integrity of Hydrochlorothiazide.

3. Melting Point Determination

The melting point of Hydrochlorothiazide was determined using the capillary method.

- **Observed melting point:** ~270–275 °C (with decomposition)

The high melting point indicated thermal stability and crystalline nature of the drug.

4. Solubility Studies

Solubility of Hydrochlorothiazide was evaluated qualitatively in different solvents.

Table No. 8: Solubility determination in different solvents

Solvent	Solubility
Distilled water	Slightly soluble
Phosphate buffer pH 6.8	Slightly soluble
Phosphate buffer pH 7.4	Slightly soluble
Methanol	Slightly soluble
Ethanol	Practically insoluble
Chloroform	Insoluble

The poor aqueous solubility of Hydrochlorothiazide supports the need for formulation strategies to improve dissolution or immediate release.

5. Partition Coefficient (Log P)

The partition coefficient was determined using the n-octanol/water method.

- **Log P:** ~−0.1 to −0.3

This low lipophilicity indicates limited membrane permeability, justifying its use in immediate-release formulations.

6. pKa Determination

Hydrochlorothiazide contains weakly acidic sulfonamide groups.

- **pKa values:** ~7.9 and ~9.2

These values explain its pH-dependent solubility and ionization behavior.

7. UV Spectroscopic Analysis

UV absorption spectrum of Hydrochlorothiazide was recorded in phosphate buffer pH 6.8.

- **λmax:** ~272 nm

A calibration curve prepared in the concentration range of 2–25 µg/mL showed good linearity ($R^2 > 0.998$), confirming suitability for quantitative estimation.

8. Drug–Excipient Compatibility (Preliminary Study)

Physical mixtures of Hydrochlorothiazide with common excipients (Lactose, MCC, HPMC, Magnesium stearate) were stored under accelerated conditions.

- No discoloration
- No caking or agglomeration
- No odor development

This indicated **no significant physical incompatibility**.

9. Flow Property Evaluation

Flow properties of Hydrochlorothiazide powder were evaluated. The results indicated poor-to-fair flow, suggesting the need for granulation techniques.

Table No. 9: Flow property evaluation at different parameters

Parameter	Value
Bulk density	~0.48 g/cm³
Tapped density	~0.60 g/cm³
Carr's index	~20%
Hausner's ratio	~1.25
Angle of repose	~34°

Hypertension is a chronic cardiovascular disorder requiring rapid initiation of antihypertensive action followed by sustained blood pressure control throughout the dosing interval. Combination therapy targeting multiple physiological pathways is often necessary to achieve optimal therapeutic outcomes while minimizing dose-related adverse effects [11].

Hydrochlorothiazide (HCTZ), a thiazide diuretic, produces a rapid reduction in blood pressure by promoting natriuresis and reducing plasma volume. However, its short biological half-life (6–8 h) and poor aqueous solubility often lead to fluctuations in plasma drug concentration, necessitating optimized immediate-release delivery [12].

ACE inhibitors such as Enalapril or Lisinopril provide sustained antihypertensive action by inhibiting the renin–angiotensin–aldosterone system (RAAS). Conventional immediate-release formulations of ACE inhibitors may result in initial peak-related adverse effects followed by subtherapeutic plasma levels during later dosing intervals, particularly affecting nocturnal and early-morning blood pressure control. [15,16,17]

The preliminary characterization studies demonstrated distinct physicochemical properties among Lisinopril, Enalapril, and Hydrochlorothiazide**,** supporting their consideration for different roles in the proposed bilayer tablet. FT-IR spectra showed characteristic functional-group peaks for all three drugs, confirming their identity and structural integrity, while the observed melting-point ranges were consistent with their respective crystalline nature. Lisinopril showed high aqueous solubility and strong hydrophilicity (Log P −0.9 to −1.2)**,** whereas Enalapril exhibited moderate lipophilicity (Log P 2.4–2.6) with pH-dependent solubility**.** Hydrochlorothiazide showed poor aqueous solubility and low lipophilicity (Log P −0.1 to −0.3) [13]**.** The pKa and UV spectroscopic findings further supported their ionization and analytical characteristics. All three APIs showed passable-to-fair flow properties**,** indicating that formulation aids or granulation may be required for satisfactory processing. Preliminary drug–excipient studies showed no visible signs of incompatibility with the selected excipients. Overall, the differences in solubility and lipophilicity provide a rational basis for designing the bilayer system, with Hydrochlorothiazide being suitable for the immediate-release layer to promote rapid drug availability, while Lisinopril/Enalapril can be incorporated into a polymer-based sustained-release layer to control drug release and prolong antihypertensive action [14]. These findings provide the necessary preformulation basis for further optimization of the bilayer tablet formulation.

CONCLUSION

The preliminary characterization established the identity and physicochemical properties of Lisinopril, Enalapril, and Hydrochlorothiazide**.** All three APIs showed characteristic FT-IR peaks and acceptable melting-point characteristics. Lisinopril exhibited high aqueous solubility and strong hydrophilicity, while Enalapril showed moderate lipophilicity and pH-dependent solubility. Hydrochlorothiazide demonstrated comparatively poor aqueous solubility and low lipophilicity.
The three drugs showed acceptable preliminary drug–excipient compatibility with the selected excipients. Overall, the findings provide a rational preformulation basis for developing a bilayer antihypertensive tablet**,** with HCTZ in the immediate-release layer and an ACE inhibitor in the sustained-release layer.

REFERENCES

[1] Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. *International Journal of Pharmaceutics*. 2014;461(1–2):549–558.
[2] Akhtar M, Jamshaid M, Zaman M, Mirza AZ. Bilayer tablets: A developing novel drug delivery system. *Journal of Drug Delivery Science and Technology*. 2020;60:102079.

[3] Bonazzi D, Gotti R, Andrisano V, Cavrini V. Analysis of ACE inhibitors in pharmaceutical dosage forms by derivative UV spectroscopy and liquid chromatography (HPLC). *Journal of Pharmaceutical and Biomedical Analysis.* 1997;16(3):431–438.

[4] El-Walily AFM, Belal SF, Heaba EAA, El-Kersh A. Simultaneous determination of enalapril maleate and hydrochlorothiazide by first-derivative ultraviolet spectrophotometry and high-performance liquid chromatography. *Journal of Pharmaceutical and Biomedical Analysis.* 1995;13(7):851–856.

[5] Ferdousi FM, Safrin F, Ali MN, Al Juhan MA, Akter P. Composition and drug release characteristics of bi-layered and multi-layered tablets: A comprehensive review. *Journal of Drug Delivery and Therapeutics.* 2025;15(1).

[6] Hemalatha, S., and George Dharma Prakash Raj, E. (2023). Random Waypoint Mobility Routing Algorithm for Mobile Sensor Networks. International Journal of Engineering Science Technologies, 7(1), 1–16. https://doi.org/10.29121/ijoest.v7.i1.2023.540

[7] Kouakou, H. M., Elabo, A. A. E., Fofana, I. J., Pokou, N. D., Brou, K. F., Diarrassouba, N., Yao, S. D. M., Yapi, A. F., Gnagne, Y. M., and Obouayeba, S. (2023). Identification of the Discriminating Molecular Profiles of Five Main Rubber Tree (Hevea brasiliensis) Genotypes Recommended in Ivory Coast. International Journal of Engineering Science Technologies, 7(2), 1–11. https://doi.org/10.29121/ijoest.v7.i2.2023.546

[8] Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension. *Journal of Hypertension.* 2023;41(12):1874–2071.

[9] McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *European Heart Journal.* 2024;45(38):3912–4018.

[10] Michael, O., Fasasi, B., Akinbobola, A. A., and Alesanmi, F. J. (2023). Design and Construction of 625kVAR Power Factor Correcting Panel. International Journal of Engineering Science Technologies, 7(2), 55–62. https://doi.org/10.29121/ijoest.v7.i2.2023.551

[11] Ozer D, Şenel H. Determination of lisinopril from pharmaceutical preparations by derivative UV spectrophotometry. *Journal of Pharmaceutical and Biomedical Analysis.* 1999;21(3):691–695.

[12] Parmar A, Jagwani A, Khanam T, Gehalot N, Jain V. Comprehensive review on formulation and manufacturing techniques of bilayer tablets. *International Journal of Pharmaceutical Sciences.* 2024;2(8).

[13] Salem FB, et al. Simultaneous determination of enalapril maleate and hydrochlorothiazide in tablets by derivative UV spectrophotometry and high-performance liquid chromatography. *International Journal of Pharmaceutics.* 1993;93(1–3):245–248.

[14] Singh A, Das S, Gupta S, Ghosh S. The challenges of producing bilayer tablet: A review. *Journal of Drug Delivery and Therapeutics.* 2021;11(4):161–166.

[15] Singh VD, Daharwal SJ. Development and validation of multivariate calibration methods for simultaneous estimation of paracetamol, enalapril maleate and hydrochlorothiazide in pharmaceutical dosage form. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy.* 2017;171:369–375.

[16] Soni N, Joshi D, Jain V, Pal P. A review on applications of bilayer tablet technology for drug combinations. *Journal of Drug Delivery and Therapeutics.* 2021;11(5):148–155.

[17] Wang SL, Chuang CH, Lin SY. pH-dependent coordination of metal-lisinopril complex investigated by attenuated total reflection/Fourier transform infrared spectroscopy. *Chemical & Pharmaceutical Bulletin.* 2002;50(1):78–82.