RESEARCH PAPER

Formulation and In Vitro Characterization of a Mucoadhesive Microsphere of Dolutegravir for Enhanced Oral Bioavailability

Gayke A U[1]*, Palade Vaishanvi[2], Patil S D[3], Shinde V S[4], Avhad P S[5], Jain U N [6]

[1]Department of Pharmaceutics, SND College of Pharmacy ,Yeola
[2]Department of Pharmaceutics, SND College of Pharmacy ,Yeola
[3]Department of Pharmaceutical Chemistry, SND College of Pharmacy ,Yeola
[4]Department of Pharmaceutics, SND College of Pharmacy ,Yeola
[5]Matoshri Institute of Pharmacy ,Dhanore
[6]Department of Pharmaceutical Chemistry,RJS College of Pharmacy ,Kotamgoam
Corresponding author: Dr Amol U Gayke, amolgayke6687@gmail.com

ABSTRACT

Dolutegravir (DTG), a potent antiretroviral agent, requires an effective delivery system to improve gastrointestinal residence time and sustain drug release. The present study aimed to develop and optimize mucoadhesive microspheres of Dolutegravir using the solvent evaporation method and a Box–Behnken Design (BBD). Polymer concentration, drug-to-polymer ratio, and stirring speed were selected as independent variables, while particle size, entrapment efficiency, and cumulative drug release were evaluated as responses. The optimized formulation consisted of 1.5% polymer concentration, a 1:3 drug-to-polymer ratio, and a stirring speed of 1000 rpm. The optimized microspheres exhibited a particle size of 268.00 ± 3.61 µm, entrapment efficiency of 86.90 ± 1.03%, drug loading of 28.64 ± 0.94%, and zeta potential of −21.47 ± 1.18 mV. In vitro release studies demonstrated sustained drug release, achieving 71.80 ± 0.46% release over 24 h. The findings suggest that the developed mucoadhesive microspheres are a promising oral controlled-release system for enhanced Dolutegravir delivery.

Keywords: Dolutegravir, Mucoadhesive microspheres, Box–Behnken design, Controlled drug release, Oral bioavailability

How to cite this article: Gayke AU, Vaishanvi P, Patil SD, Shinde VS, Avhad PS, Jain UN. Formulation and In Vitro Characterization of a Mucoadhesive Microsphere of Dolutegravir for Enhanced Oral Bioavailability. Int J Drug Deliv Technol. 2026;16(65s):1134-1139. DOI: 10.25258/ijddt.16.65s.115

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection continues to be a major global public health concern despite significant advances in antiretroviral therapy (ART). The widespread use of highly active antiretroviral therapy (HAART) has considerably reduced HIV-related morbidity and mortality, transforming HIV infection from a fatal disease into a manageable chronic condition.1 However, successful long-term treatment requires maintaining adequate drug concentrations, minimizing adverse effects, and ensuring patient adherence to therapy.[2] Therefore, the development of novel drug delivery systems capable of improving therapeutic efficacy and patient compliance remains an important area of pharmaceutical research.

Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTI) that has emerged as a preferred first-line antiretroviral agent for the treatment of HIV-1 infection. It inhibits the HIV integrase enzyme, thereby preventing the integration of viral DNA into the host genome and effectively suppressing viral replication 3. Dolutegravir possesses several advantages, including potent antiviral activity, a high genetic barrier to resistance, favorable pharmacokinetic properties, and good tolerability, making it a key component of modern ART regimens 4.

Despite its therapeutic benefits, the oral bioavailability of Dolutegravir can be influenced by several physiological and formulation-related factors. Variations in gastrointestinal transit time, food effects, and interactions with polyvalent cations may affect drug absorption and therapeutic outcomes 5. In conventional oral dosage forms, rapid transit through the gastrointestinal tract may reduce the contact time available for absorption, thereby limiting the extent of drug uptake. Consequently, the development of advanced oral delivery systems capable of enhancing gastrointestinal residence time and improving absorption is highly desirable.

Mucoadhesive drug delivery systems have attracted considerable attention as an effective approach for enhancing oral bioavailability. Mucoadhesion refers to the ability of a material to adhere to the mucus layer covering biological membranes. By remaining attached to the gastrointestinal mucosa for prolonged periods, mucoadhesive systems can increase drug residence time, improve drug absorption, reduce dosing frequency, and enhance therapeutic effectiveness 6 . Such systems are particularly useful for drugs that require prolonged contact with absorptive surfaces for optimal bioavailability.

Among various mucoadhesive dosage forms, microspheres have gained significant importance due to their ability to provide controlled and sustained drug release. Microspheres are free-flowing spherical particles composed of biodegradable or biocompatible polymers capable of encapsulating therapeutic agents within a polymeric matrix. These systems offer several advantages, including protection of the drug from degradation, improved stability, controlled release behavior, and enhanced absorption 7. The incorporation of mucoadhesive polymers further increases their potential to prolong gastrointestinal residence and improve drug bioavailability.

The performance of mucoadhesive microspheres depends largely on the type and concentration of polymers used in the

formulation. Natural polymers such as chitosan, sodium alginate, pectin, and xanthan gum are widely used because of their excellent biocompatibility, biodegradability, and mucoadhesive properties. Synthetic polymers such as carbopol, hydroxypropyl methylcellulose (HPMC), and polyvinyl alcohol (PVA) contribute to controlled drug release and mechanical stability 8. Mucoadhesion occurs through various mechanisms, including hydrogen bonding, electrostatic interactions, van der Waals forces, and interpenetration of polymer chains with mucin molecules present in the mucus layer 9.

Various techniques have been employed for the preparation of mucoadhesive microspheres, including solvent evaporation, spray drying, emulsification-crosslinking, coacervation, and ionotropic gelation. Among these methods, ionotropic gelation is particularly advantageous because it is simple, cost-effective, reproducible, and suitable for heat-sensitive drugs. The technique involves ionic crosslinking between polymer chains and multivalent ions, resulting in the formation of stable microspheres capable of sustained drug release 10.

Therefore, the present study was undertaken to formulate and characterize mucoadhesive microspheres of Dolutegravir with the aim of enhancing oral bioavailability. The developed microspheres were evaluated for their physicochemical properties, drug entrapment efficiency, mucoadhesive characteristics, and in vitro drug release behavior. The successful development of a mucoadhesive microsphere system may provide an effective strategy for improving the therapeutic performance of Dolutegravir and enhancing treatment outcomes in HIV-infected patients 11.

MATERIAL AND METHOD

Dolutegravir was procured from Taj Pharma India Limited, Vapi, Gujarat, India. Chitosan, ethylcellulose, polyvinyl alcohol (PVA), and mannitol were obtained from Merck Pvt. Ltd. and Qualigens Fine Chemicals, India. Analytical-grade reagents and solvents, including glacial acetic acid, dichloromethane, ethanol, phosphate buffer salts, sodium hydroxide, and hydrochloric acid, were procured from Qualigens Fine Chemicals, India.

PREFORMULATION STUDIES

Preformulation studies were conducted to evaluate the physicochemical properties and compatibility of Dolutegravir with selected polymers (PLGA, chitosan, and ethylcellulose). Organoleptic characteristics such as color, odor, and appearance were assessed visually. The maximum absorption wavelength (λmax) was determined using a UV–Visible spectrophotometer by scanning a 10 µg/mL drug solution in the range of 200–400 nm. Calibration curves were prepared in 0.1 N HCl and phosphate buffer (pH 6.8). Drug–polymer compatibility was investigated using FTIR spectroscopy (4000–400 cm^{-1}) and DSC analysis (30–300°C) to identify potential interactions and thermal behavior.12

PREPARATION OF FORMULATION

OPTIMIZATION OF FORMULATION

The present study aimed to develop and optimize Dolutegravir-loaded mucoadhesive microspheres using a Box–Behnken Design (BBD). Three formulation and process variables—polymer concentration (X_1), drug-to-polymer ratio (X_2), and stirring speed during emulsification (X_3)—were evaluated for their effects on particle size, entrapment efficiency, and cumulative drug release. The statistical design enabled efficient optimization with a reduced number of experimental runs and helped identify the formulation exhibiting desirable microsphere characteristics and sustained drug release suitable for oral mucoadhesive delivery.

EXPERIMENTAL DESIGN

Dolutegravir-loaded mucoadhesive microspheres were developed using a three-factor, three-level Box–Behnken Design generated by Design-Expert® software. A total of 15 experimental runs were performed, including center points. The independent variables selected for optimization were polymer concentration (X_1), drug-to-polymer ratio (X_2), and stirring speed (X_3), each studied at low (−1), medium (0), and high (+1) levels. The selected factor levels allowed evaluation of both individual and interaction effects of the variables and facilitated efficient optimization of the microsphere formulation.13

PROCEDURE :

Fifteen Dolutegravir-loaded mucoadhesive microsphere formulations were prepared according to the Box–Behnken Design matrix generated using Design-Expert® software. Accurately weighed quantities of Dolutegravir and the selected polymer(s) were dissolved in dichloromethane to form the internal organic phase. Separately, a 0.5% w/v polyvinyl alcohol (PVA) solution was prepared as the external aqueous phase. The organic phase was added dropwise into the aqueous phase under continuous stirring at the speed specified for each formulation run. Emulsification was continued for 4 h to allow complete solvent evaporation and hardening of the microspheres. The formed microspheres were recovered by centrifugation, washed with distilled water, dried in a vacuum oven at 40°C for 24 h, and stored in airtight containers until further evaluation. The prepared formulations were characterized for particle size, entrapment efficiency, and cumulative drug release, and the experimental data were analyzed using Design-Expert® software to identify the optimized formulation.

Table 02. Experimental Design for Box–Behnken Design

Run	Factor 1A:Polymer concentration% w/v	Factor 2B:Drug : Polymer ratio	Factor 3C:Stirring speedrpm	Response 1Particle sizeµm	Response 2Entrapment efficiency%	Response 3Cumulative drug release%
1	1	1:3	750	325	78.6	82.4
2	1.5	1:3	1000	268	86.9	71.8
3	1.5	1:2	750	311	80.8	80.1
4	2	1:1	750	315	80.1	80.9
5	1	1:2	500	348	74.5	86.3
6	1.5	1:3	500	336	76.3	84.5
7	2	1:2	1000	301	82.5	77.6
8	1.5	1:2	750	309	81.4	78.9
9	1	1:2	1000	272	86.1	72.6
10	2	1:2	500	362	72.3	88.1
11	1	1:1	750	318	79.6	81.5
12	1.5	1:1	1000	288	84.3	75.4
13	2	1:3	750	325	78.7	82.2
14	1.5	1:1	500	358	73	87.5
15	1.5	1:2	750	321	79.2	81.9

STATISTICAL ANALYSIS

The experimental data obtained from the Box–Behnken Design were analyzed using Design-Expert® software. A quadratic polynomial model was developed to evaluate the effect of polymer concentration, drug-to-polymer ratio, and stirring speed on particle size, entrapment efficiency, and drug release. Model

significance was assessed using ANOVA, F-value, p-value, and R^2 statistics. Response surface plots were generated to study variable interactions, and numerical optimization using the desirability function was performed to obtain the optimized microsphere formulation.

PHYSICOCHEMICAL CHARACTERIZATION OF MICROSPHERES

The prepared Dolutegravir mucoadhesive microspheres were characterized to evaluate their physicochemical properties and formulation performance.14

DETERMINATION OF PERCENTAGE YIELD

The percentage yield of the microspheres was determined by comparing the practical yield obtained after drying with the theoretical yield of the formulation components.

PARTICLE SIZE AND POLYDISPERSITY INDEX

Particle size and PDI were measured using a dynamic light scattering (DLS) particle size analyzer (Zetasizer) after dispersing the microspheres in distilled water.

DETERMINATION OF ZETA POTENTIAL

Zeta potential was determined using a Zetasizer to evaluate the surface charge and colloidal stability of the microspheres.

DETERMINATION OF DRUG ENTRAPMENT EFFICIENCY

Drug entrapment efficiency was determined by extracting Dolutegravir from the microspheres and analyzing the drug content using a UV–Visible spectrophotometer at the predetermined λmax.

DETERMINATION OF DRUG LOADING CAPACITY

Drug loading capacity was calculated from the amount of drug present in the microspheres relative to the total weight of the dried microspheres.

FLOW PROPERTIES OF MICROSPHERES

The flow properties of the prepared microspheres were evaluated using standard micromeritic parameters to assess their handling and processing characteristics.

DETERMINATION OF BULK DENSITY

Bulk density was determined by measuring the volume occupied by a known weight of microspheres before compaction.

DETERMINATION OF TAPPED DENSITY

Tapped density was determined by measuring the volume occupied by the microspheres after mechanical tapping.

IN VITRO DRUG RELEASE STUDY

The in vitro drug release study of Dolutegravir mucoadhesive microspheres was performed using a USP Dissolution Apparatus Type II (paddle method). Microspheres equivalent to 50 mg of Dolutegravir were placed in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 50 rpm. Samples were withdrawn at predetermined time intervals up to 24 h and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The samples were filtered and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Dolutegravir. The cumulative percentage drug release was calculated and plotted against time to evaluate the controlled-release behavior of the microsphere formulation and for subsequent drug release kinetic analysis.

RESULTS

Table 1. Independent variable Design

Factor	Level used, actual (coded)	Level used, actual (coded)	Level used, actual (coded)
Independent Variables	Low (-1)	Medium (0)	High (+1)
X1 = Concentration of Polymer (mg)	1.0	1.5	2.0
X2 = Drug : Polymer ratio	1:1	1:2	1:3
X3 =Stirring speed	500	750	1000

Table 4. DoE matrix with experimental responses

Run	Factor 1A:Polymer concentration% w/v	Factor 2B:Drug : Polymer ratio	Factor 3C:Stirring speedrpm	Response 1Particle sizeμm	Response 2Entrapment efficiency%	Response 3Cumulative drug release%
1	1	1:3	750	325	78.6	82.4
2	1.5	1:3	1000	268	86.9	71.8
3	1.5	1:2	750	311	80.8	80.1
4	2	1:1	750	315	80.1	80.9
5	1	1:2	500	348	74.5	86.3
6	1.5	1:3	500	336	76.3	84.5
7	2	1:2	1000	301	82.5	77.6
8	1.5	1:2	750	309	81.4	78.9
9	1	1:2	1000	272	86.1	72.6
10	2	1:2	500	362	72.3	88.1
11	1	1:1	750	318	79.6	81.5
12	1.5	1:1	1000	288	84.3	75.4
13	2	1:3	750	325	78.7	82.2
14	1.5	1:1	500	358	73	87.5
15	1.5	1:2	750	321	79.2	81.9

Table 5. Composition and Response Profile of Optimized Formulation

Parameter	Optimized Formulation Result
Optimized batch	Run 2
Polymer concentration	1.5% w/w
Drug: Polymer ratio	1.3% w/w
Stirring speed	1000 rpm
Particle size	268
Entrapment efficiency	86.9
Cumulative drug relaease	71.8
Model signafigance	$p < 0.05$

Table 6. Physicochemical Characterization of Optimized Dolutegravir Microspheres

Parameter	Value (Mean ± SD)
Percentage Yield (%)	82.36 ± 1.24
Particle Size (µm)	268.00 ± 3.61
Polydispersity Index	0.284 ± 0.012
Zeta Potential (mV)	−21.47 ± 1.18
Entrapment Efficiency (%)	86.90 ± 1.03
Drug Loading (%)	28.64 ± 0.94

Table 7. In Vitro Drug Release of Optimized Dolutegravir Microspheres

Time (h)	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)	Mean ± SD (%)
1	12.4	12.9	12.7	12.67 ± 0.25
2	21.6	22.1	21.9	21.87 ± 0.25
4	34.8	35.4	35.1	35.10 ± 0.30
6	46.2	46.8	46.5	46.50 ± 0.30
8	56.7	57.3	57.0	57.00 ± 0.30
12	66.9	67.5	67.2	67.20 ± 0.30
24	71.3	72.2	71.9	71.80 ± 0.46

PREFORMULATION STUDIES

The preformulation studies demonstrated the suitability of Dolutegravir for microsphere formulation. Organoleptic evaluation showed that the drug was a white to slightly off-white, odorless crystalline powder. UV spectrophotometric analysis revealed a λmax of 259 nm, and the calibration curve exhibited excellent linearity in the concentration range of 2–12 µg/mL with a correlation coefficient (R^2) of 0.999. FTIR spectra of the drug–polymer mixtures retained the characteristic peaks of Dolutegravir without significant shifts, indicating the absence of drug–polymer interactions. DSC analysis showed a characteristic melting endotherm at approximately 188–190°C, confirming the crystalline nature of the drug and its compatibility with the selected polymers. These findings confirmed the physicochemical stability and suitability of Dolutegravir for the development of mucoadhesive microspheres.

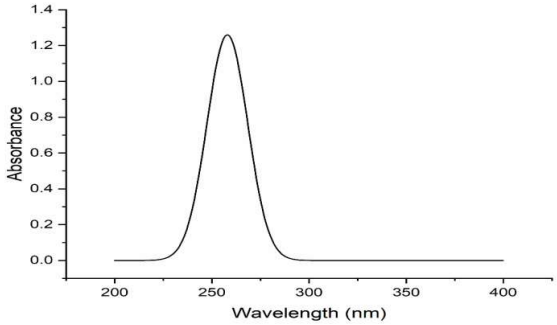

Figure Maximum absorption wavelength (λmax) of Dolutegravir

DRUG-EXCIPIENT COMPATIBILITY STUDIES

BOX–BEHNKEN DESIGN MATRIX AND EXPERIMENTAL RESPONSES

The prepared Dolutegravir mucoadhesive microsphere formulations were evaluated for three dependent responses: particle size, entrapment efficiency, and cumulative drug release. The experimental response values obtained for all 15 runs are presented below.The optimized microsphere formulations exhibited particle size values ranging from 268 to 362 µm, indicating a significant influence of formulation and process variables on microsphere formation. Entrapment efficiency varied between 72.3% and 86.9%, demonstrating the ability of the selected polymers to effectively encapsulate Dolutegravir. The cumulative drug release ranged from 71.8% to 88.1%, reflecting the sustained-release characteristics of the microsphere system. Higher stirring speeds generally produced smaller microspheres with improved entrapment efficiency and lower drug release, whereas lower stirring speeds resulted in larger microspheres with faster drug release. These findings confirmed that the selected formulation variables significantly influenced

the physicochemical characteristics and release behavior of the developed mucoadhesive microspheres.

OPTIMIZED FORMULATION SELECTION

Statistical analysis confirmed that the quadratic model was suitable for optimization of the Dolutegravir mucoadhesive microsphere formulation. Among all formulations, Run 2 was selected as the optimized formulation based on its desirable combination of minimum particle size, maximum entrapment efficiency, and controlled drug release. Run 2 contained 1.5% w/v polymer concentration, 1:3 drug-to-polymer ratio, and a stirring speed of 1000 rpm, producing microspheres with a particle size of 268 µm, entrapment efficiency of 86.9%, and cumulative drug release of 71.8%. These results indicated that Run 2 provided the most favorable balance between microsphere size, drug encapsulation, and sustained-release performance, making it suitable for further characterization and evaluation.

PHYSICOCHEMICAL CHARACTERIZATION OF OPTIMIZED DOLUTEGRAVIR MICROSPHERES

The optimized Dolutegravir mucoadhesive microspheres exhibited satisfactory physicochemical and flow properties, confirming the effectiveness of the optimized formulation variables. The percentage yield was found to be 82.36 ± 1.24%, indicating efficient recovery of microspheres during the solvent evaporation process. The mean particle size was 268.00 ± 3.61 µm with a polydispersity index (PDI) of 0.284 ± 0.012, demonstrating a relatively uniform particle size distribution. The microspheres showed a zeta potential of −21.47 ± 1.18 mV, suggesting adequate colloidal stability and reduced tendency for particle aggregation.The optimized formulation exhibited a high entrapment efficiency of 86.90 ± 1.03%, indicating effective incorporation of Dolutegravir within the polymeric matrix, while the drug loading capacity was 28.64 ± 0.94%, confirming good drug-carrying potential. Evaluation of flow properties revealed a bulk density of 0.44 ± 0.01 g/cm³ and tapped density of 0.51 ± 0.01 g/cm³. The Carr's compressibility index (13.73 ± 0.27%) and Hausner's ratio (1.16 ± 0.01) indicated good flowability, which was further supported by an angle of repose of 27.23 ± 0.41°.

Overall, the optimized Dolutegravir microspheres demonstrated good production yield, uniform particle size distribution, adequate surface charge, high drug entrapment, acceptable drug loading, and excellent flow characteristics, indicating their suitability as a controlled-release mucoadhesive drug delivery system.

Figure2 Image of Optimized microspheres formulation

IN VITRO DRUG RELEASE STUDY

The optimized Dolutegravir mucoadhesive microspheres exhibited a sustained and controlled drug release profile in 0.1 N HCl (pH 1.2) over a period of 24 h. The cumulative drug release increased gradually from 12.67 ± 0.25% at 1 h to 71.80 ± 0.46% at 24 h, indicating prolonged release of Dolutegravir from the polymeric matrix. The initial release may be attributed to surface-associated drug, followed by controlled diffusion through the PLGA-based microsphere matrix. The sustained release behavior demonstrated the ability of the optimized formulation to extend drug release over an extended period, supporting its potential application as an oral controlled-release mucoadhesive drug delivery system

CONCLUSION :

The present study successfully developed and optimized Dolutegravir-loaded mucoadhesive microspheres using the solvent evaporation technique and a Box–Behnken Design approach. Preformulation studies confirmed the suitability of Dolutegravir for formulation development, demonstrating favorable physicochemical properties and compatibility with the selected polymers, namely PLGA, chitosan, and ethylcellulose. The optimization process established the significant influence of polymer concentration, drug-to-polymer ratio, and stirring speed on particle size, entrapment efficiency, and drug release behavior.

The optimized microsphere formulation exhibited desirable physicochemical characteristics, including a percentage yield of 82.36%, particle size of 268.00 µm, polydispersity index of 0.284, zeta potential of −21.47 mV, entrapment efficiency of 86.90%, and drug loading of 28.64%. Micromeritic evaluation demonstrated good flow properties, indicating suitability for handling and processing. In vitro drug release studies revealed a controlled and sustained release profile, with 71.80% cumulative drug release over 24 h, confirming the ability of the polymeric matrix to prolong drug release.

Overall, the developed mucoadhesive microspheres represent a promising oral controlled-release delivery system for Dolutegravir, with potential to enhance gastric residence time, improve therapeutic efficacy, and reduce dosing frequency. Further in vivo studies are warranted to establish clinical performance and bioavailability enhancement.

REFERENCE

1. World Health Organization. Global HIV statistics and HIV fact sheet. Geneva: WHO; 2024.

2. De Clercq E. Antiretroviral drugs. Curr Opin Pharmacol. 2010;10(5):507-15.

3. Min S, Song I, Borland J, Chen S, Lou Y, Fujiwara T, et al. Pharmacokinetics and safety of Dolutegravir. Antimicrob Agents Chemother. 2010;54(1):254-8.

4. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva J, et al. Dolutegravir versus raltegravir in antiretroviral-naive adults. Lancet. 2013;382(9893):700-8.

5. Reese MJ, Savina PM, Generaux GT, Tracey H, Humphreys JE, Kanaoka E, et al. In vitro investigations into Dolutegravir interactions. Drug Metab Dispos. 2013;41(2):353-61.

6. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009;71(3):505-18.

7. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. New Delhi: Vallabh Prakashan; 2012.

8. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive drug delivery systems. Biomaterials. 1996;17(16):1553-61.

9. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005;57(11):1556-68.

10. mucoadhesive microspheres. Drug Dev Ind Pharm. 2005;31(4-5):417-27.

11. Shargel Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of

12. L, Yu ABC. Applied Biopharmaceutics and Pharmacokinetics. 8th ed. New York: McGraw-Hill Education; 2022.

13. Nikam, B. A., & Gayke, A. U. (2022). Formulation development and evaluation of immediate release tablet of paracetamol and orphenadrine citrate by direct compression method. Journal of Science and Arts, 22(3), 735-754.

14. Shinde, G, Jadhav, R., Godge, R,Vikhe, D. Formulation, optimization, and standardization of orodispersible herbal tablets using design of experiments (DOE). Journal of Applied Pharmaceutical Research,2025; 13(4), 313-323.

15. Singh I, Kamboj S, Rana V. Quality by design based fabrication of iron oxide induced mucoadhesive microspheres for enhanced bioavailability of cinnarizine. Curr Drug Deliv. 2017;14(8):1154-1169.