GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

Check for updates

Design and characterization of solid lipid nanoparticles of Ibrutinib

Manikanta Chikka, K. Anie Vijetha * and M. Sunitha Reddy

Centre for Pharmaceutical Sciences, UCESTH, JNTUH

GSC Biological and Pharmaceutical Sciences, 2025, 33(02), 025–032

Publication history: Received on 24 September 2025; revised on 30 October 2025; accepted on 01 November 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.33.2.0423

Abstract

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor used in the treatment of B-cell malignancies, faces significant limitations due to its poor aqueous solubility and low oral bioavailability. To address these challenges, the present study aimed to develop and characterize solid lipid nanoparticles (SLNs) of Ibrutinib using the homogenization–bath sonication method. Preformulation studies, including FTIR and PXRD, confirmed no chemical interaction between Ibrutinib and excipients and revealed conversion of the drug from crystalline to amorphous form, thereby enhancing solubility. Gelucire 44/14 was selected as the optimal lipid, with Labrasol and Tween 80 chosen as lipophilic and hydrophilic surfactants, respectively, based on their emulsification efficiency and stability enhancement properties. Among the formulations developed (S1–S6), formulation S6 showed the most favorable characteristics: a particle size of 132.6 nm, PDI of 0.219, zeta potential of –31.2 mV, and entrapment efficiency of 96%. In vitro drug release of S6 demonstrated a biphasic pattern with an initial burst followed by sustained release, achieving 99.5% release over 24 hours. Drug release kinetics followed the Korsmeyer-Peppas model, suggesting a combined diffusion and erosion mechanism. Stability studies conducted at 40 ± 2 °C and 75 ± 5% RH for one month indicated no significant deviation in physical parameters or drug content, confirming the robustness of the formulation. In conclusion, the optimized SLN formulation of Ibrutinib successfully improved solubility, sustained drug release, and exhibited excellent stability, making it a promising approach for enhancing therapeutic efficacy.

Keywords: Ibrutinib; Solid Lipid Nanoparticles; Sustained Release; Particle Size; Bruton's Tyrosine Kinase.

1. Introduction

Ibrutinib is an orally administered, first-in-class Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of various B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström's macroglobulinemia. Despite its clinical success and broad therapeutic potential, Ibrutinib's development is significantly challenged by its poor aqueous solubility and limited oral bioavailability. Classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, Ibrutinib exhibits high membrane permeability but poor solubility, which limits its absorption and contributes to variable pharmacokinetics[1,2].

To overcome these limitations, nanotechnology-based drug delivery systems—particularly Solid Lipid Nanoparticles (SLNs)—have emerged as a promising strategy. SLNs are submicron colloidal carriers composed of physiological lipids that remain solid at room and body temperatures. They combine the advantages of traditional carriers like liposomes and polymeric nanoparticles, such as biocompatibility, controlled release, physical stability, and protection of labile drugs from chemical degradation[3,4].

The nanoencapsulation of Ibrutinib in SLNs addresses its key pharmaceutical challenges. By reducing particle size to the nanometer range, SLNs significantly increase the drug's surface area, enhancing dissolution rate and solubility. The lipid matrix not only protects Ibrutinib from enzymatic degradation but also facilitates lymphatic uptake, thereby

* Corresponding author: K. Anie Vijetha

bypassing first-pass metabolism, which is a major hurdle in oral Ibrutinib therapy. Moreover, SLNs enable controlled and sustained drug release, potentially improving therapeutic efficacy while minimizing systemic toxicity and dosing frequency[5-8].

2. Materials

Ibrutinib was generously gifted by Natco Pharma Ltd. Various lipids including Gelucire 44/14, Glyceryl monostearate, Stearic acid, Cetyl alcohol, and Glyceryl monooleate were procured from A.S. Chemicals. Surfactants such as Tween 80, Tween 20, Span 80, PEG 200, PEG 400, Pluronic F-68, Labrasol, Capryol 90, and Transcutol P were obtained from Finar and Gattefosse. Analytical-grade solvents including methanol and ethanol were sourced from Merck. All other reagents used were of analytical grade.

2.1. Methods

2.1.1. Determination of λmax

A 10 mg quantity of Ibrutinib was dissolved in methanol and scanned using a UV-Visible spectrophotometer in the 200–400 nm range. The λmax was identified at 260 nm[2,8,9].

2.1.2. Calibration Curve of Ibrutinib

A standard stock solution (100 µg/mL) was prepared in methanol. Serial dilutions (2–14 µg/mL) were measured at 260 nm. A linear calibration curve was established to quantify drug content[2,8,9].

2.1.3. Drug-Excipient Compatibility

Fourier Transform Infrared (FTIR) spectroscopy was used to assess chemical interactions. Pure drug, excipients, and 1:1 drug–excipient physical mixtures were analyzed for characteristic peak shifts or disappearance in the 4000–400 cm^{-1} range using the KBr pellet technique[2-9].

2.1.4. Partition Coefficient (log P)

Using the shake-flask method, Ibrutinib was equilibrated between n-octanol and water. The concentration in each phase was analyzed spectrophotometrically to calculate log P, which was found to be approximately 0.872[10-14].

2.1.5. Powder X-Ray Diffraction (PXRD)

PXRD patterns of pure Ibrutinib and SLN formulations were compared in the 2θ range of 10°–50° using Cu-Kα radiation to determine crystallinity and confirm amorphous transformation[15-17].

2.1.6. Solubility Studies

Ibrutinib solubility was tested in various surfactants and lipids. Excess drug was added to each excipient and shaken at 37 ± 0.2°C for 72 hours. Samples were centrifuged, filtered (0.45 µm), and analyzed by UV-Vis spectroscopy to identify suitable components for formulation[18].

2.1.7. Preparation of Solid Lipid Nanoparticles (SLNs)

SLNs were prepared using a homogenization–bath sonication technique. The lipid (Gelucire 44/14) was melted and mixed with Ibrutinib and Labrasol. Separately, Tween 80 was dissolved in water and added dropwise to the lipid phase at equal temperature. The pre-emulsion was homogenized at 3000 rpm for 6 hours, followed by sonication for 2 hours. The final dispersion was cooled, filtered, and dried[19-24].

2.1.8. Formulation Design

Six formulations (S1–S6) were developed by varying the concentrations of Labrasol (25–100 mg) and Tween 80 (50–100 mg) while keeping the drug (50 mg) and lipid (200 mg) constant in 10 mL volume.

2.1.9. Characterization of SLNs

Particle Size and Zeta Potential

Measured using Dynamic Light Scattering (DLS) at 25°C. Polydispersity index (PDI) and zeta potential were also determined to assess stability.

Entrapment Efficiency

Unentrapped drug was separated by centrifugation. The SLNs were lysed using methanol, and total drug content was analyzed using UV-Visible spectrophotometry.

In Vitro Drug Release

Evaluated using a dialysis bag method in methanolic PBS (pH 7.4, 50:50 v/v) at 37 ± 0.5°C. Aliquots were withdrawn at regular intervals up to 92 hours and analyzed at 260 nm[25-28].

2.1.10. Accelerated Stability Studies

Optimized formulation (S6) was stored at 40 ± 2°C and 75 ± 5% RH for 1 month. Parameters such as particle size, PDI, zeta potential, and drug content were monitored for stability assessment[29].

3. Results and Discussion

The analytical and preformulation studies conducted for the development of Ibrutinib-loaded solid lipid nanoparticles (SLNs) provided a foundational understanding of the drug's physicochemical characteristics and its compatibility with various excipients. UV-Visible spectrophotometric analysis revealed a maximum absorption wavelength (λmax) of 260 nm, which was used for all subsequent quantitative evaluations. A calibration curve constructed in the concentration range of 2–14 µg/mL exhibited excellent linearity, confirming the reliability of UV spectroscopy for Ibrutinib analysis, with a high correlation coefficient (R^2). Furthermore, the partition coefficient (Log P) was calculated to be 0.872, indicating moderate lipophilicity, which is favorable for both encapsulation into lipid matrices and oral bioavailability enhancement.

In the preformulation studies, FTIR spectroscopy was employed to examine potential interactions between Ibrutinib and the selected excipients. The characteristic peaks of the drug were retained in the physical mixtures, indicating no significant chemical interactions or incompatibilities, thereby confirming the formulation's stability. PXRD analysis showed that pure Ibrutinib exhibited sharp crystalline peaks, while the optimized SLN formulation demonstrated a significant reduction in crystallinity, suggesting an amorphous nature. This transition is crucial as it implies enhanced solubility and dissolution rate of the drug when incorporated into the SLN matrix.

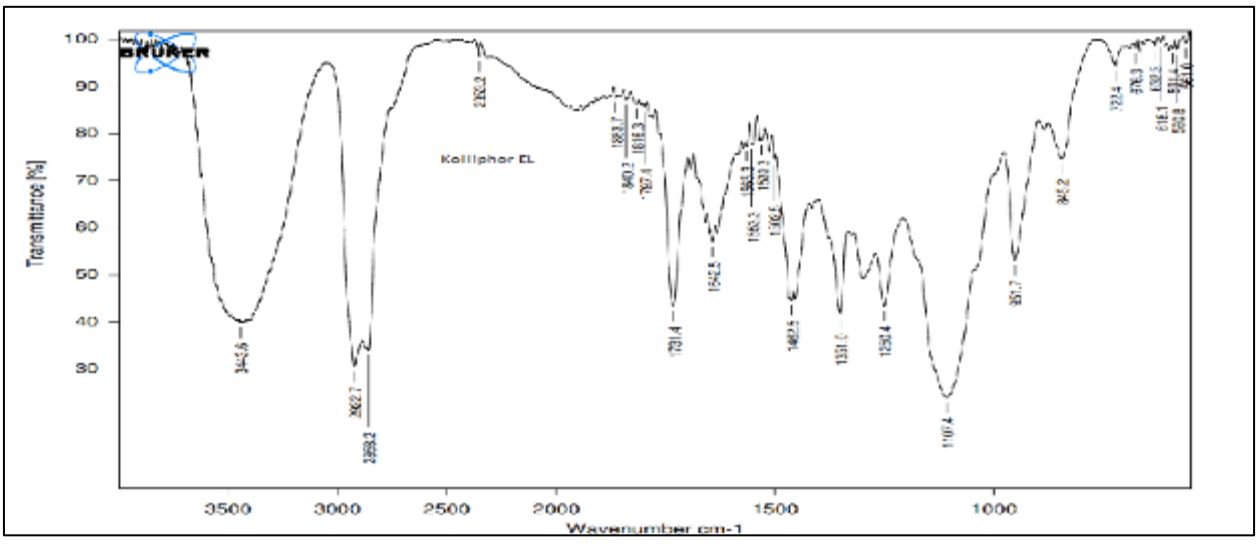

Figure 1 Spectrum IR of Ibrutinib

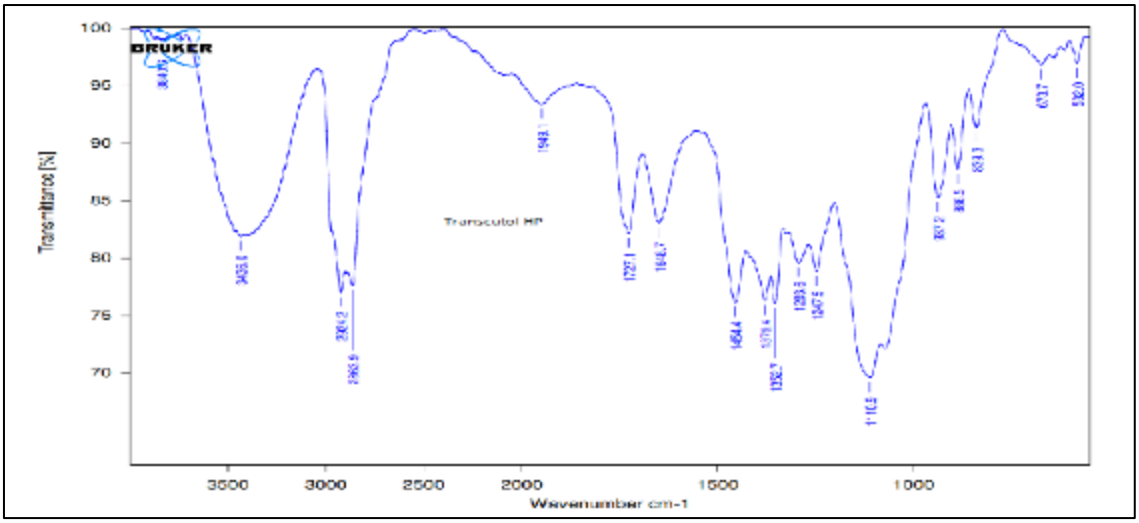

Figure 2 Spectrum IR of Optimized Solid Lipid Nanoparticle

For excipient selection, Gelucire 44/14 emerged as the most suitable solid lipid due to its superior solubilizing capacity for Ibrutinib. Labrasol was selected as the lipophilic surfactant because of its excellent emulsification properties, and Tween 80 was chosen as the hydrophilic surfactant for its ability to stabilize the formulation and improve zeta potential. The SLNs were prepared using the homogenization–bath sonication method, which allowed for efficient size reduction and uniform dispersion. Six different formulations (S1 to S6) were developed by varying the concentrations of surfactants while keeping the drug and lipid content constant.

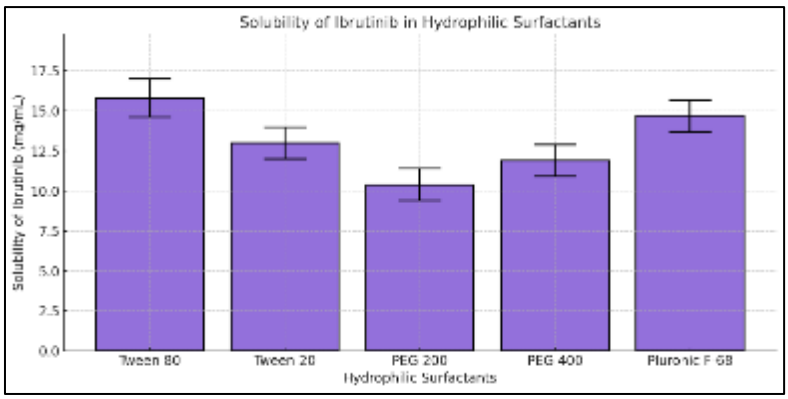

Figure 3 Solubility of Ibrutinib in various Hydrophilic Surfactants

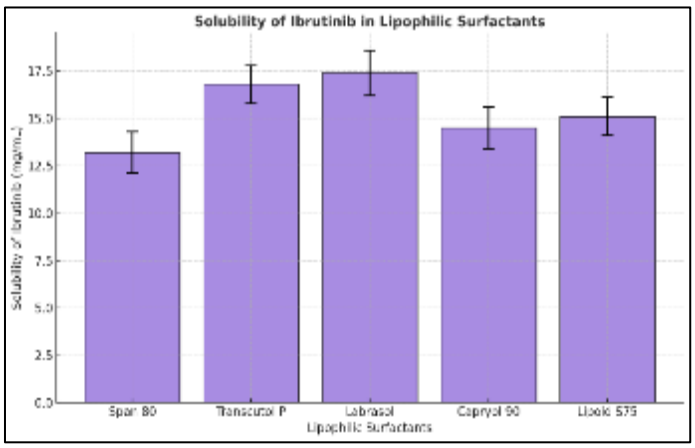

Figure 4 Solubility of Ibrutinib in various Lipophillic Surfactants

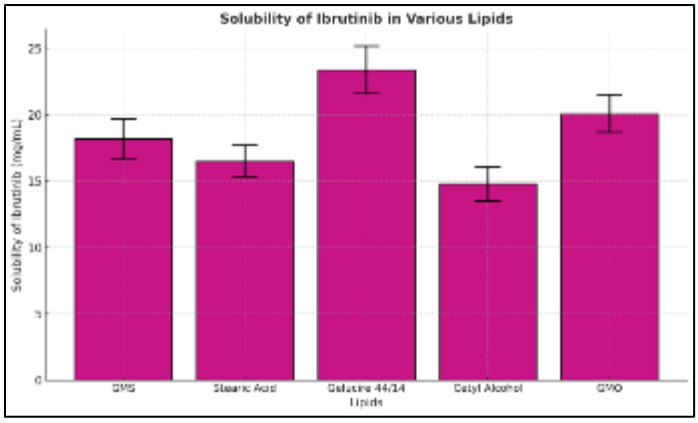

Figure 5 Solubility of Ibrutinib in various Lipids

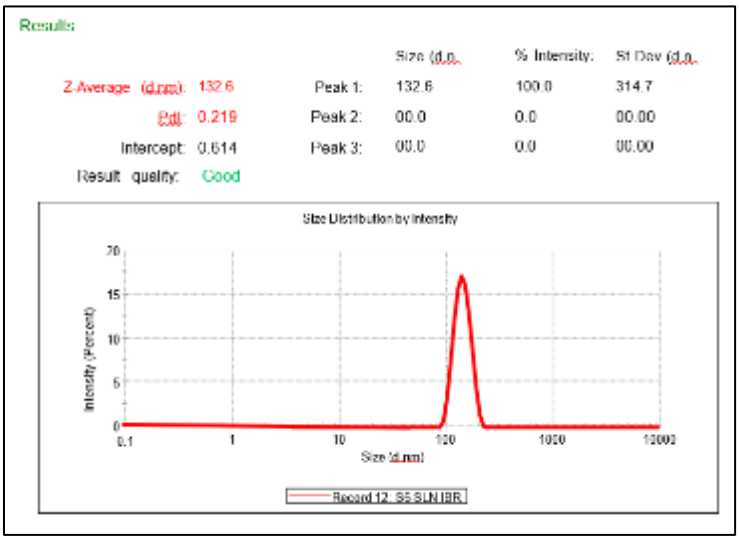

Figure 6 Size and PDI of Optimized formulation S6 (IBR SLN)

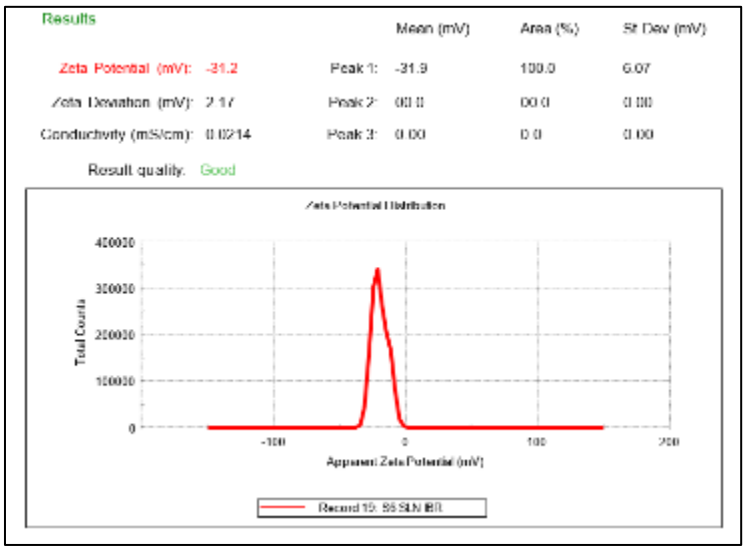

Figure 7 Zeta potential of Optimized formulation S6 (IBR SLN)

Characterization of the optimized formulation, S6, demonstrated highly desirable physicochemical attributes. The average particle size was found to be approximately 132.6 nm, which is ideal for enhanced bioavailability and cellular

uptake. The polydispersity index (PDI) was 0.219, indicating a narrow and uniform particle size distribution. A zeta potential of -31.2 mV confirmed strong electrostatic stability, reducing the risk of particle aggregation. Entrapment efficiency was impressively high, reaching up to 96% for S6, while drug loading was also optimized, suggesting that the formulation can effectively carry and retain the therapeutic agent.

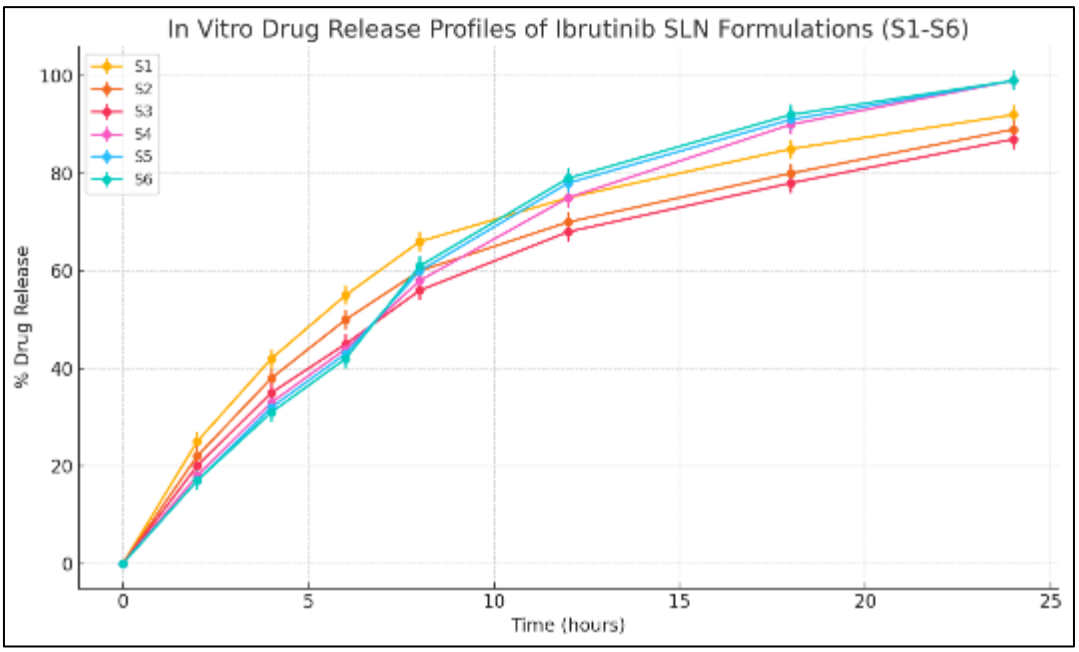

Figure 8 Drug release from Ibrutinib SLN (S1-S6)

In vitro drug release studies using the dialysis bag method in a 50:50 methanol:phosphate buffer saline (PBS) medium at pH 7.4 revealed a biphasic release profile for S6. An initial burst release was observed, likely due to surface-associated drug, followed by a sustained release phase extending up to 24 hours, culminating in approximately 99.5% cumulative drug release. This sustained profile is highly beneficial for maintaining therapeutic drug levels over an extended duration. Kinetic modeling of the release data showed the best fit with the Korsmeyer–Peppas model, indicating that the drug release was governed by a combination of diffusion and erosion mechanisms.

Stability studies conducted under accelerated conditions (40 ± 2°C / 75 ± 5% RH) over one month demonstrated minimal changes in critical quality attributes, affirming the robustness of the formulation. After storage, S6 maintained a particle size of 137.59 nm, a PDI of 0.267, and a zeta potential of -30.4 mV, with drug content remaining at 99.34%. These findings underscore the physical and chemical stability of the optimized Ibrutinib SLN formulation, highlighting its potential for effective and patient-compliant cancer therapy.

4. Conclusion

The study successfully developed a stable and optimized solid lipid nanoparticle (SLN) formulation of Ibrutinib (S6). The formulation demonstrated enhanced solubility and improved oral bioavailability. It exhibited a sustained drug release profile for up to 24 hours, which is ideal for reducing dosing frequency. High entrapment efficiency ensured effective drug loading within the lipid matrix. The optimized SLNs showed uniform particle size, low PDI, and good zeta potential, indicating physical stability. FTIR and PXRD analyses confirmed drug-excipient compatibility and amorphization of the drug. Accelerated stability studies confirmed that the formulation remained stable without major deviations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Cheng, Y., Zhao, P., Wu, S., Yang, T., Chen, Y., Zhang, X., ... & Li, Y. (2019). Cisplatin and ibrutinib co-loaded lipid–polymer hybrid nanoparticles for synergistic treatment of non-small cell lung cancer. *Molecular Pharmaceutics*, 16(10), 4387–4398. https://doi.org/10.1021/acs.molpharmaceut.9b00494

[2] Zhang, Y., Wang, Y., Tang, L., He, Y., & Zhou, Y. (2021). Nanotechnology strategies to improve the bioavailability of ibrutinib. *International Journal of Nanomedicine*, 16, 2139–2151. https://doi.org/10.2147/IJN.S300981

[3] Zhang, J., Tang, J., Wang, Y., Lu, J., Zhou, Y., Li, X., ... & Liu, Y. (2022). Development of lipid-based nanoparticles for ibrutinib delivery to enhance oral bioavailability and therapeutic efficacy. *Drug Delivery and Translational Research*, 12(3), 720–732. https://doi.org/10.1007/s13346-021-00977-4

[4] Liao, Y., Ma, X., Sun, H., Zhou, Y., & Zhang, Y. (2018). Overcoming ibrutinib resistance using dual-drug nanoparticles that co-deliver BTK inhibitor and PI3K inhibitor. *Journal of Controlled Release*, 285, 36–45. https://doi.org/10.1016/j.jconrel.2018.07.027

[5] Burger, J. A., & O'Brien, S. (2018). Ibrutinib for the treatment of chronic lymphocytic leukemia and other B-cell malignancies. *Drugs*, 78(4), 435–445. https://doi.org/10.1007/s40265-018-0870-3

[6] Alexis, F., Pridgen, E., Molnar, L. K., & Farokhzad, O. C. (2008). Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular Pharmaceutics, 5(4), 505–515. https://doi.org/10.1021/mp800051m

[7] Danhier, F., Feron, O., & Préat, V. (2010). To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of Controlled Release, 148(2), 135–146. https://doi.org/10.1016/j.jconrel.2010.08.027

[8] Makadia, H. K., & Siegel, S. J. (2011). Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers, 3(3), 1377–1397. https://doi.org/10.3390/polym3031377

[9] Sahana, B., Santra, K., Basu, S. K., & Mukherjee, B. (2010). Development of biodegradable polymer-based tamoxifen citrate-loaded nanoparticles and effect of some manufacturing process parameters on them: A physicochemical and in vitro evaluation. International Journal of Nanomedicine, 5, 621–630. https://doi.org/10.2147/IJN.S12136

[10] Shakeel, F., Haq, N., Alanazi, F. K., & Alsarra, I. A. (2011). Solubility and thermodynamic function of anticancer drug 5-fluorouracil in various solvents. *Journal of Chemistry*, 8(1), 469–474. https://doi.org/10.1155/2011/614239

[11] Avdeef, A. (2012). Absorption and drug development: Solubility, permeability, and charge state (2nd ed.). Hoboken, NJ: Wiley-Interscience.

[12] Bae, Y. H., & Park, K. (2011). Targeted drug delivery to tumors: Myths, reality and possibility. Journal of Controlled Release, 153(3), 198–205. https://doi.org/10.1016/j.jconrel.2011.06.001

[13] Cheng, Y., Zhao, P., Wu, S., Yang, T., Chen, Y., Zhang, X., ... & Li, Y. (2019). Cisplatin and ibrutinib co-loaded lipid–polymer hybrid nanoparticles for synergistic treatment of non-small cell lung cancer. Molecular Pharmaceutics, 16(10), 4387–4398. https://doi.org/10.1021/acs.molpharmaceut.9b00494

[14] Zhang, Y., Wang, Y., Tang, L., He, Y., & Zhou, Y. (2021). Nanotechnology strategies to improve the bioavailability of ibrutinib. International Journal of Nanomedicine, 16, 2139–2151. https://doi.org/10.2147/IJN.S300981

[15] Sharma, D., Maheshwari, R., Tekade, R. K., & Tekade, M. (2020). Nanoparticles in the treatment of hematologic malignancies. In R. K. Tekade (Ed.), Nanotechnology-based approaches for targeting and delivery of drugs and genes (pp. 365–390). Academic Press. https://doi.org/10.1016/B978-0-12-819660-1.00013-9

[16] Zhang, J., Tang, J., Wang, Y., Lu, J., Zhou, Y., Li, X., ... & Liu, Y. (2022). Development of lipid-based nanoparticles for ibrutinib delivery to enhance oral bioavailability and therapeutic efficacy. Drug Delivery and Translational Research, 12(3), 720–732. https://doi.org/10.1007/s13346-021-00977-4

[17] Liao, Y., Ma, X., Sun, H., Zhou, Y., & Zhang, Y. (2018). Overcoming ibrutinib resistance using dual-drug nanoparticles that co-deliver BTK inhibitor and PI3K inhibitor. Journal of Controlled Release, 285, 36–45. https://doi.org/10.1016/j.jconrel.2018.07.027

[18] Yalkowsky, S. H., & He, Y. (2003). Handbook of aqueous solubility data. CRC Press.

[19] Bala, I., Hariharan, S., & Kumar, M. N. V. R. (2004). PLGA nanoparticles in drug delivery: The state of the art. Critical Reviews™ in Therapeutic Drug Carrier Systems, 21(5), 387–422. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i5.10

[20] Mehnert, W., & Mäder, K. (2001). Solid lipid nanoparticles: Production, characterization and applications. Advanced Drug Delivery Reviews, 47(2-3), 165–196. https://doi.org/10.1016/S0169-409X(01)00105-3

[21] Shah, R. M., Malherbe, F., Eldridge, D., Palombo, E. A., & Harding, I. H. (2014). Physicochemical characterization of solid lipid nanoparticles (SLNs) prepared by a novel microemulsion technique. Journal of Colloid and Interface Science, 428, 286–294. https://doi.org/10.1016/j.jcis.2014.04.019

[22] Jain, S., Jain, P., Umamaheshwari, R. B., & Jain, N. K. (2003). Transfersomes—A novel vesicular carrier for enhanced transdermal delivery: Development, characterization, and performance evaluation. Drug Development and Industrial Pharmacy, 29(9), 1013–1026. https://doi.org/10.1081/DDC-120024622

[23] Yuan, H., Wang, L. L., Du, Y. Z., You, J., Hu, F. Q., & Zeng, S. (2007). Preparation and characteristics of nanostructured lipid carriers for control-releasing progesterone by melt-emulsification. Colloids and Surfaces B: Biointerfaces, 60(2), 174–179. https://doi.org/10.1016/j.colsurfb.2007.06.019

[24] Honary, S., & Zahir, F. (2013). Effect of zeta potential on the properties of nano-drug delivery systems—A review (Part 1). Tropical Journal of Pharmaceutical Research, 12(2), 255–264. https://doi.org/10.4314/tjpr.v12i2.19

[25] Parhi, R., Suresh, P., & Pattnaik, S. (2016). Development and characterization of solid lipid nanoparticles: A review. Journal of Applied Pharmaceutical Science, 6(9), 170–183. https://doi.org/10.7324/JAPS.2016.60925

[26] Nair, R., Kumar, A. C., & Kumria, R. (2013). Solid lipid nanoparticles–natural lipids based drug delivery systems. International Research Journal of Pharmacy, 4(1), 9–16. https://doi.org/10.7897/2230-8407.04103

[27] Iqbal, J., Shahnaz, G., & Ahmad, H. (2022). Development and characterization of ibrutinib-loaded SLNs for improved oral bioavailability and controlled drug release. AAPS PharmSciTech, 23(6), 161. https://doi.org/10.1208/s12249-022-02318-5

[28] Kaur, G., Mehta, S. K., & Rana, D. (2020). Preparation, optimization, and evaluation of ibrutinib-loaded lipid nanoparticles for improved delivery. Materials Science and Engineering: C, 112, 110872. https://doi.org/10.1016/j.msec.2020.11087.

[29] ICH (International Conference on Harmonisation). (2003). *ICH Q1A(R2) – Stability Testing of New Drug Substances and Products*. Geneva: ICH Harmonised Tripartite Guideline.