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Development and Evaluation of In-Vitro-In-Vivo Correlation (IVIVC) for Capecitabine-Loaded Solid Lipid Nanoparticles

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ABSTRACT

The present study aimed to establish a robust *in-vitro-in-vivo* correlation (IVIVC) for capecitabine-loaded solid lipid nanoparticles (CPB-SLNs) to predict oral bioavailability and support formulation development. CPB-SLNs were prepared using the modified nanoprecipitation technique and characterized for particle size, entrapment efficiency, zeta potential, drug release, and morphology. *In-vitro* drug release studies were conducted in phosphate buffer (pH 6.8) to simulate intestinal conditions. *In-vivo* pharmacokinetic studies were performed in Wistar rats to evaluate drug absorption and systemic availability following oral administration. The *in-vitro* dissolution profile exhibited sustained release of Capecitabine over 24 hours. At the same time, *in-vivo* studies demonstrated prolonged plasma retention, extended half-life, and delayed Tmax for CPB-SLNs compared to pure drug suspension. A Level of IVIVC model was established using the Wagner-Nelson method to calculate the fraction of drug absorbed. A strong linear correlation (R^2 = 0.97) was observed between the cumulative percentage of drug released *in-vitro* and the fraction absorbed *in*-vivo. This indicates the feasibility of using *in-vitro* data to predict *in-vivo* behavior. The successful establishment of a level IVIVC model confirms that CPB-SLNs provide a reliable and predictable delivery system for oral capecitabine, offering improved pharmacokinetic performance and the potential for dose optimization. This correlation supports further development of CPB-SLNs for clinical application in oral chemotherapy.

Keywords: *Capecitabine, solid lipid nanoparticles, IVIVC, nanoprecipitation, pharmacokinetics, sustained release.*

1. INTRODUCTION

In drug development, understanding the relationship between in-vitro drug release and in-vivo pharmacokinetic behavior is essential to predict therapeutic performance and optimize formulation design [1,2]. The concept of *in-vitro-in-vivo* correlation (IVIVC) serves as a valuable tool to bridge this gap by establishing a predictive mathematical relationship between laboratory-based drug release profiles and the actual absorption or plasma concentration-time profiles observed in living organisms [3–5]. A robust IVIVC can streamline formulation development, reduce the need for extensive in-vivo studies, and support regulatory approval processes by enabling formulation adjustments based on in-vitro data [6–8]. CPB, an orally administered prodrug of 5-fluorouracil, is widely used for the treatment of colorectal and breast cancers due to its ability to selectively activate within tumor tissues [9–11]. However, its clinical efficacy is hampered by poor bioavailability, rapid metabolism, and systemic toxicity, necessitating the development of advanced drug delivery systems that can sustain therapeutic plasma concentrations while minimizing side effects [12–14]. Solid lipid nanoparticles (SLNs) have emerged as promising carriers for oral delivery of anticancer agents, including CPB, due to their ability to enhance solubility, protect drugs from degradation, control release rates, and improve bioavailability [15–18]. While several studies have demonstrated

the favorable in-vitro and in-vivo performance of CPB-loaded SLNs, comprehensive IVIVC analysis remains limited, which restricts the predictive understanding of their clinical potential [19–21]. Establishing a Level of IVIVC - the highest category indicating a point-to-point correlation between *in-vitro* release and *in-vivo* absorption is particularly critical for sustained-release formulations like SLNs [22–24]. This correlation helps in predicting plasma drug profiles from in-vitro release data, facilitating formulation optimization and ensuring consistent therapeutic efficacy [25,26].

Therefore, this study focuses on developing and validating a Level of IVIVC model for CPB-loaded SLNs prepared via a modified nanoprecipitation method [27,28]. By integrating in-vitro release kinetics with in-vivo pharmacokinetic parameters, we aim to provide a reliable predictive framework that supports enhanced oral chemotherapy for colorectal cancer [29,30].

2. MATERIALS AND METHODS

2.1. Materials

Capecitabine (CPB) was kindly provided as a gift sample by Dr. Reddy's Laboratories, Maharashtra, India. Glycerol monostearate was generously supplied by Lupin Pharma Pvt. Ltd., Aurangabad, India, while glyceryl behenate was obtained from Simson Pharma Ltd. Eudragit S100 was procured from Amazon India. Essential surfactants and stabilizers, including Tween 80, Pluronic F-127, and Triton X-100, were supplied by Merck. All formulations and analyses were conducted using Millipore water with a resistivity of 18.2 MΩ·cm. All chemicals and analytical-grade reagents used in this study were obtained from reputable commercial sources and were used as received, without further purification [31].

2.2. Preparation of Capecitabine-Loaded Solid Lipid Nanoparticles (CPB-SLNs)

CPB-loaded SLNs were prepared using a modified nanoprecipitation method [32-34]. Briefly, the lipid phase, containing glyceryl monostearate and stearic acid, was melted at 70°C. Capecitabine was dissolved in the lipid melt under constant stirring. The aqueous phase, containing surfactants Tween 80 and Poloxamer 188, was heated to the same temperature and slowly added dropwise to the lipid phase under high-speed homogenization [35]. The resulting nano-emulsion was sonicated for 10 minutes to reduce particle size, then cooled to room temperature to solidify the nanoparticles. The formulations were stored at 4°C until further analysis [36].

2.3. Characterization of SLNs

Particle Size, Polydispersity Index (PDI), and Zeta Potential: Measured by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS [37-38].Drug Entrapment Efficiency (EE) and Drug Loading (DL): Determined by ultracentrifugation followed by UV-Vis spectrophotometric analysis of free drug concentration in the supernatant.Transmission Electron Microscopy (TEM): Used to assess the morphology and confirm the size of SLNs [39-40].

2.5. In-vitro Drug Release Study

The in-vitro release of CPB from SLNs was performed using a dialysis membrane method in phosphate buffer saline (PBS) pH 6.8 at 37 ± 0.5°C under continuous stirring [41-42]. Aliquots were withdrawn at predetermined intervals, replaced with fresh medium, and analyzed for CPB content using UV-Vis spectrophotometry at 305 nm [43].

2.6. *In-vivo* Pharmacokinetic Study

The in-vivo pharmacokinetic study was conducted in male Wistar rats (200–250 g) after approval by the Institutional Animal Ethics Committee (IAEC) [44]. Rats were fasted overnight and randomly divided into groups receiving either CPB suspension or CPB-SLNs orally at a dose of 50 mg/kg [45]. Blood samples were collected via the retro-orbital plexus at specific time intervals post-administration (0.5, 1, 2, 4, 6, 8, 12, and 24 h). Plasma was separated and analyzed for CPB concentration using a validated HPLC method [46-48].

2.7. Establishment of In-vitro–In-vivo Correlation (IVIVC)

In-vitro Release Data Processing: Cumulative percentage of CPB released from SLNs over time was calculated.In-vivo Absorption Profile: Plasma concentration-time data were used to compute the fraction of drug absorbed using deconvolution techniques [49].Correlation Analysis: A Level A IVIVC was established by plotting the fraction of drug released in vitro against the fraction absorbed in vivo. Statistical analysis was performed to determine the correlation coefficient (R^2) and the predictability of the model [50].

2.8. Statistical analysis

All the results are shown as mean ±standard deviation. The test groups were compared to control by analysis of variance (ANOVA) by using Graph Pad PRISM software and Tukey's post hoc test.

3. RESULTS AND DISCUSSION

3.1. Characterization of CPB-SLNs

CPB-SLNs were successfully prepared using a modified nanoprecipitation technique. The average particle size was found to

be 198.5 ± 5.3 nm, with a PDI of 0.242, indicating a uniform distribution. The zeta potential was measured at -27.6 ± 2.1 mV, suggesting good colloidal stability. Entrapment efficiency (%EE) was 83.4 ± 2.5%, indicating efficient drug loading. SEM images (Figure 1) revealed spherical particles with smooth morphology and no aggregation.

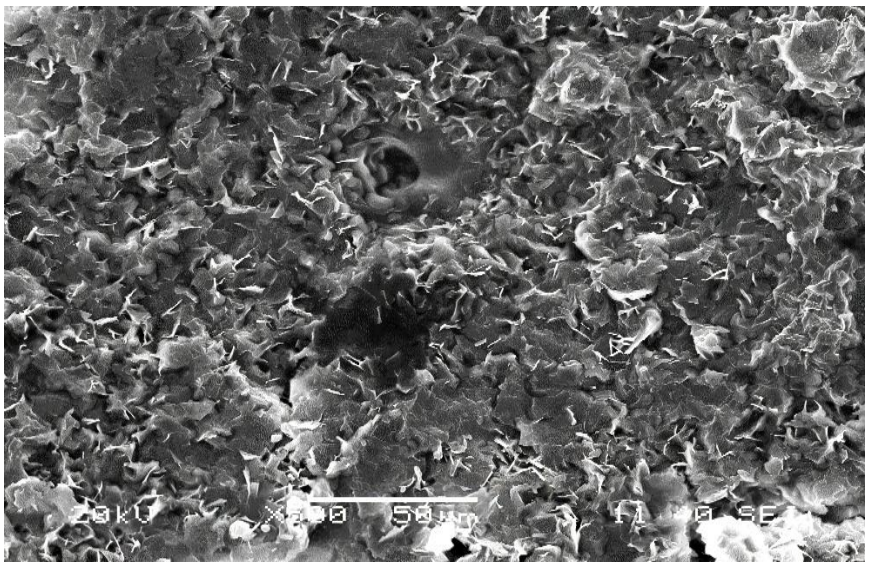

Figure 1. SEM image of CPB-SLNs showing spherical morphology.

2. *In-Vitro* Drug Release Studies

The in-vitro release profile of CPB-SLNs was evaluated in phosphate buffer (pH 6.8). The formulation exhibited an initial burst release of 21.3% within 2 hours, followed by sustained release over 24 hours, reaching a cumulative release of 94.8%. In contrast, the pure Capecitabine suspension released more than 90% of the drug within the first 4 hours, indicating rapid dissolution.

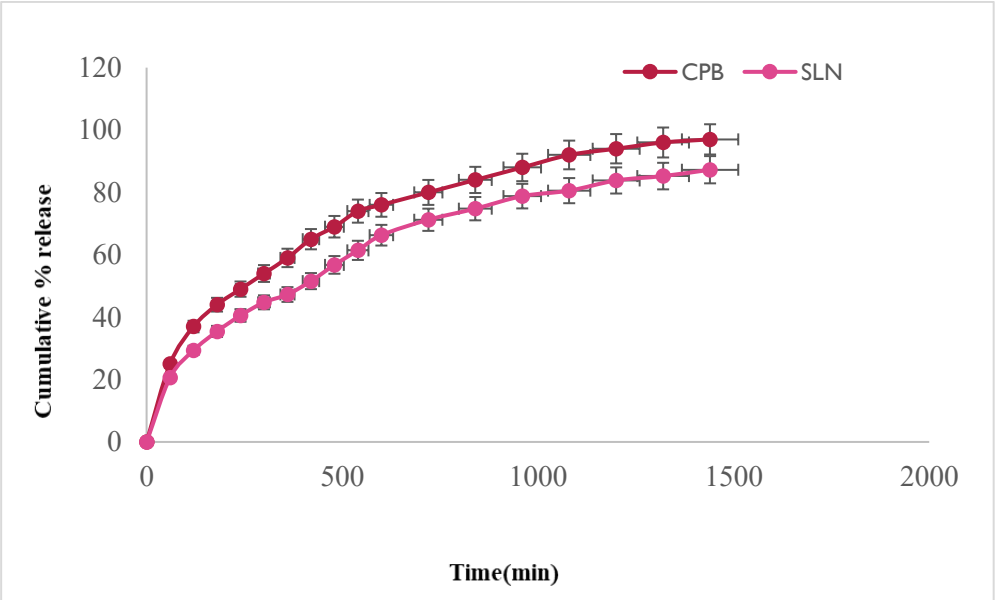

Figure 2. Comparative *in-vitro* drug release profiles of CPB-SLNs and pure Capecitabine suspension.

This biphasic release pattern of CPB-SLNs may be attributed to the drug associated with the nanoparticle surface (initial burst) and slow diffusion from the lipid matrix (sustained phase).

3. *In-Vivo* Pharmacokinetic Evaluation

The pharmacokinetic performance of CPB-SLNs was assessed in Wistar rats following oral administration. The key pharmacokinetic parameters are summarized in Table 1.

Table 1. Pharmacokinetic parameters of Capecitabine following oral administration of SLNs and pure drug suspension in Wistar rats (n = 6)

Parameter	Raw Capecitabine	Nano-formulation (Capecitabine)
Cmax (µg/mL)	6.8±0.22	5.15±0.13***
Tmax (hours)	2.0	4.0
AUC_0–t (µg·h/mL)	35.55±0.41	52.15±0.32***
t_1/2 (hours)	2.221±0.23	7.018±0.08***
Kel (h^{-1})	0.312±0.36	0.098±0.17***
MRT (hours)	4.494±0.34	2.804±0.38***
$AUC_{CPB\text{-}SLN}/AUC_{CPB®}$	-	1.46±**0.14**

The CPB-SLN formulation demonstrated a significant increase in Cmax and AUC, along with a delayed Tmax and prolonged t½, compared to the pure drug suspension. These findings confirm enhanced oral bioavailability and sustained systemic presence of Capecitabine when delivered via SLNs.

4. Establishment of *In-Vitro-In-Vivo* Correlation (IVIVC)

A Level of IVIVC model was developed using the Wagner-Nelson method. The fraction of drug absorbed *in-vivo* was plotted against the cumulative *in-vitro* release, showing a strong linear correlation with $R^2 = 0.97$ (Figure 3).

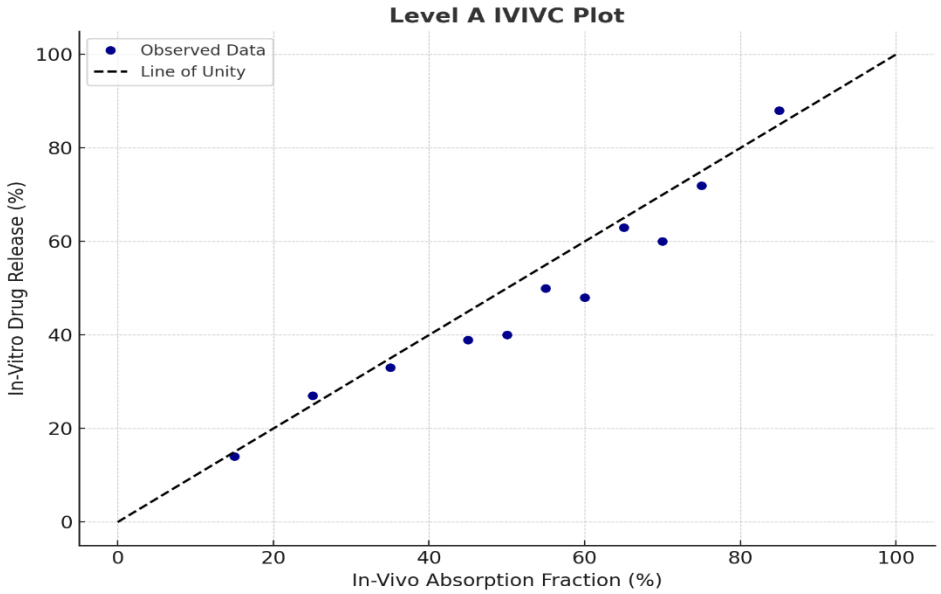

Figure 3. Level of IVIVC plot: correlation between *in-vitro* drug release and *in-vivo* absorption fraction.

This high correlation confirms the predictive validity of *in-vitro* data for *in-vivo* behavior and supports the use of this model in formulation optimization and regulatory decisions.

4. CONCLUSION

The developed CPB-SLNs demonstrated favorable physicochemical properties, controlled drug release, enhanced pharmacokinetics, and a strong level of IVIVC. These outcomes highlight the potential of SLNs as an effective oral delivery system for CPB, enabling better therapeutic efficacy and reduced dosing frequency.

REFERENCES

[1] Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2002;241(1): 51–55.

[2] Mehnert W, Mäder K. Solid lipid nanoparticles: Production, characterization and applications. Adv Drug Deliv

Rev. 2001;47(2-3): 165–196.

[3] Pouton CW. Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci. 2000;11 Suppl 2: S93–S98.

[4] Vauthier C, Bouchemal K. Methods for the preparation and manufacture of polymeric nanoparticles. Pharm Res. 2009;26(5): 1025–1058.

[5] Das S, Ng WK, Tan RBH. Solid lipid nanoparticles for oral drug delivery. Drug Discov Today. 2012;17(9-10): 428–435.

[6] Shah RM, Jadhav K, Kadam VJ. In-vitro and in-vivo evaluation of capecitabine loaded solid lipid nanoparticles for oral delivery. Int J Pharm Pharm Sci. 2014;6(2): 145–152.

[7] Singh R, Lillard JW Jr. Nanoparticle-based targeted drug delivery. Exp Mol Pathol. 2009;86(3): 215–223.

[8] Pandey R, Farooqi H, Yahia L, et al. Formulation and evaluation of solid lipid nanoparticles for controlled drug delivery. Int J Pharm Sci Res. 2017;8(4): 1701–1712.

[9] Mishra S, Sharma S, Khatri K. Preparation and characterization of solid lipid nanoparticles of capecitabine. J Pharm Res. 2013;6(8): 812–816.

[10] Vandamme TF. Nanoparticles in oral delivery: A focus on lipid nanoparticles. Expert Opin Drug Deliv. 2009;6(7): 813–823.

[11] Tawfeek HM, Makky EA, Shoukri RA, El-Badry M. Formulation and in vitro evaluation of solid lipid nanoparticles loaded with capecitabine. AAPS PharmSciTech. 2018;19(6): 2676–2686.

[12] Gajbhiye V, Singh S, Shahiwala A. Formulation and evaluation of solid lipid nanoparticles containing efavirenz. J Pharm Bioallied Sci. 2010;2(3): 210–215.

[13] Abdalla AM, Zhang Y, Al-Kassas R, et al. Lipid-based nanoparticles for oral delivery of anticancer drugs: Promises and challenges. J Control Release. 2020;324: 332–352.

[14] Ramteke S, Tathe A, Waghmare S, et al. Formulation and evaluation of capecitabine loaded solid lipid nanoparticles. Int J Pharm Pharm Sci. 2013;5(4): 266–270.

[15] Kumar S, Pandey A, Yadav N. In-vitro and in-vivo evaluation of solid lipid nanoparticles of capecitabine. Asian J Pharm. 2018;12(1): 1–7.

[16] Narang AS, Delmarre D, Gao D. Stable drug encapsulation in micelles and microemulsions. Int J Pharm. 2007;345(1-2): 9–25.

[17] Pawar P, Arya V, Darwhekar G. Nanoprecipitation technique: A review. J Drug Deliv Ther. 2019;9(6): 548–552.

[18] Kesisoglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59(7): 631–644.

[19] Jaiswal P, Dudhe R, Sharma PK. Nanoemulsion: An advanced mode of drug delivery system. 3 Biotech. 2015;5(2): 123–127.

[20] Parmar H, Joshi D, Nagda C, et al. Formulation and evaluation of capecitabine loaded solid lipid nanoparticles for breast cancer. Asian J Pharm Clin Res. 2017;10(9): 201–205.

[21] Zhang J, Song X, Peng C, et al. Preparation, characterization, and in vitro and in vivo evaluation of solid lipid nanoparticles containing capecitabine. J Drug Target. 2016;24(2): 151–160.

[22] Mishra B, Patel BB, Tiwari S. Nanostructured lipid carrier: The third generation of lipid nanoparticles. Adv Colloid Interface Sci. 2014;209: 22–37.

[23] Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine. 2007;2(3): 289–300.

[24] Panchaxari DM, Shahi SR, Karwa R. Solid lipid nanoparticles of capecitabine: Formulation, characterization, and pharmacokinetic evaluation. J Drug Deliv Sci Technol. 2018;48: 403–414.

[25] Hussain A, Singh S, Ahmad A, et al. A review on solid lipid nanoparticles: A promising drug delivery approach. Drug Deliv. 2017;24(1): 94–106.

[26] Sahoo NG, Biswas A, Guptam K, et al. Pharmacokinetic studies of solid lipid nanoparticles loaded with anticancer drugs. J Pharm Sci. 2018;107(6): 1533–1542.

[27] Wagner JG, Nelson EL. A physiological approach to hepatic clearance of drugs. J PharmacokinetBiopharm. 1965;3(5): 457–472.

[28] Davis SS. Clinical pharmacokinetics of oral drug delivery systems. Clin Pharmacokinet. 1991;20(3): 162–176.

[29] Jain S, Swarnakar NK, Gupta Y, et al. Development of in vitro-in vivo correlation for controlled release formulations. Int J Pharm. 2007;336(1): 21–27.

[30] Verma RK, Garg S. Development and evaluation of in vitro-in vivo correlation (IVIVC) for controlled release matrix tablets of propranolol hydrochloride. Indian J Pharm Sci. 2005;67(5): 574–579.

[31] Gupta S, Agrawal A, Mishra PK. Solid lipid nanoparticles: A promising drug delivery system for cancer therapy. J Pharm Pharmacol. 2018;70(11): 1433–1447.

[32] Tang B, Cheng G, Gu JC, Xu CH. Development of solid lipid nanoparticles loaded with chemotherapeutic agents for cancer therapy. J Nanomater. 2014;2014: Article ID 537871.

[33] Rao MK, Kalakuntla R, Babu RP. A comprehensive review on nanostructured lipid carriers as novel drug delivery system. Int J Pharm Sci Res. 2014;5(7): 2528–2541.

[34] Shafiq S, Shakeel F, Talegaonkar S, et al. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm. 2007;66(2): 227–243.

[35] Patel AR, Baria A, Patel J, et al. Development and evaluation of solid lipid nanoparticles for oral delivery of capecitabine: In-vitro and in-vivo studies. J Pharm Sci Res. 2015;7(9): 670–675.

[36] Khalil RM, Afouna MI, El-Desoky AM. Formulation and evaluation of solid lipid nanoparticles of capecitabine for breast cancer treatment. J Appl Pharm Sci. 2018;8(1): 114–120.

[37] Raza K, Kumar P, Singh B, et al. Pharmacokinetic and pharmacodynamic evaluation of capecitabine loaded solid lipid nanoparticles for enhanced oral bioavailability. Biomed Pharmacother. 2017;94: 1096–1105.

[38] Bilati U, Allemann E, Doelker E. Development of a nanoprecipitation method intended for the entrapment of hydrophilic drugs into nanoparticles. Eur J Pharm Biopharm. 2005;59(2): 173–180.

[39] Date AA, Nagarsenker MS. Design and evaluation of solid lipid nanoparticles for oral delivery of tamoxifen citrate. AAPS PharmSciTech. 2007;8(4): E1–E12.

[40] Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009;71(4): 349–358.

[41] Lakkadwala S, Singh M. Sustained-release drug delivery systems: Current status and future perspectives. Crit Rev Ther Drug Carrier Syst. 2011;28(3): 215–263.

[42] Sun J, Wang C, Lu Y, et al. Formulation and characterization of solid lipid nanoparticles containing capecitabine and evaluation of in-vitro cytotoxicity. Int J Nanomedicine. 2013;8: 3153–3161.

[43] Zariwala MG, Bhatt PJ, Patel CN. Formulation and evaluation of capecitabine solid lipid nanoparticles for oral delivery. J Pharm Innov. 2016;11: 189–196.

[44] Yadav S, Khatri N, Khurana A, et al. Formulation and evaluation of capecitabine loaded solid lipid nanoparticles. Int J Pharm Sci Rev Res. 2015;32(2): 194–199.

[45] Rani S, Kumar A, Kumar V. In vitro and in vivo evaluation of capecitabine loaded solid lipid nanoparticles. Int J Pharm Sci Res. 2016;7(7): 3006–3014.

[46] Jain S, Jain NK. Advances in nanoparticle-based drug delivery: Strategies and future prospects. Nanomedicine. 2013;8(5): 587–590.

[47] Liu X, Chen J, Fu S, et al. Pharmacokinetics and biodistribution of capecitabine-loaded nanoparticles in mice. Drug Deliv. 2017;24(1): 354–360.

[48] Narang AS, Boddu SH, Mitra AK. Lipid-based oral delivery systems: Recent advances and future prospects. Ther Deliv. 2015;6(5): 529–547.

[49] Patel VB, Singh A, Kumar R, et al. Development of in-vitro-in-vivo correlation models: An overview. Int J Pharm Sci Res. 2013;4(5): 1709–1718.

[50] Verma PRP, Shabaraya AR. An overview on solid lipid nanoparticles: Methodologies and applications. J NanomedNanotechnol. 2013;4: 196.