6. Summary and Conclusion

6.1. Summary

- USFDA approved polymer (PCL) carrier based nanoparticles of berberine was prepared successfully using nanoprecipitation technique.
- Process variables such as needle size 26 G (0.45 mm i.d), injection rate (6 ml/min) and stirring rate (800 rpm) were optimized for preparation of nanoparticles.
- Selected aqueous phase (pH 4.5 phthalate buffer), stabilizer (F-68) and QbD based optimization of drug to polymer ratio (1:3) and stabilizer concentration (50 mM) play a key role in achieving higher entrapment efficiency (82%), optimal particle size (196.71 ±1.47), narrow polydispersity index (0.153 ± 0.012 nm) and zeta potential -26.3 ± 0.8 mV).
- It can be concluded that prior selection of aqueous phase, stabilizer and methodical optimization of formulation variables would be helpful to achieve higher entrapment of hydrophilic drugs by nanoprecipitation method.
- BBR - NP were efficiently surface coated using vitamin E TPGS (1 % w/v).
- BBR-SCNP have particle size (208.48 ± 1.07 nm), PDI (0.166 ± 0.002) and ZP(-10.32 ± 1.2 mV).

- FT-IR studies confirmed the co existence of vitamin E TPGS in BBR - SCNP.
- The solid state characterizations such as DSC confirmed amorphous state of BBR in both of the formulations i.e. BBR - NP and BBR - SCNP.
- PXRD assured that BBR was in amorphous state in BBR – SCNP.
- TEM images indicate that particles of both of the formulations are of in spherical shape. Tiny surrounding layer was observed in TEM images of BBR-SCNP.
- BBR exhibited sustained drug release pattern and around 82% of the drug was released from nanoformulations in 24 h.
- No significant difference was observed in drug release studies of both of the formulations (BBR-NP and BBR-SCNP).
- Both of the formulations followed non-ficikian drug release mechanism.
- Insignificant changes in the particle properties for 180 days of storage period indicate the stability of both of the formulation.
- The quantitative and morphological characterization tools illustrated that surface coated BBR NP (BBR – SCNP) were stable at different SBFs and plasma compared to uncoated NP (BBR – NP).
- It is also demonstrated that STC (bile salt) played crucial role in prevention of particles aggregation at SBF (pH 6.8).

- It is suggested that administration of NP via oral route may be preferable after meals as secretion of bile salts due to meals can help in absorption of NP through intestine without aggregation.
- The result indicates that vitamin E TPGS surface coating is helpful in maintenance of stability of BBR nanoparticles at systemic conditions (pH 6.8 and 7.4).
- The AUC of BBR-NP was 3.23 and 1.52 folds higher compared to BBR aqueous solution and BBR with verapamil treated group, respectively.
- It indicates that encapsulation of BBR in nanosize form enough to circumvention of P-gp efflux effect.
- Pharmacokinetic study revealed that oral bioavailability of BBR increased by 3.5 folds for BBR – SCNP formulations compared to BBR aqueous solution whereas it was 1.70 folds compared to group which received combination of BBR and verapamil.
- Nanosize of the formulation and surface coating with vitamin E TPGS (P-gp efflux inhibition excipient) cumulatively facilitated higher absorption of drug as well as reduced elimination of drug. Ultimately, it leads to higher bioavailability of BBR and longer retention of NP in systemic circulation.

- The results indicate that administration of BBR in surface coated nanoformulation would be beneficial for enhancement of its bioavailability and longer retention in systemic circulation.
- The haemolysis, LDH assay and platelet aggregation results confirmed that both type of NP were compatible for systemic use. In addition, haemocompatibility studies also indicated that BBR, PCL, surface coater; vitamin E TPGS and its concentration (1% w/v) were found to be safe for systemic use.
- Sub acute oral dose toxicity studies for 28 days such as evaluation of intestine, liver and kidney histopathology and biochemical estimations indicated that BBR-SCNP developed were safe for long use.
- The present work demonstrated that simplified Naplet; smart technology is useful for effective oral delivery of nanomedicines.
- This work paves an alternative way for oral administration of nanoformulations without compromising the characteristics of nanoparticles.
- The Naplet smart technology is convenient and offers simple preparation methodology compared to existing methods i.e by avoiding the other expensive steps in preparation like freeze drying or lyophilization.

- The uncoated and coated naplet weight was found to 25 ± 2 and 27 ± 3 mg, respectively.
- The batch (5) containing binding agent (0.50 mg w/w; 2%) and disintegrating agent (0.75 mg w/w; 3%) showed better redispersion of nanoparticles from naplet (90 %), fast disintegration time (29 sec), optimal hardness (5.2 kg/cm^2) and permissible friability (0.059 %).
- The particle and surface morphology (SEM and TEM) characterizations revealed that nanoparticles retained their physical state in naplet.
- The absence of disintegration and drug release from coated naplet in acidic medium (pH 1.2) illustrated the gastric resistant ability of naplet.
- Insignificant changes in the Naplet properties such as resdispersion, particle size, PDI and zeta potential for 180 days of storage period indicate the stability of Naplet.
- Therefore, it can protect the nanoparticle from exposure to acidic environment in the stomach due to enteric coating.
- Thus, it can be concluded that developed technology has great potential for development of oral delivery of nanoparticles dosage form as a naplet.

6.2. Conclusion

BBR loaded polymeric nanoparticles were successfully prepared with high entrapment efficiency by nanoprecipitation technique. Pharmacokinetic studies revealed that developed BBR NP are capable to evade the P-gp recognition and as a result improve its absorption and systemic bioavailability in comparison to group treated with BBR and verapamil (P-gp inhibitor). It was observed that surface coating with vitamin E TPGS is helpful in maintenance of NP stability and longer retention in systemic conditions. *In-vitro* haemocompatibility studies and *in-vivo* toxicity studies demonstrated the safety profile of developed nanocarrier systems. Thus, vitamin E TPGS coated polymer based NP offer promising delivery system for improved bioavailability of Berberine chloride. It can be concluded that enhancement in the bioavailablity of BBR may improve the therapeutic efficacy of the drug by reducing the dose and dosage frequency. Ultimately, it may improve patient compliance. Further, the developed Naplet smart technology is feasible approach for oral administration of nanoparticles without compromising the characteristics of nanoparticles and its stability in the GIT.