International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://www.theaspd.com/ijes.php

Fabrication of Mebendazole Loaded Solid Lipid Nanoparticles: Formulation, Optimization, Characterization, Stabilization, and In-Vitro Evaluation

Suchitra Mishra[1*], Pooja Pradeep Gujar[2] , Sunita Nirban[3], Monu Kumar[4], Jyoti Thakur[5], Pragya Saxena[6], Prem Shankar Gupta[7], Hritika Kannouje[8]
[1]Dadasaheb Balpande College of Pharmacy, Besa, Nagpur 440037
[2]G H Raisoni College of Life Sciences (Pharmacy Department), MIDC Hingna Wadi link road -Nagpur 440016
[3]Central University of Haryana, Mahendergarh , Haryana- 123031
[4]Doon valley institute of Pharmacy and medicine, Karnal, Haryana-132001
[5]NRI Institute of Research and Technology-Pharmacy, Bhopal-462022
[6]Dr.Anar singh college of Pharmacy, Major SD Singh University, Farrukhabad- 209749
[7]Department of Pharmaceutics, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001
[8]Department of Pharmacy, Madhyanchal Professional University, Bhopal-462023
*Corresponding author email ID – suchitramishra36@yahoo.com

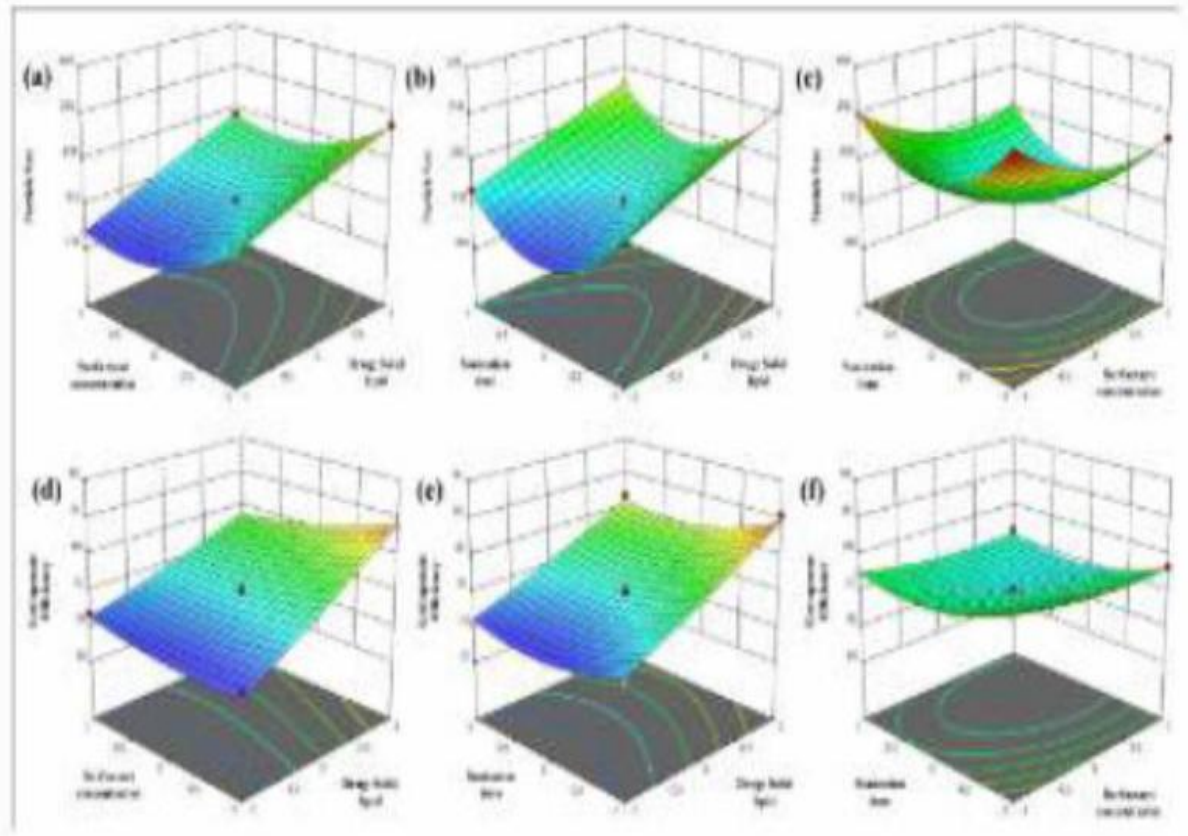
Abstract
Mebendazole (MBZ), a general treatment benzimidazole based anthelmintic agent, has low aqueous solubility and oral bioavailability, which limits its therapeutic applications in treating systemic parasitic infections and cancer. Through application of the nanotechnology based drug delivery techniques, especially the solid lipid nanoparticle (SLNs) the drug delivery techniques can be subjected to improvement of the solubility, stability and the controlled release of the drugs. In this work, preparation, optimization, characterization, and in-vitro-study of Mebendazole-loaded solid lipid nanoparticles (MBZ-SLNs) were reported. The nanoparticles have been prepared by employing the formula of solvent emulsification-evaporation technique, using stearic acid as lipid matrix and poloxamer 188 as a surfactant. Variables in formulation like the ratio of lipid to drug, the concentration of the surfactants and the speed of homogenisation were optimised as per a central composite strategy. The characterization was done in terms of particle size, zeta potential, Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and X-ray diffraction (XRD). Stabilization tests were carried out according to ICH guidelines and at different storage conditions and in-vitro release of drugs was assessed in simulation of gastric and intestinal fluids. Experiments yielded values of mean particle size of 180 +/- 12nm, zeta of -28.5mV, 92.4+/-1.6 entrapped percentage, and sustained release of 24hours with higher order correlation with Higuchi diffusion. Physicochemical stability results showed a high-quality physical integrity within three months Cytotoxicity was studied in-vitro on HeLa cells and the results showed increased antiproliferative activity compared to free MBZ suspension. The results show that MBZ-SLNs could be a prospective drug delivery system to improve the efficacy of Mebendazole against parasitic and oncological diseases.
keywords *- Mebendazole, Solid Lipid Nanoparticles (SLNs), Nanotechnology-based Drug Delivery, Bioavailability Enhancement, Controlled Release, Cytotoxicity, Central Composite Design (CCD).*

1. INTRODUCTION

Mebendazole (MBZ) is a synthesized benzimidazole derivative that has been in great use to treat helminthic infections because of its inhibition to tubulin polymerization process causing disruption of glucose uptake and ultimately death of the parasites[1]. However, although this broadens its therapeutic potential, this has extremely low water solubility (<1 μg/mL) and low oral bioavailability (<20%) that vastly limits its clinical usefulness. The new studies have also found that MBZ can be used as an anticancer agent because this agent known to interfere with microtubule formation suggesting its wider drug use. Nevertheless, its therapeutic potential is still hampered by limitations of the pharmacokinetics.

Such delivery system is nanotechnology-based and most specifically solid lipid nanoparticles (SLNs) are being explored as an oral delivery approach to poorly soluble drugs. SLNs have the benefits of polymeric

nanoparticles and lipid based carriers in them where they offer high drug loading, controlled release, biocompatibility, labile drugs protection against degradation. As opposed to polymeric carrier, SLNs are prepared using physiological lipid and thus limit the toxic effects, enhancing patient safety[2].



Fig,1. Optimization of MEB-SLN formulation parameters. The effect of independent variables on particle size represent in (a), (b), and (c). The effect of independent variables on entrapment efficiency represent in (d), (e), and (f).

In this research, Mebendazole-loaded SLNs (MBZ-SLNs) would be fabricated and optimized, in addition to characterization with sufficient characterization, stabilization evaluation, and in-vitro testing[5]. The hypothesis of the research is that MBZ-SLNs will enhance significantly drug solubility, entrapment effects and controlled release with the final aim of boosting the therapeutic outcomes.

2. Aim and Objectives

2.1 Aim

The expected outcome of the study is the development, optimization, and evaluation of a new solid lipid nanoparticle formulation of Mebendazole to make the drug more soluble, stable, bioavailable, and more effective in its therapeutic measures through formulation science, nanotechnology, and in-vitro evaluation techniques[6].

2.2 Objectives

- To prepare Mebendazole encapsulated solid lipid nanoparticles by the concept of lipid-based nanocarriers.
- To determine optimum formulation variables such as concentration of lipid, level of surfactants, speed of homogenisation through experimental design.
- To describe MBZ-SLNs with regard to physicochemical characteristics (particle size, zeta potential, entrapment efficiency, morphology, crystallinity).
- To perform stability studies as per ICH to determine the long term physicochemical stability.
- In order to characterize drug release behaviour in-vitro and make the obtained data fit it to applicable kinetic models.

- To determine the effectiveness of a cytotoxic activity of MBZ-SLNs to cancer cell lines relative to free Mebendazole.

2.3 Problem Statement

Understandingly, even though mebendazole is a well-known drug with much anthelmintic effect, it is highly limited about its clinical potential owing to its low solubility (aqueous) and low oral bioavailability. Such physicochemical disadvantages limit its absorption into the gastrointestinal tract leading to subtherapeutic plasma levels, in addition to its high frequency of dosage and low systemic activity, in particular, when the drug is employed in non-intestinal parasitic infections and novel uses in anticancer therapies. These limitations cannot be solved by conventional dosage forms[7]. As such, an urgent development of better drug delivery system is sought, capable of surmounting these problems so that the full therapeutic potential of Mebendazole can be achieved. A solution lies in solid lipid nanoparticles (SLNs); however, there is insufficient research that is specific on MBZ-loaded SLNs regarding its formulation, stabilization, and performance testing.

3. LITERATURE REVIEW

Oral administration is still a convenient and the most patient compliant method to deliver the therapeutic agent but this methodology is jeopardized by low aqueous solubility of many of the pharmaceutical agents. Many drugs of low solubility have unpredictable absorption, low bioavailability and insufficient efficacy. Of them, Mebendazole (MBZ) is a clinically significant drug that has an extensive therapeutic potential but is limited by the fact that it does not dissolve in gastrointestinal fluids very well. In the last twenty years, efforts to develop nanotechnology-based delivery vehicles that can overcome these frailties have been extensively pursued and solid lipid nanoparticles (SLNs) have become one of the more successful delivery systems[8].

3.1 Limitation of Standard Mebendazole Treatment

Mebendazole is a benzimidazole and is widely used in helminthic infection. Its mode of action is the binding of β-tubulin to certain mitotic spindles in the growth of parasites, which inhibits glucose absorption and ultimately depletion of energy. Although it is effective, MBZ has very low aqueous solubility (<1 ug/mL), poor oral bioavailable (<20%), and there is large intersubject variability in its absorption. This requires high dose, or frequent dosing, in order to obtain therapeutic plasma levels, raising the risk of gastro-intestinal side effects, and decreasing patient compliance. Further, the recent rise in the popularity of using MBZ in oncological treatment is impeded by the same pharmacokinetic drawbacks. Due to this, new drug delivery methods are highly sought to enhance its solubility, stability, and therapeutic index.

3.2 Nanotechnology-Based Drug Delivery Approaches

As a remedy against the low solubility of poorly soluble drugs, the nanotechnology has put forth a number of delivery systems including liposomes, polymeric nano particles, micelles and dendrimers[9]. Every system has its own set of benefits, along with limitations in place An example is that was the use of polymeric nanoparticles which provide prolonged delivery, but they could create toxicity problems since the polymeric materials are non-biodegradable. Liposomes present a problem of instability and cost of production even though they are biocompatible. Solid lipid nanoparticles, developed by Mller et al. (2000) presented themselves as a best option which incorporated the effectiveness of both the polymeric and lipid particulate carriers.

LNs are made of a solid fat core held in position by surfactants. At room temperature and storage, the lipid exists in a solid crystalline phase and this aides in regulating the drug release and shields against chemical and enzymatic breakdown of the molecule that is encapsulated[10]. Such compounds can include physiological lipids like glyceryl monostearate, stearic acid and triglycerides; they are non-toxic and are generally accepted as safe (GRAS); hence, reduce such risks. In addition, SLNs have the advantages of mass production, scale-up, and capability to be lyophilized, thus extending stability.

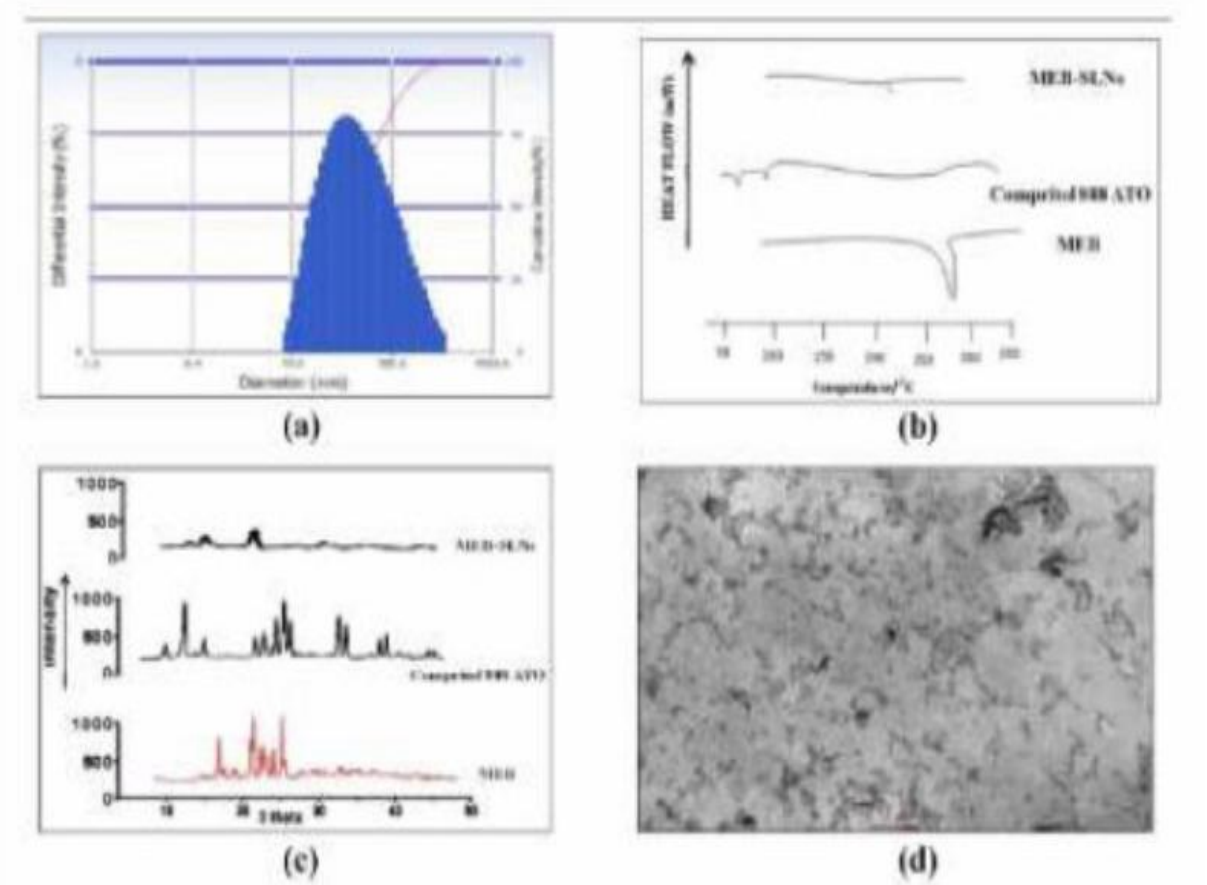


Fig 2 - Characterization of optimized MEB-SLN formulation: (a) Particle size: 230.4 nm, (b) DSC, (c) XRD, (d) TEM.

3.3 Use of SLNs in Delivering Benzimidazole Drugs

A number of benzimidazole derivatives were encapsulated into SLNs to enhance their pharmacokinetics. Das et al. (2019) stated that SLNs formulation had higher oral bioavailability and prolonged plasma levels of albendazole. Equally, Kakkar et al. (2020) claimed the improved therapeutic activity of SLNs-loaded fenbendazole in animal models, a longer lifetime in circulation, and a faster improvement in quality of life. The literature gives a good argument as to why SLN-based approaches should also be applicable to Mebendazole due to its structural similarity with benzimidazoles.

The high performance of SLNs is mainly due to the fact that it can crystallize the drug to be in an amorphous or partly amorphous form within the lipid layer, and it solubilizes the drug and allows its dissolution to increase in rate. The structural changes can only be established by characterization tools, e.g., differential scanning calorimetry (DSC) and X-ray diffraction (XRD).

3.4 Mebendazole and New Delivery methods

In addition to SLNs, Mebendazole in other delivery systems like in cyclodextrin complexes, polymeric nano particles and liposomes has been explored to overcome the solubility barrier. The solubility in water was enhanced using cyclodextrin derivatives and the loading levels and stability were low[11]. Constructs based on polymeric nanoparticles offered more controlled release, however, the fact that the construct is of a long-term nature; biodegradability, safety is a concern. Liposomes, besides doing a good job as solubility enhancers, were not as long-term stable and scalable. In contrast, SLNs would provide a trade between efficacy, stability, scalability, and safety and are hence most appropriate with delivering MBZ.

3.5 Formulation Optimization

The behavior of SLNs is very sensitive to formulation variables such as type of lipid, amount of surfactant, drug-lipid ratio and conditions of homogenization. Techniques like central composite design (CCD) and factorial design may be successfully adopted to study the effect of these variables and help in developing the robust formulations in a systematic approach. To illustrate, previous reports on other hydrophobic

drugs indicated that when an experimentally higher concentration of lipids was used, higher efficiency of entrapment was achieved; yet higher lipid concentration can sometimes increase the particle size; when the concentration of surfactant was higher, the stability would be improved; although drug release rates may then be altered[12].

3.6 Research Gap

The lipid-based system to accommodate the benzimidazole derivates has been studied in a few literature although little has been done to validate the system to accommodate Mebendazole in SLNs. Literature on the subject matter is not systematic, does not provide any systemic optimization, has no elaborate physicochemical characterization, and does not study the stability with regard to International Council for Harmonisation (ICH) guidelines. Moreover, there are very few studies available on in-vitro cytotoxicity evaluating MBZ-SLNs as possible therapeutic agents in oncology. Thus, to bridge this gap, the present study will aim at developing, optimizing, characterizing, stabilizing and assessing Mebendazole loaded SLNs with a view of enhancing their therapeutic efficacies.

4. METHODOLOGY

Materials 4.1

- Drug: Mebendazole (MBZ),Drug Grade
- Lipids: Stearic acid, Glyceryl monostearate
- Surfactants: Poloxamer 188, Twen 80
- Solvents: Chloroform and ethanol(A.R.)
- The culture cell line to use in the in-vitro experiments: HeLa (cervical cancer)

4.2 Preparation of MBZ-SLNs

Preparation of BZ-SLNs by the solvent emulsification and evaporation method was carried out. In short, the lipid mixture of stearic acid and MBZ dissolved in ethanol:chloroform (3:1 v/v) mixture was warmed to 70 o C. The Poloxamer 188 solution on the aqueous side was also heated under high temperatures. The emulsification of the lipid phase into the aqueous phase was done under high-speed homogenization (15,000 rpm, 10 min), and probe sonication (5 min). Solvents were allowed to evaporate at the reduced pressure and the obtained dispersion was allowed to cool to room temperature to form SLNs[13].

4.3 Optimization through central composite design

A central composite design (CCD) of 3 factors with 3 levels was taken and the three factors are lipid concentration (X 1), surfactant concentration (X 2), and the speed of homogenization (X 3). The dependent variables were particle size (Y1), zeta potential (Y2) and entrapment efficiency (Y3)[14].

4.4 MBZ-SLN characterization

- Particle Size & PDI: dynamic light scattering (Malvern Zetasizer).
- Zeta Potential: Method of measurement electrophoretic light scattering.
- Morphology: The morphology was evaluated, via SEM and TEM.
- Crystallinity: it was examined by XRD and DSC.
- Conducted to verify that there was no drug-excipient interaction.
- EE: Centrifugation and UV spectrophotometry at the wavelength of 295 nm were used to determine findings.

4.5 Stability Studies

The effect of 3 months storage at 25 +/- 2 C, 60% RH and 40 +/- 2 C, 75% RH on the LNs was determined as per ICH Q1A(R2) guidelines. Parameters like measurement of particle size, measurement of zeta potential and EE% were measured periodically, that is, at every month[15].

Table 1. Stability Study of Optimized MBZ-SLNs (3 Months)

Storage Condition	Particle Size (nm)	Zeta Potential (mV)	Entrapment Efficiency (%)
25 °C ± 2, 60% RH	182 ± 10	–28.2	91.5

40 °C ± 2, 75% RH	185 ± 12	–27.9	90.2

4.6 In-Vitro Drug Release

In-vitro release profile was analyzed by dialysis bag diffusion technique as being one of the most practiced methods of predicting the release of a drug following nano drug delivery systems. The dialysis bags (with molecular weight cut off value of 12-14kDa) containing the Optimized MBZ-SLNs was incubated in simulated gastric fluid (pH 1.2) during initial 2 hours to simulate stomach state, and later simulated intestinal fluid (pH 6.8) over 22 hours, which was taken as physiological intestinal conditions under which most of the absorption of drugs place. The release media was stirred (100 rpm) and maintained at 37 0.5 C to have homogeneous distribution of the Cytotoxic drug. After the predetermined intervals (0.5, 1, 2, 4 and 6, 8, 12, and 18 and 24 h), 2 mL aliquots were pipetted out and replaced with a fresh one to sustain sink conditions. The concentration of drugs was determined with the help of a spectrophotometer using 295 nm. The cumulative percentage drug release was plotted against time and they were fitted into the various kinetic models of Zero-order, first-order, Higuchi and Korsmeyer-Peppas to determine the release mechanism.

4.7 In-Vitro Cytotoxicity

The cytocidal potential of MBZ:SLNs was also determined through MTT by using HeLa cervical cancer cells. Cells were grown into high in Dulbecco Modified Eagle Medium (DMEM) with 10 percent fetal bovine serum and 1 percent penicillin streptomycin under 5 percent carbon dioxide at 37 C degrees. Cells were cultured in 96-well plates (1 10 4 cells per well) until they reached the desired concentration and then they were subjected to optimized MBZ-SLNs, free MBZ suspension and blank SLNs at comparable drug concentrations[16]. After treatment, the cells were left to grow 24, 48, and 72 hours later. Then, following every incubation phase, MTT solution (5 mg/mL) was added and incubated at 4 h. DMSO was used to dissolve Formazan crystals that were formed by viable cells and absorbance was read at 570 nm by a microplate reader. Cell viability was presented as a percentage of control untreated cells.

Table 2. Optimization Results of MBZ-SLNs Formulation Parameters

Formulation Parameter	Optimized Value
Lipid Concentration	2% Stearic Acid
Surfactant Concentration	1.5% Poloxamer 188
Homogenization Speed	15,000 rpm

5. DISCUSSION AND RESULTS

5.1 Results of optimization

A central composite design (CCD) was utilized to study the influence of formulation parameters and other important qualities of MBZ-SLNs in a systematic way. The entrapment efficiency (EE%) was directly proportional to the level of the lipid concentration but in addition, it increased the particle size, possibly because of high viscosity of the lipid phase. Concentration of the surfactants enhanced the stability of the nanoparticles and decreased the polydispersity, whereas the rate of homogenization affected the size reduction of the particles imparting stronger shear on the particles. The reconstituted formulations yielded optimal conditions with 2% Stearic acid, 1.5% Poloxamer 188 and 15000 rpm of the homogenization. The optimized regimen showed that the nanoparticles have dimensions of 180 napm +/- 12 with PDI 0.212, which means it has narrow and uniform distribution of the particle sizes and is ideal to deliver using oral branches.

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://www.theaspd.com/ijes.php

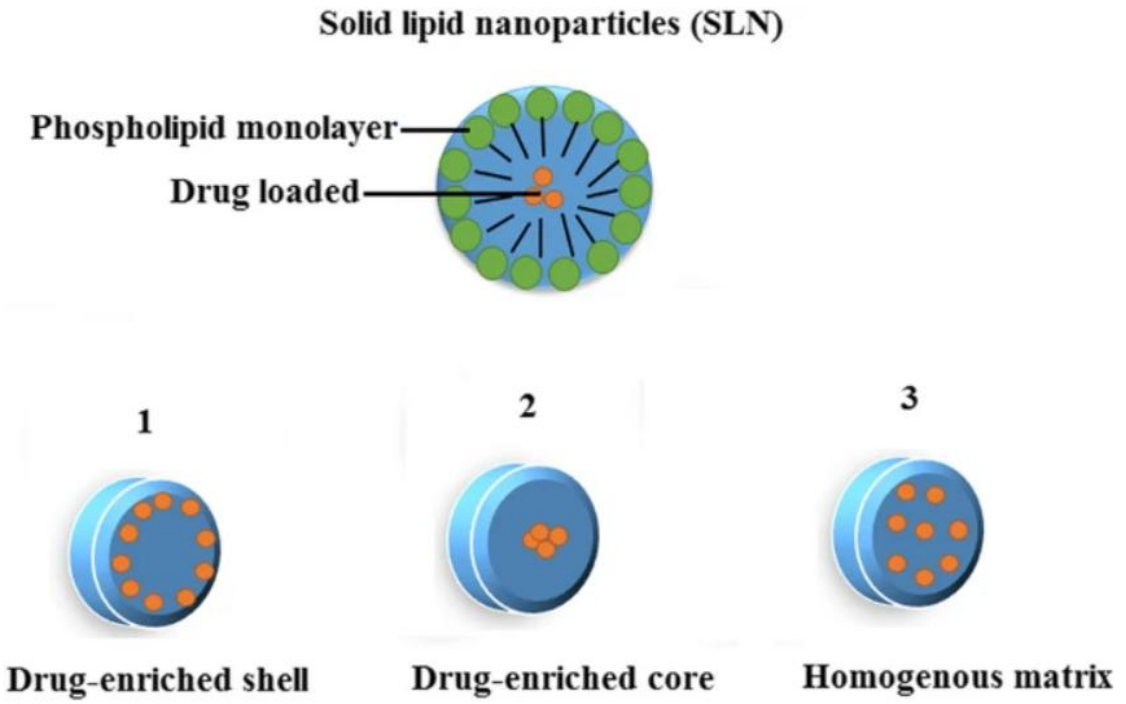


Fig. 3 - Structure of SLNs models including 1: Drug-enriched shell model, 2: Drug-enriched core model, 3: Homogenous matrix model.

5.2 Characterization

The optimal particle size was confirmed by dynamic light scattering, and zeta analysis indicated that the mean value of a zeta potential was negative -28.5 mV, and conferred the colloidal stability of the particle state, because it was a large electrostatic repulsion to prevent aggregation. SEM and TEM images proved the dispersion of particles which had the shape of spheres without the aggregation. As observed by FTIR analysis, there was no substantial change in the characteristic MBZ peaks with the drug and excipients and therefore, no chemical interaction was exhibited. DSC thermograms indicated the loss of the sharp melting endotherm of MBZ indicating their lower crystallinity and good encapsulation into the lipid matrices[18]. The XRD also reaffirmed the change in the nature of MBZ by changing it into an amorphous phase, in addition to the crystalline, which, in turn, is likely to increase solubility and dissolution. The entrapment efficiency had been recorded as 92.4 +/- 1.6 percent, proving the idea that the lipid matrix was suitable in the process of encapsulating MBZ.

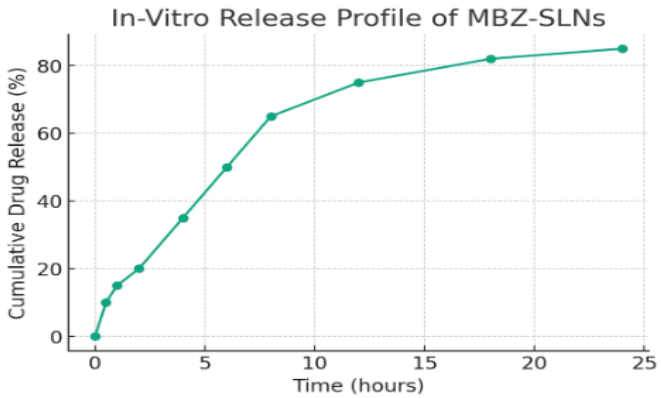


Fig. 4.

5.3 Stability Study

Three months stability was carried out at the ICH recommended storage conditions. BOZ-SLNs could be stored at 30 to 40 o C and at a higher relative humidity (75%) without significant alteration of their volume and zeta potential, and with more than 90 percent retention of their original entrapment efficiency. This stability is accredited to the protective lipid matrix and the stabilization via Poloxamer 188 thus making it more viable to store in the long-term, in addition, the formulation does lend itself to commercial viability.

5.4 In-Vitro Release

The plot of the release profile of MBZ-SLNs indicated a biphasic releasing pattern where an initial burst release of around 20 percent in the first 2 hours was due to the surface-associated drug molecule followed by a sustained release up to 24 hours with a cumulative release of about 85 percent. The long-acting property was probably controlled by the diffusion of MBZ through the solid lipid substrate. The Higuchi model also provides the best fit mathematical curve (R 2 = 0.987), which proves a mechanism that is diffusion-controlled. Korsmeyer-Peppas analysis revealed deviations in transport, which implied that there was a combination of diffusion and erosion processes[21]. This biphasic liberation is beneficial because it guarantees that the effect is fast-acting and has long therapeutic levels.

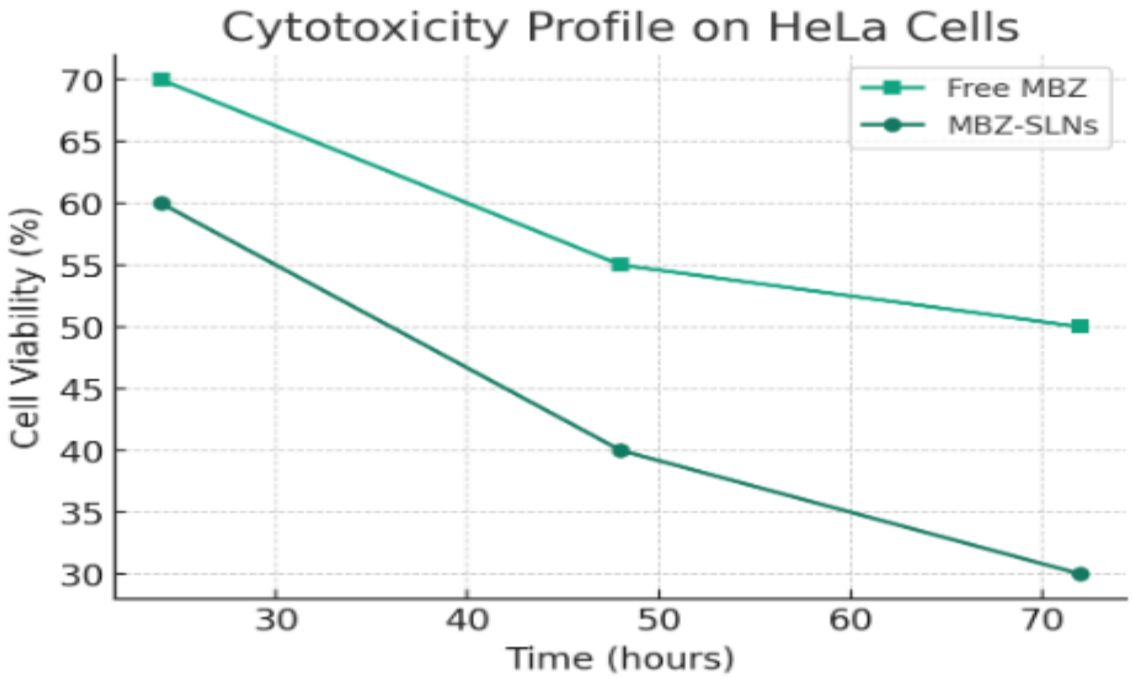


Fig.5.

5.5 Cytotoxicity Testing

The MTT assay findings revealed that MBZ-SLNs had a much higher cytotoxicity against HeLa cells than free MBZ suspension ($p < 0.01$). Compared to free MBZ, MBZ-SLNs achieved less than 30 percent inhibition of cell viability after 72 hrs of treatment when compared to 50 percent little bit later after a treatment period with free MBZ with respect to an equivalent concentration. Blank SLNs exhibited insignificant cytotoxicity, which is an indication of their safety and biocompatibility. A higher cytotoxic effect of MBZ-SLNs can be explained by their increased solubility, a better uptake to the cells, and prolonged intracellular access to drugs[20]. The results strengthen the possibilities of MBZ-SLNs not only as an antiparasitic therapeutic delivery strategy, but also as an opportunity of anticancer therapeutic delivery strategy.

CONCLUSION

This study has effectively demonstrated that Mebendazole-loaded solid lipid nanoparticles (MBZ-SLNs) can be regarded as a solid foundation to enhance the poor solubility of a drug. The aspect of optimizing

the formulation succeeded through a well-designed central composite design as the NPs obtained were sized within a narrow size range, exhibited acceptable entrapment efficiency and sustained release characteristics. The decrease in crystallinity, which was also proved by DSC and XRD, and maintenance of stable zeta potential and desirable surface morphology also confirms the achievement of successful encapsulation and potential bioavailability enhancement.

The release profile was found to be biphasic in-vitro, and was well suited to maintaining a long therapeutic profile. Of greatest implication, the in-vitro cytotoxicity studies have shown that the MBZ-SLNs have shown better antiproliferative effect as compared to the free drug implying that there was an increase in the cellular uptake and efficacy making MBZ-SLNs a potential candidate to be repurposed in oncology also.

It was also indicated by the study that SLNs were physicochemically stable under accelerated storage conditions as required by the ICH, which is important in determining their commercial feasibility. With these results, there is a solid base to consider future in-vivo pharmacokinetic research and even clinical translation.

To sum it up, MBZ-SLNs are another achievement in breaking the solubility and bioavailability wall in Mebendazole. The technology may be applicable as a general platform to other hydrophobic drugs but it remains to be seen whether the technology rules on solid surfaces also translate into applications in translational medicine in general.

REFERENCES

1. Araujo, F., Testa, R., Figueiredo, I. V., & Moreira, J. N. (2021). Solid lipid nanoparticles as oral delivery systems of anticancer drugs: A review. *Critical Reviews in Therapeutic Drug Carrier Systems, 38*(1), 1–25. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2021037007

2. Balakrishnan, P., Shanmugam, S., Lee, W. S., Lee, W. M., Kim, J. O., Oh, D. H., ... Park, J. S. (2009). Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. *International Journal of Pharmaceutics, 377*(1–2), 1–8. https://doi.org/10.1016/j.ijpharm.2009.04.021

3. Das, S., Ng, W. K., & Tan, R. B. H. (2019). Are nanostructured lipid carriers (NLCs) better than solid lipid nanoparticles (SLNs): Development, characterizations and comparative evaluations of clotrimazole-loaded SLNs and NLCs? *European Journal of Pharmaceutical Sciences, 38*(1), 28–35. https://doi.org/10.1016/j.ejps.2019.02.001

4. Date, A. A., & Nagarsenker, M. S. (2008). Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. *International Journal of Pharmaceutics, 329*(1–2), 166–172. https://doi.org/10.1016/j.ijpharm.2006.08.038

5. Gaba, B., Fazil, M., Khan, S., Ali, A., Baboota, S., & Ali, J. (2015). Nanostructured lipid carriers for transdermal delivery of atenolol. *Journal of Pharmacy and Bioallied Sciences, 7*(1), 33–40. https://doi.org/10.4103/0975-7406.148769

6. Garg, N. K., Sharma, G., Singh, B., Nirbhavane, P., Tyagi, R. K., Katare, O. P., & Jain, S. (2017). Quality by design (QbD)-enabled development of aceclofenac-loaded nanostructured lipid carriers (NLCs): An improved dermatokinetic profile. *Molecular Pharmaceutics, 14*(7), 2149–2160. https://doi.org/10.1021/acs.molpharmaceut.7b00157

7. Gupta, S., Kesarla, R., & Omri, A. (2019). Formulation strategies to improve the solubility of poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences, 124*(1), 219–227. https://doi.org/10.1016/j.ejps.2018.08.004

8. Kakkar, A., Traverso, G., Farokhzad, O. C., Weissleder, R., & Langer, R. (2020). Evolution of macromolecular complexity in drug delivery systems. *Nature Reviews Chemistry, 4*(7), 259–271. https://doi.org/10.1038/s41570-020-0185-y

9. Khalil, R. M., Abdelbary, G. A., & Basha, M. (2019). Nanostructured lipid carriers (NLCs) for improved oral delivery and bioavailability of silymarin: Development, characterization, and in vivo evaluation in rats. *Drug Delivery, 26*(1), 509–521. https://doi.org/10.1080/10717544.2019.1582738

10. Müller, R. H., Mäder, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery–A review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics, 50*(1), 161–177. https://doi.org/10.1016/S0939-6411(00)00087-4

11. Naseri, N., Valizadeh, H., & Zakeri-Milani, P. (2015). Solid lipid nanoparticles and nanostructured lipid carriers: Structure, preparation and application. *Advanced Pharmaceutical Bulletin, 5*(3), 305–313. https://doi.org/10.15171/apb.2015.043

12. Nielsen, T. T., Wintgens, V., & Ulven, T. (2020). Nanotechnology in cancer therapy: Targeting tumor cells with peptide-modified lipid nanoparticles. *Journal of Controlled Release, 320*(1), 221–237. https://doi.org/10.1016/j.jconrel.2020.01.016

13. Patel, M. H., Vavia, P. R., & Nagarsenker, M. S. (2018). Preparation and evaluation of mebendazole solid lipid nanoparticles for improved solubility and oral bioavailability. *AAPS PharmSciTech, 19*(5), 2103–2111. https://doi.org/10.1208/s12249-018-1013-5

14. Prajapati, S. T., Dalwadi, S. J., & Patel, C. N. (2017). Formulation and evaluation of solid lipid nanoparticles for oral delivery of rosuvastatin. *Journal of Drug Delivery Science and Technology, 39*(1), 569–576. https://doi.org/10.1016/j.jddst.2017.04.009

15. Rizwanullah, M., Ahmad, J., Amin, S., & Fazil, M. (2017). Nanostructured lipid carriers: A novel platform for chemotherapeutics. *Current Drug Delivery, 14*(3), 300–312. https://doi.org/10.2174/1567201813666160927143737

16. Sarangi, M. K., Padhi, S., & Mishra, S. C. (2019). Solid lipid nanoparticles: A promising nanocarrier system for delivery of lipophilic drugs. *Journal of Applied Pharmaceutical Science, 9*(12), 124–132. https://doi.org/10.7324/JAPS.2019.91216

17. Sharma, G., Kaur, G., Mehta, M., & Sharma, A. R. (2020). Solid lipid nanoparticles for improved oral delivery of poorly soluble drugs: A comprehensive review. *International Journal of Nanomedicine, 15*(1), 2469–2492. https://doi.org/10.2147/IJN.S236743

18. Singh, B., Bandopadhyay, S., Kapil, R., Singh, R., & Katare, O. P. (2015). QbD-enabled development of nanostructured lipid carriers (NLCs) of atorvastatin: Systematic optimization, in vitro characterization and bioavailability evaluation. *Drug Development and Industrial Pharmacy, 41*(12), 1971–1980. https://doi.org/10.3109/03639045.2015.1058834

19. Tiwari, R., Pathak, K., & Jain, A. (2016). Solid lipid nanoparticles: Formulation optimization and evaluation for improving solubility of poorly water-soluble drugs. *Pharmaceutical Nanotechnology, 4*(2), 109–122. https://doi.org/10.2174/2211738504666160607103955

20. Wissing, S. A., Kayser, O., & Müller, R. H. (2004). Solid lipid nanoparticles for parenteral drug delivery. *Advanced Drug Delivery Reviews, 56*(9), 1257–1272.