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Fabrication and Optimization of Terbinafine Hydrochloride Solid Lipid Nanoparticles (TBH-SLNs) using a Modified Solvent Emulsification Technique

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Abstract

The modified solvent emulsification technique was employed to fabricate TBH-SLN dispersions. Formulations were prepared with varying concentrations of excipients to determine the optimal formulation parameters. The influence of various process parameters on SLN formulation was assessed based on average particle size, evaluated, formulations F20 and R20 demonstrated the smallest particle size and polydispersity index, highest zeta potential, and controlled drug release from SLNs. polydispersity index, zeta potential, and in vitro drug release. Among the batches evaluated, formulations F20 and R20 demonstrated the smallest particle size and polydispersity index, highest zeta potential, and controlled drug release from SLNs.

Key words : Solid lipid nanoparticles, Antifungal, Terbinafine, Optimization, Supermolecules.

Therapeutic drugs are delivered using solid lipid nanoparticles. In order to facilitate the trapping of API, SLNs are often created by incorporating a solid form of lipid into an o/w kind of emulsion with the aid of a stabilizer. Because SLNs are made up of physiological supermolecules, the body already has the pathways for lipid transportation and metabolism to verify the carrier's in vivo destination.[2,7] They are also essential for several targeting modes because they are stable for a long time and simple to rescale when compared to other mixture systems.[6,8] SLNs include a wide range of medications from different pharmacological categories, including antifungals, vitamins, steroids, and cancer-fighting medicines.[10,13,14] SLNs are also frequently employed for topical treatments since it is believed that they transport medications to the site of action[1]. [5]For increased efficacy, these SLN formulations also provide improved localization, occlusiveness, controlled release, and skin association[15].

Oral and topical antifungal medications are used to treat fungal infections of the skin, scalp, or nails. Terbinafin hydrochloride (TBH) is a commonly used medication that has been shown to be well tolerated when taken orally or topically to treat fungal infections of the skin[4]. However, the topical route was more appropriate for drug administration due to inadequate bioavailability and hepatic first pass metabolism (about 40%)[11]. Both the systemic load and the systemic adverse effects of the active pharmaceutical ingredients (API) can be reduced thanks to it[16]. By focusing on particular body cells, controlled medication delivery systems are among the most effective methods for treating illnesses[9]. Therefore, the benefits of nanotechnology, a revolutionary medication delivery technique, include timing and site specificity[12]. The ability of nanoparticles to target the cells or receptors at the site of action has been demonstrated.Therefore, this may be useful in overcoming the pharmacokinetic disadvantages of medications[3].

Preparation of Solid Lipid Nanoparticles (SLNs) : Solid lipid nanoparticles (SLNs) containing TBH were prepared by Solvent emulsification technique. In this method Dissolve TBH in lipid and heat. Dissolve OLMS surfactant in water. Combine lipid phase with aqueous phase under stirring. Continue stirring and cooling and add other excipients. Optimize parameters like stirring rate, sonication time, and cooling temperature (refer to Table-1). This process aims to optimize the formulation of TBH-SLNs by varying concentrations of excipients and adjusting process parameters for improved physicochemical properties of the nanoparticles.

Table-1. Formulation of TBH-SLN dispersion at different process parameters

Formulation	Batch	Stirring rate rpm			Stirring time hr			Sonication time min				Cooling Temperature speed	
F1	B20	2000											
F2	B20		3000										
F3	B20			4000									
F4	B20	2000			1								
F5	B20	2000				1.5							
F6	B20	2000					2						
F7	B20	2000			1			0					
F8	B20	2000			1				10				
F9	B20	2000			1					20			
F10	B20	2000			1						30		
F11	B20	2000			1			0				Slow	
F12	B20	2000			1			0					Fast

Formulation Development of TBH-SLN : The formulation development of Terbinafine Hydrochloride-loaded Solid Lipid Nanoparticles (TBH-SLN) was carried out following Quality by Design (QbD) principles. The entrapment efficiency (EE) for the twenty batches of TBH-SLN ranged from 46.33% to 75.66% w/w, indicating variability in the ability of the SLNs to encapsulate the drug. The percentage drug loading of TBH-SLNs varied between 13.31% and 19.99% w/w, reflecting the proportion of the drug encapsulated relative to the total weight of the SLNs. The mean diameter of the TBH-SLNs ranged from 58.75 μm to 155.42 μm, indicating differences in particle size which can influence drug release and stability. The process yield of TBH-SLNs was found to range from 47.36% to 75.16% w/w, showcasing the efficiency of the production process.

The regression analysis indicates that the drug-to-lipid ratio (X1) and surfactant 67 concentration (X3) are critical factors influencing the % entrapment efficiency of TBHSLNs. The model fits well with an $r2r2$ value of 0.9807, indicating a high degree of correlation between the predicted and actual values. These findings underscore the importance of optimizing these factors to achieve maximum entrapment efficiency in TBH-SLN formulations.

Preparation and Evaluation of Optimized Solid Lipid Nanoparticles Dispersion :

Optimized formulae for TBH-SLN obtained from numerical optimization and desirability function. The color and odor of SLN noted. Stability evaluated by centrifugation at 2000 rpm for 30 minutes.

Determination of Average Particle Size (APS) and Polydispersity Index (PDI):

Photon Correlation Spectroscopy (PCS) technique used to Determine the average particle size and polydispersity index of the SLN. SLN formulations diluted with double distilled water to concentrations between 0.001% to 1% mass to minimize particle interaction in concentrated samples.

Zeta Potential (ZP):- ZP measurements performed with electric field strength of 23 V/m at 25°C. ZP values provide insight into the stability of the SLN dispersion, with higher absolute values indicating greater stability. This detailed analysis and preparation process ensure that the TBH-SLN formulation is optimized for desired physicochemical properties, stability, and efficacy.

Entrapment Efficiency (EE) and Drug Loading (DL): The percentage of drug entrapped in solid lipid nanoparticles (SLNs) can be determined by calculating the entrapment efficiency (EE) and drug loading (DL). This is done by measuring the concentration of the drug in the supernatant SLN dispersion after ultracentrifugation. Here's how the calculations are performed:

Entrapment Efficiency (EE): EE (%)=(TD–$TSTD$)×100EE (%)=(TDTD–TS)×100

Where: TD = Total mass of drug, $TSTD$ = Total mass of drug in supernatant, $TLTL$ = Total mass of lipid

Drug Loading (DL): DL (%)=(TD–$TSTL$)×100DL (%)=(TLTD–TS)×100

Transmission Electron Microscopy Study (TEM): Transmission electron microscopy (TEM) is used to study the particle size, shape,

and morphology of solid lipid nanoparticles. In this study, the SLN dispersion is diluted with water, and a drop of the dispersion is placed on a copper grid coated with a thin film of carbon. After drying for 45 minutes, the sample is examined under the transmission electron microscope to visualize the nanoparticles.

Stability Study of SLN Dispersion: The stability of solid lipid nanoparticles (SLNs) is evaluated over twelve months according to International Council for Harmonisation (ICH) guidelines under various storage conditions, including refrigeration and different temperature and humidity conditions. Samples are withdrawn at specific intervals and evaluated for physical appearance, clarity, particle size, polydispersity index (PDI), and entrapment efficiency.

The investigation into the formulation of SLN dispersion involved assessing the impact of different excipient concentrations and process parameters on various factors such as particle size, polydispersity index, and zeta potential. The results of this evaluation are summarized in tables-2.

Table 2. TBH-SLN dispersions with variable process parameters and their evaluated results for particle size and polydispersity index

Formulations	Particle Size	Polydispersity Index
F1	287.1	0.282
F2	287.1	0.315
F3	284.9	0.372
F4	280.5	0.286
F5	278.3	0.289
F6	279.4	0.288
F7	278.3	0.287
F8	271.7	0.396
F9	266.2	0.41
F10	254.1	0.537
F11	275	0.3
F12	270.6	0.281

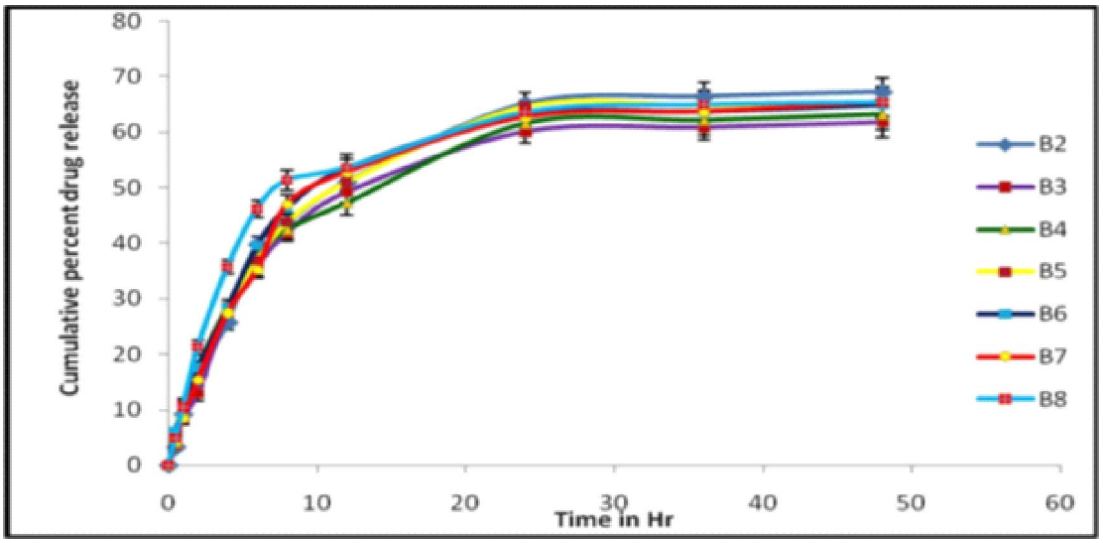

Figure 1. In vitro release profile of formulation B2 to B8

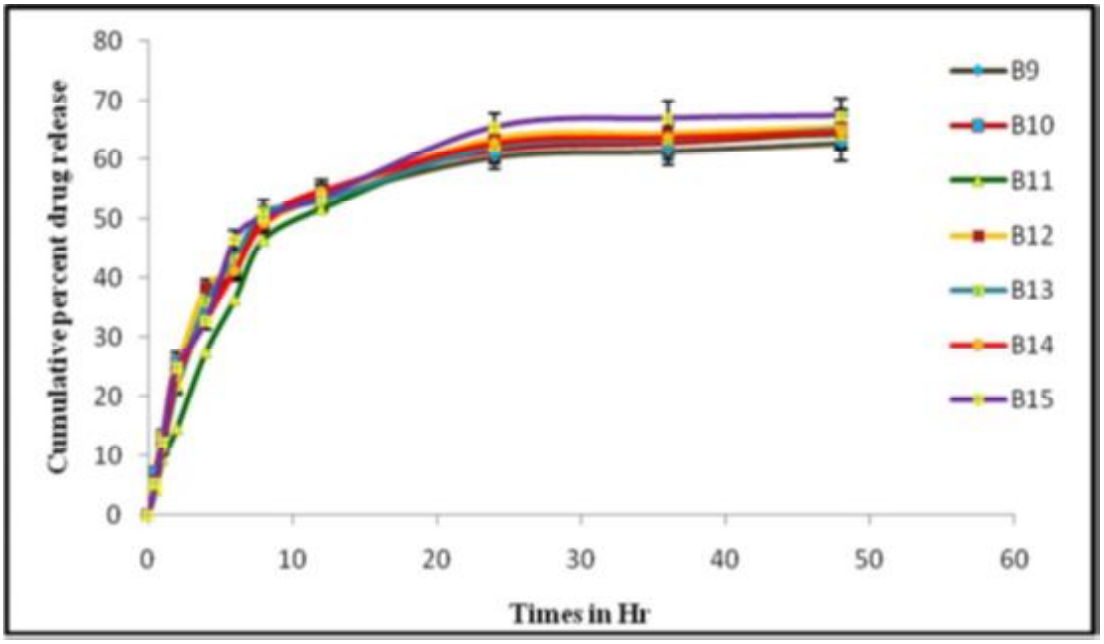

Figure 2. In vitro release profile of formulation B9 to B15

The investigation into the in vitro release of TBH from TBH-SLNs was conducted, with the corresponding data. It was observed that different formulation excipients and their varying concentrations significantly influenced particle size, PDI, and the in vitro drug release profile. To ensure consistency, constraints regarding minimum particle size and PDI for TBH-SLN dispersion were applied in selecting formulations for the drug release study. Formulation B1, characterized by larger particle size and PDI, was consequently excluded from the release profile analysis. The drug release profiles corresponding to these formulations are illustrated in figures 1, 2 and 3.

The drug release patterns varied across formulations B2 to B8, reflecting the influence of different excipients used in each formulation. Specifically, formulations B2 and B5, which contained 5% OLML and 3% OLMS respectively, exhibited the highest and most gradual increase in drug release. Conversely, formulation B6, which had a higher surfactant concentration (6% OLMS), displayed an initial burst release within the first half hour, followed by sustained release. Formulation B8, containing 5% DMSO, showed erratic drug release behaviour.

Formulations B9 and B10, incorporating 1.5% and 5% acetone respectively, exhibited an initial burst release, with 6.2% and 7.39% drug release within the first half hour. In contrast, formulation B13, containing 0.05% TPGS, demonstrated enhanced release after the initial half hour. Notably, formulation B15, with 1.5% TPGS, displayed the highest drug release at the 24-hour mark. These findings indicate distinct drug release patterns among the various formulations.

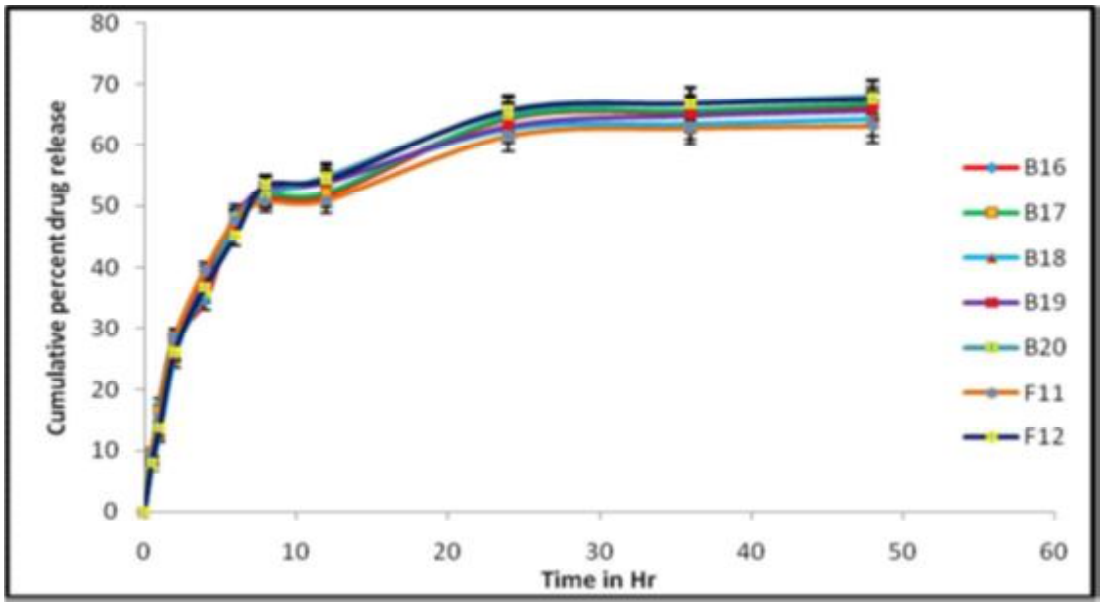

Figure 3. In vitro release profile of formulation B16 to F12

Formulations B16 and B17, containing higher concentrations of TPGS at 3.5% and 5%, respectively, exhibited comparatively lower drug release rates than formulation B15. Conversely, formulation B20, incorporating 0.3% stearyl amine, and F12, with a faster cooling temperature during the preparation of hot TBH-SLN dispersion, demonstrated consistent and maximal drug release.

The influence of formulation ingredients and process parameters on the particle size and PDI of TBH-SLN dispersions. The data indicates that both particle size and PDI increase with higher lipid content. For formulations BS1 to BS8, particle sizes ranged from 231±2.79 nm to 278±3.19 nm, and PDI ranged from 0.241±0.005 to 0.369±0.01. The optimized BS9 TBHSLN formulation had a particle size of 261.25±2.38 nm and a PDI of 0.268±0.01. Zeta potential values reflect the stability of nanoparticles in the SLN dispersion. For batches BS1 to BS8, zeta potentials ranged from 11.7±0.16 mV to 24.9±0.41 mV. The optimized BS9 TBH-SLN batch exhibited a zeta potential of 23.98±0.27 mV, indicating good stability.

Variations in lipid and organic solvent concentrations significantly impacted the EE and DL of Terbinafine in the formulations. The EE for formulations BS1 to BS8 ranged from 87.45±2.26% to 91.65±1.69%, while drug loading ranged from 15.05±0.58% to 22.86±0.46%. The optimized BS9 TBH-SLN batch showed an EE of 91.35±2.35% and a drug loading of 19.692±0.95%.

Consistent with the particle size analysis, TEM images of the BS9 TBH-SLN (Figure 4) confirmed that the nanoparticles were within the nanometric range and were spherical in shape.

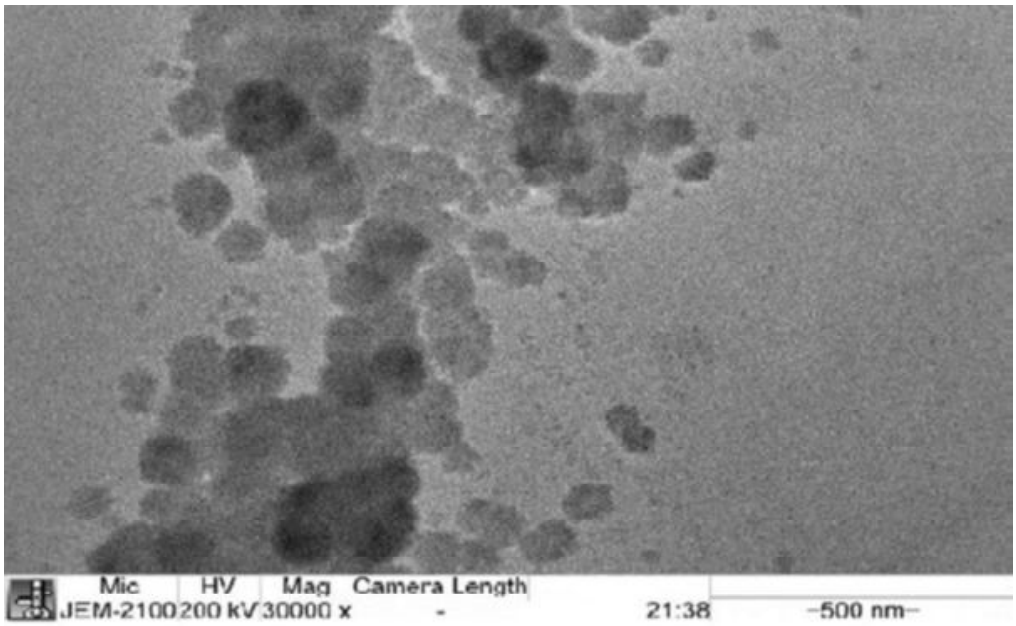

Figure 4:- The TEM image of BS9 TBH-SLN.

To assess the impact of storage temperature on the stability of the optimized BS9 TBH-SLN dispersion, the samples were evaluated over a 12-month period following ICH guidelines. This involved storing the dispersions under four different conditions and monitoring their physical and chemical stability represented in figure 5, 6 and 7.

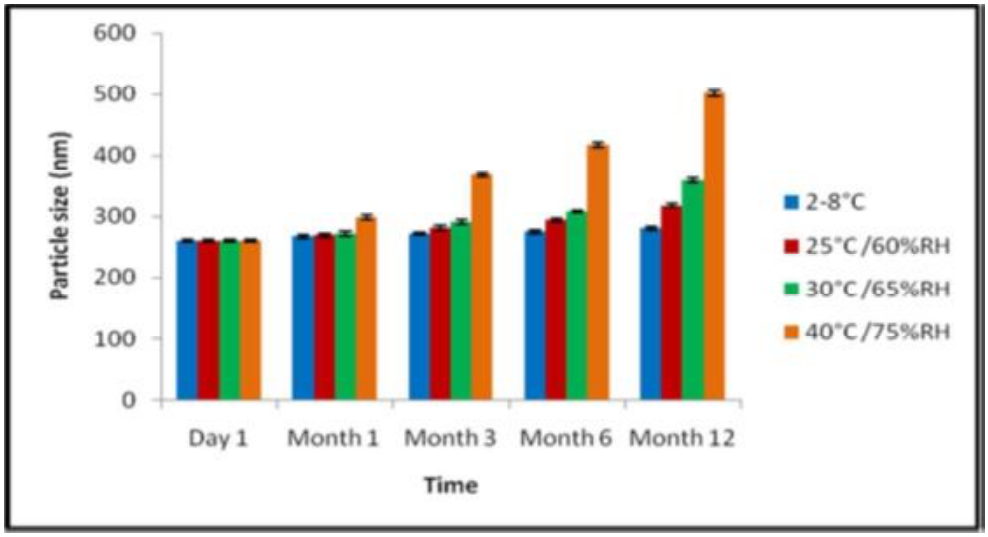

Figure 5. Stability data of BS9 TBH-SLN as per ICH guidelines evaluated based on average particle size

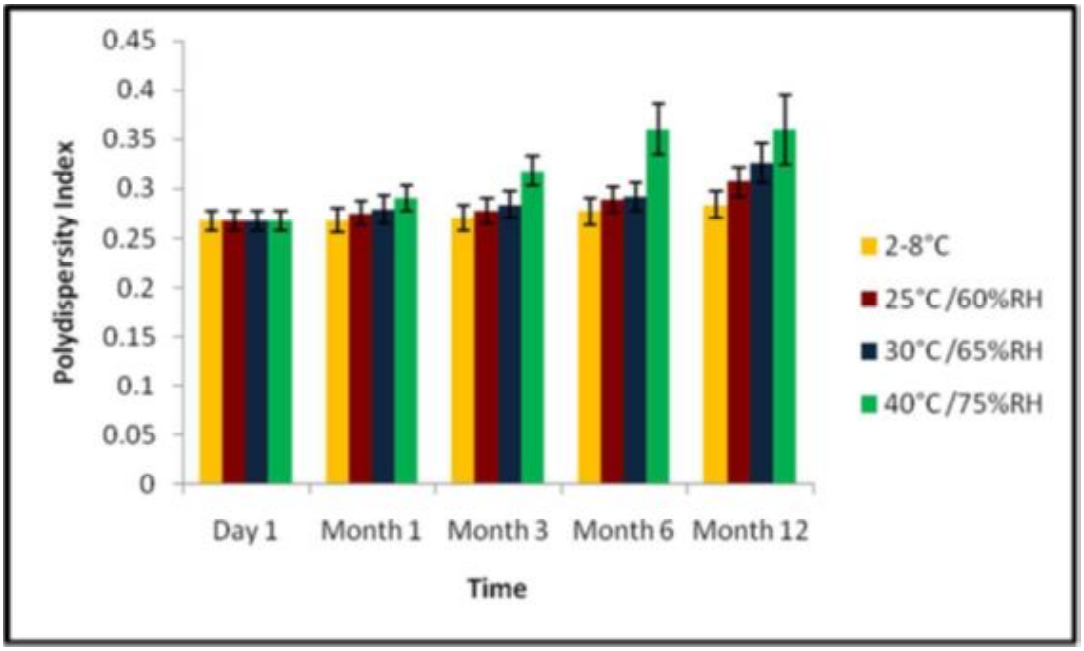

Figure 6. Stability data of BS9 TBH-SLN as per ICH guidelines evaluated based on PDI

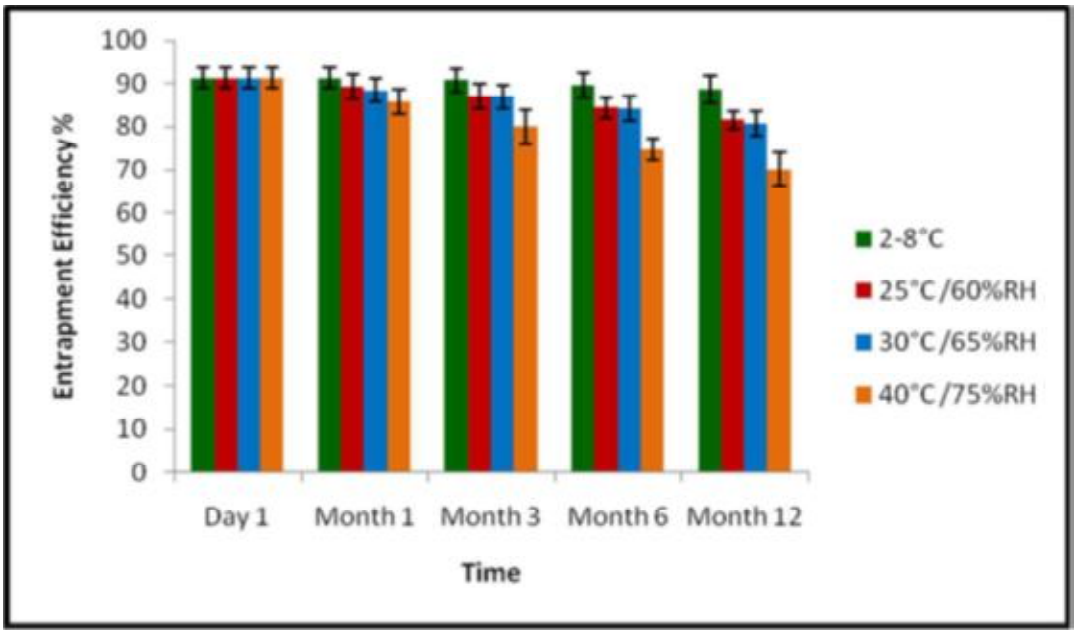

Figure 7. Stability data of BS9 TBH-SLN as per ICH guidelines evaluated based on Entrapment efficiency (%).

The modified solvent emulsification technique was employed to fabricate TBH-SLN dispersions. Formulations were prepared with varying concentrations of excipients to determine the optimal formulation parameters. The influence of various process parameters on SLN formulation was assessed based on average particle size, evaluated, formulations F20 and R20 demonstrated the smallest particle size and polydispersity index, highest zeta potential, and controlled drug release from SLNs. polydispersity index, zeta potential, and in vitro drug release. Among the batches evaluated, formulations F20 and R20 demonstrated the smallest particle size and polydispersity index, highest zeta potential, and controlled drug release from SLNs.

The optimization process utilizing a 23 factorial design resulted in the development of the optimized BS9 TBH-SLN dispersion composed of 5% OLML, 4% OLMS, 0.5% DMSO, and 1.5% TPGS. This formulation exhibited desirable characteristics including a particle size of 261.25±2.38 nm, a PDI of 0.268±0.01, a ZP of 23.98±0.27 mV, an EE of 91.35±2.35%, and a DL of 19.692±0.95%. The dispersion was further evaluated for color, odor, and stability, demonstrating its suitability for further use.

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