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RESEARCH ARTICLE

Formulation and Characterization of Liquisolid Tablets for Improving Dissolution of Telmisartan

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SUMMARY

The current study's objective was to create liquisolid tablets (LST) to improve the dissolution profile of telmisartan (TLS), a poorly soluble medication Biopharmaceutical Classification System (BCS) class II. To prepare LST, the following ingredients were used: microcrystalline cellulose (MCC) as the carrier, polyethylene glycol 600 (PEG 600) as the vehicle, croscarmelose sodium (CCS) as the superdisintegrant, and Aerosil 200 as the coating material. The tablet quality control tests, flow characteristics, and interactions between the medication and the excipient were assessed for each formulation. Higuchi, Korsmeyer-Peppas (KP), zero order, and first-order models were utilized to investigate the in vitro drug release (IVDR) kinetics for various batches. When the optimized formulation (TC3) was evaluated for stability at 75±5% RH and 40±2ºC, it was shown to be steady for a maximum of three months. No interaction between the medication and excipients was confirmed by Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) investigations. The solubility studies were used to guide the selection of the dissolution medium. Comparing the TC3 to the conventional marketed tablet (MKT), TELVAS 20, a notable improvement in dissolution was observed. After three months of storage, there was no discernible change in the tablet's characteristics or the drug release profile.

Key Words: *Dissolution, Poorly soluble, Stability, TLS.*

Telmisartanın Çözünmesini İyileştirmek İçin Sıvı Katı Tabletlerin Formülasyonu ve Karakterizasyonu

ÖZ

Mevcut çalışmanın amacı, Biyofarmasötik Sınıflandırma Sistemi (BCS) sınıf II'de zayıf çözünen bir ilaç olan telmisartanın (TLS) çözünme profilini iyileştirmek için sıvılaştırılmış katı tabletler (LST) oluşturmaktı. LST'yi hazırlamak için şu bileşenler kullanıldı: taşıyıcı olarak mikrokristal selüloz (MCC), taşıyıcı olarak polietilen glikol 600 (PEG 600), süper dağıtıcı olarak kroskarmeloz sodyum (CCS) ve kaplama malzemesi olarak Aerosil 200. Her formülasyon için tablet kalite kontrol testleri, akış özellikleri ve ilaç ile yardımcı madde arasındaki etkileşimler değerlendirildi. Çeşitli partiler için in vitro ilaç salım (IVDR) kinetiğini araştırmak için Higuchi, Korsmeyer-Peppas (KP), sıfırıncı ve birinci dereceden modeller kullanıldı. Optimize edilmiş formülasyon (TC3), %75±5 RH ve 40±2ºC'de kararlılık açısından değerlendirildiğinde, en fazla üç ay boyunca kararlı olduğu gösterildi. İlaç ve yardımcı maddeler arasında herhangi bir etkileşim, Fourier Dönüşümlü Infrared Spektroskopisi (FTIR) ve Diferansiyel Taramalı Kalorimetri (DSC) araştırmaları ile doğrulanmadı. Çözünme ortamının seçimi için çözünürlük analizi kullanıldı. TC3 piyasada bulunan geleneksel tablet (MKT), TELVAS 20 ile karşılaştırılarak, çözünmede kayda değer bir iyileşme gözlemlendi. Üç aylık depolamadan sonra, tabletin özelliklerinde veya ilaç salım profilinde fark edilebilir bir değişiklik olmadı.

Anahtar Kelimeler: *Çözünme, Zayıf çözünürlük, Stabilite, TLS.*

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INTRODUCTION

Many potentially novel medications fall into either BCS class IV (low solubility and low permeability) or BCS class II (low solubility and high permeability), and many of them show poor water solubility. The most crucial factors affecting bioavailability are the drug's solubility and dissolution behavior (Yadav et al., 2010). Poorly water-soluble drugs have numerous challenges while developing dosage forms for oral administration because of their low bioavailability (Javadzadeh et al., 2007). One crucial factor in achieving the appropriate drug concentration in the systemic circulation (Peddi et al., 2013) and demonstrating a pharmacological response is solubility.

Due to their limited solubility in the gastrointestinal tract (GIT), drugs that poorly soluble in water will naturally release their contents slowly. The task at hand for these medications is to optimize their rate of solubility or dissolution. This ultimately enhances bioavailability and absorption. For many pharmaceutical formulations, dissolution is the rate-limiting step. Solid dispersions (Merisko-Liversidge et al., 2003), inclusion complexes with β-cyclodextrins (Jarowski et al., 1992), micronization (Barzegar et al., 2005), liquisolid (LS) technology (Nokhodchi et al., 2011), spray drying technique (El-Houssieny et al., 2010), use of surfactants (Nighute et al., 2009), use of co-solvents (Millard et al., 2002), self-emulsification and self-micro emulsification (Balakrishnan et al., 2009), use of pro-drugs and drug derivatization (Tanino et al., 1998), formation of solid solutions or amorphous solids (Kapsi et al., 2001), and microencapsulation (Li et al., 2008) are some of the techniques for increasing drug solubility. The LS systems are the creative method to improve poorly soluble drug dissolution and *in vivo* bioavailability (Tiong et al., 2009).

The technology of solutions in powder form utilized to create "liquid medication," gave rise to the idea of LST. Solid medications dispensed in appropriate, vehicles for non-volatile liquids are called "liquid medication" (Nagabandi et al., 2011). The idea of LS allows for the physical blending process to be used with specific excipients such as carrier and coating material to transform a liquid into an easily compressible, seemingly dry, and free-flowing powder. LS is described by (Spireas et al., 1999). To achieve a suitable flowable and compressible LS system, Spireas has developed a model to determine the right amounts of coating material and carrier. The excipients ratio (R) is the carrier/coating ratio.

$$R = Q/q \quad (1)$$

As a result, R is the ratio of the coating material (q) to the carrier material (Q) weights. The ideal value of R is 20. The weight ratio of the liquid drug (W) to Q in the LS system is known as the liquid loading factor (Lf) (Kasturi et al., 2021).

$$Lf = W/Q \quad (2)$$

The surface area of the medication accessible for disintegration and wetting qualities is greatly enhanced by the LS system. It is reasonable to anticipate that the LS system of water-insoluble compounds will exhibit improved medication dissolution, leading to increased bioavailability. The ideas behind the construction of LS are to use powdered liquid medications, such as drug solutions, suspensions, or liquid drugs. LS describes the process of combining liquid pharmaceuticals with appropriate additives, also known as transporters and coating materials, to create powder combinations that appear dry, loose-flowing, non-stick, and compressible (Kavitha et al., 2011) (Spireas, 2002).

A potent and specific angiotensin II type 1 (AT1) receptor antagonist used to treat essential hypertension is TLS (Kolatkar et al., 2007, 2005).BCS class II medication TLS has an aqueous solubility of 0.09 μg/mL (Tran et al., 2008). Its solubility varies with pH, nearly becoming insoluble within the pH 3–9 range. Furthermore, its nature is strongly hydrophobic (log P = 3.2) (Sangwai et al., 2013). Poor drug water solubility is linked to irregular and sluggish drug absorption, slow drug breakdown, and ultimately, low and insufficient oral bioavailability (43%) (Wienen et al., 2000). Solid systems for liquid medications are created using LST technology. The current study is to formulate LST of TLS and its characterization.

MATERIALS AND METHODS

Materials

TLS was gifted by Indchemie Health Specialties Pvt ltd (Sikkim, India). PEG 600, Aerosil 200, croscarmelose sodium (CCS), and Hydrochloric acid (HCl) were acquired from Mumbai, India's S D Fine-Chem Ltd. We bought microcrystalline cellulose (MCC) from Signet Pharma in Mumbai. Analytical grade solutions, reagents, and other chemicals were all utilized. Marketed tablet (MKT) *TELVAS 20,* Aristo Pharmaceuticals Pvt. Ltd. Batch no: SPF231027 Sikkim was procured from a local pharmacy.

Analytical techniques for TLS in vitro estimation and formulations

Based on in vitro tests, the amount of TLS in the formulations was estimated using UV-visible spectrophotometric analytical methods. The pure medication and standard calibration curves were scanned for this procedure. Using an HCl buffer with a pH of 1.2, standard calibration curves were prepared.

Lamda max determination

100 mg of TLS was transferred to 100 ml volumetric flask and make up the volume upto the mark with 0.1N HCl to get concentration of 1000 µg/ml of standard stock solution. Further 5 milliliters was pipetted out from the above stock solution and transferred to a 50 ml volumetric flask make up the volume upto the mark with 0.1N HCl to obtain the concentration of 100 µg/ml (Padmavathi et al., 2013). Further 5 ml of solution was pipetted out from 100 µg/ml TLS solution and transfer to 10 ml volumetric flask, make up the volume upto the mark with 0.1N HCl to get concentration of 50 µg/ml. Then the 50 µg/ml solution was scanned in UV–visible spectrophotometer, and the λmax was observed at 290 nm.

Calibration curve for TLS

A concentration of 1000 µg/ml standard stock solution (Tatane et al., 2011) was obtained by adding 100 mg of TLS medication to 100 ml of 0.1NHCl solution. Five milliliters of the solution was taken out from standard stock solution and diluted with fifty milliliters of 0.1 N HCl solution to create a concentration of 100 µg/ml. The 100 µg/ml solution was diluted using the same HCl buffer pH 1.2 to produce a sample solution at 10, 20, 30, 40, and 50 µg/ml concentrations. The absorbance corresponding to the concentrations was calculated at a 290 nm wavelength. A curve for calibration for pure TLS was made by plotting the measured absorbance against the respective concentrations.

Compatibility study

FTIR

The FTIR allows (Milam et al., 2013) the identification of functional groups in a variety of compounds and drug-excipient incompatibility. Using the KBr pellet method, the FTIR analysis (Bruker, αE, Germany) of antihypertensive medications was completed. To create a transparent pellet, a small portion of the mixture was squeezed at 10 kg per centimeter with a hydraulic press. The pellet remained inside the specimen container of the FTIR spectrophotometer and scanned between 4000 and 400 $cm^{-1.}$

DSC

The examination of potential incompatibilities between dosage forms' medication excipients is predicted using DSC (Shimadzu DSC-50, Japan). Drug and individual excipient physical mixes in a 1:1 ratio were prepared and subjected to DSC analysis (Milam et al., 2013). In a DSC pan, individual samples and a physical combination of the medication and excipients were weighed to a maximum of 5 mg. For efficient heat conduction, the sample pan was crimped and scanned between 50 and 300^0C. A 20^0C min^{-1} heating rate was employed, and the resulting thermogram was examined for signs of interaction. The thermograms were then compared (Jaydip et al., 2020).

Preparation of LST

Spireas provided instructions for preparing TLS liquid-solid pills (Spireas et al., 1999; Swamy et al., 2013). To create a homogeneous dispersion, the weighed amount of TLS was combined with the non-volatile solvent (PEG 600), heated to $(80–90)^0C$,

and then sonicated for 15 minutes. The carrier material (MCC) was then added to the melt in predetermined volumes, and following a standard mixing process, the resultant wet mass was mixed with the coating material (Aerosil 200). After spreading the powder mixture evenly, it was let to stand for five minutes. After scraping the powder mixture, it was combined with CCS as superdisintegrant and mixed for an additional minute. A Rimek rotary tablet press machine was utilized to compress the LS powder admixtures, under pressure, into tablets with concave punches with the necessary weight. Table 1 displays the ingredients of LST.

Table 1. Composition of LST

Batches	TLS (mg)	PEG600 (W)	MCC (Q)	Aerosil 200 (q)	CCS	Total Weight (mg)	Lf = W/Q	R = Q/q
TC1	20	100	200	10	8	338	0.5	20
TC2	20	100	200	10	16	346	0.5	20
TC3	20	100	200	10	24	354	0.5	20

Characterization LST of TLS

Pre-compression parameters

The angle of repose (AOR), tapped and bulk density, and Carr's index (C.I.) parameters were measured by specific procedures for prepared granules (Sahoo et al., 2015). The fixed funnel technique was used to measure the granular repose angle. AOR is determined by the classical method. Granules were to flow through the funnel freely and land on the spotless surface. The funnel was positioned so that its bottom tip would not make contact with the upper portion of the granule pile. Equation below is used to calculate AOR.

$$\tan=h/r \quad (3)$$

$$=\tan^{-1}(h/r) \quad (4)$$

Where the AOR measured in degrees, h is the heap's height in centimeters, and r is the circular support's (cone's) radius in centimeters.

The mass of an untapped powder sample divided by its bulk volume is known as the bulk density of a powder. A 100 ml graduated cylinder with a readable 1 ml is taken in order to determine the bulk density. Then it is fitted to bulk density apparatus (Sisco, India). When the bulk volume is leveled and the needed powder is carefully added to the cylinder without compacting, it is marked to the closest graded unit. Bulk density is then computed.

The bulk volume is determined using a measuring cylinder. A suitable 100 ml graduated cylinder readable 1 ml is taken and graduated measuring cylinder containing a powder sample fitted to bulk density apparatus is mechanically tapped. 10, 500, and 1250 taps on the powder sample were carried out, and the corresponding volumes V_{10}, V_{500}, and V_{1250} to the nearest graduated unit were noted. V_{1250} is the tapped volume if the difference between V_{500} and V_{1250} is less than or equal to 1 ml. If the difference between V_{500} and V_{1250} exceeds 1 ml, continue in increments, such as 1250 taps, until the difference between subsequent measurements is less than or equal to 1 ml. Next, compute tapped density by dividing the powder mass by the tapped volume.

The following formula was utilized to calculate C.I. (Saeedi et al., 2021).

$$\% \text{ C.I} = 100 \quad (5)$$

H.R. was computed by dividing the tapped density by the bulk density.

Post-compression parameters of LST

Appearance of the tablets

Tablets were chosen randomly from each batch and formulation, and their surface texture, shape, overall elegance, consistency, color, and odor were all examined (Jadhav et al., 2011).

Thickness

Utilizing a Vernier calliper, the thickness (Jadhav et al., 2011) of each LS tablet was determined.

Hardness

Utilizing the Monsanto hardness tester,(Jadhav et al., 2011) the tablets' hardness was measured.

Friability

The friability of LST was tested using a Roche friabilator (Gandhi et al., 2011). Twenty pills were added to the chamber after the group was weighed. Over the course of the friabilator's 100 revolutions, the tablets experienced the combined consequences ofshock and abrasion because the plastic chamber holding them dropped them six inches away with each revolution. The pills are then weighed one more and finished (Naureen et al., 2022).

Weight variation test (WVT)

Weight variation was assessed for each prepared LST in accordance (Suthar et al., 2016) with the USP monograph. Each of the twenty tablets is weighed individually, the average weight is established, and the weights of each tablet are compared to the average to conduct the WVT. After calculating the % weight deviation, the results were compared to the USP requirements (Patil et al., 2022).

Uniformity of drug content test

Each batch of LS pills contained ten tablets, (The USP 26-National Formulary, 2003)which were triturated to create a powder.A 100 ml volumetric flask filled with 0.1N HCl was allowed to dissolve the powder weight equivalent to one tablet over the course of 24 h using a magnetic stirrer. After the solution was suitably diluted, then it was filtered using Whatman filter paper No. 1, and then subjected to spectrophotometric analysis.

Disintegration test

The disintegration test was finished in accordance with IP 1996's strategy for uncoated tablets. The assembly was placed in the suitable vessel, preferably a 1000 ml beaker, and suspended in the liquid medium (water). The fluid volume so that the wire mesh, at its highest position, is at least 25 mm below the liquid's surface and, at its lowest point, is at least 25 mm above the container's base. A thermostat was utilized to raise the liquid's temperature and keep it at 37 ± 2^0C. The apparatus was run for a predetermined amount while the assembly was suspended in a beaker filled with 1000 milliliters of pure water. The tablet's breakdown time was also noted. Ultimately, the liquid was removed from the assembly (Tiwari et al., 2021).

***In vitro* dissolution study (IVDS)**

IVDS was performed with USP type II (paddle) equipment (Electrolab, India). The pill is stored in 900 ml of HCl buffer pH 1.2 dissolution medium with a 75 rpm rotating stirrer, (Senthil et al., 2011) which keeps the dissolution media at 37±0.5^{0}C for the necessary number of hours. At predetermined time intervals five milliliter aliquots were withdrawn by a sampling cannula then filtered using a 0.45-µm cellulose acetate filter. They replaced with equivalent amount of HCl buffer pH 1.2 solutions to the dissolution medium. The samples were suitably diluted and analyzed for absorbance with a UV/Visible Spectrophotometer at λmax of 290 nm. To ascertain the release profile of different batches, the percentage CDR was plotted against time.

Model-independent approach for dissolution comparison

Results of the IVDR profile were expressed as mean ± Standard Deviation (S.D). The model independent approach uses a difference factor (f1) and similarity factor (f2) to compare dissolution profiles (Sahoo et al., 2015). The f1 calculates the percent difference between the two curves at each time point and relative error between two curves. It is expressed as

$$f1 = / \times 100 \quad (6)$$

Where n is the sampling number, Rj and Tj are the percent dissolved of the reference and test products at each time point j.

The f2 is a logarithmic transformation of the sum squared error of differences between the test Tj and reference products Rj over all time points.

$$f2 = 50 \times \log [1+^{2}]^{-0.5} \times 100 \quad (7)$$

Where wj is an optional weight factor, the two release profiles are considered to be similar if f1 value is lower than 15 (between 0 to 15), and f2 value is more than 50 (between 50 to 100).

IVDR kinetic study

To ascertain the method of release from tablets, the formulation's release data was investigated utilizing the Higuchi model, first-order kinetics, zero-order kinetics, Korsmeyer-Peppas (KP) equations, and the Hixson Crowell model (Senthil et al., 2011). The Higuchi model showed the percentage CDR versus square root of time. The KP model showed the log % CDR versus log time. The Hixson and Crowell model showed the drug proportion left in the matrix as a cube root vs. time, first-order log % drug remaining to release vs. time and the zero-order model, which showed the percentage CDR versus time, were the kinetic models that were used.

Accelerated Stability Study (ASS)

For three months, the tightly sealed tablets were kept in stability chambers at 40±2^{0}C/75±5% RH (Thermo Lab Scientific Equipment Pvt. Ltd., Mumbai, India) for ASS (ICH Harmonized Tripartite Guidelines, 2003). The tablets were removed from the container regularly to be checked for IVDS, drug content, and other characteristics.

Statistical Analysis of Data

The experiment results were presented as mean ± S.D values (Rani et al., 2004). The degree of significance was ascertained using a paired and one-sided Student t-test. At $p < 0.05$, the difference was deemed statistically significant, whereas at $p > 0.05$, it was considered non-significant.

RESULTS AND DISCUSSION

Analytical methods for the estimation of TLS

The drug content and IVDS of TLS were estimated by obtaining a calibration curve in a pH 1.2 HCl buffer. The estimated λmax at a standard concentration of TLSin the HCl buffer, pH 1.2 was observed to be 290 nm. Regression values (R^2), which were found to be 0.9995, demonstrated the linearity of the calibration curve for HCl buffer pH 1.2. Y= 0.0205X-0.0015 calibration curves were used to derive the straight-line equations for drug content and IVDS. The scanning graph for λmax of TLS in HCl buffer pH 1.2 was presented in Figure 1. The values of absorbance to corresponding concentration in different buffer for TLS were presented in Table 2 and calibration curve was presented in Figure 2. The analytical parameters for UV-visible spectroscopic method (Systronics double beam India) were presented in Table 3.

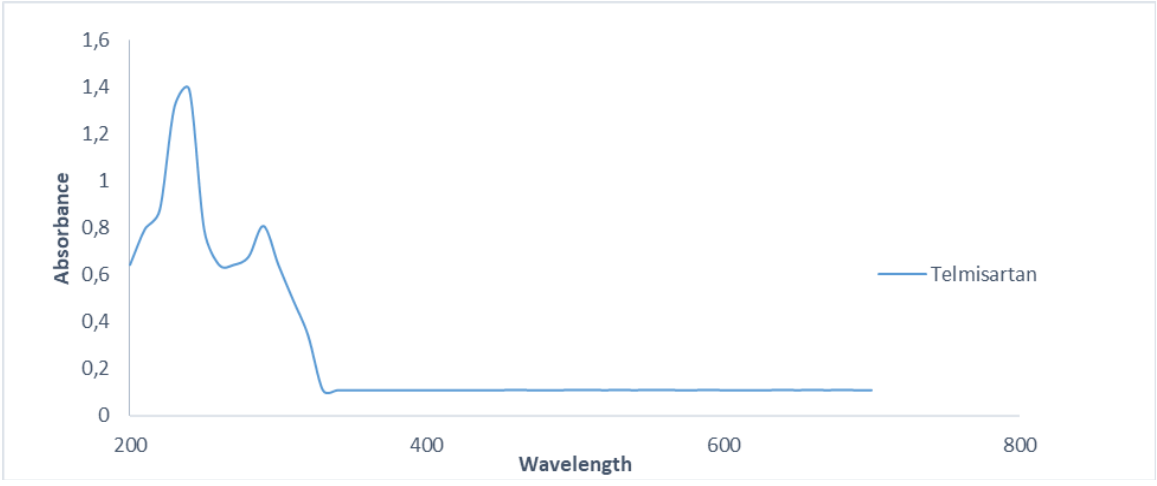

Figure 1. Scanning spectrum curve of TLS in HCl buffer pH 1.2

Table 2. Absorbance values to the corresponding concentration of TLS in HCl buffer pH 1.2 at 290 nm

Concentration (µg/ml)	Absorbance (Mean ± S.D.)
0	0
10	0.207 ± 0.013
20	0.414 ± 0.011
30	0.601 ± 0.017
40	0.815 ± 0.015
50	1.036 ± 0.018

Where S.D. is Standard Deviation, n 3

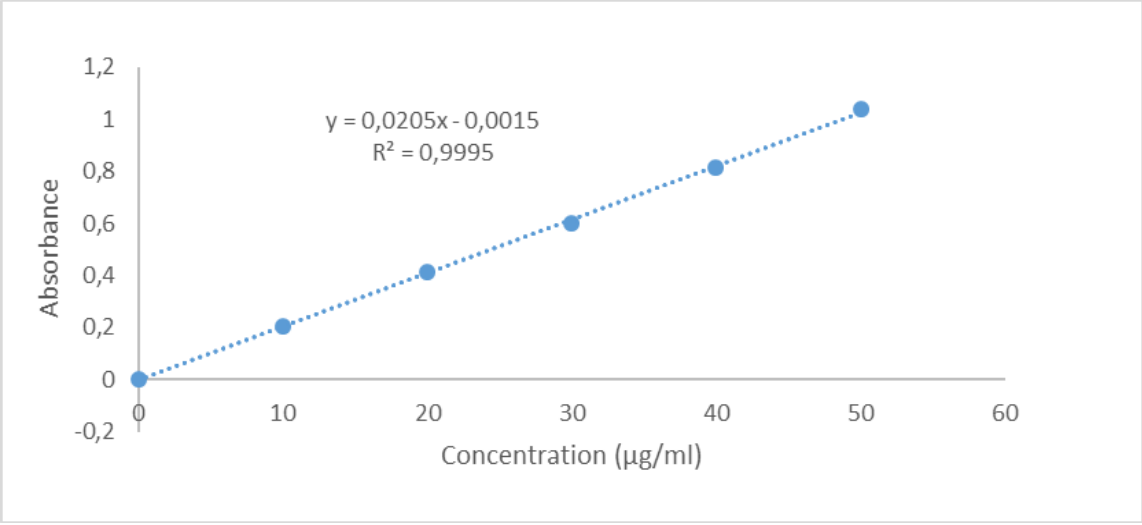

Figure 2. Calibration curve of TLS in HCl buffer pH 1.2 at 290 nm

Table 3. Analytical parameters of TLS for the development of the UV method

Parameters	Values for HCl buffer pH 1.2
λmax (nm)	290
Beer's law limit (µg/ml)	0-50
Regression equation	Y = 0.0205X-0.0015
Slope	0.0205
Intercept	0.0015
Correlation coefficient (R^2)	0.9995

Compatibility study

FTIR study

Pure TLS's FTIR spectra revealed the drug's distinctive peak at 2955.38 cm^{-1} caused by the aromatic group's C-H stretching vibration, the carbonyl group at 1693.19 cm^{-1} (Figure 3), and the C=C. The physical mixture's FTIR spectrum showed that the medication's unique peaks (at 1693.19 cm^{-1} and 1459.85 cm^{-1}) remained unchanged and did not exhibit any interaction, as demonstrated by the aromatic bend and stretch at that location (Figure 4). Consequently, there was no appreciable distinction between the FTIR spectra and those obtained for their physical mixing, indicating compatibility.

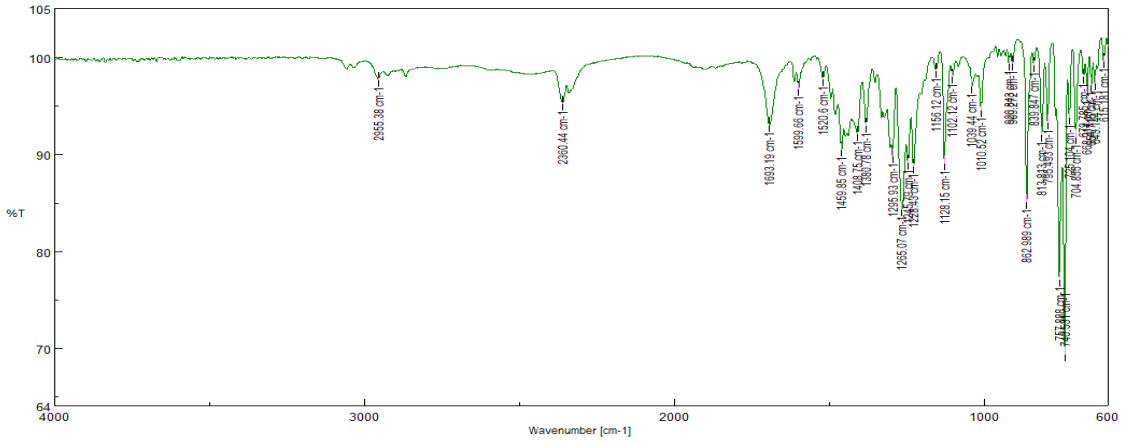

Figure 3. FTIR study of TLS

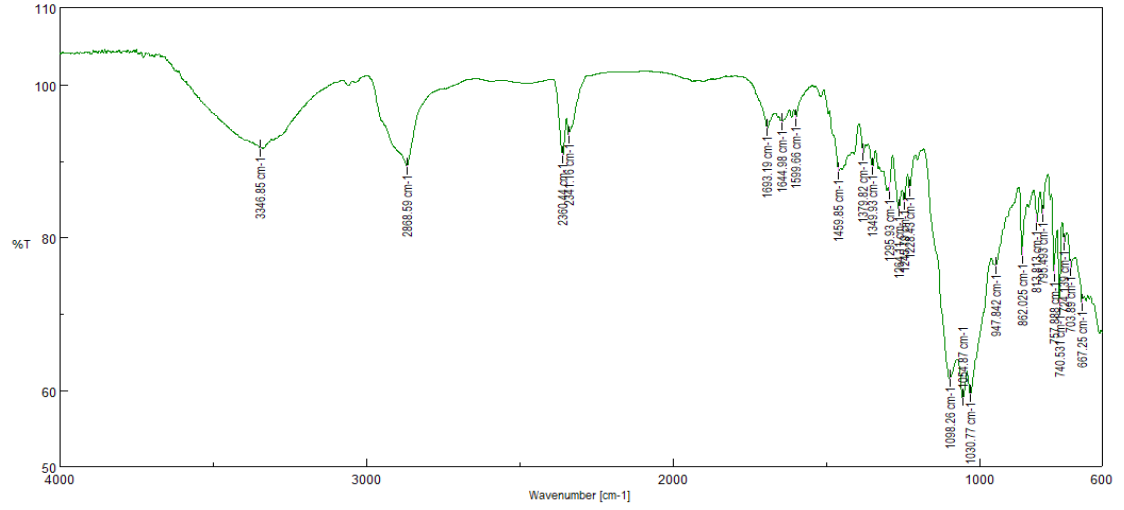

Figure 4. FTIR spectroscopy study of TC3

The formulation spectra also show the distinctive absorption peaks of TLS without much of a shift, suggesting no interaction between TLS and the additions (Swamy et al., 2013).

DSC Study

DSC thermogram of pure drug, and physical mixture of excipients used for LS formulations were obtained and shown in figure 5 and 6. Out of 3 formulations one formulation was found to be good i.e. TC3. DSC thermogram showed an endothermic peak at 275.42 ^{0}C which is corresponding melting point of drug. DSC thermogram showed a peak at 268.75 ^{0}C in TC3 formulation. Hence, physical mixture showed that there was compatibility with the drug.

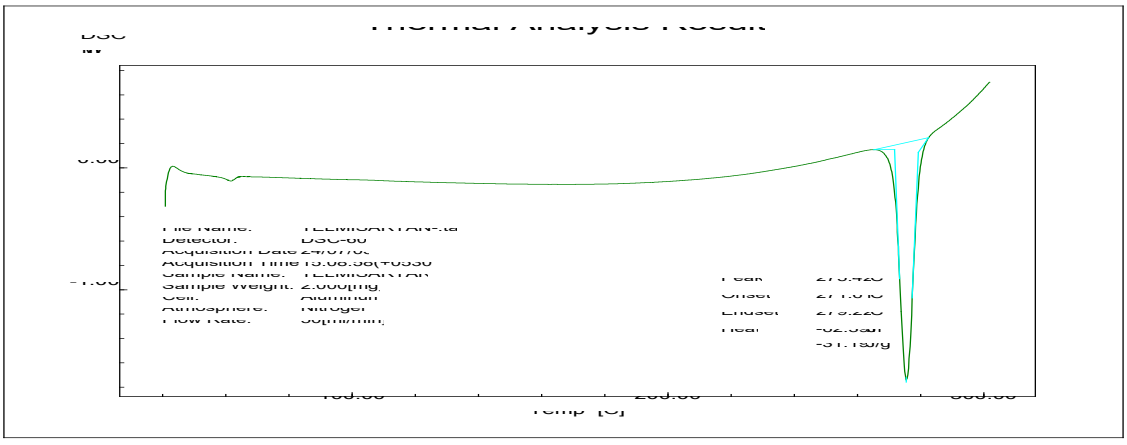

Figure 5. DSC thermogram of TLS

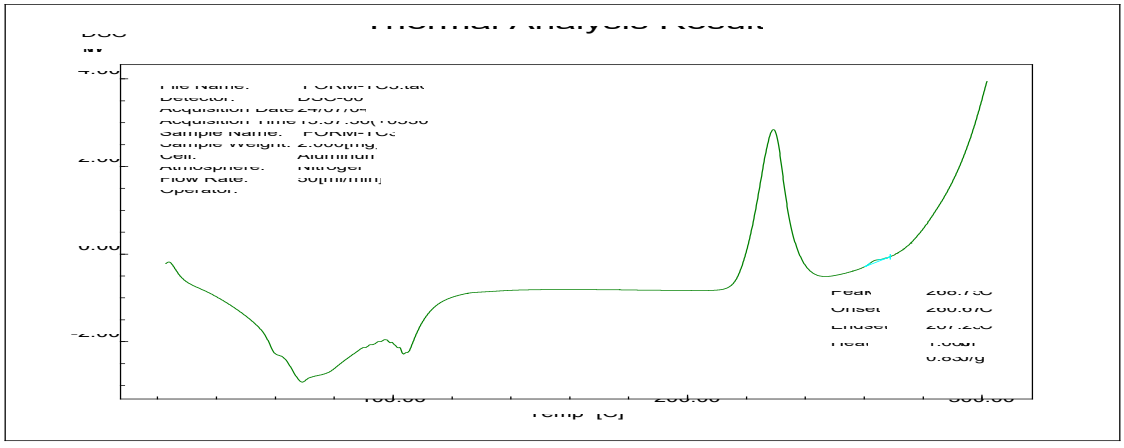

Figure 6. DSC thermogram of TC3

Since the steep peak at 266.45 on the TLS DSC thermogram is identical to the drug's melting point, it indicates no drug-excipient interaction (Mishra et al., 2023).

Characterization LST of TLS

Pre-compression parameters

All formulations had an angle of repose between 32.01 ± 1.60 and 47.2 ± 2.36. All formulations' bulk densities of TLS fell between 0.16 ± 0.008 and 0.26 ± 0.013 g/ml. It was discovered that the tapped densities ranged from 0.20 ± 0.01 to 0.35 ± 0.017 g/ml. These findings indicated that the formulation powders were TC1-poor, TC2-fair, and TC3-good, in that order. The range of results for Carr's index across all TLS formulations was 11.54 ± 0.57 to 30 ± 1.5. The optimized formulation TC3's C.I. value ranges from 5 to 15%, indicating excellent granule flow properties. In contrast, the TC2 formulation's C.I. value ranges from 16 to 20%, indicating fair granule flow properties. The granules of TLS had H.R. values ranging from 1.13 ± 0.05 to 1.42 ± 0.07 in all formulations. When the granule H.R. is less than 1.25, it typically shows that the TLS formulations TC2 and TC3 under investigation have outstanding flow properties. However, TC1 had a weak flow. According to the pre-compression parameter data, all TLS formulations' dry granules had good flow characteristics, making it easier to manufacture LST. Table 4 displays it.

Table 4. Pre-compression parameters of powder blend

Batches	AOR (degree) ± S.D (n = 3)	Bulk density (g/ml) ± S.D (n = 3)	Tapped density (g/ml) ± S.D (n = 3)	C.I (%) ± S.D (n = 3)	H.R ± S.D (n = 3)
TC1	47.2 ± 2.36	0.26 ± 0.013	0.3 ± 0.015	30 ± 1.5	1.42 ± 0.07
TC2	36.50 ± 1.83	0.16 ± 0.008	0.20 ± 0.01	20.43 ± 1.021	1.25 ± 0.06
TC3	32.01 ± 1.60	0.30 ± 0.015	0.35 ± 0.017	11.54 ± 0.57	1.13 ± 0.05

N.B.-Each value is given as mean± S.D.

CI values ranged from 11.5 to 15.5, while AOR values varied from 28.89° to 34.07° among the pre-compression investigations. H.R. results ranged from 1.12 to1.19 indicating good powder mix flow, which is very much needed for final processing into tablets (Swamy et al., 2013)

Post compression parameters

All of the TLS LSTs were found to have identical morphological features. It was discovered that every tablet had a smooth, concave, round, and white surface. The TLS LST ranged in average thickness from 5.67 ± 0.28 to 6.5 ± 0.47 mm. It was within permissible bounds, with average value variations not exceeding ± 5%. Every TLS LST had a hardness ranging from 2 ± 0.19 to 3 ± 0.11 kg/cm^2. All formulations had a percentage friability ranging from 0.08±0.0008% to 0.11 ± 0.001%. The % friability for each formulation was good in the current trials. The range of weight variation for the average pill weight was 2.9 ± 0.016 to 3.53 ± 0.017 percent. All of the formulations fell within the permitted range. The drug content percentages for TLS LST were discovered to be within allowable bounds, ranging from 97.98 ± 1.04 % to 99.12 ± 1.25 %. Within the defined range, the disintegration time of TLS LST was determined to be 2.20 ± 0.16 to 5.94 ± 0.21 minutes. Table 5 refers to it.

Table 5. Post-compression parameters of LST.

Batches	Thickness (mm) ± S.D (n = 10)	Hardness (kg/cm^2) ± S.D (n = 10)	%Friability (%) ± S.D (n = 20)	%Weight variation (%)^b ± S.D (n = 20)	%Drug content (%) ± S.D (n = 10)	Disintegration time (min) ± S.D (n = 10)
TC1	5.67 ± 0.28	2 ± 0.19	0.11 ± 0.001	2.9 ± 0.016	97.98 ± 1.04	5.94 ± 0.21
TC2	6.34 ± 0.56	2.5 ± 0.11	0.08 ± 0.0008	3.44 ± 0.017	98.26 ± 1.06	5.16 ± 0.19
TC3	6.5 ± 0.47	3 ± 0.11	0.10 ± 0.001	3.53 ± 0.017	99.12 ± 1.25	2.20 ± 0.16

N.B.-Each value is given where mean± S.D.

LS compacts ranged in hardness from 3.8 to 4.6 kg/cm^2. For LS compacts, the friability value varied from 0.5 to 0.72%. The drug content ranges from 91.29 ± 0.03 to 94.62 ± 0.01 %, whereas the thicknesses vary from 5.80 ± 0.01 to 5.87 ± 0.02 mm. The disintegration time ranges from 185 to 276 seconds (Swamy et al., 2013).

IVDS

After 30 minutes, the % cumulative drug release (% CDR) of TLS for TC1, TC2, TC3, and MKT was 85.63%, 92.97%, 98.30%, and 88.95%, respectively. Figure 7 displays the graph, which was created by plotting the % CDR (Y-axis) against time (X-axis). The % CDR of optimized formulation is highest as compared to others because of its high concentration of CCS. Significantly (p 0.05) higher values of % CDR of TC3 compared to MKT further indicate superiority of developed formulation over MKT.

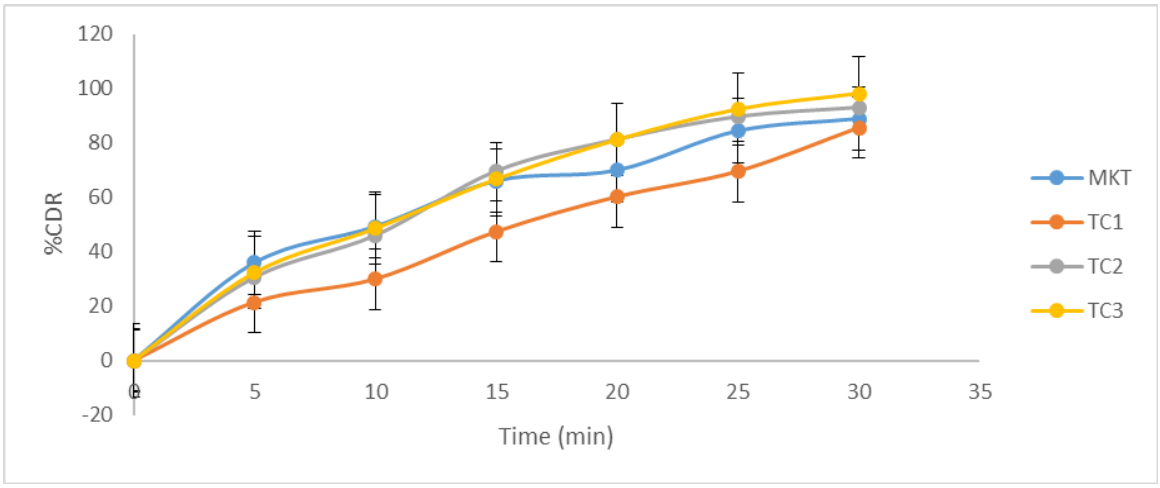

Figure 7. IVDS is showing TLS release from various fabricated formulations TC1-TC3 and MKT (n=3).

From the dissolution profile data for TLS LS compacts, a % CDR of 85.97 to 94.05 was recorded for the formulations at the end of 60 min. The drug surface available for dissolution is significantly increased with LS compacts because the drug is present in a non-volatile component solution, meaning that the drug is available in a molecularly distributed state in the dissolving media (Swamy et al., 2013). According to the data, the medication started to release from the compacts at minute five, and after sixty minutes, 70.00% to 93.28% of the drug was visible in the dissolving media. The commercial formulation of TLS, recognized for its favorable in-vitro drug release profile, was contrasted with the F5 formulation, which demonstrated the maximum release (Mishra et al., 2023)

The reason for the high dissolving rate of LST is that their formulations have a drug solution in a non-volatile vehicle that is used to generate the LS compact, which significantly increases the amount of drug surface area available for dissolution. As a result, compared to MKT, the surface area of the medication that is available for dissolving in an LS compact is significantly larger (Kalbhor et al., 2020).

Model-independent approach for dissolution comparison

IVDR profiles of developed formulations TC1-TC3 were compared with commercial tablet TELVAS 20. The values of f1 and f2 were depicted in Table 6. From the data TC3 formulation was found to best among all showing f2 value 80.5 and f1 value 2.4.

Table 6. Estimation of f1 and Similarity f2 of TC1-TC3

Formulations	f1	f2	Observation
TC1	34	49.25	Dissimilar
TC2	3	68	Similar
TC3	2.4	80.5	Similar

IVDR kinetic study

The TC3 exhibits a non-Fickian transport mechanism and KP release kinetics, as shown from the kinetic. TC3 was determined to be the optimal formulation among the three developed formulations. The R^2 values were 0.953, 0.912, 0.986, 0.999, and 0.987 for the zero-order, first- order, Higuchi, KP, and Hixson-Crowell models, respectively. In comparison to other models, it was discovered that the KP model had the highest R^2 value due to its excellent linearity. It therefore adheres to KP kinetics. The KP model n's release exponent for the TC3 formulation was found to be 0.650, which appears to support Non-Fickian diffusion. It is shown in Table 7.

Table 7. Fitting of IVDR data in various mathematical models

Models	Zero-order		First-order		Higuchi		KP			Hixson-Crowell	
Batches	R^2	K_0	R_1^2	K_1	R_H^2	K_H	R_K^2	Kp	N	R^2	Ks
TC1	0.991	2.738	0.933	0.059	0.941	15.35	0.975	5.61	0.785	0.972	0.069
TC2	0.932	3.088	0.989	0.092	0.979	18.19	0.977	10.77	0.654	0.992	0.094
TC3	0.953	3.199	0.912	0.126	0.986	18.71	0.999	11.15	0.650	0.987	0.111

ASS

ASS was determined for TC3. It was noted that no discernible alterations had occurred to optimized batch's weight variation, physical appearance, friability, drug content etc. There was no significant (p 0.05) difference between TC3 accelerated values vs. initial values of TC3 parameters. Hence it was confirmed that TC3 was found to be stable. Table 8 displays it.

Table 8. Comparative physicochemical analysis of TC3

Parameters	Initial	Following thirty days	Following sixty days	Following ninety days
Physical appearance	White, circular, and concave smooth surface	Nothing alters	Nothing alters	Nothing alters
Thickness (mm) ± S.D (n = 10)	6.5 ± 0.47	6.5 ± 0.47	6.5 ± 0.47	6.4 ± 0.47
Hardness (kg/cm^2) ± S.D (n = 10)	3 ± 0.11	3 ± 0.11	3 ± 0.11	3 ± 0.11
Friability (%) ± S.D (n = 20)	0.10 ± 0.001	0.10 ± 0.001	0.10 ± 0.001	0.9 ± 0.001
Weight variation (%) ± S.D (n = 20)	3.53 ± 0.017	3.53 ± 0.017	3.52 ± 0.017	3.51 ± 0.017
Drug content (%) ± S.D (n = 10)	99.12 ± 1.25	99.12 ± 1.25	99.12 ± 1.25	98.12 ± 1.25
Disintegration time (min)± S.D (n = 10)	2.20 ± 0.16	2.20 ± 0.16	2.19 ± 0.22	2.19 ± 0.23

N.B. Every value is presented as mean ± S.D.

CONCLUSION

According to the current study's findings, LST shows great promise in enhancing the dissolving of medications that are difficult to dissolve, such as TLS. It was discovered that the LST made with Aerosil 200 and MCC was a superior product, exhibiting an enhanced dissolution profile and satisfactory tableting qualities. When compared to commercial tablets, IVDS showed an improvement in dissolution from LST tablets. The medication and excipients did not interact, according to the FTIR spectra. According to stability experiments, aging did not affect the LS formulation's capacity to dissolve. Ultimately, it may be said that TC3's LST can more effectively lessen the adverse effects of traditional tablets.

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AUTHOR CONTRIBUTION STATEMENT

Chinmaya Keshari Sahoo (CKS) gave the concept and idea for research, Nidhi Shree (NS) performed the literature survey and research work. CKS, and Amiyakanta Mishra (AKM) reviewed the research data, manuscript, and approved the final version.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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