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RESEARCH PAPER

Formulation and Evaluation of Telmisartan Nanoparticles via the Evaporative Antisolvent Precipitation Technique

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ABSTRACT

Telmisartan is an antihypertensive agent belongs to angiotensin II receptor blockers which is used to alleviate hypertension and cardiovascular disorders owing to its effective competitive blockade of the AT1 receptor. According to the biopharmaceutical classification system, telmisartan is a class II drug with low solubility and high permeability. NPs are generally defined as carriers with sizes ranging between 1 and 1000 nanometers in diameter that can encapsulate or absorb drugs and deliver them to the desired region. Nanoparticles are considered one of the most promising recent techniques for improving the solubility of Class II drugs. Telmisartan nanoparticles were prepared via an evaporative antisolvent precipitation technique. Telmisartan (100 mg) was dissolved in dichloromethane (DCM; 10 ml of dichloromethane). The polymers (PEG, PVA, or PVP) were dissolved in 100 ml of water at different concentrations via a magnetic stirrer until a homogenous solution was obtained. The drug mixture was then stirred until nanoparticles formed. Formula F2 which composed of 100 mg telmisartan and PVP as stabilizer in concentration of 0.5 mg/ml has the lowest average particle size (259 nm) and this could be due to the high affinity of PVP for both hydrophobic and hydrophilic surfaces, indicating that PVP has a relatively high affinity for telmisartan. Telmisartan nanoparticles were synthesized via antisolvent precipitation. At different concentrations, the PVP, PVA, and PEG stabilizers produced nanoparticles. Unlike conventional telmisartan, the synthesized nanoparticles were released wholly and rapidly.

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INTRODUCTION

Telmisartan (TEL) belongs to angiotensin II receptor blockers (ARBs) which alleviates hypertension and cardiovascular disorders owing to its effective competitive blockade of the AT1 receptor [1]. TEL meets certain pharmacokinetic requirements; it has low oral bioavailability, ranging from 42-58%, owing to its poor water solubility (0.004 g/L) but high permeability and high first-pass metabolism. Thus, this solubility is inappropriate for absorption and requires higher loading, which leaves patients with possible side effects and variability in therapeutic outcomes [2]. To overcome these constraints, nanoparticle-based delivery systems have been used to improve TEL bioavailability and therapeutic value [3].

NPs are generally defined as carriers with sizes ranging between 1 and 1000 nanometers in diameter that can encapsulate or absorb drugs and deliver them to desired areas [4]. NPs offer several advantages, including enhanced solubility, improved dissolution rates, and increased antimicrobial activity [5]. NPs can be composed of many materials, such as biodegradable polymers, lipids, and surfactants. In addition, the system can be manipulated to achieve the desired rate of release and biodistribution of drugs [6]. Among the more significant challenges in drug development, controlling the solubility of poorly soluble drugs has constituted a significant problem; however, the advancement of NPs provides a complete solution. Their small size is beneficial because they deliver a large surface area/volume ratio, which enhances their dissolution in body fluids. Furthermore, NPs can preserve the amorphous state of a drug, which dissolves better than the crystalline form does [7]. Additional dispersion in aqueous environments is evident when hydrophobic drugs are encapsulated in hydrophilic NPs such as liposomes or micelles. Nanosuspensions and surface-modified particles have the advantages of enhancing aqueous stability and preventing drug–particle aggregation. These mechanisms greatly increase drug solubility and bioavailability and ensure delivery [8]. The preparation of TEL NPs aims to enhance bioavailability of the drug by increasing aqueous solubility through particle size reduction, which leads to a larger effective surface area.

MATERIALS AND METHODS

Materials

TEL was purchased from Hetero Drugs Limited (India). Methanol, hydrochloric acid, polyvinyl pyrrolidine (PVP) K30, polyvinyl alcohol (PVA) cold water soluble, and polyethylene glycol 8000 (PEG) were obtained from Himedia Limited (India). Dichloromethane was purchased from J. T. Baker (Germany).

Determination of TEL solubility

The solubility of TEL in different media was determined by dissolving excess TEL in distilled water, phosphate buffer (pH 6.8), and dichloromethane. The solutions were incubated for 48 h with regulatory agitation, filtered, and examined spectrophotometrically at 297 nm [9].

Preparation of TEL nanoparticles

Solvent-antisolvent evaporative method was used to prepare TEL NPs. TEL (100 mg) was dissolved in dichloromethane (DCM; 10 ml of dichloromethane). PEG, PVA, and PVP were dissolved in 100 mL of water at varying

Table 1. The major composition of telmisartan nanoparticles.

No. of Formula	Concentration of TEL mg/ml	PVP mg/ml	PVA mg/ml	PEG mg/ml
1	10	0.25	-	-
2	10	0.5	-	-
3	10	1	-	-
4	10	2	-	-
5	10	-	0.5	-
6	10	-	1	-
7	10	-	2	-
8	10	-	-	0.5
9	10	-	-	1
10	10	-	-	2

concentrations and thoroughly mixed using a magnetic stirrer to obtain a homogeneous solution. The drug mixture was dropwise added under continuous magnetic stirring at 1500 rpm. After the complete addition of the drug solution, stirring was continued for an additional 2 hours at the same rate [10]. The different ratios of polymers used for preparing the NPs formulas are listed in Table 1.

Characterization of TEL nanoparticles

NPs characterized for particle size, zeta potential and polydispersity index determination

The particle size and zeta potential were measured to characterize the prepared NPs. Additionally, the size uniformity of the dispersed NPs was studied by measuring their polydispersity index (PDI) via dynamic light scattering (DLS) (Microtrac, USA) at a scattering angle of 90° at room temperature. Measurements of the formulas were done in triplicate for each [11].

Fourier transform infrared spectroscopy (FTIR)

Infrared spectra were obtained using an FTIR spectrophotometer (Bruker Tensor 37, Germany) to analyze pure TEL and each ingredient used in formulations F2, F5, and F8, ensuring no chemical interactions occurred during formulation [12].

Differential Scanning Calorimetry

DSC thermograms were obtained using a differential scanning calorimeter (Shimadzu, Japan). Each sample (2–5 mg) was placed in a pierced aluminum pan and heated from 30°C to 300°C at a rate of 10°C/min under a nitrogen flow of 50 mL/min [13].

Measurement of entrapment efficiency

The entrapment efficiency of the NPs was determined via a 10 ml portion, which was subsequently centrifuged at 7000 rpm for 10 min (Centrifuge-CL008). The supernatant layer then was removed, and the amount of unincorporated drug in the supernatant was measured spectroscopically at 297 nm (Shimadzu, Japan) [14].

In vitro dissolution

The dissolution test was conducted using 0.1N HCl (900 mL, pH 1.2) at 37°C, a USP II device with paddle spinning at 50 rpm. Dissolution tests of both TEL NPs and a TEL standard were used. Five millilitres of each sample was extracted via a syringe filter at various intervals over the course of six hours. A UV spectrophotometer was used to measure the amount of TEL dissoluted at λmax = 297 nm. The findings are displayed as the average value of three records [15].

Analysis of statistics

The experimental results are expressed as the mean ± standard deviation (SD). Statistical analysis was done using one-way analysis of variance (ANOVA), and a significance determined when *P*

Table 2. Particle size, polydispersity index (PDI) and zeta potential (mV) for TEL nanoparticle formulations (n=3, mean± SD).

Formula no.	PARTICLE SIZE	PDI	ZETA POTENTIAL
F1	730 ±0.08	0.338 ±0.164	98.8 ±0.53
F2	259.2 ±0.38	0.205 ±0.002	80.5 ±0.36
F3	502.1 ±0.37	1.290 ±0.427	69.4 ±0.24
F4	704 ±0.95	0.451 ±0.553	52.6 ±0.39
F5	513.6 ±0.126	0.432 ±0331	32.8 ±0.48
F6	937.3 ±0.22	0.481 ±0.336	11.8 ±0.57
F7	768 ±0.121	0.293 ±0.279	15.4 ±0.71
F8	456.3 ±0.128	0.27 ±0.21	32.9 ±0.44
F9	1227.6 ±0.12	0.621 ±0.565	61.2 ±0.344
F10	3272 ± 0.135	0.315 ±0.263	100.2 ± 0.33

< 0.05.

RESULTS AND DISCUSSION

TEL solubility

The solubility of TEL was 0.014 mg/ml in water, 0.000401 mg/ml in phosphate buffer (pH 6.8) and 18.33 mg/ml in dichloromethane. The results showed that TEL is highly soluble in dichloromethane (18.33 mg/ml) and dissolves remarkably well in dichloromethane (DCM) because dichloromethane has a lipid solubility that is complementary to the structure of TEL. Its moderate polarity and weak hydrogen bonding interactions characterize this solvent as appropriate for dissolving nonpolar compounds through van der Waals and dipole–dipole forces [16].

NP size, polydispersity index (PDI) and zeta potential (mV)

Table 2 shows the results of the particle size, polydispersity index (PDI), and zeta potential (mV) of the TEL NPs; all the prepared TEL NPs formulations had particle sizes within the nanoscale range, with wide variations from 259.2 to 3272. Formulas F2, F5, and F8 were found to have the smallest average particle size, and therefore, were selected for further evaluation. Among these, PVP (used in F2) resulted in the smallest particle size and PDI. This may be attributed to PVP's strong affinity for both hydrophilic and hydrophobic surfaces, which likely enhances its ability to adsorb TEL more effectively than PEG8000 and PVA [17].

Fourier transform infrared spectroscopy (FTIR)

The results of the infrared spectroscopy of the TEL, F2, F5, and F8 are shown in Fig. 1. The prominent peaks include a wide envelope at 3100-3500 cm^{-1} from O–H stretching of carboxylic acid and a strong peak at 1700 cm^{-1} from C=O stretching. These results demonstrated that there were no chemical interactions between TEL and other ingredients [18].

Differential Scanning Calorimetry

Fig. 2 displays the differential scanning calorimetry (DSC) results. The DSC thermogram of TEL exhibited sharp endothermic peaks at 269.8°C, which represent its melting point. The same peak absence in the final selected formula suggests that there were no interactions between the used excipients and TEL during the process of formulation [19].

Entrapment Efficiency

The entrapment efficiency (EE) results are

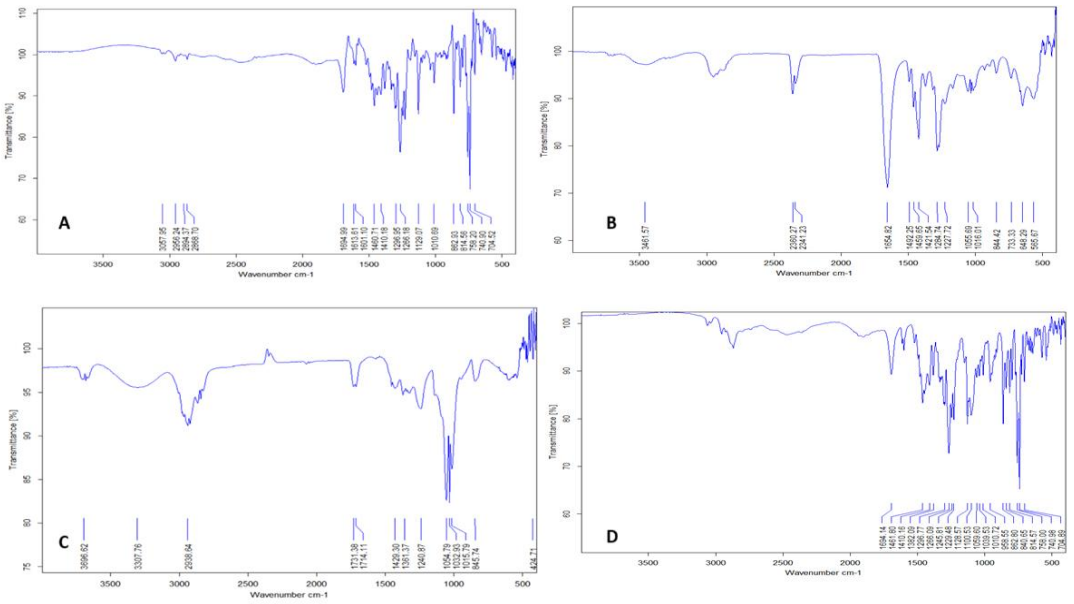

Fig. 1. IR spectra of A:TEL, B: F2, C: F5, D: F8.

shown in Table 3. The highest entrapment efficiency was 99.89% for F9.

In vitro dissolution

Comparative release profile analysis revealed that TEL effectively enhanced the release profile of the nanoparticle-based formulation (TEL nanoparticles; F2) compared with that of the standard formulation (standard TEL). The number of TEL nanoparticles increased and remained at ~87% at 180 min, which could indicate nearly complete drug dissolution, whereas the standard TEL remained at less than 19%. This finding shows that the TEL formulation improved the solubility,

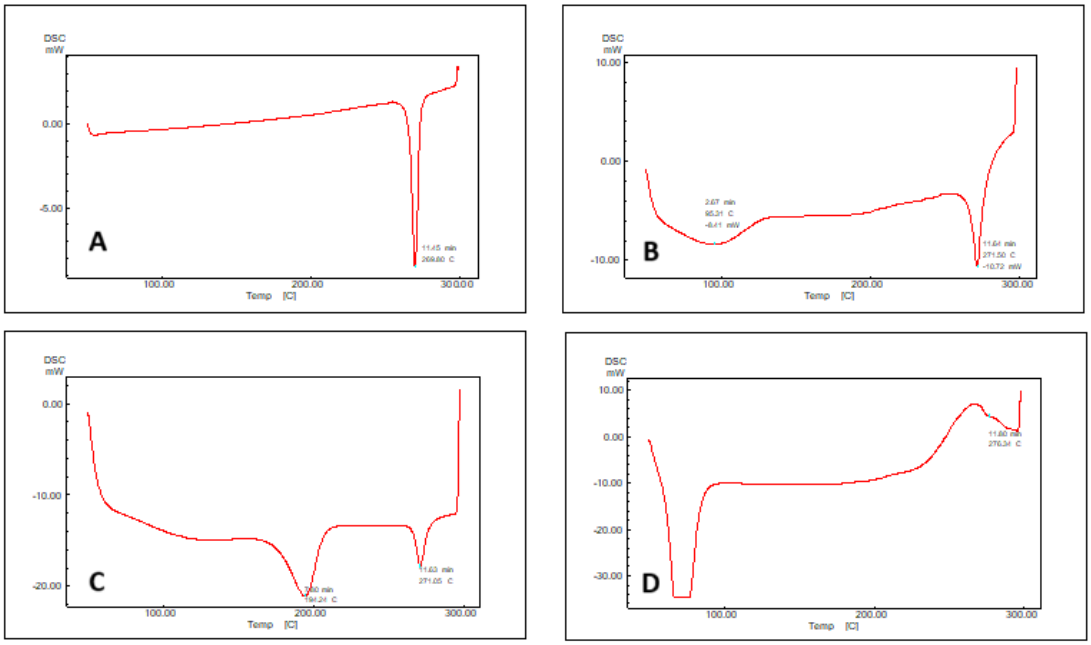

Fig. 2. DSC thermograms of A: TEL, B: F2, C: F5 and D: F8.

Table 3. Entrapment efficiency of TEL nanoparticle formulations (n=3, mean ±SD).

Formula	EE%
F1	98.01±0.22
F2	97.17±0.32
F3	99.24±0.43
F4	95.94±0.54
F5	98.71±0.23
F6	99.23±0.12
F7	98.82±0.54
F8	98.37±0.42
F9	99.89±0.65
F10	97.31±0.12

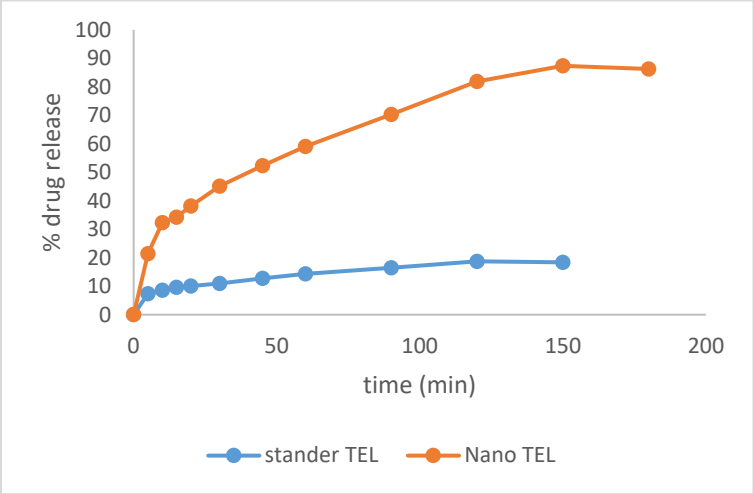

Fig. 3. Release profile of TEL nanoparticles and plane TEL (n=3, mean±SD).

dissolution rate, and overall release efficiency of the nanoparticles, making it a better formulation for the delivery of TEL [20]. Fig. 3 shows the release profiles of the standard TEL and TEL nanoparticles.

CONCLUSION

This study successfully formulated and evaluated TEL nanoparticles via the evaporative antisolvent precipitation technique. The results demonstrated that nanoparticle-based formulations significantly increased the solubility and dissolution rate of TEL, overcoming its inherent low aqueous solubility. Among the stabilizers used, PVP provided the most favourable characteristics, yielding the smallest particle size and highest dissolution efficiency. In vitro release studies confirmed that TEL nanoparticles exhibited rapid and nearly complete drug release compared with conventional TEL. These findings highlight the potential of nanoparticle-based drug delivery systems to improve the bioavailability and therapeutic efficacy of poorly soluble drugs such as TEL. Future studies should explore in vivo pharmacokinetic and pharmacodynamic evaluations to validate these results and assess their clinical applicability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Liu D, Wu P, Gu W, Yang C, Yang X, Deng X, et al. Potential of angiotensin II receptor blocker telmisartan in reducing mortality among hospitalized patients with COVID-19 compared with recommended drugs. Cell discovery. 2022;8(1):91-91.
2. Nugraha YP, Unique IGANP, Miyake T, Rahmah R, Indra I, Soewandhi SN, et al. Structural Characterization and Pharmaceutical Evaluation of Telmisartan Hydrochloride Salts. Crystals. 2024;14(2):151.
3. Shrimal P, Jadeja G, Patel S. Microfluidics nanoprecipitation of telmisartan nanoparticles: effect of process and formulation parameters. Chemical Papers. 2020;75(1):205-214.
4. Khan Y, Sadia H, Ali Shah SZ, Khan MN, Shah AA, Ullah N, et al. Classification, Synthetic, and Characterization Approaches to Nanoparticles, and Their Applications in Various Fields of Nanotechnology: A Review. Catalysts. 2022;12(11):1386.
5. Hantosh AM, Rajab NA, Abachi FT. Synthesis and antimicrobial activity of new 1,2,3,4-tetrahydropyrimidine-5-carbonyl glycinate silver nanoparticle derivatives. International journal of health sciences. 2022:8930-8948.
6. Khan S, Hossain MK. Classification and properties of nanoparticles. Nanoparticle-Based Polymer Composites: Elsevier; 2022. p. 15-54.
7. Mohanraj VJ, Chen Y. Nanoparticles - A review. Tropical

Journal of Pharmaceutical Research. 2007;5(1).
8. Haroon Anwar S. A Brief Review on Nanoparticles: Types of Platforms, Biological Synthesis and Applications. Research and Reviews Journal of Material Sciences. 2018;06(02).
9. Park J, Cho W, Cha K-H, Ahn J, Han K, Hwang S-J. Solubilization of the poorly water soluble drug, telmisartan, using supercritical anti-solvent (SAS) process. Int J Pharm. 2013;441(1-2):50-55.
10. Kakran M, Sahoo NG, Li L, Judeh Z, Wang Y, Chong K, et al. Fabrication of drug nanoparticles by evaporative precipitation of nanosuspension. Int J Pharm. 2010;383(1-2):285-292.
11. Mohanty D, Gilani SJ, Zafar A, Imam SS, Kumar LA, Ahmed MM, et al. Formulation and Optimization of Alogliptin-Loaded Polymeric Nanoparticles: In Vitro to In Vivo Assessment. Molecules (Basel, Switzerland). 2022;27(14):4470.
12. Ali Ashoor J, M. Mohsin J, Mohsin HM, W. Mahde B, M. Gareeb M. Permeability Enhancement of Methotrexate Transdermal Gel using Eucalyptus oil, Peppermint Oil and Olive Oil(Conference Paper)#. Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683 - 3597 , E-ISSN : 2521 - 3512). 2022;30(Suppl.):16-21.
13. Menczel JD, Andre R, Kohl WS, Krongauz VV, Lőrinczy D, Reading M, et al. Fundamentals of DSC. The Handbook of Differential Scanning Calorimetry: Elsevier; 2023. p. 1-189.
14. Teaima M, Abdelmonem R, Adel YA, El-Nabarawi MA, El-Nawawy TM. Transdermal Delivery of Telmisartan: Formulation, in vitro, ex vivo, Iontophoretic Permeation Enhancement and Comparative Pharmacokinetic Study in Rats. Drug Des Devel Ther. 2021;15:4603-4614.
15. The Enhancement Solubility of Oral Flurbiprofen by Using Nanoemelsion as Drug Delivery System. International Journal of Pharmaceutical Research. 2020;12(sp1).
16. Ha E-S, Kim J-S, Lee S-K, Sim W-Y, Jeong J-S, Kim M-S. Solubility and modeling of telmisartan in binary solvent mixtures of dichloromethane and (methanol, ethanol, n-propanol, or n-butanol) and its application to the preparation of nanoparticles using the supercritical antisolvent technique. J Mol Liq. 2019;295:111719.
17. Abdelghany AM, Elamin NY, Younis S, Ayaad DM. Polyvinyl pyrrolidone/ carboxymethyl cellulose (PVP/CMC) polymer composites containing CuO nanoparticles synthesized via laser ablation in liquids. J Mol Liq. 2024;403:124857.
18. Rahman A, Sravani GJ, Srividya K, Priyadharshni ADR, Narmada A, Sahithi K, et al. Development and Validation of Chemometric Assisted FTIR Spectroscopic Method for Simultaneous Estimation of Valsartan and Hydrochlorothiazide in Pure and Pharmaceutical Dosage Forms. J Young Pharm. 2020;12(2s):s51-s55.
19. Chella N, Narra N, Rama Rao T. Preparation and characterization of liquisolid compacts for improved dissolution of telmisartan. Journal of drug delivery. 2014;2014:692793-692793.
20. Khafeef Hk, Rajab NA. Eplerenone Crystal Nanosuspension for Solubility Enhancement: Preparation and Evaluation. Maaen Journal for Medical Sciences. 2023;2(2).