ORIGINAL ARTICLE

Pharmaceutical Development of Ticagrelor Nanoparticle and Dapagliflozin Dual Component Capsule

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Abstract

Introduction: Ticagrelor (TCG) is a platelet aggregation inhibitor used to manage acute coronary syndrome. Dapagliflozin propanediol monohydrate (DPM), a sodium-glucose cotransporter-2 inhibitor, for type 2 diabetes also provides cardiovascular benefits. Recent studies highlight that coadministration of these two drugs produces additive protective effects against cardiovascular problems and nephropathy in secondary complication of diabetes. **Materials and Methods:** The TCG nanoparticles (TCG NPs) were prepared via ionic gelation using chitosan and sodium tripolyphosphate, DPM tablets were prepared by the direct compression method using suitable excipients, and dual-component (DC) capsules were prepared by manual filling. **Results and Discussion:** TCG NP were optimized with a particle size of 729.8 nm with an acceptable polydispersity index, positive zeta potential, and a high drug loading efficiency of 95.65%, while the amorphous state contributed to enhanced solubility. DPM tablets showed robust physical properties and rapid dissolution consistent with immediate release. The DC capsule exhibited uniformity in content and weight, rapid disintegration (7.5 min), and rapid drug release following first-order kinetics with quasi-Fickian diffusion. Stability tests confirm good stability. **Conclusion:** This dual-drug in a DC capsule demonstrates feasibility for simultaneous oral therapy of TCG NP and DPM, with future work recommended for bioavailability study.

Key words: Dapagliflozin, dual component capsule, ionic gelation method, nanoparticle and tablet in capsule technology, ticagrelor

INTRODUCTION

Diabetic nephropathy is a common complication of diabetes mellitus.[1] Approximately 30–40% of patients with diabetes mellitus develop diabetic nephropathy. Recent studies highlight that the coadministration of ticagrelor (TCG) and dapagliflozin produces additive protective effects against diabetic cardiomyopathy and diabetic nephropathy complications.[2] TCG is used as an antiplatelet agent.[3] TCG is a Biopharmaceutics Classification System (BCS) Class IV drug[4] with poor bioavailability; to improve that, various formulation approaches are used.[5] Chitosan (CH) nanoparticle formulations significantly enhance the solubility and dispersibility of various poorly water-soluble compounds, ranging from phytochemicals to pharmaceutical actives, leading to better release profiles and bioavailability.[6] Dapagliflozin propanediol monohydrate (DPM) is a sodium–glucose cotransporter-2 inhibitor primarily used for the treatment of diabetes mellitus, heart failure, and chronic kidney disease.[7,8] DPM is a BCS Class III drug.[9] Currently, administration of these two drugs in cardiovascular diseases, diabetic nephropathy, As per patient aspect, especially the elder patients, has poor adherence to therapy, which can result in treatment failure, progression to the disease condition, ultimately leading to death. Hard gelatin capsules help reduce pill burden, simplify dosing, and are especially useful for elderly patients who need to take multiple medications.[10]

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MATERIALS AND METHODS

Materials

TCG and DPM were donated by Saimirra Innopharm Pvt. Ltd., Chennai, India. CH and microcrystalline cellulose were purchased from Sigma-Aldrich. Tripolyphosphate (TPP) and polyvinylpyrrolidone were procured from Loba Chemie. Lactose monohydrate and magnesium stearate were procured from HiMedia. Talc was purchased from Nice Chemicals. "00" hard gelatin capsules were procured from Yarrow Chem. Unless otherwise stated, all chemicals and solvents were analytical grade.

Methods

Preformulation studies

The TCG[11,12] and DPM[13] stock solutions were prepared and analyzed using a double-beam UV-visible spectrometer. The melting points of TCG and DPM were determined by a digital melting point instrument. The solubility of TCG and DPM was evaluated in various solvents, including water, methanol, and ethanol, by the saturation solubility method.[14,15] Drug and physical mixture compatibility was analyzed through a Fourier Transform Infrared (FTIR) Spectrophotometer.[16]

Formulation process

Formulation of nanoparticles by the ionic gelation technique using low-, medium-, and high-molecular weight CH were dissolved in a 1% acetic acid solution and TCG was dissolved in ethanol and TPP in water with a ratio of 7:3:3 for the preparation of TCG nanoparticles (TCG NP). The CH solution was placed on a magnetic stirrer under stirring conditions, and then the TCG solution was added drop by drop to the CH solution. After appearing opalescent to the suspension, add the cross-linking agent TPP solution. The mixture was homogenized at 7000 rpm for 2 min before lyophilization.[17] Further optimization was done using a homogenization process. TCG NP was freeze-dried to get powder. DPM and all other excipients were accurately weighed and passed through a #25 mesh. The powder was blended in a mortar and pestle for 15 min. The blending was further continued for 1 min after the addition of the lubricant, magnesium stearate. The final mixture was subjected to direct compression using a 7-mm concave punch.[15] The capsule-filling process was initiated by manually inserting the pre-compressed tablet into the body of a "00" hard gelatin capsule to provide a stable base. Subsequently, the accurately weighed TCG NP powder equivalent to 60 mg of TCG was gently loaded. The capsule was then locked onto the body.[18,19]

Evaluation of TCG NP

The TCG NP was tested for various parameters by Malvern Zeta Size.

Drug content

The freeze-dried powder 10 mg was measured by dissolving in ethanol for TCG NP. Further, the stock solution was diluted with the same solvent and measured in ultraviolet (UV)-visible spectroscopy to evaluate the concentration.[20]

Morphological study by atomic force microscopy (AFM)

The surface morphology of drug-entrapped TCG NP was determined using AFM. The sample was placed securely onto the AFM stage or holder. The sample should be clean and flat to ensure accurate measurements.[21]

Morphological study by scanning electron microscopy (SEM)

Structural morphology of TCG NP with CH: TCG:TPP weight ratio 7:3:3 was carried out using SEM.[16]

Structural characterization by X-ray diffraction (XRD)

To determine the nature of TCG NP, powder XRD analysis was performed using an Empyrean Series III diffractometer.[16]

Characterization of DPM tablets

The common quality assessment tests of tablets were weight variation, thickness and diameter,[22] friability, disintegration test,[22,23] hardness,[15] content uniformity[24] [Table 1] was analyzed.

Evaluation of DC capsule dosage form

The DC capsule is evaluated for the weight uniformity test [Table 2], disintegration test[25] and content uniformity.[24]

In vitro drug release studies

Dissolution test of capsule dosage form is performed using USP Apparatus 2. The dissolution medium consisted of (1% w/v polysorbate solution) for TCG NP[26] and pH 1.2 (0.2M HCl buffer) for DPM tablets,[13] respectively, with a volume of 900 mL at 37.0 ± 0.5°C at 75 rpm.

In vitro drug release kinetics

The DC capsule dosage form is subjected to kinetic modeling.[27] The kinetic modeling is performed using the DD solver.

Stability studies

A stability study was performed under the different conditions as per the International Conference on Harmonisation (ICH) guidelines, with a necessary study for 6 months.[28]

Table 1: Characterization of DPM tablet

Evaluation parameter	Observed results
Weight variation test	98.24±1.53 mg
Thickness	3.1±0.08 mm
Diameter	6.9±0.07 mm
Friability	0.25±0.07%
Hardness	40.83±2.85 N
Disintegration	5.12±0.55 min
Content uniformity	99.44±0.91%

DPM: Dapagliflozin propanediol monohydrate

Table 2: Characterization of DC capsule

Evaluation parameter	Components	Observed results
Weight uniformity test	Capsule	490.70±2.48 mg
	Tablet	98.75±0.54 mg
	Nanoparticle powder	271.48±1.56 mg
	Empty capsule shell	119.84±1.44 mg
Content uniformity	Ticagrelor	99.05±1.55%
	Dapagliflozin	99.28±0.77%
Disintegration test	Capsule dosage form	7.51±0.21 min

DC: Dual component

RESULTS AND DISCUSSION

Preformulation studies

UV analysis was performed for both TCG and DPM, and the maximum lambda max was observed, followed by a plotted standard curve. The melting point of TCG was found to be 141°C, and DPM was found to be 77°C. The solubility studies showed that TCG is freely soluble with ethanol, methanol and practically insoluble with water. The solubility studies of DPM confirmed that it was soluble in methanol, freely soluble in ethanol and very slightly soluble in water. FTIR studies confirmed that no physical interaction occurred within the drugs and excipient mixture.

Formulation process

TCG NP were successfully prepared by the ionic gelation method using a ratio of CH:TCG:TPP (7:3:3), followed by homogenization and lyophilization. DPM tablets were formulated by direct compression using suitable excipients. Finally, a DC capsule was assembled by DPM tablet with TCG NP powder into a "00" size hard gelatin capsule.

Evaluation of TCG NP

The low molecular weight CH nanoparticle formulation showed higher positive zeta potential, smaller size and best polydispersity index (PDI) compared to medium and high molecular weight CH nanoparticle formulations. Low and high molecular weight CH NPs were stable, whereas medium molecular weight CH NP are unstable after 30 min of preparation. With this study, low molecular weight is taken with the ratio of CH: TCG:TPP as 7:3:3 for the formulation of nanoparticles. Homogenization cycle of CH, the drug, and TPP for nanoparticles formulation is optimized using a 1% w/v concentration of each component. The TCG NP had a particle size of 696.4 nm, PDI of 0.453, with a zeta potential of +36.5 mV. The optimization of the homogenization process for drug-loaded nanoparticles was carried out up to 5 cycles of 7000 rpm, and the impact of homogenization was evaluated by measuring particle size (729.8 nm), PDI (0.430), and zeta potential (+25.6 mV). During nanoparticle formulation, it was observed that the first cycle reduced particle size. However, the second cycle increased particle size due to the introduction of mechanical energy, which led to higher particle density and a consequent decrease in specific surface area. Subsequent cycles (third, fourth, and fifth) resulted in a reduction of particle size compared to the second cycle, but the size remained larger relative to the first cycle. Hence, homogenization 1 cycle for 2 min was fixed as optimum for these formulations.

Drug content

Drug content for TCG was 0.22 mg in 1 mg of TCG NP, corresponding to 95.65 % comparing to the theoretical drug content.

Morphological study by AFM

Formulated TCG NPs were analyzed using AFM, which showed an average size of 212.36 nm for 65536 nanoparticles. The maximum size observed is 515.11 nm, with an average roughness of 51.58 nm. The morphology of the TCG NP was found to be irregular in shape, as depicted in [Figure 1].

Morphology study by SEM

Further, freeze-dried formulated TCG NP are analyzed using the SEM. The analysis revealed that the CH nanoparticles exhibited irregular to hemispherical morphology with an observed size range of approximately 325 to 788 nm, as depicted.

Structural characterization by XRD

XRD analysis of the formulated nanoparticle is performed in the range of 5 to 90° (2θ). A diffuse, broad peak is observed between 10° and 30° (2θ) prooves amorphous nature of TCG NP shown in [Figure 2].

Characterization of DPM tablet

The characterization of DPM tablets, including weight variation, thickness and diameter, friability, hardness, disintegration time, and content uniformity, demonstrated

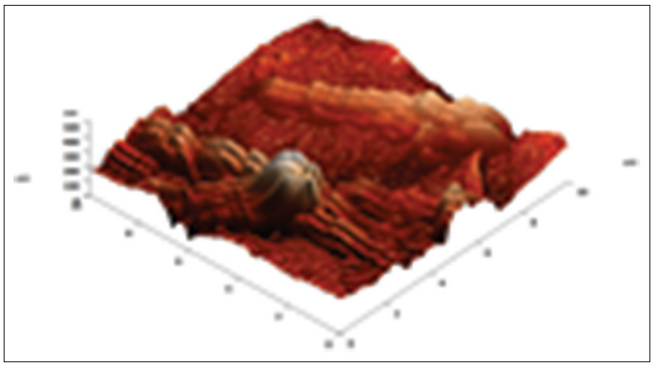

Figure 1: 3D atomic force microscopy imaging of ticagrelor nanoparticles

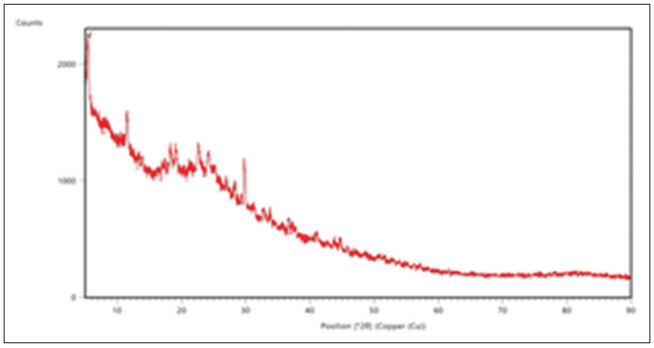

Figure 2: X-ray diffraction of ticagrelor nanoparticles

that all parameters fell within their respective ideal ranges. The data are presented in [Table 1].

Evaluation of DC capsule dosage form

The characterization of the DC capsule, including the weight uniformity test, content uniformity and disintegration time, demonstrated that all parameters fell within their respective ideal ranges. The data are shown in [Table 2]. The *in vitro* drug release profiles of the prepared formulations are compared with those of conventional products. At 5 min, 30.95% of TCG is released from the nanoparticles, whereas 98.49% was released at 120 min. In comparison, the conventional product released 15.89% at 5 min and 97.99% at 120 min. These results indicate that the nanoparticle formulation of TCG demonstrates an improved release profile compared to the conventional product. DPM showed a rapid release, with 46.9% of the drug released at 5 min and 98.21% within 60 min. The conventional product exhibited a similar release profile, with 50.13% released at 5 min and 99.89% at 60 min. These findings suggest that the release profiles of the prepared and conventional formulations of DPM are nearly equivalent. The release kinetics of TCG NP and DPM tablets, along with their respective conventional products, followed first-order release and the Korsmeyer–Peppas model exhibited a quasi-Fickian diffusion mechanism and confirms non-swellable matrix diffusion kind of release. The Higuchi model confirms that the release kinetics are fairly non-linear. The stability study of the DC capsule dosage form confirms the suitability of the method for stable formulation.

CONCLUSION

A dual-component (DC) capsule loaded with TCG NP and a DPM tablet is formulated. Low molecular weight CH demonstrated a greater ability to produce stable nanoparticles compared to the other two molecular weights of CH in our formulation. The polymer: drug: TPP ratio (7:3:3) resulted in a stable zeta potential of +36.5 mV, with a particle size of 696.4 nm and a PDI of 0.453. Further optimization was carried out using a homogenization process up to five cycles. Among these, the first cycle was considered optimal for our formulation, yielding a zeta potential of +25.6 mV, particle size of 729.8 nm, and PDI of 0.430 with a drug content of 95.65%. The structural morphology of the TCG NP by AFM provided high-resolution topographical images indicating an irregular shape, surface roughness of approximately 51.58 nm and an average size of 212.36 nm. In contrast, SEM revealed an irregular to hemispherical shape. Structural characterization by XRD analysis confirmed an amorphous nature for TCG NP, suggesting enhanced solubility. The DPM tablet was prepared and evaluated for weight variation, thickness and diameter, hardness, friability, disintegration and drug content to confirm acceptable physical and performance characteristics. Evaluation of the final capsule dosage form confirmed compliance with pharmacopeial limits for uniformity of weight, disintegration, content uniformity, and *in vitro* drug release. *In vitro* dissolution kinetics demonstrated a first-order release profile with quasi-Fickian diffusion for both the nanoparticle and tablet components, supporting their immediate-release behavior. The formulated capsule dosage form remained stable as per ICH guidelines.

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