Guar gum based oral films for hypertensive urgencies

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ABSTRACT
Guar gum (GG) is a natural film forming biopolymer used as a drug delivery media for Telmisartan (TS). TS is a poorly water-soluble anti-hypertensive agent with low bioavailability. The present work has been hypothesized by converting TS into nanocrystals by high shear homogenisation to enhance the solubility thereby the bioavailability is expected to get enhanced. TS-NC-GG-OF was formulated by solvent casting method using GG by varying the disintegrant ratio. Telmisartan nanocrystals showed particle size of 441.70±35.28 nm, surface charge of −20.86±0.55 mV and reduced crystalline pattern. The amount of TS present per mg of nanocrystals is 0.33 mg. The developed TS-NC-GG-OF was circular, creamy white colour with desired physicochemical properties. The in vitro release studies performed by beaker model showed an immediate release pattern. This proof of concept specifies that the TS-NC-GG-OF may be a better choice for hypertensive emergencies using the natural excipient Guar gum.

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1. Introduction
Guar gum (GG) is an agro-based, non–ionic, hydrophilic and neutral polysaccharide derived from Cyamopsis Tetragonolobus (Leguminosae) (Thombare et al. 2016). Due to

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the presence of the hydroxyl groups (mannose and galactose), GG gets dispersed in water and improves the viscosity/gelling/thickening properties with the aid of intermolecular hydrogen bonding (Thombare et al. 2016). GG was also reported for its blood pressure reduction effect and slowing the gastric emptying time especially in type-2 diabetes mellitus patients (Liu et al. 2020). Hypertension is a chronic medical condition of elevated blood pressure (≥140/90 mm Hg). Telmisartan (TS) is an orally active BCS class II drug and an efficacious anti-hypertensive agent (Angiotensin II receptor antagonist) (Gosse 2006). The major hinderance for anti-hypertensive drugs are the low bioavailability and requirement of rapid onset of action especially in cases of emergencies. Nanocrystals (NCs) are crystalline particles with dimension ranging from 10-1000 nm. Challenges of BCS class II drugs may be overcome by conversion into nanocrystals by high shear homogenisation, which may ultimately improve the bioavailability, improve the dosage proportionality and dissolution potential of the drug (Junyaprasert and Morakul 2015). Drugs may be converted into nanocrystals before they are incorporated into oral films so as to improve drug solubility and promote immediate drug release (Karagianni and Peltonen 2020; Germini and Peltonen 2021). Thus, the nanocrystal-based drug delivery system is a potent novel approach for improving the effectiveness of hypertension treatment (Katteboinaa et al. 2009). Recently the severity of Diabetes (Cicciù et al. 2019) has been focussed through oral film technology. The use of natural biomaterials in drug delivery can contribute to safe, non-toxic as well as effective therapy (Cicciù et al. 2019). Hence, the present study aimed to develop a fast-dissolving telmisartan loaded guar gum sublingual film for the treatment of hypertension.

2. Results and discussion

2.1. Development of Telmisartan Nanocrystals (TS-NCs)

TS-NCs were developed by dispersing TS in Tween 80 and PVP K30 solution followed by high shear homogenisation at 15,000 rpm which led the formation of reduced particles size with increased encapsulation efficiency and redispersibility. These TS-NCs, were observed to be white and crystalline nature after drying at room temperature. Tween 80, a non-ionic surfactant is used as an absorption enhancer, stabilizer and to prevent particles clustering during the development of the nanocrystals. The characterization results showed that the particle size, depends upon the homogenization rate, polymer concentration and aqueous phase volume. The average particle size and zeta potential was 441.70 ± 35.28 nm and -20.86 ± 0.55 mV. Due to the negative zeta potential, aggregation and flocculation can be avoided, assuring both steric and electrostatic stabilization (Shen et al. 2013). The low value of polydispersity index (<0.4) indicates narrow size distribution. It was found that 1 mg of TS-NCs contained 0.33 mg of TS. In XRD analysis TS-NCs exhibited several sharp peaks but the XRD pattern showed reduction in peak intensities compared to TS. The difference in the peak intensities and the reduction in crystallinity may be due to homogenization process as the cavitation forces, collision and shear forces determine the breakdown of drug particles to nanometre scale improving solubility (Sharma and Sriganesan 2018).
2.2. Development and characterization of TS-NC-GG-OF

The oral film was developed by solvent casting method with the components as mentioned in Table S1 (as supplementary). Here in aqueous GG was treated with TS-NCs (60.66 mg TS-NCs equivalent to 20 mg of pure TS) and mixed well under magnetic stirring for 2 h at 200 rpm. To this solution, other excipients were added and stirred to promote encapsulation of the TS in guar gum. Finally, the obtained dispersion was casted in a petri dish and dried at room temperature for 24 h, stored at 4°C. TS-NC-GG-OF was creamy white in colour with a shiny appearance. The formed films were flexible, smooth, homogenous and easily peelable indicating that guar gum used as the polymer had good film forming properties. The film formation of GG was due to intermolecular hydrogen bonding (Patel et al. 2014).

The characteristics of the films are shown as supplementary in Table S2 (as supplementary). A uniform thickness and average weight of the TS-NC-GG-OF was found, which ranged from 0.9 ± 0.10 mm to 1.2 ± 0.05 mm and 39.39 ± 1.3 mg to 50.68 ± 1.3 mg. Uniformity of thickness is directly proportional to the dose accuracy of the film and the weight varied with small standard deviation hence showing uniform distribution of the components in the film. The films were found to endure without breakage for >200 times thus, showing better flexibility. The pH of the film ranges from 6.65 to 6.88 which is nearer to neutral and hence it is less irritant to the sublingual mucosa. The amount of TS present in 100 mg of the TS-NC-GG-OF ranges from 38.25% to 93.35%.

The invitro release profile was observed by beaker dissolution method with phosphate buffer of pH 6.6 as the dissolution medium. The invitro release studies showed that the drug release was higher in the formulation that had higher amount of disintegrants (Figure S1 as supplementary). This may be due to the presence of SSG disintegrants which supports break down of film into smaller parts thereby increasing the surface area promoting rapid release of the drug. The TS-NC-GG-OF-3 showed increased release of 93.63% within 4 h compared to the other formulations. Further immediate disintegrating pattern was confirmed within 1 h of the investigation. Thus, the results showed that TS-NC-GG-OF gets rapidly released which may be effectively used for hypertensive urgencies with improved patient compliance. Further investigations like permeation studies, invivo studies and stability studies are required to gain more data on drug delivery by GG films.

3. Conclusion

From this investigation, TS can be successfully converted into stable nanocrystals with acceptable range of particle size, charge and drug loading efficiency. The TS-NC-GG-OF was formulated by solvent casting with guar gum and different disintegrant ratio. All formulations showed good physicochemical property while TS-NC-GG-OF-3 exhibited superior dissolution and TS release rate compared to other formulations with immediate release profiles. The limitations of the developed film include the small drug load which may be overcome by its expected superior bioavailability. Due to the growing interest in the commercial formulation of safe and effective drug delivery systems, oral film technology may show promising application in future. Thus, TS-NC-GG-OF’s may be a potential tool for the improved treatment of hypertension with quick onset of action.
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Disclosure statement

No conflict of interest was reported by the authors.

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