Formulation of Double-Layered Orally Disintegrating Microparticles Containing Desmopressin

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ABSTRACT SUMMARY

The aim of this study was to formulate desmopressin (DSM) double layered orally disintegrating granules (ODM). To keep the mechanical and chemical integrity of ODMs, a two-step coating process incorporating aqueous drug layer coating after organic coating was used. The prepared ODMs had round shape with total amount of impurities less than 1.5% which ensured the ODMs were produced with mechanically and chemically stable process. ODMs were evaluated for its in vitro disintegration time and in vitro dissolution profile.

INTRODUCTION

Nocturia is defined as feeling of urgent need to urinate during night, which may affect sound sleep. Nocturnal enuresis defined as uncontrollable leakage for patients more than 5 years old, the age after which development of bladder control occurs².

The first-line treatment for nocturia and nocturnal enuresis is the administration of synthetic peptide, desmopressin. Desmopressin helps relieve bladder symptoms for patients with bladder emptying or storage problems, or diabetes insipidus by reducing urine production³.

Currently, desmopressin is available as many types of dosage forms such as injections, nasal sprays and tablets. However, the target patient population of DSM is mostly pediatric and geriatric patients, which may have problems with administering conventional dosage form such as tablets. Furthermore, people with these kinds of symptoms usually fear water intake. Therefore, orally disintegrating tablets (ODT) has recently been marketed in some countries.

Good mouthfeel of a dosage form is reported to be affected by its particle size and morphology, as well as water solubility⁴. Therefore, for good mouthfeel, the target particle size was set below 300 μm, and watersoluble sucrose beads were used as core particles despite their weak mechanical strength. Also, desmopressin contains disulfide bonds, which are reported to cause chemical instability. Therefore, the prepared ODMs were monitored carefully for their chemical impurities as well as well as size distribution.

In our study, we have formulated ODMs containing DSM by coating DSM onto sucrose beads with a fluid-bed coating process.

EXPERIMENTAL METHODS

The coating process was carried out using a lab-scale fluid bed coater (Micro Fluid Bed®, Dalton Co.,Ltd.). Hydroxypropyl cellulose was dissolved in the coating solution to give solution concentration 2.5 wt%. Talc was added as an anti-tacking agent (1 wt%). For the drug layering, DSM was added to the coating solution and sprayed to the microparticles to result in 0.2% weight gain for sucrose beads. Either ethanol solution (70 wt. %) or distilled water was used as solvent.

The dissolution rate of drugs from ODMs and commercial product (Minirin®, Ferring) was evaluated according to United States Pharmacopoeia (USP). Samples were withdrawn at predetermined time intervals of 5, 10, 15, 30 and 45 minutes and analyzed by a validated HPLC method.

The in vitro disintegration study was performed by placing a unit dosage corresponding to 0.2 mg DSM in a petri dish filled with 10 mL of water. To aid drug disintegration, the petri dish was fixed on the bottom of a shaking water bath and was shaken at 100 rpm, 37 °C. The excipients remaining after disintegration was compared with marketed ODT (Aricept®, Eisai Inc.). It was selected because of its dosage form and widespread use.

The particle size distribution of DSM ODMs was analyzed using laser diffraction technique (Mastersizer 2000, Malvern Instruments, Ltd.) In addition, the morphologies of ODMs were evaluated using scanning electron microscopy (SEM) (JSM-6700F, JEOL Ltd.)

RESULTS AND DISCUSSION

Few studies have covered a coating process on small sized microparticles (ca. 100 μm) has been reported. This is because coating becomes more sensitive to process parameters and formulations as size become smaller. However, to have it is vital to have diameter of final product smaller than 300 μm for good mouthfeel. Therefore, we have prepared DSM ODMs by coating drug layer on sucrose beads with diameter of 100 μm.

For sucrose beads coated with aqueous coating solution, they showed severe deformations in its shape (Fig 1(b)) and higher fraction of fine particles, supported by a low Dv0.1 value (Fig 2), which is defined as the maximum particle diameter below which 10% of the sample volume exists and is mainly used to monitor presence of fine particles. In contrast, the organic coating process preserved the original round shape of sucrose beads (Fig 1(c)) and had smaller fraction of fine particles (Fig 2). However, the organic coated microspheres had...
significantly higher amount of impurities \((5.559 \pm 0.325\%)\) than raw DSM \((1.362 \pm 0.077\%)\). The USP limits for DSM tablets are 1.5% for total impurity amount, which implied organic drug coating is inappropriate for drug coating. It is supposed that higher rate of evaporation during organic coating have exposed drug to more oxidative environment, resulting in higher rate of peptide bond breakage.

To address these morphological and chemical instability problems, an organic-aqueous two-step coating process was selected. In short, the sucrose beads were first coated with an organic subcoating to have mechanical stability, and aqueous drug solution was coated on the beads as a second layer for chemical stability. The resultant double-layered DSM ODMs had total amount of chemical impurities of \(1.390 \pm 0.212\%\), which complied with the USP limits. They also maintained the round shape and had smoother surface than original sucrose beads. The median size was smaller than 200 \(\mu m\). The dissolution rate was faster than conventional product, which showed ca.100% release in 5 min (Fig 3). *\textit{In vitro} disintegration test showed fast disintegration time \((15.33 \pm 2.89 \text{ s})\) and had finer size of remaining water insoluble excipients suggesting a good mouthfeel (Fig 4).

**CONCLUSION**

In the present study, a double-layered desmopressin orally disintegrating microparticles was successfully developed by using organic-aqueous two-step coating process. The results obtained from the study revealed that prepared DSM ODMs have round shape with small size and had fast disintegration time along with high release rate with fewer water-insoluble excipients. The prepared product may improve patient compliance by having fast disintegration time and good mouthfeel, being a good candidate for alternative dosage form than conventional tablet.

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