Formulation and Evaluation of Torsemide Pellets for Extended Drug Release by Extrusion-spheronization Method

Narender Karra¹, P. Narayana Raju¹, R. Sivakumar²

¹Department of Pharmaceutics, Malla Reddy Institute of Pharmaceutical Sciences, Maisammaguda, Secunderabad, Telangana, India, ²Department of Pharmaceutical Chemistry, Geetanjali College of Pharmacy, Cheeryal, Medchal, Telangana, India

Abstract

Aim and Objective: The main objective of this study was to formulate extended release pellets of torsemide, a pyridine–sulfonyl urea type loop diuretic. Materials and Methods: The preparations of torsemide pellets were prepared by extrusion-spheronization method. The prepared pellets were then coated with ethyl cellulose of different grades and Eudragit L30 D 55 and Eudragit NM 30 D grades at different concentrations as release retardant polymers using fluid bed processor, in this formulation hydroxypropyl methylcellulose used as a pore former and binder, microcrystalline cellulose PH101 as diluents and water used as a solvent. Results: The prepared pellets were evaluated for drug content, in vitro dissolution, differential scanning calorimetry (DSC), Fourier transforms infrared (FTIR), and scanning electron microscopy (SEM). The drug release was extended up to 24 h and drug release was depended on polymer grade and polymer proportion. The optimized formulation showed 99 ± 0.11 release in 24 h. The DSC and FTIR studies were showed the compatibility of the drug with a polymer, i.e., no drug-polymer interaction. Using SEM, it was shown that the torsemide pellets were porous and spherical in shape. Accelerated stability studies showed good similarity with the initial formulation indicated good stability for 6 months. In vivo, pharmacokinetic studies were conducted in rabbits by parallel design and pharmacokinetic parameters were calculated. Conclusion: By the above results, it can be concluded that the above-prepared pellets of torsemide could be able to extend the drug release by avoiding problems such as dose dumping, more gastric residence time, and improve the patient compliance. In vivo studies in rabbits were shown the increased half-life and bioavailability for a long duration.

Key words: Extended release dosage forms, extrusion-spheronization, pellets, torsemide

INTRODUCTION

In recent years, there has been a growing interest in the field of pelletization to produce spherical pellets, which can be changed into several dosage forms such as tablet and capsule or can be administered as such. Pelletization involves size enlargement process and if the final agglomerates are spherical in shape in size range of 0.5–2.0 mm, they are called pellets.¹ ³ Using a multiple-unit dosage form, pellets offer several advantages: Pellets disperse freely in the gastrointestinal tract and thus maximize drug absorption, reduce peak plasma fluctuations, and minimize side effects; high local concentrations of drug are avoided; there is flexibility in the development of oral dosage forms as pellets, so different drug substances (e.g., incompatible drugs) can be formulated and blended into a single dosage form; and immediate- and controlled-release pellets can be mixed to achieve the desired release pattern.¹ ³ This present study was aimed to prepare extended release pellets of torsemide by extrusion-spheronization method. Then, the spheroids were coated by fluid bed processor. Extrusion spheronization involves shaping the wet mass into cylinders called extrusion and breaking up the extrudate and rounding of the particles into spheres called spheronization.¹ ³

Address for correspondence:
Narender Karra,
Malla Reddy Institute of Pharmaceutical Sciences,
Maisammaguda, Secunderabad, Telangana, India.
Phone: +91-9959468402.
E-mail: narenderreddy.karra@gmail.com

Received: 05-06-2018
Revised: 15-06-2018
Accepted: 21-06-2018
Dry mixing→wet massing→extrusion→spheronization→
drying→screening

Production of uniform size pellets with high drug loading capacity
is the major goal of the extrusion/spheronization technique.\[9-11\]

Torsemide is a new generation loops diuretic belonging to
pyridine-sulfonylurea class and has been used for the treatment
of both acute and chronic congestive heart failure, liver
cirrhosis, and arterial hypertension. It exerts longer duration
of action with a bioavailability of 80% and elimination half-
life of 3–4 h compared with other loop diuretics.\[12-14\]

The main objective of this study was to formulate extended
release pellets of torsemide by extrusion-spheronization
method to extend the drug release to increase the patient
compliance by preventing dosing frequency.

This pellet formulations as these are multi-particulate systems
there was less chances of dose dumping, gastric irritation due to
reduced gastric emptying time and more stable to gastric fluids.

MATERIALS AND METHODS

Torsemide was obtained as a gift sample from Dr. Reddy’s
Laboratories, Hyderabad, hydroxypropyl methylcellulose
(HPMC) was obtained from Colorcon Asia, ethyl cellulose
and Eudragit of different grades were obtained from Tini
Pharma Pvt., Ltd. All other chemicals and reagents used in
the study were of analytical grade.

Construction of calibration curve of torsemide

**Determination of \( \lambda_{\text{max}} \)**

**Preparation of 0.1N hydrochloric acid**

A known volume of 8.5 ml hydrochloric acid is dissolved
in distilled water, and the volume is made up to 1 L (USP
21\textsuperscript{st} Revision, NF 16\textsuperscript{th} Edition page no:1430).

Accurately weighed 100 mg of a drug of torsemide was
dissolved and diluted to 100 ml using 0.1N HCl to get
1 mg/ml solution. From the stock solution, further dilutions
were made to get 10 μg/ml concentrations. The resultant
solution is scanned in the range of 200–400 nm by ultra-
visible spectrophotometer to get absorption maximum
(\( \lambda_{\text{max}} \)).

**Preparation of calibration curve**

From the above-prepared stock solution, different
concentration (1–10 μg/ml) solutions are prepared using
0.1N HCl solution. The absorbance of these solutions is
measured at \( \lambda_{\text{max}} \) (263 nm) by UV-spectrophotometer.
A standard curve is plotted using concentration on X-axis
and the absorbance obtained on Y-axis. The calibration curve
obtained is shown in Figure 1.

The formulation for torsemide pellets by extrusion-
spheronization and different process parameters for the
development of were shown in Table 1, and the procedure for
preparation is as follows.

**Pellets preparation by coating on spheroids**

In this method, initially, granules of torsemide were prepared by
wet granulation method using water as granulation fluid. The drug
torsemide, microcrystalline cellulose (MCC), and hydroxypropyl
cellulose (HPC) were mixed thoroughly, and water was added to
study the binding property and finally selected one best formula
of good binding property for further study. The prepared wet
granules were then passed through the extruder; finally, spheroids
were prepared. The prepared spheroids were dried and made
ready for the further coating process.

**Coating solution preparation**

The polymer ethyl cellulose of 4 cps, 7 cps, and 10 cps was
taken separately. The polymers were mixed with HPMC
separately. Take IPA and methylene dichloride in a separate
vessel and to this add triethyl acetate citrate and stir for
15 min to get uniform dispersion. To the above solution
slowly, the polymer mixture was added and stirred for 45 min
for complete formation of solution.

**Eudragit based coating solution**

Eudragit based coatings are direct polymer aqueous based.
Coating dispersions can be used directly as coating solutions.
The coating process was similar as mentioned in the Eudragit
coating (EC) based coating system.

Different percentage of coating was applied such as 5%,
10%, and 15% for EC based coating and 10%, 20%, and 30% for
Eudragit based coating solutions. The composition was
showed in Table 2.
Karra, et al.: Extended release pellets of torsemide

Asian Journal of Pharmaceutics • Apr-Jun 2018 • 12 (2) • 148

Evaluation of prepared pellets

The prepared pellets were subjected to various evaluation tests. They are evaluated for parameters drug content, in vitro drug release, differential scanning calorimetry (DSC), Fourier transforms infrared (FTIR), and scanning electron microscopy (SEM) and also accelerated studies were performed for 6 months.

**Drug content**

Drug content was estimated by UV visible spectrometer at 263 nm.

**Drug excipient compatibility studies**

To know the compatibility between drug and polymer used, compatibility studies were performed using DSC and FTIR.

**DSC**

Thermal properties of pure drug were evaluated by DSC using Mettler Star SW 8.10. Accurately weighed 5–6 mg samples were hermetically sealed in aluminum pans and heated at a rate 50°C/min from 50°C to 250°C temperature range under nitrogen flow of 25 ml/min.[15]

**FTIR studies**

The pure torsemide drug and formulations with ethyl cellulose, Eudragit was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press (press pellet technique). The pellets were analyzed in the frequency range between wave numbers 4000 and 400/cm at 4/cm resolution.[16]

**RESULTS AND DISCUSSION**

In this present study, torsemide pellets were prepared by extrusion-spherization method. The prepared pellets were assayed for drug content, and drug content was found in the range of 90–95%. The prepared pellets were porous in nature.

<table>
<thead>
<tr>
<th>Table 1: Formulation of torsemide pellets and various parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td><strong>T1</strong></td>
</tr>
<tr>
<td>Torsemide</td>
</tr>
<tr>
<td>MCC PH 101</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
</tr>
<tr>
<td>Water</td>
</tr>
<tr>
<td>Binding property</td>
</tr>
<tr>
<td><strong>Granulation parameters</strong></td>
</tr>
<tr>
<td>Addition of water</td>
</tr>
<tr>
<td>Impeller speed</td>
</tr>
<tr>
<td>Chopper speed</td>
</tr>
<tr>
<td>Kneading time</td>
</tr>
<tr>
<td>Impeller speed</td>
</tr>
<tr>
<td>Chopper speed</td>
</tr>
<tr>
<td>Property of extrudes</td>
</tr>
<tr>
<td>Th. weight of pellets mg</td>
</tr>
<tr>
<td>Screen size</td>
</tr>
<tr>
<td>Screw extrusion speed</td>
</tr>
<tr>
<td>Spheronization speed</td>
</tr>
<tr>
<td>Spheronization time</td>
</tr>
<tr>
<td>Drying time</td>
</tr>
</tbody>
</table>

MCC: Microcrystalline cellulose

[15] Accurately weighed 5–6 mg samples were hermetically sealed in aluminum pans and heated at a rate 50°C/min from 50°C to 250°C temperature range under nitrogen flow of 25 ml/min.

[16] The pellets were analyzed in the frequency range between wave numbers 4000 and 400/cm at 4/cm resolution.
and spherical in shape was known by scanning electron microscopy. It was shown in Photograph 1.

DSC and FTIR study was conducted on the pure drug and prepared pellets. DSC thermogram of pure torsemide showed an endothermic peak at 164.8°C, the mixtures of drug and polymers also showed similar endothermic peaks indicates no drug-polymer interaction. DSC thermogram and FTIR spectra of torsemide pure drug and mixtures were shown in Figures 4 and 5.

FTIR spectra of pure torsemide shown peaks at N-H stretch at 3385.12/cm, C=O stretch (amide) 1685.12/cm, and S=O stretch (sulfonyl) at 1350.53\textsuperscript{−1}. Similar peaks were observed with mixtures, indicates no drug-polymer interaction.

In vitro dissolution studies were performed by USP dissolution apparatus-II. A total of 15 formulations were prepared based on the difference in the concentration of coating solution and type of coating. Here, two polymers EC and Eudragits were used for coating. This C1, C2, and C3 formulations were prepared using ethyl cellulose of different grades and EC 10CP5 with high viscosity extended the release or retarded the release rate more, compared to less viscous polymers. The release was extended up to 24 h.

Formulations E1 (Eudragit L30 D55) and E2 (Eudragit NM 30D) with different concentrations of Eudragit were prepared. In the E2-30% which is more viscous extended the drug release up to 24 h.

Among these entire formulations, C3-15% was shown 95% drug release in 24% h and Eudragit NM30D was shown 99% drug release in 24 h indicates this polymer at this concentration was more suitable to extend the drug release.

The release kinetics showed that the release was followed first-order kinetics. The kinetics was best fitted to the Higuchi model and clearly indicates that the release mechanism was diffusion controlled. Peppas n values found between 0.2 and 0.5 clearly indicates that the release was Fickian diffusion. The dissolution studies for optimized formulation had shown in Table 3.
The optimized formulation had shown similar properties after 6 months of stability studies, i.e., in vitro drug release shown in Figure 2, drug content, and physical appearance.

**In vivo pharmacokinetic study**

In vivo studies were conducted in healthy Rabbits (New Zealand, White) by parallel design. The plasma kinetic data were assessed with KINETIKA 5.0 software. Figure 3 shows the mean comparative data plot of the mean plasma concentration of the TORSEMIDE in both test (ER formulation) and reference (conventional formulation). The mean peak plasma concentration of test (T) formulation $C_{\text{max}}$ 1810 ng/ml was gradually reached in 2.45 h. Whereas in case of conventional reference formulation (R) the maximum plasma concentration was 28760 ng/ml, which was reached in 1.18 h. The concentration maximum of the test formulation (T) was lower when compared with reference (R) formulation.

The result of the present study revealed that the maximum plasma drug concentration reached in less time with reference sample and more time with test sample indicates the drug was slow and extended in comparison with a reference sample.

**CONCLUSION**

An extrusion-spheronization method was successfully applied to formulate torsemide extended release pellets. Using scanning electron microscopy, it was shown that the torsemide pellets were in a spherical shape and porous in nature. The in vitro release profiles indicated that the release of torsemide from the pellets exhibited a first-order release and followed diffusion mechanism. DSC and FTIR studies also showed the compatibility between drug and polymers. The stability studies also showed that the formulations had same physical properties and drug content and drug release after 6 months of study. The in vivo plasma profile of extended-release formulations in rabbits was shown the availability of the drug for a long time indicated by $C_{\text{max}}$, $T_{\text{max}}$, and AUC. The present work demonstrates the feasibility of extended delivery torsemide utilizing rate controlling polymers.

**REFERENCES**


Source of Support: Nil. Conflict of Interest: None declared.