RESEARCH ARTICLE

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

Narender Karra[1], P. Narayana Raju[1], R. Sivakumar[2]

[1]Department of Pharmaceutics, Malla Reddy Institute of Pharmaceutical Sciences, Maisammaguda, Secunderabad, Telangana, India, [2]Department 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 caloriemetry (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 dosages 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.[1,2] 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.[3-5] 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.[6-8]

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 λ 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 21st Revision, NF 16th 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 (λmax).

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 λmax (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.

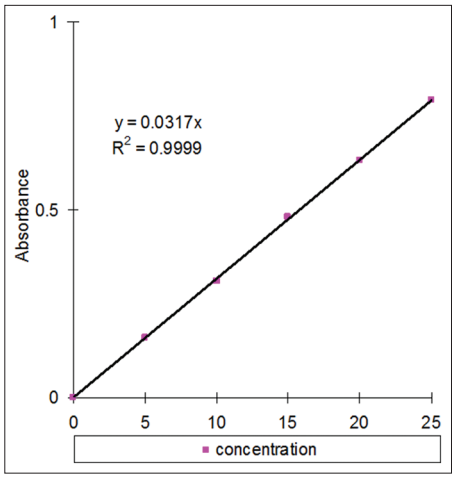


Figure 1: Calibration curve of torsemide at λ_{max} 263 nm

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 get the granules different ratios of HPC and MCC were used 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.

Table 1: Formulation of torsemide pellets and various parameters

Ingredients	Mg/unit					
	T1	T2	T3	T4	T5	T6
Torsemide	20	20	20	20	20	20
MCC PH 101	50	50	60	70	80	90
Hydroxypropyl cellulose	0	5	10	15	15	15
Water	Qs	Qs	Qs	Qs	Qs	Qs
Binding property	Poor	Fair	Good	Good	Excellent	Excellent
Granulation parameters						
Addition of water	6 min	6 min	6 min	6 min	6 min	6 min
Impeller speed	Slow	Slow	Slow	Slow	Slow	Slow
Chopper speed	Off	Off	Off	Off	Off	Off
Kneading time	2 min	2 min	2 min	2 min	2 min	2 min
Impeller speed	Slow	Slow	Slow	Slow	Slow	Slow
Chopper speed	Slow	Slow	Slow	Slow	Slow	Slow
Property of extrudes	Fine Particle	Fine Particles	Good/Brittle	Good/Brittle	Good	Excellent
Th. weight of pellets mg	70	75	90	105	115	125
Screen size	0.8 mm					
Screw extrusion speed	30 rpm					
Spheronization speed	1500 rpm					
Spheronization time	6 min					
Drying time	24 h					

MCC: Microcrystalline cellulose

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 caloriemetry (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

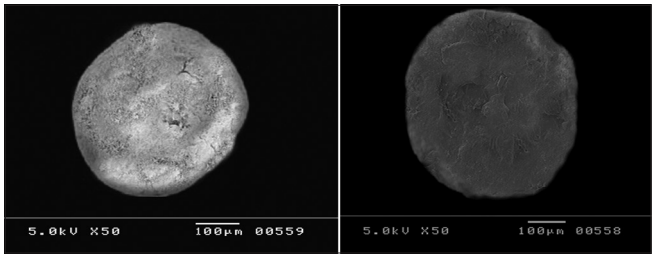
The pure torsemide drug and formulations with ethyl cellulose, Eudragit was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press (press pellet technique). The pellets were analyzed in the frequency range between wave numbers 4000 and 400/cm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

In vitro drug release studies

Dissolution studies for each prepared formulation were performed in a calibrated dissolution test apparatus (LABINDIA), equipped with paddles (USP apparatus II method). 900 ml of 0.1N HCL solution was used as a dissolution medium. The paddles were operated at 50 rpm, and the temperature was maintained at 37°C ± 0.5°C throughout the experiment. Dissolution samples were withdrawn from the apparatus at regular intervals, i.e., 1, 2, 3… up to 24 h and replaced with equal volume of dissolution medium to maintain the volume throughout the experiment. Samples were withdrawn at various time intervals and were suitably diluted with same dissolution medium, and the amount of drug released was estimated by chromatographically at 263 nm.

RESULTS AND DISCUSSION

In this present study, torsemide pellets were prepared by extrusion-spheronization 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



Photograph 1: Scanning electron microscopy of (1) drug + EC pellets (2) drug + eudragit pellets polymer

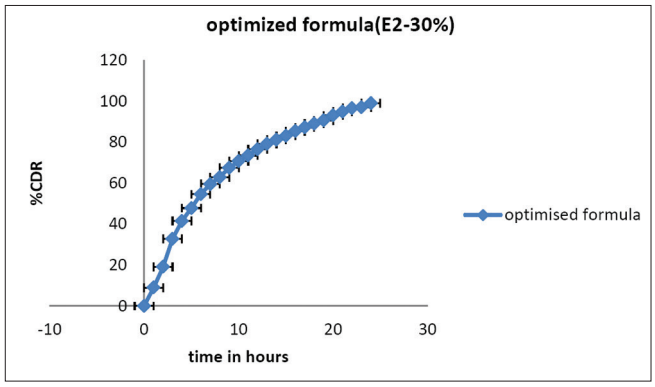


Figure 2: Cumulative percentage CDR for optimized formulation

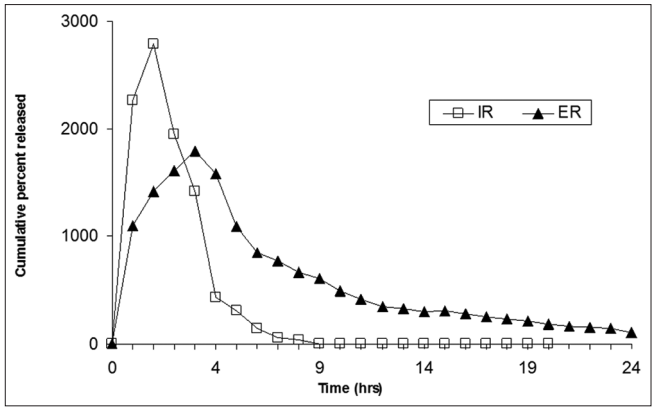


Figure 3: Comparative plasma profiles of TORSEMIDE 20 mg conventional formulation (R) with TORSEMIDE 20 mg extended release pellets formulation (T)

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^{-1}. Similar peaks were observed with mixtures, indicates no drug-polymer interaction.

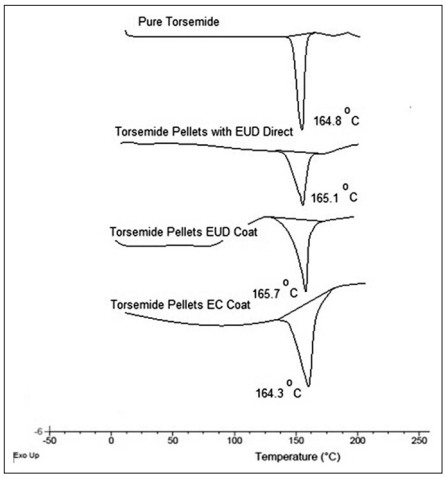


Figure 4: Differential scanning caloriemetry thermogram of pure torsemide and torsemide with different polymers

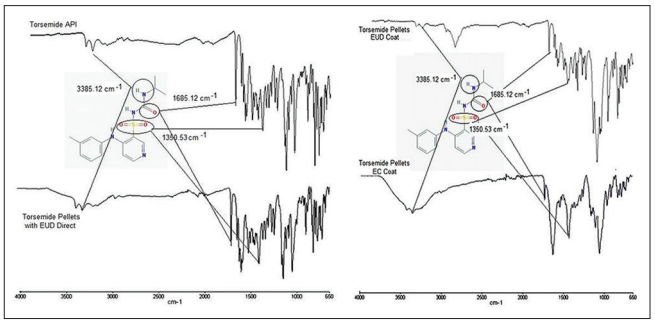


Figure 5: Fourier transforms infrared spectra of pure drug and drug mixture

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 10CPS 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.

Table 2: Formulation of coating solution

Ingredients	C1	C2	C3
Ethyl cellulose 4 cps	30	**	**
Ethyl cellulose 7 cps	**	30	**
Ethyl cellulose 10 cps	**	**	30
HPMC	5	5	5
Triethyl citrate	10	10	10
IPA	200	200	200
MDC	100	100	100
Eudragit coating solution	E1	E2	
Eudragit L30 D 55	12.5	**	
Eudragit NM 30 D	**	12.5	
Water	Qs	Qs	

HPMC: Hydroxypropyl methylcellulose

Table 3: *In vitro* drug release from optimized formula (E2-30%)

Time in hours	%release	Time in hours	%release
0	0	13	79.2±0.52
1	9±0.97	14	81.2±0.78
2	19.1±0.85	15	83.1±0.65
3	32.8±0.95	16	85.4±0.48
4	41.5±1.12	17	87.2±0.77
5	47.8±0.98	18	89.1±0.63
6	54.6±0.87	19	90.6±0.24
7	59.5±0.85	20	93.1±0.59
8	62.9±0.35	21	94.9±0.86
9	67.4±0.54	22	96.6±0.98
10	70.7±0.55	23	97±0.82
11	73.5±0.64	24	99±0.11
12	76.5±0.36		

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 show 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_{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_{max}, Tmax, and AUC. The present work demonstrates the feasibility of extended delivery torsemide utilizing rate controlling polymers.

REFERENCES

1. Jadhav NR. Pelletization by extrusion spheronization technique: An excipient review. Drug Deliv Lett 2012;2:1-14.
2. Ahir AA. Pelletization technology: Methods and applications-a review. Res J Pharm Tech 2015;8:131-8.
3. Singh R, Poddar SS, Chivate A. Sintering of wax for controlling release from pellets. AAPS Pharm Sci Tech 2007;8:E1-9.
4. Sellassie IG, Gordon RH, Fawzi MB. Evaluation of a high-speed pelletization process and equipment. Drug Dev Ind Pharm 1985;11:1523-41.
5. Ghebre-Shellasie I. Pellets: A General Overview. Pharmaceutical Pelletization Technology. New York: Marcel Dekker Inc; 1989; 6-7. Vervaet C, Baert L, Remon J. Extrusion spheronisation: A literature review. Int J Pharm 1995;116:131-46.
6. Ramireddy GV. Formulation and evaluation of sustained release pellets of Bosentan by fluidized bed coating process. Eur J Biomed Pharm Sci 2017;4:312-8.
7. Mezreb N, Charrueau C, Boy P, Allain P, Chaumeil JC. Production of carbopol 974P and carbopol 971P pellets by extrusion spheronization. Optimization of the processing parameters and water content. Drug Dev Ind Pharm 2004;30:481-90.
8. Santosh H, Veiga F, Pina M, Sousa JJ. A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets. Eur J Pharm Sci 2004;21:119-29.
9. Bhaskaran S, Lakshmi PK. Extrusion spheronization-a review. Int J Pharm Tech Res 2010;2:2429-33.
10. Wang Z, Sun J, Wang Y, Liu X, Liu Y, Fu Q, *et al.* Solid

self-emulsifying nitrendipine pellets: Preparation and *in vitro*/*in vivo* evaluation. Int J Pharm 2010;383:1-6.
11. Trivedi NR, Rajan MG, Johnson JR, Shukla AJ. Pharmaceutical approaches to preparing pelletized dosage forms using the extrusion spheronization process. Crit Rev Ther Drug Carr Syst 2007;24:1-40.
12. Preobrazhenskii DV, Nekrasova NI, Khoseva EN, Arystanova A, Talyzina IV, Pataraia SA. Torasemide is the effective loop diuretic for long-term therapy of arterial hypertension. Kardiologiia 2011;51:67-73.
13. Jain S, Yadav SK, Patil UK. Preparation and evaluation of sustained release matrix tablet of furosemide using natural polymers. Res J Pharm Tech 2008;1:374-6.
14. Macharla A, Velmurugan S, Rao PV. Design and evaluation of torsemide controlled release matrix tablets. Asian J Pharm Clin Res 2015;8:159-63.
15. Skoog DA, Holler FJ, Nieman T. Principles of Instrumental Analysis. 5th ed. New York: Saunders College Publishing; 1998. p. 805-8.
16. Lin SY, Wang SL. Advances in simultaneous DSC-FTIR microspectroscopy for rapid solid-state chemical stability studies: Some dipeptide drugs as examples. Adv Drug Deliv Rev 2012;64:461-78.

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