Drug Development and Industrial Pharmacy, 35:252–258, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802277680

informa
healthcare

Multiparticulate Drug Delivery System of Aceclofenac: Development and In Vitro Studies

Gopal Venktesh Shavi, Usha Nayak, Ranjith Kumar Averineni, Karthik Arumugam, Srinivasa Reddy Meka, Udupa Nayanabhirama, and Pandey Sureshwar

Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, India

The aim of this study was to develop an enteric-coated multi-unit dosage form containing aceclofenac, a nonsteroidal anti-inflammatory drug. The pellets were prepared by using extrusion/spheronization method, and the core pellets were coated with a pH-sensitive poly(meth) acrylate copolymer (Eudragit L100-55) to achieve site-specific drug release. The formulated pellets were characterized for percentage yield, size distribution, surface morphology studies, drug content, and flow properties. In vitro dissolution test was used for comparison of drug release profiles of various coated pellets. The practical yield was found to be 90–95%. The particle size of enteric-coated pellets was found to be in the range of 0.59–0.71 mm. The pellets were spherical in shape and surfaces of pellets were found to be rough and showing micropores. Enteric-coated pellets showed good flow properties and in vitro dissolution profile. Dissolution tests were carried out in a USP type II dissolution apparatus in media-simulating pH conditions of the gastrointestinal tract. The release of the aceclofenac from formulated pellets was established to be minimum in the pH 1.2 (<5%) for a period of 2 h, and at pH 6.8, it shows the maximum release (85 ± 5% release within 1 h) which indicates gastric resistance of the formulated pellets. The 20% wt/wt enteric-coated pellets were compared to that of marketed product (tablets), it was observed that pellets showed better release profile. The study concluded that the formulated multiparticulate dosage forms can be used as an ideal drug delivery system for the aceclofenac.

Keywords enteric-coated pellets; aceclofenac; eudragit L100-55; NSAID; multiparticles

INTRODUCTION

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective nonsteroidal anti-inflammatory agent having remarkable anti-inflammatory, analgesic, and antipyretic properties and potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. One of the major side effects associated with the use of nonsteroidal anti-inflammatory drug (NSAID) is gastrointestinal (GI) irritation. Though aceclofenac is well tolerated than other NSAID, it also shows some adverse events affecting mainly the GI system (abdominal pain, dyspepsia, ulcerative stomatitis, etc.) (Pareek, Chandanwale, Oak, Jain, & Kapoor, 2006). Irritation can vary from minor gastric discomfort to ulceration and bleeding of the mucosa and is not only caused by the inhibition of the prostaglandin synthesis but is probably also because of direct contact of the drug with the mucosa (Debunne, Vervaet, Mangelings, & Remon, 2004). The development of a suitable drug delivery system may reduce the contact time of the drug with the gastric mucosa, while the application of an enteric coating may offer additional protection (Aabakken, Olaussen, Mowinckel, & Osnes, 1992). Polymeric coatings have been used since many years to control drug release from solid pharmaceutical dosage forms (Bando & McGinity, 2006). Enteric polymeric coatings play an important role in protecting drugs that are susceptible to acidic or enzymatic degradation in the stomach. These coatings also function to protect the gastric mucosa from irritating compounds such as NSAID. In addition, multiple-unit drug delivery systems such as pellets are known to reduce the risk of local irritation of the mucosa, and since they also show less variable gastric emptying times, enteric-coated pellets of aceclofenac were prepared (Huyghebaert, Vermeire, Rottiers, Remaut, & Remon, 2005).

Multiple-unit sustained release dosage forms, such as pellets, are believed to have many therapeutic advantages in comparison with the single-unit dosage forms. They can distribute in the GI tract homogeneously, thus maximizing drug absorption and reducing peak plasma fuctuations, minimizing the risk of local GI tract irritation and dose dumping, decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient (Bashaiwoldu, Abraham, & Podczeck, 2004; Chopra, Podczeck, Newton, & Alderborn,

Address correspondence to Srinivasa Reddy Meka, Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal 576104, India. E-mail: ms.reddy@manipal.edu

2002; Hu, Liu, Tang, & Zhan, 2006). In this study, aceclofenac pellets were prepared by extrusion/spheronization method, and Eudragit L100-55 was used as enteric coating polymer. Extrusion/spheronization is an established technique in pharmaceutical industry, which results in spherical pellets in a typical size range between 0.5 and 2 mm. These pellets possess high density, small particle size distribution, and regular shape (Alvarez, Concheiro, Gómez-Amoza, Souto, & Martínez-Pacheco, 2002; Sriamornsak, Nunthanid, Luangtana-anan, & Puttipipatkhachorn, 2007). The enteric polymer, Eudragit L100-55, is an anionic copolymer based on methacrylic acid and ethyl acrylate, with free carboxyl groups in a ratio of 1:1 with the ester groups. The carboxylic groups begin to ionize in aqueous media at pH 5.5 and above, rendering the polymer resistant to the acidic environment of the stomach but soluble in intestinal fluid (Lin & Larry, 2001; Paulsson & Singh, 1999; Zheng & McGinity; 2003).

This study was conducted to develop a release controlling film coat around aceclofenac core pellets with Eudragit L100-55. Therefore, the aim of this study was to develop an enteric-coated multiparticulate formulation, which ensures primary protection of the aceclofenac against the harmful GI influences and subsequently releases the drug in intestine.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as gift sample from Lupin Research Park (Pune, India). Avicel PH101 was obtained from FMC Biopolymers (Philadelphia, PA, USA). Lactose and polyvinylpyrrolidone (PVP K-30) were procured from BASF Corporation (Ludwigshafen, Germany). Eudragit L100-55 was procured from Rohm Polymers (Philadelphia, PA, USA). Magnesium stearate was purchased from S. D. Fine-Chem Limited (Mumbai, India).

Methods

Preparation of Aceclofenac Pellets by the Method of Extrusion/Spheronization

The enteric-coated pellets of aceclofenac were prepared by using extruder spheronizer. The composition of core pellets is given in Table 1. Lactose, Avicel PH 101, Aceclofenac, and PVP K-30 were thoroughly mixed and the granulating fluid (water) was added in small increments until a homogenous damp mass was achieved. The wet mass was passed through the extruder (Umang Pharmatech Pvt Ltd., UICE-Lab, Mumbai, India) equipped with screw and screen with a 0.5-mm aperture at 60 rpm, and the extruded material was put in a spheronizer having plate diameter 2.0 mm for 5 min at 1,000 rpm until spherical pellets were obtained. The pellets were then dried in a vacuum oven at 40°C for 24 h. After drying of the spheronized product at 40°C, sieving analysis was performed using standard sieves. The maximum pellets were retained on 30 mesh (0.59–0.71 mm) and were used for enteric coating.

Coat Application by Pan Technology

For aqueous polymer coating, 50 g of core pellets (0.4–0.6 mm) were used. The composition of coating solution is given in Table 2. Eudragit L100-55 and PEG 6000 were dispersed/dissolved separately in water. Titanium dioxide, purified talc, and tween-80 were triturated to get paste-like mass, and it is added to Eudragit L100-55 dispersion (30% wt/wt). The PEG 6000 solution was mixed with Eudragit L100-55 dispersion using magnetic stirrer for 30 min. The coating solution was passed through sieve of aperture size 0.149 mm to get a clear dispersion and used for coating. The pellets were coated in a modified traditional coating pan and operated under the following conditions.

- Inlet air temperature: 30–35°C
- Pan speed: 30 rpm
- Atomizing air pressure: 1 bar
- Spray rate: 2–2.5 g/min
- Spray nozzle diameter: 0.8 mm.

The coating solution was applied when the pellet bed in the coating pan reached 30°C. The aqueous dispersion was stirred continuously throughout the coating process to prevent sedimentation of insoluble particles. The pellets were coated until the desired film weight was deposited (A1, 15% wt/wt; A2, 20% wt/wt; and A3, 25% wt/wt). The coating level (based on polymer in coating) was calculated from the weight difference between the coated and the uncoated pellets. The coated pellets were lubricated using Aersoil 200 and talc (0.5% wt/wt; 1:1).

TABLE 1
Composition of Aceclofenac Core Pellets

Ingredients	Concentration (% wt/wt)
Aceclofenac	20.03
Avicel PH 101	38.79
Lactose	38.79
PVP K-30	2.39

TABLE 2
Composition of Coating Solution

Enteric Coating	A1 (15% wt/wt)	A2 (20% wt/wt)	A3 (25% wt/wt)
Eudragit L100-55	7.0	9.3	11.62
Purified talc	2.1	2.8	3.5
Titanium dioxide	0.69	0.92	1.15
PEG 6000	0.69	0.92	1.15
Tween-80	0.26	0.34	0.42

Characterization of Pellets

Size. For size characterization, 25-g samples of pellets were sieved through a nest of sieves. Sieves with aperture sizes of 0.84, 0.71, 0.59, 0.42, and 0.297 mm were used; the samples were shaken for 5 min on a vibrating shaker (CISA, Barcelona, Spain). The amount retained on each sieve was weighed and plotted as percentage weight fraction versus size (Rodriguez et al., 2001).

Content Uniformity. Accurately weighed samples of the enteric-coated pellets (100 mg) from all the formulations were dissolved in methanol, filtered, and analyzed spectrophotometrically (UV-1601PC, Shimadzu, Tokyo, Japan) for aceclofenac content at 275 nm after suitable dilution with phosphate buffer pH 6.8. All experiments were performed in triplicate.

Micromeritic Properties. The packing ability was evaluated from the changes in volume due to rearrangement and packing occurring during tapping. The Carr's Compressibility Index (CC (%)) and Hausner ratio (HR) of the coated pellets were computed on the basis of tapped bulk density and poured bulk densities. Tapped bulk density (ρ_t) was determined by taking 25 g of the pellets in 50-mL measuring cylinder and tapping it to a constant volume in a bulk density apparatus (Cambell Electronics, Mumbai, India). Poured bulk density (ρ_p) was determined by three-tap method using the same apparatus. Carr's Compressibility Index (CC) and Hausner's ratio (HR) are calculated as follows:

$$\mathrm{CC}(\%) = \frac{100(\rho_t - \rho_p)}{\rho_t}$$

$$\mathrm{HR} = \frac{\rho_t}{\rho_b}.$$

Scanning Electron Microscopy

The shape and surface morphology of the enteric-coated pellets were studied by scanning electron microscopy (SEM) (JEOL, JSM 50A, Tokyo, Japan). The samples were mounted on double-sided adhesive tape that has previously been secured on copper stubs and then analyzed. The accelerating voltage was 5 kV.

Infrared Spectroscopy

Infrared (IR) spectroscopy was conducted using a Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu), and the spectrum was recorded in the wavelength region of 4,000–400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, mixture of drug & polymer and formulated pellets) in KBr and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed using DSC-60 (Shimadzu) calorimeter to study the thermal behavior of the drug alone and the enteric-coated pellets. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60), and operating software (TA 60). The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 mL/min) at a scanning rate of 5°C/min from 24 ± 1 to 250°C. Empty aluminum pan was used as a reference. The physical mixture of drug with excipients for compatibility studies was prepared by triturating the drug with excipient in a dried mortar for 5 min.

In Vitro Dissolution Study

In vitro dissolution studies were carried out using the USP type II dissolution apparatus (Electrolab, Mumbai, India). Accurately weighed pellets (n = 3) containing the equivalent of about 100 mg of aceclofenac were introduced in the dissolution medium. The dissolution was carried out in 900 mL 0.1 N HCl for 2 h at 37 ± 2°C at a speed of 75 rpm, and subsequently, the dissolution medium was replaced with the phosphate buffer (pH 6.8). The samples were withdrawn at predetermined intervals and analyzed using UV spectrophotometer (UV-1601PC; Shimadzu) at 275 nm.

Stability Studies

After determining the drug content, the optimized pellets were charged for the accelerated stability studies according to ICH guidelines (40 ± 2°C and 75 ± 5% RH) for a period of 6 months in stability chamber (Thermolab, Mumbai, India). The samples were placed in USP type I flint vials and hermetically sealed with bromobutyl rubber plugs and aluminium caps. Vials containing pellets (n = 3) were taken out at 15, 30, 60, 90, and 180 days and evaluated for the drug content and physical changes.

RESULTS AND DISCUSSION

The aceclofenac pellets were prepared by using extruder spheronizer and coated with an acrylic polymer Eudragit L100-55 using PEG 6000 as plasticizer. The prepared pellets were evaluated for various physical and micromeritic properties along with in vitro dissolution studies.

Practical Yield, Drug Content, and Particle Size

The practical yield of pellets was found to be 90–95%. Drug content of all the formulations was found to be in the range of 92–96%. The weight distribution data of the core pellets indicated that majority (>90%) of the pellets fall in the size range 0.59–0.71 mm. The particle size distribution is shown in Figure 1. Those which were retained on 20 mesh (0.84 mm) were the doublets and triplets, whereas those that passed through 50 mesh (0.297 mm) were the fines.

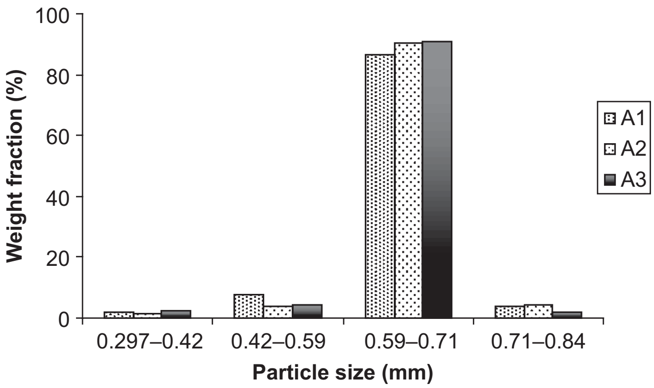

FIGURE 1. Particle size distribution of enteric-coated pellets.

IR, DSC, and SEM Studies

The possible interaction between the drug and the excipients were studied by IR spectroscopy and DSC. IR spectra of pure aceclofenac and the prepared pellets are shown in Figure 2. Pure aceclofenac showed major peaks at 3319.3, 2970.2, 2935.5, 1716.5, 1589.2, 1506.3, 1479.3, 1344.3, 1280.6, 1255.6, and 665.4 cm^{-1} (Muatlik, Usha, Reddy, Ranjith, & Pandey, 2007; Mutalik, Anju, Manoj, & Usha, 2008). The results revealed no considerable changes in the IR peaks of aceclofenac in the prepared formulation when compared to pure drug, thereby indicating the absence of any interaction.

The results of DSC studies are given in Figure 3. Pure aceclofenac showed a sharp endotherm at 155.54°C corresponding to its melting point (Mutalik et al., 2007; Mutalik et al., 2008), where the pellets showed melting endotherm of 152.7°C. There was no appreciable change in the melting endotherms of the aceclofenac as compared to pure drug. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between drug and excipient used in the preparation.

The SEM photomicrographs of pellets are given in Figure 4. The surface morphology study showed good sphericity and smooth surface and also revealed that the pellets were discrete and devoid of cracks.

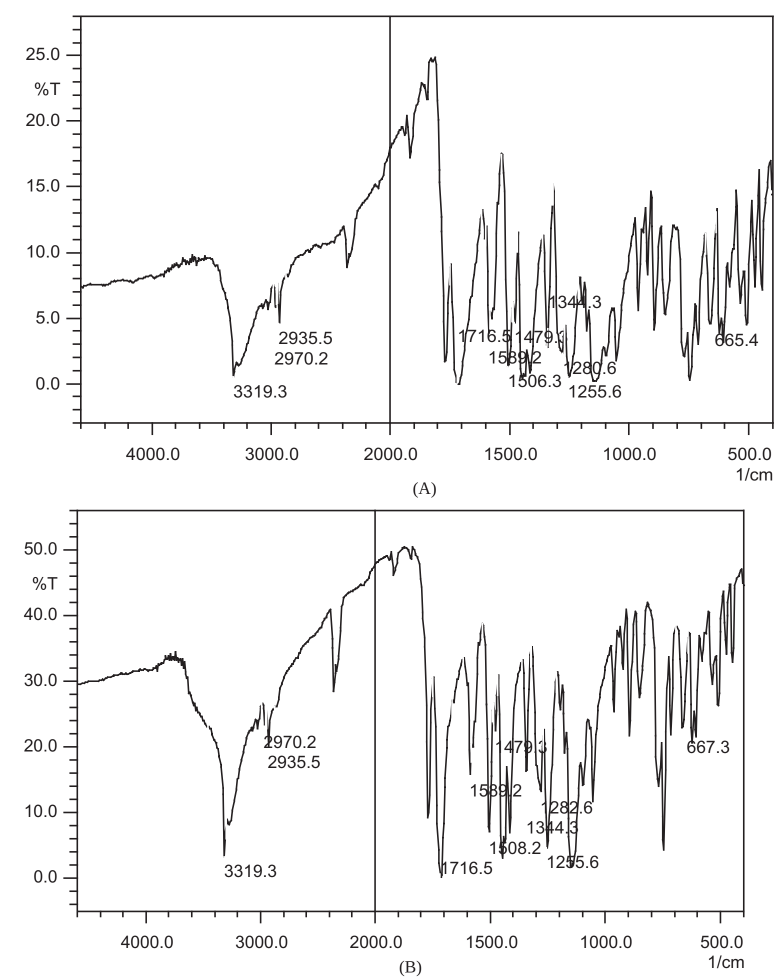

FIGURE 2. Infrared spectra of (A) aceclofenac and (B) formulation A2.

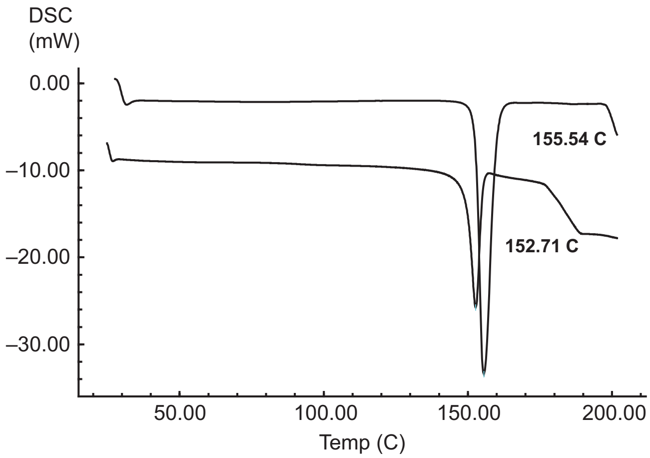

FIGURE 3. DSC thermograms of aceclofenac (155.54°C) and formulation A2 (152.71°C).

TABLE 3
Micromeritic Properties of Enteric-Coated Pellets

Parameters	Pure Drug	A1 (15% wt/wt)	A2 (20% wt/wt)	A3 (25% wt/wt)
Poured density	0.51 ± 0.08	0.66 ± 0.02	0.62 ± 0.01	0.67 ± 0.005
Tapped density	0.74 ± 0.12	0.68 ± 0.01	0.64 ± 0.01	0.7 ± 0.01
Carr's index (%)	31.08	2.94 ± 0.5	3.15 ± 0.2	4.28 ± 0.3
Hausner's ratio	1.45	1.03 ± 0.01	1.03 ± 0.02	1.04 ± 0.02
Angle of repose	46.92	20.4 ± 3.1	21.5 ± 1.2	22.8 ± 1.7

Micromeritic Properties

The micromeritic properties of the pure drug and the formulations are given in Table 3. The pellets exhibited good flow properties as evident from the micromeritic properties. The Carr's Index and Hausner's ratio values for pure drug were 29.99 and 1.42%, respectively. For pellets, those values ranged from 2.94 ± 0.5 to 4.28 ± 0.3 and 1.03 ± 0.01 to 1.04 ± 0.02, indicating good compressional characteristics of pellets. In evidence to this, the angle of repose values of pellets further supported for good flow properties when compared to pure drug. The pure drug alone showed 46.92° (Aulton, 1990) and that of pellets were in the range of 20.4° to 22.8°. The improvement in flowability helps in easy filling of pellets into capsule dosage form or filling of the pellets into the tablet die cavity.

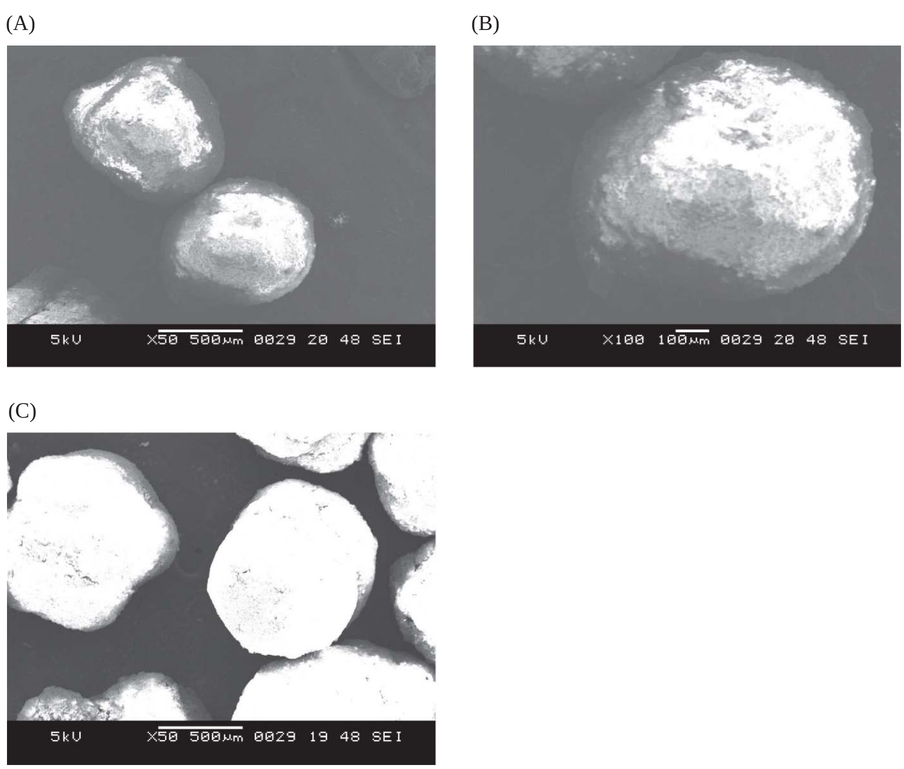

FIGURE 4. Scanning electron microscopy (SEM) photographs of enteric-coated pellets.

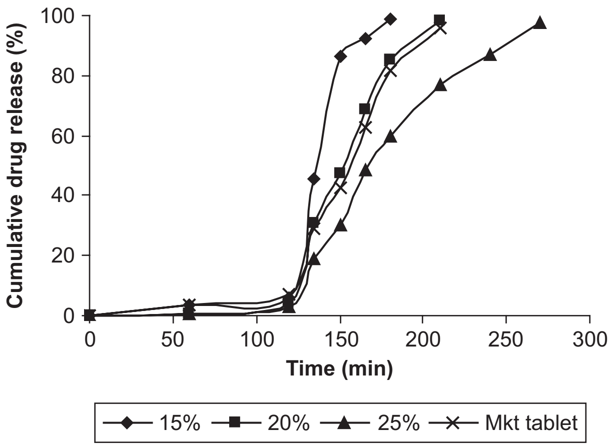

FIGURE 5. Influence of various coating levels (15, 20, and 25% wt/wt) on in vitro release of core pellets coated with Eudragit L100-55 dispersion.

Dissolution Study

A polymeric membrane provides a certain amount of resistance to drug diffusion from the drug reservoir to the surrounding medium. The drug entity from film-coated dosage forms may be transported through a hydrated swollen film or a network of capillaries filled with the dissolution media (Rahman & Yuen, 2005). Dissolution studies indicated that factors such as coating thickness would affect drug release from the coated pellets. Drug release from coated pellets depends to a greater extent on coating levels of the polymeric dispersion applied on core pellets as shown in Figure 5. Dissolution was carried out in two media, namely simulated gastric fluid (acidic buffer, pH 1.2) for the first 2 h and simulated intestinal fluid (phosphate buffer pH 6.8) for subsequent hours. The results of dissolution study demonstrate the influence of thickness of coating on the release of drug from pellets (Shivakumar, Sarasija, & Desai). The formulation (EC coated pellets) A1 showed 5 ± 0.82% drug release whereas A2 showed 3 ± 0.58% drug release and A3 showed 2 ± 0.42% drug release in pH 1.2 (0.1 N HCl) buffer. The EC pellets A2 showed 85 ± 5% release in 75 min, whereas A1 showed 85 ± 5% release in 30 min and A3 showed 85 ± 5% release in 120 min in phosphate buffer, pH 6.8. The dissolution profile of pellets was compared with that of Hifenac marketed tablet (film coated, 100 mg dose). The cumulative percent release of marketed tablet in 0.1 N HCl buffer was high, 6 ± 0.78%. But the in vitro release of formulation A2 was comparable with that of marketed formulation. A faster release was observed with 15% wt/wt compared with 20 and 25% wt/wt coating levels. This variability in the drug release from pellets might be because of the difference in the coating thickness of pellets. The release rate from the coated pellets seemed to be inversely proportional to the thickness of the polymer coat. A similar inverse relationship between the thickness of polymer coat and the rate of drug release has been reported (Rahman & Yuen, 2005).

Stability Studies

The results of accelerated stability studies indicated that pellets did not show any physical changes during the study period and the drug content was found to be more than 96% at the end of 6 months. The percent of drug content ($n = 3$; $M \pm SD$) in pellets were as follows: 0 day, 100.00 ± 0.00; 15 days, 99.23 ± 0.72; 30 days, 98.95 ± 0.51; 60 days, 98.12 ± 0.34; 90 days, 97.31 ± 0.27; 180 days, 96.18 ± 0.32. This indicates that the formulated pellets are quite stable at accelerated storage conditions of ICH guidelines.

CONCLUSION

The enteric-coated pellets containing aceclofenac were successfully prepared by using extruder spheronizer. The drug release rates varied according to the amount of coating applied on the pellets. The prepared EC pellets of aceclofenac increased the lag time of drug by preventing releasing in stomach followed by rapid release in intestine. So the formulated pellets may reduce the gastric irritation and showed better release in comparison with the marketed product.

ACKNOWLEDGMENTS

We thak the Department of Science and Technology (DST), New Delhi, India, for providing the infrastructure facilities to carry out the research work.

REFERENCES

Aabakken, L., Olaussen, B., Mowinckel, P., & Osnes, M. (1992). Gastro-duodenal lesions associated with two different piroxicam formulations. An endoscopic evaluation. *Scand. J. Gastroenterol., 27*, 1049–1054.

Alvarez, L., Concheiro, A., Gómez-Amoza, J. L. Souto, C., & Martínez-Pacheco, R. (2002). Effect of microcrystalline cellulose grade and process variables on pellets prepared by extrusion–spheronization. *Drug Dev. Ind. Pharm., 28*, 451–456.

Aulton, M. E. (1990). *Pharmaceutics: the Science of dosage form design* (vol. 1, 2 ed.) London: Churchill Livingstone.

Bando, H., & McGinity, J. W. (2006). Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit® S100:L100 dispersion. *Int. J. Pharm., 323*, 11–17.

Bashaiwoldu, F., Abraham, B., & Podczeck, J. M. N. (2004). The application of non-contact laser profilometry to the determination of permanent structural change induced by compaction of pellets II. Pellets dried by different techniques. *Eur. J. Pharm. Sci., 22*, 55–61.

Chopra, R., Podczeck, F., Newton, J. M., & Alderborn, G. (2002). The influence of pellet shape and film coating on the filling of pellets hard shell capsules. *Eur. J. Pharm. Biopharm., 53*, 327–333.

Debunne, A., Vervaet, C., Mangelings, D., & Remon, J. (2004). Compaction of enteric-coated pellets: Influence of formulation and process parameters on tablet properties and in vivo evaluation. *Eur. J. Pharm. Sci., 22*, 305–314.

Hu, L., Liu, Y., Tang, X., & Zhan, Q. (2006). Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. *Eur. J. Pharm. Biopharm., 64*, 185–192.

Huyghebaert, N., Vermeire, A., Rottiers, P., Remaut, E., & Remon, J. P. (2005). Development of an enteric-coated, layered multi-particulate formulation for ileal delivery of viable recombinant Lactococcus lactis. *Eur. J. Pharm. Biopharm., 61*, 134–141.

Lin, A. Y., & Larry, L. (2001). Augsburger. *AAPS Pharm. Sci., 3*(2), 1–12.

Muatlik, S., Usha, A. N., Reddy, M. S., Ranjith, A. K., & Pandey, S. (2007). Improved bioavailability of aceclofenac from spherical agglomerates: Development, *in vitro* and preclinical studies. *Pak. J. Pharm. Sci., 20*(3), 218–226.

Mutalik, S., Anju, P., Manoj, K., & Usha, A. N. (2008). Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan-based solvent change approach. *Int. J. Pharm., 350* (1-2), 279–290.

Pareek, A., Chandanwale, A. S., Oak, J., Jain, U. K., & Kapoor, S. (2006). Efficacy and safety of aceclofenac in the treatment of osteoarthritis: a randomized double-blind comparative clinical trial versus diclofenac—an indian experience. *Curr. Med. Res. Opin., 22*(5), 977–988.

Paulsson, M., & Singh, S. K. (1999). Colloidal and thermal characteristics of concentrated dispersions of polymethacrylate-based latices for aqueous enteric coating. *J. Pharm. Sci., 88*(4), 406–411.

Rahman, N. U., & Yuen, K. H. (2005). Eudragit NE40-drug mixed coating system for controlling drug release of core pellets. *Drug Dev. Ind. Pharm., 31*, 339–347.

Rodriguez, E. C., Torrado, J. J., Nikoakakis, I., Torrado, S., Lastres, J. L., & Malamataris, S. (2001). Micromeritic and packing properties of diclofenac pellets and effets of some formulation varibles. *Drug. Dev. Ind. Pharm., 27*(8), 847–855.

Shivakumar, H. N., Sarasija, S., & Desai, B. G. (2006). Design and evaluation of pH sensitive multi-particulate systems for chronotherapeutic delivery of diltiazem hydrochloride. *Indian J. Pharm. Sci., 68*(6), 781–787.

Sriamornsak, P., Nunthanid, J., Luangtana-anan, M., & Puttipipatkhachorn, S. (2007). Alginate-based pellets prepared by extrusion/spheronization: A preliminary study on the effect of additive in granulating liquid. *Eur. J. Pharm. Biopharm., 67*, 227–235.

Zheng, W., & McGinity, J. W. (2003). Influence of eudragit NE 30 d blended with eudragit_ l 30 D-55 on the release of phenylpropanolamine hydrochloride from coated pellets. *Drug Dev. Ind. Pharm., 29*(3), 357–366.