Using Extrusion–Spheronization to Develop Controlled-Release Formulations of Azithromycin

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The authors develop matrix-based controlled-release formulations of azithromycin using extrusion–spheronization. The effectiveness of several excipients for controlling the release were studied for this high-dose and highly water-soluble drug.

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Azithromycin (AZI) is a semisynthetic, acid-stable erythromycin derivative with a broad spectrum of activity and improved tissue pharmacokinetic characteristics compared with erythromycin (1). Perorally administered immediate-release formulations of AZI are absorbed rapidly and pharmacokinetically exhibit a two-compartment model (therapeutic range 0.1–0.4 mg/mL) with a relatively long elimination half-life (~60 h) (2). AZI therapy with immediate-release formulations is associated with various adverse effects such as nausea, vomiting, abdominal cramping, headache, and dizziness. Conventional immediate-release formulations have a more-pronounced incidence of adverse effects as result of higher peak plasma concentrations of AZI (1). One approach to eliminating the peak plasma concentration of AZI is by collapsing the two-compartment behavior of AZI into one compartment and developing a controlled-release drug delivery system (CRDDS). The CRDDS releases AZI at a predetermined rate, eliminating the undesired peak plasma concentration; reducing or eliminating unwanted side effects; and resulting in a better dosage regimen.

Extrusion–spheronization generates multiunit matrix-based particulate systems that produce multiparticulates with spherical shape, good flow properties, low friability, and uniform packing characteristics. Pellets can accommodate high drug loads, and modified drug release can be achieved by incorporating release-modifying agents such as ethylcellulose, acrylic polymers, chitosan, and glyceryl monostearate (3–5). Moreover, pellets can be compressed to single-unit dosage forms or coated to deliver a drug at a desired rate at the same site or at various sites within the gastrointestinal tract (GIT) (6).

Extrusion–spheronization was used to develop a matrix-based controlled-release formulation of AZI based on pharmacokinetic principles. Various approaches to modifying the formulation composition or process were adopted to achieve the target drug-release profile and to test the feasibility of using various excipients for successful extrusion–spheronization. The pellets' particle size, size distribution, crushing strength, and density were evaluated, and the yield was calculated. Drug-release mechanisms and kinetics were elucidated, and the stability of a selected formulation under accelerated temperature and humidity conditions was evaluated.

Table I: Compositions of azithromycin pellet formulations prepared using extrusion–spheronization (50-g batch size).

Batch code	Quantity of ingredients (%w/w)								Granulating liquid (quantity used in grams)	Moisture content*	Parameters studied
	AZI	MCC	LAC	EC	GMS	MC	CW	MS			
ES01	40	60							Water (24.09)	24.32	Granulating liquid
ES01A	40	60							BA1 10% w/w (20.07)	23.15	
ES01B	40	60							BA2 20% w/w (21.09)	26.92	
E03	25	65		10					BA1 10% w/w (28.81)	26.05	Water-insoluble
ES04	25	50		25					BA1 10% w/w (21.27)	23.01	excipients
ES05	25	35		15	25				BA1 10% w/w (17.00)	20.03	Waxy material and
ES06	25	20		15	40				BA1 10% w/w (13.30)	15.04	combination of waxy
ES07	35	25		15	25				BA1 10% w/w (16.96)	23.95	material with water-
ES08	25	50			25				Water (19.50)	24.96	insoluble excipients
ES09	30	30		10	30				BA3 30% w/w	14.03	
									Dispersion (20.45)		
ES10	30	35		25				10	BA1 10% w/w (20.60)	14.01	
ES11	26.65	20					53.35		BA1 10% w/w (15.0)	10.97	Melt granulation
ES12	30	55				15			BA1 10% w/w (14.20	19.05	Hydrophilic
ES13	35	55				10			BA1 10% w/w (15.52)	23.10	water-swellable
ES14	35	45	10			10			BA1 10% w/w (17.56)	26.06	polymer
ES02	40	40	15						BA2 20% w/w (19.47)	26.06	Water-soluble
ES15	40	35	25						BA2 20% w/w (16.70)	23.01	excipients

*Moisture content was measured as the percent weight loss on wet basis.
Key to abbreviations: AZI (azithromycin); MCC (microcrystalline cellulose); LAC (lactose); EC (ethylcellulose); GMS (glyceryl monostearate); MC (methocel K4M); CW (carnuaba wax); MS (magnesium starate); BA1 (hydroxypropyl methylcellulose); BA2 (polyvinyl pyrolidone); and BA3 (ethylcellose).

Materials and methods

Materials. AZI (lot number MHZ1101011) was procured from Kopran Ltd. (Maharashtra, India). Carnauba wax, directly compressible lactose, and microcrystalline cellulose (MCC PH101) were gift samples from Panacea Biotec Ltd. (New Delhi, India). Glyceryl monostearate, magnesium stearate, and polyvinyl pyrrolidone K30 (PVP) were purchased from a local market. Hydroxypropyl methylcellulose (HPMC) was gifted by Parke-Davis (Mumbai, India) Ltd. Methocel K4M and ethylcellulose were gifted by Colorcon Asia Pvt. Ltd. (Mumbai, India) and Dabur Research Foundation (New Delhi, India), respectively. All materials were used as received.

Theoretical design of the CRDDS. To calculate the dose and release rate of AZI, a two-compartment model was collapsed into a one-compartment model (7) using the reported pharmacokinetic properties of AZI (8). The desired maximum steady-state concentration was 0.390 mg/mL (2) and the time of drug delivery (t_{del}) from the dosage forms was 14 h, which was selected on the basis of the average GI transit time. Assuming first-order release (basically exhibited by envisaged matrix system), a first-order release rate of (kr) 0.164/h was obtained.

The serum concentration versus time profile of AZI after a 500-mg intravenous administration to a healthy male population (average weight of 74 kg) is shown in Figure 1 (8). The absorption phase of the curve was generated using the required absorption rate constant of 0.164/h—that is, a first-order drug release rate from CRDDS (drug absorption becomes a function of release from the delivery system in the case of a controlled-release product) and pharmacokinetic principles (back feathering). From the generated single-dose serum concentration versus time profile of perorally administered AZI, the steady-state concentration was predicted using superposition (8, 9) and the dose was calculated to achieve the desired steady-state AZI concentration according to the following equation:

$$DM_{desired} = (\text{Target concentration}_{desired} \div \text{Target concentration}_{test}) \times DM_{test}$$

in which $DM_{desired}$ is the dose needed to load in the system to attain a desired peak steady-state concentration (Target concentration$_{desired}$). DM_{test} is a preliminary reasonable maintenance dose needed for the calculation test based on a conventional dose. Similarly, Target concentration$_{test}$ is a theoretical plasma concentration within the therapeutic limits initially required in the calculation.

The dose of AZI for a once-a-day CRDDS to provide a maximum desired steady-state level of 0.390 mg/mL was 506.4 mg (~500 mg), which was to be released at a controlled rate of 0.164/h according to first-order kinetics.

Preparation and characterization of pellets. Accurately weighed quantities of ingredients were thoroughly mixed in a polythene bag for 15 min (dry mixing), followed by the gradual addition of the required amount of freshly prepared binder solution to prepare a wet mass. The prepared wet mass then was extruded through a 1-mm diameter screen using a roller extruder (model 10, Caleva Process Solutions, Dorset, UK). The extrudates were spheronized at 2650 rpm in a spheronizer (model 120, Caleva)

Table II: Physical characteristics of various pellet formulations prepared using extrusion–spheronization.

Batch code	Total yield (%)	Product yield (%)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Pellet strength (N)	Mean pellet size (μm)	Quality of pellets*
ES01	55.65	78.61	0.63	0.66	14.28	1.16	7.15	533.17	Good
ES01A	51.25	84.73	0.68	0.68	12.76	1.19	10.49	556.31	Good
ES01B	64.32	72.98	0.64	0.75	14.28	1.16	7.15	633.32	Good
ES02	65.25	37.31	0.57	0.65	11.76	1.13	5.49	793.57	Average
ES03	54.50	58.13	0.56	0.64	13.63	1.15	11.71	719.35	Poor
ES04	58.25	94.58	0.54	0.63	12.50	1.14	8.93	537.07	Average
ES05	58.50	74.84	0.59	0.66	10.34	1.11	6.68	696.35	Good
ES06	54.00	74.85	0.56	0.64	11.76	1.13	5.16	615.62	Average
ES07	59.75	69.95	0.60	0.62	10.50	1.11	5.44	631.70	Good
ES08	48.90	66.05	0.66	0.72	10.00	1.11	5.81	652.83	Good
ES09	66.25	84.74	0.62	0.68	8.57	1.09	6.67	552.12	Good
ES10	74.37	75.73	0.57	0.63	10.00	1.11	7.11	603.27	Good
ES11	32.12	88.70	0.51	0.57	10.09	1.13	5.82	561.31	Average
ES12	37.50	60.52	0.63	0.66	5.50	1.05	15.55	620.55	Poor
ES13	33.20	90.66	0.60	0.62	4.00	1.04	15.21	569.05	Average
ES14	58.12	87.17	0.58	0.66	11.76	1.13	5.88	542.67	Average
ES15	52.00	78.15	0.60	0.64	7.40	1.08	6.12	534.42	Good

*Good rating denotes spherical-shape pellets; average rating denotes oval-shape pellets; and poor rating denotes dumbbell-shape pellets.

fitted with a cross-hatch cut stainless-steel friction plate (120-mm diameter, 3 × 3 mm^2 pitch, 1-mm depth). Spheronization time was varied from 2 to 5 min, depending on the formula. Prepared pellets were kept at room temperature for 12 h for drying before being packed in plastic bottles.

Preparation of tablets. Pellets were compressed using a single-punch tablet machine (Cadmach India Ltd., Ahmedabad, India) fitted with 12.75-mm round, flat-faced punches. For each tablet, 680 mg of pellets (equivalent to 250 mg of AZI) were weighed, filled into the die, and compressed. Tablet hardness was kept constant (17–19 kp) for all formulations. To study the effect of compression on the release rate, pellets were compressed at three applied pressures to generate tablets of high (23 kp), moderate (18 kp), and low hardness (12 kp). To study the effect of tablet dimension on the *in vitro* release of AZI, tablets of various diameter and thickness also were made.

***In vitro* drug release studies.** Dissolution testing of various pellet formulations (pellets equivalent to 250-mg AZI) and tablet formulations was performed in a sodium phosphate buffer (pH 6.0, 900 mL) using the paddle method at 50 rpm and 37 ± 0.5 °C. At various time intervals, 2.0-mL samples were withdrawn, filtered (0.45-μm syringe filter, Sartorius Corp., Goettingen, Germany), suitably diluted, and analyzed using high-performance liquid chromatography (HPLC) (10).

Release profiles comparison. To compare two formulations, dissolution data were fitted to the fit factors f_2 (similarity factor) and f_1 (dissimilarity factor) (11). The mean dissolution time (MDT) (12) also was calculated to compare the dissolution characteristics of the formulations.

Release kinetics and mechanism. To establish the drug-release kinetics and mechanism, drug-release data were fitted into various drug-release kinetic models, including zero-order, first-order, Higuchi, Hixon-Crowell, Baker-Lonsdale, Hopfenberg, Korsenmeyer, and Peppas. The criteria for selecting the most appropriate model were based on the highest coefficient of determination (R^2), the smallest sum of squared residuals (SSQ), the standard error, and the akaike information criteria (AIC). The *F*-statistic was applied to determine whether correlations occurred by chance (13, 14).

Stability studies. An optimized formulation was isothermally stressed to study the stability under accelerated temperature and relative humidity (RH) conditions (40 °C and 75% RH) for three months. Test samples withdrawn every month were subjected to various tests, including visual inspection for any appreciable change on the tablet surface, assay, hardness, friability, and dissolution. HPLC and differential scanning calorimetry were used as analytical tools to characterize the stability of AZI in tested formulation.

Results and discussion

Formulation optimization. Initially, a base formulation was prepared using a combination of MCC and AZI. MCC was incorporated into the base formulation for imparting moisture retaining and distribution ability to extrusion–spheronization (15). Various formulation and process modification approaches were used at various stages of formulation development to achieve the target release profile. The following describes these approaches and their effects on product quality. Ingredient compositions of the formulations are shown in Table I.

Effect of granulating fluid, binding agents. To assess the effect of binding agents on the physical properties and release rate, base formulations of AZI were prepared with various granulating liquids such as water and aqueous polymeric solutions of HPMC and PVP. Because of the water-holding capacity of the polymeric solutions, a less amount of granulating fluid (compared with water) was required to provide sufficient moisture

Table III: Comparison of drug-release profiles of tablets prepared from various AZI pellets using model-dependent and model-independent parameters.

	First-order kinetic model parameters*							Model-independent parameters			
										MDT	
Batch code	R^2	k_1	SE	SSQ	F	AIC	R	f_2	f_1	Tablets	Pellets
ES01	0.046	0.171	0.752	6.224	0.536	27.770	0.484	15.90	89.84	1.527	0.219
ES01A	0.059	0.146	0.599	3.957	0.694	21.880	0.514	16.13	89.11	0.362	0.277
ES01B	0.684	0.424	0.592	3.857	17.494	21.549	0.983	24.50	61.18	1.251	0.303
ES02	0.930	0.171	0.212	0.494	146.290	−5.176	0.969	57.41	12.78	6.826	0.252
ES03	0.897	0.201	0.213	0.502	95.511	−4.972	0.899	23.85	60.04	2.552	0.274
ES04	0.676	0.200	0.352	1.365	22.948	8.049	0.943	30.38	43.69	2.693	0.287
ES05	0.981	0.154	0.076	0.063	576.930	−31.981	0.982	48.08	17.54	7.376	0.308
ES06	0.938	0.076	0.086	0.082	166.898	−28.466	0.976	34.95	34.77	10.12	0.356
ES07	0.932	0.368	0.266	0.775	151.410	0.686	0.974	52.20	16.14	4.914	0.125
ES08	0.969	0.142	0.077	0.065	344.890	−31.494	0.974	41.76	24.62	7.714	0.125
ES09	0.822	0.119	0.377	1.565	50.744	9.823	0.975	42.14	24.99	8.844	0.125
ES10	0.687	0.344	0.568	3.558	24.100	20.500	0.825	25.80	53.26	1.547	0.125
ES11	0.439	0.045	0.100	0.111	8.634	−24.600	0.752	33.38	33.14	1.156	0.249
ES12	0.818	0.242	0.265	0.773	49.750	0.648	0.950	47.67	18.20	6.122	0.246
ES13	0.843	0.256	0.307	1.036	58.900	4.460	0.889	38.16	27.03	7.753	0.125
ES14	0.606	0.352	0.552	3.353	16.940	19.728	0.900	42.96	25.08	4.372	0.125
ES15	0.989	0.175	0.064	0.045	1071.68	36.314	0.984	72.40	06.61	5.957	0.125

*R^2 is the coefficient of determination; k_1 is the first-order drug-release rate constant per hour; SE is the standard error of *y*-estimation; SSQ is the sum of squared residuals; F is the observed F value for the F statistic; AIC is the akaike information criterion; R is the correlation coefficient; MDT is the mean dissolution time in hours; f_2 is the similarity factor; and f_1 is the dissimilarity factor.

content to the wet mass (see Table I, formulations ES01A and ES01B). Moreover, polymeric solutions significantly improved mean pellet size and size distribution (see Table II). In the case of PVP, however, mean pellet size was greater compared with HPMC (633 versus 556 μm). Examination of the bulk and tap density data indicated that the density of the pellets increased when water was replaced with a granulating agent (HPMC and PVP). Changes in density may be attributed to the formation of more-uniform spherical pellets with binding agents. Binding agents also enhanced the flow characteristics of the pellets, indicated by lower Carr's index and Hausner ratio values (see Table II).

Although using granulating fluids provided a significant advantage over using water with respect to the pellets' physical properties, little influence was observed in the respective release profiles (see Figure 2). Changing the binding agent from PVP to HPMC, however, decreased the amount of AZI released during the initial hour. Prolonged AZI release may have attributed to an increase in pellet hardness because pellets made with HPMC exhibited higher hardness compared with pellets made with PVP (16).

Effect of water-soluble excipients. Various concentrations of lactose, a water-soluble excipient, were incorporated into the base formulation to improve the quality of the pellets (see Table I). Including lactose in formulations ES02 and ES15 decreased the amount of granulation fluid to 23.01% w/w moisture content for 25% w/w lactose compared with 26.92% w/w for a formulation without lactose (see Table I). In formulation ES02 (15% w/w lactose), a higher moisture content (more than 25% w/w) from overwetting led to agglomeration. A decreased proportion

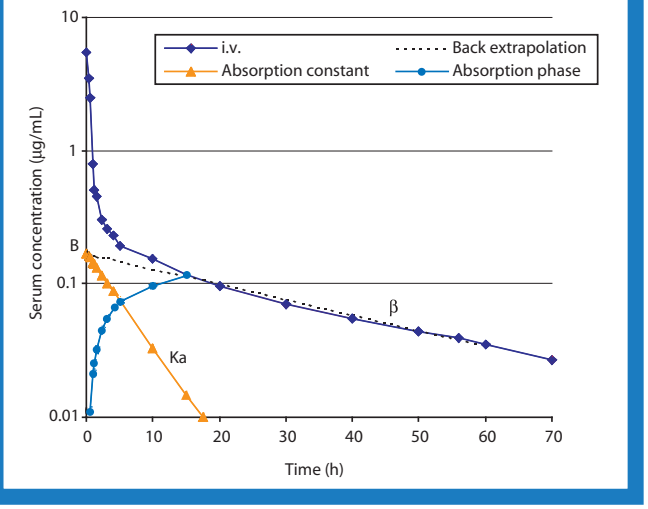

Figure 1: Collapsing of a two-compartment model to a one-compartment model. The rate of absorption is slower than the rate of distribution. (B = 0.17 mg/mL; k_a= 0.164/h; β = 0.026/h). For the calculation of dose and release rate, a serum concentration–time profile of AZI after 500-mg administration to a healthy male population with an average weight of 74 kg was used from the literature (9).

of MCC (which can hold a large amount of freely mobile water in the wet stage) in a formulation reduces water-holding capacity (17, 18) and leads to fast agglomeration.

Incorporating lactose in the base formulation produced a large fraction of pellets in the lower size range, thereby reducing the mean pellet size from 633 (ES1B) to 534 μm (ES15) (see

Table IV: Effect of various tableting parameters on the release rate of AZI tablets prepared from pellets from ES15.

Parameters studied	Pellets size (μm)	Weight (mg)	Hardness (kp)	Thickness (mm)	Diameter (mm)	f_2 factor	f_1 factor
Pellet size	355–710	680	18.2	4.50	12.75	72.47	7.47
	710–1000	676	17.2	4.52	12.75	61.56	10.15
	>1000	686	17.1	4.47	12.75	71.42	6.62
Hardness	355–710	669	12.8	4.92	12.75	42.44	28.17
	355–710	680	18.2	4.50	12.75	72.47	7.47
	355–710	678	23.2	3.95	12.75	48.38	19.30
Thickness/ weight	355–710	680	18.2	4.50	12.75	72.47	7.47
	355–710	805	18.3	5.90	12.75	65.71	8.66
Diameter/ weight	355–710	547	17.1	4.44	10.05	62.60	8.86
	355–710	680	18.2	4.50	12.75	72.47	7.47

Table V: Kinetic and statistical parameters obtained on fitting drug-release data of ES15 tablets prepared from pellets of extrusion–spheronization in various mathematical models.*

Parameter	Zero order	First order	Higuchi	Hixson-Crowell	Baker-Lonsdale	Hopfenberg	Peppas
Parameters for assessing model fit							
R	0.924	-0.991	0.993	0.988	0.985	0.978	0.994
R^2	0.854	0.981	0.987	0.976	0.970	0.957	0.989
F	68.57	1071.68	338.783	532.166	365.325	468.292	595.321
SSQ	2133.73	0.045	160.994	0.386	0.007	0.017	0.015
AIC	103.65	−36.196	57.435	−8.374	−58.991	−48.27	−50.368
Parameters for kinetic equation							
Slope	4.484	-0.079	26.350	0.162	0.020	0.034	n = 0.612
k	11.201	0.174	26.350	0.162	0.020	0.034	0.176
SE (slope)	0.557	0.002	1.289	0.007	0.100	0.001	0.024
SE (y-est)	13.92	0.064	6.473	0.179	0.026	0.014	0.041

*k is the release rate constant with units of % per hour, % per (hour)$^{1/2}$, and (%)$^{1/3}$ per hour for zero-order, Higuchi, and Hixson-Crowell models, respectively. Units of k for the first-order, Baker-Lonsdale and Hopfenberg models are (h^{-1}). For the Peppas model, the units of k are h^{-n}. R is the correlation coefficient; F is the observed F-statistic value; SSQ is the sum of squared residuals; SE (slope) is the standard-error of slope; AIC is the akaike information criterion; R^2 is the coefficient of determination; SE (y-est) is the standard error of the y estimation.

Table II). The shift in the pellet-size distribution toward a lower size was attributed to the crystalline nature of the lactose, which lacked the cohesiveness and plasticity to form the pellets (19). Total yield and product yield remained unchanged. Formulation ES02 exhibited a large mean pellet size (793 μm) because of uncontrolled agglomeration resulting from an overwetting of the wet mass. The Carr's index and Hausner ratio values decreased, which indicated better flow properties in the presence of lactose as a filler in the base formulation. An insignificant difference in the crushing strength of the pellets containing 15% and 25% w/w lactose indicated the pellets' strength was not affected by the presence of lactose (see Table II). In addition, incorporating water-soluble excipients increased the drug release (see Figure 3) because the high aqueous solubility of the lactose caused channels or cracks to form on the pellets' surface (20, 21)

Effect of water-insoluble, hydrophobic excipients. Using water-insoluble excipients retards the release rate (22, 23) from a matrix system because they impart hydrophobicity in the matrix. Various concentrations ethylcellulose, a water-insoluble excipient, were added to the base formulation to retard the release of AZI. Mean pellet size increased (ES03) and then decreased (ES04) when the concentration of ethylcellulose increased 0–10% and 10–25% w/w, respectively. Average pellet size was higher (720 μm) at 10% concentration level because of the high degree of agglomeration resulting from the large volume of granulating liquid used in this batch. In formulation ES04, pellet fragmentation occurred at high concentrations of ethylcellulose and resulted in smaller size pellets compared with pellet sizes in ES01A. Although total and product yields were improved, spherical pellets were not produced because of the low spheronizing properties of ethylcellulose (21, 24). No significant changes were observed in bulk and tap density values, which was further substantiated by the observed Carr's index and Hausner ratio values (see Table II). AZI release was retarded as a function of an increase in concentration of ethylcellulose from 10 to 25% in base the formulation (see Figure 4). Because of the highly water soluble nature of AZI, however, an initial-burst effect was observed, which was further pronounced by the pellets' high surface area and pores created by the release of AZI (24, 25).

Effect of hydrophilic-swellable polymers. Hydrophilic swellable polymers, commonly used as matrix-forming material in CRDDS, control drug release by penetrating water into the matrix, hydrating and swelling the polymer, diffusing the dissolved drug, and the eroding the gelatinous polymeric layer (26, 27).

Preparing the wet mass with Methocel K4M was difficult because of its tendency to form a tacky mass, which affected the total yield from 52% (ES01A) to 33% (ES13) (see Table II). On the other hand, mean pellet size increased from 589 to 620 μm as the concentration of Methocel K4M was increased from 10 to 15%. In addition, long dumbbell-shaped pellets were obtained instead of spherical pellets. The crushing strength of the pellets, however, improved to 15 N, which can be attributed to better cohesiveness provided by the polymer (28).

With respect to drug release, a 70% release of AZI within 1 h indicated the unsuitability of a hydrophilic swellable polymer as a retardant for highly water-soluble drugs. A synergetic

Table VI: Stability study results of ES15 tablets prepared from pellets of extrusion–spheronization after 0, 1, 2, and 3 months of storage in screw-capped HDPE bottles under accelerated stability conditions of 40 °C and 75% RH.

Evaluated parameters	0 month	1 month		2 months		3 months	
		Control*	Test**	Control*	Test**	Control*	Test**
AZI peak positions (T_m °C) during DSC analysis	121.74	119.70	120.38	119.76	119.74	120.31	119.89
Heat of transitions (ΔH, J/g) during DSC analysis	13.86	7.74	7.38	8.69	9.97	10.91	10.39
Drug content (% of labeled content) mean (SD)	104.32 (0.20)	99.59 (2.05)	108.19 (0.15)	101.65 (1.64)	101.32 (0.24)	96.78 (1.69)	99.64 (0.54)
Hardness (kp) mean (SD)	19.74 (1.37)	-	-	-	-	17.98 (1.78)	18.54 (1.68)
Friability (%)	0.203		-	-	-	0.201	0.186
Similarity factor***, f_2	-	63.65	63.08	64.53	64.39	82.76	62.57
Dissimilarity factor***, f_1	-	8.88	10.49	8.74	9.83	3.70	10.55

*Control samples were kept at 4 °C in refrigerator
**Test samples were kept at 40 °C and 75% RH in a stability chamber.
***Release profile of 0-month sample was taken as the reference profile.

effect of swelling property of Methocel K4M and a disintegrating property of MCC could be the reason for the immediate release of drug (28, 29).

Effect of waxy materials. Waxy materials are hydrophobic in nature and a potential release retardant for controlled-release matrix systems (30, 31). Two waxy materials (glyceryl monostearate and carnauba wax) with varying degrees of lipophilicity were used as formulation components on the assumption that they would make the matrix hydrophobic and retard drug release.

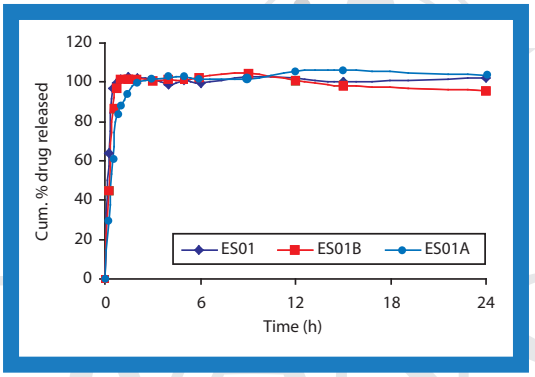

Figure 2: Effect of granulating fluids on the *in vitro* release profile of AZI from pellet formulations prepared by extrusion–spheronization. ES01 is water; ES01A is 10%w/w HPMC; and ES01B is 20% w/w polyvinyl pyrrolidone K30.

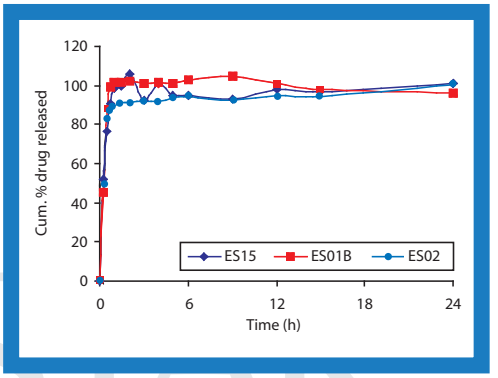

Figure 3: Effect of water-soluble excipients on the *in vitro* release profile of AZI from pellet formulations. ES01B is 0% w/w lactose; ES02 is 15% w/w lactose; and ES15 is 25% w/w lactose.

Glyceryl monostearate and carnauba wax were incorporated to obtain formulations ES08 and ES11 using two different processes. For ES08, AZI was mixed with a dry-powder form of glyceryl monostearate and then granulated with water. At a high concentration of glyceryl monostearate (25%), flaking occurred during spheronization, but this effect was reduced by initially melting the glyceryl monostearate in hot distilled water and then adding the drug to form the slurry before mixing with MCC (30). For ES11, AZI was dispersed in molten carnauba wax by continuous stirring and then dried. The dried mixtures were milled to obtain granules, which were mixed with other dry-powder excipients and granulated with an aqueous solution of polymeric binder (32).

Total yield from ES11 was very low (33.20%) compared with ES08 (48.90%) because of the loss of material during melt granulation (see Table II). Product yield (pellets in the size range of 355–710 μm), however, was from ES11. In addition, the pellets' density and crushing strength decreased as carnauba wax was incorporated into the formulations. On the other hand, glyceryl monostearate resulted in better yield, crushing strength, and density (see Table II). These results suggest that carnauba wax had unfavorable effects on the spheronizing property of the powdered mix, findings also supported by poor pellet shape (rough, dumbbell-shape pellets). It can be attributed to the hydrophobicity and poor molding capacity of carnauba wax. Even in these formulations the initial burst effect was observed as shown in Figure 6 owing to the formation of a poor matrix (30).

Effect of polymer–excipient combinations. On the basis of the results obtained using various excipients and polymers, we concluded that only water-insoluble excipients and glyceryl monostearate retarded the release rate of AZI from CRDDS effectively, with an initial-burst release that could not be controlled by these excipients alone. Because using ethylcellulose and glyceryl monostearate resulted in good quality pellets, various combinations of ethylcellulose and glyceryl monostearate were made as retardants to overcome the problem of an initial burst.

Ethylcellulose and glyceryl monostearate were added in various proportions with an aqueous polymeric solution of HPMC as the granulating liquid. Using glyceryl monostearate in for-

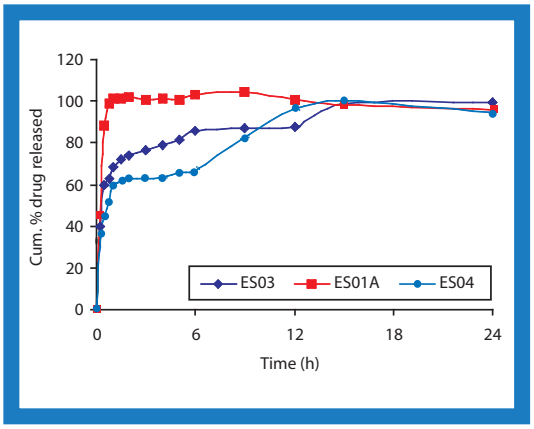

Figure 4: Effect of water-insoluble excipients on the *in vitro* release profile of AZI from pellet formulations. ES01A is 0% w/w ethylcellulose; ES03 is 10% w/w ethylcellulose; and ES04 is 25% w/w ethylcellulose.

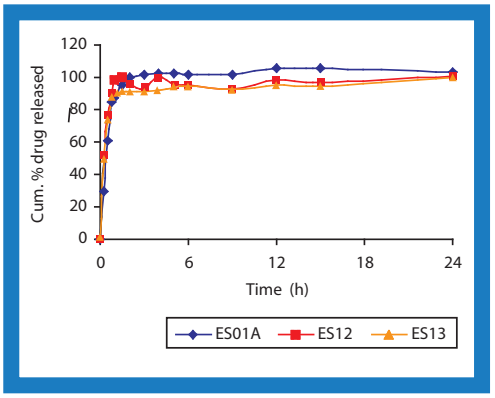

Figure 5: Effect of hydrophilic-swellable polymers on the *in vitro* release profile of AZI from pellet formulations. ES01A is 0% w/w Methocel K4M-HS1; ES12 is 15% w/w Methocel K4M-HS1; and ES13 is 10% w/w Methocel K4M-HS1.

mulations ES05 and ES06 decreased the amount of granulation fluid required for extrusion–spheronization. As the concentration of glyceryl monostearate was increased from 25% (ES05) to 40% (ES06), the amount of granulating liquid required for extrusion decreased from 17.0 to 13.30 g. This decrease was attributed to the reduced amount of MCC in the formulation (glyceryl monostearate was incorporated at the expense of MCC). No significant change in the required amount of granulation liquid was observed, however, when the AZI concentration was increased from 25 (ES05) to 35% (ES07) and the ethylcellulose and glyceryl monostearate concentration was kept constant. This was attributed to the water-holding capacity of AZI, which was incorporated to compensate the amount of MCC in formulation (33). In contrast, the required amount of granulating liquid increased when magnesium stearate was used in place of glyceryl monostearate (ES10). A possible reason for this was the presence of a higher concentration of ethylcellulose in ES10 compared with other formulations (ES05, ES06, and ES07), which has a higher moisture-holding capacity than glyceryl monostearate (34).

Results of evaluating pellets made with all combinations demonstrated that combinations of a water-insoluble excipient (ethylcellulose) and a waxy material (glyceryl monostearate) could easily be incorporated into the pellets by extrusion–spheronization. When excipients were used in various proportions, the total and product yield remain unchanged (see Table II). Mean pellet size decreased as the concentration of glyceryl monostearate increased, although most of the pellets fell in the size range of 355–710 μm (see Table II). In contrast, pellet density and crushing strength decreased as glyceryl monostearate concentration increased (see Table II). The lack of glyceryl monostearate to provide sufficient cohesiveness to the wet mass may be the reason for the decrease in pellet size, density, and crushing strength (30).

For ES09, an aqueous dispersion of ethylcellulose was used as a granulating agent in place of the binder HPMC, expecting that the presence of a film-forming polymer in the matrix would help in the preparation of better quality pellets and in controlling the drug release (35). To increase the solids content in the formulation, a greater amount of aqueous dispersion was used. Total and product yields and increased significantly (see Table II) compared with other formulations. Pellet crushing strength also increased.

The release profile clearly shows that a combination of excipients produced a better matrix that had a greater retarding effect than a matrix made with ethylcellulose or glyceryl monostearate alone (ES03, ES08) (see Figure 7). A combination of both excipients increased the lipophilicity of the pellet matrix, which decreased the effective penetration and wettability of the dissolution medium. Consequently, the dissolution of the drug within the pellets was slower; hence the rate of AZI release was slower. An initial-burst release was observed in all formulations and could not be prevented, even after an aqueous dispersion of film-forming polymer was used as a granulating agent (ES09).

Pellet compression. On the basis of the pellet formulation results (see Table I) and the presence of an initial-burst release,

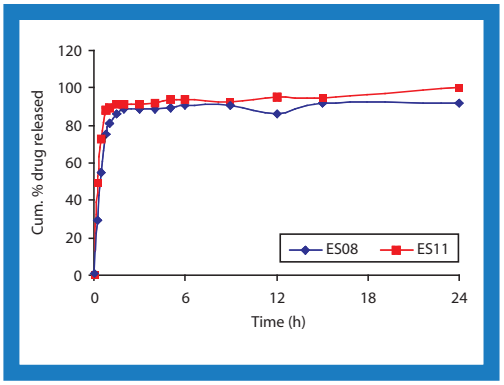

Figure 6: Effect of low-melting point waxy materials on *in vitro* release profile of AZI from pellet formulations. ES08 is 25% w/w GMS and ES11 is 53.35% w/w GMS.

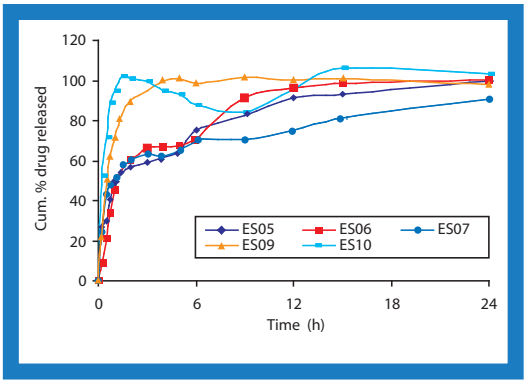

Figure 7: Effect of polymers–excipients combination on *in vitro* release of AZI from pellets prepared by extrusion–spheronization. ES05 is 15:25% w/w EC:GMS; ES06 is 15:40% w/w EC:GMS; ES07 is 15:25% w/w EC:GMS; ES09 is 10:30% w/w EC:GMS; and ES10 is 25:10% w/w EC:MS.

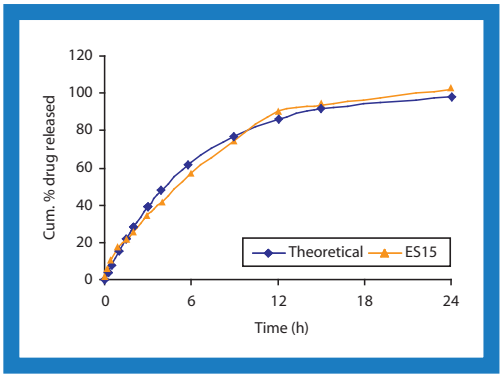

Figure 8: *In vitro* drug release profile of ES15 tablets prepared from pellets and comparison to the theoretical desired release profile.

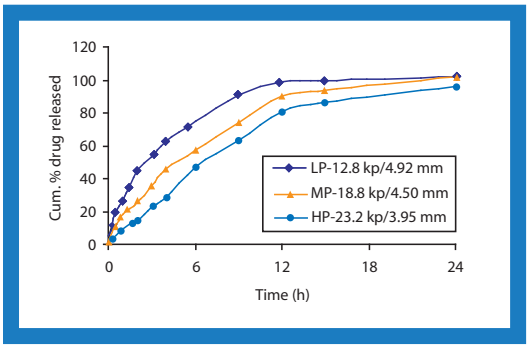

Figure 9: Effect of compression force and tablet hardness on the *in vitro* release profile of AZI from ES15 tablets. LP denotes low pressure; MP denotes medium pressure; and HP denotes high pressure.

we concluded that none of the approaches were successful to achieve the formulation with a release profile close to the theoretical calculated desired release profile. Two different approaches can be taken to prevent this initial burst: coating pellets with suitable release-retarding polymers or compressing the pellets. We decided to compress the pellets as an additional step in preparing a CRDDS for AZI using extrusion–spheronization. All pellet formulations in the 355–710 μm size range were compressed with a single-punch tablet machine. MDT values confirmed that AZI release from these tablets was better controlled than corresponding release profiles obtained from pellets (see Table III). This improved control over the AZI release was attributed to the close packing of the pellets after compression and to the formation of a matrix structure having limited porosity. Compression into single-unit tablets also reduced the surface area exposed to the dissolution medium, which prevented the initial-burst release observed with the pellets.

Selecting a tablet formulation. To select a formulation having a release profile close to the desired profile, we determined the model-independent parameters f_2, f_1, and MDT and the first-order kinetic model parameters R, R^2, standard error of y-estimation (SE), AIC, SSQ, and F statistic from the AZI release profiles of various tablet formulations (14) (see Table III). Model-independent parameters showed that the f_2 values of the ES02, ES07, and ES15 tablets were greater than 50, compared with the desired-release profile. MDT values of these formulations also were close to the desired values. These results suggest similarity among the drug-release profiles from three tablet formulations and the desired-release profile of the AZI formulation. On fitting the dissolution data to the first-order kinetic equation, however, results of ES02 and ES07 tablets indicated very poor correlations, characterized by the values of R^2, SSQ, AIC, and the F-statistic. Only the ES15 formulation fit well to the first-order kinetic model and exhibited a drug-release rate (0.174/h) close to the desired release value (0.164/h) with good correlations (*i.e.,* high R, R^2, and F statistic and low SE, SSQ, and AIC values) (see Figure 8). On the basis of these results, we selected the ES15 formulation for further development as first-order kinetic controlled-release tablets of AZI. The effect of pellet size and tablet dimensions on the drug-release characteristics were studied.

Effect of pellet size. The effect of pellet size on the tablets' drug-release properties was studied using various size fractions of pellets of ES15 (retained on 16 sieve, >1000 μm; 16/22 sieve, 710–1000 μm; and 22/44 sieve 355–710 μm) to prepare tablets of 680 mg weight (see Table IV). For all tablets, $f_2 < 50$ and $f_1 < 15$, indicating the similarity of the release profiles (see Table IV). Release was independent of the pellet size used to prepare the tablets. During compression, some of the pellets were crushed, forming a uniform matrix (clearly seen in scanning electron micrographs). Thus, a release-retardation effect was achieved because of the close packing of the matrix, irrespective of pellet size. Similarity in terms of AZI-release properties of various-size fractions of pellets indicates that all size fractions (total yield) can be used for tablet preparation, which increases the output of the extrusion–spheronization process.

Effect of tablet structural integrity. AZI tablets from ES15 were broken into two parts using a tablet hardness tester (Erweka, Germany). Tablets were kept between the arms of the hardness tester and a force was applied until fracture occurred, exposing radial fracture surfaces. Weights of the broken tablets were checked, and only those weighing ±2% to the respective intact tablet weights were used for the dissolution studies. Halved tablets showed faster release during the initial 1–4 hours, compared with intact tablets of the same weight. Although the f_2 and f_1 values were 51.97 and 14.91, respectively, indicating a similarity of drug release, the halved tablets had a distinct, faster initial drug release. This release was attributed to the broken tablets' increase in exposed surface area as well as the fast dissolution of AZI that on the exposed surface of the tablets.

Effect of tablet dimensions. The effects of tablet weight, hardness, thickness, and diameter on the release rate of AZI were studied by preparing tablets (ES15) of various dimensions (see Table IV). Pellets of ES15 were compressed using three different pressures (low, medium, and high) to produce 12.75 mm diameter tablets of low (12.8 kp), moderate (18.8 kp), and high (23.2 kp) crushing strength, with respective thicknesses of 4.92, 4.50, and 3.95 mm for 680-mg tablets. As expected, drug release decreased as tablet hardness and compression force increased (see Figure 9). It is possible that during the tableting process at a high compression force (>17kp), some pellets undergo fragmentation and generate fines. Such fines fill the interstitial spaces between the intact pellets more effectively, which enhances the interparticulate binding between the pellets, thus forming a continuous matrix (35) (see Figure 10). Correlation of the SEM photos with the release results confirms that compressing pellets at higher pressures to produce tablets of closely packed pellets helps control the release of AZI.

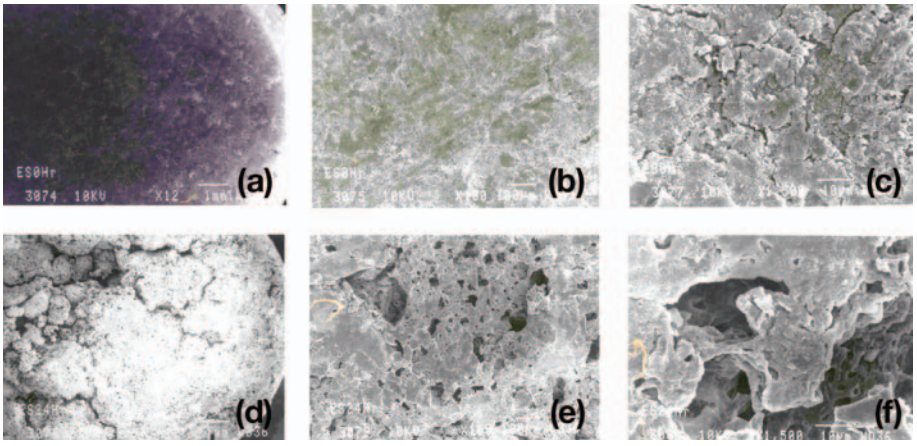

Figure 10: Scanning electron micrographs of ES15 tablet showing the initial outer surface morphology (A, B, and C at magnifications of 12, 100, and 1500×, respectively) and after a 24-h period of dissolution study (D, E, and F at magnifications of 12, 100, and 1500×, respectively).

To assess the effect of thickness on tablet weight, tablets of 4.50- and 5.90-mm thicknesses were produced by compressing 680- and 805-mg ES15 pellets to obtain tablets of the same hardness (17–19 kp) and diameter (12.75 mm). Drug-release profiles from these tablets showed that tablet thickness and weight were not the controlling factors for drug release (see Table IV). Tablets having higher thickness and weight (thus increased tablet surface area) and the same hardness showed similar release profiles. We also studied the effects of tablet diameter and weight on the release rate by making tablets of 10.05- and 12.75-mm diameter. The tablets were made by compressing 545- and 680-mg ES15 pellets. Tablet hardness (17–19 kp) and thickness (4.4–4.5 mm) were kept constant. Drug release was similar for various tablet diameters of the same thickness (see Table IV).

On the basis of all of these results, we concluded that tablet dimensions did not play a significant role in controlling drug release from the AZI tablets prepared from ES15 pellets, especially when these pellets were compressed under high pressures (17–19 kp). The close packing of pellets in tablets was irrespective of tablet weight or dimensions.

Effect of media pH on drug release. Because orally administered formulations pass through various pH environments in the GIT, we performed dissolution studies in media having 1.2–6.8 pH. To simulate the environment of the GIT, a pH change dissolution method (*i.e.,* changing the pH of the dissolution medium while running the dissolution test) was used (29). AZI release was independent the drug-release medium's pH. The f_2 value (theoretical release profile was taken as reference) was 65.36, indicating the similarity of dissolution profiles. The f_1 value, calculated to be 9.11, thereby indirectly indicating the similarity among the release profiles.

Release kinetics and mechanism elucidation. Dissolution data fitted into first-order release kinetic, Higuchi, and Baker-Lonsdale models indicated that drug release was controlled by a drug concentration–dependent diffusion process (see Table V). This result suggested that the tablets were heterogeneous granular matrix systems, which control the release by diffusion through channel or capillaries in the matrices. SEM photographs of the matrix taken 24 h after the dissolution experiment also showed that matrix was intact and that channels had formed throughout the matrix (see Figure 10). Dissolution data were also well fitted in Baker-Lonsdale model, indicating that discrete pellets were the release-controlling units. These results all indicate that retardation of drug release from the tablets could be attributed to the close packing of pellets. The close packing effectively retarded the penetration of dissolution medium into tablets and consequently prolonged the drug release from tablets, thereby circumventing the problem of the initial burst release that was observed with pellets.

Poor fitting of the dissolution data to the Hopfenberg model (confirmed by a low R^2 value) clearly ruled out the possibility of erosion being the release-controlling mechanism (37). This result was supported by the intact tablet structure remaining after 24 h. Fitting data to the Hixson-Crowell model could not be explained because the tablets' dimensions did not diminish during dissolution.

Drug-release data fit well in the Higuchi and first-order kinetic models. To further define diffusion kinetics, we analyzed dissolution data with the Peppas model. The value of the exponent n obtained after treating the data was 0.64, which suggested the drug release was non-Fickian anomalous diffusion (38).

Accelerated temperature stability studies. No changes in the DSC thermograms confirmed that the AZI tablets were unaffected after three-month storage under accelerated conditions (see Table VI). Transition temperature and heat of fusion values were close to the expected values. Moreover, there were no signs of visually distinguishable changes in appearance, texture, and color of formulation. The test product's AZI content and friability were comparable with those of the control samples and within limits (±10%). In all cases, $f_1 < 15$ and $f_2 > 50$, compared with these values for the control samples. On the basis of these results, we concluded that the formulation was stable under accelerated stability test conditions for three months.

Conclusion

Desired drug-release profiles for once-a-day, first-order kinetic CRDDS of AZI were developed on the basis of drug pharmacokinetics (collapsing principles) and a method of superposition. Preparation of a matrix systems for CRDD for AZI was successful only after the prepared pellets were compressed. These pellets were stable in under accelerated stability conditions for three months. The solubility of the drug and the pellets' large surface area resulted in an extensive burst release. In addition, a higher dose of AZI made it necessary to incorporate drug in higher proportion in the delivery system, which resulted in a higher fraction of drug available on the pellet surface contributing to a pronounced burst effect. Therefore, compression can effectively prevent an initial-burst effect. Compression pressure

was a critical factor in avoiding an initial burst release. A high pressure (hardness >17 kp) was necessary to obtain a drug release profile close to the desired release profile. The drug release data fitted to a first-order release kinetics model indicated that drug release was concentration dependent.

References

1. J.D. Christopher and L.B. Barradel, "Azithromycin: A Review of Its Pharmacological Properties and Use as Three-Day Therapy in Respiratory Tract Infection," *Drugs* **51,** 483–505 (1996).
2. W.A. Ritschel and G.L. Kearns, "Pharmacokinetic Parameters of Important Drugs," in *Handbook of Basic Pharmacokinetics* (American Pharmaceutical Association, Washington, DC, 1999), pp. 479–503.
3. S.R. Goskonda and S.M. Upadrashta, "Avicel RC-591/Chitosan Beads by Extrusion–Spheronisation Technology," *Drug Dev. Ind. Pharm.* **19** (8), 915–927 (1993).
4. D. Blanque, "Some Factors Influencing the Formation and *In Vitro* Drug Release from Matrix Pellets Prepared by Extrusion–Spheronization," *Int. J. Pharm.* **119** (2), 203–211 (1995).
5. S.H. Neau, M.Y. Chow, and M.J. Durrani, "Fabrication and Characterization of Extruded and Spheronized Beads Containing Carbopol 974P, NF Resin," *Int. J. Pharm.* **131** (1), 47–55 (1996).
6. A. Sood, Y. Ashokraj, and R. Panchagnula, "Use of Extrusion–Spheronization to Develop Controlled-Release Dosage Forms for Diltiazem Hydrochloride," *Pharm. Technol.* **28** (4), 62–83 (2004).
7. W.A. Ritschel, "Biopharmaceutics and Pharmacokinetic Aspects in the Design of Controlled-Release Peroral Drug Delivery Systems," *Drug Dev. Ind. Pharm.* **15** (6,7), 1073–1107 (1989).
8. G. Foulds, R.M. Shepard, and R.B. Johnson, "The Pharmacokinetics of Azithromycin in Human Serum and Tissues," *J. Antimicrob. Chemother.* **25** (suppl. A), 73–82 (1990).
9. W.A. Ritschel and G. Sathyan," Development and Pharmacokinetic Evaluation of Controlled-Release Dosage Form of Lithium Carbonate in Beagle Dogs," *Lithium* **1,** 209–214 (1990).
10. R. Gandhi, C.L. Kaul, and R. Panchagnula, "Validated HPLC Method for *In Vitro* Analysis of Azithromycin by Using Electrochemical Detection," *J. Pharm. Biomed. Anal.* **23** (6), 1073–1079 (2000).
11. J.W. Moore and H.H. Flanner, "Mathematical Comparison of Dissolution Profiles," *Pharm. Technol.* **20** (6), 64–74 (1996).
12. W.D. Lindner and B.C. Lippold, "Drug Release from Hydrocolloid Embeddings with High or Low Susceptibility to Hydrodyanamic Stress," *Pharm. Res.* **12** (11), 1781–1785 (1995).
13. A. Sood and R. Panchagnula, "Drug Release Evaluation of Diltiazem CR Preparations," *Int. J. Pharm.* **175** (1), 95–107 (1998).
14. P. Costa and J.M.S. Lobo, "Modeling and Comparison of Dissolution Profiles," *Eur. J. Pharm. Sci.* **13** (2), 123–133 (2001).
15. M. Law, D.B. Deasy, and J.P. McLaughlin, "Comparison of Two Commercial Brands of Microcrystalline Cellulose for Extrusion–Spheronization," *J. Microencaps.* **14** (6), 713–723 (1997).
16. J. Varshosaz, R.A. Kennedy, and E.M. Gipps, "Effect of Binder Level and Granulating Liquid on Phenylbutazone Pellets Prepared by Extrusion–Spheronization," *Drug Dev. Ind. Pharm.* **23** (6), 611–618 (1997).
17. K.E Fielden *et al.,* "Thermal Studies on the Interaction of Water and Microcrystalline Cellulose," *J. Pharm. Pharmacol.* **40** (10), 674–678 (1988).
18. D. Bains, S.L. Boutell, and J.M. Newton, "The Influence of Moisture Content on the Preparation of Spherical Granules of Barium Sulphate and Microcrystalline Cellulose," *Int. J. Pharm.* **69** (3), 233–237 (1991).
19. P.J Harrison, J.M Newton, R.C. Rowe, "The Characterization of Wet Powder Masses Suitable for Extrusion–Spheronization," *J. Pharm. Pharmacol.* **37** (10), 686–691 (1985).
20. A.M. Juppo *et al.* "Compression of Lactose Glucose and Mannitol Granules," *J. Pharm. Pharmacol.* **47** (7), 543–549 (1995).
21. A. Sood, Y. Ashokraj, and R. Panchagnula, "Multiunit Matrix-Based Particulate System (MUMPS) for Controlled Delivery of Nifedipine: Formulation Development using Extrusion–Spheronization and *In Vitro* Evaluation," *Pharm. Technol.* 28 (11), 84–102 (2004).
22. S.R. Goskonda, G.A. Hileman, and S.M. Upadrashta, "Controlled Release Pellets by Extrusion–Spheronization," *Int. J. Pharm.* **111** (1), 89–97 (1994).
23. S.R. Goskonda, G.A. Hileman, and S.M. Upadrashta, "Development of Matrix Controlled Release Beads by Extrusion-Spheronization Technology Using a Statistical Screening Design," *Drug Dev. Ind. Pharm.* **20** (3), 279–292 (1994).
24. A. Sood and R. Panchagnula, "Development and *In Vitro* Evaluation of Matrix-Based CR Pellets for Diltiazem HCL Using Extrusion and Spheronization," *J. Pharm. Pharmacol.* **50** (suppl.), 181 (1998).
25. US Patent 6068859, "Controlled-Release Formulations of Azithromycin," Pfizer Inc., New York, NY (2000).
26. V. Iannuccelli *et al.,* "Effect of Loading Method on the Drug Release from Cross-Linked Carboxymethylcellulose Beads," *J. Controlled Release* **23** (1), 13–20 (1993).
27. R. Chatlapalli and B.G. Rohera, "Physical Characterization of Hydroxypropyl methylcellulose and Hydroxyethylcelloluse and Investigation of Their Use as Pelletisation Aid," *Int. J. Pharm.* **161** (2), 179–193 (1998).
28. J. Herman *et al.,* "The Dissolution Rate and Bioavailability of Hydrochlorthiazide in Pellet Formulations," *J. Pharm. Pharmacol.* **40** (3), 157–160 (1988).
29. P.J. Cox *et al.,* "Development and Evaluation of Multiple-Unit Oral Sustained-Release Dosage Form for s(+)-Ibuprofen: Preparation and Release Kinetics," *Int. J. Pharm.* **193** (1), 73–84 (1999).
30. E.S. Ghali, G.H. Klinger, and J.B. Schwartz, "Thermal Treatment of Beads with Wax for Controlled Release," *Drug Dev. Ind. Pharm.* **15** (9), 1311–1328 (1989).
31. F. Zhou, C. Vervaet, and J.P. Remon, "Matrix Pellets Based on the Combination of Waxes, Starches, and Maltodextrins," *Int. J. Pharm.* **133** (1–2), 155–160 (1996).
32. K.K. Peh and K.H. Yuen, "Development and In Vitro Evaluation of a Novel Multiparticulate Matrix Controlled-Release Formulation of Theophylline," *Drug Dev. Ind. Pharm.* **21** (13), 1545–1555 (1995).
33. G.A. Stephenson *et al.,* "Solid-State Investigations of Erythromycin Dihydrate: Structure, NMR Spectroscopy and Hygroscopicity," *J. Pharm. Sci.* **86** (11), 1239–1244 (1997).
34. P.R. Katikaneni *et al.,* "Ethylcellulose Matrix Controlled Release Tablets of a Water-Soluble Drug," *Int. J. Pharm.* **123** (1), 119–125 (1995).
35. A.M. Dyer, K.A. Khan, and M.E. Aulton, "Effect of Polymer Loading on Drug Release from Film-Coated Ibuprofen Pellets Prepared by Extrusion–Spheronization," *Drug Dev. Ind. Pharm.* **21** (16), 1841–1858 (1995).
36. T.P. Foster and E.L. Parrott, "Effect of Processing on Release from an Inert, Heterogeneous Matrix," *Drug Dev. Ind. Pharm.* **16** (8), 1309–1324 (1990).
37. H.B. Hopfenberg, in *Controlled Release Polymeric Formulations*, D.R. Paul and F.W. Harris, Eds. (American Chemical Society, Washington, DC, 1976), pp. 26–31.
38. N.A. Peppas, "Analysis of Fickian and Non-Fickian Drug Release from Polymers," *Pharm. Acta. Helv.* **60,** 110–111 (1985). **PT**