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Research Article

Effects of Processing on the Release Profiles of Matrix Systems Containing 5-Aminosalicylic Acid

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Abstract. The aim of this study was to investigate the influence of different processing methods on the profiles of 5-aminosalicylic acid dissolution from controlled-release matrix systems based on Eudragit® RL and Eudragit® RS water-insoluble polymers. The pure polymers and their mixtures were studied as matrix formers using different processing methods, *i.e.*, direct compression, wet granulation of the active ingredient with the addition of polymer(s) to the external phase, wet granulation with water, and wet granulation with aqueous dispersions. In comparison with the directly compressed tablets, tablets made by wet granulation with water demonstrated a 6–19% increase in final drug dissolution, whereas when polymers were applied in the external phase during compression, a 0–13% decrease was observed in the amount of drug released. Wet granulation with aqueous polymer dispersions delayed the release of the drug; this was especially marked (a 54–56% decrease in drug release) in compositions, which contained a high amount of Eudragit RL 30D. The release profiles were mostly described by the Korsmeyer–Peppas model or the Hopfenberg model.

KEY WORDS: controlled release; matrix tablet; polymethacrylates; release kinetics.

INTRODUCTION

Controlled-release formulations are coming increasingly into the focus of attention, as they are designed to decrease the number of administrations through the incorporation of high doses of the active compounds, thereby enhancing patient compliance, which is crucial in the therapy of chronic diseases (1). Reservoir and matrix (also called monolithic) systems are commonly used in modified-release formulations because of their simplicity and cost-effective manufacturing. A number of manufacturing routes have been devised for the preparation of controlled-release systems, including polymer-based matrices, reservoir-type systems, bilayered tablets, and gastroretentive systems (2–8). Matrix systems involve active ingredients and excipients embedded into a matrix, where the active pharmaceutical ingredient (API) can be dispersed or dissolved. Conventional methods, such as direct compression, wet granulation, or hot melt extrusion, are employed to prepare these systems (9).

Release modeling behavior is indispensable for prediction of the dissolution behavior of drugs from delivery systems. The *in vitro* dissolution testing of solid dosage forms is frequently applied to reveal drug release mechanisms, the resulting data improving of value for the assessment and interpretation of possible risks such as dose dumping, interactions, and effects of food on bioavailability. Two basic types of equipment are generally accepted: apparatus 2 (paddle apparatus) and apparatus 4 (flow-through cells) (10,11). Apparatus 2 (paddle apparatus) is widely applied in view of its simplicity, robustness, and standardizability, and considerable experience has accumulated from its use. Guidelines recommend its utilization for the testing of immediate- and modified-release dosage forms (12).

Conventionally, plastic polymers, including acrylates and ethylcellulose, are used to form insoluble matrices due to their inertness and high drug-embedding ability. Chemically, Eudragit® RS (E RS) and Eudragit® RL (E RL) are copolymers of ethyl acrylate, methyl methacrylate, and a low content of a quaternary ammonium salt of a methacrylic acid ester. Such salts make the polymers permeable. E RS has a lower permeability than that of E RL as it contains fewer trimethylammonioethyl methacrylate groups (13). The polymers swell pH independently and release the incorporated drugs *via* diffusion and erosion. The rate-limiting step is the liquid penetration into the matrix, and the dissolution therefore correlates strictly with this. Eudragit® dispersions are utilized as film-forming agents (14), but the matrix-forming capacities have not been adequately described.

5-Aminosalicylic acid (5-ASA) was used as API in the present study; it is commonly utilized for the first-line treatment of mild-to-moderate inflammatory bowel diseases such as Crohn's disease (15). Orally administered 5-ASA is absorbed rapidly and almost completely from the small intestine (16–18). Nonetheless, time-controlled delivery systems are advantageous in the treatment of inflammatory bowel diseases, and as orally administered dosage forms are greatly preferred to rectal

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ABBREVIATIONS: E RS, Eudragit® RS; E RL, Eudragit® RL; 5-ASA, 5-Aminosalicylic acid; E RL 30D, Eudragit® RL 30D aqueous dispersion; E RS 30D, Eudragit® RS 30D aqueous dispersion; DC, Direct compression; S_{12}, Spreading coefficient.

administration (19). Controlled release is generally achieved through coating, and most commercial drugs are available as coated tablets; ethylcellulose is occasionally applied for this purpose.

The present study focused on the profiles of dissolution from inert matrix systems. Monolithic matrix tablets were prepared by direct compression and wet granulation and were investigated as regards their dissolution profiles; the morphology and structure of the granules prepared were characterized in order to evaluate the differences in the amount of API released. In the case of wet granulation with a binder, the rate of release was low. Prior to the preparation of the matrices, we performed a study to determine the surface properties of the matrix formers and 5-ASA. This revealed that 5-ASA is more hydrophilic than the polymers. The effects of processing on matrix formulations are rarely studied. An overall understanding of the basic relations and of the effects of the processing methods is indispensable in the development of matrix systems, as the interactions that can occur during processing can influence the drug release and stability.

The various processing methods may result in products with different physical properties, including morphology, and whose dissolution can suffer a retardation effect or a sudden, unexpected burst. There may be differences in capillary force, the driving force in coalescence in film formation, especially if wet granulation is applied.

Direct compression is the most convenient method by which to prepare solid dosage forms, due to its cost and time effectiveness, although some excipients and APIs are unsuitable for compression in this way, because of their poor flowability. In our study, the compressed sample was applied for comparison and not as the final dosage form. Since 5-ASA possesses poor flow properties, appropriate processing techniques are required. The simplest and most common method is granulation, particularly wet granulation. This has the advantages that the particles are approximately spheroids and a number of options are available for production (although its utilization with moisture-sensitive APIs is limited) (20).

The polymers were applied alone or in combination and in the form of a powder or an aqueous dispersion in the formulations. In the combinations, different ratios of E RS and E RL (1:1, 1:9, and 9:1) were examined.

MATERIALS AND METHODS

Materials

5-Aminosalicylic acid was purchased from Alfa Aesar, while Eudragit® RL PO (E RL PO), Eudragit® RS PO (E RS PO), and the aqueous dispersions E RL 30D and E RS 30D were kindly donated by Evonik Rhöm GmbH, Darmstadt, Germany. Distilled water was applied as solvent for wet granulation. Distilled water and diiodomethane (Sigma–Aldrich, Steinheim, Germany) served as the probe liquids to assess the polar and disperse components of the surface energy.

Preparation of Matrix Tablets

The tablets were prepared by means of four different processing methods: direct compression, compression of the wet-granulated API with polymer(s) in the external phase, compression of the wet-granulated API and polymers, and wet granulation of the API with aqueous dispersion(s) of the polymer(s). Each processing method included five different tablet formulations. The tablets were compressed with a hydraulic press (Specac Inc., Graseby, UK); samples were pressurized at 10 kN with a dwell time of 10 s, the punch was 13 mm in diameter, and the tablets were flat-shaped. The tablets usually contained 50% 5-ASA and 50% polymer, but in the samples prepared with polymer dispersions, the amount of the API was increased up to 88%. The processing methods were as follows (Table I):

1. Direct compression: a mixture of 5-ASA and solid polymer (s) in mass a ratio of 1:1 was blended in a rotating shaker mixer (Turbula mixer, W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 min before direct compression. The comprimates weighed 400 mg and contained 200 mg API. These samples were denoted by the code DC.
2. Wet granulation of the API: 5-ASA was granulated with distilled water in a high-shear granulator (ProCepT nv, Zelzate, Belgium; kneading parameters: chopper speed, 3,000 rpm; impeller speed, 1,000 rpm; rate of liquid dosing, 5 mL/min). The wet mass was forced through a 1.2-mm mesh sieve to achieve a more homogeneous particle size. The granulation was performed in a stainless steel vessel: Preliminary results have shown that the work of adhesion was less in a steel vessel than in a glass one. Drying was carried out under ambient conditions (25°C, 60% relative humidity) for 24 h. The polymer(s) was (were) added to the external phase before compression: A mixture of granulated 5-ASA and solid polymer(s) in a mass ratio of 1:1 was blended in a rotating shaker mixer (Turbula mixer, W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 min before compression (G5ASA).

Table I. Composition of Tablets

Tablet code	5ASA (mg)	E RS (mg)	E RL (mg)	Total (mg)
DC1	200	200	0	400
DC2	200	0	200	400
DC3	200	100	100	400
DC4	200	20	180	400
DC5	200	180	20	400
G5ASA1	200	200	0	400
G5ASA2	200	0	200	400
G5ASA3	200	100	100	400
G5ASA4	200	20	180	400
G5ASA5	200	180	20	400
G1	200	200	0	400
G2	200	0	200	400
G3	200	100	100	400
G4	200	20	180	400
G5	200	180	20	400
GD1	350	50	0	400
GD2	350	0	50	400
GD3	350	25	25	400
GD4	350	5	45	400
GD5	350	45	5	400

The abbreviations refer to the preparation methods: *DC* direct compression, *G5ASA* 5-aminosalicylic acid granulated with water, *G* mixture of 5-aminosalicylic acid and polymer(s) granulated with water, *GD* 5-aminosalicylic acid granulated with polymer dispersion(s)

Table II. Contact Angles and Surface Free Energies of Raw Materials and Their Mixtures

Composition	Contact angle water Θ_w (°)±*SD*	Contact angle diiodomethane Θ_d (°)±*SD*	Suface free energy γ_s (mN/m)	Disperse component γ_s^d (mN/m)	Polar component γ_s^p (mN/m)	Polarity *P* (%)
5ASA	32.5±*1.86*	20.2±*1.10*	73.0	43.1	29.9	41.0
E RL PO	71.0±*1.37*	19.9±*1.40*	55.0	43.7	11.3	20.6
E RS PO	70.2±*1.29*	22.8±*0.82*	54.6	42.8	11.8	21.6
DC1	38.1±*3.68*	16.4±*2.74*	71.1	44.1	27.1	33.8
DC2	41.2±*3.25*	14.2±*2.30*	70.0	44.5	25.5	36.4
DC3	39.9±*3.76*	16.7±*2.15*	70.3	44.0	26.3	37.4
DC4	40.4±*3.79*	15.1±*1.68*	70.3	44.3	25.9	36.9
DC5	39.7±*2.36*	14.4±*2.72*	70.7	44.5	26.2	37.1

5-ASA 5-aminosalicylic acid, *E RS* Eudragit® RS, *E RL* Eudragit® RL, *E RL 30D* Eudragit® RL 30D aqueous dispersion, *E RS 30D* Eudragit® RS 30D aqueous dispersion, *DC* direct compression

3. Wet granulation of the API and polymers: a mixture of 5-ASA and solid polymer(s) in a mass ratio of 1:1 was blended in a rotating shaker mixer (Turbula mixer, W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 min before granulation. The mixture was granulated with distilled water in a high-shear granulator (ProCepT nv, Zelzate, Belgium; kneading parameters: chopper speed, 3,000 rpm; impeller speed, 1,000 rpm; rate of liquid dosing, 5 mL/min). The wet mass was forced through a 1.2-mm mesh sieve to achieve a more homogeneous particle size. The granulation was performed in a stainless steel vessel. Drying was carried out under ambient conditions (25°C, 60% relative humidity) for 24 h. These samples were denoted as G.
4. 5-ASA was granulated with the polymer dispersion(s) in a high-shear granulator until an appropriate wet mass was achieved. The process parameters were as follows: chopper speed, 3,000 rpm; impeller speed, 1,000 rpm; rate of liquid dosing, 6 mL/min. The wet mass was forced through a 1.2-mm mesh sieve to achieve a definite range of particle size. These samples were denoted as GD.

Contact Angle Measurements

The wetting properties of the initial materials and their mixtures were determined with the OCA 20 Optical Contact Angle Measuring System (Dataphysics Instruments GmbH, Filderstadt, Germany). Ten parallel measurements were made. Contact angles were measured with the use of distilled water and diiodomethane as polar and apolar test liquids, respectively, which were dispensed by means of an automatic syringe. The tablets were compressed with a hydraulic press equipped with a highly polished stainless steel punch and die (Specac Inc., Graseby, UK) 13 mm in diameter, under a force of 50 kN. The Wu equation was used to calculate the surface free energy. The spreading coefficient (S_{12}) was determined according to the following equation (21):

$$S_{12} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d}+\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}-\frac{\gamma_1}{2}\right] \quad (1)$$

where γ^d refers to the disperse component of surface free energy, and γ^p refers to the polar component.

Table III. Spreading Coefficient

Composition	Spreading coefficient (S_{12})
5ASA(1)+E RS PO(2)	−26.25
5ASA(1)+E RL PO(2)	−26.40

5-ASA 5-aminosalicylic acid, *E RS PO* Eudragit® RS powder, *E RL PO* Eudragit® RL powder

Water Uptake

Water uptake was determined with an Enslin apparatus, consisting of a glass filter and pipette, with an accuracy of 0.01 mL. The tablets were measured with analytical accuracy prior to being placed onto the filter, and the water uptake was recorded in milliliters at predefined time points. Three parallel measurements were performed.

Dissolution Tests and Release Modeling

Dissolution tests were carried out in an Erweka DT 700 dissolution apparatus (Erweka GmbH, Heusenstamm, Germany), using a paddle method. The dissolution medium was 900 mL of phosphate buffer solution of pH6.8 (adjusted according to the Ph. Eur.). The dissolution temperature was maintained at 37±0.5°C, and the rotation speed was set at

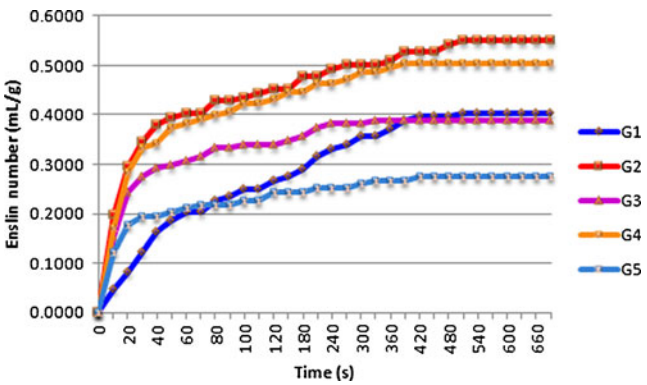

Fig. 1. Water uptake of wet-granulated samples prepared with water

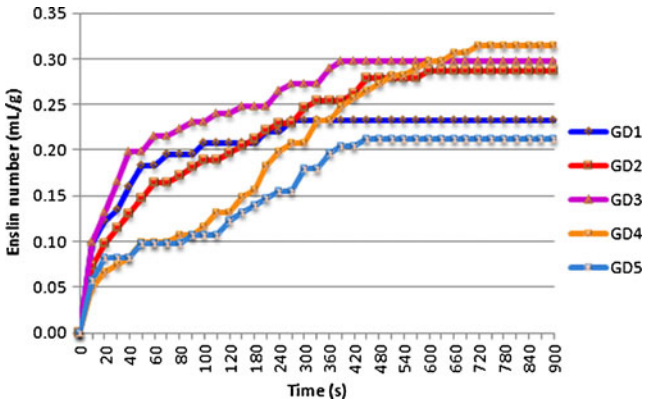

Fig. 2. Water uptake of wet-granulated samples prepared with polymer dispersions

50 rpm. Samples (5 mL) were automatically collected from the dissolution medium at 1, 2, 3, 4, 5, 6, 7, and 8 h. Three replicates were tested for each tablet formulation batch. Absorbance was measured spectrophotometrically (Unicam Helios Alpha, Spectronic Unicam, Cambridge, UK) at λ_{max}= 331 nm.

The resulting dissolution data were subjected to statistical analysis. Mathematical models were used to describe the dissolution profiles of 5-ASA from the matrices. Several mathematical equations were applied to find the one best characterizing the drug release.

Microscopic Structure of the Granules

Photographs of wet-granulated samples were taken with the aid of a scanning electron microscope (SEM) (Hitachi 4700, Hitachi Ltd., Tokyo, Japan). A sputter coating apparatus (Polaron E5100, Polaron Equipment Ltd., Greenhill, UK) was used to induce electric conductivity on the surface of the samples. The air pressure was 1.3–13 mPa.

Table IV. Formulations Dissolving According to the Korsmeyer–Peppas Model

Sample	*k*	*n*	R^2
DC1	10.4439	0.568	0.9995
DC3	18.6222	0.723	0.9960
DC5	11.7439	0.641	0.9978
G5ASA1	10.7166	0.520	0.9995
G5ASA3	13.1529	0.780	0.9997
G5ASA5	11.6521	0.512	0.9960
G1	12.4556	0.567	0.9990
G5	17.5289	0.642	0.9951
GD1	9.9416	0.630	0.9994
GD2	13.2166	0.611	0.9983
GD3	14.3930	0.623	0.9996
GD4	10.8783	0.597	0.9996
GD5	9.6666	0.607	0.9964

k rate constant, *n* release exponent, *DC* direct compression, *G5ASA* 5-aminosalicylic acid granulated with water, *G* mixture of 5-aminosalicylic acid and polymer(s) granulated with water, *GD* 5-aminosalicylic acid granulated with polymer dispersion(s)

Table V. Formulations Dissolving According to the Hopfenberg Model

Sample	*k*	*n*	R^2
DC2	0.1337	2	0.9936
DC4	0.1207	2	0.9924
G5ASA2	0.1268	2	0.9919
G5ASA4	0.1230	2	0.9995

k rate constant, *n* release exponent, *DC* direct compression, *G5ASA* 5–aminosalicylic acid granulated with water

RESULTS AND DISCUSSION

Contact Angle Measurements

The measurement of contact angles revealed that 5-ASA is polar and, with the presence of the same amount of highly water-insoluble polymers, did not cause a dramatic decrease in the polarity (Table II). The calculated spreading coefficient indicated that the polymer spreads on the surface of 5-ASA (Table III). Nonetheless, the fine polymer particles did not evenly cover the API crystals with their large surface and could therefore presumably not greatly reduce the polarity of the API. Knowledge of the surface free energy permits a deeper insight into how a material behaves during wetting. This property is crucial because the extent of wetting of a solid surface influences the dissolution: If there is no wetting, the solid system will not dissolve (22).

Water Uptake

The determination of water uptake kinetics is highly recommended prior to formulation as this influences the dissolution. Water was taken up more rapidly by the samples prepared by the wet granulation of the mixture of API and polymers than by the samples prepared by the granulation of the API with aqueous polymer dispersions. The curves revealed that the wetting rate was more uniform in the case of the wet-granulated samples (Fig. 1), while the more compact structure of the granules produced from the dispersions resulted in a slower water uptake due to the prevailing hydrophobic features (Fig. 2). For the wet-granulated samples prepared from the aqueous dispersions, the water uptake capacity correlated with the dissolution rate.

Dissolution Study and Release Modeling

The Korsmeyer–Peppas model was found to be the most suitable for the fitting of the drug dissolution curves in the majority of the cases, where not only diffusion but also erosion was involved in the drug release (Table IV). In four cases,

Table VI. Characterization of Exponent of Korsmeyer–Peppas Equation

Release exponent (*n*)	Drug transport mechanism
0.5	Fickian diffusion
$0.5<n<1$	Non-Fickian transport
1	Case II transport
$n>1$	Super case II transport

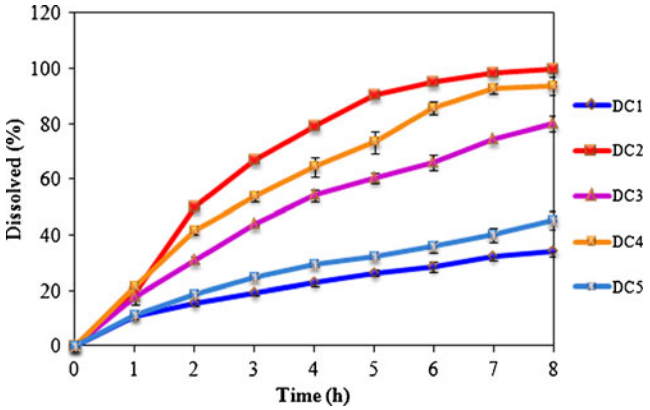

Fig. 3. Dissolution curves of tablets prepared by direct compression

however, when heterogeneous erosion occurred on the surface of the tablet, the Hopfenberg model was the most suitable (Table V).

The release exponent (n) was $0.45<n<0.89$ (for cylindrical tablets), and the diffusion mechanism was therefore anomalous; the drug transport mechanism was non-Fickian diffusion. This indicated the coupling of erosion and diffusion mechanisms, leading to drug release controlled by multiple processes.

Korsmeyer–Peppas Model

This model, a semiempirical model that can be used to analyze data on drug release from polymers (23), implies that the fractional release of drug is exponentially related to the release time, *i.e.*, a power law equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t/M_∞ is a fraction of drug released at time t, k is the rate constant, and n is the release exponent.

Fickian Diffusion (or Diffusion-Controlled Drug Release)

The equation of Fick's second law:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{3}$$

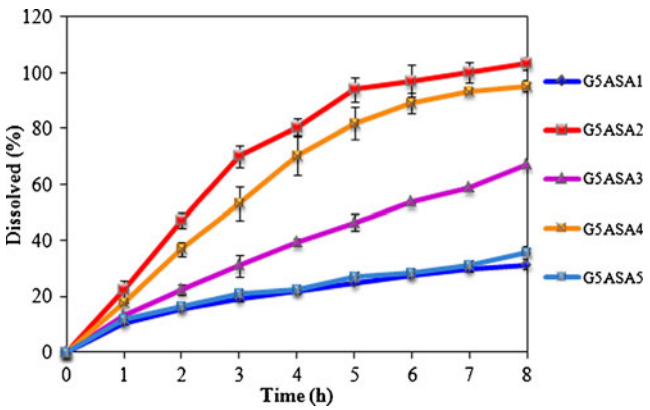

Fig. 4. Dissolution curves of tablets containing polymers in the external phase

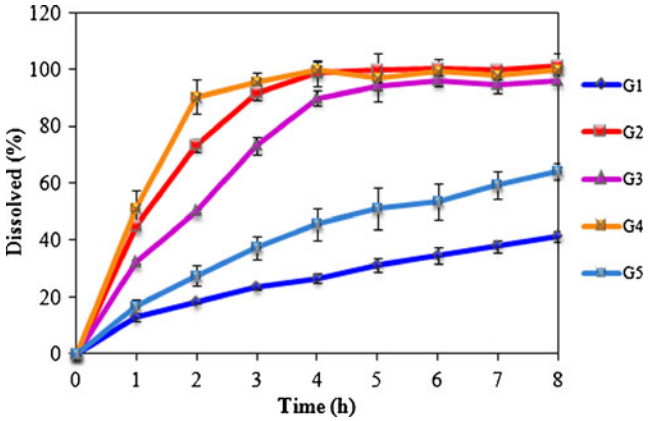

Fig. 5. Dissolution curves of wet-granulated samples prepared with water

can be used to express the diffusion of a drug from a polymer in the form of a plane sheet of thickness. D is the diffusion coefficient of the drug, and C is the concentration of the drug.

Crank's solution (24) of this equation for the initial and boundary conditions ($t=0$; $-Lx<L$; $C=C_0$ and $t>0$; $x=\pm 2L$; $C=C_1$) is:

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{L^2}\right)^{\frac{1}{2}}\left\{\pi^{-\frac{1}{2}} + \sum_{n=1}^{\infty}(-1)^n ierfc\left(\frac{nL}{\sqrt{Dt}}\right)\right\} \tag{4}$$

where M_t is the total amount of substance diffused from the sheet at time t, M_∞ is the corresponding quantity after an infinite time, and ierfc is the integrated error function. For positive t values, ierfc approximates to 0, and we obtain

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

where $k = 2\frac{D}{\sqrt{\pi L^2}}$.

Non-Fickian Diffusion

For diffusion that deviates from the Fickian equation, such as drug release from swellable polymer systems, the same equation can be used, where k is now an experimentally determined parameter characteristic of the structure and

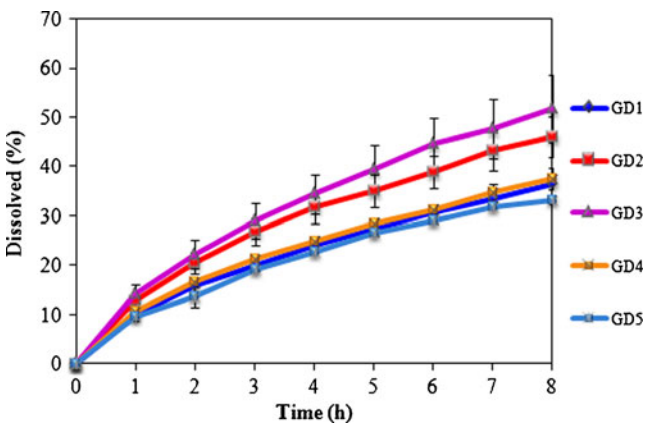

Fig. 6. Dissolution curves of wet-granulated samples prepared with polymer dispersions

Fig. 7. Morphology of granules prepared by wet granulation with water (**a** G3, **b** G4, **c** G5)

geometry of the dosage form. Peppas used an n value to characterize different release mechanisms (Table VI) (25).

The equation was later modified to accommodate the lag time (T):

$$\frac{M_t}{M_\infty} = k(t - T)^n \tag{6}$$

Hopfenberg Model

This model can be used to analyze the release of drug from surface-eroding devices. Hopfenberg developed an equation describing the drug release from several geometries (slabs, spheres, and cylinders) displaying heterogeneous erosion (26):

$$\frac{M_t}{M_\infty} = 1 - (1 - kt)^n \tag{7}$$

where M_t/M_∞ is the fraction of drug released at time t, k is the rate constant, and n is the release exponent. k is equal to k_0/C_0A_0, where k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix, and A_0 is the initial radius of a sphere or a cylinder or the half-thickness of a slab. The value of n is 1, 2, and 3 for a slab, a cylinder, and a sphere, respectively.

During the design of the present study, the directly compressed formulations were intended to serve as comparators. Depending on the permeability of the applied polymer, the degree of release achieved was nearly complete (highly permeable compositions) or incomplete (formulations with low permeability) (Fig. 3). Formulations with lower permeability (DC1 and DC5) and the formulation containing polymers in a ratio of 1:1 followed the Korsmeyer–Peppas model, where both diffusion and erosion occur. The Hopfenberg model was applicable for the tablets prepared with a high amount of E RL PO (a highly permeable polymer).

The tablets containing wet-granulated API and polymers in the external phase exhibited a similar dissolution profile to that of the directly compressed samples: the highly permeable matrices were described by the Hopfenberg model, and the remaining formulations by the Korsmeyer–Peppas model. The latter formulations were associated with lower levels of dissolution (a 3–13% reduction in the total amount of API released) (Fig. 4).

Wet granulation resulted in significant and somewhat unexpected changes, each wet-granulated formulation generally releasing more API than the amount released by the directly compressed samples. The samples containing a higher amount of E RS PO (G1 and G5) could be described by the Korsmeyer–Peppas model, while the highly permeable matrices provided a fast, burst-like dissolution that could not be described by any mathematical model (Fig. 5). These formulations are therefore not suitable for the achievement of extended drug release.

Prolonged drug release was observed for the aqueous dispersions, which served as binder and matrix former: All of these formulations displayed an approximately 50% decrease in the total amount of drug released as compared with the directly compressed samples, and each of the dissolution curves could be fitted with the Korsmeyer–Peppas model (Fig. 6). These findings indicated that the use of aqueous polymer dispersions allows extended and steady drug release.

Morphology of Granules

The SEM pictures revealed that some of the initial orthorhombic crystals of 5-ASA remained intact, but rounded particles also developed during the wet granulation with water

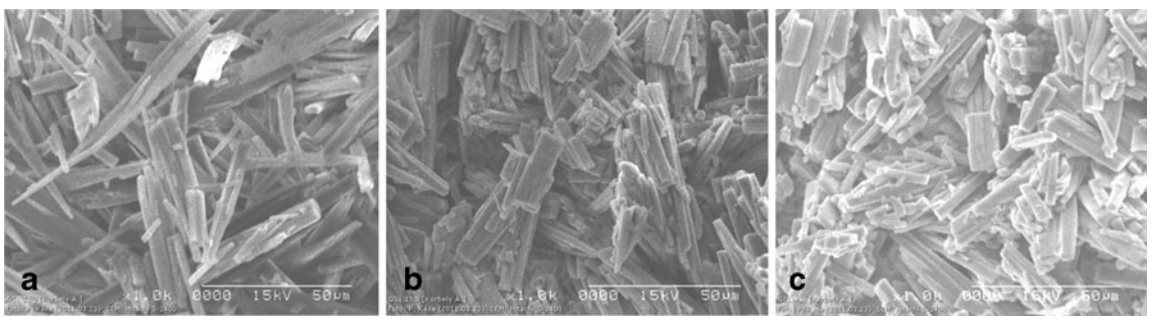

Fig. 8. Morphology of granules prepared by wet granulation with polymer dispersions (**a** GD3, **b** GD4, **c** GD5)

(Fig. 7). The polymers formed an amorphous network. On wet granulation with the polymer dispersions, it was observed that the 5-ASA was converted into sharp, needle-like crystals as a result of rapid recrystallization (Fig. 8). Some 5-ASA crystals were not covered by the thin polymer film layer because of the relatively large amount of 5-ASA. The polymer particles dispersed with high specific surface area were homogeneously distributed in the bulk, and this contributed to film formation. It is presumed that the aqueous dispersion formed a film in the granules, providing them with a compact inner texture and consequently prolonged drug release. Coalescence of latex particles could occur in the dispersions and a relatively continuous film layer could form. This film was able to retain the 5-ASA and prolong dissolution. In contrast, such a process could not occur (or only partially) in the solid polymers where there was insufficient moisture for the complete solvation of the polymeric chains, and the linkages could not form to retain the 5-ASA molecules and protect them, despite the higher amount of polymers. This draws attention to the fact that an appropriate ratio of the polymers in the matrix is a critical point during formulation.

CONCLUSIONS

This study focused on how different granulation methods affect dissolution and its kinetics from inert matrix systems. The polymers applied were designed to ensure time-controlled release. The study revealed that the properties of the excipients can provide tailored drug release, but the pharmaceutical processing method can also contribute to the rate of drug release. Consequently, a wet granulation technique, which involves only granulation of the active compound (*e.g.*, to improve its physical properties) and the application of matrix-forming polymers as an external phase during tableting, may result in a highly similar profile to that observed with directly compressed tablets. Nonetheless, wet granulation affecting both the active substance and polymer excipients may accelerate the dissolution process. In contrast, the use of matrix formers in aqueous dispersions, which simultaneously function as binding materials in the granulation, can lead to prolonged release. Thus, if more retarded drug release is required, this kind of process can promote a long-lasting drug dissolution effect. It is noteworthy that the matrix systems with low permeability released the API according to the Korsmeyer–Peppas model, *i.e.*, diffusion was the determining mechanism during dissolution, while the Hopfenberg model was applicable to the higher water-permeable matrices as a result of the surface erosion.

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