Drug Development and Industrial Pharmacy, 2011, 37(4): 456–464

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.522191

informa
healthcare

ORIGINAL ARTICLE

Suitability of a flat die press for the manufacture of pharmaceutical pellets by extrusion/spheronization

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Abstract

Background: Flat die presses are commonly used for the compaction of food, wood, waste, feedstuff, and chemicals. Because of their large capacity, low price, and high production speed, flat die presses represent a promising alternative for conventional extruders used in the pharmaceutical industry. In this work the feasibility of using the flat die press 14-175 for the manufacture of pharmaceutical pellets by extrusion/spheronization was investigated. *Method*: Pellet formulations containing different model drugs (theophylline, paracetamol, hydrochlorothiazide, or furosemide) and excipients (lactose, mannitol, dicalcium phosphate dihydrate, or starch) with different solubility properties were produced using κ-carrageenan as pelletization aid. Pellets with high and low drug strength were tested. The prepared pellet formulations were assessed in terms of size, size distribution, shape, and release properties. *Result*s: All pellet formulations showed a high yield of the pelletization process and a narrow size distribution. The median aspect ratio was approximately 1.1 indicating acceptable roundness with exception of the pellets produced with high dose of furosemide because of the small-sized needle-shaped active ingredient. The dissolution profiles of the produced formulations showed fast drug release with low standard deviation thus suggesting good batch uniformity. *Conclusion*: The flat die press is a promising choice for the production of pellets by wet extrusion/spheronization with high formulation robustness.

Key words: Aspect ratio, dissolution, equivalent diameter; κ-carrageenan, tensile strength, 10% interval

Introduction

Pharmaceutical pellets can be defined as isometric agglomerates having a narrow size distribution and a smooth surface structure[1]. Typical mean diameter for pellets produced in the pharmaceutical industry varies in the range between 300 μm and 2 mm. As a well-established multiparticulate dosage form, pellets are gaining increased interest in the pharmaceutical field because of their several benefits over monolithic dosage forms. The reduced or eliminated risk of dose dumping and the homogenous distribution in the GI tract leading to maximized drug absorption, limited peak plasma fluctuations, and minimized irritation of mucosa resulting from high local concentration of some active ingredients encountered in case of single-unit dosage forms are well-known benefits of multiparticulate drug delivery systems[2,3,4]. Furthermore, the feasibility of producing dosage forms with different drug strengths starting from the same pellet batch by simply varying the capsule fill weight[5] or the percentage of pellets in a multiparticulate tablet as well as the possibility of combining several incompatible active ingredients in one dosage form or mixing pellets with different release properties to achieve a desired liberation profile and hence allowing high therapeutic flexibility make these systems an attractive choice for pharmaceutical formulators. The excellent flow properties of pellets are also quite beneficial for a reproducible die or capsule filling leading to uniform drug content[6]. Pellets also show the big advantage of spherical shape and smooth surface over irregular-shaped granules, which are key factors for a simple and efficient film coating with lower amount of the coating agent needed[4]. Last but not least a relatively rapid, gradual and to some extent predictable gastric emptying of small particles independently of the feeding state was associated with minimal influence on the transit time in the upper intestine and lowered inter- and intra-subject variability

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(Received 21 May 2010; accepted 5 Sep 2010)

of drug plasma concentration compared with conventional single-dose solid forms[3,7,8].

Various methods are used to produce pellets such as direct pelletization, spray layering, spray congealing, tableting, and extrusion/spheronization[4,9–18].

The production of pellets through extrusion/spheronization is a well-established technique in the pharmaceutical industry and is particularly advantageous over most other methods in terms of robustness, good reproducibility, feasible high drug loading, as well as the high density and the narrow size distribution of the pellets obtained with this method. Moreover, the continuous nature of the extrusion process is particularly profitable for a high throughput when coupled with multiple spheronizers operating in parallel[5,19].

Extruders are generally classified according to the way the pressure is applied to force the wetted mass through defined openings into screw extruders, sieve- or basket-type extruders, roll extruders, and ram extruders.

Flat die presses fall in the category of roll extruders and are commonly used in the food, plastic, chemical, and recycling industries for the compaction and pelletization of wood, fertilizers, feeding stuff, chemicals, as well as the production of substitute refuse-derived fuel. The operating principle of flat die presses lies in forcing a bulk product through a flat die plate with defined orifices by means of a rotating roller. The resulting extrudates are then cut with a simultaneously rotating knife to the desired length.

Because of their high capacities, high production speed, reduced costs, and limited place requirements, flat die presses represent attractive alternatives for conventional extruders. Preliminary studies using specially designed plates with small die openings revealed the potential use of the flat die press 14-175 for preparing pharmaceutical extrudates[20]. In this work, the feasibility of using the mentioned flat die press for the preparation of small pharmaceutical pellets by wet extrusion/spheronization was investigated.

The flat die press 14-175

The flat die press 14-175 (Figure 1) is a laboratory die press developed by the company Kahl for small production-scale and research purposes. It consists of a feeding system (F), a processing area (P), a gearbox (G), and a control unit (C).

The feeding system is illustrated in Figure 2a and consists of a reservoir tank (RT) from which the previously wetted mass is transferred to two feeding screws (FS). The reservoir tank contains a stirrer (ST) to avoid product bridging. The feeding screws and the stirrer are driven by the same motor (M) and rotated simultaneously. The bulk material is fed volumetrically into the processing area.

The processing area (Figure 2b) includes two rollers (R) with a diameter of 130 mm and breadth of 29 mm and a die plate (DP) of 175 mm diameter. The two rollers

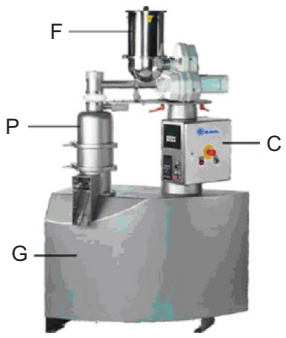

Figure 1. The flat die press 14-175: (F) feeding system, (P) processing area, (G) gearbox, (C) control unit.

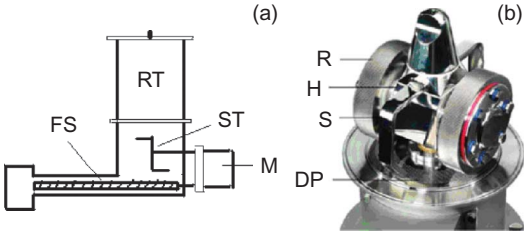

Figure 2. (a) Feeding system: (RT) reservoir tank, (FS) feeding screws, (ST) stirrer, (M) motor; (b) processing area: (R) roller, (H) roller head, (S) scraper, and (DP) die plate of the flat die press 14-175.

are fixed to the two sides of a roller head (H). The surface of the rollers is ribbed to avoid slippage and to ensure a proper material uptake. The roller head sits on an axis and is fixed to it using fitted keys. The roller head is driven by the axle thus inducing the rotation of the rollers over the die plate. The rollers are also freely rotatable. Two scrapers (S) are mounted on the roller head.

The die plate is fixed to the casing and lies under the rollers. Die plates (Figure 3a) are made of a non-corrosive hard material to withstand the high pressure and friction during processing. The die plate is changeable and consists of a flat disk with a high number of dies (up to 9818 for a plate with 0.4 mm die diameter).

The dies for all plates are cylindrical with a conical inlet. The outlets can be tiered to achieve the desired path length while maintaining a sufficient plate thickness to withstand work conditions (Figure 3b). The breadth of the die strip is 29 mm.

The control unit consists of two control windows: one for the feeding system allowing the variation of the rotational speed of the feeding screws and another for the processing area controlling the speed of the axle and consequently that of roller and the knife.

Working principle

The bulk product is delivered from the feeding system through the discharge pipe to the processing area whereby a material layer is built. The rollers roll over the material layer compressing it and forcing it into the press channels leading to the formation of strands which are

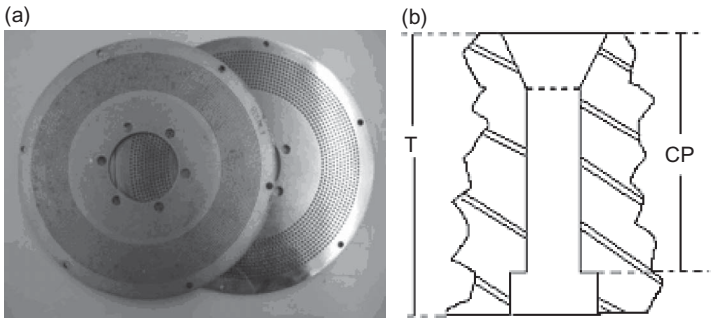

Figure 3. (a) Examples of the die plates supplied with the flat die press 14-175; (b) schematic of the compression channels: (T) thickness of the plate and (CP) compression path.

cut upon leaving the lower side of the die plate to the desired length using a knife with adjustable distance to the plate through the addition of metal rings with different thicknesses. The distance between the rollers and the die plate is also adjustable. Larger space between the two compression elements (roller and die plate) leads to a thicker product layer and higher pre-compression before passing through the dies.

The extrudates fall down over a rotating dish and are driven by a centrifugal force to the outlet of the die press.

The mechanism of extrusion in the die press is illustrated in Figure 4. After a material layer is built on the die plate, the ribbed roller surface allows the entry of the material under the roller leading to a pre-compression followed by forcing the material in the dies where it is subjected to a friction force from the die walls. The process is continued until the compression force through the die is higher than the friction force and a strand is formed[21]. The friction force depends on the roughness of the dies, the friction coefficient between the plate and the compressed material, the side pressure working against the expansion of the extrudates, and the surface area of the die.

The extrusion process in the flat die press can be influenced through a number of factors such as the properties of the material subject to extrusion, the moisture content of the worked mass, the feeding rate, the distance between the rollers and the die plate, the distance between the rollers and the knife, the length of the extrusion channels, the diameter of the dies, the type of metal, the processing of the rollers and the die plate, and the friction value of the press channel walls[22,23]. In this study, the process parameters were kept constant and the versatility and formulation robustness of the flat die press were investigated. Various formulations containing different model drugs and excipients with different solubilities were tested. Pellets with low and high drug strength were produced. The prepared pellets were assessed in terms of size, size distribution, shape, and drug release.

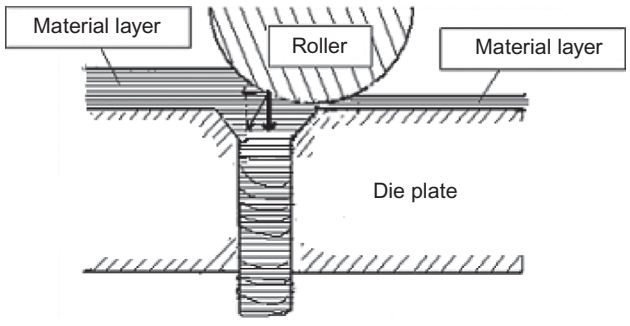

Figure 4. Schematic illustration of the extrusion process in the flat die press.

Materials and methods

Materials

The materials used were theophylline monohydrate (BASF, Ludwigshafen, Germany), paracetamol BP/PH EUR/USP Powder APC 178 (Atabay, Gebze, Turkey), hydrochlorothiazide (Unichem, Mumbai, India), furosemide PH EUR (Arandy, Hyderabad, India), κ-carrageenan (Gelcarin® GP 911 NF; FMC, Philadelphia, PA, USA), α-lactose monohydrate (Granulac® 200; Meggle, Wasserburg, Germany), mannitol 60 (Roquette, Lestrem, France), dicalcium phosphate dihydrate (Dicafos® C92-14; Chemical Fabric Budenheim, Budenheim, Germany), starch (Meritena® 142; Tate and Lyle, Saint Nicaise, France), and deionized water.

Methods

Characterization of the active ingredients

Particle size. The particle size of the active ingredients (n = 3) was determined using a laser diffraction system (Helos/KF-Magic; Sympatec GmbH, Clausthal-Zellerfeld, Germany) coupled with a dry dispersion device (Vibri, Rodos T4.1; Sympatec GmbH) at a feed rate of 80%. The data were analyzed using the corresponding analysis software (Helos; Sympatec GmbH).

Morphology. The particle shape of the active ingredients used was examined using scanning electron microscopy (LEO VP 1430; Carl Zeiss, Jena, Germany). Before scanning, the dried samples were sputter-coated with

gold for 180 seconds under argon (Agar Manual Sputter Coater B7340; Agar Scientific, Stansted, UK).

Production of pellets by extrusion/spheronization

Four pellet formulations with high drug strength (Table 1) and twelve pellet formulations with low drug strength (Table 2) were produced by extrusion/spheronization.

The dry powders were mixed (2 kg) in a laboratory-scale blender (LM; Bohle, Ennigerloh, Germany) for 30 minutes at 35 rpm, then every 500 g was wetted with different amounts of deionized water for each formulation using a high shear mixer (Mini-MGT; Bayer, Leverkusen, Germany) for 5 minutes at 420 rpm. The wetted mass was supplied to a flat die press 14-175 (Amandus Kahl, Reinbek, Germany) at a feeding screw rate of 100 rpm and extruded at a roller speed of 30 rpm through a flat plate with 5049 dies of 0.6 mm diameter and 1:3 length to diameter ratio. The distance between the rollers and the die plate was adjusted to 0.5 mm and that between the die plate and the knife to 3 mm. Collected extrudate batches of approximately 300 g were transferred into a spheronizer (RM300; Schlueter, Neustadt/Ruebenberge, Germany) and were spheronized for 6 minutes at a temperature of 25°C and a spheronization speed of 1500 rpm. The resulting pellets were then transferred to a fluid bed dryer (GCPG1; Glatt, Dresden, Germany) and dried for 20 minutes at 60°C. The amount of water leading to the roundest pellets for each formulation is shown in Tables 1 and 2. The optimized pellet batches were used for further characterization. Additionally, the formulation with 80% hydrochlorothiazide was produced in triplicate.

Table 1. Pellet formulations with high drug strength and amount of water used for extrusion/spheronization based on the weight of solid components.

Ingredients (%)	The	Par	Hyd	Hyd-b	Hyd-c	Fur
Theophylline	80					
Paracetamol		80				
Hydrochlorothiazide			80	80	80	
Furosemide						80
κ-Carrageenan	20	20	20	20	20	20
Deionized water	52	50	52	52	52	54

Characterization of the prepared pellets

Yield of the pelletization process. The yield of the pelletization process (i.e., the fraction of pellets with a diameter between 400 and 1000 μm) was determined using a sieving system (Retsch, Haan, Germany) coupled with a vibration apparatus (AS200 control; Retsch) at an amplitude of 1.5 over 3 minutes.

Image analysis. The particle size and particle size distribution (mean and median Feret's diameter, median equivalent diameter, and 10% interval) as well as the shape factors (roundness factor and aspect ratio) were determined with the help of an image analysis system consisting of a stereo microscope (Leica MZ 75; Leica, Cambridge, UK), a ring light with cold light source (Leica KL 1500), a digital camera (Leica CS 300 F), and an image-analyzing software (Qwin; Leica). Five hundred pellets of the chosen yield size fraction of each pellet formulation were analyzed at a suitable magnification (1 pixel = 7 μm). For each pellet, 64 Feret's diameters and the projected area (A) were measured. The equivalent diameter was quoted as $d_{eq} = \sqrt{(4A/\pi)}$ and the 10% interval was calculated as the percentage of pellets with a dimensionless diameter (obtained by dividing the individual equivalent diameters by their median $d_d = d_{eq} / d_{eq50}$) between 0.9 and 1.1[24].

The aspect ratio was calculated as the ratio between the maximum Feret's diameter and the Feret's diameter perpendicular to it. The roundness factor was quoted as the ratio of the particle area A to the area of a sphere with a diameter equal to the maximum Feret's diameter d_{max} of the measured particle: $\text{Roundness} = A/\pi(d_{max}/2)^2$.

Mechanical strength. The mechanical properties of pellets were characterized using a texture analyzer (TA.XT2i; Stable Micro Systems, Godalming, UK) at a loading rate of 0.01 mm/s. The fracture force (F) of 55 pellets per formulation was determined as the first peak of the recorded force displacement curve. The diameter (d) of each pellet in the crushing direction was also determined. The tensile strength of the pellets was calculated after introducing the correction factor suggested by Shipway and Hutchings[25] according to the formula $\sigma = 1.6F/(\pi * d^2)$.

Table 2. Pellet formulations with low drug strength and amount of water used for extrusion/spheronization based on the weight of solid components.

Ingredients (%)	TheLac	TheMan	TheDic	TheSta	HydLac	HydMan	HydDic	HydSta	FurLac	FurMan	FurDic	FurSta
Theophylline	10	10	10	10								
Hydrochlorothiazide					10	10	10	10				
Furosemide									10	10	10	10
Lactose	70				70				70			
Mannitol		70				70				70		
Dicafos			70				70				70	
Starch				70				70				70
κ-Carrageenan	20	20	20	20	20	20	20	20	20	20	20	20
Deionized water	46	43	56	89	46	44	56	90	48	45	58	92

Release studies. Dissolution studies were carried out according to the monographs of the United States Pharmacopoeia 30 (2007) at 37°C ± 0.5°C using 900 mL of the appropriate medium and the appropriate apparatus (Sotax AT6; Sotax AG, Basel, Switzerland) for each substance (Table 3).

Results and discussion

Amount of water needed for extrusion/spheronization

Pellets were successfully obtained with all tested formulations at high and low drug strength. The amount of water needed for extrusion varied between the different formulations and was as expected higher for the formulations containing poorly soluble ingredients (Tables 1 and 2). Thus, high-dose formulations containing the poorly soluble active ingredients hydrochlorothiazide and furosemide required a higher amount of water than that needed for the formulation with the more soluble paracetamol. The same applied for the formulations with low drug strength with less amount of water required for the extrusion of formulations containing lactose and mannitol as soluble fillers in comparison with those containing the insoluble dicalcium phosphate dihydrate. The formulation prepared with starch as a filling agent required a considerably higher amount of water than all the other studied formulations because of the higher water-binding ability of starch by swelling. An increased amount of water required for the extrusion of poorly soluble ingredient was reported by Baert et al.[26] and was explained by the fact that soluble components dissolve in the liquid phase leading to an increased liquid/solid ratio in the mass subject to extrusion and hence reduced amount of water is required to achieve the same degree of plasticity needed for extrusion. The extrusion time was less than 10 minutes for all formulations which was expected given the high number of extrusion channels in the die plate used (5049 dies).

Table 3. Test conditions used in the release studies of the prepared pellet formulations.

Active ingredient	Medium	Apparatus	Wavelength for UV detection
Theophylline	Deionized water	1	272
Paracetamol	Phosphate buffer pH = 5.8	1	346
Hydrochlorothiazide	Hydrochloric acid 0.1 N	2	272
Furosemide	Phosphate buffer 5.8	1	274

Yield of the pelletization process and size distribution of the prepared pellets

All pellet formulations showed a high yield of the pelletization process (the yield varied in the range 86.5–97%) (Table 4). The median equivalent diameter was between 580 and 730 μm (Figure 5a) and a narrow size distribution was obtained for all prepared pellet formulations as indicated by the values of 10% interval lying above 50%[24] (Table 4). A narrow pellet size distribution leads to a defined specific surface area, which is of vital importance for a reproducible dissolution pattern of the formulated active ingredients[27].

Pellet shape

The pellets were spheronized at a high spheronization speed (1500 rpm for 6 minutes). Pre-experiments with

Table 4. Yield of the pelletization process (size fraction between 400 and 1000 μm), mean and median Feret's diameter, mean and median roundness factor, and 10% interval of the prepared pellet formulations (n = 500).

		Feret's diameter			Roundness factor		
Formulation	Yield (%)	Mean (μm)	CV[a] (%)	Median (μm)	Mean (μm)	Median (μm)	10% Interval (%)
The	96.3	670	11.1	677	0.857	0.858	64.2
Par	97.3	702	10.8	704	0.863	0.868	60.8
Hyd	89.9	701	9.8	707	0.846	0.848	68.4
Fur	97.0	682	12.8	677	0.823	0.827	57.8
TheLac	93.2	692	10.3	695	0.856	0.860	65.4
TheMan	92.4	705	11.1	706	0.856	0.862	66.6
TheDic	95.8	638	10.6	637	0.849	0.849	65.2
TheSta	92.6	630	10.6	628	0.875	0.882	65.8
HydLac	86.5	717	9.8	719	0.852	0.854	68.8
HydMan	90.5	703	12.2	703	0.848	0.850	60.2
HydDic	87.0	648	9.9	652	0.848	0.850	70.6
HydSta	91.1	616	11.4	612	0.866	0.870	62.4
FurLac	95.5	732	10.1	734	0.847	0.847	64.0
FurMan	92.9	753	10.7	750	0.843	0.846	66.2
FurDic	97.0	674	11.8	680	0.843	0.844	63.0
FurSat	94.0	596	11.7	598	0.860	0.864	60.8

[a]Coefficient of variation.

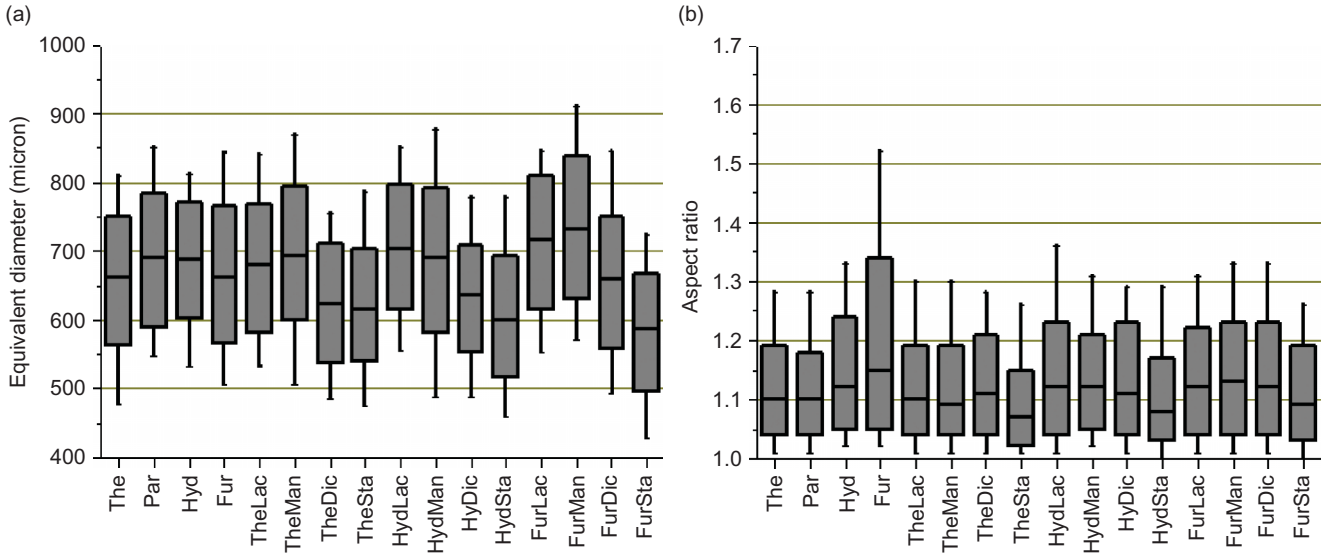

Figure 5. (a) Equivalent diameter; (b) aspect ratio of the prepared pellet formulations (×1, ×10, ×50, ×90, ×99, $n = 500$).

lower spheronization speeds resulted in dumbbell-shaped pellets. This may be explained as suggested by Thommes and Kleinebudde[28] by the fact that the extrusion through a high number of holes results in reduced speed of the extrudates through the dies and hence low shearing of the extruded mass. This leads in the case of κ-carrageenan as pelletization aid to decreased plasticity of the produced extrudates because the water-binding capacity of κ-carrageenan remains high at low shearing (rheodestruction of carrageenan gels being mentioned by Hänsel et al.[29]). Consequently less water is lost to the surface to lubricate the spheronized mass and higher level of energy is needed to break the extrudates at the beginning of the spheronization and to ensure subsequent sufficient plastic deformability throughout the rest of the process.

Good roundness of the pellets is a key factor for a successful subsequent coating and reduced amount of film-forming agent needed to achieve a desired functionality[27]. Several shape factors can be used to assess the roundness of pellets with both roundness factor and aspect ratio as the most powerful distinguishing tools[30]. The roundness factor of the prepared pellets is given in Table 4. The aspect ratio is a simple parameter particularly commonly used to evaluate the roundness of pellets obtained by extrusion/spheronization[31]. A low aspect ratio indicates good roundness of the pellets and generally pellets with a mean aspect ratio less than 1.1 are classified as good whereas those with a mean aspect ratio higher than 1.2 are considered of poor quality[32]. The pellets prepared in this study were of acceptable roundness as expressed by the values of median aspect ratio lying around 1.1 except for those prepared with 80% furosemide (Figure 5b). The poor roundness of the latter could be probably attributed to the small-sized needle-shaped active ingredient (Figure 6). Small needles can interlock during processing resulting in a decreased plasticity of the extrudates subject to spheronization[33]. The pellets prepared with low drug loading of furosemide had markedly lower aspect ratio. A better roundness of the high-strength furosemide pellets could be probably expected upon using higher amounts of the pelletization aid. The negative effect of the needle-shaped active ingredient was not observed in case of the large needle-shaped particles of paracetamol. The formulation with high dose of paracetamol possessed a good roundness with a median aspect ratio of 1.1. It seems therefore that a significant particle interlocking is more likely associated with small needles rather than large ones.

The pellets produced with starch as filler showed particularly low aspect ratio compared with the other formulations. This might be attributed to the higher water-binding capacity of starch through swelling leading to higher plasticity of extruded mass and hence a facilitated deformation during subsequent spheronization.

Mechanical resistance

Sufficient mechanical strength of pellets is necessary for any further handling such as filling into capsules or coating processes as well as to avoid any loss during storage or transportation. The prepared pellet showed sufficient mechanical strength (Figure 7). The type of filler used in the pellets with low drug strength had an influence on their mechanical resistance. The pellets containing the highly brittle dicalcium phosphate dihydrate possessed a higher tensile strength compared with those containing lactose or mannitol. Same observation was made for the pellet prepared with starch as a filling agent.

Drug release

Defined dissolution profile is crucial for a reproducible pharmaceutical bioavailability of the active ingredient

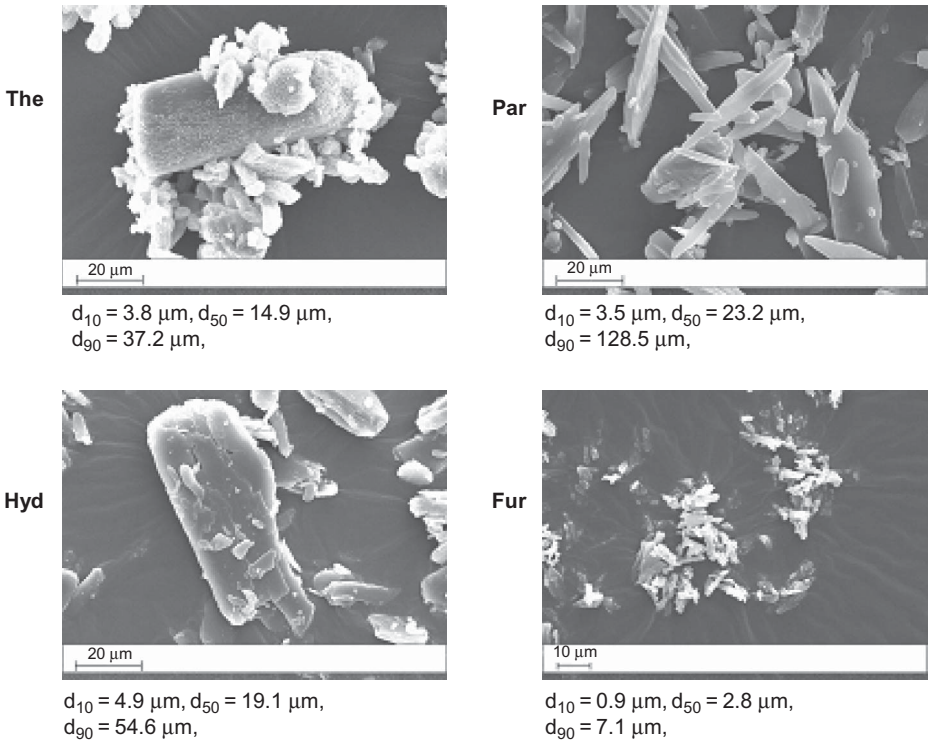

Figure 6. SEM micrographs and particle size of the active ingredients: (The) theophylline, (Par) paracetamol, (Hyd) hydrochlorothiazide, and (Fur) furosemide.

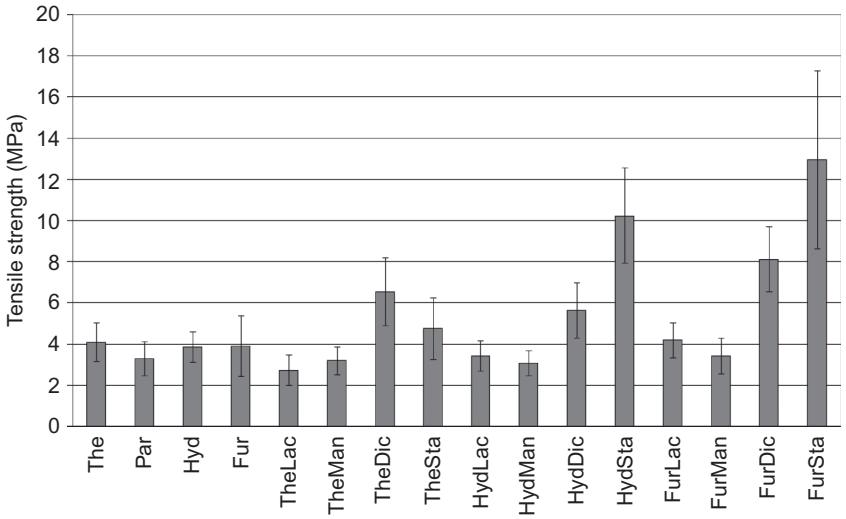

Figure 7. Tensile strength of the prepared pellet formulations (mean and standard deviation, $n = 55$).

being delivered. The dissolution profiles of the high- and low-dose pellets are illustrated in Figure 8. All prepared pellet formulations released the drug rapidly, regardless of the solubility of their active ingredients as expected with pellets made using κ-carrageenan as pelletization aid in general. The standard deviation was low for most formulations indicating batch uniformity. The replicate experiments with the formulation with high strength of hydrochlorothiazide also show good batch conformity (Figure 9).

Conclusion and outlook

The flat die press is a promising choice for the production of pharmaceutical pellets by extrusion/spheronization with high formulation robustness. The pellets obtained in this work showed narrow size distribution, low aspect ratio, and small variation in the release of their active ingredients.

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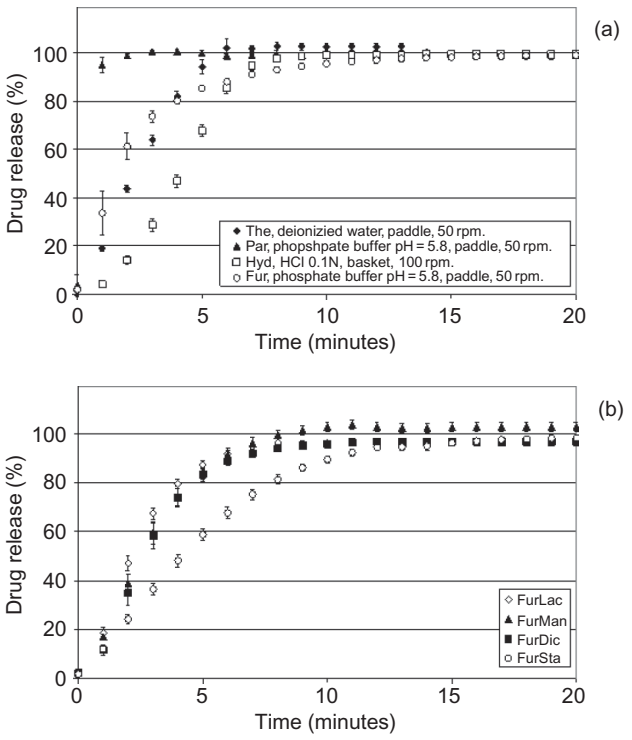

Figure 8. Release profiles of the pellets prepared using the flat die press 14-175: (a) high-dose pellet formulations; (b) pellet formulations with low drug strength ($n = 6$).

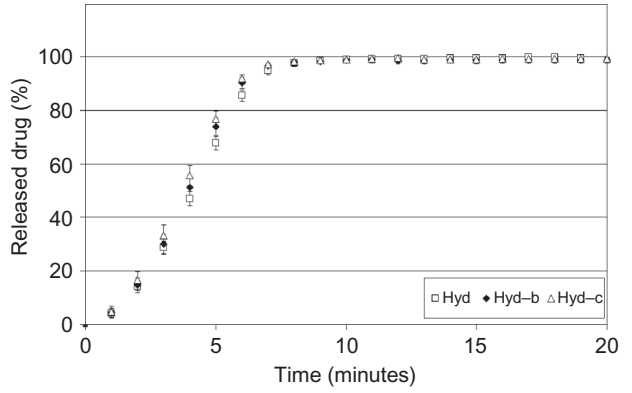

Figure 9. Release profiles of the different replicates of the pellet formulation containing 80% hydrochlorothiazide.

through the high number of dies a higher throughput than that obtained with the twin screw extruder. Moreover, the simple working principle of the flat die press leads to a robust extrusion process. A main disadvantage of the flat die press is, however, the lack of an integrated wet massing, which is not the case of the twin screw extruder. Therefore, when using a volatile granulation liquid it is preferable to use a twin screw extruder to minimize the possible liquid evaporation.

Optimization of the flat die press for pharmaceutical purposes is of particular importance. The dosing system should be particularly improved to avoid the accumulation of the wetted mass on the walls of the reservoir tank and of the cylinder surrounding the dosing screws in case of highly wetted materials. Furthermore, the mounting of the die press is laborious as the adjustment of the distance between the die plate and the knife as well as between the roller and the die requires the addition of distance rings. Thus, variation of these distances in one experiment requires a dismantling of the processing area and the removal of the rollers which is quite laborious. A temperature control of the process area is necessary for heat-sensitive products as well as any hot-melt extrusion intended to be done in this equipment. Further experiments should be done to assess the feasibility of producing extrudates with smaller diameter (with die plate having channels with less than 0.5 mm).

Acknowledgment

The authors thank Dr. Sternowsky and the company Kahl for the supply of the flat die press 14-175 and the die plate used in this work as well as for the delivered technical information.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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