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European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 317–326
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Review article

Roll compaction/dry granulation: pharmaceutical applications

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Received 12 January 2004; accepted in revised form 4 April 2004

Available online 1 July 2004

Abstract

Roll compaction/dry granulation (RCDG) is an agglomeration process of growing importance. New machine generations and improvements in instrumentation and process control have resulted in an increasing number of pharmaceutical applications of RCDG. This literature review illustrates the progress and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.

Keywords: Roll compaction; Dry granulation; Tablets; Excipients; Herbal dry extracts; Immediate release; Controlled release

1. Introduction

Roll compaction/dry granulation (RCDG) is an agglomeration process, which has been known since the end of the 19th century. It is widely used in many industries. Although, RCDG has been used in the pharmaceutical industry since more than 50 years, it has recently drawn increasing attention [1]. The present review article is mainly focused on pharmaceutical applications of roll compaction/dry granulation.

Dry granulation is a controlled crushing of pre-compacted powders densified by either slugging or passing it between two counter-rotating rolls. The advances of roll compaction over slugging are [2,3]:

- Greater production capacity
- More control over operating parameters and dwell time
- Minimal need for powder lubricant

Due to the large pressure exerted in the roll gap, the powder is transformed into a compact. Compaction in a roll press is a continuous process. Friction between the material and roll surface brings the powder towards the narrow space between the rolls (gap), where the powder is exposed to high stresses leading to the formation of a compact. If the rolls are smooth, fluted or knurled, the material will be compacted into dense ribbons (flakes, sheets, strips), whereas pocket rolls will form briquettes.

The space between the rolls, where different mechanisms occur, is generally divided into three zones (Fig. 1): (1), the feeding zone, where the stresses are small and densification is solely due to rearrangements of particles; (2), the compaction zone, where the pressing forces become effective and the particles deform plastically and/or break; (3), the extrusion zone. The transition between the feeding zone and the compaction zone is called the nip or gripping angle (α) [4].

Funakoshi et al. [5] and Miller [3] defined the following requirements for successful roll compaction:

- Adequate powder supply to the gripping zone
- Powder entering the gripping zone must be completely conveyed into the narrowest part of the roll gap
- Compaction pressure should be distributed as uniformly as possible over the entire roll-gripped mass
- Vacuum de-aeration must be adequately and effectively distributed before the nip roll region

Choosing the dry granulation process by roll compaction has product as well as process advantages. In general, a major advantage of dry granulation over wet granulation is the absence of water or any organic solvents. Therefore, this methodology is especially attractive for drugs, which are

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doi:10.1016/j.ejpb.2004.04.014

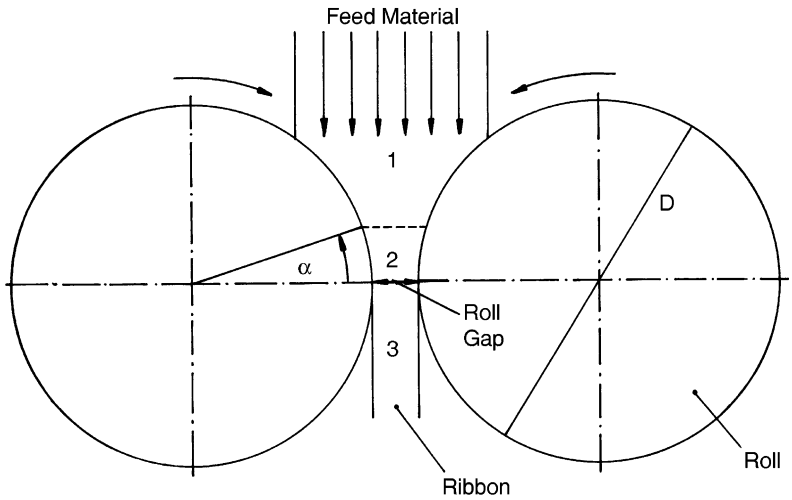

Fig. 1. Roll compactor and different zones: 1, feed zone; 2, compaction zone; 3, extrusion zone.

moisture or heat sensitive. In addition, this process is environmentally friendly. Also the roll compaction technique provides an efficient and easily automated process [6]. The process is easily scalable, which offers conceptual simplicity and low operational costs. However, compaction in a roll press is still not fully understood [4].

Only few models are available in the literature to predict the behaviour of granular materials during roll compaction [7]. In the mid-1960s Johanson [8] developed the first model, which is capable of predicting the material behaviour undergoing continuous shear deformation between the rolls. The material is assumed to be isotropic, frictional, cohesive and compressible. The Johanson model, which was further developed, was widely used for the layout of roll presses [9,10]. Other models summarized by Dec et al. were based on the slab method and on finite element analysis [7]. Nevertheless, to date most current industrial roll compacting practices are largely based on trial-and-error techniques.

The aims of roll compaction/dry granulation are an improved handling of the powders due to a larger particle size and a better flowability. Dust problems are minimised or avoided and the die filling during tableting is improved. Also, this is achievable by increasing the bulk density because less air will escape during tableting process. Sometimes the capping of tablets might also be reduced. Roll compaction/dry granulation can be used, if the drug or the excipient is poorly flowing or sensitive to heat or moisture. It can also be used for densification of powders prior to encapsulation.

2. Parameters

2.1. Equipment

Only few suppliers of roll compactors are established in the pharmaceutical field. The machine design differs between suppliers (Fig. 2) [10,11]. However, important improvements were implemented by different suppliers during the last decades. The suppliers provide machines in different sizes. Furthermore, the process control depends to a certain extent on the layout of the equipment. For example, if the two rolls are fixed, the compaction force will greatly vary with the fluctuating mass flow. In the case of one movable roll the compaction force can be kept constant by changing the gap width in case of fluctuating mass flow. Another important factor is the roll diameter. Since the nip angle is independent from the roll diameter, a higher roll diameter will result in a higher densification at a constant gap width. Therefore, some machine suppliers only offer machines with the same roll diameter but varying roll width, whereas other suppliers offer machines with different roll diameters. Due to the importance of the machine layout, Table 1 assigns the suppliers of roll compactors to papers based on their machines.

Some of the equipment variables are [1,3,4,7,9–11,46]:

- Rolls mounted in a horizontal (Bepex, Freund, Fitzpatrick, Komarek, Sahut-Conreur), vertical (Alexanderwerk) or inclined (Gerteis) position (Fig. 2)
- Two fixed rolls vs. one fixed and one movable roll (adjustable hydraulic force)
- Roll surface: smooth, knurled (fluted, grooved) or pocket design

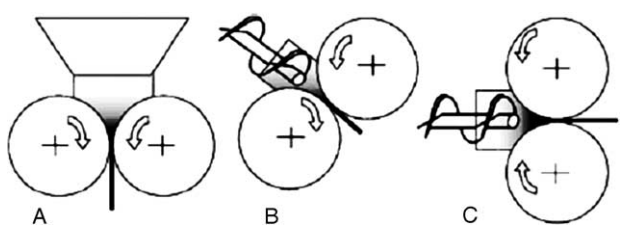

Fig. 2. Configuration of roll compactors (taken from Guigon and Simon [4]).

Table 1
Suppliers of roll compactors and papers based on the respective equipment

Supplier	Published work
Alexanderwerk	Skinner, 1999 [12]
Bepex/Hosokawa	Hakanen, 1993/1995 [13,14]; Salonen, 1997 [15]; Rocksloh, 1999 [16]
Fitzpatrick	Cohn, 1966 [17]; Li, 1990 [18]; Falzone, 1992 [19]; Inghelbrecht, 1997/1998 [20–23]; Gereg, 2002 [6]
Freund/Vector	Funakoshi, 1977 [5]; Parrott, 1981 [2]; Kawashima, 1993 [24]; Sheskey, 1996 [25]; Murray, 1998 [26]; Sheskey, 1999 [27]; Rocksloh, 1999 [16]; Turkoglu, 1999 [28]; Habib, 2000 [29]; Horisawa, 2000 [30]; Ohmori, 2000 [31,32]; Mitchell, 2003 [33]; Zinchuk, 2004 [34]
Gerteis	Lammens, 2000 [35]; Shlieout, 2000 [11]; Rambali, 2001 [36]; Shlieout, 2002 [37]; Bultmann, 2002 [38]; Eggelkraut-Gottanka, 2002 [10,39]; Schiller, 2003 [40]; Freitag, 2003 [41,42]
Hutt	Jaminet, 1966 [43]; Arnaud, 1998 [44]
Komarek	Simon, 2000 [45]; Guigon, 2003 [4]
Sahut-Conreur	Dehont, 1989 [46]; Jerome, 1991 [47]; Hervieu, 1994 [48]

- Sealing system: flat rolls with side seal vs. concavo-convex/rim rolls
- Roll diameter
- Roll width
- Feeding system (gravity feeder vs. force feeder with one or two screws)
- Powder de-aeration unit (Vacuum can avoid leakage of non-compacted powder, compressed air inside the compact, and a disturbance of the feeding by upwards airflow.)

2.2. Process

The main process variables are:

- Compaction pressure/specific compaction force (i.e. compaction force per cm of roll width)
- Speed of feeding screws (vertical vs. horizontal)
- Roll speed

2.3. Formulation

The formulation variables including the use of binders and lubricants as compaction aids will be discussed in the subsequent sections.

3. Pharmaceutical applications

In most cases roll compaction/dry granulation is performed prior to tableting. Thus, the properties of the resulting tablets are of main interest. However, in some studies the granules per se were the focus of interest and, therefore, they were characterised. Only in a few studies the properties of the ribbon were investigated and related to granule and tablet properties.

3.1. Early studies and basic formulations

The first pharmaceutical applications of RCDG were published in 1966 (Jaminet and Hess, and Cohn et al.). In a very informative paper Jaminet and Hess [43] investigated the effect of different binders on the properties of briquettes, granules and tablets. The addition of binders to a lactose starch mixture decreased significantly the amount of non-compacted material. The strength of the briquettes was tested by a bending method. The addition of ethylcellulose increased the strength, whereas carbowax 4000 decreased the strength in all cases. The addition of celluloses changed the strength in different ways, depending on the process parameters during roll compaction and the concentration of cellulose. The addition of a small amount of water resulted in a lower amount of non-compacted material and decreased the strength of the briquettes. The particle size distribution of the granules was strongly dependent on the process parameters during dry granulation and the strength of the briquettes. Strong briquettes resulted relatively in coarse granules. Tablet strength was strongly influenced by the type and amount of added binder. The addition of a lubricant prior to roll compaction appeared to be effective. The authors propose the formulation in Table 2 as a starting point for the development of drug containing formulations.

Cohn et al. [17] used the RCDG technique to optimise the process variables of a basic granulation in which other drugs could be added and directly compressed into tablets. Potassium chloride was selected as the test material. The influence variables studied were the oil pressure during compaction, the roll speed, the feed screw speed and the amount of added moisture. Critical response variables were the amperage of the roll compactor, the amount of non-compacted material and the hardness of the tablets. One of the major difficulties of the compactor was the leakage of powders between roll seals. A simple relationship between

Table 2
Starting formulation for RCDG proposed by Jaminet and Hess [43]

Material	Content (%)
Corn starch	30
Lactose	63
Talc	2
Macrogol 4000	1
Microcrystalline cellulose	4

the variables and the responses did not exist. However, it was possible to find the optimal settings of the influence variables.

In a conventional flat roll compactor the screw feeder cannot adequately deliver the powder to the gripping and the compressing zone because the stationary side seals act as a resistance to the powder flow. Funakoshi et al. [5] studied the factors affecting the distribution of compacting pressure during the process of dry granulation with a roll compactor. The compaction pressure distribution was estimated by measuring the load needed for drilling the ribbon at different places. Lactose powder was used and mixed with small amount of riboflavin as a second pressure indicator. The used rolls were designed as a concavo-convex pair that exactly kept their mutual fit while rotating. The flanges formed by the concavity of the concave roll at both its ends, called rims, were subjected to several experimental variations in the angles of wall slopes, namely, 45,65,75 and 90°. The overall effect was that the pressure of compaction was adjusted uniformly over the whole width of the rolls, and the best result was obtained at a rim angle of 65°. The roll compacting system used here was superior, in the sense of compression uniformity to conventional roll compactors.

Parrott [2] applied RCDG to eight different pharmaceutical powders using a concavo-convex roll compactor under a pressure of 140 kg/cm^2. A ridge height of 7 mm and an angle of 65° resulted in a uniform compression force. The median particle size and the bulk density increased for all materials and the lowest increase was observed for lactose and dibasic calcium phosphate. This was explained by the brittle nature of the respective flakes, which might be fractured in the oscillating granulator to produce a smaller median diameter. The primary effect of compaction was to increase bulk density but little effect, if at all, was noticed on flowability. For lactose and dibasic calcium phosphate the compaction had a negative influence on flowability.

Malkowska and Khan [49] used slugging/dry granulation in order to study the effect of re-compression on the properties of tablets made of different direct compression excipients. Re-compression reduced generally the tablet strength and this reduction was more significant when the initial compaction was carried out at a higher pressure. The re-working potential of the direct compression excipients was calculated by determining the area under the tensile strength/re-compression pressure profile expressed as percentage of the area under the initial tensile strength/pressure profile. The re-working potential depended on the nature of the material and on the initial compaction pressure. The reason for the reduction of tensile strength during re-compression was attributed to the work-hardening and the production of robust granules, which may increase the resistance to deformation compared to the starting material. Interestingly, both types of excipients, plastically deforming (MCC and DC starch) and brittle were capable of being work hardened. The mechanism of work-hardening was observed for RCDG by numerous authors. However, Jerome et al. [47] reported improvements in compactibility of powdered cellulose after RCDG.

3.2. Preparation of directly compressible excipients

An ideal excipient for direct compression is a material with good flowability and compactibility. In many cases, an agglomeration is required to produce a directly compressible excipient. Li and Peck [18] agglomerated maltodextrin by fluidized bed granulation and RCDG. Fluidized bed granulation produced highly porous granules of a low bulk density, whereas RCDG resulted in granules with a significantly low degree of intragranular porosity with high bulk density. The roll compacted granules exhibited a better flowability in terms of gravimetric and volumetric flow rate. From Heckel plots a higher yield pressure was determined for the roll compacted granules indicating a higher resistance to deformation. Tableting of roll compacted granules gave rise to compacts with lower tensile strength which was explained in terms of work hardening. For tablets of the same porosity the roll compacted granules achieved a lower tablet tensile strength.

Mollan and Celik [50] compared five maltodextrins prepared by spray drying, fluidised-bed agglomeration and roll compaction/dry granulation with other commonly used excipients in direct compression. Propranolol hydrochloride was used as an active drug. Low crushing strength and high friability values for the tablets made of RCDG granules indicated a higher sensitivity against the lack of lubricant. The higher yield value for RCDG maltodextrin derived from Heckel plots indicated more brittle deformation behaviour compared to the other types, which behaved more plastically/elastically. In a further study, the same authors [51] compared the tableting behaviour of five maltodextrins prepared by spray drying, fluidised-bed agglomeration and RCDG. The roll compacted maltodextrin was more robust to increased magnesium stearate concentrations than the other maltodextrins, evaluated by the tablet crushing force. This was attributed to a larger surface area, higher bulk density, and more fragmentary failure behaviour for the roll compacted maltodextrin compared with the other maltodextrins.

Cellactose was compared with other lactose–cellulose blends, which were processed by extrusion/spheronisation and by slugging/dry granulation [52,53]. Horisawa et al. [30] produced microcrystalline cellulose granules by different techniques including roll compaction/dry granulation. Beten et al. [54] reported that slugging process had a negative influence on the compactibility of microcrystalline cellulose.

Hakanen and Laine [13] used the acoustic emission during roll compaction to characterise the process. Over-compaction of microcrystalline cellulose could be detected by this method. At a compaction force of 30 kN the product was broken into two pieces and turned yellow at its edges.

This 'capping' phenomenon was noticed by an enhancement of acoustic emission in the region of about 17–23 kHz. In a later study, Salonen et al. [15] showed that the integrated acoustic relaxation emission (ARE) as a function of the compressive force is a characteristic of the compacted powder. They compared microcrystalline cellulose with maize starch and related the ARE to the Young's modulus and the cohesive energy density of the materials. Bultmann [38] reported multiple compaction of microcrystalline cellulose up to ten passes in a roll compactor. The amount of fines could be reduced by multiple compactions. At the same time flow properties were improved and the mean granule size was increased. However, the tablet tensile strength decreased to a high degree with increasing the number of passes. All changes were most pronounced during the first two passes.

Inghelbrecht and Remon [22] compared the influence of the roll compaction process on the granule friability of four different types of lactose with different particle size, bulk density, and morphology using the second order polynomial model. Pressure was the most crucial parameter followed by the roll speed and then the horizontal screw speed. The best quality was obtained at a high pressure with a low horizontal screw speed. However, roll compaction of spray-dried lactose was difficult. A gradual decrease of lactose quality was observed by the following order: α-lactose monohydrate 200 M, anhydrous β-lactose, α-lactose monohydrate 90 M and finally spray-dried α-lactose. In a previous study [20], a non-linear model was required to describe the friability of plastically deforming drum-dried waxy maize starch. Selkirk et al. [55] and Riepma et al. [56] investigated the effects of slugging/dry granulation of lactose on tablet structure. Kochhar et al. [57] evaluated the effects of slugging and recompression on different pharmaceutical excipients and their blends.

3.3. Compaction of drugs and drug formulations

Some drugs have low and inconsistent bulk and tap densities accompanied with very fine and inconsistent particle sizes. If the material also exhibits poor flow properties and poor compactibility, RCDG might be used to overcome the raw material difficulties. Habibet al. [29] used the antimicrobial agent Nisin to evaluate the effect of single, double and triple compaction on a roll compactor. Direct compression was not suitable due to the poor flowability of Nisin, and it produced capping tablets with extensive fragmentation in a subsequent coating process. Three lots of Nisin were used in the study. Although single pass roll compaction improved the material characteristics, at least three passes were necessary to produce acceptable flowability for compression and to minimize the lot-to-lot variability of raw material. With increasing number of roll compaction passes the tablet capping decreased. After three passes, excellent tablets were produced which could withstand the vigorous agitation during coating.

If the dose of a drug is high, direct compression can cause problems, especially for drugs with low bulk density. Required die volume, die filling and de-aeration during tableting are critical. A densification of the powder mixture is beneficial in these cases. Tablets with a fraction of 95.24% ibuprofen were produced using roll compaction/dry granulation [26]. Roll pressure and speed (fixed ratio of roll speed and feed screw speed) were varied on three levels between 30 and 120 kg/cm^2 and 6/9 rpm to 17/30 rpm, respectively. None of the studied compactor variables had a significant effect on tablet crushing strength or disintegration time. Due to the low concentration of excipients in the formula used, the authors proposed that the effect of varying roll compactor machine setting is largely influenced by the compaction properties of ibuprofen. These compaction properties were not further characterised. For dissolution, a statistically significant although small influence of the interaction between roll pressure and speed was observed.

Inghelbrecht and Remon [21] compared seven different types of microcrystalline cellulose (MCC) with ibuprofen as a mainly fragmenting model drug. The addition of 25% of ibuprofen to all MCC types, except to Avicel CE-15 (co-processed product with guar-gum), resulted in a poor granule quality compared to the pure MCC. A progressive increase of the ibuprofen concentration from 25% to 75% improved the granule quality again. It was postulated that a small amount of ibuprofen disturbed the binding properties of the plastic deforming MCC, which was compensated by the fracturing and sintering ability of the drug at higher concentrations. A general conclusion could not be drawn due to the influence of roll compaction on tablet mechanical strength. During tablet production a decrease in the plastic deformation ability was observed for the MCC due to work hardening. A fast drug release was seen for the MCC tablets containing 75% ibuprofen.

Acetaminophen shows elastic deformation and produces weak compacts. Therefore, it is difficult to produce tablets without a prior agglomeration process. Turkoglu et al. [28] studied a RCDG process by varying binder type (HPMC, PEG, Carbopol) and concentration (5,10,20%), the number of roll compactor passes and the addition of microcrystalline cellulose during tableting. The results of the tablet properties (ejection force, crushing strength, friability, and disintegration time) were modelled using artificial neural networks (ANN) and genetic algorithms. Out of 42 experiments, 30 were used to train the network and 12 were used to test the prediction capacity of neural network and genetic algorithm. Genetic algorithm predictions of tablet characteristics were much better than the ANN. Based on these data, an optimisation was performed for an immediate release tablet formulation with 20% HPMC after two roll compaction passes. Skinner et al. [12] optimised a tablet formulation for acetaminophen using RCDG process with fine-particle hydroxypropylcellulose (HPC) as binder. Acetaminophen, MCC and different amounts of HPC

(4,6,8%) were roll compacted at three different compaction pressures (30,40,50 bar). Tablets were produced and evaluated at 5 different compression forces. RCDG increased the average particle size and bulk density in all cases. Capping of tablets was decreased, when roll compaction was performed at higher compaction pressure and/or with a higher HPC level. HPC showed suitable properties as a tablet binder with good physical characteristics. Falzone et al. [19] also used acetaminophen as drug in their investigation to study the influence of roll compactor parameters on particle size distribution and recompression of materials. The effect of the roll compactor parameters depended greatly on the investigated material. Only the compressibility factor of acetaminophen blend could be modelled by a quadratic regression model. All three roll compactor variables, the roll speed, the horizontal feed speed and the vertical feed speed as well as some interactions had a significant effect on the compressibility factor. The mean particle size of the granules was less than or equal to the size of the starting material. SEM studies confirmed that fragmenting of the acetaminophen crystals during roll compaction may lead to this observation. A general model for the materials could not be determined, because the actual effects of the compactor parameters depended on the bonding and deformation characteristics of the compacted material.

Gereg and Cappola [6] developed a method to determine whether a drug candidate, excipient or formulation is suitable for RCDG. Various lactose materials were used as model compounds. Process parameters were determined at laboratory-bench scale, and these parameters were directly transferred to large-scale process equipment. The laboratory-bench scale equipment was a hydraulic press suitable for slugging of the test material. Flat punches of 28.58 mm diameter were used in the milling study. Milling was either performed manually or by a mechanical cone mill using a 1.0 mm sieve or 1.0 and 1.2 mm screens, respectively. The selected compaction pressure was transferred from the hydraulic press to a production-scale roll compactor. Both methods for densifying crystalline lactose resulted in a product with similar density, compactibility and suitable powder flow. In spite of differences in bulk density and Carr index, the two granulation methods were considered to be equivalent for practical purposes. The density and hardness properties of tablets produced using both types of precompacted products were comparable. Recently, Zinchuk et al. [34] used microcrystalline cellulose as model material and solid fraction and tensile strength of ribbons as key properties. The roll compaction process was simulated on a laboratory scale compaction simulator. When compacted to the same solid fractions, real and simulated ribbons exhibited similar compression behaviour and equivalent mechanical properties. Although the simulation could not account for some roll compaction aspects like nonhomogeneous ribbon density and material bypass, it enabled prediction of the effects of critical parameters, such as roll speed, pressure and radius, on the properties of ribbons. Furthermore, constant ribbon solid fraction and/or tensile strength were proposed as scale up factors for the roll compaction process.

Badway et al. [58] compared the chemical stability of an ester prodrug prepared using blends, slugging/dry granulation or wet granulation. Formulations manufactured using the dry and wet granulation processes contained disodium citrate as a pH modifier. Although aqueous wet granulation of a hydrolysable drug is usually avoided, tablets and capsules manufactured by wet granulation were more stable in this case than those manufactured by the dry granulation process. This was attributed to the more uniform distribution of the pH modifier.

3.4. Granulation of inorganic materials

Parrott [2] showed a linear relationship between the logarithm of applied pressure during roll compaction and the bulk or drop density of the resulting granules for both magnesium carbonate and calcium carbonate. At a compaction pressure of 140 kg/cm^2, the bulk density of the granulated magnesium carbonate and calcium carbonate was 3.0 and 2.5 times higher than the bulk density of the starting material, respectively, whereas the flowability was slightly improved after roll compaction.

Freitag and Kleinebudde [41] compared the powder and granule properties and also the tableting behaviour of four types of magnesium carbonate with and without RCDG. It was found that even low specific roll compaction forces were suitable for increasing the mean particle size and to improve the flowability significantly. For all types of magnesium carbonate, the tensile strength of tablets made of granules was lower than those made of starting material. Increasing specific compaction force diminished the tensile strength of tablets and resulted in higher apparent mean yield pressure values derived from Heckel plots. The degree of densification during tableting, calculated as ratio of the relative density of the tablets to the relative density of the feed material (powder or granules), might be related to the achieved tensile strength. A high degree of densification could be realized for starting materials with a low relative tapped density. The partial loss in compactibility required the use of low load during roll compaction. The attempt to densify by compaction only to the degree necessary for nonfriable granules has been described before [6]. This improves the flowability without noticeable effect on the compactibility. A further study [42] described the addition of powdered cellulose as a binder to the magnesium stearate.

3.5. Granulation of herbal dry extracts

Herbal dry extracts often possess a considerable hygroscopicity due to their hydrophilic components like sugars or organic acids. Furthermore, extracts often show poor flow and compression properties making

a compaction/ granulation step necessary prior to tableting [40]. Tablets prepared using plant dry extracts appear heterogeneous and their taste and smell are often unacceptable. This usually requires a film coating using a non modifying polymer like HPMC.

Rocksloh et al. [16] compared tablets made of different plant extracts with those made of granulated plant extracts. The aim was to optimise the crushing strength and disintegration time of a high-dose plant extract tablet. Different types of fillers, disintegrants, lubricants and glidants were used. Furthermore, various batches of plant extracts were dry granulated with and without a lubricant after processing on two different roll compactors at different varied process parameters. Subsequently, crushing strength and disintegration time were evaluated by different techniques using 873 and 406 samples, respectively. Artificial neural networks (ANN) were found to be more successful in characterising the effects, which influence crushing strength and disintegration time than the conventional multivariate method (PLS, partial least squares). The predictive ability of the PLS algorithm was low. The main advantage of ANN might be expressed in its ability to describe nonlinear correlations between input and output data. Such advantage was also reported by Inghelbrecht et al. [20], who evaluated the friability of tablets by a second order polynomial and ANN.

Eggelkraut-Gottanka et al. [10] investigated the influence of roll compaction parameters on granule and tablet quality of a dry herbal extract from St. John's wort (*Hypericum perforatum* L.). Eight different extract batches, four concentrations of magnesium stearate and five compaction forces were studied. The roll compaction/dry granulation resulted in a larger particle size and improved the flowability. Tableting the granulated extract instead of the extract powder effectively reduced not only dust and feeding problems during the tableting process but also prevented capping. The incorporation of 2 and 5% magnesium stearate into the roll compacted extract reduced significantly the sticking of the dry herbal extracts to the punch faces without affecting the crushing strength of the tablets. Formulations containing granulated extracts with 5% magnesium stearate were readily compressed without the need to add magnesium stearate in the external phase of the tableting mixture. Disintegration and dissolution were faster for tablets made of granulated material. Thus, granulated extracts led significantly to improved tablet quality. Dry granulation levelled out the differences in technological properties between the eight dry herbal extracts. In a further study [39] the authors used a 3^3 factorial design to study the influence of the amount of magnesium stearate, the roll compaction force and the granulating sieve size on the mean particle size of granulated extracts and the disintegration time of tablets containing these granulated extracts. Increasing the compaction force and the granulating sieve size resulted in increased mean particle size. The disintegration time slightly increased with increasing magnesium stearate concentration and with decreasing compaction force. The negative effect of magnesium stearate on the disintegration time was reduced after the incorporation into the granulated extract without affecting its lubrication properties.

Schiller et al. [40] compared the stability of film-coated tablets, prepared from non-compacted Eschscholtzia californica Cham. dry extract or prepared from dry granules made of the extract. A lubricant was required for roll compaction to prevent the hygroscopic plant extract material from adhering onto the press rolls. The different batches of the plant dry extract material showed varying compaction behaviours, which was explained by the different origin and composition mainly different organic acids. Exposing the film coated tablets to different relative humidities showed that tablets prepared with non-compacted extract powder adsorbed more water compared to those produced with compacted material. The hygroscopicity of the herbal extracts was decreased after roll compaction due to the decrease in material surface area.

3.6. Immediate release formulations and enhanced dissolution

The effectiveness of nine commonly used polymers as dry binders during the manufacture of an immediate release tablet was investigated [25]. Three binder levels (6.2, 12.5, 25%) and three roll compaction pressures (1, 3, 6t) were studied. High initial roll pressures resulted in tablets with lower crushing strengths and high friability values, particularly at high binder levels. This was attributed to the work-hardening during the first compaction step, which resulted in an increased resistance to deformation during recompression. For most binders the crushing strength increased with increasing level of binder amount. Granulations produced at the lowest roll compaction pressure usually led to granules with smaller diameter compared to those produced at higher compaction pressures. In general, the drug release times were a function of tablet binder concentration rather than the level of applied roll pressure. This was not true for pregelatinised corn starch and microcrystalline cellulose.

Mitchell et al. [33] used HPMC (K3LV Premium) to enhance the rate of dissolution for naproxen, nifedipine and carbamazepine. Three different means of combining HPMC and drug were utilized: dry-blending of drug and polymer to produce a simple physical mixture, compacting the blends by either roll compaction or slugging with subsequent milling. Both roll compaction and slugging processes enhanced the dissolution rate of sparingly soluble drugs compared to the physical mixture preparation or the pure drug. The roll compaction and slugging methods produced comparable drug dissolution behavior.

The microenvironment surfactant effect is believed to be the mechanism, in which the compaction/milling process enhances the drug dissolution properties. In this mechanism,

the dissolution of HPMC will create a local surfactant concentration in the boundary layer surrounding the drug particles, providing a lower-energy pathway for drug dissolution. The compaction processes are believed to be particularly effective in enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the HPMC particles during drug dissolution. In contrast, in a physical mixture the drug and HPMC particles will quickly disperse and separate in the dissolution medium. In conclusion, slugging/roll compaction combined with dry granulation was reported to be an easily scalable process, which requires neither solvents nor heat and it can effectively enhance the dissolution properties of the sparingly soluble drugs.

3.7. Controlled release formulations

Sheskey and Hendren [27] studied the influence of (a) the process variables: roll speed, feed-screw speed and roll pressure, (b) the equipment variable: roll surface design and (c) the formulation variable: HPMC polymer level, on a model controlled-release formulation. The model formulation contained 10% anhydrous theophylline and 20–60% HPMC. Tablets from compacted material showed a lower crushing strength compared to tablets prepared by direct compression. However, the effect of the roll compaction process variables was minimal. Increasing the fraction of HPMC resulted in a lower crushing strength. The process variables during roll compaction and the applied tablet compression force did not alter the drug release from tablets, whereas varying the HPMC ratio did affect that behavior.

Kawashima [24] produced granules using binary mixtures of acetaminophen and pulverized low-substituted hydroxypropylcellulose by slugging and RCDG and then compared the granules with the corresponding physical mixture. RCDG granules prepared at different roll compaction pressures were continuously compressed by a single-punch tableting machine, whereas continuous compression of the physical mixture was difficult due to its extremely low bulk density. The drug release rates from tablets increased with increasing roll compaction pressure. The drug release from the tablets was widely controlled (i.e. from rapid to sustained release) by employing granules prepared under low to high roll compaction pressures (0.2–8 MPa).

Juang and Storey [59] reported the effects of different compositions and manufacturing processes on drug dissolution rates for swelling controlled release devices. The processing difference included wet granulation and dry roll compaction. A formulation containing Carbopol, sodium citrate and povidon was granulated, tableted and then coated. Roll compaction resulted in a 30% higher extent of swelling and the product continued to swell for more than twice the length of time compared to the wet granulation product.

Ohmori and Makino [31,32] developed bilayer tablets with an immediate release portion and a sustained release portion. The sustained release layer consisted of 10% water-soluble drug, 20% excipients and 60% HPMC 2208. The tensile strength of tablets made of the sustained release layer notably decreased with increasing roll compaction pressure. The compactibility of the sustained release layer manufactured by direct compression was superior to that manufactured by dry granulation. Furthermore, an increase in roll compaction pressure increased the number of laminated bilayer tablets. Lamination of the sustained release layer caused the cracking of the bilayer tablets but not the separation of the two layers.

Saravanan et al. [60] produced HPMC based extended release tablets for cephalexin and compared wet granulation with slugging/dry granulation. Tablets prepared with materials from dry granulation showed a slower release of cephalexin. A clear explanation was not provided. The authors suggested, the presence of higher moisture in granules prepared by a dry granulation technique ($5.5 \pm 0.96\%$ compared to $4.7 \pm 0.22\%$ after wet-granulation) resulted in faster swelling of the HPMC matrix, which might reduce the pore size through which diffusion of drug occurs. The addition of polysorbate 80 further reduced the dissolution of cephalexin which was again explained by the faster wetting and swelling of the HPMC matrix.

Rambali et al. [36] used bio-adhesive characteristics to optimise the dry granulation process for the production of buccal tablets. Dry granulation was preferred to direct compression, because it gave better powder flow characteristics and improved compressibility depending on the drug load. In a factorial design the influence of compaction force, gap width, roll type, and sieve aperture on the mean granule size and the characteristics of the tablets were investigated. The granule size was influenced by the compaction force, the roll type and the sieve aperture. Tablet strength was higher for granules produced at a low compaction force, a larger gap width and a smooth roll. The influence of the compaction force was explained by the work-hardening effect. The relative standard deviation of the tablets was not affected by the influential variables studied. In a fractional factorial design with tablet compression pressure as additional factor the dissolution profile and the bio-adhesive characteristics were optimised. A high compression pressure and a ribbed roll tended to make the dissolution profile more linear. The compaction process parameters were important for the buccal tablet characteristics.

4. Problems and suggested solutions

Some reported problems of RCDG and means to avoid these problems are briefly summarized in the following list:

- High amount of fines/leakage of un-compacted material
  - Use of concave rolls for sealing, because non compacted material occurs due to leakage between roll side seals (5)

- Recycling of fines: this is commonly used in other industries; however, if the composition of the fines differs from the total composition this will result in an inhomogeneity of the final product. Furthermore, multiple compaction of the material can have a negative effect on the compactibility.
- Vacuum de-aeration

- Loss in compactibility

  Many authors have reported a loss in compactibility, which is more pronounced at higher roll compaction forces. The mechanism of work hardening was proposed to explain the loss in compactibility [49]. The loss in compactibility occurs predominantly for plastically deforming materials but it is also described for brittle and fragmenting materials including inorganic materials.

  Generally, the roll compaction force should be as high as necessary to achieve the desired granule characteristics but as low as possible to avoid the loss in compactibility.

  Overcompaction can result in discolored, extremely hot, severely cracked or plasticized ribbons. A splitting of ribbons can also be observed [14].
- Homogeneity of the compact

  The stress exerted on the compact is neither homogeneous on the roll width nor constant versus time [4]. The heterogeneity distribution is periodical. The period of the phenomenon is the period of the screw feeder. The fluctuations have the same period as the screw [4]. A pattern on the ribbons can be determined [35].

  Using a conventional side seal system the strength of the ribbon is not constant. In the central part a higher strength is observed compared to the peripheral parts. The profile can be improved by using a rim roll system [5].
- Sticking to the rolls
  - Addition of lubricants [10,38,39,44]
  - Multiple compactions [38]

During the past few years, the field of RCDG is developing fast and further results can be expected in the near future. However, RCDG has its inherent limitations and is not the universal solution to all problems concerning agglomeration. A lot of work is necessary to develop the understanding of the fundamental phenomena and to establish new applications of RCDG.

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