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Review

Tableting of coated pellets[1]

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Abstract

Oral sustained/controlled release multiple unit dosage forms are becoming more popular when compared to single unit dosage forms. With regard to the final dosage form, the multiparticulates are usually formulated into single unit dosage forms such as filling them into hard gelatin capsules or compacting them into tablets. Although there is abundant literature available on the preparation of pellets and on coating technology, only a few dozen research articles have addressed the issue of compaction of coated pellets into tablets. This review provides an update on this research area and discusses the important formulation and process parameters necessary to obtain pellet-containing tablets, which, ideally, have the same properties, in particular drug release properties, as the individual coated pellets.

Keywords: Beads; Coating; Compaction of pellets; Multiparticulates; Multiple unit dosage forms; Oral controlled release; Pellets; Tableting

1. Introduction

Oral controlled release drug delivery systems can be classified into two broad groups: single unit dosage forms (e.g. tablets or capsules) and multiple unit dosage forms (e.g. pellets, granules or microparticles). Although similar drug release profiles can be obtained with both dosage forms, multiple unit dosage forms offer several advantages [1,2]. The multiparticulates spread uniformly throughout the gastrointestinal tract. High local drug concentrations and the risk of toxicity due to locally restricted tablets can be avoided. Premature drug release from enterically coated dosage forms in the stomach, potentially resulting in the degradation of the drug or irritation of the gastric mucosa, can be reduced with coated pellets because of a more rapid transit time when compared to enterically coated tablets. The better distribution of multiparticulates along the GI-tract could improve the bioavailability, which potentially could result in a reduction in drug dose and side effects. Inter- and intra-individual variations in bioavailability-caused for example by food effects-are reduced. With coated single dose dosage forms, the coating must remain intact during the drug release phase; damage to the coating would result in a loss of the sustained release properties and dose dumping. If not compressed, the mechanical strength of the coating of pellets is not as critical as with tablets since unwanted dose dumping from pellets is practically nonexistent. Various drug release profiles can be obtained by simply mixing pellets with different release characteristics; in addition, a more rapid onset of action can be achieved easier with pellets than with tablets.

With regard to the final dosage form, the multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular, especially in the USA, where hard gelatin capsules have been tampered (Tylenol®). The advantages of tableting

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multiparticulates include a reduced risk of tampering and less difficulties in oesophageal transport when compared with capsules. Large volume tablets generally have a higher patient compliance than capsules; a higher dose strength could be administered with tablets. Tablets from pellets can be prepared at lower cost when compared to pellet-filled capsules because of the higher production rate of tablet presses. The expensive control of capsule integrity after filling is also eliminated. In addition, tablets containing multiparticulates could be scored without losing the controlled release properties. Scored tablets allow a more flexible dosing regimen.

Compaction of coated multiparticulates into tablets could either result in disintegrating tablets providing a multiparticulate system during GI-transit or in intact tablets due to the fusion of the multiparticulates in a larger compact. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in gastrointestinal fluids. The pellets should not fuse into a non-disintegrating matrix during compaction. The drug release should not be affected by the compaction process. The challenges of formulating pellets into tablets are evident. With reservoir-type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; it can deform, but should not rupture. Without sufficient elasticity of the film, the coating could rupture during compression and the extended release properties would be lost. In addition, the bead core should also have some degree of plasticity, which can accommodate changes in shape and deformation during tableting.

The aim of most studies on the compaction of pellets is to convert a multiple unit dosage form into a single unit dosage form containing the multiparticulates, with this single unit dosage form having the same properties, in particular drug release properties, as the individual multiparticulates. This article reviews the key variables affecting the compaction and performance of coated pellets (reservoir-type drug delivery systems) including the type and amount of polymer coating and the proper selection of pellet core and tableting excipients. Smaller particles (e.g. microcapsules or microspheres) or matrix-type pellets are not discussed.

2. Polymer coating

Polymers used in the film-coating of solid dosage forms fall in two broad groups based on either cellulosic or acrylic polymers [3,4]. The acrylic polymers are marketed under the trade name Eudragit® and the major cellulosic polymer used for controlled release is ethyl cellulose. Many of these polymers have been formulated into aqueous colloidal dispersions (e.g. latexes or pseudolatexes) in order to overcome problems associated with the use of organic polymer solutions. The polymeric coating of the pellets must remain intact during compression in order to control the drug release. Besides its permeability properties, which govern the drug release, the mechanical properties of the particular polymer coating have to be determined in order to investigate its suitability for the coating of pellets to be compressed into tablets.

2.1. Ethyl cellulose

Ethyl cellulose films cast from the plasticized pseudolatexes, Aquacoat® and Surelease®, were very brittle and weak with low values for puncture strength and elongation ($< 5\%$) [5]. The mechanical properties of Aquacoat® films were similar for different plasticizers (brittle, with elongation values $< 2\%$ in most cases). Curing of the pseudolatex-cast ethyl cellulose films had minimal effects on their mechanical properties.

Most studies on the compaction of pellets coated with ethyl cellulose revealed a damage to the coating with a loss of the sustained release properties. This is not surprising because of the weak mechanical properties of ethyl cellulose.

The drug release from compressed niacin/microcrystalline cellulose pellets coated with the aqueous colloidal ethyl cellulose dispersion, Surelease® (7% w/w), was much faster when compared to the release of the uncompressed pellets [6]. At higher compression pressures, the pellets were fractured and simultaneously underwent fusion. This resulted in a slight decrease in drug release when compared to the release from compacts compressed at lower compression pressures.

The compaction of diltiazem HCl pellets coated with ethyl cellulose resulted in a faster drug release irrespective of the formulation used when compared to the release from noncompressed pellets [7]. The tensile properties of free films as a function of plasticizer were measured. The elongation varied between 0.93 and 4.28% for different plasticizers. This is obviously too low to result in flexible films, which deform and do not rupture during compression.

Coating pellets with Surelease® to coating levels of 10, 15, and 20% w/w changed the deformation characteristics of the uncoated pellets from being brittle and elastic to plasto-elastic properties [8,9]. Increasing the coating level reduced the pressure necessary to obtain the same in-die porosity, indicating an easier compressibility of the coated pellets. An increased coating level, however, caused a decrease in tensile strength (10% coating $> 15 > 20 >$ uncoated pellets), and a reduction in the yield pressure of the pellets and an increase in the elastic recovery upon ejection. The polymer caused an additional expansion because of its elastic characteristics. The ability of the pellets to deform, both plastically or elastically, increased with increasing coating level. Increasing the punch velocity resulted in a reduc-

tion in the tensile strength of the compacts and an increase in both yield pressure and elastic recovery values. The punch velocity dependence of these variables was greater with pellets coated with higher coating levels. As shown with dissolution studies, the coated pellets lost their sustained release properties during compaction, regardless of the coating level and the compaction pressure. This was attributed to the formation of cracks within the coating and to the fragmentation of the pellets.

Potassium chloride crystals coated with an organic solution of ethyl cellulose were more resistant to compaction than crystals coated with the pseudolatexes, Aquacoat® or Surelease® [10]. The sustained release properties of the pseudolatex-coated crystals were lost after compaction. Possible reasons given were the incomplete fusion of the colloidal particles, the presence of additives in the coating and the migration of KCl into the film during the coating process. Coatings prepared from organic solution were mechanically stronger than coatings prepared from the pseudolatexes [5].

To reduce the damage to ethyl cellulose coated pellets, the compressed pellets were put in an oven at 70°C for 24 h to obtain a retardation in the drug release [11]. The storage at elevated temperature resulted in a decrease in drug release, however, after 30 min, still 55% of chlorpheniramine maleate was released. The results showed that a certain amount of ruptures was sintered during exposure of the tablets to temperatures above the glass transition temperature.

In order to overcome the brittle character of ethyl cellulose, multilayered beads consisting of approximately 10 alternating layers of ethyl cellulose (Aquacoat®), drug or cushioning agent (mannitol) were prepared [12]. Drug release patterns indicated that still all polymer layers were ruptured during compression. Mannitol was not effective as a cushioning agent. At higher compression forces and coating levels in excess of 15%, non-disintegrating matrices with useful sustained release properties were obtained.

2.2. Acrylic polymers

When compared to the ethyl cellulose films, films prepared from acrylic polymers are more flexible and therefore more suitable for the coating of pellets to be compressed into tablets [5]. Films of Eudragit NE 30D, a poly (ethylacrylate-methylmethacrylate) dispersion, were very flexible. The elongation was in excess of the elongation limit of 365% achievable with the puncture test device. The dispersion has a minimum film-forming temperature of around 5°C and did not require the addition of plasticizers in contrast to the other dispersions evaluated. The molecular structure of the polymer, which is based on acrylic esters, indicates the lack of strong interchain interactions (e.g. hydrogen bonds), thus explaining the flexible character of the polymer films. With plasticized Eudragit RS and RL 30 D, which are dispersions based on the cationic polymer, poly (ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate chloride), flexible films were obtained with elongation values in excess of 125%. The enteric acrylic latex, Eudragit L 30D (poly (methacrylic acid-ethylacrylate) with a ratio of 1:1) resulted in weak and brittle films (elongation < 1%) when compared to the other Eudragit polymers. A possible explanation could be strong interchain hydrogen bonding caused by the presence of the carboxyl groups.

Crystals, granules and pellets were coated with various aqueous acrylic polymer dispersions (Eudragit NE 30D, RS/RL 30D and L 30D-55) and compressed into fast disintegrating tablets [13,14]. Multiparticulates coated with flexible polymers (Eudragit NE 30D) and plasticized Eudragit RS/RL 30D) could be compressed without significant damage to the coating. No or only small changes in drug release were found with coatings with elongation values in excess of 75%. These films have enough elasticity to deform on coated pellets during compression without rupture. Very little difference in drug release was observed between the compressed granules and the noncompressed granules, containing theophylline coated with an Eudragit RL/RS dispersion. Enteric coatings based on Eudragit L30D-55, a methacrylic acid-ethylacrylate copolymer, were brittle and the compression of the pellets resulted in film damage. This damage could be avoided by mixing the enteric polymer with the flexible Eudragit NE 30D. Heterogenous films, which retained their enteric properties, were obtained after the addition of Eudragit NE 30D.

However, with bisacodyl pellets, the drug release with these mixed films did not fulfill the requirements of the USP for enteric dosage forms [15]. New, more flexible, enteric polymers were developed by Röhm for the compression of coated pellets [16]. The ethyl acrylate monomer was replaced with methyl acrylate or with methyl acrylate/methyl methacrylate in order to give more flexible films, which allows the compression without damage of the polymeric coating. The glass transition temperature is in the range of 45–60°C, which is much lower when compared to the USP/NF methacrylic acid copolymers used for enteric coating. A copolymer of methacrylic acid:methacrylate (20:80) dissolves at pH 6, while a copolymer composed of methacrylic acid:methacrylate:methylmethacrylate (10:65:25) dissolves at a higher pH, pH 7.2. The addition of 5–10% triethyl citrate resulted in elongation values up to 300%. While no retardation in drug release was observed with compacted pellets coated with Eudragit L 30D-55 with doubling the amount of coating from 12.5 to 25%, the drug release was reduced with the new enteric polymers, which had an elongation at break

in excess of 50%. Release in gastric juice of tableted bisacodyl pellets was < 5% after 2 h. Films made from Eudragit L 30D-55 are too brittle to adjust to the deformation of the pellets and an increase in coating thickness did not avoid the film rupture.

The effect of compression force on the dissolution from Eudragit NE 30D-coated theophylline pellets was evaluated in a range of 6–20 kN [17]. A compaction force of 15 kN was required to obtain tablets with a smooth surface. At lower compression forces, the tablets were granular in appearance. At 6 kN, the dissolution was faster than from the untableted pellets. The compaction-induced pellet deformation was practically complete at 6 kN and no change in dissolution rate was observed upon increasing the compression force to 20 kN. The increase in drug release rate was not attributed to rupturing of the polymeric film, but to a thinning of the flexible film because of stretching.

3. Pellet core

As described above, without sufficient flexibility of the film, the coating could rupture during compression and the sustained release properties would be lost. Besides the coating, the bead core also will affect the compaction behavior of the coated pellets. The bead core should also have some degree of elasticity, which can accommodate changes in shape and deformation during tableting. It should deform and recover after compression without damage to the coating.

The compaction properties of uncoated beads (bead cores), which were prepared by an extrusion/spheronization process from well-known tablet excipients including microcrystalline cellulose, lactose and dicalcium phosphate dihydrate, were investigated [18]. Microcrystalline cellulose is a plastic material, lactose consolidates by fragmentation and then by plastic deformation while dicalcium phosphate dihydrate consolidates primarily by fragmentation. Pellets could be formed from microcrystalline cellulose, however, neither lactose nor dicalcium phosphate formed beads by themselves. Beads were formed after the addition of 22.5% of microcrystalline cellulose. Although microcrystalline cellulose powder is known to be very compressible and forms hard tablets at low compression forces, microcrystalline cellulose beads were not compressible and formed soft tablets. Very few bonds are formed between the beads as shown on scanning electron micrographs. Lactose/microcrystalline cellulose beads were more compressible and exhibited more fracture than the microcrystalline cellulose beads. Dicalcium phosphate/microcrystalline cellulose beads underwent plastic flow more easily than the other two bead formulations, had a higher degree of fracture and were more compressible. The authors concluded that any desired compaction profile could be obtained by changing the bead formulation.

Similar results were obtained by Wang et al. [19]. Compacts prepared from lactose/microcrystalline beads had different compaction/consolidation behaviors than powders of the same composition. The tensile strength of compacts prepared from powders increased with increasing microcrystalline cellulose content, while compacts prepared from extruded/spheronized beads showed the opposite trend. The poor compactibility and bonding ability of microcrystalline cellulose-rich beads was attributed to the loss of the plasticity of microcrystalline cellulose during the granulation process and the confinement of the fibrous nature of microcrystalline cellulose because of strong granule bounderies formed during extrusion/spheronization.

The compression behavior of microcrystalline cellulose pellets (prepared by extrusion-spheronization) with different porosities and mechanical properties was investigated by Johansson et al. [20]. Scanning electron micrographs revealed that the size and appearance of the pellets within the compact were similar to the characteristics of the original pellets. This indicated that the microcrystalline cellulose pellets kept their integrity under compression and did not fragment into smaller particles. The major mechanism of compression appeared to be deformation and not fragmentation. An increased pellet porosity increased the degree of deformation of the pellets during compression and the tensile strength of the tablets because of the formation of stronger intergranular bonds. The tensile strength of tablets prepared with lubricated pellets was lower when compared to tablets prepared with unlubricated pellets. This supported the argument that pellet deformation and not fragmentation occurred during compression. In a subsequent study, the tableting properties of pellets of varying porosity consisting of dicalcium phosphate (80%, a brittle material) and microcrystalline cellulose (20%, a ductile material) were investigated [21]. An increase in pellet porosity led to an increased tensile strength and a decreased air permeability of the compacts. The reduction in tensile strength caused by the addition of a lubricant, magnesium stearate, decreased with increasing pellet porosity. Scanning electron micrographs revealed fracture across individual beads for tablets made with high porosity pellet and fracture around intact pellets for low porosity pellets. Lubricated tablets fractured around the pellets.

The compaction behavior of uncoated pellets prepared from microcrystalline cellulose alone or in combination with 10% propranolol HCl and either 10% lactose or 10% dicalcium phosphate was compared to that of the powders with an integrated compaction research system [22,23]. Porosity changes, the Heckel equation, the total work of compaction and average power consumption were used for the comparison. The

pellets required lower compression pressures than the powders to obtain the same porosities, however, the tensile strength of the compacts prepared from the powders was significantly higher than the tensile strength of compacts prepared from the pellets. The powders, which compacted primarily by plastic deformation, produced strong compacts whereas their pellets exhibited elastic deformation and brittle fragmentation resulting in compacts of lower tensile strength. The pressure required to achieve the predetermined porosity was lower with microcrystalline cellulose than with the other powder formulations, indicating a decrease in compressibility of microcrystalline cellulose upon the addition of lactose, dicalcium phosphate or propranolol HCl. Unlubricated pellets required higher pressures than lubricated (magnesium stearate) pellets to achieve the same porosity, however, the strength of the lubricated compacts was weaker. The compacts disintegrated in the order of microcrystalline cellulose > microcrystalline cellulose/drug/dicalcium phosphate > microcrystalline cellulose/drug/lactose. Compacts made from pellets were highly friable and disintegrated within 5 s. The addition of microcrystalline cellulose to the pellets resulted in acceptable friability and still low disintegration times (1 min). The mechanical strength of the compacts increased with additives such as microcrystalline cellulose and decreased with the inclusion of pregelatinized starch, soy polysaccharide or magnesium stearate as external additives.

Theophylline:microcrystalline cellulose (1:10) pellets were prepared by extrusion/spheronization using ethanol/water mixtures in varying ratios as granulating fluid [24]. Increasing the amount of water in the mixture resulted in harder and less porous pellets and a slower drug release. Water granulated pellets were not very compressible, whereas pellets prepared with 95% ethanol had excellent compressibility. This was attributed to the weaker character of the ethanol-granulated pellets, which ruptured during compaction, forming new surfaces for bonding. The stronger, water-granulated pellets resisted rupturing and less surfaces were available for bonding as shown on photomicrographs.

Harder pellets coated with Eudragit L30D-55 were able to resist the compression forces better when compared with softer, more porous pellets, which deform easier and therefore resulted in a higher degree of film rupture [15]. Minimal damage to coated pellets was found when the elastic and tensile properties of the coating and the uncoated pellet were similar [25].

The size of the pellets also affects the compaction properties and the drug release from the compacted pellets. At the same coating level, smaller pellets were more fragile than larger pellets. This was attributed to the reduced film thickness of the smaller pellets because of the larger surface area [11]. On the contrary, Ragnarson et al. found that increasing the particle size resulted in more damage to the coating, as indicated by larger differences between the release profiles of tableted and uncompressed pellets [26]. Since the drug release is proportional to the surface area of the coated beads, smaller pellets, however, require more coating to obtain the same drug release profiles [27].

It can be concluded from the above studies that the compaction of pellets and the mechanical properties of the resulting compacts are quite different from the powdered excipients.

4. Tableting excipients

Various inert excipients have to be used to assist the compaction process and to prevent the rupture and damage of the coated pellets. The ideal filler materials used for the tableting of pellets should prevent the direct contact of the pellets (e.g. polymer coatings) and act as cushion during compression. Theoretically, 29% of excipient are needed to fill the void space between densely packed spheres. A layer has to be formed between the pellets to prevent adhesion or fusion of the coated pellets. The excipients should result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release.

Besides their compaction properties, the excipients have to result in a uniform blend with the coated pellets, avoiding segregation and therefore weight variation and poor drug content uniformity of the resulting tablets. In order to avoid segregation during the flow of the pellet-excipient mixture, excipients with a larger particle size or drug-free placebo pellets could be used as diluents.

The variation in weight and drug content uniformity was minimized when using higher pellet concentrations or larger particle size fractions (e.g. granules) of the inert excipients [15]. It was found that, at a 30% w/w pellet concentration, granules of Avicel have to be added in order to achieve sufficient drug content uniformity. Above a pellet content of 50%, the variations are acceptable, even with nongranulated excipients. However, the exclusive use of larger granules as fillers increased the drug release from the tableted pellets. Lower damage to the coating was achieved by using the minimum amount of granules (20%) and using the rest of the excipients in the form of finely divided powders. In addition, the coated pellets could be prepared with a smaller size in order to approach the particle size of the inert excipients. Smaller pellets would also improve the content uniformity of low dose drugs. However, particle size is an important factor affecting the drug release and, in general, thicker coatings have to be applied to smaller pellets in order to obtain the same drug release profiles when compared to larger pellets.

The protective effect of different tableting excipients on the compression of theophylline granules coated with Eudragit RS was studied indirectly through dissolution studies [28]. The order of the least damage to the coating was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate (Di-Tab). These results were in good agreement with the yield pressure of the excipients. If the tablet matrix has a lower yield pressure than the pellet/pellet coating, the energy of compaction is predominantly absorbed by the matrix, resulting in a preferential deformation of the matrix and not the pellets. However, even at low compression forces, there was some damage to the coating membranes. A combination of 50% microcrystalline cellulose, 25% polyethylene glycol 3350 and 25% crospovidone was most suitable for minimizing the damage to the coating. Increasing the compression force mostly resulted in an increase in dissolution rate because of particle crushing, however, with PEG 3350 and Di-Tab, it resulted in a decrease in dissolution rate because of particle bonding.

The hardness of compacts increased with increasing compression force, and decreased with increasing amounts of pellets [15]. Above 90% w/w pellets, stable compacts could not be prepared. The hardness of the tablets was also influenced by the type of fillers. Tablets with sufficient hardness could be prepared with up to 50% pellet content with Avicel PH 101 and Bekapress D2 (calciumhydrogenphosphat, dihydrate) and with up to 70% pellets with Cellactose (75% α-lactose, monohydrate/25% cellulose). At higher pellet contents, the friability of the tablets was too high. Decreasing the amount of lubricant, magnesium stearate, to 0.25% resulted in stronger tablets. At the same pellet content, tablets prepared with Avicel or Bekapress D2 disintegrated faster than Cellactose. No effect of compression force (range 5–25 kN) was observed with the four excipients. Increasing the pellet content increased the amount of drug released, indicating a higher proportion of damaged pellets. At a lower pellet content, the excipients act as cushions while the pellets deform to a larger extent at a higher pellet content. The fillers had very little effect on the drug release at low pellet content (< 10%). At higher pellet contents the ingredients could be ranked in the following order: Polyethylene glycol 6000 < Cellactose < Avicel PH 200 < Bekapress D2. Bekapress D2 resulted in the highest damage to the coated pellets as indicated by the fastest drug release because of its fragmentation and high density. Avicel and Cellactose are more porous fillers and can therefore absorb higher compression forces. Low damage of the pellets was also observed with polyethylene glycol 6000, however, at higher pellet contents, tablets with insufficient hardness were obtained. Polyethylene glycol 6000 fused during compression. Because of the high density of Bekapress, the volume percentage of the pellets was higher when compared to the other fillers. This can explain the higher damage of the pellets. Bekapress had a true density of 2.63 g/cm^3, Cellactose of 1.53 g/cm^3 and Avicel PH 200 of 1.52 g/cm^3. Scanning electron micrographs also revealed the penetration of filler particles into the coating, this, however, did not affect the drug release significantly.

Chlorpheniramine maleate pellets were manufactured using a rotor granulator (Glatt GPCG-1) and then coated with an aqueous ethyl cellulose pseudolatex plasticized with 24% dibutyl sebacate to weight gains of 25, 30 and 35% [11]. An HPMC-overcoat was applied in order to reduce tackiness/sticking during curing at 60°C for 1 h. The fillers evaluated for the compaction of the pellets included microcrystalline cellulose (Avicel PH 101, PH 200), spray dried lactose, sorbitol, pregelatinized starch, compressible sugar and PEG 8000. Microcrystalline cellulose provided tablets disintegrating within 10 s, while the tablets prepared with the other fillers disintegrated within 7–10 min. PEG 8000 tablets actually eroded over a 35 min period. The coated pellets had sustained release properties, however, the polymeric coatings did not withstand the compaction. The ethyl cellulose coating was too weak and ruptured resulting in a more rapid drug release. Even at the lowest compression force of 5 kN, rupture of the coating occurred irrespective of the filler used.

A patent has been issued on the use of microcrystalline cellulose in concentrations between 10 and 50% w/w with coated granules in order to prevent fracture of the coated granules and to result in a tablet matrix of sufficient hardness [29].

The placebo pellets should be mechanically weaker than the coated pellets and fragment during compression in order to fill the voids between the pellets and give good bonding [23]. However, this concept did not work with coated ibuprofen pellets, which were weaker than drug-free microcrystalline cellulose or lactose pellets. Various dry powder mixes with large particle size excipients, such as Avicel PH 200 and Meggle lactose EP, grade 20, were evaluated. Weak and friable tablets were formed with lactose as the single or major filler; the addition of microcrystalline cellulose resulted in stronger, less friable tablets with a faster disintegration. At < 40% external excipient level, the tablets were too friable. The compaction of the pellets resulted in slightly faster drug release; the pellets were deformed, but were basically intact.

Tablets containing modified-release theophylline pellets with rapid disintegration ('flash disintegration', disintegration time < 1 min) were prepared by Flament et al. [17]. A rapid disintegration of the tablet into the individual pellets within the GI-tract is desirable in order to keep the advantages of multiparticulate drug delivery systems. The active pellets contained 75%

theophylline and 25% inert excipients and were coated with Eudragit NE 30 D. Tablets compressed from only active pellets were too weak. The active pellets were mixed with inert granules, which were prepared by wet granulation from microcrystalline cellulose, lactose powder and various disintegrants. The active pellets were then blended with the inert granules followed by tableting. Uniform mixtures were obtained with inert granules having a mean diameter close to that of the active pellets. Noncompressed inert granules containing 50% starch resulted in disintegration times of 30 s. These granules then facilitated the rapid disintegration of the tablets in water. Microcrystalline cellulose was used to compensate for the low compressibility of starch and to improve the hardness of the tablets produced. The optimal formula of the inert granules was microcrystalline cellulose:cornstarch, 1:1. No lubricant was required for the compression, this being favorable with respect to the disintegration time and uniformity of the blend.

An effervescent tablet containing coated multiparticulates was developed to rapidly disintegrate in the mouth into the individual particles (Orasolv®-technology) [30]. The effect of various excipients on the tablet hardness and disintegration time was investigated. Surprisingly, increasing the level of the effervescent agent 4-fold did not affect the in vivo disintegration time and increasing the concentration of Ac-Di-Sol, a popular disintegrant, actually increased the disintegration time. The disintegration time could be decreased with increasing Avicel concentrations.

The compression of acetylsalicylic acid pellets coated with Eudragit RS resulted in a reduction in drug release at filler (microcrystalline cellulose) concentrations of $< 5\%$ when compared to the noncompressed pellets [31]. This effect was attributed to the fusion of the acrylic coatings during the compression, resulting in a nondisintegrating matrix. Tablets containing in excess of 15% microcrystalline cellulose had similar drug release profiles to the uncompressed pellets. The amount necessary to fill the voids between the multiparticulates can be estimated from the tapped density of the particles.

The drug release from tablets containing pellets with damaged coatings and therefore faster drug release could be reduced through the addition of water-insoluble excipients such as polymers or waxes prior to the compaction of the pellets. Phenazone pellets coated with Eudragit RS 100 were mixed with different additives and compressed into tablets [32]. The release from the compressed pellets was faster than the release from the uncompressed pellets, this being attributed to deformation or rupturing of the coating. The addition of powdered Eudragit RSPM to the pellets prior to compression retarded the drug release. It was speculated that the powdered polymer acted as a repairing agent for the broken parts of the pellet coats. Granulating the coated pellets and microcrystalline cellulose with a 20% solution of Eudragit RS in acetone resulted in a retarding effect. Using the enteric polymer, Eudragit S, as a granulating agent, resulted in a faster drug release. This was attributed to the dissolving action of acetone for the polymer coat during granulation. Increasing the compressional force increased the drug release, probably because of deforming of the pellets and rupturing of the coats. The addition of an equal quantity of a hydrophobic excipient, castor wax, to ethyl cellulose-coated granules, which were damaged upon compression, retarded the drug release [6].

5. Conclusions

The challenges in preparing tablets from coated pellets are evident. Various formulation and process parameters have to be optimized in order to obtain tableted reservoir-type pellets having the same properties, and, in particular, release properties as the original, uncompacted pellets. The most important variable is the type of polymer selected for the coating of the pellets. The polymer coating must remain intact during compaction in order to extend the drug release. Traditionally used polymers for the coating of solid dosage forms which do not resist the mechanical stress during compaction (e.g. ethyl cellulose) are not suitable for the preparation of compacted pellets. The polymers have to be flexible enough to not rupture. The formulations of the pellet core and the final tablet have to be carefully selected in order to prevent the rupture of the coating, and to obtain tablets with proper content uniformity, hardness and rapid disintegration. Key variables include the pellet:excipient ratio and the compression force. Microcrystalline cellulose appears to be the excipient of choice because of its good compaction and disintegration properties. However, even under optimized conditions, ethyl cellulose-coated pellets lost their extended release properties.

On reviewing the literature on compacted beads, it was evident, that only few studies have addressed the compaction of matrix-type pellets, a multiparticulate system potentially showing less problems under compaction.

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