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TABLETING OF COATED MULTIPARTICULATES: A REVIEW

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of a medical condition known as dementia, which effects the brain and hence memory. The National Institute of Health predicts, if the current trend continues, there will be more than 8.5 million AD patients by the year 2030 in USA alone. Although there is no cure for dementia if AD type at present alternative pharmacologic treatment modalities can reduce the symptoms of cognitive improvement and slow disease progression. Nootropic agents like, piracetam and cholinesterase inhibitors like, Donepezil® are commonly used for improving memory, mood and behavior. However, the resulting adverse effects of these drugs have limited their use and it is worthwhile to explore the utility of traditional medicines in the treatment of various cognitive disorders. The present work was undertaken to assess the potential of latex of *Calotropis procera* as a nootropic agent in mice. Elevated plus maze was employed to assess the memory of mice. Whole brain Ache activity was also measured. Diazepam (1 mg/kg, i.p.) and Scopolamine (0.4 mg/kg,i.p.) were used to induce amnesia in mice. *C. procera* (100 and 200 mg/Kg, p.o.) was administered for 3 successive days to both young and old aged mice. *C. procera* deceased transfer latencies indicating improvement in learning and memory and it also reversed amnesia induced by Scopolamine, diazepam and natural ageing. Hence *C. procera* can be employed as a memory restoration agent in patients suffering from amnesia.

Key words: Acetylcholinestrase activity; Memory; *Calotropis procera.*

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INTRODUCTION

Oral controlled release dosage forms comprising multiparticulates provide various advantages over single unit dosage forms: risk reduction of local irritation; less variable bioavailability; decrease of inter and intra-individual variation in bioavailability

and various drug release profiles can be obtained by simple mixing pellets with different release characteristics. The preparation of multiparticulates in easy administrative form (single dosage form) can be manufactured by filling multiparticulates into hard gelatin capsules or compression them into tablets. The latter offers some advantages such as protection of tampering, reduction of difficulty in esophageal transport and less production cost. Preferably, tablets containing beads should disintegrate rapidly into individual beads and drug release should not be affected by the compression[1]. Tableting of reservoir type multiparticulates is more challenging than tableting of matrix type multiparticulates in term of film damage during compression. Parameters affecting the tableting of reservoir type pellets: polymer coating, pellet cores, tableting excipients and tableting process parameters (tableting machine speeds and pellets loading) are needed to be considered.

Polymer coating

The polymer coating is the most important parameter among key parameters for tableting of coated pellets. Polymers used in the film coating can be divided as cellulosic polymers, acrylic polymers and polyvinyl acetate. The film coating should be highly elastic and flexible enough to adapt to the deformation of pellets without rupturing[2]. Polymeric coating should contain sufficient mechanical stability and remain intact during compression in order to control drug release. Lehmann et al. (1994)[3] have revealed that at least 75% of elongation at break was required for compression of coated pellets without or with small damage of release controlling film. Solvent based coatings have been found to be more flexible and have a higher degree of mechanical stability than aqueous-based ones, and therefore less affected by compaction[4]. Ethyl cellulose films cast from the plasticized pseudolatexes, Aquacoat®, and Surelease® were very brittle and weak with low values of puncture strength and elongation (< 5%). The possible explanation could be incomplete fusion of latex spheres; molecular weight change due to the pseudolatex manufacture; stabilizer; stabilizer and plasticizer used in the formulation[2]. Comparing to ethyl cellulose films, the films prepared from acrylic and polymers and polyvinyl acetate are more flexible and therefore more suitable for the coating of pellets to be compressed into tablets. The flexible films reported to withstand the compression of pellets are Eudragit® NE 30D, Eudragit® RS 30D, Eudragit® RL 30D, Eudragit® FS 30D, (Wagner et al., 2000a and b) and Kollicoat® SR30D. Bodmeier and Paeratakul (1994) found that films of Eudragit® NE30D dispersion were very flexible with the elongation value in excess of 365%. With plasticized Eudragit® RS and RL30D, which are dispersions based on the cationic polymer, flexible films were obtained with elongation values in excess of 125%. Plasticized Kollicoat® SR30D became flexible with elongation values > 137% and coated pellets could be compressed into tablets with negligible damage[5, 6, 7, 8]. The new enteric coating Eudragit® FS 30D was introduced as flexile film former and suitable for the tableting of coated beads. Coated pellets of this polymer coating (with 10% TEC plasticization) were compressible[9, 10].

Tableting of multiparticulates coated with brittle films (ethylcellulose and enteric films) would result in the damage of coating. The blends of flexible and brittle polymer for pellet tableting were investigated. The damage of enteric film (Eudragit® L 30D) during compression could be avoided with increasing film flexibility by blending the enteric polymer with flexible Eudragit® NE 30D [11]. The coating thickness can play a role in protecting the film integrity during compression. Thicker coatings would increase in the mechanical strength of film to withstand the damage during the compression better than a thinner coating [12].

The approach of multiple layered coating with different enteric coating on lansoprazole pellets was claimed to improve flexibility against tableting of pellets, stability of drug and taste of pellets [13]. Since triethyl citrate had an unpleasant bitter taste and showed incompatibility with lansoprazole, PEG 6000 was applied in inner and outer of enteric coating.

Pellet core

Pellet cores also affect the compaction behavior of coated pellets. The core should contain some degree of elasticity, which can accommodate changes in shape during compression. The desirable mechanical properties of the core should be strong, not brittle and have a low elastic resilience [14].

Soft pellet cores have been used to prepare reservoir type pellets [13]. These soft pellets were prepared by a powder layering method using sucrose crystal as seed, adherent powder (a mixture of Lactose D80, Aerosil and Kollidon 25 as adherent) and binder dispersion (Eudragit® NE30D, sucrose and water). Adherent powder was poured into the coating pan during the spraying of the binder dispersion on sucrose crystal. The deformation of single pellets with and without maximum crushing strength has been presented from hard pellets (prepared by extrusion-spheronization) and soft pellets, respectively.

The incorporation of a soft waxy material: glyceryl behenate[15]; glyceryl monostearate [16], [17] polyethylene glycol 6000 [18]; paraffinic wax[19], into pellet forming matrix in order to modify the compactability and to protect reservoir pellets has been studied. The improvement on deformation behavior is attribute to increasing pellet slide past each other; reduction in pellet thickness and porosity; facilitation of pellet deformation at low pressures.

Extrusion-spheronization pellets (40-80% ibuprofen, blends of Eudragit® RS PO/RL PO, Avicel® PH 101 and PVP K30 as binder) have been prepared[20]. The cured pellets containing 40% or 60% drug and more Eudragit® RS PO in the polymer blend underwent plastic deformation without fracture under mechanical tests. The change of Eudragit pellets from glassy to rubbery state upon curing was responsible for the observed plastic behavior of the cured pellets. These results revealed that thermal treatment of Eudragit based pellets could be advantageous in the production of plastic pellets that are intended to be coated and compressed into tablets.

Pellet porosity can play a role on the compaction pattern and thereby affects the polymer coat integrity during compression. The pellet porosity was found to control the degree of deformation that the pellets underwent during compressio[21]. The degree of deformation caused by a reposition of primary particles within the pellet, seemed to be controlled by the total air volume surrounding the primary particles in the pellets. Increasing 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. This was confirmed through a study of drying rate effect on porosity and compaction behavior of microcrystalline cellulose pellets[22]. An increased drying rate gave more porous pellets, due to decreased pellet densification during the drying process which were more deformable and which formed tablets of a higher tensile strength. However, the incorporation of dicalcium phosphate dihydrate resulted microcrystalline cellulose pellets less compressible during compaction and the pore structure of the tablets more closed[23]. This suggested that the primary particles are harder, it will be more difficult for them to flow within the pellet and the pellets will thus be more rigid and less prone to deform and densify during compression.

The similar finding of the pellet porosity on the degree of deformation was found[24]. The compaction behavior of EC reservoir pellets; extrusion-spheronisation pellets (containing microcrystalline cellulose and salicylic acid) and coated with EC, of three different porosities was investigated. Insignificant effect of the coating on the compression behavior of the pellets was shown. Compacted pellets of high porosity were highly densified and deformed, while drug release was unaffected. In contrast, drug release of compacted pellets of low porosity was markedly increased while there was only slight densification and deformation.

Tableting excipients

The ideal tableting excipients used for compression of coated pellets should prevent the direct contact of pellets and act as cushioning agent during

tablets compression. The excipients should result in robust tablets at low compression force, rapidly disintegrating and no influence on drug release [1].

To obtain desired tablets: acceptable content uniformity of pellets, without the direct contact of pellets and absence of coating rupture, pellet to excipient proportion and compression are needed to be considered. Theoretically, 29% of excipient is needed to fill the void space between closely packed pellets in tablet formulation [25]. Soft tableting materials: carrageenan[26]; chitosan and alginates [27] were used as soft excipients to avoid the damage of coat during compression. Deformable of kappa carrageenan was presented by deformation with minimal fragmentation of drug matrix pellets of this material [28].

The attempts to overcome the segregation of pellets and excipients have been performed by (1) tableting of pellets with comparable size of granulated excipients or cushioning pellets or (2) adhesion (spraying or granulation) of cushioning agent on pellets to be compressed.

Tunón et al. (2003) [24] showed that ethylcellulose coated pellets could withstand the compression with an incorporation of microcrystalline cellulose pellets with different physical properties. The reservoir pellets were shown to undergo extensive deformation and densification during compaction and more preserved with small size and high porosity microcrystalline cellulose pellets.

Hot tableting of coated pellets could be applied when low melting point materials are incorporated as cushioning excipient. The successful tableting of ethylcellulose coated pellets into tablets were performed using PEG 3000 granules as cushioning excipient and processed at 56 °C with 1 kN [29]. EC coated pellets were compressed and embedded within molten PEG. Additional layer coating of cushioning agents on pellets was applied to avoid segregation and to protect coated pellets during tableting.

Ethylcellulose coated pellets with sufficient coating (about 8% weight gain) were less damaged during compaction by blending with soft pellets (30% glyceryl mono- stearate, 20% microcrystalline cellulose and 50% barium sulphate) and disintegrant pellets[30]. The soft pellets added restricted the drug pellets from deforming and to hold the tablet together by deformation during the compaction. Similar result, compression of coated pellets into tablets with incorporation of wax beads (paraffinic wax) as cushioning materials was investigated by Vergote et al [31].

The adhesion of cushioning agent on coated pellets to be compressed has been applied studied. Altaf et al. (1999)[32] used polyethylene oxide as the cushioning agent by spray coating on ethylcellulose coated pellets and microcrystalline cellulose was coated on the top. The compacted PEO layered beads with 5% sodium starch glycolate (Explotab®) disintegrated into individual beads and provided sustained release up to 8 h. However, it was postulated that the PEO was hydrated and formed a gel that acts as a sealant for the cracks formed in the ruptured polymer coating. The overcoating of HPMC as a protective layer to minimize coating film damage during compression was studied[33], but this layer affected drug release behavior also. The fast applying compressible excipient onto coated pellets by centrifugal granulation method was introduced by Pan et al[34]. In this granulation process, binder solution was sprayed in parallel with powder excipients. However, the influence of some cushioning agent (sodium alginate) on the drug release retard was observed.

Tableting process parameters

The proper adjustment for tablet shape, having the smallest surface area/volume ratio, would result in better pellet protection during compression was found by Wagner et al [35]. The influence of tableting machine speeds on the film coating integrity is one parameter needed to be considered. Increasing the machine speeds led to increasing the bisacodyl release from Eudragit® FS30D after 2 h in pH 1, indicating an increase of coating damage[36].

The loading of coated pellets in compressed tablets is needed to be concerned for good drug uniformity and preventing segregation of coated pellets. Beckert et al[37] found that mixtures with 30% w/w pellets showed good uniformity with granulated excipients. With 50-70% w/w pellets in a tablet, good content uniformity was found. This

can be explained by the formation of a percolating cluster of the pellets, which prevented segregation. A threshold of at least 50% w/w, corresponding to 30 % vol. /vol. pellet content has to be reached. The maximum achievable pellet content is reached by a rhombic lattice and is 71% v/v. However, damages of pellets and coatings during tableting increase upon increasing the pellet content of the mixture[14] with higher coated pellets loading, non-segregating mixtures of coated pellets and filler-binders are necessary to obtain tablets of uniform weight and drug content. Granules or pure microcrystalline cellulose, having a large surface area and a fibrous surface texture built a close percolating infinite cluster stabilizing the pellets at their location in the mixture [38].

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