International Journal of Pharmaceutics 384 (2010) 87–92

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Mechanical properties of excipients do not affect polymer matrix formation

Lipika Chatterjee*, Thomas Rades, Ian G. Tucker

School of Pharmacy, University of Otago, Dunedin, Otago 9054, New Zealand

ARTICLE INFO

Article history:
Received 29 December 2008
Received in revised form
21 September 2009
Accepted 30 September 2009
Available online 9 October 2009

Keywords:
Matrix tablets
Eudragit-RLPO
Excipients
Mechanical properties
Coalescence

ABSTRACT

Coalescence of polymer particles has been identified as a crucial step in film formation on tablets, pellets and granules. Though the significance of thermal treatment on matrix dosage forms is well established the process of coalescence in matrix formation and the forces driving it remain unexplored. The aim of this study was to investigate whether stresses in tablets, caused by deformation of excipient during compression, provide a driving force for polymer matrix formation. Polymer matrix tablets containing Eudragit-RLPO, a pH independent and permeable polymer at two levels 10 and 40% (w/w) were prepared by direct compression. Either lactose monohydrate (brittle) or mannitol (plastic) was used as a diluent at 80 or 50% (w/w) and indomethacin, a model drug was present at 10% (w/w). Tablets from each formulation type were prepared at two compression pressures either 221 MPa (above the yield pressure of both excipients) or 74 MPa (below the yield pressure of both excipients). Tablets from each formulation type compressed at the two compression pressures were thermally treated at 40 °C (below T_g) or 70 °C (above T_g) for 24 h. The rotating basket (100 rpm) method was used for the release studies conducted at 37 °C in 900 ml phosphate buffer (0.2 M) pH 7.2 as the dissolution medium. Morphological characteristics of the tablets were observed by scanning electron microscopy. Differences in tablet structure due to the formulation and processing variables were further evaluated by disintegration and tensile strength testing. Data from this factorial study were analysed by analysis of variance. Excipient mechanical properties determine matrix properties only at low polymer level independent of curing temperature and at high polymer level cured at 40 °C only. Though lactose and mannitol have different mechanical properties and therefore different deformation behaviors, this did not influence the properties of tablets containing 40% (w/w) polymer cured at 70 °C, suggesting stresses in these tablets are not a significant driving force for matrix formation.

1. Introduction

Matrix tablets consist of a drug either dispersed or dissolved in an inert matrix forming agent, prepared by conventional methods like direct compression, wet granulation or hot melt extrusion (Krajacic and Tucker, 2003; Zhu et al., 2006; Azarmi et al., 2002; Azarmi et al., 2005). Thermoplastic polymers, which on thermal treatment (curing) above their glass transition temperature (T_g) undergo a transition from the glassy to the rubbery state, are generally used to form stable matrix networks (Heller, 1987). It has been speculated that curing causes polymer chain movement and entanglement, followed by inter-diffusion of polymer chains (coalescence) thereby redistributing it throughout the matrix (Omelczuk and McGinity, 1993; Billa et al., 1998). Post-compression thermal treatment of matrices enhances the bonding strength, increases tortuosity and decreases porosity leading to increased tensile strength and decreased drug release (Omelczuk and McGinity, 1993; Billa et al., 1998; Shao et al., 2001).

The mechanism of coalescence of polymer latexes in film formation from has been discussed since the 1950 (Dillon et al., 1951; Brown, 1956; Sheetz, 1965; Tent and Nijenhuis, 2000) and the capillary force driving coalescence in film formation may also drive matrix formation particularly if wet granulation is used in manufacturing. The heterogeneous nature of matrices consisting of drug, polymer and other excipients suggests however, that the process of coalescence is more complex in matrix formation than in films (Krajacic and Tucker, 2003). Krajacic and Tucker (2003) observed that the coalescence process of matrix tablets prepared at 20 °C above the polymer minimum film forming temperature of −8 °C, continued in acidic pH medium at 37 °C during release studies. They speculated that since water could not evaporate in those conditions, coalescence could not be driven by capillary force. Although the matrix system has been studied extensively, and it has been shown that curing alters the release properties (Omelczuk and McGinity, 1993; Billa et al., 1998; Shao et al., 2001), no one has discussed the actual forces which drive these changes in matrix systems. Possibilities are: capillary forces (see above); surface tension of the

* Corresponding author.
E-mail address: chali858@student.otago.ac.nz (L. Chatterjee).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.09.047

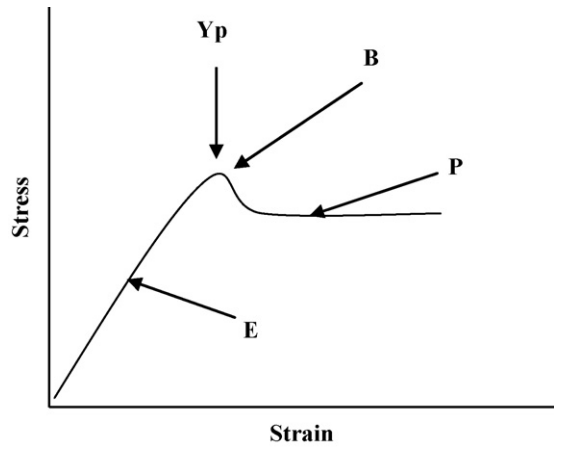

Fig. 1. Stress–strain profile indicating elastic deformation (E), brittle fracture (B) and plastic deformation (P).

polymer as discussed in the sintering process (Dillon et al., 1951); stresses locked in the compressed matrix tablet. These potential forces drive viscoelastic flow of the polymer particles in the rubbery state bringing them into contact. Subsequently inter-particle diffusion of polymer macromolecular chains leads to the formation of a stable matrix.

The aim of this paper was to test the hypothesis that stresses due to 'frozen elastic deformations' (Shlieout, 2000) contribute to the formation of the stable matrix on curing. This was tested by preparing matrices with two different excipients (lactose monohydrate and mannitol) with different mechanical properties (brittle and plastic), at low and high compression pressures, to produce matrices with different internal stresses.

During tableting, on compaction, the particles of the powder mix undergo rearrangement, deformation and bond formation (Armstrong, 1996; Paronen and Iikka, 1996). Depending on the stress applied the particles may exhibit elastic (E) or plastic deformation (P) or brittle fracture (B) or a combination of these (Nyström and Karehill, 1996; Rowe and Roberts, 1996). The yield pressure (Yp) corresponds to the maximum pressure a material can tolerate before it deforms permanently (Narayan and Hancock, 2003). The linear portion of the stress–strain profile (Fig. 1) represents elastic deformation at pressures below Yp and is usually reversible. However relaxation of elastically deformed materials may be restricted by the plastically deformed materials surrounding it resulting in internal stresses—'frozen elastic deformation' (Shlieout, 2000). We expect that tablets made from excipients with different mechanical properties will have different internal stresses. We hypothesize that these stresses in tablets, caused by 'frozen elastic deformation' of excipients, provide a driving force for polymer matrix formation.

In the present study, Eudragit-RLPO, a pH independent and permeable polymer was used as the matrix forming agent at two levels (10 and 40%, w/w), indomethacin (10%, w/w) was used as the model drug and lactose monohydrate (brittle) or mannitol (plastic) were used as diluents. The Yp of lactose is reported as 178 and 183 MPa and that of mannitol as 90 MPa (Rowe and Roberts, 1996; Narayan and Hancock, 2003); hence two compression pressures 74 MPa (below Yp) and 221 MPa (above Yp) and were selected to prepare the matrix tablets.

2. Materials and methods

Indomethacin was from DHY Pharmaceutical Co. Ltd. (Ningbo, China); Eudragit-RLPO was gifted by Evonik Industries (Darmstadt, Germany). Lactose monohydrate was bought from Lactose New Zealand (Hawera, New Zealand) and mannitol was from M&B Laboratory Chemical (Victoria, Australia). Sodium hydroxide and potassium dihydrogen phosphate were purchased from Ajax Finechem (Auckland, New Zealand).

2.1. Raw material characterization

2.1.1. Particle size and density measurement

Particle size measurements of the polymer and indomethacin were carried out using a laser diffraction analyser (Mastersizer X Malvern Instruments, UK) and the true densities were determined by helium pycnometry (AccuyPyc 1330 Micromeritics Instruments Corporation, USA). Mannitol and lactose monohydrate were sieved (Retsch AS 200 basic, Germany) to a size range of 125–250 μm. Indomethacin and Eudragit-RLPO were used as-received. Experiments were carried out in duplicate.

2.1.2. Thermal analysis

Thermal analyses of indomethacin, Eudragit-RLPO, mannitol and lactose were performed by differential scanning calorimetry (DSC) using a TGA Instruments Q100, USA in pin holed aluminium pans. Samples (5–10 mg) were heated at 10 K/min over a temperature range of 30–250 °C. Thermogravimetry (TGA Instruments Q50, USA) analysis was performed at a heating rate of 10 K/min over a temperature range of 30–180 °C. Experiments were carried out in duplicate.

2.2. Preparation of matrix tablets

2.2.1. Percolation threshold study

Formulations contained 10, 20, 30, 40 or 50% (w/w) Eudragit-RLPO, 10% (w/w) indomethacin and either lactose monohydrate or mannitol to 100% (w/w). The ingredients were gently mixed in a mortar by geometric dilution. Tablets (500 mg) were prepared using a laboratory press (F. Carver Inc., USA) equipped with a 13 mm flat faced punch set at 221 MPa with a dwell time of 2 min. The punch set was swabbed with a thin film of magnesium stearate solution (5%, w/v) in methanol to prevent sticking. After compression, tablets were treated at 70 °C for 24 h (Clayson oven, New Zealand) and then, stored over silica gel at ambient temperature.

2.2.2. Excipient mechanical properties and correlation with other variables of the polymer matrix tablet

A full factorial study was constructed. Matrices containing 10 or 40% (w/w) Eudragit-RLPO, 10% (w/w) indomethacin and either lactose or mannitol to 100% (w/w) were prepared, as above, at two compression pressures of 221 MPa (above excipient Yp) or 74 MPa (below excipient Yp). After compression, tablets were thermally treated at either 40 or 70 °C for 24 h and then stored over silica gel at ambient temperature.

2.3. Tablet morphology

The surfaces of matrix tablets were observed by scanning electron microscopy (SEM) after sputter coating with 10 nm of gold palladium (Emitech 575X High Resolution Sputter Coater, E M Technologies Ltd., England). The coated tablets were mounted on aluminium stubs with double sided carbon tape and observed at 3.0 kV using the field emission SEM (JEOL 6700F, Japan). The accelerating voltage was either 3 or 5 kV; probe current was 8 and both SEI (secondary) and LEI (lower secondary) detectors were used.

2.4. Drug release

The drug release from tablets of various formulations was conducted using a USP dissolution apparatus 1 (Erweka DT 600, Germany). The test was performed in 900 ml phosphate buffer pH 7.2 USP medium (0.2 M) at 37 °C and baskets were rotated at