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# Mechanical properties of excipients do not affect polymer matrix formation

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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

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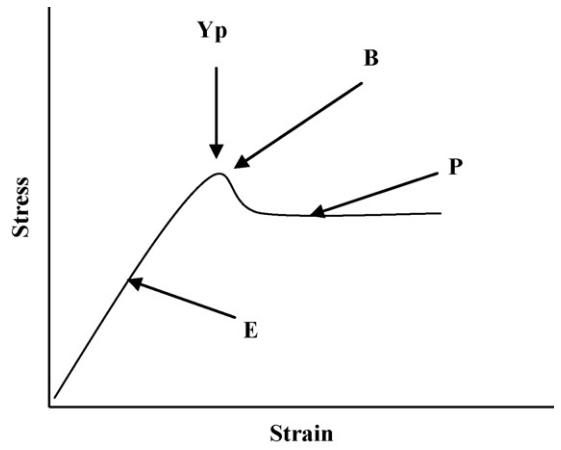


**Fig. 1.** Stress–strain profile indicating elastic deformation (E), brittle fracture (B) and plastic deformation (P).

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

100 rpm. Samples (5 ml) were collected with replacement over a period of 8 h. Tests were carried out in triplicate. Samples were analysed by a validated UV spectroscopy (CARY Varian, Australia) method at 318 nm.

### 2.5. Disintegration test

The disintegration test was performed in a USP disintegration apparatus (Shang Hai Huang Hai, China) using 800 ml of phosphate buffer pH 7.2 USP medium (0.2 M) at 37 °C ($n = 3$).

### 2.6. Mechanical test (tensile strength)

The load ($F$) required to break the thermally treated tablets ($n = 5$) from each formulation type was determined by diametrical compression (Erweka TBH-450IC Erweka GmbH, Germany) at a constant speed of 2.3 mm/s. The tensile strength ($\sigma_t$) of tablet was calculated as follows (Fell and Newton, 1970):

$$\sigma_t = \frac{2F}{\pi D h}$$

where $D$ and $h$ are the diameter and thickness of the tablet.

### 2.7. Statistical analysis

Data from the drug release, disintegration and tensile strength studies were statistically analysed by ANOVA using Minitab15 (Minitab Inc., USA) at significance of $p < 0.05$.

## 3. Results and discussion

### 3.1. Raw material characterisation

The melting point of indomethacin at 161 °C confirmed the drug to be the stable polymorphic form (γ indomethacin). The glass transition temperature ($T_g$) of Eudragit-RLPO was recorded at 56 °C. The melting point of lactose monohydrate and mannitol were noted at 215 and 168 °C, respectively. Differential scanning calorimetry (DSC) data of physical mixtures of Eudragit-RLPO and indomethacin cured at 70 °C for 24 h confirmed absence of solid-state plasticization.

The true densities of the materials measured by helium pycnometry are listed in Table 1 and the volume mean diameter of indomethacin and Eudragit-RLPO were recorded as 88 and 84 μm.

### 3.2. Effect of Eudragit-RLPO concentrations on polymer matrix formation

Percolation theory, initially used in the study of powder compaction behaviour of binary systems has been extended to understand and predict behaviour of more complex controlled release hydrophilic matrix systems (Blattner et al., 1990; Leuenberger et al., 1996; Melgozaa et al., 2001; Miranda et al., 2006, 2007). According to this theory, a percolating system consists of a large number of sites that are occupied by the components of the system. When the neighbouring sites in the system are occupied by the same component particles they form a cluster. This is termed

**Table 1**
True density of raw material measured by helium pycnometry.

| Raw material | Density (g/cm$^3$) |
|---|---|
| Indomethacin | 1.381 |
| Eudragit-RLPO | 1.92 |
| Mannitol | 1.49 |
| Lactose MH | 1.55 |

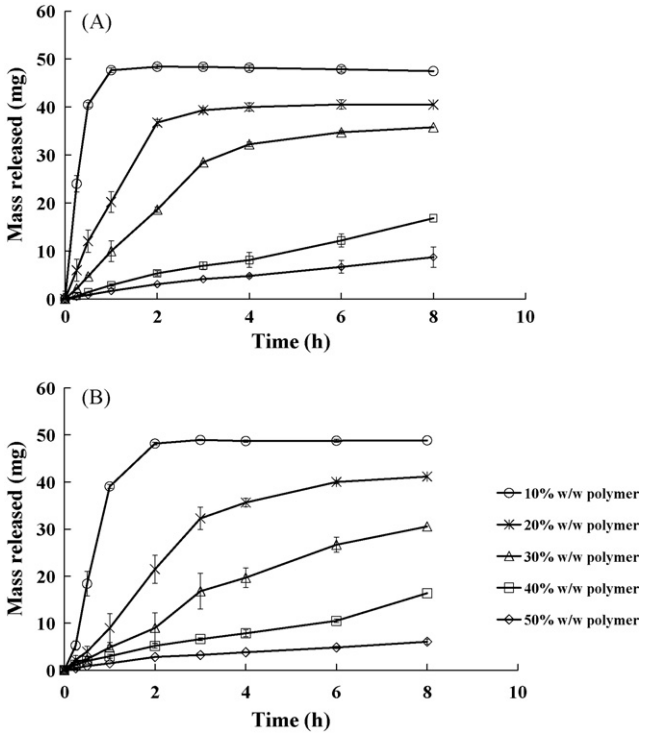


**Fig. 2.** Effect of polymer (Eudragit-RLPO) levels on drug release from (A) lactose and (B) mannitol containing matrices prepared at 221 MPa and cured at 70 °C, 24 h. Data presented are mean ± S.D. ($n = 3$).

site percolation and when bonds are formed between these clusters of particles it is called bond percolation (Leuenberger et al., 1996). Tablet formation may involve a combination of site and bond percolation. Since matrices are a mix of drug, polymer and other excipients, above a critical concentration of a component, there is a high probability that percolating clusters of that component will exist throughout the tablet (Leuenberger et al., 1996). At this critical concentration, termed the percolation threshold, significant changes in matrix properties such as abrupt changes in disintegration and drug release behaviours may be observed (Leuenberger et al., 1996; Fuertes et al., 2006; Miranda et al., 2006, 2007).

Initially, the effect of increasing polymer concentration on drug release behaviour from either lactose or mannitol containing matrices compressed at 221 MPa and cured at 70 °C for 24 h was studied. The abrupt change in the shape of the drug release curves for both lactose (Fig. 2(A)) and mannitol (Fig. 2(B)) tablets above 30% (w/w) polymer suggests a change in the release mechanism and hence in tablet structure. According to percolation theory, low polymer levels (e.g. 10 and 20%, w/w) are below the percolation threshold of the polymer so there are few polymer clusters, but there are continuous lactose or mannitol (80 and 70%, w/w) networks throughout the matrix. These water-soluble excipient networks rapidly disintegrated (at <25 min at 10%, w/w polymer and <80 min at 20%, w/w polymer) resulting in complete drug release in 2 h. The sharp change in slope between 30 and 40% (w/w) polymer levels suggests that the polymer clusters are percolating the entire tablet. At 40 and 50% (w/w) polymer, the presence of the continuous insoluble polymer network throughout the matrix maintained the integrity of these tablets resulting in slow and incomplete release over 8 h.

### 3.3. Effect of mechanical properties of excipients on drug release, disintegration time and tensile strength of Eudragit-RLPO matrices

Matrix tablets were characterised by drug release, disintegration time and tensile strength tests. Statistical analysis of these

**Table 2**
*p*-Values for three-factor interactions for matrix properties obtained by ANOVA using a general linear model.

| Interactions | Drug release | Tensile strength |
|---|---|---|
| Excipient type × polymer level × curing temperature | 0.009 | 0.156 |
| Excipient type × polymer level × compression pressure | 0.487 | 0.024 |
| Excipient type × compression pressure × curing temperature | 0.261 | 0.222 |

data revealed significant main effects (e.g. for release: polymer level > curing temperature > excipient). That is, the type of excipient had a significant effect ($p < 0.05$) on release which might suggest that the mechanical properties of the excipients are affecting coalescence of the polymer particles. This however, is not so for the reasons discussed below.

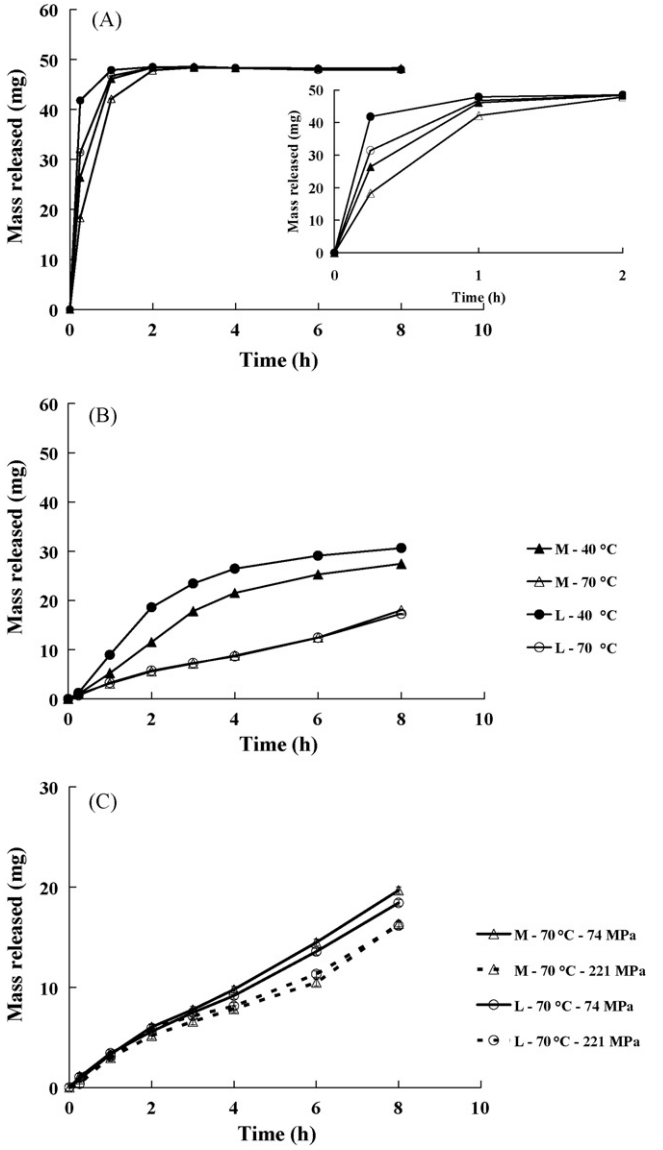


**Fig. 3.** Effect of type of excipient (M—mannitol, L—lactose), curing temperature and polymer level on average drug release from (A) 10% (w/w) Eudragit-RLPO matrices (insert shows release in first 2 h), (B) 40% (w/w) Eudragit-RLPO matrices, (C) 40% (w/w) Eudragit-RLPO matrices prepared at 74 and 221 MPa and cured at 70 °C. Experiments were performed in 900 ml phosphate buffer pH 7.2 at 37 °C in a USP basket apparatus at 100 rpm. Data are means. Pooled standard errors are within the symbols.

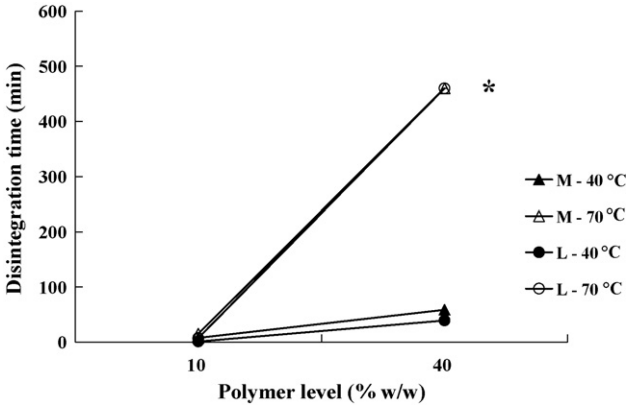


**Fig. 4.** Effect of type of excipient (M—mannitol, L—lactose), curing temperature and polymer level on average disintegration time of Eudragit-RLPO matrices. Disintegration time experiments were performed in phosphate buffer pH 7.2 at 37 °C. Data presented are means. Pooled standard errors are within the symbols. *Tablets did not disintegrate in 8 h.

**Table 3**
*p*-Values for two-factor interactions for matrix properties obtained by ANOVA using a general linear model.

| Interactions | Drug release | Tensile strength |
|---|---|---|
| Excipient type × polymer level | 0.844 | 0.001† |
| Excipient type × compression pressure | 0.112 | 0.134 |
| Excipient type × curing temperature | 0.001† | 0.551 |
| Polymer level × compression pressure | 0.564 | 0.001 |
| Polymer level × curing temperature | 0.057 | 0.001 |
| Compression pressure × curing temperature | 0.979 | 0.001 |

† Significant two-factor interactions involving excipient type.

There were statistically significant interactions between the type of excipient (mannitol-plastic, lactose-brittle) and other formulation (polymer level) and processing variables (compression pressure and curing temperature) reflecting the complexity of these systems (Table 2). Thus, it is not possible to discuss the effect of the mechanical properties of the excipients in isolation, but rather mechanical properties must be considered in relation to other factors with which it interacts.

### 3.3.1. *Interaction between excipient type, polymer level and curing temperature*

The highly significant interaction between excipient type, polymer level and curing temperature on drug release (Table 2) and

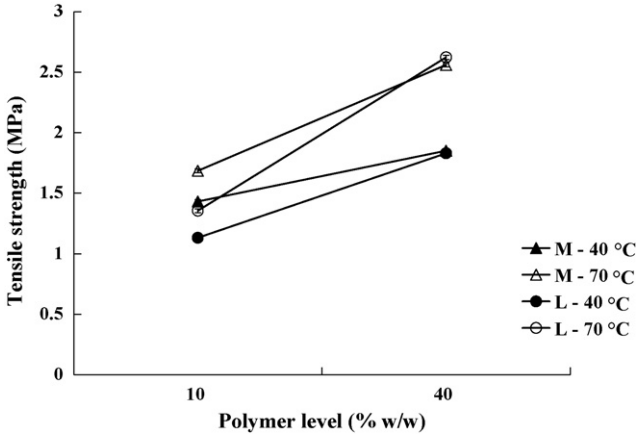


**Fig. 5.** Effect of type of excipient (M—mannitol, L—lactose) at 10 and 40% polymer level on average tensile strength of Eudragit-RLPO matrices. Data are presented as means. Pooled standard errors are within the symbols.

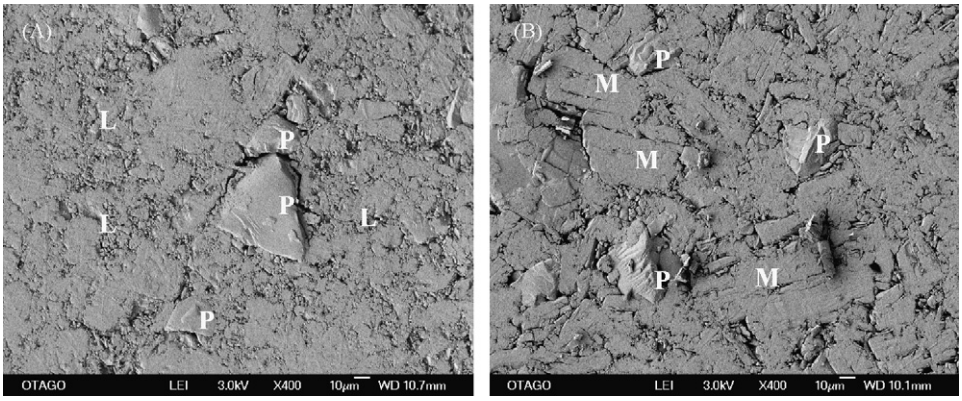


**Fig. 6.** Surface structure of 10% (w/w) Eudragit-RLPO (P) matrices prepared at 221 MPa and cured at 70 °C for 24 h: (A) lactose monohydrate—L and (B) mannitol—M.

disintegration time indicates that the effect of the type of excipient depends on the polymer level and curing temperature. The difference in release behaviour (Fig. 3(A)) and disintegration (Fig. 4) at 10% polymer are minor and reflect the difference in compaction behaviour of lactose and mannitol. At 40% polymer (Fig. 3(B)) excipient type had a clear effect in 40 °C tablets (lactose > mannitol) when there is no polymer coalescence (<$T_g$) whereas at 70 °C, the type of excipient was not important (Fig. 3(B)) irrespective of compression pressure (Fig. 3(C)). So, the excipient effect only occurs on 40 °C treated tablets and must relate to the differing behaviours of lactose and mannitol on compaction. But lactose and mannitol mechanical properties do not result in different behaviours at 70 °C, that is, coalescence of polymer is independent of the mechanical properties of the excipients. We postulated that 'frozen elastic deformation' could be a driving force for coalescence of the polymer, but this hypothesis is not supported by the release and disintegration data.

Although for tensile strength, there was no significant three-factor interaction between the type of excipient, polymer level and curing temperature, there were significant two-factor interactions but only one of these involved the type of excipient (excipient type × polymer level) (Table 3). Mannitol matrices were significantly ($p < 0.05$) stronger than lactose matrices only at the 10% (w/w) polymer level (Fig. 5) that is below the percolation threshold of the polymer where coalescence is of little importance. At 40% polymer level there was no difference in mannitol and lactose tablets supporting the conclusion that the mechanical properties of the excipient do not influence matrix formation.

### 3.3.2. Interaction of excipient type, polymer level and compression pressure

There was no significant interaction of excipient type, polymer level and compression pressure on drug release and disintegration time ($p = 0.114$) and only a marginally significant interaction on the tensile strength (Table 2). Further, there was no significant interaction between excipient type and compression pressure (Table 3). This too supports the conclusion that 'frozen elastic deformation' is not a driving force for coalescence.

During tableting, excipients undergo deformation depending on their inherent mechanical property. At 221 MPa (above Yp) lactose fractured into a large number of smaller sized particles thereby increasing the total surface area (Fig. 6(A)). SEM showed polymer particles surrounded by smaller (<10 μm) lactose particles whereas mannitol particles underwent plastic deformation and flattened at 221 MPa (Fig. 6(B)). It has been reported that the newly formed lactose particles due to brittle fracture are held by relatively weak attraction forces over the inter particle distance (Fuhrer, 1996).

Plastic materials like mannitol are preferred over highly fragmenting materials due to their ability to form larger bonding surface areas (Nyström and Karehill, 1996). Studies suggest that the decrease in surface area during compaction actually reflects the involvement of those surface areas in inter-particulate bond formation (Fuhrer, 1996; Nyström and Karehill, 1996). SEM showed the differences in matrix structure due to the different deformation behaviour of lactose and mannitol in 10% (w/w) polymer matrices cured at both 40 and 70 °C but this was not so clear in 40% (w/w) polymer matrices.

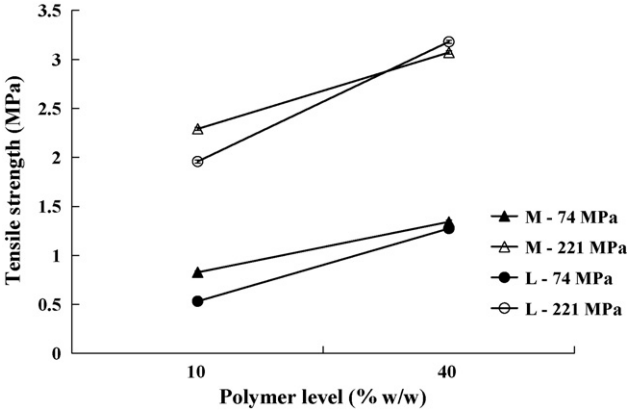


**Fig. 7.** Effect of type of excipient (M—mannitol, L—lactose), compression pressure and polymer level on average tensile strength of Eudragit-RLPO matrices. Data are presented as means. Pooled standard errors are within the symbols.

As expected for both polymer levels the matrices compressed at 221 MPa were always stronger than those compressed at 74 MPa. At 10% (w/w) polymer the mannitol matrices were significantly stronger than the lactose matrices whereas no such difference was observed at 40% (w/w) polymer (Fig. 7). The excipient network governed the matrix hardness in lower polymer matrices whereas the polymer network provided strength to higher polymer matrices, but the strength was independent of the mechanical properties of the excipients (lactose and mannitol).

## 4. Conclusion

All four variables (polymer content; thermal treatment; excipient mechanical property and compression pressure) influence the polymer matrix properties and they interact and so they cannot be considered independently. The percolation threshold for the Eudragit-RLPO was observed between 30 and 40% (w/w). The presence of infinite excipient particle clusters in 10% (w/w) polymer (80%, w/w excipient) matrices define the matrix properties whereas at 40% (w/w) polymer there are networks of both excipient and polymer. High polymer level matrices cured above polymer $T_g$

retarded the drug release, increased the tensile strength and disintegration time significantly probably due to coalescence of polymer particles. Mechanical property (deformation behaviour) of excipient plays an important role only at low polymer level irrespective of curing temperature and at higher polymer level only at curing temperatures below the $T_g$. Since there were no differences in the properties of lactose and mannitol matrices cured above $T_g$, it is concluded that in these systems, internal stresses do not provide a driving force for coalescence of the polymer particles.

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## References

Azarmi, S., Farid, J., Nokhodchi, A., Bahari-Saravi, S.M., Valizadeh, H., 2002. Thermal treating as a tool for sustained release of indomethacin from Eudragit RS and RL matrices. Int. J. Pharm. 246, 171–177.

Azarmi, S., Ghaffari, F., Löbenberg, R., Nokhodchi, A., 2005. Mechanistic evaluation of the effect of thermal-treating on Eudragit RS matrices. Farmaco 60, 925–930.

Billa, N., Yuen, K.H., Peh, K.K., 1998. Diclofenac release from Eudragit-containing matrices and effects of thermal treatment. Drug Dev. Ind. Pharm. 24, 45–50.

Blattner, D., Kolb, M., Leuenberger, H., 1990. Percolation theory and compactability of binary powder systems. Pharm. Res. 7, 113–117.

Brown, G.L., 1956. Formation of films from polymer dispersion. J. Polym. Sci. 22, 423–434.

Dillon, R.E., Matherson, L.A., Bradford, E.B., 1951. Sintering of synthetic latex particles. J. Colloid Sci. 6, 108–117.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametrical compression test. J. Pharm. Sci. 59, 688–691.

Fuertes, I., Miranda, A., Millan, M., Isidoro, C., 2006. Estimation of the percolation thresholds in acyclovir hydrophilic matrices. Eur. J. Pharm. Biopharm. 64, 336–342.

Fuhrer, C., 1996. Interparticulate attraction mechanisms. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, vol. 71. Dekker, New York, pp. 1–17.

Heller, J., 1987. Use of Polymers in Controlled Release of Active Agents. In: Robinson, J., Lee, V. (Eds.), Controlled Drug Delivery, vol. 29. Dekker, New York, pp. 179–212.

Krajacic, A., Tucker, I.G., 2003. Matrix formation in sustained release tablets: possible mechanism of dose dumping. Int. J. Pharm. 251, 67–78.

Leuenberger, H., Leu, R., Bonny, J.D., 1996. Application of percolation theory and fractal geometry to tablet compaction. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, vol. 71. Dekker, New York, pp. 133–164.

Melgozaa, L.M., Rabascob, A.M., Sandovala, H., Caraballo, I., 2001. Estimation of the percolation thresholds in dextromethrophan hydrobromide matrices. Eur. J. Pharm. Sci. 12, 453–459.

Miranda, A., Milan, M., Caraballo, I., 2006. Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery. Int. J. Pharm. 311, 75–81.

Miranda, A., Milan, M., Caraballo, I., 2007. Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophyllic matrix tablets. J. Pharm. Sci. 96, 2746–2756.

Narayan, P., Hancock, B., 2003. The relationship between the particle properties, mechanical behavior, and surface roughness of some pharmaceutical excipient compacts. Mater. Sci. Eng., A A355, 24–36.

Nyström, C., Karehill, P.G., 1996. The importance of intermolecular bonding forces and the concept of bonding surface area. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, vol. 71. Dekker, New York, pp. 17–54.

Omelczuk, M.O., McGinity, J.W., 1993. The influence of thermal treatment on the physical–mechanical and dissolution properties of tablet containing poly(DL-lactic acid). Pharm. Res. 10, 542–548.

Paronen, P., Iikka, J., 1996. Porosity-pressure functions. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, vol. 71. Dekker, New York, pp. 55–56.

Rowe, R.C., Roberts, R.J., 1996. Mechanical properties. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, vol. 71. Dekker, New York, pp. 283–284.

Shao, Z.J., Farooqui, M.I., Diaz, S., Krishna, A.K., Muhammad, N.A., 2001. Effects of formulation variables and post-compression curing on drug release from a new sustained-release matrix material: polyvinylacetate-povidone. Pharm. Dev. Technol. 6, 247–254.

Sheetz, D.P., 1965. Formation of films by drying of latex. J. Appl. Polym. Sci. 9, 3759–3773.

Shlieout, G., 2000. Investigation of the mechanical properties of two polyvinyl alcohols and their influence on drug release. Drug Dev. Ind. Pharm. 26, 499–505.

Tent, A.V., Nijenhuis, K.T., 2000. The film formation of polymer particles in drying thin films of aqueous acrylic lattices. J. Colloid Interface Sci. 232, 350–363.

Zhu, Y., Shah, N., McGinity, J., 2006. Controlled release of a poorly water-soluble drug from hot-melt extrudates containing acrylic polymers. Drug Dev. Ind. Pharm. 32, 569–583.