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Matrix formation in sustained release tablets: possible mechanism of dose dumping

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Abstract

Conditions under which poly(ethyl acrylate, methyl methacrylate) 2:1 (poly(EA-MMA), Eudragit NE) forms a stable matrix were investigated in tablets with diclofenac sodium (DS) as an active substance. DS was granulated with the aqueous polymer dispersion. Granules and/or tablets were cured under various temperature and humidity conditions. A six position rotating disk (200 rpm) apparatus was used for the release studies conducted in 37 °C acid then phosphate buffer (0.4 M) pH 6.8 or buffer only as the dissolution media. Morphological characteristics of the tablet surface were observed under SEM. Changes in tablet structure upon curing were evaluated through changes in tablet mechanical characteristics. Modulus of rupture, Young's modulus, AUC, $AUC_{<max}$, $AUC_{>max}$, where $AUC = AUC_{<max} + AUC_{>max}$, were determined by the three-point bending test. Some poorly cured tablets dose-dumped when placed directly into buffer but not if first placed in acid and then buffer. A higher content of polymer in the matrix, led to formation of a stronger polymer network upon higher curing temperature and/or longer curing duration, whereas relative humidity had a minor effect.

Keywords: Dissolution; Dose dumping; Granulation; Matrix; Sustained release; Tensile strength

1. Introduction

Reservoir and matrix tablets are common sustained release (SR) dosage forms, in part, due to their apparent simplicity of formulation and production. Reservoir systems consist of a drug/excipient core coated with a controlling membrane, whereas matrix systems comprise drug/excipient embedded within a matrix. Typically, polymers are used for the coating and matrix materials. They can be classified as either hydrophobic (polyethylene, polypropylene, ethylcellulose) or hydrophilic (hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, derivatives of polylactoglycolic acid, polymethacrylates). Although originally applied as organic solutions, polymethacrylates are now commonly used as aqueous dispersions of latex particles (200 nm diameter).

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Research on polymer film formation on tablet surfaces has demonstrated the essential process of coalescence of the latex particles (Brown, 1956; Bauer et al., 1998). This coalescence occurs provided the processing temperature is above the minimum film forming temperature (MFT; McGinity and Lehmann, 1997; Bauer et al., 1998) and depends on capillary forces created by the evaporation of water (Brown, 1956; Bauer et al., 1998; Obara et al., 1999). When the processing temperature is at least 20 °C above the MFT, film formation occurs in seconds to minutes (Bauer et al., 1998). Typically this is the case for soft polymers, whereas for hard polymers with higher MFTs, the processing temperature is usually closer to MFT, so film formation can take hours to days (Bauer et al., 1998). Although these principles are well-known for film coating, there are few reports dealing with latex coalescence in matrix dosage forms where the process is likely to be more complex given the mix of latex particles, drug and excipients and the competitive distribution of water. Nevertheless, heating of tablets has been shown to be important.

Omelczuk and McGinity (1993) reported that the thermal treatment of theophylline matrix tablets above the glass transition temperature (Tg) decreased drug release in comparison with untreated tablets. This was explained by an annealing effect that caused stronger compaction and more effective distribution of polymer throughout the matrix. Tsai et al. (1998) granulated conventional excipients, such as lactose and dibasic calcium phosphate (DCP) with the film-forming polymers poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1 (Eudragit RS 30D), poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit RL 30D) and ethylcellulose (Surelease). Granulated excipients were directly compressed to fabricate SR captopril tablets. Billa et al. (1998) suggested that thermal treatment led to a greater particle coalescence of poly(ethyl acrylate, methyl methacrylate) 2:1 (Eudragit NE 40D) resulting in higher tortuosity and lower porosity of the matrix. Consequently, release of diclofenac sodium (DS) was sustained.

More research is required for a detailed mechanistic understanding of matrix formation in these systems. This is important not only to allow predictability of release from matrix tablets, but also to control the potential for poorly formed matrix tablets to dose-dump.

The aim of the present study was to investigate conditions under which the polymer matrix is formed and, hence, the dependence of drug release on matrix formation. We also show that dose dumping can occur in poorly formed matrix tablets and that this behaviour could be dependent on the gastric residence time of the tablet.

Poly(ethyl acrylate, methyl methacrylate) 2:1 (poly(EA-MMA)) in the form of an aqueous dispersion (Eudragit NE 40D) was investigated as a matrix-forming polymer and DS was used as a model drug. Preliminary results of this work were presented previously (Tucker and Krajacic, 2001).

2. Materials and methods

2.1. Materials

DS, regular (min 70% particles <45 μm), produced by Sekhsaria Chemicals Ltd. (Bombay, India), was used as received. Poly(EA-MMA) in the form of 40% aqueous dispersion, produced by Röhm Pharma (Darmstadt, Germany), was received as a gift from Plastral Trading (NZ) Ltd. (Auckland, New Zealand) and used as a binder. It has a Mw = 800 000, an MFT of 5 °C and Tg of −8 °C. Hydrochloric acid (concentrated), di-sodium hydrogen orthophosphate, anhydrous and potassium di-hydrogen orthophosphate were produced by APS Chemicals Ltd. (Seven Hills, Australia) and used for the preparation of the dissolution media.

2.2. Methods

2.2.1. Granulation and compression

DS was granulated by hand with an aqueous dispersion of poly(EA-MMA) (DS:poly(EA-MMA) = 6:1 and 3:1 mass ratio). Duplicate batches of each formulation were dried for 48 h under ambient conditions of 20, 23 and 26 °C

Table 1
Curing conditions of tablets of group I granules

	Cured tablets			
	37 °C		50 °C	
DS:poly(EA-MMA) = 6:1 DS:poly(EA-MMA) = 3:1	1 h	12 h	1 h	12 h

Table 2
Curing conditions of granules (group II) and tablets

Uncured granules Cured granules: 50 °C/1 h	Uncured tablets	Cured tablets (50 °C/1 h)

DS:poly(EA-MMA) = 3:1.

Table 3
Curing conditions of granules (group III) and tablets

Uncured granules over silica gel/4 °C/2 days Cured granules: 33% RH/4 °C/2 days Cured granules: 81% RH/4 °C/2 days	Tablets: 0 day, then 37 °C/1 h	Tablets: 4 °C/2 days then 37 °C/1 h

DS:poly(EA-MMA) = 3:1.

(groups I, II, III) prior to compression with a laboratory press (F. Carver Inc, USA). In a preliminary study, the ambient drying temperature was 18 °C.

To determine the effect of the curing temperature of the tablets on drug release, tablets from group I were stored at 37 and 50 °C for 1 and 12 h, prior to release testing (Table 1).

To determine the effect of curing temperature of the granules and/or tablets on drug release, half of the granules from group II were cured at 50 °C for 1 h, prior to compression. Half of the tablets produced from uncured and cured granules were cured at 50 °C for 1 h, prior to release testing (Table 2).

Humidity effects were assessed by storing granules from group III at 4 °C for 2 days over silica gel, or at 33 or 81% RH. Tablets made from these granules were stored for 0 or 2 days at 4 °C and then treated at 37 °C for 1 h prior to release testing (Table 3).

2.2.2. Release studies

A six position rotating disk (200 rpm) apparatus (Tianjin University Radio Factory, China) was used for the release studies. Phosphate buffer (0.4 M) pH 6.8 was used as the dissolution medium. Samples were drawn at standard times up to 180 min and analysed by a validated spectrophotometric assay (290 nm). All studies were conducted at 37 °C.

2.2.3. Scanning electron microscopy (SEM)

Uncured and cured (50 °C/1 h) tablets, withdrawn after 45 min of release and dried overnight, were attached with double-sided carbon tape on the aluminium stubs, coated (Bio-Rad coating system) with Au–Pd alloy (18% Au+20% Pd) and observed with a scanning electron microscope (Cambridge S360 stereo scan microscope) at magnification of 800 ×.

2.2.4. Tensile strength studies (three-point bending test)

Tests were performed on tablets from each group (I, II, III) cut into bars and stored at 4 °C, at least 24 h prior to tensile strength studies. Modulus of rupture was determined by the three-point bending test (Instron 1193), from the force required to fracture the bar, according to the formula:

$$\text{Modulus of rupture [MPa]} = \frac{3FL}{2wd^2},$$

where F is force causing fracture (N), L is distance between supports (mm), w is width of the sample (mm), d is depth of the sample (mm).

Young's modulus was calculated as the slope of the linear portion of the tensile stress versus elongation curve in the range from 0 to maximum tensile stress.

Area under the tensile stress versus elongation curve (AUC) was expressed as AUC in the range where tensile stress increased to its maximal value ($AUC_{<max}$) and AUC in the range after the maximum ($AUC_{>max}$). Generally, $AUC = AUC_{<max} + AUC_{>max}$.

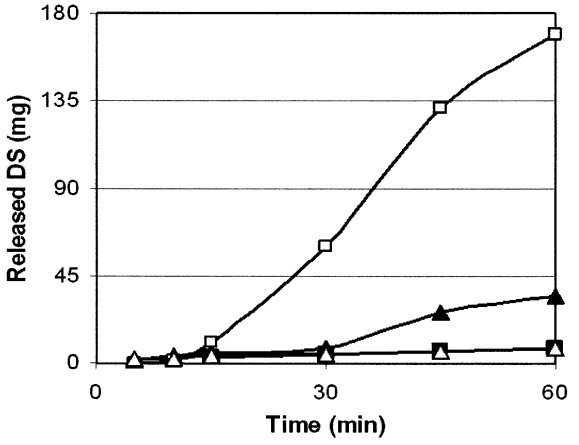

Fig. 1. Effect of various treatments on the release of DS from matrix tablets in a rotating disk apparatus at 37 °C. (■) 0.1 M HCl (60 min at 37 °C)+phosphate buffer, 0.4 M; (▲) phosphate buffer, 0.4 M; (□) pretreatment in 0.1 M HCl (60 min at 8 °C)+phosphate buffer 0.4 M; (△) pretreatment at 37 °C (overnight)+phosphate buffer 0.4 M.

2.2.5. Statistical analysis

The release data were analysed by a repeated measures ANOVA using MINITAB 12.1 at a significance level of $P < 0.05$.

3. Results and discussion

In the preliminary study tablets pretreated with acid (0.1 M HCl) at 37 °C for 1 h, showed a SR when placed in pH 6.8 buffer, whereas those put directly into buffer swelled and disintegrated rapidly within 1 h (Fig. 1). Since the acid pretreated tablets were simultaneously exposed to 37 °C and aqueous medium prior to release (DS is insoluble in acid), it raised the question whether temperature and/or moisture were influencing the matrix structure. An alternative explanation could be precipitation of diclofenac acid on the tablet surface.

In order to test these postulates, tablets were exposed to cold acid at 8 or 37 °C, prior to release studies. Pretreatment in cold acid did not sustain drug release; DS release was significantly higher in comparison to release even from tablets without pretreatment (Fig. 1). Consequently, the moisture effect and precipitation of diclofenac acid on the tablet surface do not explain the effect. Pretreatment at 37 °C prior to release markedly decreased DS release resulting in a dissolution profile similar to that from tablets pretreated in acid at 37 °C. This suggested temperature as the factor with the main influence on matrix structure(Fig. 1).

This release behaviour provides a possible mechanism for dose dumping from matrix tablets of this type. Tablets can remain in the stomach for variable times (from minutes to hours) depending on the fed/fasting state and dosing in relation to housekeeper waves. It is well known that continuous intake of small meals throughout the day can delay gastric emptying, and, hence, the emptying of tablets for more than 10 h. Further, gastric emptying follows a circadian rhythm, being slower in the afternoon than in the morning (Swarbrick and Boylan, 1995). The data in Fig. 1 suggest that a matrix tablet cleared from the stomach in a short time could dump its dose in the intestine, whereas a tablet retained more than one hour would have a SR. Presumably, this would not occur if the tablet was completely cured prior to administration.

Billa et al. (1998) found that tablets prepared from DS:poly(EA-MMA):microcrystalline cellulose granules showed SR after thermal treatment of granules and tablets. As drug release was not detectable at pH 1 and 4, they suggested pH dependence of drug release. Indeed, DS is insoluble at low pHs, therefore, drug release will be low, independently of thermal treatment. However, our data suggest that matrix tablets of this type can continue to undergo a curing process at 37 °C in dilute acid. This is surprising since current theory says that coalescence of polymer latex particles, at least for film formation, is driven by evaporation of water and the resultant capillary forces. These forces bring about coalescence of latex particles above the MFT. When tablets are immersed in dilute acid, evaporation is clearly not possible, so the driving force for the assumed latex particle coalescence can not be the evaporation of residual moisture within the tablet. Kidokoro et al. (2001) studied tablets containing ibuprofen granulated with hot, melted poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methylacrylate chloride) 1:2:0.1 (commercially available in a powder form as Eudragit RS PO). They found that

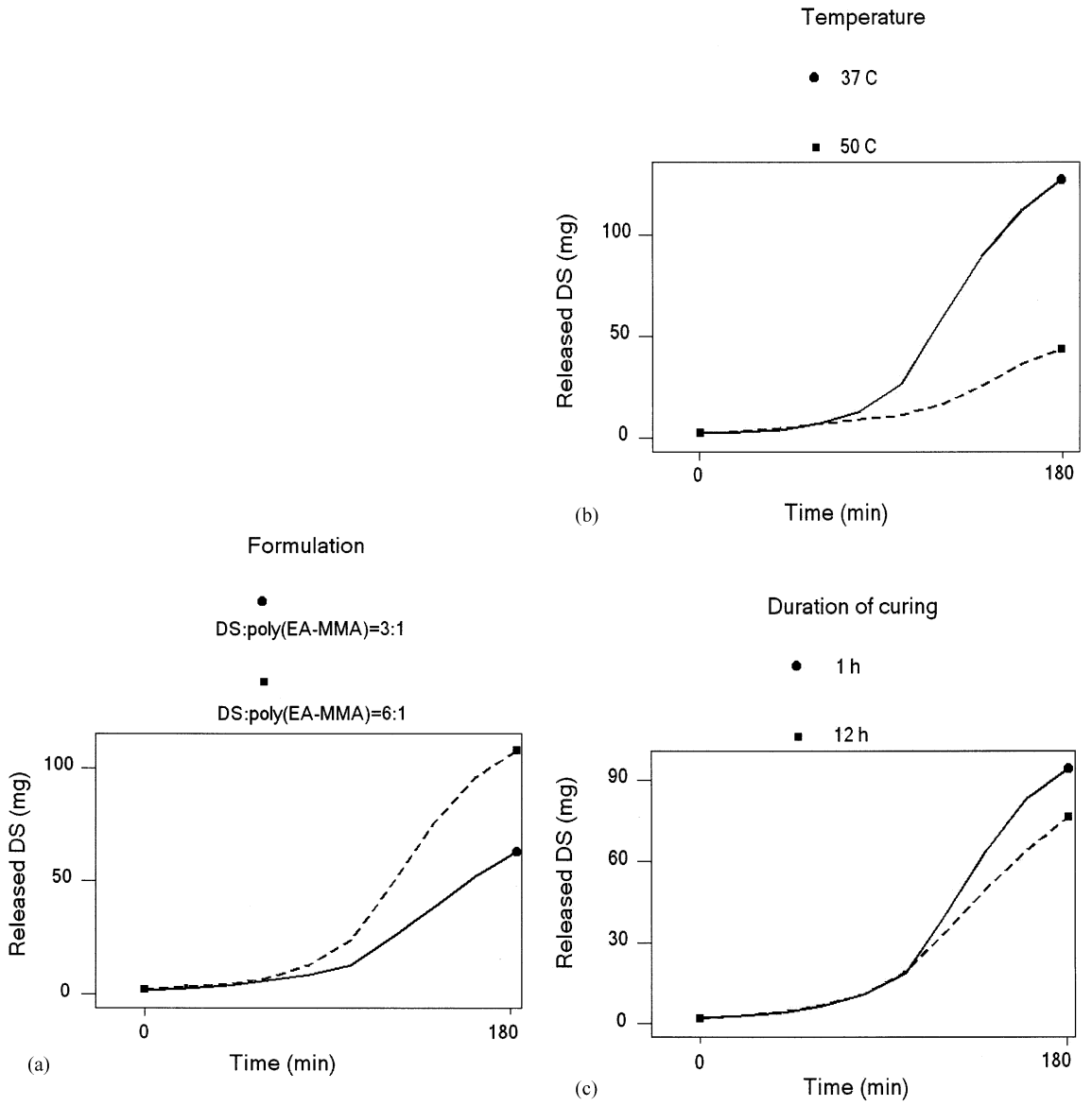

Fig. 2. Effect of (a) polymer content, (b) curing temperature and (c) curing time on the release of DS at pH 6.8 and 37 °C. Results are group means.

ibuprofen was incorporated in the polymer during processing and had a plasticising effect enabling structural changes in the tablets due to the coalescence of plasticised polymer particles. Porosity of the tablets was reduced, therefore, drug release rate decreased.

To investigate how temperature and time influenced curing and, hence, drug release, tablets with different drug–polymer ratios (DS:poly(EA-MMA) = 6:1 and DS:poly(EA-MMA) = 3:1) were cured at 37 and 50 °C for 1 and 12 h (group I).

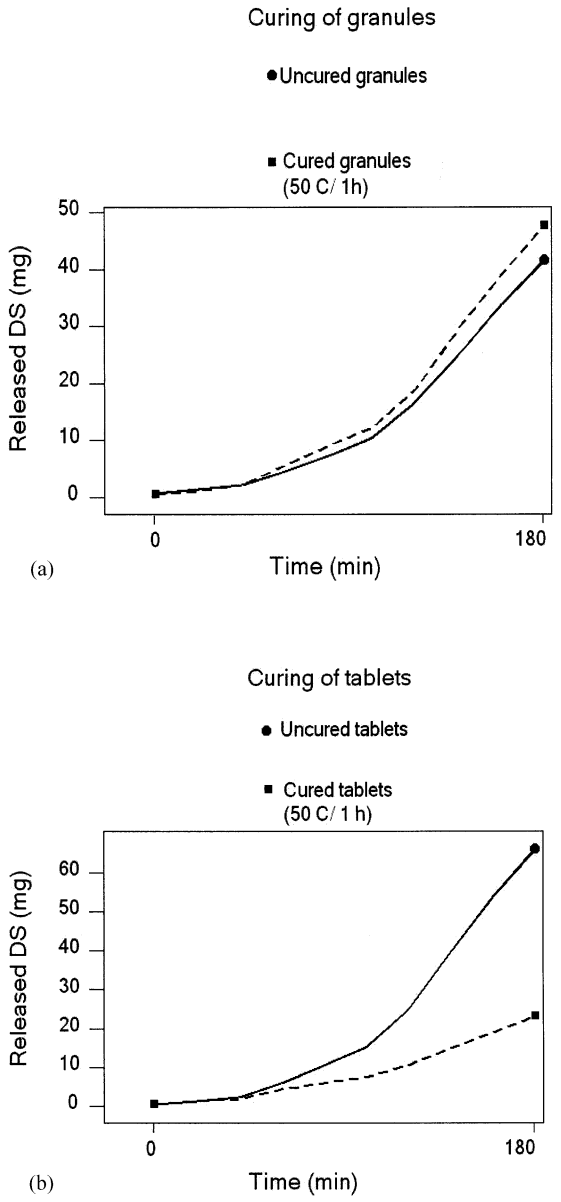

Fig. 3. Effect of (a) curing of the granules and (b) curing of the tablets on the release of DS at pH 6.8. Results are group means.

ANOVA demonstrated that higher polymer content, higher curing temperature and/or longer curing time decreased drug release rate (Fig. 2). Interactions between polymer content and curing temperature, polymer content and curing time, as well as curing temperature and curing time, were not significant.

Granules from group II were cured prior to compression to determine whether or not increased temperature influenced drug release in the same way as in the group I (curing of tablets made from uncured granules). It was found that curing of granules did not markedly affect drug release (Fig. 3a); however, curing of the tablets made from uncured granules again had a major influence on drug release (Fig. 3b). Only cured tablets made from uncured granules remained intact for extended times during release studies. Even cured tablets made from cured granules disintegrated within 3 h suggesting that cured granules did not compress into tablets with a stable matrix (Fig. 4).

Tablets made from group III granules (dried at 26 °C) released DS markedly slower than the tablets in the preliminary study and slower than tablets from groups I and II. Although the MFT of the poly(EA-MMA) is reported to be below 10 °C (McGinity and Lehmann, 1997; Bauer et al., 1998), the release rate of DS still varied inversely with the granule drying temperature (18–26 °C). It has been reported for polymer films (Bauer et al., 1998), that latex particle coalescence followed by film formation depends on the processing temperature and it occurs in minutes if the processing temperature is at least 20 °C above polymer Tg. When polymer is used as a binder in granules, coalescence of the polymer latex particles occurs during drying. However, we found that even drying for 48 h at a temperature of 26 °C, that is 34 °C above the Tg and 18 °C above the MFT, did not lead to complete curing of the granules since further curing at 50 °C/1 h affected release. However, subsequent storage at 4 °C of the dried granules under different RHs had a minor effect on release as did storage of the tablets at 4 °C, made from uncured granules (data not shown) indicating that RH without increased temperature did not influence drug release rate.

Change in tablet surface morphology was observed under SEM of tablets from group I granules. The differences in appearance of tablet surfaces are understandable in terms of the different polymer contents. Tablets with a 6:1 drug:polymer ratio showed larger cavities left after drug dissolution (Fig. 5). After curing, although mor-

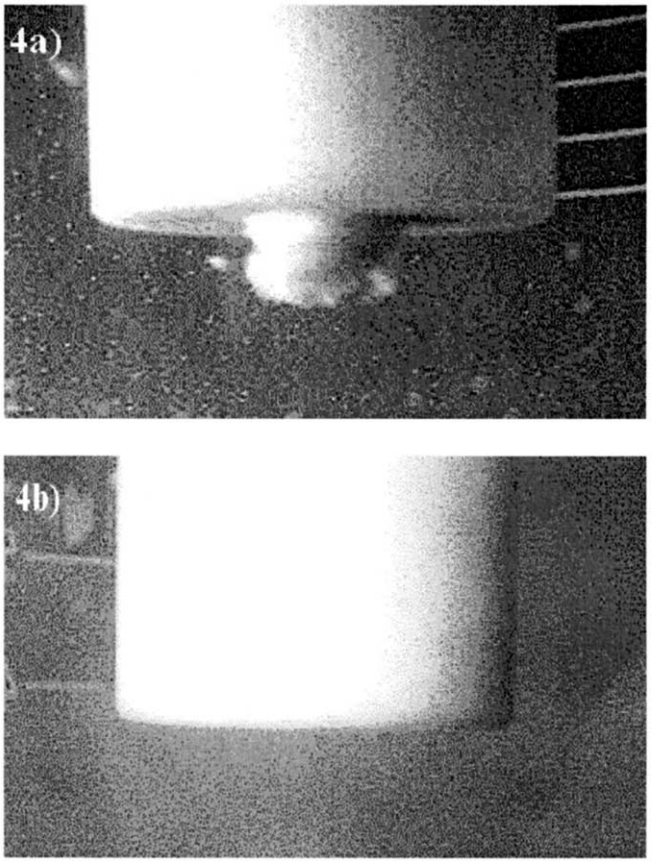

Fig. 4. Typical behaviour of (a) uncured tablet made from cured granules and (b) cured tablet made from uncured granules in the rotating disc apparatus after 45 min of release.

phological differences among formulations were still present, the amount of released drug (seen as empty holes) was markedly decreased. Consequently, the curing step was found necessary for the stabilisation of drug release. Similarly, Amighi and Moës (1997) demonstrated the importance of the curing step for SR of theophylline from pellets coated with the same type of polymer (poly(EA-MMA)).

Curing of the granules and tablets not only affected the release characteristics of the tablets, but also influenced their mechanical properties. When an increasing force was applied to a tablet bar, it first underwent elastic deformation followed by plastic flow to varying extents for the different tablet treatments prior to cracking of the bars (Fig. 6). The cracking process varied for different tablet formulations giving rise to marked differences in the $AUC_{>max}$.

Uncured tablets from group I were brittle and the modulus of rupture was independent of the formulation (Table 4, Fig. 7). However, tablets cured at 50 °C/1 h exhibited a short plateau at the maximum tensile stress, the stress-strain curve being parallel to the x-axis. Maximum tensile stress was spread over a certain elongation range, indicating changes in structure in comparison to the uncured tablets. Cured tablets, near the maximum tensile stress, became ductile during loading and flowed under nearly constant stress. The behaviour is typical of plastic materials. Additionally, the modulus of rupture and Young's modulus decreased in cured tablets. As the Young's modulus (modulus of elasticity) represents the relative

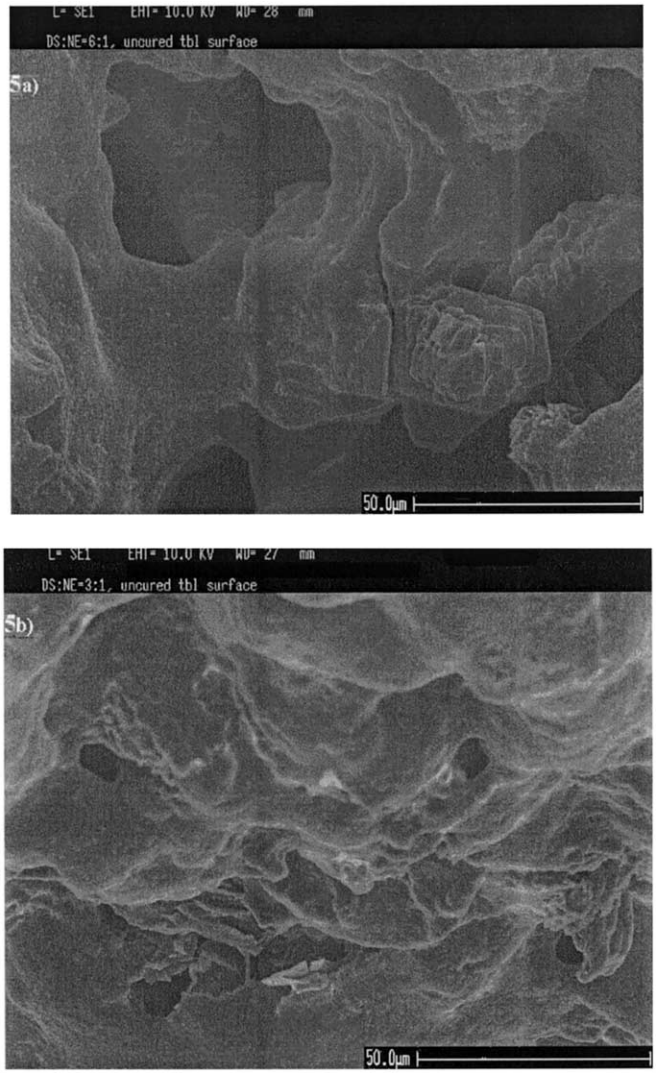

Fig. 5. Dependence of changes in tablet surface morphology on the formulation and curing step. (a) DS:poly(EA-MMA) = 6:1, uncured tablets; (b) DS:poly(EA-MMA) = 3:1, uncured tablets; (c) DS:poly(EA-MMA) = 6:1, cured (50 °C/1h) tablets; (d) DS:poly(EA-MMA) = 3:1, cured (50 °C/1h) tablets.

stiffness of the material, its decrease represents decrease in stiffness of the cured tablets. Therefore, a lower force was needed for the elongation and plastic deformation of the tablet bars, resulting in final breaking. $AUC_{<max}$ increased with an increase in polymer content, but decreased with curing. $AUC_{>max}$, is usually neglected but it appears a useful measurement of stepwise fracturing of the tablet. It increased with curing indicating increased toughness of the samples. Samples from group III showed the same behaviour (data not shown).

When granules were cured at 50 °C/1 h (group II), the tablet behaviour was different. Young's modulus decreased as before, but $AUC_{<max}$ for cured tablets (50 °C/1 h) produced from the cured granules (50 °C/1 h) increased in comparison to uncured tablets (Table 5). Thus it seemed that curing of both granules and tablets generally increased matrix toughness. However, curing of

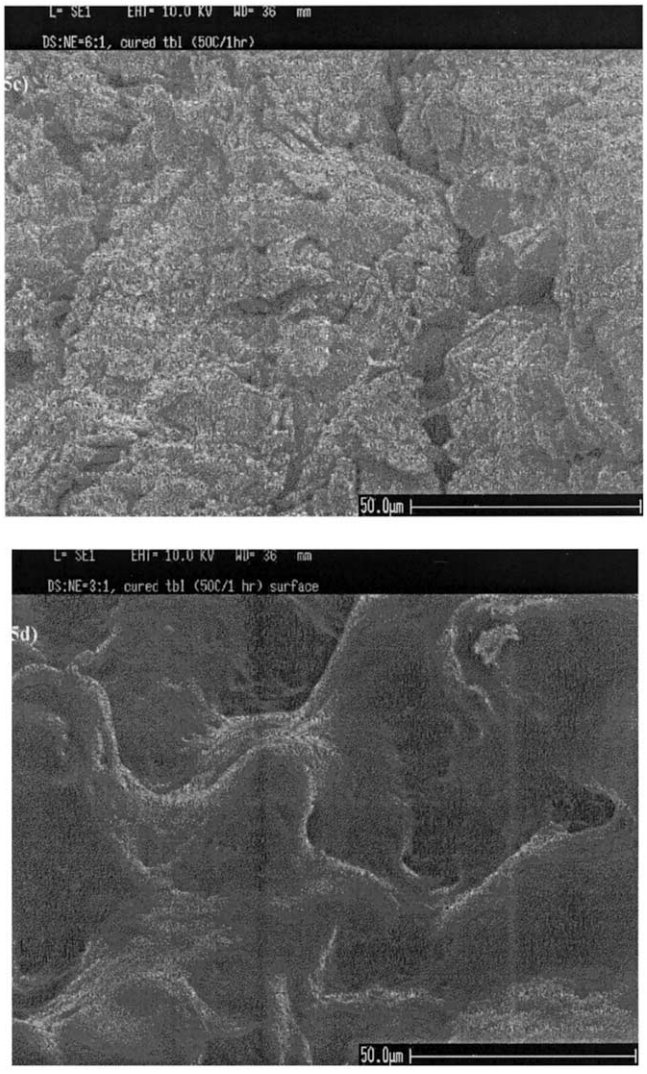

Fig. 5 (*Continued*)

the granules of this group of samples did not lead to prolonged drug release because it disabled formation of a stable matrix so that tablets disintegrated within 3 h.

It is possible that heating of the tablets enabled latex particle coalescence and further formation of bridges both within and between previously cured granules. We noted that $AUC_{>max}$ in cured tablets produced from uncured granules (group I) was higher than $AUC_{>max}$ in cured tablets produced from cured granules (group II) where partial coalescence within granules had already occurred, resulting in reduction of polymer particles available for coalescence between granules. As $AUC_{>max}$ refers to breaking of the tablet bars (Fig. 6), we therefore, suggest that $AUC_{>max}$ indicates the matrix toughness.

Changes in release and mechanical properties of polymer films on storage have been reported. Gutierrez-Rocca and McGinity (1993) found that physical ageing of both aqueous and solvent cast poly(methacrylic acid, ethyl acrilate) 1:1 films

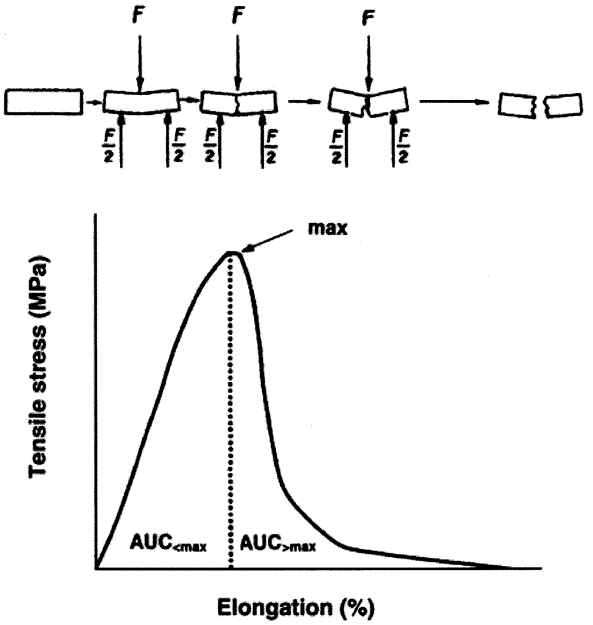

Fig. 6. Deformation of tablet bar on application of force (F) in the three-point bending test.

(commercially available as Eudragit L 100–55 and Eudragit L 30D), resulted in decreased elasticity, but increased tensile strength of the films. The extent of the mechanical changes of the polymer films depended on production and environmental factors. However, the situation is likely to be more complicated for matrices. For example, Westermarck et al. (1998) noted that a more porous structure and a greater number of small pores in granules increased the compactibility of the granules. Thus curing of poly(EA-MMA)-drug granules may alter intragranular porosity due to latex coalescence and this would affect their compaction behaviour and the properties of the resultant tablets. These complexities require further investigation.

Table 5
Effect of curing of tablets made from cured granules (group II) on mechanical properties

Tablets	DS:poly(EA-MMA) = 3:1	
Curing conditions	Uncured	50 °C/1 h
Modulus of rupture(MPa)	1.30±0.1	1.4±0.1
Young's modulus (10 kPa)	29.0±0.9	18.6±1.2
$AUC_{<max}$ (100 MPa)	3.1±0.2	5.5±0.7
$AUC_{>max}$ (100 MPa)	0.9±0.1	1.5±0.0

Results are expressed as mean±S.E.M.

4. Conclusion

Polymer content, curing temperature and curing time of the granules and/or tablets influence drug release rate. As the amount of polymer increases, stronger polymer networks are formed upon higher curing temperature and/or curing duration resulting in an increase in tablet toughness and plasticity, reflected in changes in tablet mechanical characteristics, and a decrease in drug release rate.

However, the results suggest that the process of matrix formation cannot be understood in the same way as the process of film formation. Since drug release was sustained upon placing the tablets in 37 °C acid, water evaporation, could not occur, and so cannot be understood as a driving force for matrix formation. Furthermore, literature suggests 20 °C above Tg as film formation occurs within minutes. However, our results show that even

Table 4
Effect of curing of tablets made from uncured granules (group I) on mechanical properties

Tablets	DS:poly(EA-MMA) = 6:1		DS:poly(EA-MMA) = 3:1	
Curing conditions	Uncured	50 °C/1 h	Uncured	50 °C/1 h
Modulus of rupture(MPa)	1.5±0.1	1.0±0.1	1.3±0.0	1.0±0.0
Young's modulus (10 kPa)	28.5±2.6	22.0±1.5	20.1±0.9	14.7±0.7
$AUC_{<max}$ (100 MPa)	3.8±0.3	2.8±0.4	4.5±0.2	3.5±0.2
$AUC_{>max}$ (100 MPa)	0	0.6±0.1	0.5±0.3	2.25±0.1

Results are expressed as mean±S.E.M.

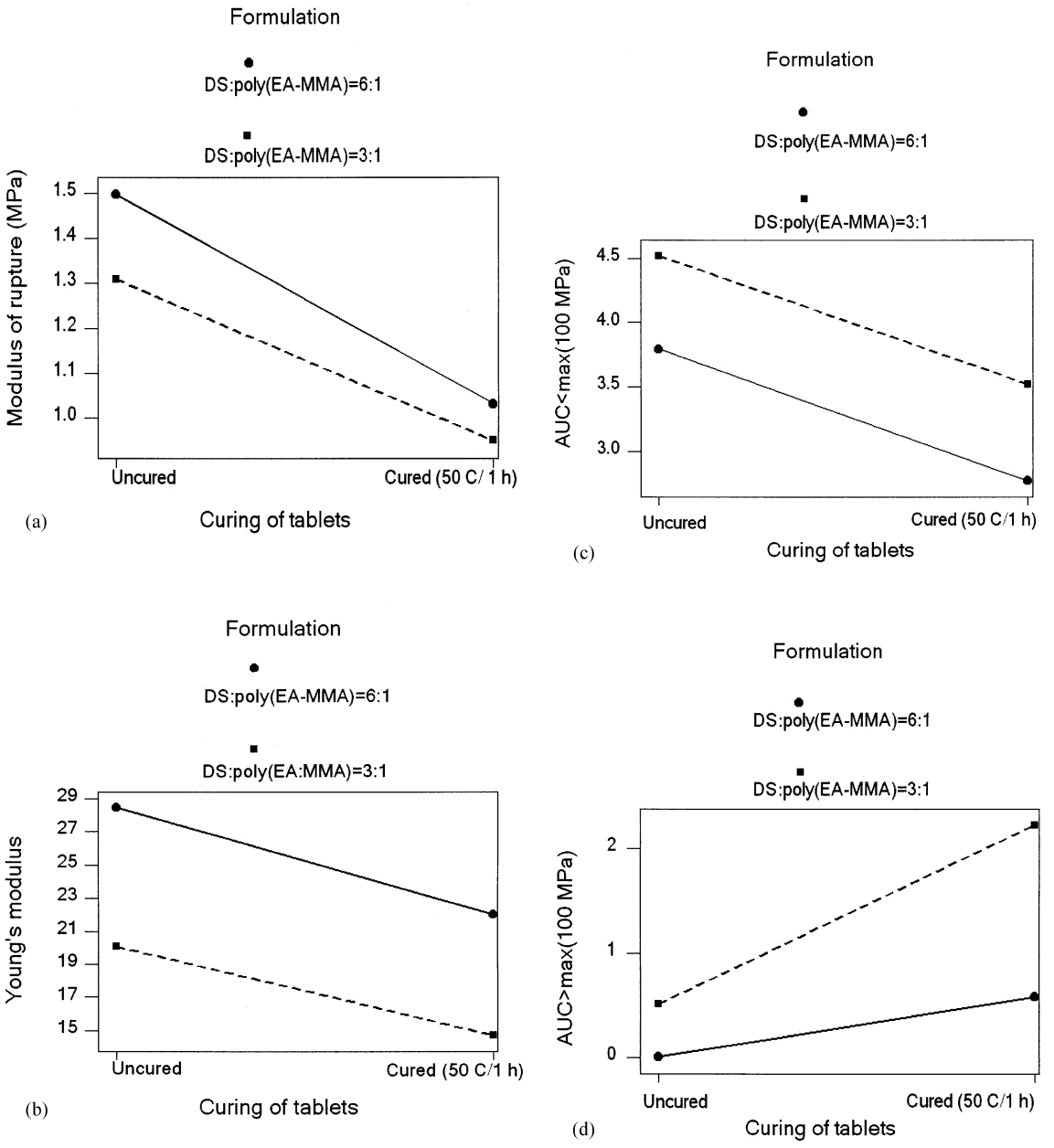

Fig. 7. Effect of the formulation and curing (group I) on the mechanical properties of tablet bars: (a) modulus of rupture, (b) Young's modulus, (c) $AUC_{<max}$, (d)$AUC_{>max}$. Results are group means.

34 °C above the Tg cannot enable completion of matrix formation, even within hours, as additional heating at 50 °C/1 h brings about further changes in mechanical properties and drug release rate.

Formation of a polymer matrix or meshwork within tablets of this type depends on the formulation, processing and storage conditions of the tablets. If the matrix is incompletely formed prior

to tablet ingestion by a patient, the curing process can continue in stomach acid at 37 °C so that the release characteristics of such tablets may depend on gastric residence time. This provides a possible explanation for dose dumping from this type of SR tablets.

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