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European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 1004–1013
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Modulation of drug release kinetics of shellac-based matrix tablets by *in-situ* polymerization through annealing process

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Received 11 December 2007; accepted in revised form 22 January 2008
Available online 5 February 2008

Abstract

A new oral controlled release matrix tablet based on shellac polymer was designed and developed, using metronidazole (MZ) as a model drug. The shellac-based matrix tablets were prepared by wet granulation using different amounts of shellac and lactose. The effect of annealing temperature and pH of medium on drug release from matrix tablets was investigated. The increased amount of shellac and increased annealing temperature significantly affected the physical properties (i.e., tablet hardness and tablet disintegration) and MZ release from the matrix tablets. The *in-situ* polymerization played a major role on the changes in shellac properties during annealing process. Though the shellac did not dissolve in acid medium, the MZ release in 0.1 N HCl was faster than in pH 7.3 buffer, resulting from a higher solubility of MZ in acid medium. The modulation of MZ release kinetics from shellac-based matrix tablets could be accomplished by varying the amount of shellac or annealing temperature. The release kinetics was shifted from relaxation-controlled release to diffusion-controlled release when the amount of shellac or the annealing temperature was increased.

Keywords: Shellac; Matrix tablets; Release kinetics; Annealing; *In-situ* polymerization

1. Introduction

Oral controlled release dosage forms are the most common type of dosage forms that offer highest attention in the area of novel drug delivery systems. Such systems offer numerous advantages compared to conventional dosage forms including improving efficiency, reduced toxicity, and improved patient compliance [1]. Controlled release is usually accomplished employing a membrane or matrix. Matrix type formulations are prepared from either non-swellable lipophilic excipients or swellable hydrophilic polymers [1]. Compressed polymeric matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications [2]. They are usually easy and economical to formulate. Drug release from matrix tablets is controlled by either the formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into tablet and also movement of dissolved solutes out of the matrix tablets [3,4] or the dissolution or erosion of the polymeric matrices [4,5]. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, whereas poorly water-soluble drugs are released predominantly by erosion mechanisms. The contribution of each release mechanism to the overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the

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doi:10.1016/j.ejpb.2008.01.027

gel barrier that forms around the tablet. The hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release [6,7], any change in the properties of the hydrated surface layer caused by a change in pH, is likely to influence the performance of hydrophilic polymer, especially pH dependent polymer, as a sustained release carrier. Water-insoluble polymers, similar to lipophilic matrix agents, were frequently used in the preparation of sustained release tablets [5]. As the matrix system passes through the gastrointestinal tract, the active drug is slowly released and absorbed.

In the view of their abundance and biodegradability, natural polymers have been used in drug delivery applications. Shellac, a natural polymer secreted by lac insects (*Laccifer lacca*), has been used in food and pharmaceutical products, due to its excellent film-forming and protective properties. Shellac has been mostly used for enteric film coating and sugar coating (during sub-coating or gloss coating process) of pharmaceutical products, especially for health supplements and nutraceuticals. However, the low stability and low solubility in alkaline pH of shellac made it less attraction. The stabilization of native shellac by various methods has been reported [8–11]. Recently, micronized shellac was combined with other water-insoluble polymers and then coated on pellets by a dry powder coating technique [12]. Pearnchop et al. [13] has preliminary reported the application of shellac as moisture-protective and taste-masking coatings and as a binder for extended-release matrix tablets. However, there is no study exploring the possibility of shellac as a major excipient for the preparation of matrix tablets. Therefore, the first objective of this study was to investigate the possibility of using shellac as a matrix polymer excipient for oral controlled release drug delivery. Metronidazole (MZ), a nitroimidazole derivative with activity against anaerobic protozoa, aerobic and microaerophilic bacteria, was used as a model drug. Common adverse effects of MZ involve the gastrointestinal tract with high doses. Therefore, reduction of side effects of MZ while prolonging its action using controlled oral dosage forms is highly desirable. The second objective was to study the effect of shellac concentration and annealing temperature on MZ release in both acidic and neutral media to simulate the gastrointestinal conditions. The MZ release mechanism from the shellac-based matrix tablets was also characterized.

2. Materials and methods

2.1. Materials

Metronidazole (MZ, Luotian Hongyuan Biochemical, P.R. China) was used as a model drug. Shellac (Thananchai Part., Thailand), lactose monohydrate (Wyndall, New Zealand), polyvinyl pyrrolidone (PVP K30, P.C. Drug Center, Thailand), colloidal silica (Aerosil 200, Germany), magnesium stearate (Glaxo Wellcome Vidhyasom, Thailand) were used as tablet excipients in this study. Other reagents used were of analytical grade.

2.2. Characterization of native shellac and annealed shellac

To study the effect of annealing on shellac properties, native shellac was heated at 40, 60, 80 and 100 °C for 24 h in an oven (model UT6760, Heraeus, Germany). The annealed shellac was then kept at room temperature before evaluation and compared with native shellac.

2.2.1. Acid value and insoluble solid

Acid value (AV) was determined by acid-base titration method adapted from the United States Pharmacopeia (USP) [14], as previously described [11]. An accurately weighed of 3 g of finely ground shellac sample was dissolved in ethanol overnight and finally adjusted to the total weight of 39 g with ethanol. The solution was centrifuged and filtered through Whatman filter paper (average pore size of 11 microns). The 26-g filtrate (equivalent to 2 g of shellac) was titrated with 0.1 N sodium hydroxide vs. The end point was determined from the inflection points of potentiometric titration curves using pH meter instead of using color indicator due to dark color of shellac. The insoluble solid on filter paper was washed with excess ethanol and dried at 70 °C until the dried weight was constant, and then the percentage of insoluble solid was calculated.

2.2.2. Differential scanning calorimetry (DSC)

Shellac samples were dried over silica gel and pulverized with agate mortar. DSC curves of ground samples were recorded using a differential scanning calorimeter (model Sapphire, Perkin-Elmer, USA). Each sample (5–6 mg) was accurately weighed into an aluminum pan. The measurements were performed between 10 and 250 °C at a heating rate of 10 °C/min.

2.3. Preparation of shellac-based matrix tablets

Shellac-based matrix tablets containing metronidazole were prepared using the wet granulation method. Metronidazole, shellac and lactose were separately passed through a #80 mesh screen and mixed in plastic bag for 10 min. The 30% w/w of PVP K30 solution was added to the powder mixture and mixed by using planetary mixer (model K55S, KitchenAid, USA). Sufficient water was added as necessary for making damp mass. The damp mass was then passed through a #16 mesh screen and dried at 40 °C for 24–48 h. The dried granule was sieved through a #18 mesh. Colloidal silica (1% w/w) and magnesium stearate (1% w/w) were added and mixed in plastic bag for 5 min. Tablets were compressed, using the single-punch tableting machine (Yeo Heng, Thailand) with a 9.6 mm flat-faced punch. The weight and hardness of tablets were controlled to 300 ± 10 mg and 100 ± 10 N, respectively. The compositions of the shellac-based matrix tablets are given in Table 1.

Table 1
Formula of shellac-based matrix tablets (per 1500 tablets)

Composition	Weight (g, dry basis) Shellac content (% w/w)						
	0%	5%	10%	20%	30%	40%	50%
Metronidazole	150.0	150.0	150.0	150.0	150.0	150.0	150.0
Shellac	–	22.5	45.0	90.0	135.0	180.0	225.0
Lactose	277.5	255.0	232.5	187.5	142.5	97.5	52.5
PVP K30	13.5	13.5	13.5	13.5	13.5	13.5	13.5
Colloidal silica	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5

To study the effect of annealing temperature on properties of shellac-based matrix tablets, the tablets were heated at 40, 60, 80 and 100 °C for 24 h in an oven (model UT6760, Heraeus, Germany). The annealed tablets were kept at room temperature before characterization.

2.4. Physical characterization of shellac-based matrix tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h, at room temperature. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed tablets (model AC210 S, Sartorious, Germany). The thickness of ten tablets was measured individually using an electronic micrometer (model G, Peacock, Japan). The hardness of ten tablets was determined by hardness tester (model PTB311, Pharmatest, Germany). Disintegration testing was performed at 37 °C both in simulated gastric fluid (without enzyme) and phosphate buffer pH 7.3 using a disintegration apparatus (model DT 3, Sotax, Switzerland). The disintegration times were reported as mean values of six determinations.

2.5. In-vitro release studies

The dissolution studies were carried out using USP dissolution apparatus, type II, (model DT 70, Erweka, Germany) equipped with paddles which was operated at the speed of 50 rpm. Nine hundred milliliters of either 0.1 N HCl (pH 1.2) or phosphate buffer (pH 7.3), as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to 37 ± 0.5 °C. The amount of drug released was measured at the suitable time interval and was then determined spectrophotometrically (model Lambda 2, Perkin-Elmer, Germany) in a 1-cm quartz cell at 277 and 320 nm for MZ release in 0.1 N HCl and buffer pH 7.3, respectively. Each *in-vitro* release study was performed in triplicate.

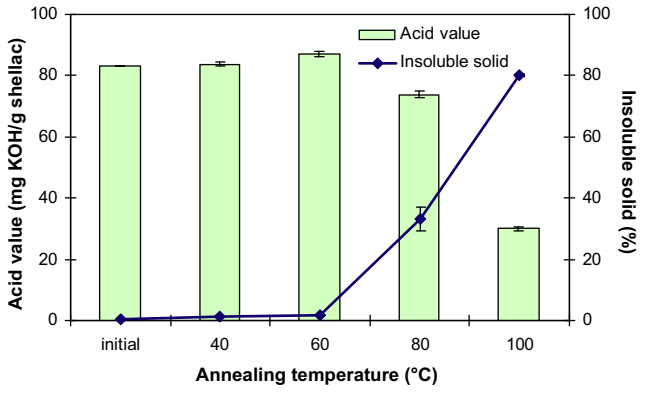

Fig. 1. Effect of annealing temperature on acid value and percent insoluble solid of shellac.

2.6. Morphological examination of tablets

Morphological examination of the tablets was carried out using a digital microscope (model QX5, Digital Blue, P.R. China). Photo imaging was performed on each tablet formulation after release study in different media (i.e., 0.1 N HCl and phosphate buffer pH 7.3) for 8 h. The tablets were taken out from the medium and were photo-

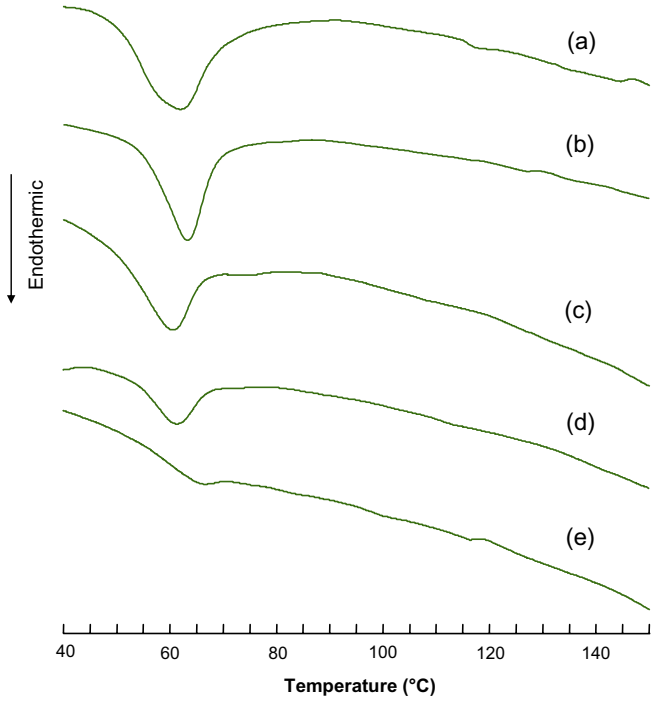

Fig. 2. DSC curves of native shellac (a) before annealing and after annealing at (b) 40 °C, (c) 60 °C, (d) 80 °C and (e) 100 °C.

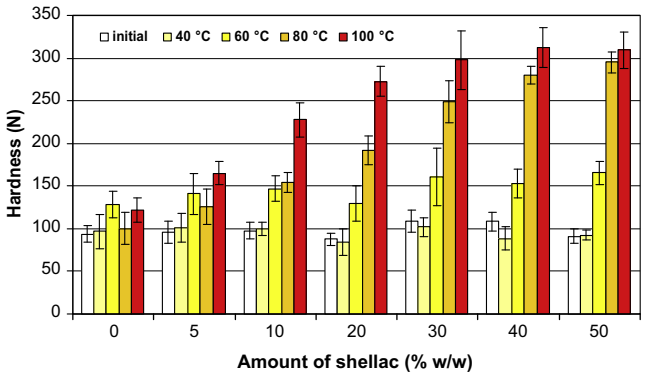

Fig. 3. Effect of annealing temperature (i.e., 40–100 °C) on hardness of shellac based matrix tablets.

graphed by a digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate.

2.7. Analysis of release data

The mechanism of drug release from shellac-based matrix tablets during dissolution tests was determined using zero-order, first-order, Higuchi and the exponential equation (Korsmeyer–Peppas equation). The Korsmeyer–Peppas equation demonstrated below is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved [15].

$$\frac{M_t}{M_f} = kt^n$$

where k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism and M_t/M_f represents the drug dissolved fraction at time t. When determining the n exponent, only the portions of the release profile where $M_t/M_f \leqslant 0.6$ were employed to provide the accurate values [15].

2.8. Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Analysis of variance (ANOVA) and Levene's test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., USA). *Post hoc* testing ($p < 0.05$) of the multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene's test was insignificant or significant, respectively.

3. Results and discussion

3.1. Effect of annealing temperature on shellac properties

To study the effect of annealing on shellac properties, native shellac was heated at 40, 60, 80 and 100 °C for

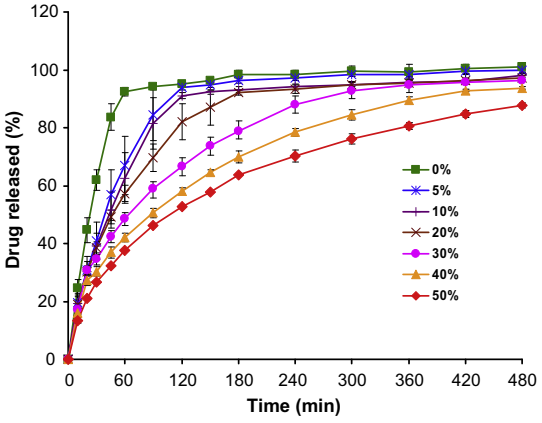

Fig. 4. Effect of amount of shellac (i.e., 0–50% w/w) on drug release in 0.1 N HCl.

Table 2
Effect of annealing temperature on disintegration time of shellac-based matrix tablets in 0.1 N HCl and pH 7.3 buffer

Medium	Shellac (% w/w)	Disintegration time (min)				
		Initial	40 °C	60 °C	80 °C	100 °C
0.1 N HCl	0	18.0 ± 0.7	20.0 ± 2.5	16.9 ± 1.5	20.2 ± 1.6	19.5 ± 1.5
	5	26.8 ± 0.4	30.6 ± 2.1	30.0 ± 3.5	32.8 ± 1.9	57.0 ± 2.5
	10	33.6 ± 0.7	34.6 ± 1.1	32.6 ± 2.4	68.3 ± 6.0	>120
	20	47.3 ± 3.4	50.4 ± 4.0	53.8 ± 4.8	>120	>120
	30	98.0 ± 3.6	103.7 ± 1.0	>120	>120	>120
	40	>120	>120	>120	>120	>120
	50	>120	>120	>120	>120	>120
Buffer pH 7.3	0	39.6 ± 0.3	39.3 ± 4.4	37.6 ± 3.2	38.8 ± 5.0	38.4 ± 0.9
	5	50.3 ± 8.2	52.6 ± 3.3	52.1 ± 4.1	72.6 ± 5.7	103.4 ± 6.1
	10	61.9 ± 2.8	66.6 ± 2.0	62.3 ± 2.9	153.9 ± 31.1	>180
	20	101.8 ± 2.6	96.8 ± 9.0	93.2 ± 5.0	>180	>180
	30	148.0 ± 17.8	164.6 ± 5.6	139.6 ± 5.7	>180	>180
	40	>180	>180	>180	>180	>180
	50	>180	>180	>180	>180	>180

The means of six replicates and standard deviations are reported.

24 h in an oven. Both native shellac and annealed shellac were characterized and compared. DSC was used as a preliminary tool for studying thermal behavior of shellac samples. The native shellac and annealed shellac (at 60 °C) demonstrated endothermic peak due to melting around 50 °C while the shellac annealed at 80 and 100 °C did not clearly show endothermic peak. The result suggested that the polymerization process was occurred after annealing at high temperature. The acid value (AV) and insoluble solid were the indicative parameters for polymerization of shellac, as previously reported [11]. Shellac molecules consisted of a large amount of hydroxyl and carboxyl groups. The polymerization could occur by the esterification among the functional groups and resulted in a reduction of carboxyl groups (expressed by AV) and an increase of insoluble solid [11]. Therefore, AV and insoluble solid of shellac and corresponding annealed samples were determined (Fig. 1). The decreased AV and increased insoluble solid were clearly observed after annealing at 80 and 100 °C. The results agreed with those observed in DSC (Fig. 2), confirming that the polymerization was occurred.

3.2. Physical properties of shellac-based matrix tablets

Shellac-based matrix tablets were prepared by wet granulation using shellac and lactose as matrix excipients at various ratios. Some of the obtained tablets were annealed at different temperatures (i.e., 40, 60, 80, and 100 °C) for 24 h. The comparison of hardness of the matrix tablets without and with shellac (5–50% w/w) is shown in Fig. 3. The hardness of the plain tablets (with no shellac) and the shellac-based matrix tablets ranged from 90 to 110 N, at room temperature. The increased amount of shellac in the formulation did not affect the hardness of the tablets. The annealing temperature seemed to influence the hardness of the matrix tablets but no significant difference was found for the plain tablets. In case of the tablets containing shellac, the increased annealing temperature influenced the tablet hardness. The effect of annealing temperature was more apparent when the tablets containing higher amount of shellac. It was because the *in-situ* polymerization occurred during annealing resulting in stronger tablets, as discussed above.

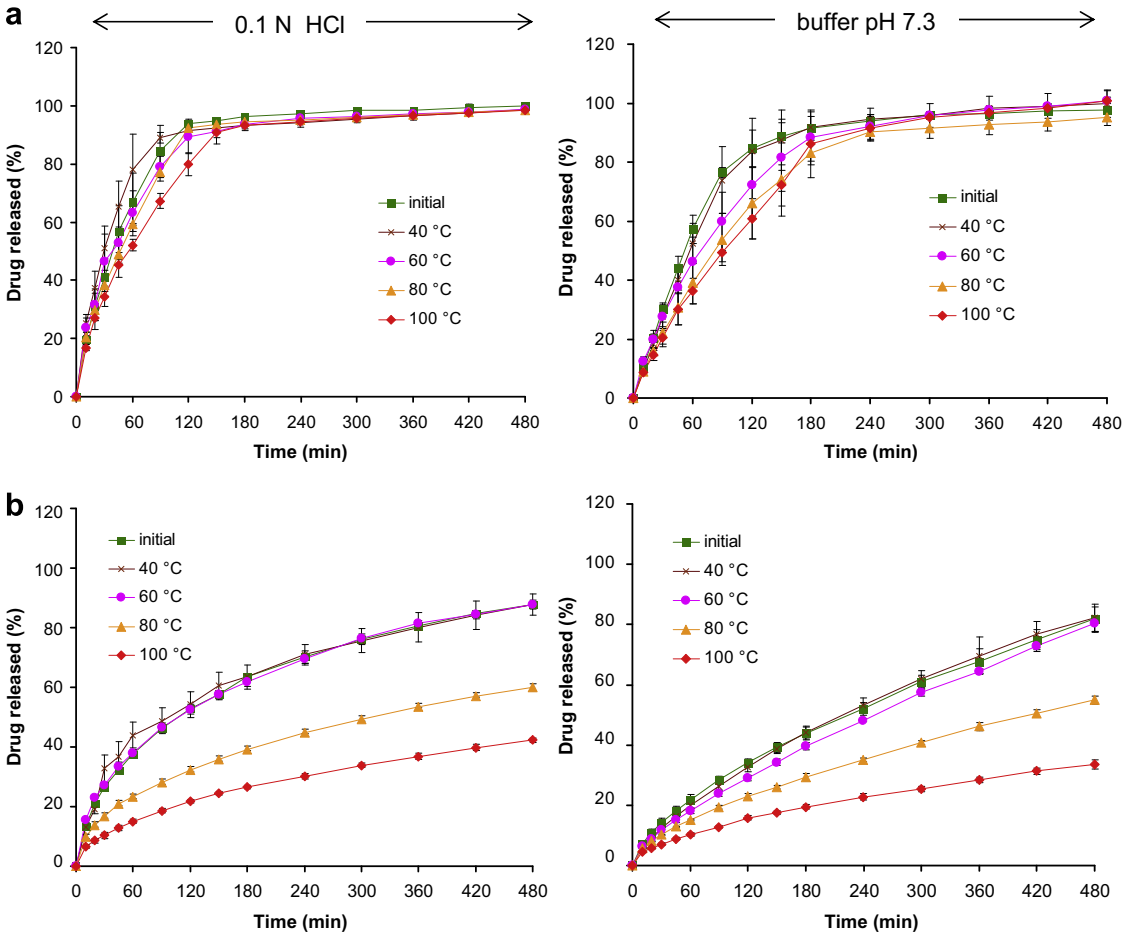

Fig. 5. Effect of annealing temperature on percent drug released of (a) 5% w/w shellac-based matrix tablets and (b) 50% w/w shellac-based matrix tablets, in 0.1 N HCl and pH 7.3 buffer.

The disintegration times of shellac-based matrix tablets are given in Table 2. The plain tablets containing no disintegrant but lactose, which could be dissolved in aqueous medium, so that they could dissolve or erode as time progressed, e.g., about 17–20 min in 0.1 N HCl and 38–40 min in pH 7.3 buffer. As MZ dissolved more quickly in acid medium, it could form the porous structure in the tablets and enhance tablet dissolution in 0.1 N HCl. Incorporation of shellac, which is not dissolved in acid condition, significantly delayed the tablet disintegration (dissolution) in 0.1 N HCl. The annealing effect on the disintegration time of shellac-based matrix tablets was clearly observed. The increased annealing temperature and shellac amount also significantly retarded the tablet disintegration. This could be seen in both 0.1 N HCl and pH 7.3 buffer. The tablets containing more than 40% w/w shellac, even at initial condition, did not disintegrate even after 120 min in 0.1 N HCl or 180 min in pH 7.3 buffer, which is a desired matrix behavior. The polymerization of shellac at high temperature may be the major reason for the non-disintegration of the matrix tablets. At higher temperature, the non-disintegration of tablets was found at lower concentration of shellac, suggesting the lower critical points for polymerization. After the test in pH 7.3 buffer, however, the tablets were decreased in size. This is probably due to the dissolution or erosion of the shellac-based matrices. The results suggested that shellac-based matrix tablets that annealed at high temperature can be used as compressed non-disintegrating matrices for sustained/controlled release tablets.

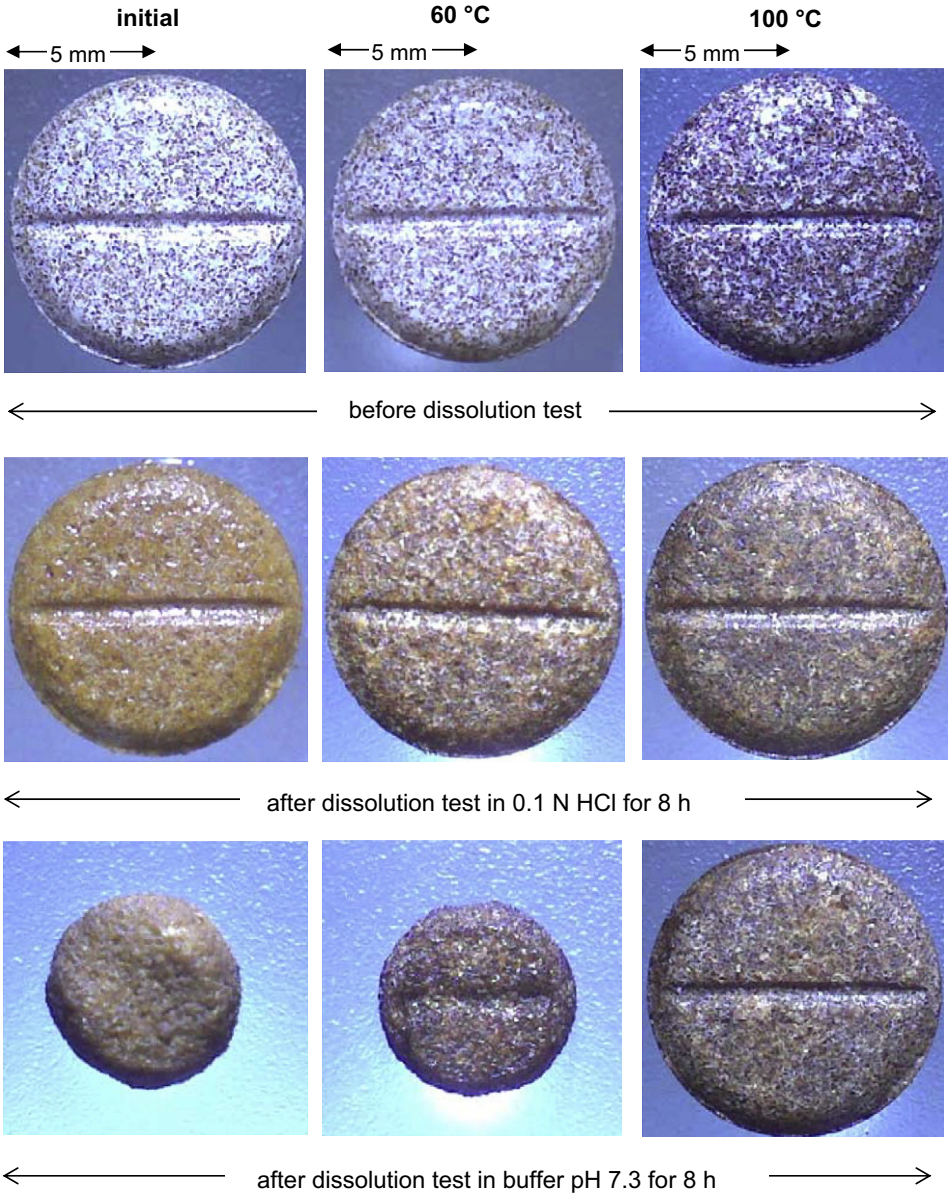

Fig. 6. Photoimages of 50% w/w shellac-based matrix tablets before and after annealing and dissolution test.

3.3. Release behavior of shellac-based matrix tablets

The release profiles of MZ from some shellac-based matrix tablets in 0.1 N HCl (pH 1.2) are shown in Fig. 4. The drug release from matrix tablets was influenced by the amount of shellac. Drug release from the plain tablets without shellac was quite rapid with essentially complete release within 1–2 h. Matrix tablets containing shellac could sustain drug release in 0.1 N HCl for at least 6–8 h, especially the tablets containing 40–50% w/w shellac. Fig. 5 demonstrates the effect of annealing temperature on drug release from matrix tablets containing 5% and 50% w/w. MZ release from matrix tablets containing 5% w/w shellac was fairly rapid, similar to that from the plain tablets. Most of the MZ released within 3 h when tested in SGF and about 4 h in pH 7.3 buffer.

Although the shellac-based matrix tablets were not disintegrated or dissolved in acid condition due to the enteric properties of shellac (pK_a of native shellac is about 6.7 [9]), the drug release in 0.1 N HCl was slightly faster than that in pH 7.3 buffer (Fig. 5a and b). This is probably due to the fact that MZ, a weakly basic drug, could be ionized at the pH below its pK_a ($pK_a = 2.5–2.6$). Because of the dissolution of shellac at higher pH, the poor solubility of MZ was compensated. It is considered that MZ release from shellac-based matrix tablets in acidic medium is primarily driven by diffusion through the matrices and water-filled pores while that in pH 7.3 buffer is mainly driven by erosion or dissolution of the matrices.

The annealing temperature affected the drug release from the matrix tablets, even though it was not quite obvious when using 5% w/w shellac. On the contrary, the MZ

Table 3
Mathematic modeling and drug release kinetics from shellac-based matrix tablets in 0.1 N HCl

Conditions		Correlation coefficient (r^2)				Parameters obtained from Korsmeyer–Peppas model	
Shellac (%)	Temperature (°C)	Zero order	First order	Higuchi	Korsmeyer–Peppas model	Diffusional exponent (n)	Kinetic constant (k)
0	Initial	n/a	n/a	n/a	n/a	0.8601	0.0340
	40	0.9989	0.9927	0.9881	0.9958	0.7548	0.0430
	60	0.9975	0.9936	0.9843	0.9951	0.8225	0.0321
	80	0.9830	0.9136	0.9976	0.9928	0.7273	0.0312
	100	0.9900	0.9619	0.9981	0.9934	0.8339	0.0284
5	Initial	0.9996	0.9681	0.9900	0.9976	0.7016	0.0384
	40	0.9991	0.9950	0.9890	0.9937	0.6324	0.0582
	60	0.9450	0.9222	0.9607	0.9658	0.5626	0.0634
	80	0.9949	0.9479	0.9969	0.9990	0.5987	0.0501
	100	0.9815	0.9156	0.9987	0.9982	0.6348	0.0406
10	Initial	0.9964	0.9560	0.9972	0.9997	0.6489	0.0434
	40	0.9813	0.9092	0.9997	0.9977	0.6554	0.0403
	60	0.9937	0.9446	0.9954	0.9984	0.6667	0.0373
	80	0.9970	0.9574	0.9942	0.9970	0.5831	0.0459
	100	0.9775	0.8890	0.9979	0.9986	0.6380	0.0324
20	Initial	0.9805	0.9107	0.9997	0.9979	0.6201	0.0462
	40	0.9951	0.9424	0.9970	0.9997	0.6446	0.0382
	60	0.9824	0.9098	0.9999	0.9977	0.6499	0.0405
	80	0.9691	0.8618	0.9997	0.9991	0.5419	0.0395
	100	0.9499	0.8297	0.9950	0.9954	0.5381	0.0385
30	Initial	0.9422	0.8162	0.9862	0.9736	0.5397	0.0541
	40	0.9637	0.8646	0.9985	0.9968	0.5742	0.0450
	60	0.9783	0.9097	0.9992	0.9973	0.5784	0.0451
	80	0.9685	0.8700	0.9997	0.9999	0.4925	0.0417
	100	0.9476	0.8051	0.9985	0.9983	0.5034	0.0348
40	Initial	0.9515	0.8292	0.9916	0.9833	0.4915	0.0565
	40	0.9615	0.8551	0.9983	0.9977	0.5568	0.0408
	60	0.9546	0.8542	0.9971	0.9977	0.4914	0.0581
	80	0.9566	0.8252	0.9984	0.9977	0.5496	0.0283
	100	0.9472	0.7955	0.9986	0.9993	0.4942	0.0279
50	Initial	0.9548	0.8341	0.9973	0.9952	0.5324	0.0418
	40	0.8850	0.7366	0.9590	0.9525	0.5595	0.0400
	60	0.9589	0.8577	0.9981	0.9984	0.4796	0.0532
	80	0.9446	0.7966	0.9984	0.9994	0.4688	0.0339
	100	0.9550	0.8134	0.9994	0.9988	0.4961	0.0201

Note. n/a, not applicable.

release from shellac-based matrix tablets (50% w/w) was obviously slower than that from matrix tablets containing lower amount of shellac (Fig. 5b) and the profound effect of annealing temperature was apparently shown. In 0.1 N HCl, the shellac-based matrices were not disintegrated and adhesive in nature but represented a tough and rubbery texture (Fig. 6). The enteric properties of shellac have an effect on the integrity of the tablets in acid condition [9]. After dissolution test in pH 7.3 buffer, the erosion/dissolution of shellac-based matrices (initial tablets and tablets annealed at 60 °C) was seen (Fig. 6). However, the matrix tablets annealed at 100 °C were not eroded after testing in pH 7.3 buffer. It is likely that the *in-situ* polymerization during the annealing at high temperature played a major role in the integrity of the matrix tablets, as discuss above. Besides, the tablets annealed at high temperature (i.e., 100 °C) were also the hardest tablets. This contributed to the slower drug release.

3.4. Analysis of release data

The mechanism of drug release from polymer-based matrices is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms [6,16,17]. Previous report [6] showed that the release of MZ in acidic medium showed a good fit into Korsmeyer–Peppas equation but also fitted well with zero-order release model, in neutral medium. Higuchi model is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix. A good fit to Korsmeyer–Peppas equation indicated combined effect of diffusion and erosion mechanisms for drug release [15]. In case of Fickian release (diffusionally controlled release), the n have the limiting values of 0.45 for release from cylinders. Case II transport or relaxation-controlled release, the exponent n is 0.89 for the release from

Table 4
Mathematic modeling and drug release kinetics from shellac-based matrix tablets in pH 7.3 buffer

Conditions		Correlation coefficient (r^2)				Parameters obtained from Korsmeyer–Peppas model	
Shellac (%)	Temperature (°C)	Zero order	First order	Higuchi	Korsmeyer–Peppas model	Diffusional exponent (n)	Kinetic constant (k)
0	Initial	0.9932	0.9237	0.9991	0.9972	0.8857	0.0174
	40	0.9849	0.9691	0.9642	0.9689	0.8292	0.0226
	60	0.9999	0.9413	0.9863	0.9997	0.9001	0.0141
	80	0.9924	0.9533	0.9999	0.9954	0.9565	0.0195
	100	0.9996	0.9305	0.9885	0.9999	0.9614	0.0118
5	Initial	0.9995	0.9311	0.9894	0.9999	0.9428	0.0121
	40	0.9993	0.9271	0.9899	0.9997	0.9686	0.0100
	60	0.9963	0.9400	0.9950	0.9994	0.7436	0.0220
	80	0.9965	0.9011	0.9907	0.9999	0.8123	0.0139
	100	0.9900	0.8728	0.9943	0.9985	0.7940	0.0139
10	Initial	0.9986	0.9493	0.9747	0.9990	1.0034	0.0072
	40	0.9986	0.9292	0.9915	0.9998	0.9226	0.0105
	60	0.9987	0.9242	0.9897	0.9992	0.9711	0.0094
	80	0.9983	0.9146	0.9834	0.9944	0.7036	0.0143
	100	0.9608	0.8036	0.9989	0.9981	0.6204	0.0181
20	Initial	0.9980	0.9122	0.9864	0.9988	0.8228	0.0120
	40	0.9891	0.8821	0.9959	0.9983	0.8128	0.0132
	60	0.9850	0.8732	0.9931	0.9964	0.8995	0.0103
	80	0.9665	0.8266	0.9972	0.9939	0.6480	0.0161
	100	0.9510	0.7786	0.9993	0.9974	0.5581	0.0217
30	Initial	0.9926	0.8721	0.9931	0.9992	0.7427	0.0117
	40	0.9821	0.8490	0.9984	0.9973	0.7239	0.0159
	60	0.9661	0.8587	0.9960	0.9858	0.7882	0.0137
	80	0.9781	0.8256	0.9967	0.9992	0.5867	0.0175
	100	0.9485	0.7598	0.9984	0.9950	0.5918	0.0146
40	Initial	0.9876	0.8584	0.9968	0.9992	0.7163	0.0124
	40	0.9917	0.8864	0.9915	0.9978	0.7432	0.0116
	60	0.9954	0.8898	0.9859	0.9986	0.7319	0.0124
	80	0.9768	0.8085	0.9972	0.9996	0.6083	0.0141
	100	0.9685	0.8064	0.9994	0.9997	0.5747	0.0131
50	Initial	0.9803	0.8518	0.9977	0.9999	0.6270	0.0169
	40	0.9900	0.8646	0.9918	0.9990	0.6944	0.0118
	60	0.9933	0.8688	0.9868	0.9959	0.6562	0.0129
	80	0.9838	0.8350	0.9946	0.9990	0.5957	0.0135
	100	0.9734	0.8358	0.9980	0.9973	0.5400	0.0120

cylinders. The non-Fickian release or anomalous transport of drug occurred when the n values between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation. Occasionally, values of $n > 0.89$ for release from cylinders have been observed, which has been regarded as Super Case II kinetics [15]. This mechanism could result from an increased plasticization at the relaxing boundary (gel layer).

The release kinetics for all the mathematic models is shown in Tables 3 and 4. The MZ release (in acidic medium) from shellac-based matrix tablets demonstrated a best fit into Korsmeyer–Peppas equation but fairly good fit into Higuchi equation (Table 3), suggesting a diffusion-controlled release. Also in Table 4, the release data in pH 7.3 buffer showed a good fit into Korsmeyer–Peppas model. The exception was found in some cases in which the drug release was rapid (e.g., the MZ release in 0.1 N HCl from the plain tablets) and there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. As most of the release data fitted well with Korsmeyer–Peppas equation, the release exponent (n) and the release rate coefficient (k) were then calculated (Tables 3 and 4). Most of them were non-Fickian release or anomalous transport ($0.45 < n < 0.89$), which has the Fickian and relaxation mechanisms together. It was found that the amount of shellac affected the release kinetics (Fig. 7). The increased amount of shellac decreased the 'n' value of the matrix tablets, from Case II transport (relaxation-controlled release) to Fickian transport (diffusion-controlled release).

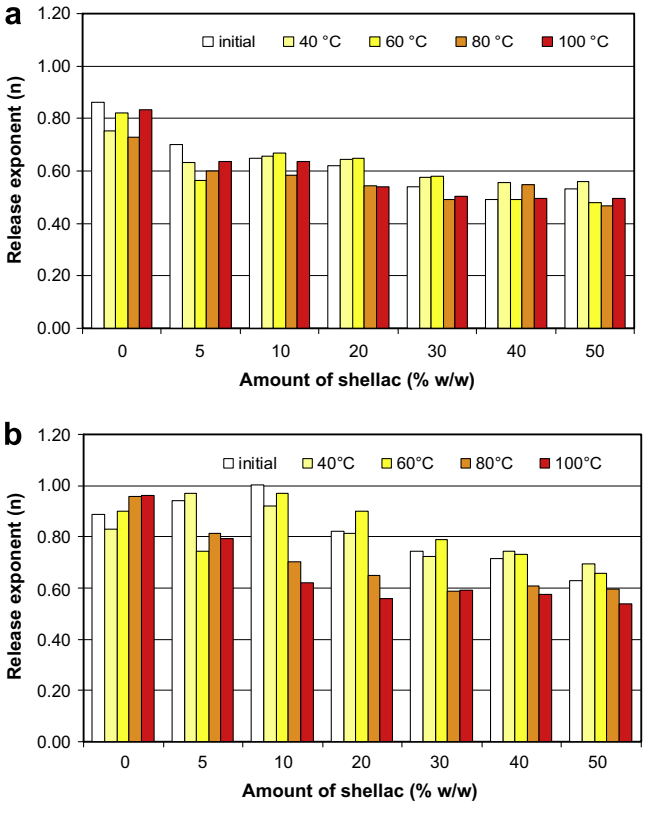

Fig. 7. Effect of annealing temperature (i.e., 40–100 °C) and concentration of shellac on diffusional exponent of metronidazole release in (a) 0.1 N HCl and (b) pH 7.3 buffer.

As illustrated in Fig. 7, the value of 'n' representing the diffusion pattern was decreased with the increase in annealing temperature, especially when the temperature of 80–100 °C was used. The polymerization of shellac resulted in the insoluble matrices with a sustained release manner, which was best fitted with the Higuchi equation and approached to the Fickian model. Similar results were observed by Cao et al. [18] in tablets with lipophilic matrices in which the drug release was controlled by diffusion or leaching through the channels of the pores and cracks of the matrix tablets. On the contrary, the 'n' values of the shellac-based matrix tablets that annealed at low temperature (60 °C or less), in pH 7.3 buffer, were higher than those annealed at high temperature, suggesting both diffusion and relaxation contributed to the release mechanisms. The photoimages of 50% w/w shellac-based matrix tablets after dissolution test in pH 7.3 buffer also confirmed these findings (Fig. 6).

4. Conclusion

Shellac-based matrix tablets were easily prepared by blending drug, shellac and other excipients, and then tableting. The increased amount of shellac significantly affected the physical properties and drug release from the matrix tablets. The *in-situ* polymerization played a major role on the changes in shellac properties during annealing process and influenced the properties of matrix tablets and their release behavior. Varying the amount of shellac or annealing temperature could alter drug release kinetics; the release kinetics was shifted from relaxation-controlled release to diffusion-controlled release when the amount of shellac or the annealing temperature was increased. The results suggest that the shellac-based matrix tablets are interesting as a simple controlled release drug delivery system.

Acknowledgements

We acknowledge the Thailand Research Fund, the Commission of Higher Education of Thailand, and Silpakorn University Research and Development Institute for financial support.

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