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EFFECTS OF MICROWAVE ON WATER AND ITS INFLUENCE ON DRUG DISSOLUTION

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Abstract—Use of water with different molecular mobilities could affect drug dissolution of a dosage form and such profile of water might be modifiable using microwave. This study investigated the effects of microwave on water and its influences on dissolution of free drugs and drugs in calcium-crosslinked alginate beads using sulphanilamide and sulphamerazine as hydrophilic and hydrophobic model drugs respectively. The water was treated by microwave at 300 W or without pre-treatment. The drug dissolution, pH and molecule mobility profiles of untreated and microwave-treated water were examined. Microwave-treated water had higher pH and water molecule mobility. The latter was characterized by higher conductivity, lower molecular interaction and crystallinity profiles. The dissolution of hydrophilic and hydrophobic free or encapsulated drugs was enhanced using microwave-treated water due to its higher molecular mobility. The untreated water of the same pH as microwave-treated water did not enhance drug dissolution. The drug dissolution from beads was increased by higher water uptake leading to matrix erosion and pore formation using microwave-treated water and was not promoted by the formation of non-crosslinked hydrated alginic acid matrix in untreated water of lower pH. Microwave treatment of water increased water molecule mobility and can promote drug dissolution.

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1. INTRODUCTION

Microwave is an electromagnetic wave with wavelengths longer than those of terahertz waves, but shorter than radiowaves [1]. It has frequencies between 300 MHz and 300 GHz. Microwave is not a form of heat, but a form of energy which manifests as heat through its interaction with materials. The transmission of microwave to an object results in vibration of molecules by induced or permanent dipoles. The intensity of vibration is dependent on the size, shape and polarizability of the molecules, as well as, the extent of intermolecular bonding of the object. Practically, the amount of energy absorbed by an object, P, is defined as:

$$P = 2\pi f E^2 E_0 E_r \tan\delta \quad (1)$$

where f = frequency of microwave, E = electric field, E_0 = dielectric constant of free space, E_r = dielectric constant of object and $\tan\delta$ = loss tangent.

Microwave has been utilized to design controlled-release alginate, alginate-chitosan, pectinate-chitosan and poly(methyl vinyl ether-co-maleic acid) beads [2–5]. The drug release characteristics of these beads were dependent on the propensity of polymer-polymer and drug-polymer interaction brought about by microwave. The microwave has also been investigated as the alternative mode to crosslink gelatin matrix which is available as microspheres suspended in a polar acetone [6]. It is found that only a short span of 10 min is required for effective crosslinking of gelatin microspheres by microwave unlike when thermal denaturation method is used [6–8]. The bioavailability of poorly water-soluble drugs is limited by their dissolution in gastrointestinal tract [9]. Kerč et al. (1998), Bergese et al. (2003) and Moneghini et al. (2008) have explored the usefulness of microwave as the tool to prepare fast-release solid dispersion [10–12]. They reported that the drug release propensity of microwave-treated sample is greatly higher than those of pure drug, samples which are untreated by microwave or treated by vacuum at 100°C, or obtained by solvent deposition method. A review of microwave application in design of drug delivery system, namely agglomerates, beads, tablets, microparticles, nanoparticles and solid dispersion, has been reported lately by Wong (2008) [4].

The process of drug dissolution proceeds through migration of drug molecules into the cavity of liquid dissolution medium and subsequent formation of bonding between drug and water molecules [13]. The lattice theory postulates that a liquid medium has crystalline or quasi-crystalline structures [14]. A proportion of volume occupied by the liquid is empty in liquid lattice network which

constitutes free volume of liquid. The dissolution and diffusion of drug molecules are accompanied by solute molecules moving from one empty cavity to another within a liquid lattice. Technically, a higher fraction of free cavity may be formed in bulk water following the transmission of microwave to water which results in vibration of water molecules, local superheating and lost of crystalline structure of water network [15]. It is hypothesized that the propensity of drug dissolution can be enhanced through employing microwave-treated liquid as dissolution medium. As dissolution profile of a drug can dictate its bioavailability, the present study sets to investigate the effects of microwave on aqueous dissolution medium and its influence on dissolution profiles of free drugs of varying degrees of hydrophobicity as well as encapsulated drugs in alginate beads.

2. MATERIALS AND METHODS

2.1. Materials

Sulphanilamide and sulphamerazine (Sigma, USA) were employed as model hydrophilic and hydrophobic drugs with the respective molecular weights of 172.2 and 264.3 g/mole. They were used as received without further purification. Sodium alginate (Manugel® DMB, ISP, USA: mannuronic acid (M)/guluronic acid (G) ratio = 0.59) was used as matrix polymer for drug encapsulation in beads with calcium chloride dihydrate (Merck, Germany) as crosslinking agent. Deionized water was used as model dissolution medium. It was obtained by means of filtration and ion exchange processes (Elga, Veolia Water Systems, UK). Other chemical employed was hydrochloric acid (Merck, Germany) for digestion of beads in atomic absorption spectrophotometric assay.

2.2. Preparation of Alginate Beads

An aqueous dispersion containing 2 %w/w of sodium alginate and 1 %w/w of drug was introduced dropwise into an aqueous solution containing 6 %w/w of calcium chloride dihydrate by extrusion through a 1.6 mm diameter orifice at a flow rate of 60 droplets/min aided by peristaltic pump (Watson-Marlow Bredel Pumps, UK). The bulk of the calcium chloride solution was subjected to magnetic stirring throughout the preparation process and the stirring was continued for an additional period of 15 min after the last addition of the sodium alginate-drug dispersion. The formed alginate beads were removed from the calcium chloride solution by filtration and washed with deionized water. Blank beads were prepared in the same manner

for all formulations, except that no drug was incorporated. All beads were oven-dried at 40 ± 0.5°C for 3 days and subsequently equilibrated to a constant weight by storing in a desiccator at 25 ± 1°C.

2.3. Microwave Treatment of Dissolution Medium

An appropriate volume of deionized water was filtered under the negative pressure. An amount of 520 g filtrate was subjected to microwave irradiation at 300 W for 10 min at 2450 ± 50 MHz (EM-G A, Sanyo, Japan). The microwave-treated water was cooled to ambient temperature and its weight was adjusted to 500 g prior to subsequent experiments on drug dissolution and calcium release.

2.4. Drug Dissolution

The dissolution profiles of free drug and drug encapsulated in alginate beads were determined using untreated water and water treated by microwave at 300 W as dissolution media. An accurately weighed amount of drug or beads was placed in 500 g of dissolution medium and agitated at 50 strokes/min using a shaker bath (Memmert GmbH+Co. KG, Germany) at 37 ± 0.2°C. Aliquots were withdrawn at various time intervals and assayed spectrophotometrically for sulphanilamide and sulphamerazine at 260 and 259.9 nm respectively (Cary 50 Conc, Varian Australia Pty Ltd, Australia). The percentage of drug dissolution was calculated with respect to drug load added to dissolution medium or drug content of beads. The drug content was expressed as the percentage of drug encapsulated in a unit weight of beads. The drug content was determined by subjecting the same sample of beads from the drug dissolution study for an additional 15 h of magnetic stirring followed by ultrasonication for at least 3 consecutive periods of 10 min before assaying for drug. Blank beads were taken as control sample. At least triplicates were carried out for each batch of sample and the results averaged. The kinetics of drug released from beads was investigated by fitting the drug release data into Korsmeyer-Peppas dissolution model as previously described [2]. The drug release rate constant (k) and release exponent (n) indicative of drug release mechanism were computed.

2.5. Calcium Release

The release profiles of calcium ions from alginate beads were examined using the similar protocol as drug dissolution study except that the aliquots were assayed using atomic absorption spectrophotometer (Z-2000, Hitachi Hi-Technologies Corporation, Japan). The percentage of

calcium release was calculated with respect to total calcium content of beads. The total calcium content was determined by subjecting alginate beads to heating in 1 : 1 ratio of 37% hydrochloric acid and deionised water mixture. The calcium content was expressed as the percentage of calcium in a unit weight of beads At least triplicates were carried out for each batch of sample and the results averaged.

2.6. Drug Aqueous Solubility

A saturated drug solution was obtained by stirring an excessive amount of drug in a 50 ml volumetric flask filled with water. The drug solution was agitated at 50 strokes/min using a shaker bath (Memmert GmbH+Co. KG, Germany) at 37 $\pm$ 0.2°C for 24 hours. Aliquots were withdrawn and assayed spectrophotometrically for sulphanilamide and sulphamerazine at 260 and 259.9 nm respectively (Cary 50 Conc, Varian Australia Pty Ltd, Australia). The calculated drug concentration represented the aqueous solubility of drug in the specified volume of water. At least triplicates were carried out for each batch of sample and the results averaged.

2.7. Bead Size and Shape

The size and shape of beads were determined using a digimatic vernier caliper system (Mitutoyo, Japan). The length and breadth were measured from each bead and its size calculated from the average of these two dimensions. The shape of bead was represented by aspect ratio which is the quotient of its length to breadth. An aspect ratio of value unity represents a perfect sphere while higher values represent greater elongation. For each formulation, 20 beads were randomly selected for measurement and the results averaged.

2.8. Scanning Electron Microscopy (SEM)

The surface structure of beads was examined using SEM technique (FEI Quanta 200F, Holland). The beads were fixed with a carbon tape onto studs, and the prepared studs were viewed directly under a scanning electron microscope at a magnification level of 1000 $\times$. Representative sections were photographed.

2.9. Bead Swelling, Erosion and Water Uptake

The analysis of bead swelling, erosion and water uptake capacity was conducted by immersing an accurately weighed bead with known size in 10 ml of untreated water or water treated by microwave at 300 W. The

bead was subjected to agitation at 50 strokes/min using a shaker bath (Memmert GmbH+Co. KG, Germany) at 37 ± 0.2°C. At specified intervals, the weight and size of wet beads were characterized after removing its surface moisture through running the bead gently over a dry petri dish till no sign of moisture left on the immediate dish surface contacted by bead. The bead was then oven-dried at 40 ± 0.5°C for 3 days and subsequently equilibrated to a constant weight by storing in a desiccator at 25 ± 1°C.

The swelling (S_I), erosion (E_I) and water uptake (WU_I) indices of bead were defined as:

$$S_I = (S_t - S_i)/S_i \cdot 100\% \tag{2}$$

where S_i = initial dry bead diameter and S_t = wet bead diameter at time, t.

$$E_I = W_i - W_{t(d)}/W_i \cdot 100\% \tag{3}$$

where W_i = initial dry bead weight and $W_{t(d)}$ = dry weight of bead collected at t.

$$WU_I = W_t - W_{t(d)}/W_{t(d)} \cdot 100\% \tag{4}$$

where W_t = wet weight of beads at t.

In computation of bead erosion and water uptake indices, the weight measurement of beads was corrected for embedded drug and calcium content at t. The response of beads towards dissolution medium was merely evaluated for their changes in polymeric domain. Ten replicates were conducted and the results averaged.

2.10. Dissolution Medium Temperature

The temperature of dissolution medium was determined using an infrared thermometer (Thermo-Hunter, Optex, Japan) with measurement conducted in a non-contact mode. The temperature of the untreated water was examined at the ambient temperature. The temperature of the microwave-treated water was examined immediately after the treatment by microwave. At least triplicates were carried out for each batch of sample and the results averaged.

2.11. Dissolution Medium pH

The pH of dissolution medium was determined by means of a pH meter (Mettler Toledo 320, China) at 25 ± 1°C. At least triplicates were carried out for each batch of sample and the results averaged.

2.12. Dissolution Medium Conductivity

The conductivity of dissolution medium was determined by means of a conductivity meter (WTW Series conductivity 720, Inolab, Germany) at 25 ± 1°C. At least triplicates were carried out for each batch of sample and the results averaged.

2.13. Dissolution Medium Crystallinity

The crystallinity state of dissolution medium was evaluated using X-ray diffractometer (Ultima IV, Rigaku Corporation, Japan) with Cu-K_α radiation generated at 40 kV and 40 mA. The X-ray diffraction was operated at a scanning speed of 3°/min, ranging from 3° to 70° (2θ). At least triplicates were carried out for each batch of sample and the results averaged.

2.14. Fourier Transform Infrared (FTIR) Spectroscopy

An appropriately weighed amount of dry potassium bromide (KBr FTIR grade, Aldrich, Germany) was ground into a fine powder using agate mortar and pestle before compressing it into a disc. Each disc was added with 30 mg of dissolution medium and scanned at a resolution of 4 cm^{-1} over a wavenumber region of 400 to 4000 cm^{-1} using a FTIR spectrometer (Spectrum RX1 FTIR system, Perkin Elmer, USA) at 25 ± 1°C. The characteristic peaks of IR transmission spectra were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

3. RESULTS AND DISCUSSION

Sulphanilamide and sulphamerazine were hydrophilic and hydrophobic drugs respectively with the former exhibited 13.6 folds of solubility in an aqueous solution (sulphanilamide solubility in untreated water = 464.4 ± 12.5 mg/100 ml; sulphamerazine solubility in untreated water = 34.2 ± 1.2 mg/100 ml). Encapsulation of sulphanilamide and sulphamerazine in alginate beads via crosslinking process using calcium chloride solution brought about the formation of matrices with sizes of 1.43 ± 0.09 and 1.20 ± 0.09 mm, aspect ratios of 1.33 ± 0.20 and 1.10 ± 0.10, drug contents of 8.71 ± 0.40 and 8.84 ± 0.60%, as well as, calcium content of 14.35 ± 1.10 and 11.78 ± 0.28% respectively (Table 1).

Table 1. Physicochemical characteristics of sulphanilamide-alginate and sulphamerazine-alginate beads.

					Drug dissolution phase					
					90 min			360 min		
Bead type	Size (mm)	Aspect ratio	Drug content (%)	Calcium content (%)	Swelling index (%)	Erosion index (%)	Water uptake index (%)	Swelling index (%)	Erosion index (%)	Water uptake index (%)
Sulphanilamide-alginate	1.43±0.09	1.33±0.20	8.71±0.40	14.35±1.10	13.33±3.87 (Untreated)[a]	40.33±4.28 (Untreated)	184.67±25.41 (Untreated)	11.04±6.60 (Untreated)	40.65±4.28 (Untreated)	108.35±25.48 (Untreated)
					13.62±6.16 (Treated)[b]	50.32±4.81 (Treated)	223.94±26.12 (Treated)	12.21±7.59 (Treated)	50.82±7.82 (Treated)	145.52±19.64 (Treated)
Sulphamerazine-alginate	1.20±0.09	1.10±0.10	8.84±0.60	11.78±0.28	10.38±5.71 (Untreated)	25.59±8.05 (Untreated)	114.30±16.08 (Untreated)	12.00±4.64 (Untreated)	34.82±5.59 (Untreated)	42.17±22.80 (Untreated)
					11.03±6.26 (Treated)	31.66±7.43 (Treated)	126.70±22.10 (Treated)	11.78±5.51 (Treated)	33.37±5.12 (Treated)	68.23±28.53 (Treated)

[a]Untreated denoted untreated water
[b]Treated denoted microwave-treated water

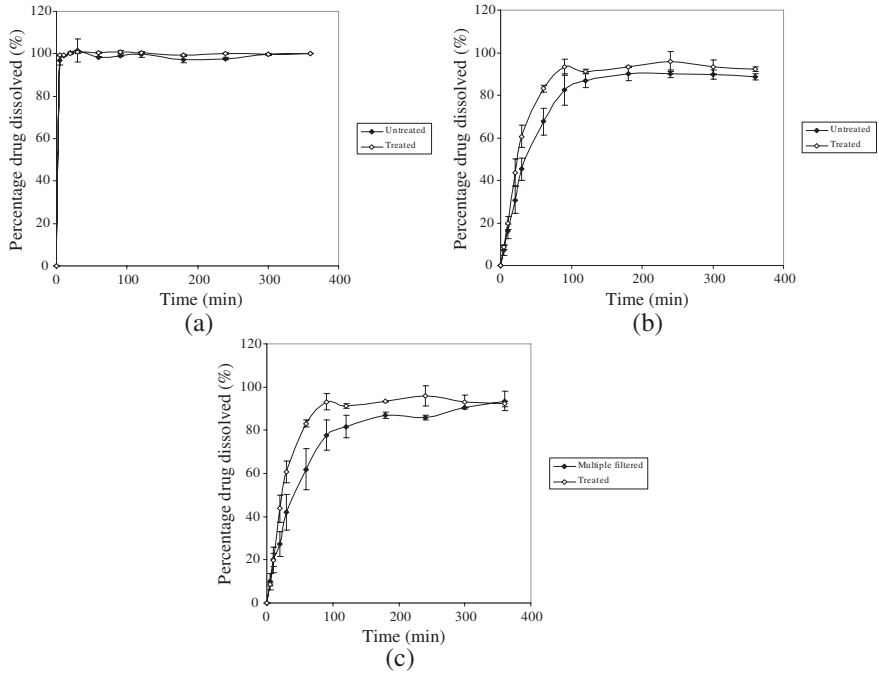

Figure 1. Dissolution profiles of free drugs (a) sulphanilamide and (b) sulphamerazine in microwave-treated and untreated water, and (c) sulphamerazine in microwave-treated and untreated, multiple filtered water.

3.1. Drug Dissolution

The dissolution profiles of free sulphanilamide and sulphamerazine in water were mainly characterized by two phases: fast and delayed dissolution phases. At the first 5 min of dissolution, the dissolution propensity of these free drugs was not markedly affected by the treatment of water with microwave (Figs. 1(a) and (b)). At the subsequent stage of dissolution, the water treated by microwave brought about a higher extent of free drug dissolution than untreated water. In comparison to sulphanilamide, the degree of free sulphamerazine dissolution was promoted to a greater extent through treating the dissolution medium by microwave.

Similar to free drugs, the release propensity of drugs embedded in alginate beads was enhanced when microwave-treated water was employed as dissolution medium (sulphanilamide: k (untreated water) $= 5.91 \pm 2.22$ %/min, k (microwave treated water) $= 18.04 \pm 3.26$ %/min; sulphamerazine: k (untreated water) $= 5.88 \times 10^{-4} \pm 4.66 \times 10^{-4}$ %/min, k (microwave treated water) $= 6.01 \times 10^{-2} \pm 2.80 \times 10^{-2}$ %/min) (Fig. 2). Nonetheless, the release extent of sulphamerazine from alginate beads in microwave-treated water was promoted to a lesser extent than the corresponding beads of sulphanilamide, unlike the cases of free drugs. Encapsulation of hydrophobic sulphamerazine in alginate beads had reduced its extent of release at 6 h of dissolution in untreated water remarkably when compared to free sulphamerazine in the same dissolution medium. The reduction in the extent of drug release was a synergistic attribute of barrier property of alginate and hydrophobic nature of sulphamerazine. This in turn negated the

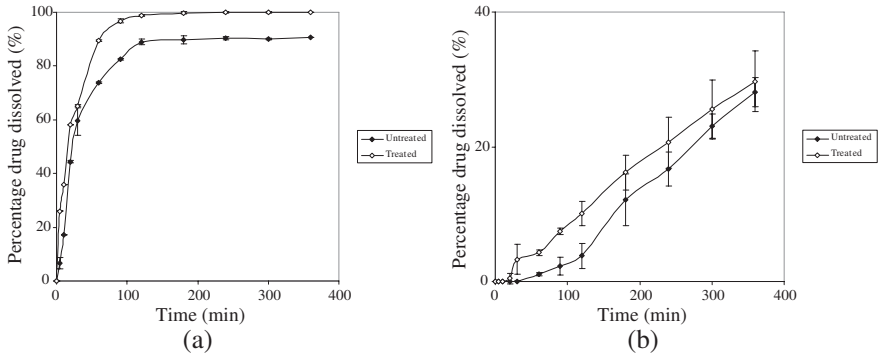

Figure 2. Drug release profiles of (a) sulphanilamide-alginate and (b) sulphamerazine-alginate beads in microwave-treated and untreated water.

sensitivity of encapsulated sulphamerazine to drug release modulation via treating the dissolution medium by microwave. With reference to drug release exponent values, the release of sulphanilamide and sulphamerazine from beads was governed largely by drug diffusion and polymer relaxation respectively (sulphanilamide: $n = 0.42 \pm 0.12$; sulphamerazine: $n = 1.50 \pm 0.49$).

3.2. Physicochemical Properties of Water

The treatment of water by microwave brought about changes in pH and mobility of water molecules (Table 2). These changes were possibly induced by the heating effect of microwave as the untreated water had a temperature of 22.0 ± 0°C whereas the water treated by microwave had a temperature of 85.2 ± 0.7°C. The pH of untreated water was lower than microwave-treated water (Student's-*t*-test, $p < 0.05$). This was likely due to the removal of carbon dioxide from water by heat in the latter. The conductivity of microwave-treated water was higher than untreated water (Student's-*t*-test, $p < 0.05$). It was envisaged that the mobility of water molecules was promoted by microwave through reducing their clustering propensity in bulk phase. This was further supported by the FTIR study of which a lower transmission intensity ratio ascribing *O-H* peak at wavenumber of 3445.5 ± 2.7 cm^{-1} to 1635.0 ± 0.5 cm^{-1} was attained by water treated with microwave (Student's-*t*-test, $p < 0.05$). In addition, X-ray diffractometry analysis indicated that microwave-treated water had a lower degree of crystallinity than untreated water (Fig. 3). The crystallinity count of microwave-treated water was significantly lower than untreated water at $2\theta = 27.94°$ (Student's-*t*-test, $p < 0.05$). The area under curve of crystallinity count-2θ plot of microwave-treated water was similarly lower than untreated water (Student's-*t*-test, $p < 0.05$). Upon heating of water by microwave, the water cluster will adopt a more mobile and less ordered structure, and an expanded

Table 2. Physicochemical characteristics of microwave-treated and untreated water.

Water type	Temperature (°C)	Conductivity (uS/cm)[a]	pH[a]	FTIR transmission intensity ratio[a]	FTIR transmission band wavenumber (cm^{-1})
Untreated	22.0 ± 0.00	0.90 ± 0.00	4.81 ± 0.04	0.3163 ± 0.0717	3448.0 ± 5.2/1634.8 ± 0.8
Microwave-treated	85.19 ± 0.68	0.97 ± 0.06	4.91 ± 0.02	0.1963 ± 0.0407	3442.6 ± 6.3/1635.5 ± 0.4

[a] Experiments conducted a 25 ± 1°C.

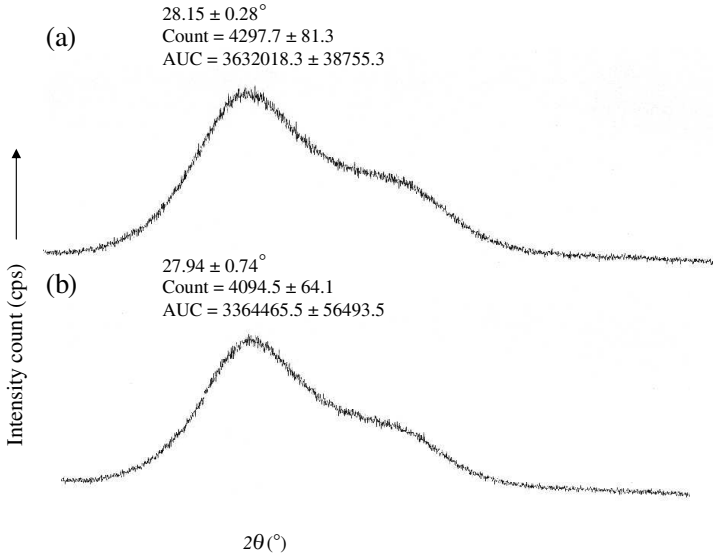

Figure 3. X-ray diffractograms of (a) untreated and (b) microwave-treated water.

water cluster can be converted into a puckered structure [16]. The tendency of water molecules to adopt a puckered structure following the irradiation by microwave was indicated by a lower inter-planar spacing d value of microwave-treated water at 27.94 ± 0.74 Å than untreated water at 28.15 ± 0.28 Å. The higher dissolution propensity of free drugs and embedded drugs from alginate beads in microwave-treated water could be attributed to this water had a higher pH value conducive for solvation of amphoteric drug [17], as well as, a greater level of mobility to generate free cavity in bulk water phase for accommodation of drug molecules.

In a further study to evaluate the significance of water molecule mobility on drug dissolution, the untreated water was subjected to multiple filtration under reduced pressure to remove its content of carbon dioxide and to keep its solution pH identical to that of water treated by microwave. Keeping the solution pH identical, it was found that the dissolution propensity of free sulphamerazine in untreated, multiple filtered water was lower than that of treated by microwave for the first 240 min of dissolution (Fig. 1(c)). The findings indicated that the dissolution behavior of drug was strongly governed by the mobility of water. The water without subjecting to the treatment of microwave had drug undergoing a lower extent of dissolution. The influence

of microwave irradiation on drug dissolution was less dependent on changes in the pH of liquid medium than mobility of water molecules. The similar mode of mechanism of microwave was identified when microwave-treated water was used to examine the activity of Ca^{2+}-dependent K^+ channels of cultured kidney cells [18]. The microwave-treated water was deemed to exhibit "solution memory" [18]. It could probably explain that the dissolution propensity of drug was higher in microwave-treated water than untreated water even if this water was re-equilibrated from 85.2 ± 0.7°C to 37 ± 0.2°C prior test and the drug dissolution test was conducted over a period of several hours.

3.3. Bead Swelling, Erosion and Water Uptake

With reference to sulphanilamide-alginate and sulphamerazine-alginate beads, the drug dissolution process was accompanied by minimal differences in swelling profile but an increase in water uptake and erosion extent of matrices when microwave-treated water was employed as dissolution medium (Table 1). The microwave-treated water molecules were more mobile and exhibited higher penetration intensity from exterior to core of beads. The containment of a higher fraction of water in beads was deemed to generate a higher level of hydrostatic pressure thereby promoting erosion and drug dissolution of matrix. The erosion characteristics of beads differed with the use of microwave-treated water. Surface morphology analysis of intact and eroded beads indicated that matrix undergoing drug dissolution in microwave-treated water tended to form deep pores, whereas beads in untreated water had inter-connecting polymeric fibrils filled in the forming pores (Fig. 4). The higher erosion extent of beads in microwave-treated water was associated with deep pore formation. This reduced the barrier for drug dissolution and promoted a higher propensity of drug release from beads.

The increase in water uptake, erosion and drug dissolution of beads in microwave-treated water was not ascribed to loss of calcium ions as the crosslinker of matrix. Fig. 5 shows that calcium ions of beads were lost to a greater degree in untreated water than microwave-treated water. The loss of calcium ions from beads could have promoted by H^+/Ca^{2+} exchange to a greater extent in the more acidic untreated water than the more mobile microwave-treated water. The pKa values of β-D-mannuronic acid and α-L-guluronic acid of alginate were 3.38 and 3.65 respectively [19]. Using guluronic acid-rich alginate with M/G ratio of 0.59 as matrix polymer, the formed beads were expected to have an excess of 5.64 percent alginic acid in the more acidic untreated water (pH = 4.81 ± 0.04) than microwave-treated water (pH = 4.91 ± 0.02) from an estimation made by Henderson-

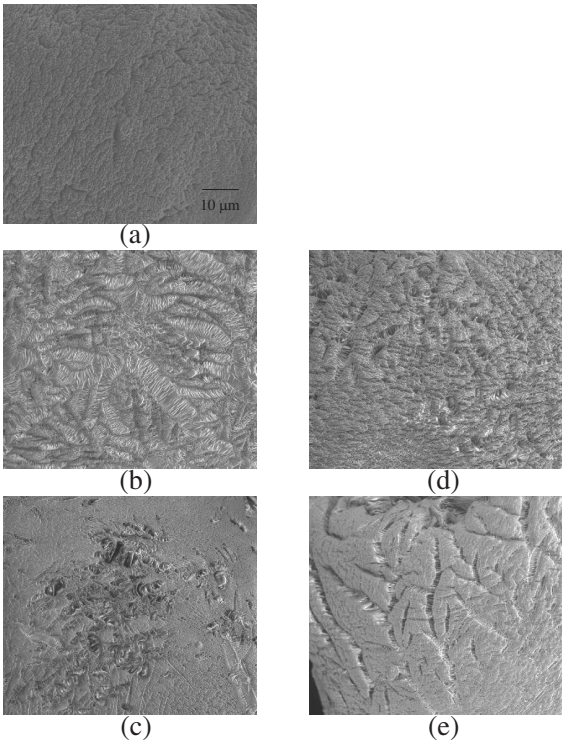

Figure 4. SEM profiles of (a) intact alginate beads and beads in untreated water at (b) 90 min and (c) 360 min, and in microwave-treated water at (d) 90 min and (e) 360 min.

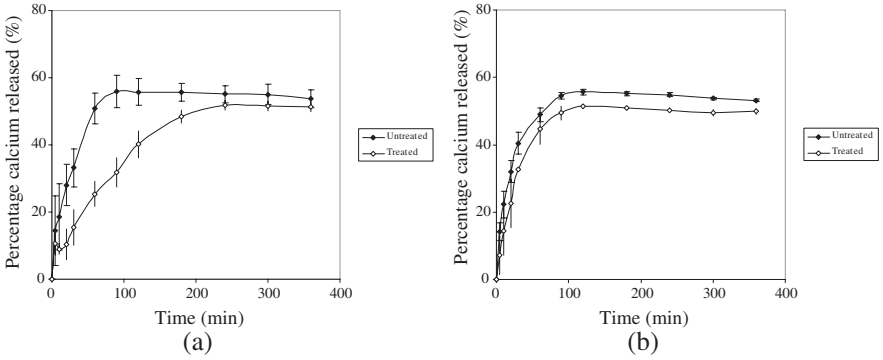

Figure 5. Calcium release profiles of (a) sulphanilamide-alginate and (b) sulphamerazine-alginate beads in microwave-treated and untreated water.

Hasselbalch and mass balance equations. The alginic acid was known to form hydrated insoluble gels and promoted drug release to a larger extent than crosslinked alginate [20, 21]. The observation of higher drug dissolution profile of alginate beads in microwave-treated water than untreated water denoted that the influence of water molecule mobility outweighed the effect of alginic acid on drug release from beads.

The sulphanilamide-alginate beads were relatively hydrophilic. The degrees of water uptake and erosion were higher in sulphanilamide-alginate beads than sulphamerazine-alginate beads in untreated water and microwave-treated water (Table 1). This aptly explained that sulphanilamide-alginate beads underwent a faster process of drug dissolution. Similar to alginate matrices reported in previous findings [22], both sulphanilamide-alginate and sulphamerazine-alginate beads demonstrated syneresis at prolonged dissolution phase. The water uptake capacity of these beads was remarkably reduced at 360 min of dissolution though changes in erosion extent of matrix were comparatively small (Table 1).

4. CONCLUSION

The use of microwave-treated water increased the dissolution propensity of both hydrophilic and hydrophobic free drugs and drugs encapsulated in calcium crosslinked alginate beads. The changes in drug dissolution were due to a rise in molecular mobility and a reduction in crystallinity of water network. Future study shall focus on the interplay effects between drug load, polymer microstructural network and water attributes on drug dissolution. This is essential to identify formulation conditions of dosage form which are critically responsive to water attribute in drug release.

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