

## INTERACTION OF TIARAMIDE HYDROCHLORIDE WITH AMBERLITE RESINS: CHARACTERIZATION OF THE INTERACTION AND MODULATION OF THE RELEASE THROUGH MICROENCAPSULATION OF THE PREPARED RESINATES

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إن عقار التيراميد هيدروكلوريد من العقاقير اللاستيرويدية المستخدمة كمضاد للالتهابات ويمتلك أيضا وُسب الشعب الهوائية ولهذا يستخدم في علاج الربو. ولأن هذا العقار له مفعول قصير الأمد فكان الهدف من هذه الدراسة إيجاد طريقة لإطالة مفعوله. ولذلك تم استخدام راتنجات التبادل الأيوني الموجبة من نوع الأمبرلايت (MB-1& IRP-69) لتحميل العقار عليها وتمت دراسة خواص الراتنجات المحملة بواسطة جهاز تقدير السعر الحراري التفاضلي وحيود الأشعة السينية والتحليل الطيفي للأشعة تحت الحمراء والميكروسكوب الإلكتروني الماسح. وبالرغم من إن انطلاق العقار من الراتنجات كان أقل من مسحوق العقار لكنه لم يكن ؛ لتحضير أنظمة ممتدة المفعول. ولذلك تمت حوصلة الراتنجات المحملة بغرض تأخير انطلاق العقار باستخدام الطريقة المحورة لتبخير الوسط المنتشر للمستحلب واستخدم بيوتيرات خلات السليلوز كمادة مغا . وبدراسة الصفات الانطلاقية للحبيبات الدقيقة أثبتت التجارب وجود إبطاء واضح في انطلاق العقار في كل من محلول حامض الهيدروكلوريك ذو الأس الأيدروجيني ، ومحلول الفوسفات المنظم ذو الأس الأيدروجيني . وقد تمت التجارب الفارماكولوجية على الجرذان بإعطاء مجموع منها عقار التيراميد هيدروكلوريد في صورة محلول أو الراتنجات المحملة أو الحبيبات الدقيقة في صورة معلق ثم إعطاء الجرذان محلول الكاراجينين (Carragenan) عن طريق الحقن تحت الجلد لقدم الجرذ. وتم قياس نسبة تثبيط انتفاخ القدم ووجد أنها تستمر لفترة أطول في حال استخدام الحبيبات الدقيقة عنه عند استخدام عقار التيراميد أو الراتنجات المحملة والغير مغلفة.

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Received in 28/12/2005 & Accepted in 9/4/2006

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*Tiaramide HCl (TAM), a basic NSAID, has high water solubility and short biological half life. The study was undertaken to prolong TAM's activity. TAM resins were prepared by a batch process and using two resins, namely Amberlite IRP-69 (RI) and Amberlite MB-1 (RII). The resins (RI/TAM & RII/TAM) were examined by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared (IR) spectrometry and scanning electron microscopy (SEM). A modified emulsion solvent evaporation method was used to produce TAM-resins coated with cellulose acetate butyrate (CAB) for more drug retardation. The microcapsules were examined using SEM. The results from DSC and XRD showed that the molecular state of the drug in the resins changed to become amorphous instead of its original crystalline form. The IR spectroscopy revealed the presence of an interaction between the drug and resin. The dissolution behavior for the resins in 0.1 N HCl or phosphate buffer (pH 7.4) was compared. TAM release was affected by the dissolution medium and resin type and was slower than that from drug powder or physical mixture. TAM release from microcapsules was slower than the uncoated resins. Additionally, the anti-inflammatory activity, using carrageenan-induced rat hind paw edema, displayed prolonged pattern in comparison with uncoated resin or free drug*

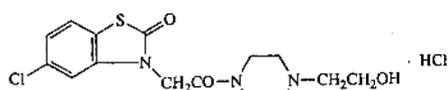
## INTRODUCTION

The ion exchange resins are crosslinked water-insoluble polymer carrying ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and hence a drug-resin complex (drug resin) is formed.<sup>1</sup> Some pharmaceutical properties of a drug prepared as a drug-resin complex are modified from pure drug including decrease drug release, taste, toxicity and stability enhancement of the drug.<sup>2-4</sup> Resins of drugs can be formulated as sustained-release suspension,<sup>5</sup> tablets<sup>6&7</sup> and microparticles.<sup>8</sup> Moreover, the coating of the complex with

some polymers has been claimed to change some of these properties more than the uncoated complex.<sup>9-11</sup> Formulation and preparation parameters of drug/ion-exchange particles microencapsulated in cross-linked chitosan were evaluated for controlled release of the water-soluble drug chlorpheniramine maleate in a suspension.<sup>8</sup> Coated ion-exchange system for phenylpropanolamine<sup>12</sup> and sulfonic acid resins loaded with dextromethorphan<sup>13</sup> were reported to obtain sustained release drug delivery systems. Similarly, coating of pseudoephedrine-dowex 50 WX8 complexes with carnauba wax for sustained release has been reported.<sup>14</sup>

Polyethyleneimine-treated calcium alginate beads loaded with the resinates were prepared by an ionic/polyelectrolyte complexation method and the effect of different formulation variables on the characteristics of the beads was investigated to develop a multi-unit sustained release dosage form of diltiazem.<sup>15</sup>

Tiaramide hydrochloride, 4-[(5-chloro-2-oxo-3-benzothiazolinyl) acetyl] -1-piperazine ethanol hydrochloride (Figure 1), is a basic NSAID and possesses analgesic and antipyretic properties.<sup>16&17</sup> In addition, it is used in treatment of bronchial asthma because it has anti-anaphylactic and bronchodilatory effect.<sup>18</sup> The plasma level of tiaramide elevated to a peak within one hour and declined linearly with a half-life of about 2 hours.<sup>19</sup> Hence, it would be beneficial if it is formulated in prolonged release dosage form.



**Fig. 1:** Structure of tiaramide hydrochloride (TAM).

Therefore, this work was carried out to investigate the molecular state of TAM prepared as resinates using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared spectroscopy (IR) and scanning electron microscopy (SEM). Then, the resinates were

subjected to microencapsulation with cellulose acetate butyrate using modified emulsion-solvent evaporation technique for more drug retardation. The dissolution of TAM from the prepared microcapsules was tested *in vitro* in 0.1 N HCl and phosphate buffer (pH 7.4) and their anti-inflammatory activity was evaluated using acute rat paw edema.

## EXPERIMENTALS

### Materials

Tiaramide HCL was obtained from Fujisawa Pharm. Co., Ltd. Osaka, Japan. Amberlite IRP-69 (Sodium form) & Amberlite MB-1 (Hydrogen form) were received from Aldrich Chem. Comp., Inc., Milwaukee, W.S., USA. Cellulose acetate butyrate was provided by FMC Co., USA. Deionized water was used throughout the study. All solvents and reagents were of analytical grade.

### Purification of ion exchange resins<sup>20</sup>

100 ml deionized water was added to the resin (5 g, < 90 μm) placed in an Erlenmeyer flask. The slurry was stirred with a magnetic bar for 30 min and allowed to settle for 15 min; then, the supernatant was removed by decantation. The resin was washed another two times according to the above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50°. The dried resin was kept in a tight vial until preparation of the resinates.

### Preparation of TAM resins

TAM resins were prepared using a batch process. Resin (1 g, < 90  $\mu\text{m}$ ) was placed in an Erlenmeyer flask and then 50 ml of 2% w/v aqueous TAM solution was added. The mixture was shaken in the water bath at 37° for 2 h (equilibrium time)<sup>21</sup> at 50 stroke/min. Then, the TAM resins (RI/TAM and RII/TAM) were separated by filtration, and washed several times with deionized water to remove any surface adsorbed drug and other ions. Resins were dried overnight at 50° and kept in a desiccator. The amount of free drug in the filtrate as well as the washing water was determined spectrophotometrically at a wavelength of 295 nm<sup>22</sup> (Shimadzu-50-02, Japan). Determinations were carried out in duplicate for each batch. The difference in weights between the initial amount of drug added and the remaining amount of drug in the solution was the amount of drug loaded onto the resins.

The physical mixtures (PMs) were prepared with the same drug content of resins by gentle mixing using pestle and mortar.

### Microencapsulation of prepared resins

Microcapsules were prepared, at 3:1 resin: polymer ratio, using modified emulsion solvent-evaporation method. One gram of resin was dispersed in solution of cellulose acetate butyrate in acetone (CAB; 0.33 g as 5% w/v). The mixture was poured into vessel containing paraffin oil (100 ml) and

span 80 (1 ml). After emulsification for 15 min, 5 ml of *n*-hexane was added dropwise at a constant rate of 1 ml/min to precipitate the coat around the resin particles. Two hours later, the microcapsules were separated by filtration and washed three times with *n*-hexane, then dried in an oven at 50° for 24 hours. The microcapsules were sized through standard sieves and the fraction size used throughout the study was in the range of 90-250  $\mu\text{m}$  since it represented the major fraction of the batch.

Drug content of the microcapsules was determined after pulverization an amount of microcapsules equivalent to 50 mg of drug then the pulverized microcapsules were transferred to 100 ml volumetric flask with the aid of 1 N HCl containing 2% NaCl. The volume was adjusted and set aside for 24 h. An aliquot was withdrawn, filtered, suitably diluted and assayed spectrophotometrically at 295 nm.

### Dissolution study

The dissolution rate for all the samples was studied using the USP paddle apparatus. The sample was accurately weighed to obtain the equivalent of 50 mg of drug and added to vessels containing 500 ml of dissolution medium (0.1 N HCl or phosphate buffer of pH 7.4). The temperature and paddle speed were set at 37  $\pm$  0.1° and 50 rpm, respectively. At suitable time intervals, samples of 5 ml volume were withdrawn and replaced with equal volume of fresh test solution. The drawn samples were filtered and assayed. The amount of drug released

was analyzed by UV spectroscopy at 295 nm.

The release kinetic of TAM from the resins was analyzed using particle diffusion-controlled model<sup>23</sup> as the following equation:

$$-\ln(1-F) = 1.59 \left\{ \frac{6}{d_p} \right\}^{1.3} D^{0.65} t^{0.65}$$

Where F is fractional release of drug from the resin,  $d_p$  is mean particle size of resin, D is apparent diffusion coefficient or diffusivity and t is time. By plotting  $-\ln(1-F)$  against  $t^{0.65}$ , the slope of this relationship could be calculated using linear regression analysis according to the following equation.

$$-\ln(1-F) = K t^{0.65}$$

Where k is the release rate constant.

The release data from micro-encapsulated resins were examined according to the common kinetic models (zero-order, first-order, Higuchi square root model). In addition, TAM release data were analyzed through 60% released using the Ritger and Peppas<sup>24</sup> equation as follows:

$$M_t/M = Kt^n$$

Where  $M_t/M$  represents the fraction of the drug released at time t, K is a constant incorporating structural and geometric characteristics of controlled release device.

### **Infrared spectroscopy (IR)**

Infrared spectra of the samples were recorded on a Hitachi 295 infrared spectrophotometer (Hitachi,

Japan). The samples were scanned over the range of 4000 to 400  $\text{cm}^{-1}$ .

### **Differential scanning calorimetry (DSC)**

DSC analysis was carried out on a differential scanning calorimeter (DSC-50 Shimadzu, Japan) at a heating rate of 10 ° per minute in the range of 25 to 350°. Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. The instrument was calibrated with pure indium and the samples (3-5 mg) were heated in hermetically sealed aluminum pans.

### **X-ray diffractometry (XRD)**

X-ray diffraction studies of the samples were performed using an automated X-ray diffractometer (Model FW 1700 series, Philips, Netherlands) with a filter  $\text{Ni CuK}_\alpha$  radiation detector, voltage 40 kV; current 30 mA and at a scanning rate of 10 mm/sec.

### **Scanning electron microscopy (SEM)**

The samples were mounted onto metal stubs using double-sided adhesive tape, vacuum-coated with a layer of gold using a sputter coater (SPI, sputter, USA). The shape, size and surface of the samples were examined with a scanning electron microscope (Joel JSM 5400LV SEM, 15 kV, Japan).

### **Anti-inflammatory study**

Anti-inflammatory studies were carried out in carrageenan-induced rat hind paw edema model.<sup>25</sup> Five

male Wistar rats weighing 180-210 g were used per group. The animals were starved for 18 h but water was allowed *ad libitum*. Group 1 received saline solution and considered as a control. Group 2 received 200 mg/kg of pure TAM dissolved in 2% w/v methylcellulose. Group 3 received resins of IRP-69 in dose 100 mg/kg equivalent to TAM, with 100 mg/kg of pure TAM in form of solution. Group 4 received microcapsules; prepared at 3:1 resins of IRP-69:CAB, at dose 100 mg/kg equivalent to TAM, with 100 mg/kg of pure TAM in form of solution. The samples were administered orally through stomach gavage followed by 1 ml water. One hour later, 0.1 ml of 1% carrageenan was injected subcutaneously into plantar surface of hind paw and the paw volume (mm) was measured with a dial caliper at 1, 2, 3, 4, 5, 6 and 7 hours after administration of carrageenan. The foot volume after injection of the inflammatory agent was compared with that before injection and the percent swelling of foot edema was calculated. The percent diminution was computed from difference in percent swelling between the treated group and the control group.<sup>25</sup>

#### Statistical analysis

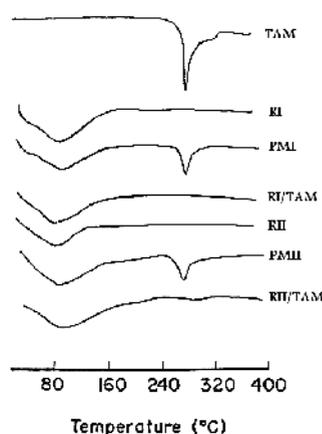
The two-tailed distribution Student's *t* test was applied to examine significance of differences. In all cases,  $P < 0.05$  was considered to be significant and highly significant for  $P < 0.01$ .

## RESULTS AND DISCUSSION

The TAM loading of the resins (RI/TAM) using Amberlite IRP-69 was  $41.56 \pm 0.42\%$  w/w, while for that (RII/TAM) using Amberlite MB-1 was  $36 \pm 0.36\%$  w/w. The difference in the loading reflected the nature of each resin. RI is strong cationic exchanger, while RII is a mixture of strong cations and anions exchanger that fact gave RI more available sites for the exchanging.

#### Differential scanning calorimetry (DSC)

Figure 2 displays the DSC curves of the TAM, resins, physical mixtures (PMs) and resins. Tiaramide has an endothermic peak at 268°,



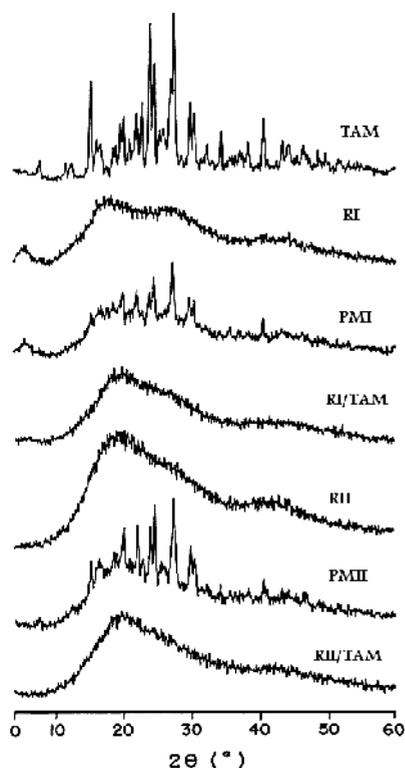
**Fig. 2:** DSC curves for samples: Tiaramide (TAM); Amberlite IRP-69 (RI); Physical mixture of RI and TAM (PMI); Resinate of RI and TAM (RI/TAM); Amberlite MB-1 (RII); Physical mixture of RII and TAM (PMII); Resinate of RII and TAM (RII/TAM).

indicating the temperature of drug melting. The thermal trace shown by resins (RI or RII) was characterized by a broad endothermic peak at 90-110° as a result of the partial dehydration process of the resins. The trace of physical mixtures (PMI or PMII) was representing the simple superimposition of TAM trace and RI or RII trace. This clearly indicated that the preparation of the physical mixture, as well as the heating, caused no interaction between the components. No peak over the range 25-350° was detected in the DSC curves of the resins suggesting the presence of resins or drug in the resins in an amorphous form.

#### X-Ray diffraction patterns (XRD)

The XRD patterns of the samples are shown in Figure 3. Tiaramide is highly crystalline drug with characteristic peaks appeared at equal to 15.07, 23.93, 24.52, 26.95, 27.93°. Physical mixtures show sharp peaks, almost at the same position, indicating that TAM kept its crystalline structure in these preparations. Resins displayed diffused peak due to their amorphous state. Halo' patterns also were given by resinsates. DSC and XRD showed that the molecular state of the entrapped drug in the resinsates changed from the crystalline to the amorphous state. From this it appeared that the drug was dispersed monomolecularly in the resinsates. In the case of physical mixtures, the molecule of drug, which was outside the resin bead, did not disperse

monomolecularly, so the crystalline state of the pure drug was presented.<sup>20</sup>

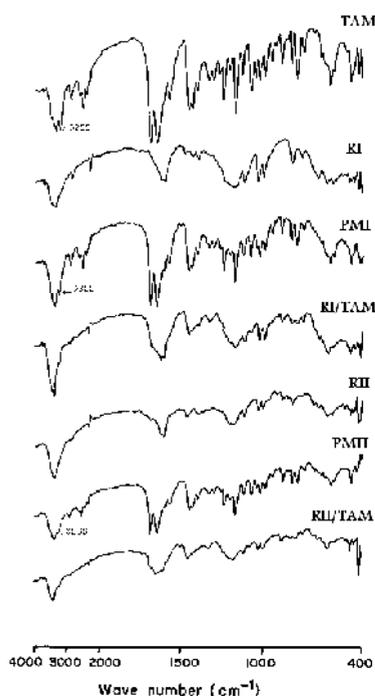


**Fig. 3:** XRD patterns for the samples: Tiaramide (TAM); Amberlite IRP-69 (RI); Physical mixture of RI and TAM (PMI), Resinate of RI and TAM (RI/TAM), Amberlite MB-1 (RII); Physical mixture of RII and TAM (PMII), Resinate of RII and TAM (RII/TAM).

#### Infrared spectroscopy (IR)

Figure 4 demonstrates the IR spectra of the samples. TAM shows the following characteristic absorption bands: 3520  $\text{cm}^{-1}$  (OH),

3255  $\text{cm}^{-1}$  ( $\text{NH}^+$ ), 1694  $\text{cm}^{-1}$  & 1653  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ), 1576  $\text{cm}^{-1}$  ( $\text{C}=\text{C}$ ; aromatic). It was observed that the physical mixtures (PMs) did not show any significant change in the position of the absorption bands of characteristic groups. These spectra appeared to be consistent with that of TAM and RI or RII. The result suggested that there was no interaction between the drug and the resin in these mixtures coinciding with the results from DSC and XRD.



**Fig. 4:** IR spectra for the samples: Tiaramide (TAM); Amberlite IRP-69 (RI); Physical mixture of RI and TAM (PMI); Resinate of RI and TAM (RI/TAM); Amberlite MB-1 (RII); Physical mixture of RII and TAM (PMII); Resinate of RII and TAM (RII/TAM).

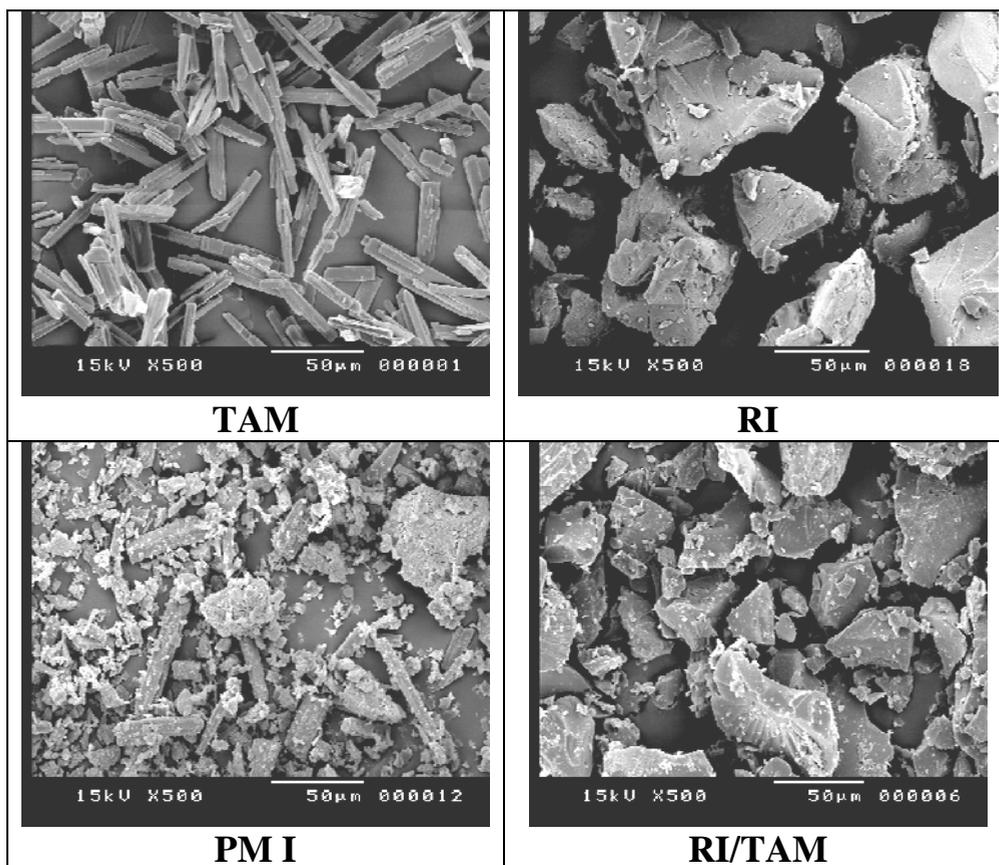
The spectra of drug-resin complexes in the region of 400-2000  $\text{cm}^{-1}$  showed the existence of major peaks of TAM prevailing the entrapment of TAM in the resins. Furthermore, the peak of the drug which appeared at 3255  $\text{cm}^{-1}$  which might be assigned to stretching vibration of the  $\text{NH}^+$  group of drug interacting with chloride ion disappeared in the complex spectra. The results could be attributed to an ionic interaction between the  $\text{NH}^+$  group in TAM and the sulphonate groups in RI or RII. These results were similar to those obtained by Akkaramongkolporn *et al.*<sup>20</sup> who showed that chlorpheniramine maleate existed in the positively charged form which interacted with the sulphonate group in the resin. Additionally, in another study, it was reported that  $\text{NH}_2^+$  group of propranolol which originally bound chloride ion was transformed to interact with the sulfonate group of resin (Amberlite IRP-69) in the complexes.<sup>26</sup> The interaction of TAM with the resins could be a contributing factor in transformation of the drug to amorphous form. Porubcan *et al.*<sup>27</sup> proposed that new chemical bonds and strong complexations could alter the crystalline structure of drug resulting in a changed XRD pattern.

#### Scanning electron microscopy (SEM)

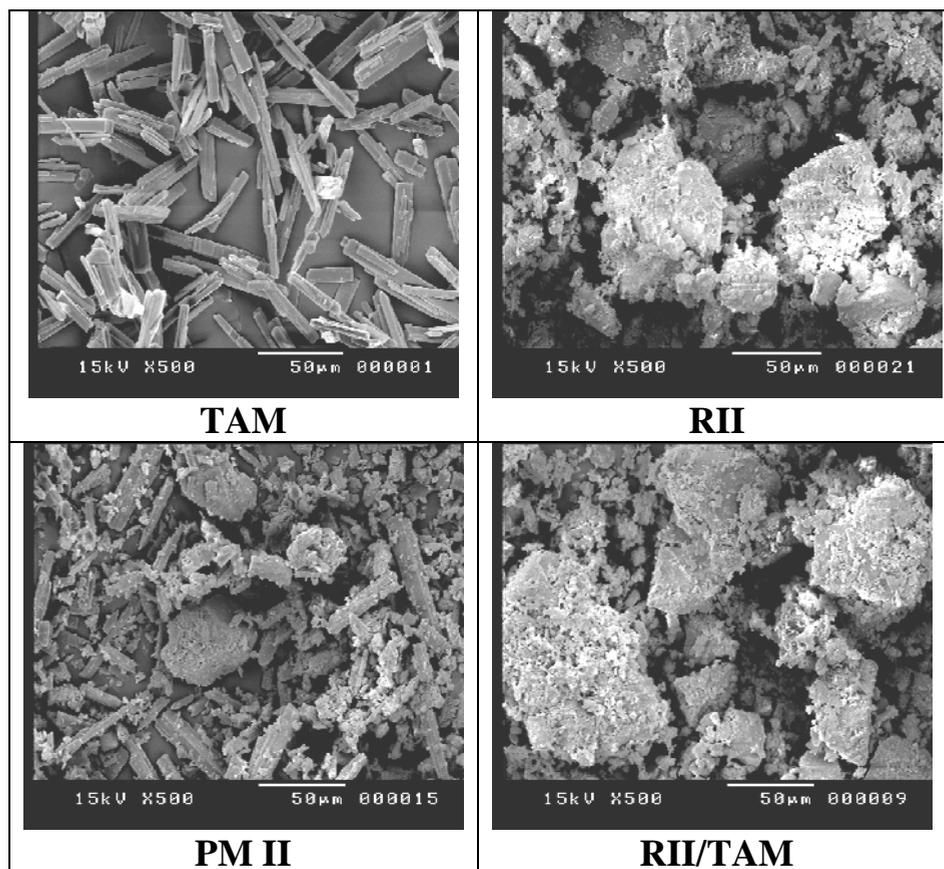
The scanning electron micrographs (SEM) for different samples are presented in Figures 5 and 6. It appeared that the drug crystals were elongated tabular form.

Both of RI and RII were irregular in shapes and appeared as separate pieces. PMI or PMII observed as a mixture of drug and the resin. It was easy to identify the individual component of TAM with RI or RII in case of PMI or PMII. RI/TAM and

RII/TAM looked different in appearance from the drug, resin or their mixture. The features of drug crystals were not easily detectable indicating formation of different compounds than the individual resin.



**Fig. 5:** Scanning electron micrographs for different systems of tiaramide and Amberlite IRP-69: Tiaramide (TAM); Amberlite IRP-69 resin (RI); Physical mixture (PMI); Resinate (RI/TAM).



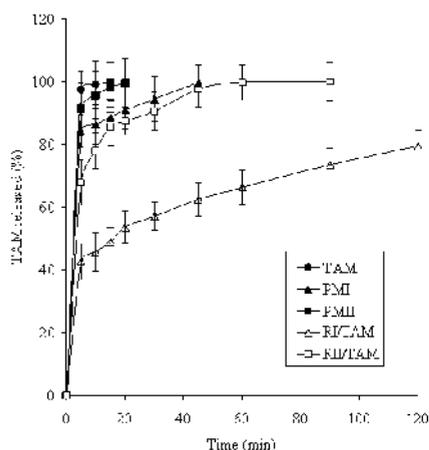
**Fig. 6:** Scanning electron micrographs for different system of tiaramide and Amberlite MB-1. Tiaramide (TAM); Amberlite MB-1 resin (RII), Physical mixture (PMII) and Resinate (RII/TAM)

#### Release study from resins

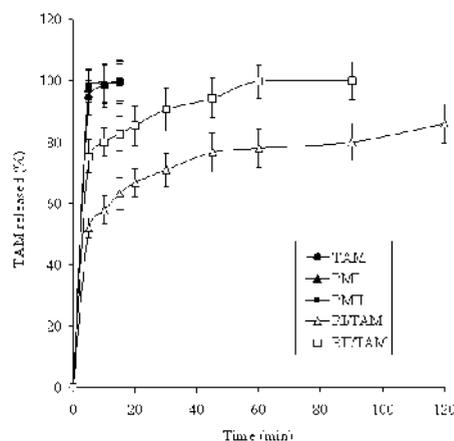
The dissolution of the drug, physical mixtures (PMs) and resins are presented in Figures 7 and 8. The PMI and PMII gave similar release rate to that of the drug suggesting no interaction between resins and TAM in that forms. However, the release rate from the resins was slower than that of drug or physical mixtures.

The slow release rate in case of the resins, in spite of the amorphous molecular state of the drug, may be attributed to their crosslinked structure which resists drug diffusion through the resin beads.<sup>26</sup> This might indicate that the molecular property of drug was not a major determinant of the release behavior of drug from the complexes. In general, the release in

0.1 N HCl was less than that in pH 7.4 in spite the higher solubility of TAM in acidic medium, as well as, the cation exchange should occur faster in acidic medium than in phosphate buffer due to the greater affinity for hydrogen ions compared to sodium or potassium ions. However, the results obtained could be presumably inferred from the difference in the concentration of different counter ions in eluting medium. This result also confirmed the presence of the drug with the resins in form of complex and its release was affected by the amount of ions in the dissolution medium.



**Fig. 7:** Dissolution rate for the samples in 0.1 N HCl: Tiaramide (TAM); Physical mixture of RI and TAM (PMI); Resinate of RI and TAM (RI/TAM); Physical mixture of RII and TAM (PMII); Resinate of RII and TAM (RII/TAM). Error bars indicates SD, n=3



**Fig. 8:** Dissolution rate for the samples in phosphate buffer (pH 7.4): Tiaramide (TAM); Physical mixture of RI and TAM (PMI); Resinate of RI and TAM (RI/TAM); Physical mixture of RII and TAM (PMII); Resinate of RII and TAM (RII/TAM). Error bars indicates SD, n= 3.

The  $-\ln(1-F)$  had a good correlation with  $t^{0.65}$ , whereas the correlation coefficients (Table 1) were  $> 0.94$ , indicating that the release of TAM can be described using particle diffusion-controlled model. In spite, the release from RIT was less than RIIT in both of the dissolution medium (Table 1), TAM release profile was very fast in initial period. So, the application of thin diffusion film could be helpful in controlling that release.

**Table 1:** Parameters of tiaramide release from its resinsates.

Resinate	Dissolution medium	K x 10 <sup>2</sup> (min <sup>-0.65</sup> )	r	Drug released (%) at different times (min)			
				5	10	15	20
RIT	0.1 N HCl	5.2	0.998	42.69	45.7	49.05	53.67
RIIT	0.1 N HCl	13.1	0.944	67.8	78.1	85.8	87.6
RIT	pH 7.4	5.8	0.983	51.97	57.77	63.2	66.7
RIIT	pH 7.4	37.3	0.949	75.25	80.03	82.72	85.4

r: correlation coefficient; K: dissolution rate constant.

### Microencapsulation of TAM resinsates

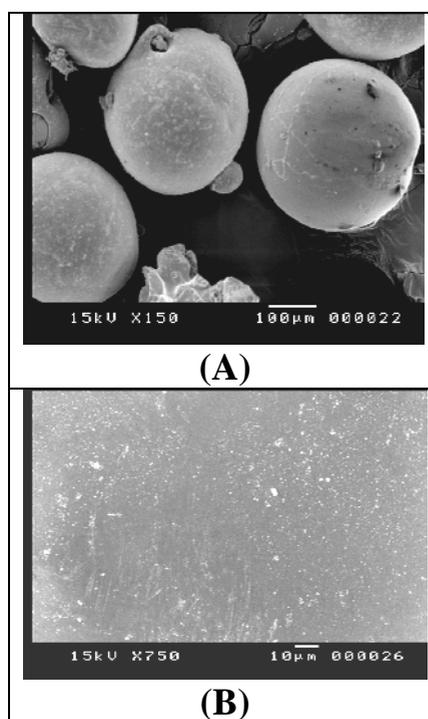
TAM resinsates were microencapsulated using modified emulsion solvent evaporation technique using cellulose acetate butyrate (CAB) as a coating material at 3:1 resinsates:CAB ratio. The percentage (w/w) of microencapsulation efficiency for microcapsules M (RI/TAM) prepared using RI/TAM was  $63.4 \pm 3.54$  while that [M (RII/TAM)] prepared using RIIT was  $66.2 \pm 4.61$ .

Figure 9 demonstrates scanning electron micrographs for microcapsules M (RI/TAM) with different magnification. The microcapsules appeared spherical in shape with absence of aggregates. The high magnification displayed smooth surface without crystals of the drug.

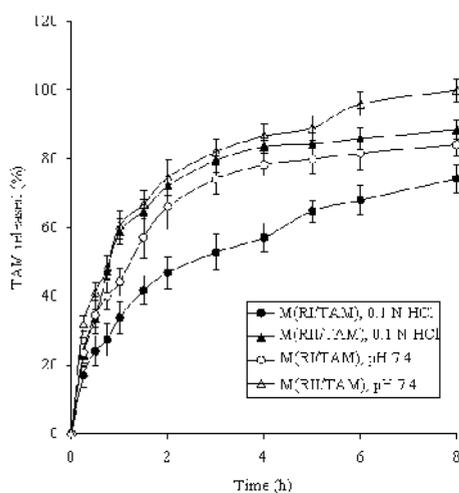
### Release study from microcapsules

In general the release from the microencapsulated resinsates was retarded and slower than from resinsates (Fig. 10). The release from M (RII/TAM) was faster than from M (RI/TAM). The release in phosphate buffer (pH 7.4) was faster than that in

0.1 N HCl. The results were in consistence with TAM release from uncoated resinsates.



**Fig. 9:** Scanning electron micrographs for microcapsules of RI/TAM [M (RI/TAM)] with different magnification: (A) X 150, (B) X 750.



**Fig. 10:** Dissolution rate for the microencapsulated resins in 0.1 N HCl (closed symbols) or phosphate buffer (pH 7.4) (open symbols): Microcapsules of RI/TAM [M(RI/TAM)]; Microcapsules of RII/TAM [M(RII/TAM)]. Error bars indicates SD, n=3.

The release data were examined according to the common kinetic models (zero-order, first-order, and Higuchi square root model). The release rate constants (K) corresponding to each mechanism and the correlation coefficients (r) are depicted (Table 2). Since, the selection of the best-fit kinetic based on the correlation coefficients (r) was difficult, TAM release data were analyzed through 60% released using the Ritger and Peppas' equation.<sup>24</sup> The value of kinetic exponent n defines the mechanism of drug release.<sup>28</sup> Table 2 comprises the values of (n) and the correlation coefficients (r) extracted from Ritger and Peppas' equation.<sup>24</sup> High correlation coefficients were obtained (r = 0.98) and values of (n) were found in the range of 0.406 to 0.516 suggesting a Fickian diffusion mechanism was operating.<sup>28</sup>

**Table 2:** Kinetic parameters of tiamide release from its microencapsulated resins.

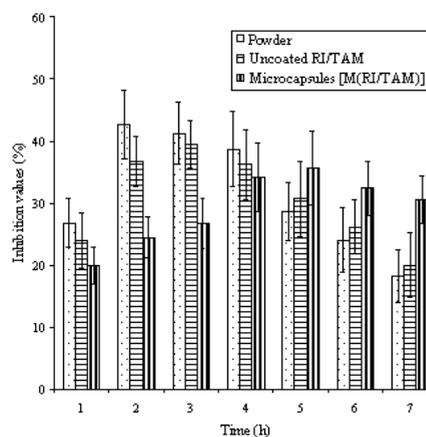
Samples	Dissolution medium	Zero-order		First-order		Higuchi's model		Ritger and Peppas equation	
		r	K <sub>0</sub> (%/h)	r	K <sub>1</sub> × 10 <sup>-2</sup> (h <sup>-1</sup> )	r	K <sub>h</sub> (%h <sup>-0.5</sup> )	r	n
MRI	0.1 N HCl	0.95	7.11	0.98	14.7	0.99	24.72	0.996	0.472
MRII	0.1 N HCl	0.90	7.34	0.93	24.2	0.93	27.3	0.978	0.521
MRI	pH 7.4	0.88	7.42	0.94	20.7	0.96	26.8	0.996	0.466
MRII	pH 7.4	0.91	8.9	0.98	43.3	0.97	28.81	0.992	0.406

r: correlation coefficient; K: dissolution rate constant; n: kinetic exponent

### Anti-inflammatory studies

Inhibitory activity of tiaramide (TAM), uncoated resinate (RI/TAM) and its microencapsulated resinate [M (RI/TAM)], on the swelling of carrageenan-induced rat hind paw edema is demonstrated in Figure 11. The experiment was conducted to evaluate the duration of action of TAM in form of microcapsules in comparison with the uncoated resinate or the pure drug. A peak inhibition of edema of about 42.6% was observed after 1 h for rats treated with TAM alone. Tsurumi *et al.*<sup>25</sup> found that the values of percent inhibition were about 20% and 40% in carrageenan-induced rat paw edema receiving tiaramide hydrochloride as 100 mg/kg and 200 mg/kg respectively. The reduced effectiveness observed with TAM powder during the late phase of carrageenan edema could be due to the drug's short duration of action. Value of peak inhibition (39.5%) appeared after 3 h for rats received resinate. However, there was insignificant difference during the late phase of carrageenin edema (5-7 h) between the rats treated with TAM alone or TAM with resinate. For rats receiving 200 mg/kg as pure TAM and M (RI/TAM) at 1:1 ratio, the peak inhibition (%) was 35.5 and occurred after 5 h. The delayed peak of anti-inflammatory response might be due to the delayed absorption of the TAM from the microcapsules fraction. The inhibition continued at higher level for 7 h than when using TAM alone or TAM with resinate. At 5 h, 6 h and

7 h the group of rats administered TAM with M (RI/TAM) showed higher inhibition percent than that administered TAM powder alone or with resinate. At 5 h the differences was not significant at 5% level of significance. But, at 6 h ( $p < 0.05$ ) and 7 h ( $p < 0.01$ ), the differences were significant and highly significant respectively. These results indicated that the presence of the resinate in the microencapsulated form prolonged TAM's duration of action.



**Fig. 11:** Inhibitory activity of tiaramide powder, uncoated resinate (RI/TAM) and its microencapsulated resinate [M (RI/TAM)], given orally, on the swelling of carrageenan-induced rat hind paw edema. Error bars indicates SD, n=5.

### Conclusion

Tiaramide hydrochloride is a NSAID that has been given orally up to three times daily for the relief of pain, inflammation or treatment of

bronchial asthma. TAM was converted to amorphous form through formation of the resins according to DSC, XRD and SEM. In spite of this form, TAM resinates gave slower release than TAM powder or the physical mixtures. In vitro release data prevailed that the micro-encapsulation of resins prolonged TAM release. Moreover, the inhibition activity of the microcapsules on the paw edema showed longer duration than powder of TAM or resins. These cation-exchange resins, as a formulation tool, can be of great value in developing new formulations for controlling TAM release.

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