Bull. Pharm. Sci., Assiut University, Vol. 33, Part 1, June 2010, pp. 43-49.

PREPARATION AND EVALUATION OF DICLOFENAC SODIUM–CELLULOSE ACETATE MICROCAPSULES USING SOLVENT EVAPORATION TECHNIQUE

Mahmoud M. Ahmed*, Sayed H. Auda, S. Abd El-Rasoul, K. I. Saleh and G. M. Zayed

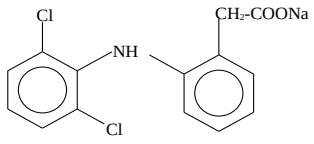
Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut branch, Assiut, Egypt

تشتمل الدراسة على تحضير حويصلات دقيقة لديكلوفيناك الصوديوم باستخدام خلات السيليولوز بطريقة تبخر المذيب في وجود مادة مكونة للمستحلب وهي عديد فينيل الكحول ، وقد أجريت تجارب تمهيدية لتحديد المدى الذي يمكن استخدامه عملياً لكل من حجم الطور الخارجي المائي، حجم الطور الداخلي العضوي ، تركيز مواد الاستحلاب ونسبة العقار مع البوليمر ، كما تم تقييم الحويصلات الدقيقة وذلك بدراسة الشكل الخارجي وخصائص السطح لها ، كما تم تعيين متوسط القطر ، وتقدير كمية الحويصلات الناتجة ومحتوى العقار بالحويصلات بالإضافة إلى دراسة معدل ذوبان العقار من هذه الحويصلات. تم بنجاح تحضير حويصلات دقيقة لديكلوفيناك الصوديوم باستخدام بوليمر خلات السيليولوز بطريقة تبخير المذيب ، وقد تأثرت خصائص الحويصلات المحضرة بعوامل الصياغة المختلفة التي درست. أظهرت النتائج عدم تأثير كمية البوليمر على شكل الحويصلات المحضرة ، كما تم الحصول على حويصلات مستديرة منفصلة ، بينما أدت زيادة كمية البوليمر إلى زيادة قطر الحويصلات ، بينما قل الناتج لزيادة لزوجة الطور العضوي ، كما زاد محتوى العقار بزيادة حجم مخلوط كلوريد المثيلين والأسيتون ، كما أظهرت النتائج عدم تكون طبقة كثيفة من عديد فينيل الكحول في التركيزات الأقل من ٠.٥% ، بينما الزيادة في تركيز عديد فينل الكحول تؤدي إلى نقص كل من حجم الحويصلات ونسبة ناتج الحويصلات. أثبتت النتائج أن عملية إذابة الديكلوفيناك صوديوم تعتمد على قيمة الأس الأيدروجيني ، كما أن العقار يذوب في الوسط القلوي بسرعة أكبر من الوسط الحامضي.

The aim of this study was the preparation of diclofenac sodium microcapsules using cellulose acetate as a polymer and polyvinyl acohol as an emulsifying agent by solvent evaporation technique. Preliminary experiments were carried out to determine practically the volume range of both the external phase, the internal organic phase, the concentration range of emulsifier and the drug to polymer ratio. The prepared microcapsules were evaluated for their morphology and surface structure, average particle size, yield, drug loading efficiency, and their release pattern. The results of these trials revealed that diclofenac sodium–cellulose acetate microcapsules were successfully prepared applying the solvent evaporation technique. The characteristics of the produced microcapsules were highly affected by the different formulation parameters. Changing the polymer content didn't affect the morphology of the produced microcapsules. The microcapsules were discrete, spherical and freely flowing. The increase in the polymer amount increased the mean particle size and decreased the yield of the microcapsules due to the increase in the internal phase viscosity. The drug loading efficiency was significantly increased with the increase in methylene chloride–acetone volume. The condensed monolayer of polyvinyl alcohol was not achieved at concentrations below 0.5%. Above this concentration, the increase in polyvinyl alcohol content decreased both the mean particle diameter and the percentage yield of the microcapsules. The release of diclofenac sodium from cellulose acetate microcapsules was pH dependent. The drug was released faster in the alkaline medium compared to acidic medium.

INTRODUCTION

Diclofenac sodium is a synthetic, non-steroidal, anti-inflammatory and analgesic compound with the following formula:



$C_{14}H_{10}Cl_2NO_2Na$ Mol. Wt.= 318.1

Received in 12/4/2010 & Accepted in 16/6/2010

*Corresponding author E-mail: m_almenshawy80@hotmail.com

Diclofenac sodium is sodium [2-(2,6-dichloro-anilino) phenyl] acetate. It is an odourless, white to off-white, crystalline, slightly hygroscopic powder. Its crystals have a melting range of 283-285°C and pka of 4. Diclofenac sodium is sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; practically insoluble in ether[1]. Diclofenac sodium has analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase. It is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosingspnodylitis, acute gout and following some surgical procedures. The usual dose by mouth is 75-150 mg daily in divided doses[2].

The emulsion solvent evaporation technique has been widely used for the formulation of different drugs into microcapsules using various polymeric materials[1]. This technique is simple and factors affecting microcapsule size distribution and drug release are easily modified[3]. These factors include, among others, type and concentration of emulsifier, volume of organic solvent and polymer composition.

Actual drug loadings often are measurably lower than expected due to loss of drug to the aqueous phase or its crystallization there. Factors that define the extent of drug loss include the volume of aqueous phase per unit weight of drug charged to the system, drug solubility in the aqueous phase under conditions used to form microcapsules, and miscibility of drugs with the carrier from which the microcapsules are formed. Aqueous phase emulsifiers may also enhance drug loss.

A number of drugs differing greatly in water solubility and chemical structure have been incorporated in microcapsules by solvent evaporation protocols that utilize an O/W emulsion. However, O/W emulsion process is more suitable for encapsulation of water insoluble drugs within water insoluble polymers[4].

The aim of this work was the preparation of diclofenac sodium microcapsules using cellulose acetate as a polymer by solvent evaporation technique.

EXPERIMENTAL

Materials and methods

Materials

Diclofenac sodium (DS): (kindly provided by El-Nasr Co. Cairo, Egypt); Cellulose acetate: (Sigma chemical Co., St. Louis USA); Polyvinyl alcohol M.W. app. 14.000 LR (PVA): Aldrich Co., (UK); Acetone and methylene chloride: (Adwic, El-Nasr Co., Cairo, Egypt). All other reagents are of analytical grade and were used as received.

Preparation of microcapsules

The microcapsules were prepared by solvent evaporation method in 250 ml beaker, using a mechanical stirrer at 400 rpm. The calculated amount of the polymer cellulose acetate (CA) was dissolved in the specified volume of methylene chloride and acetone (ratio of methylene chloride to acetone is 3:2 respectively), followed by dissolving the calculated amount of the drug (DS) to form the internal phase as shown in Table (1). The external phase was prepared by dissolving the specific amount of the polyvinyl alcohol in 120 ml distilled water. The internal phase was added drop wise to the external phase, using a 20 ml syringe at a rate of 0.5 ml/min. After complete addition of the internal phase, methylene chloride – acetone mixture was allowed to evaporate. The microcapsules were collected by filteration, washed with distilled water, left to dry at ambient conditions for 24 hrs and stored in a desiccator until used.

Microscopic examination of microcapsules

On a suitable slide, amount of the dried microcapsules was observed under an optical microscope and microscope photographs were taken at magnification powers 40 and 100x.

Determination of the particle size of microcapsules

The dried microcapsules were weighed and sized using USP standard sieve set. The fraction of microcapsules remaining on each sieve was collected and the mean particle size of the microcapsules was assigned as the percentage of microcapsules retained at each sieve multiplied by the average particle size of this sieve.

Determination of the yield of the microcapsules

The yield of the microcapsules was determined by dividing the weight of the prepared microcapsules by the original amount of the polymer and drug used and the results were expressed as a percentage.

Determination of the microcapsules content

Ten milligrams of the microcapsules were added to 25 ml pH 7.4 phosphate buffer in a 25 ml volumetric flask and left overnight. The withdrawn samples were properly diluted and measured spectrophotometrically at λ_{max} 277 nm against phosphate buffer pH 7.4 as a blank. The experiment was done in triplicate.

Release of the drug from the microcapsules

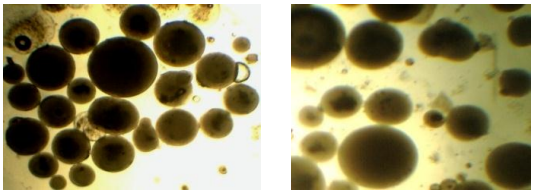
Dissolution testing of the prepared microcapsules equivalent to 100 mg diclofenac sodium (DS) was performed with the rotating paddle apparatus. The operating conditions were: Paddle spead of 50 rpm and a temperature of 37°C ± 0.5. Regarding the dissolution medium the pH shift method was used as follows[5]:

A volume of 900 ml of simulated gastric fluid, pH 1.2, was used as the release medium for two hours, followed by the addition of (8.5-12 ml) of 1 M KH_2PO_4 containing 16.75% (w/v) NaOH, in order to change the pH of the medium to 7.4. Drug release was continued in this medium for six hours. Filtered samples, 3 ml each, were removed at specified intervals throughout the whole 8 hrs. The samples were diluted appropriately with the release medium, and absorbance was measured at the predetermined λ_{max} of each medium against a blank of this medium. The withdrawn samples were replaced with equal volumes of the release medium.

RESULTS AND DISCUSSION

Microcapsule morphology

The obtained diclofenac sodium–cellulose acetate microcapsules, as seen under the optical microscope (40 and 100 x), were discrete, spherical and freely flowing ones. The microcapsules surface is smooth at both drug to polymer ratios of 1:1 and 1:2 (Fig. 1a,b).



(a) (b)

Fig. 1: Optical micrographs of the prepared microcapsules at (a) Drug: polymer ratio 1:1and (b) 1:2.

The particle size of the microcapsules

Table (1) shows the mean particle diameters of counted CA microcapsules prepared with drug to polymer ratio 1:1 and 1:2 at polyvinyl alcohol concentrations of 0.5, 1 and 2% and using 30 and 50 ml methylene chloride – acetone mixture. Upon using solvent evaporation technique, highly viscous internal phases produce larger microcapsules due to more difficult dispersion in the external phase[6]. The high viscosity results from increasing the concentration of solids in the internal phase (the drug or the polymer) or decreasing the organic solvent volume[1]. For cellulose acetate butyrate loaded with carbamazepine, the increase in microcapsules size was related to increase in the polymer amount and the decrease in organic solvent volume. The drug to polymer ratio was increased from 1:2 to 1:4 and the methylene chloride volume was decreased from 80 to 30 ml[7]. The geometric mean size of terbutaline–cellulose acetate butyrate microcapsules was increased on increasing the drug to polymer ratio[8].

The yield of the microcapsules

The percentage yield was determined as a function of the quantity of microcapsules produced to the amount of drug and polymer used. Table (2), shows the percentage yield of the prepared microcapsules. The increase in the amount of the polymer decreased the microcapsules yield, this may be attributed to the increase in the organic phase viscosity.

The effect of the polyvinyl alcohol concentration on the microcapsule yield at the two different drug to polymer ratios demonstrates that increase in the PVA concentration markedly decreased the microcapsules yield. Similar results for the D: P ratio and the emulsifier concentration effect on the microcapsule yield were obtained for carbamazepine-CAB microcapsules[7].

Table 1: Particle diameter (um) of diclofenac sodium- cellulose acetate microcapsules.

D : P ratio	Methylene chloride-acetone mixture volume	Microcapsule Diameter (μm)		
		Polyvinyl alcohol concentration (%)		
		0.5	1.0	2.0
1:1	30 ml	182.33	156.62	141.71
	50 ml	162.60	139.41	112.31
1:2	30 ml	262.31	191.42	169.9
	50 ml	273.61	176.9	147.6

Table 2: Yield of diclofenac sodium-cellulose acetate microcapsules.

D : P ratio	Methylene chloride-acetone mixture volume	Yield		
		Polyvinyl alcohol concentration %		
		0.5	1.0	2.0
1:1	30 ml	96.3	89.4	83
	50 ml	97.1	91.3	84
1:2	30 ml	92.5	86.4	79.9
	50 ml	91.0	86.1	80.3

The content of the microcapsules

Table (3) shows that the calculated theoretical drug loading value was 50% formicrocapsules prepared at 1:1 drug to polymer ratio. Microcapsules prepared with PVA concentrations of 0.5, 1 and 2%, the values of actual drug loading were 38.5, 37.3 and 36.9%, respectively, upon using 30 ml methylene chloride–acetone while the actual drug loading upon using 50 ml methylene chloride-acetone were 46.8, 44.7 and 42.3%, respectively. The mean loading efficiency were calculated and found to be 77±2.97, 74.6±3.76 and 73.8±2.88%, respectively in case of using 30 ml methylene chloride – acetone while loading efficiency upon using 50 ml methylene chloride – acetone were 93.6±4.22, 89.6±3.7, and 84.6±3.53%, respectively. The data for drug to polymer of 1:2 are given in Table (3). The increase in polymer concentration, lead to an increase in drug loading efficiency. The drug loading efficiency is increased with consequent increase in methylene chloride–acetone volume. The use of higher polymer/ organic solvent ratios increased the drug content due to higher polymer concentration at the droplet boundary at the point of precipitation. Thus a faster precipitation at the surface of the droplet occurred with consequent inhibition of drug diffusion across the phase boundary[7].

Release of diclofenac sodium from the microcapsules

Since the prepared diclofenac sodium microcapsules are intended for oral use, the release patterns were studied throughout the pH range 1.2-7.4, which approximately corresponds to the conditions met *in-vivo* (Figs. 2-5). Cellulose acetate–diclofenac sodium microcapsules equivalent to 100 mg of the drug were filled in capsule shells (size 1) and were used in the test.

Table 3: Drug loading efficiency of diclofenac sodium–cellulase acetate microcapsules

D : P ratio	1:1						1:2					
Meth. chl.-acet. vol. (ml)	30			50			30			50		
PVA concentration (%)	0.5 %	1%	2%	0.5%	1%	2%	0.5%	1%	2%	0.5%	1%	2%
Theoretical drug loading (%)	50	50	50	50	50	50	33.33	33.33	33.33	33.33	33.33	33.33
Actual drug loading (%)	38.5	37.3	36.9	46.8	44.7	42.3	24.8	23.3	22.5	28.7	27.9	26.8
Loading efficiency (%) mean+SD	77 ± 2.9	74.6 ± 3.7	73.8 ± 2.8	93.6 ± 4.2	89.6 ± 3.7	84.6 ± 3.5	74.4 ± 2.5	69.9 ± 2.8	67.5 ± 4.2	86.1 ± 2.9	83.7 ± 3.7	80.4 ± 3.7

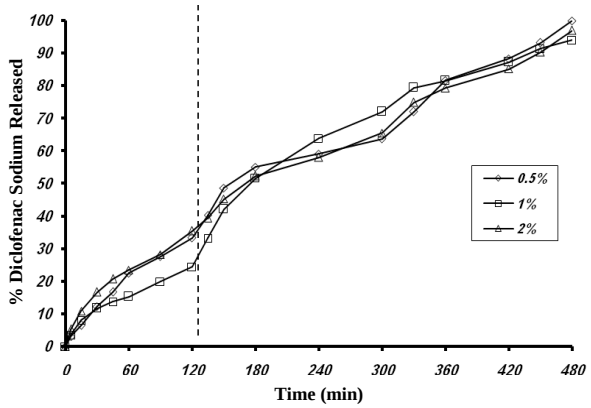


Fig. 2: Release profiles of diclofenac sodium from cellulose acetate microcapsules prepared at drug to polymer ratio of 1:1, using 30 ml methylene chloride-acetone mixture and PVA concentrations of 0.5, 1 and 2%.

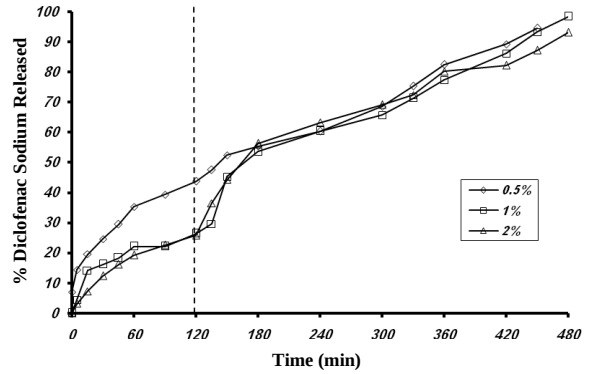


Fig. 3: Release profile of diclofenac sodium from cellulose acetate microcapsules prepared at drug to polymer ratio of 1:1, using 50 ml methylene chloride-acetone mixture and PVA concentrations of 0.5, 1 and 2%.

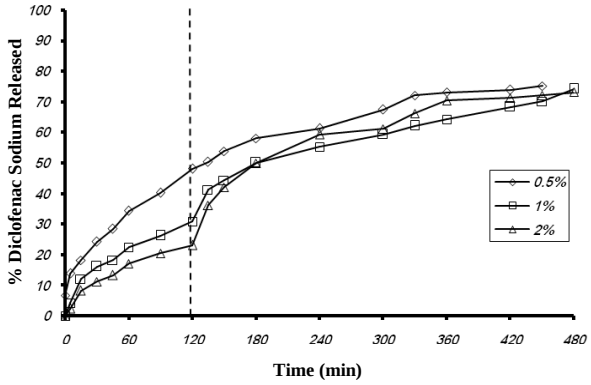


Fig. 4: Release profile of diclofenac sodium from cellulose acetate microcapsules prepared at drug to polymer ratio of 1:2, using 30 ml methylene chloride-acetone mixture and PVA concentrations of 0.5, 1 and 2%.

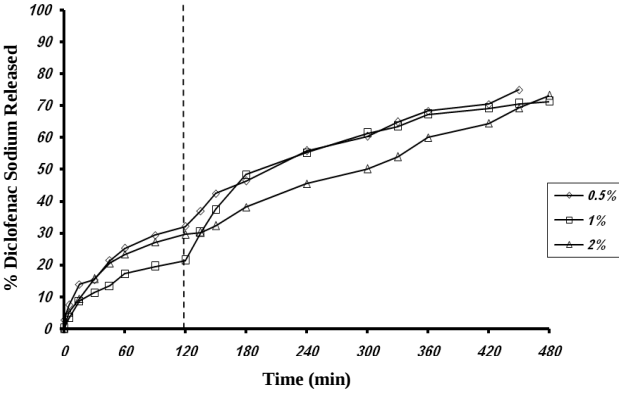


Fig. 5: Release profile of diclofenac sodium from cellulose acetate microcapsules prepared at drug to polymer ratio of 1:2, using 50 ml methylene chloride-acetone mixture and PVA concentrations of 0.5, 1 and 2%.

The release data of diclofenac sodium from cellulose acetate microcapsules prepared with different process variables were analyzed according to zero and first-order kinetics as well as, Higushi diffusion controlled mechanism. The release order of the drug was determined. It was found that the drug was released from the microcapsules according to diffusion kinetics at the different pH values (Tables 4 and 5). This Higushi diffusion release pattern was noticed rather than a zero-order pattern, at the two drugs to polymer ratios and both methylene chloride- acetone volumes. There is no effect for the change in polyvinyl alcohol concentration on the release pattern for all microcapsules. The release of the drug from the microcapsules was decreased by increasing the amount of the polymer. This delay in drug release could be attributed to the formation of thicker coating membranes or to the decrease in number of pores at the microcapsule surface at higher polymer to drug ratios. This finding for the drug: polymer ratio effect on the release profile was in agreement with the results obtained by several researchers. For example, propranolol hydrochloride encapsulated in CAB, The decrease in D:P ratio resulted in greater delay in the release rate[9]. Microcapsules of terbutaline sulfate with cellulose acetate butyrate and ethylcellulose were prepared using emulsion solvent evaporation technique. It was reported that the release was decreased as the amount of polymer increased[8]. Similar results were reported for ethyl cellulose microcapsules[1], and for cellulose propionate microcapsules[10]. On the other hand, the increase of cellulose acetate butyrate did not modify the release rate of indomethacin. As CAB is water – insoluble cellulose derivative was expected that the drug release would be by passage through the microcapsule surface pores[9]. The release medium dissolves the drug after penetrating the microcapsule wall by allowing the dissolved drug to diffuse out due to concentration gradient established between the interior of the microcapsules and the release medium[11].

Table 4: Analysis of the release data for diclofenac sodium–cellulose acetate microcapsules prepared at drug: polymer ratios of 1:1and 1:2 using 30 ml methylene chloride–acetone mixture.

PVA concentration (%)		0.5		1.0		2.0	
D:P ratio		1:1	1:2	1:1	1:2	1:1	1:2
Zero-order	K_z	11.734	8.006	11.885	7.876	9.09	8.591
	R_z	0.979	0.940	0.980	0.963	0.993	0.952
First-order	K_f	0.285	0.169	0.335	0.153	0.208	0.221
	R_f	0.986	0.986	0.982	0.990	0.976	0.964
Higuchi equation	K_h	38.321	28.954	40.97	27.63	31.212	29.34
	R_h	0.996	0.988	0.984	0.992	0.990	0.983

K_z ($mg.hr^{-1}$), K_f (hr^{-1}) and K_h ($mg/cm^2.\ hr^{½}$) are the release rate constants of zero-order, first order and Higuchi model kinetics, respectively, as well as R_z, R_f and R_h are their corresponding correlation coefficients.

Table 5: Analysis of the release data for diclofenac sodium–cellulose acetate microcapsules prepared at drug: polymer ratio of 1:1and 1:2 using 50 ml methylene chloride–acetone mixture.

PVA concentration (%)		0.5		1.0		2.0	
D:P ratio		1:1	1:2	1:1	1:2	1:1	1:2
Zero-order	K_z	9.734	9.405	10.885	8.872	11.24	9.561
	R_z	0.986	0.981	0.995	0.963	0.983	0.983
First-order	K_f	0.275	0.174	0.375	0.165	0.297	0.221
	R_f	0.936	0.992	0.900	0.984	0.986	0.981
Higuchi equation	K_h	32.321	32.743	36.98	31.12	38.997	31.354
	R_h	0.989	0.996	0.984	0.992	0.990	0.994

K_z ($mg.hr^{-1}$), K_f (hr^{-1}) and K_h ($mg/cm^2.\ hr^{½}$) are the release rate constants of zero-order, first order and Higuchi model kinetics, respectively, as well as R_z, R_f and R_h are their corresponding correlation coefficients.

Conclusion

On the basis of previous findings the following could be concluded: Diclofenac sodium–cellulose acetate microcapsules were successfully prepared applying the solvent evaporation technique. The characteristics of the produced microcapsules were highly affected by the different formulation parameters. Changing the polymer content does not affect the morphology of the produced microcapsules. Drug to polymer ratios of 1:1 and 1:2 produced discrete, spherical and freely flowing micro-capsules. The increase in the polymer amount increased the mean particle size and decreased the yield of the microcapsule due to the increase in the internal phase viscosity. The drug release from the microcapsules was markedly decreased on increasing the polymer content. Increasing the organic phase volume from 30 to 50 ml decreased the mean particle size of the produced microcapsules. No marked effect was observed for the change in organic phase volume on the percentage yield of the microcapsules. The drug loading efficiency was significantly increased with the increase in methylene chloride–acetone volume. The condensed monolayer of polyvinyl alcohol was not achieved at concentrations below 0.5%. Above this concentration, the increase in polyvinyl alcohol content decreased both the mean particle diameter and the percentage yield of the microcapsules. The release of diclofenac sodium from cellulose acetate microcapsules was pH dependent. The drug was released faster in the alkaline medium compared to acidic medium.

REFERENCES

1- Y. Srinivasa Rao, N. Malleswara Vs, K. P. and R. Chowdary, The Indian Pharmacist, 8, 63 (2009).
2- Martindale, "The Extra Pharmacopoeia", 35th Ed., The Pharmaceutical Press, London, 2007, pp. 12, 25.
3- K. S. Soppimath, A. R. Kulkorni and T. M. Aminabhavi, J. Microencap., 18, 397, (2001).
4- M. D. Dhanaraju, V. D. Sundar, S. Nandhakumar and K. Bhaskar, J. Young Pharm., 1 (4), 301 (2009).
5- N. Kondo, T. Iwao, K. I. Hirai, M. Fukuda, K. Yamanouchi, K. Yokoyama, M. Miyaji, Y. Ishihara, K. Kon, Y. Ogawa, and T. Mayumi, J. Pharm. Sci., 83, 566 (1994).
6- F. Gheorghe, C. Marieta, E. Elisabitta, N. Claudio and M. Enea, Biomat., 4337-4347 (2005).
7- P. Arnaud, C. Boue and J. C. Chaumiel, J. Microencap., 13, 407 (1996).
8- R. Ruiz, A. Sark, and O. L Sprockel, Drug. Dev. Ind. Pharm., 16, 1829 (1990).
9- Y. Pongpaibul, S. Abdel Monem, H. and C. W. Whitworth, Drug Dev. and Ind. Pharm., 15, 2547 (1989).
10- S. H. Khidr, E. M. Niazy and Y. M. El-Sayedy, J. Microencap., 15, 153 (1998).
11- J. Singh and D. H. Robinson, U.S. Pharmacist., 7, 67 (1990).