A Modified Organic Method for Preparation of Ibuprofen Microcapsules As a Sustained Release Solid Dosage Form

Issraa Rasheed Abed Al- Rahman
Alaa A. A.Rasool and Fatima A. Tawfiq
Department of Pharmaceutics, College of Pharmacy, Baghdad University, Baghdad-Iraq
Received: 02.01.2001 Accepted: 02.03.2002

ABSTRACT:

Microencapsulation is used to modify and retard drug release as well as to overcome the unpleasant effect (gastrointestinal disturbances) which are associated with repeated and overdose of ibuprofen per day.

So that, a newly developed method of microencapsulation was utilized (a modified organic method) through a modification of aqueous colloidal polymer dispersion method using ethylcellulose and sodium alginate coating materials to prepare a sustained release ibuprofen microcapsules.

The effect of core : wall ratio on the percent yield and encapsulation efficiency of prepared microcapsules was low, whereas , the release of drug from prepared microcapsules was affected by core: wall ratio ,proportion of coating material and presence of additive(PEG4000). The 2:1 core : wall ratio was compared (in weight equivalent to 300mg and 600mg drug) with Fenbid® spansule capsule 300mg and Balkaprofen® tablet 600mg respectively. It was found that the release of drug from selected ratio and Balkaprofen® tablet was more or less similar($P > 0.05$) .This sustained release ratio was encapsulated in weight equivalent to 300mg drug to be administered once daily (600mg) as two capsules as the reference. The capsules were stable within 6 months of storage at room temperature.

الخلاصة:

تستخدم طريقة التغليف المجهري للسيطرة على سرعة انطلاق العقار والتغلب على المظاهر السلبية الناتجة من لاستعمال المتكرر اليومي لعقار الايبوبروفين, لذلك تم استحداث طريقة جديدة محورة عن الطريقة المائية الغروية وسميت بالطريقة المحورة العضوية باستخدام سليلوز الاثيل والجينيت الصوديوم كمواد مغلفة لتحضير كبسولات مجهرية للايبوبروفين بطيئة التحرر. لوحظ ان تأثير نسبة المادة اللبية إلى المادة المغلِفة للعقار على كفاءة التغليف ونسبة الكبسولات المجهرية الناتجة قليل. لكن تحرر العقار من تلك الكبسولات المجهرية يتأثر بنسبة المادة اللبية إلى المادة المغلِفة, تغيير نسبة المادة المغلِفة (سليلوز الاثيل) واضافة مادة البولي أثيلين كلايكول ٤٠٠٠. تم مقارنة النسبة (١:٢) بوزن يعادل٣٠٠ ملغم, ٦٠٠ملغم من العقار مع الفنبد سبانسول كبسول ٣٠٠ ملغم و حبوب بالكابروفين ٦٠٠ ملغم على التوالي حيث أشارت النتائج إلى أن تحرر العقار من النسبة المختارة وحبوب بالكابروفين كان متشابهاً, لذلك تم احتواء تلك الكبسولات المجهرية بأوزان تعادل ٣٠٠ ملغم من الأيبوبروفين في كبسول جلاتيني صلب يصرف كبسولتين قي اليوم ليعطي تحرر بطيء للعقار مشابها لحبوب بالكابروفين.كانت ثباتية المستحضر عالية خلال فترة الخزن البالغة ٦ أشهر في درجة حرارة الغرفة.

INTRODUCTION:

Ibuprofen is a non steroidal anti–inflammatory drug used in painful and inflammatory conditions. The conventional administration of this drug may produce different side effects as gastrointestinal disturbances and patient compliance problem due to multiple dose per day .This drug is absorbed from GIT and peak plasma concentration occurs about 1-2 hours after ingestion ,90-99% of the ibuprofen is bound to plasma protein and plasma half life is about two hours[1].

Sustained release drug delivery system provides a slow release of drug over an extended period of time that can be obtained by matrix or reservoir devices formulation.

Microencapsulation (reservoir system) offers a good tool to overcome some of undesirable effects, since it has many advantages, such as; mask the bitter taste of the drugs (erythromycin [2], colistin salfate [3]), control the release of the drug (nifidipine[4]) and separate the incompatible drugs. The mechanism of action is through micro packaging technique of small particles by deposition of a thin coating material around these particles. There are different methods adapted to pharmaceutical use, these include: air suspension, phase separation coacervation, interfacial polymerization, electrostatic spraying , spray drying ,spray congealing and diffusion exchange[5].

Many drugs were encapsulated through these techniques like indomethacin[6], aspirin[7] , chloramphenicol[8] ,isoniazid[9]and nicardipine HCl[10].

The aim of the present work is to prepare a sustained release ibuprofen microcapsules as a capsule dosage form using a modified organic method and compared it with the references Fenbid® spansule capsule300mg and Blakaprofen® tablet 600mg), in addition, studying the factors that affect the releasing behavior of ibuprofen from the prepared microcapsules .

MATERIALS and METHODS:

Ibuprofen, powder supplied by SDI, Iraq; Chloroform, (BDH. Chemical LTD, Pool England); Polyethylene glycol (PEG 4000), calcium chloride and sodium alginate, (Judex laboratory reagents, Sudbury, Middlesex, England).

Fenbid® spansule capsule 300mg SKF Company, England and Balkaprofen® tablet 600mg APM Company, Jordan.

PREPARATION OF MICROCAPSULES:

A modified organic method (scheme 2) was obtained through a modification of an aqueous colloidal polymer dispersion method (scheme 1) [11].The drug was dispersed in an aqueous solution of Na–alginate (2% w/w) which is previously heated to 40ºC and added to the dispersion system of ethyl cellulose (20% w/w) in chloroform which was kept at room temperature.

Then by dropping the bubble–free dispersion through a modified separatory funnel into gently agitated calcium chloride solution (1%), a gelled beads were obtained and separated after 1–2 minutes by filtration with vacuum then rinsed with distilled water. Finally, the beads were dried at 60ºC over night.

Different core: wall ratios 2:1, 1:1 and 1:2 were prepared utilizing the same method.

2:1 core: wall ratio in weight equivalent to 300mg ibuprofen(517mg) was used to prepare different formulas as shown in table(1) in order to study the effect of PEG4000 addition and ethylcellulose proportion on the releasing profile in comparison with the sustained release reference Fenbid® spansule capsule 300mg.

Formula No.	Ibuprofen (gm)	Sodium-alginate (gm)	Ethyl cellulose (gm)	PEG4000 (gm)
Original formula	8	2	2	-
1	8	2	2	0.2
2	8	2	1.8	0.2
3	8	2	1.6	-
4	8	2	1.6	0.4

Table (1) Different Formulas of 2:1Core to Wall Ratio Ibuprofen Microcapsule Prepared by a Modified Organic Method

In addition, the release of ibuprofen from the same ratio in weight equivalent to 600mg drug (1.03g) was compared with the sustained release reference Balkaprofen® tablet 600mg.

On the other hand, the same weight of the selected ratio was compressed directly without additives into tablet dosage form using two compression forces (10×10^3 psi and 12×10^3 psi).

Also, formula 2 in weight equivalent to 600mg ibuprofen (1.07g) was compressed directly without additives into tablet dosage form using 10×10^3 psi compression force in order to investigate the effect of PEG4000 addition and ethylcellelose proportion on the release profile of compressed tabletted microcapsules. Then 1.03g of the same ratio was filled into 2 capsules of size "0" ,each of 517mg microcapsules weight, to study the release of drug from prepared capsules in comparison with Balkaprofen® tablet 600mg.Encapsulated ibuprofen microcapsules were stored at room temperature for 6 months for preliminary stability study.

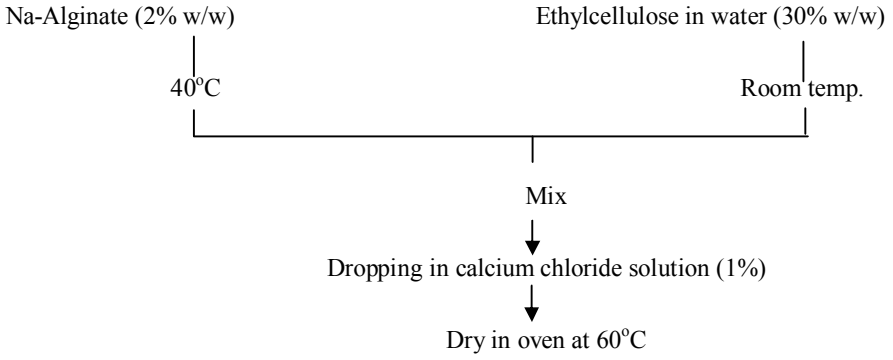
MICROCAPSULES PROPERTIES:

The properties of all prepared microcapsules were determined in order to evaluate the effect of studied variables through estimation of the following:

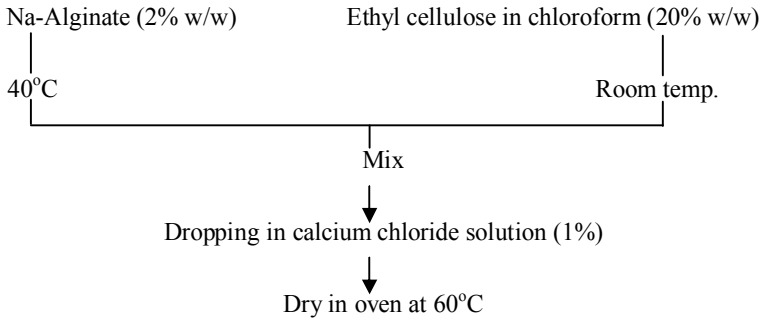
$$\text{Encapsulation efficiency} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100$$

$$\text{Percent yield} = \frac{\text{Actual wt. of microcapsules gained}}{\text{Theoretical wt. of microcapsules}} \times 100$$

Dissolution test: It was done for all prepared microcapsules and dosage forms using USP dissolution apparatus in 900 ml phosphate buffer of pH 6.8 at 37°C and a constant stirring speed of 150 rpm.



Scheme-1-Aqueous Colloidal Polymer Dispersion Method



Scheme-2-Preparation of Ibuprofen Microcapsules By a Modified Organic Method

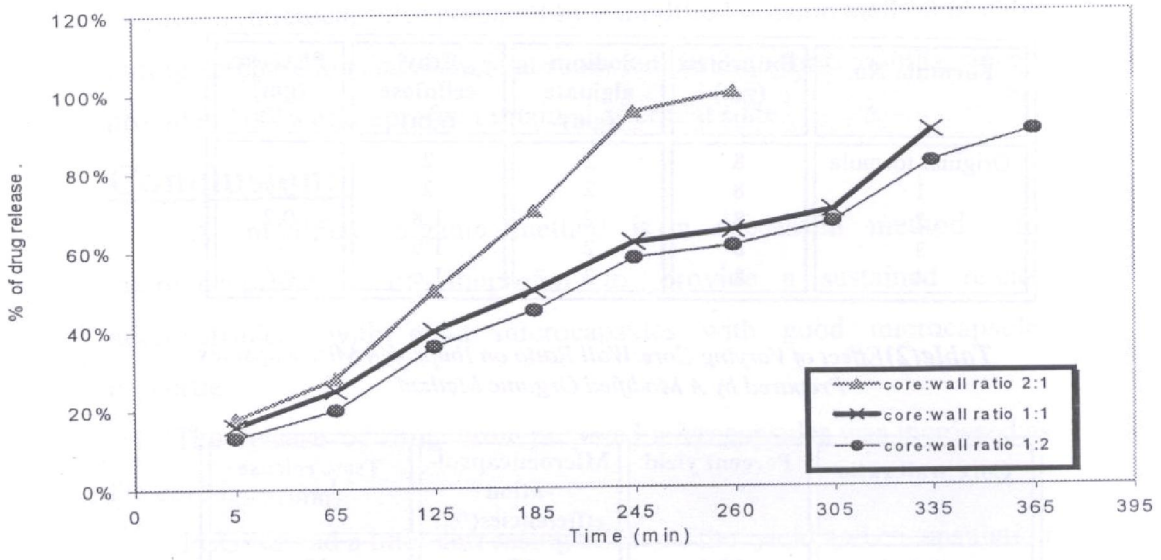
RESULTS AND DISCUSSION:

A modification of aqueous colloidal polymer dispersion method was utilized for microencapsulation of ibuprofen, through replacing the water required for ethylcellulose dispersion (30%) with chloroform (20%) as shown in scheme(2), which provided a good percent yield and encapsulation efficiency of ibuprofen microcapsules. This is due to the immiscibility of chloroform with water present in drug and sodium alginate suspension as well as its acceptable viscosity, which provided optimum conditions for microcapsules preparation. The microencapsulation data of ibuprofen are summarized in table (2).

Core:wall ratio	Percent yield	Microencapsul--ation efficiencies (%)	$T_{50\%}$ release (min)
2:1	97.5.	87	125
1:1	97.5	92	185
1:2	95	90	225

Table(2)Effect of Varying Core:Wall Ratio on Ibuprofen Microcapsules Prepared by a Modified Organic Method

It appears that no significant differences ($P>0.05$) in the encapsulation efficiency and percent yield were obtained for all prepared ratios[11], whereas, a more sustained action microcapsules was obtained as the concentration of colloid increased (figure1).



Figure(1): Effect of varying core:wall ratio on the release property of ibuprofen microcapsules prepared by a modified organic method using pH 6.8 phosphate buffer at 37ºC.

This may be related to the hydrophobic nature of ethylcellulose wall forming material, in addition to the water insoluble barrier (calcium alginate) which is formed from sodium alginate and calcium chloride gelling agent[12].

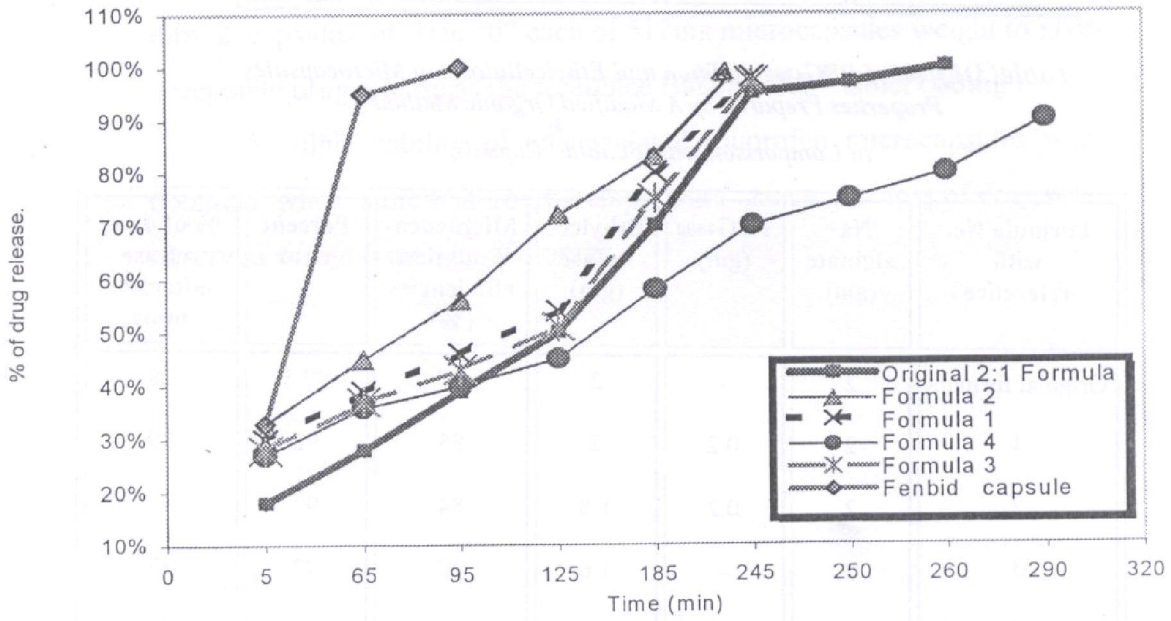
Since 2:1 core: wall ratio provided a higher release profile of ibuprofen (T50% 120mins) in comparison with other sustained release ratios 1:1 and 1:2, so that, many trails were done to prepare an acceptable sustained release solid dosage form compared with the sustained release reference Fenbid® spansule capsule 300mg (T50% 24mins), (however this product requires a dosing frequency of two times per day), utilizing this ratio to prepare different formulas by addition of PEG4000 and reduction of ethylcellulose proportion .

Microencapsulation efficiency of all prepared formulas were decreased as the proportion of PEG4000 increased and ethylcellulose decreased (table (3)).

Formula No. with reference	Na-alginate (gm)	PEG4000 (gm)	Ethylce-llulose (gm)	Microenca-psulation efficiencies (%)	Percent yield	% of drug release after 60 mins
Original formula	2	-	2	87	97.5	28
1	2	0.2	2	85	92	39
2	2	0.2	1.8	84	92	45
3	2	-	1.6	79	92	37
4	2	0.4	1.6	77	94	36
Fenbid® capsule	-	-	-	-	-	95

Table(3)Effect of PEG4000 Addition and Ethylcellulose on Microcapsules Properties Prepared by A Modified Organic Method in Comparison with Fenbid® Capsule.

Which is attributed to the interaction between PEG4000 and ibuprofen that dissolves the drug in the preparation medium [13], on the other hand ethylcellulose reduction produced unequal amount of wall forming materials with sodium alginate that provided some uncoated drug crystals on the surface of microcapsules dissolved in the dissolution medium which resulted in larger release proportion of ibuprofen at the first 60 minutes compared with untreated ratio as shown in figure (2).



Figure(2): Effect of addition of PEG_{4000} and ethylcellulose on the release profile of 2:1 core:wall ratio of ibuprofen microcapsules prepared by a modified organic method in comparison with Fenbid® capsule using pH 6.8 phosphate buffer at 37ºC.

The channeling effect of PEG_{4000} gave a higher release of drug, this could be as a result of increasing the microcapsules porosity of formula 1 and 2 compared with the original formula[14]. On the other hand, formula 2 showed a slight increase in the releasing profile of drug than formula 1 which resulted from the reduction of ethylcellulose concentration to 1.8gm[15].

In spite of lowering ethylcellulose amount to 1.6gm in formula 3 without addition of PEG_{4000}, the release of ibuprofen was lower than formula 2 but higher than the original formula.

Although, formula 4 which contains ethylcellulose (1.6gm) with PEG_{4000} (0.4gm), released initially high amount of uncoated ibuprofen crystals in comparison with the original formula due to the low percent of microencapsulation efficiency. But this followed by the formation of PEG_{4000} gelatinous barrier (0.4gm) that delayed the release of ibuprofen from reservoir system [16].

It appears that no significant difference ($P > 0.05$) concerning the $T_{100\%}$ ibuprofen release for all prepared formulas was noticed in comparison with the original formula, while, a significant difference ($P<0.05$) was observed when compared with the reference Fenbid® spansule as shown in figure (2). It was concluded that 2:1 core: wall ratio ibuprofen microcapsules prepared by a modified organic method failed to give an acceptable dissolution behavior as the reference.

Another sustained release reference was taken, Balkaprofen® tablet 600mg that required 365 minutes to provide 100% release of ibuprofen.

So that, the same ratio (2:1 core: wall) of ibuprofen microcapsules in weight equivalent to 600mg of drug was compared with this reference. No significant difference was found ($P > 0.05$)

between the releasing profile of this ratio and the reference (figure (3)). This gave a chance for preparing controlled release solid dosage form (tablet or capsule) of 600mg ibuprofen.

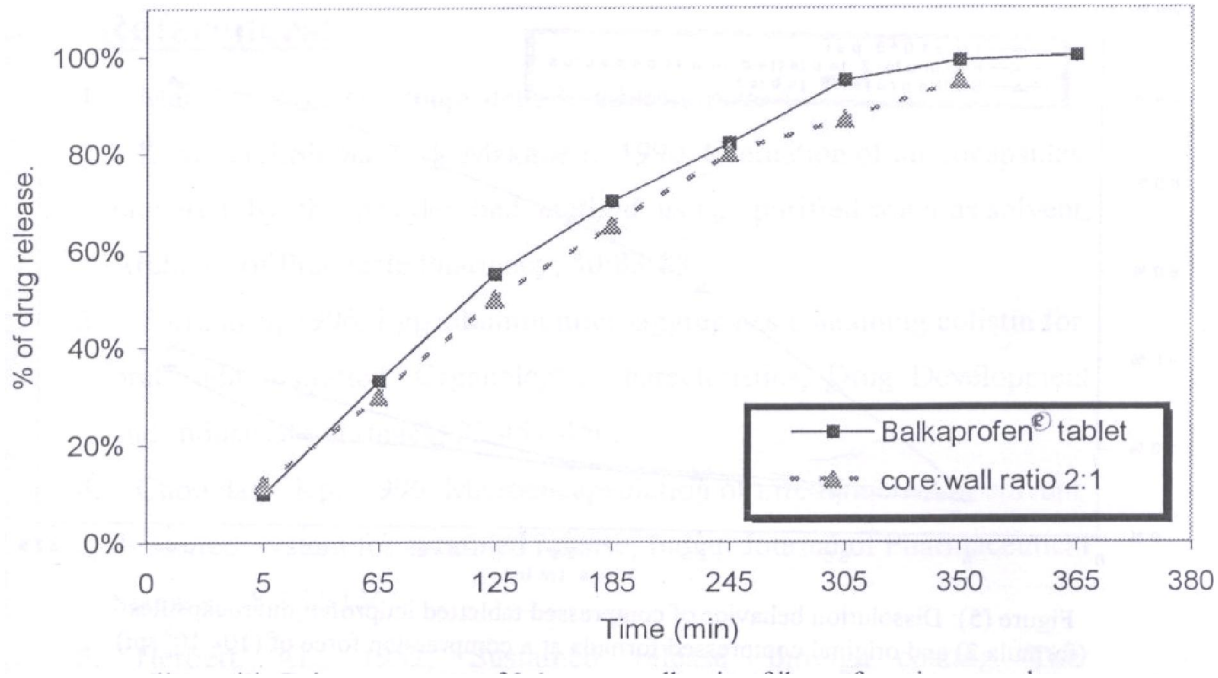


Figure (3): Release property of 2:1 core:wall ratio of ibuprofen microcapsules prepared by a modified organic method and Blakaprofen® tablet using pH 6.8 phosphate buffer at 37ºC.

Figure (4) shows that, the percent of drug released from compressed tabletted microcapsules was significantly retarded ($P< 0.05$) as the compression force increased (33% and 25% for 10×10^3 psi and 12×10^3 psi compression forces, respectively after 6 hours as well as in comparison with the uncompressed one which gave 95% within the same time).

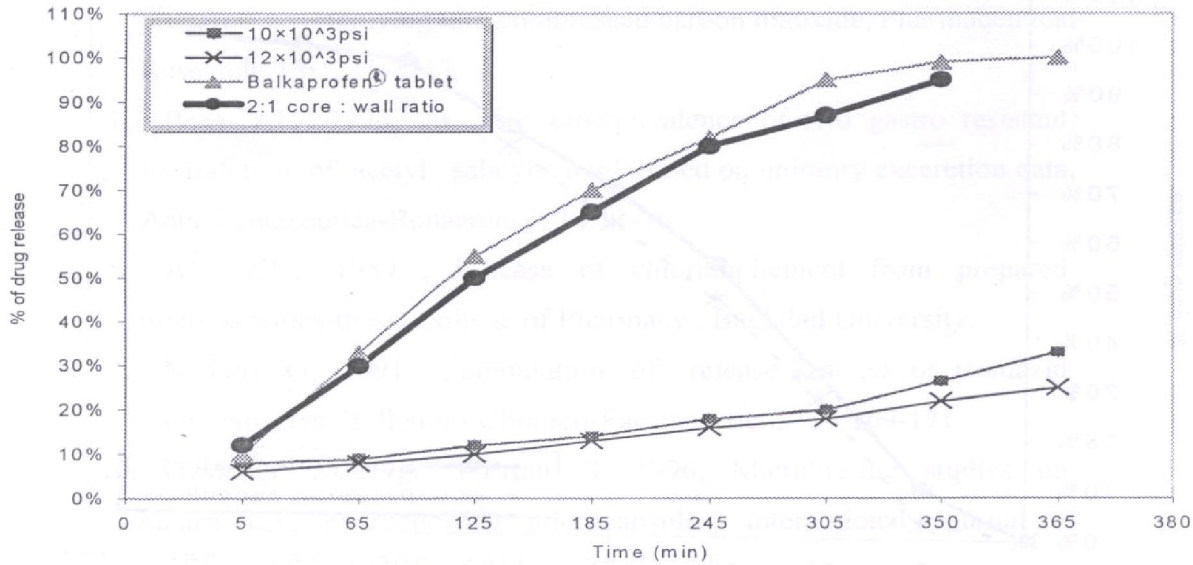


Figure (4): Effect of compression forces on the dissolution of compared tabletted ibuprofen micro prepared by a modified organic method in comparison with Balkprofen® tablet using pH 6.8 phosphate buffer at 37ºC.

This is due to continuous secondary polymer structure (matrix type formulation) produced by ethylcellulose polymer on compression which blocks most pores of microcapsules that hinders the disintegration and dissolution of tablet backbone [17].

Also it was noticed that compressed tabletted microcapsules prepared from formula 2 using 10 $\times 10^3$psi compression force which contains 0.2g PEG4000 and 1.8g ethylcellulose gave only 7% increase in the release of ibuprofen from prepared tablet (Figure (5)). This increase is due to channeling effect of PEG_{4000} and reduction of ethylcellulose proportion[15, 18].

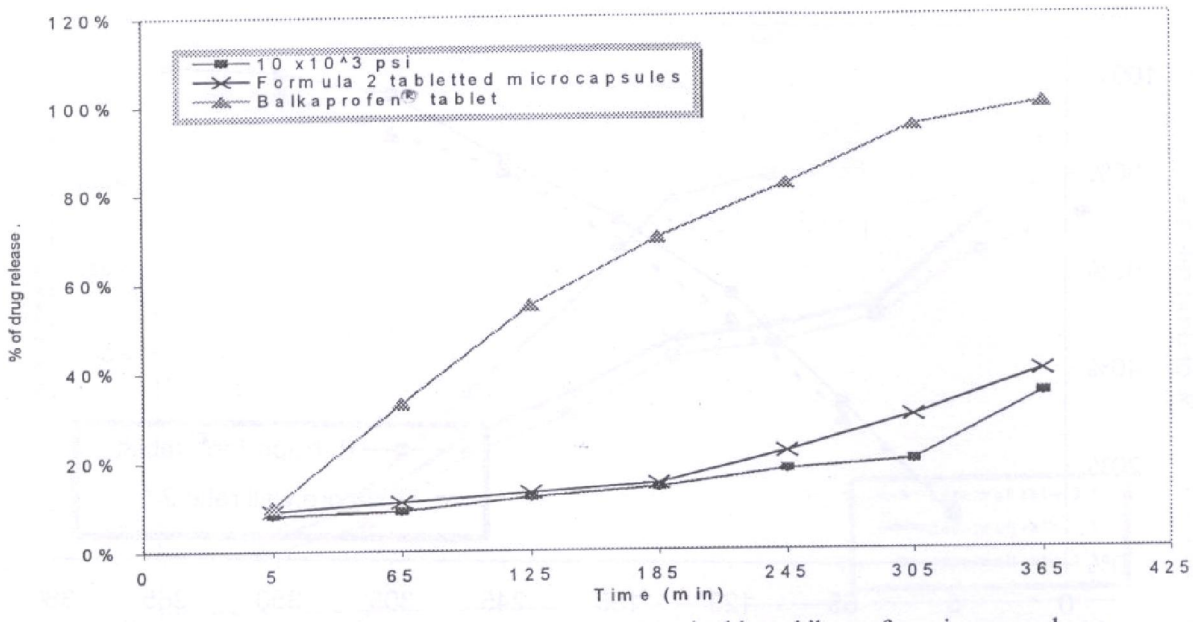


Figure (5): Dissolution behavior of compressed tabletted ibuprofen microcapsules (formula 2) and original compressed formula at a compression force of ($10x10^3$ spi) in comparison with Balkaprofen® tablet using pH 6.8 phosphate buffer at 37ºC.

The obtained results showed a difficulty in the utilization of this ratio to prepare a tablet dosage form as the reference Balkaprofen® tablet. So these findings suggest that a sustained release capsule dosage form of 300mg ibuprofen can be prepared and given to the patient in a dose of two capsules once daily (each of 0.517gm microcapsules weight) to give in vitro dissolution behavior as the reference Balkaprofen® tablet 600mg as shown in figure (6).

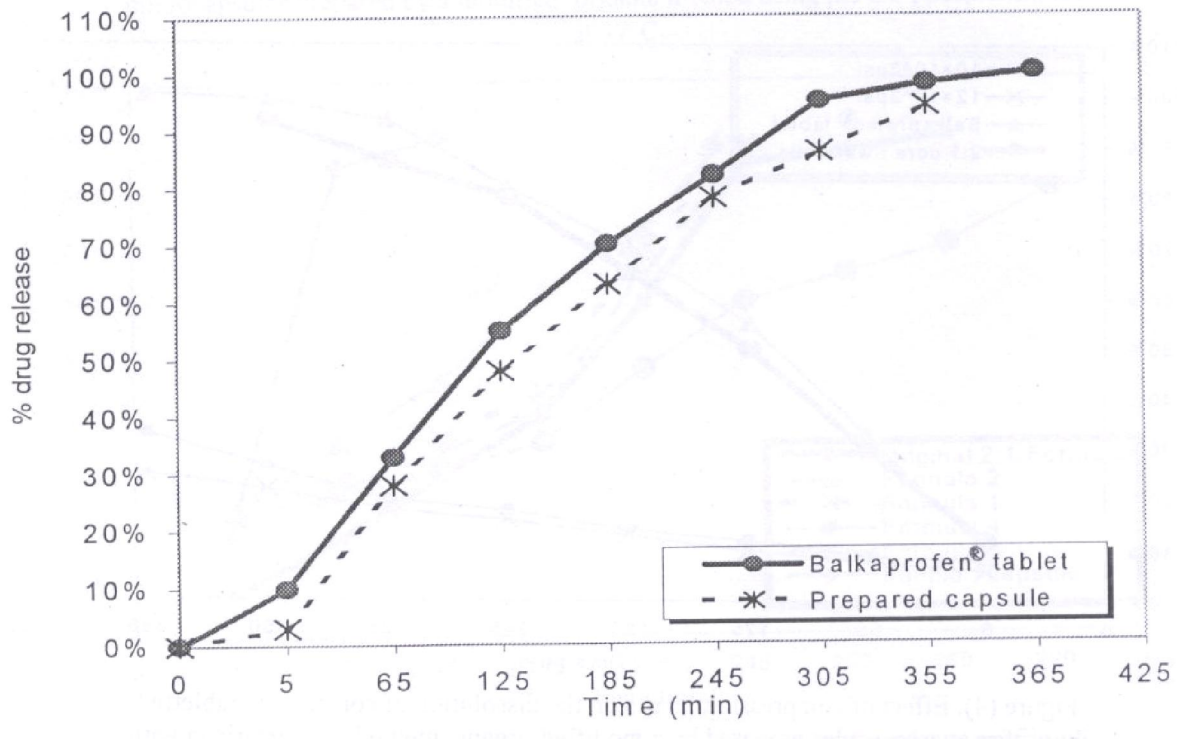


Figure (6): Comparison of dissolution of encapsulated 2:1 core:wall ratio ibuprofen microcapsules with Balkaprofen® tablet using pH 6.8 phosphate buffer at 37ºC.

The results of preliminary stability study indicated that encapsulated ibuprofen microcapsules prepared by a modified organic method is stable during preparation and storage at room temperature for 6 months, since it provided 100% of ibuprofen remained after that time.

CONCLUSION:

A modified organic method is a successful method for microencapsulation of ibuprofen to provide a sustained release microcapsules with good microcapsule properties.

The release of drug from prepared microcapsules was increased as the core increased.

PEG4000 had a little decreasing effect on the yield and encapsulation efficiency and little increasing effect on percent of drug release per time.

The selected 2:1(core :wall) ratio ibuprofen mirocapsules could not be formulated as tablet dosage form, so that, this ratio was encapsulated into 2 capsules of size "0" each of 517mg microcapsules weight to give acceptable drug release as the reference Balkaprofen® tablet 600mg .

A high stability of encapsulated ibuprofen microcapsules was obtained when stored at room temperature, since no loss of drug was observed within 6 months of storage.

REFERENCES:

1. Martin Dale, 32 edition , Ibuprofen , page 44,1999
2. Koyama I,Shimano K,Makabe E, Evaluation of microcapsules prepared by the powder bed method using purified water as solvent, Archives of Practicale Pharmacy; 1990, 50,83-88.
3. Torrado S, Egg albumin microaggregates containing colistin for oral administration: Organoleptic characteristics, Drug Development and Industrial Pahrmacy; 1996, 22,451-456.
4. Chowdary Kp, Microencapsulation of nifedipine-MCC solvent deposited system for sustained release, Indian Journal of Pharmaceutical Science, 1996, 58,152-156.
5. Herbert AL, Sustained release through coating, The Pharmaceutical Dosage Form Tablet, 1982, 3,173.
6. Bodmier R,Wang H,Dixon DJ, Polymeric microspheres prepared by spraying into compressed carbon diaoxide, Pharmaceutical Research, 1995, 12,1211-1217.
7. Pena AL, In vivo bioequivalence of two gastro resistant formulation of acetyl salicylic acid, based on uniranry exceretion data, Acta-farmaceutica-Bonaerensy; 1995, 14,11-16.
8. Ali WK, Release of chloramphenicol from prepared microcapsules-thesis,College of Pharmacy , Baghdad University 1989 ,.
9. Muhuri G, Computation of release kinetics of isoniazid microcapsules, Bollettino-Chimico-Farmaceutico, 1991, 130,169-171.
10. Ozyazici M,Sevgi F,Ertan G, Micromeritic studies on nicardipine hydrocholride microcapsules, International Journal of Pharmaceutics, 1996, 138,25-35.
11. Bodmeier R,Wang J, Microencapsulation of Drug with Aqueous Colloidal Polymer Dispersion,Journal of Pharmceutical Sciences, 1993, 82,-191-194.
12. Guler E,Sumnu M,Yazan Y, Studies on the microencapsulation of dextropropoxyphene HCL,Drug Development and Industrial Pharmacy , 1989, 15,283-293.
13. Shakhtshneider TP, Mecanochemical preparation of solid disperse systems of ibuprofen-PEG, International Journal of Pharmaceutics, 1996, 130,25-32.
14. Nokhodchi A,Farid D, Effect of various factors on microencapsulation of acetyl salicylic acid by a non-solvent addition method ,STP-Pharmaceutical Sciences, 1992, 2,279-283.
15. Chowdhary KP,Ramesh KV, Studies on microencapsulation of diltiazem, Indian Journal of Pharmaceutical Sciences, 1993, 55,52-54.
16. Khalil YI, Formulation of metformin HCL as a sustained release dosage form, thesis, College of Pharmacy , Baghdad University, 1994.
17. Vitkova M, Ethyl cellulose to prepare matrix system of hydrophilic drug by the microencapsulation process, STP-pharma-sciences, 1994, 4,486-491.
18. Sakr FM, Studies on microencapsulated granules effect of drug –binder solubilities and added diluents on core properties and microencapsulation characteristics, Journal Drug Research, 1991, 20,303-313.