

## Micro encapsulation of Naproxen By Complex Coacervation and Aqueous Colloid Dispersion Part ( 1 )

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### Abstract

Naproxen is a non steroidal anti inflammatory and antipyretic drug which has local irritation effect on the stomach, and unpleasant taste, besides bad flowability and light sensitivity .The drug was prepared as microcapsules by complex coacervation method using acacia-gelatin coating materials , and aqueous colloid polymer dispersion method ( ACPD ), using ethyl cellulose and sodium alginate coating materials . The results indicated that microcapsules prepared by 2:1 core:wall ratio is the best for both methods, with an average encapsulation efficiency (75%) and average yield (90%) .

Moreover the drug release was affected mainly by core : ratio ,pH environment and method of microencapsulation .

**Key words:** Naproxen, Microcapsule , Aqueous colloid polymer dispersion

### الخلاصة

النابروكسين هو عقار غير ستيرويدي مضاد للالتهابات وخافض للحرارة ذو اعراض مخدشة للمعدة وطعم غير مستساغ وصعوبة في جريانه اثناء التصيغ اضافة الى تاثيره الشديد بالضوء لقد تم تحضير العقار على شكل كبسولات مجهرية بطريقتي التقوسر المعقد والانتشار المائي باستعمال مواد مختلفة كالصمغ العربي الجيلاتين والسيليلوز الاثيلي اضافة الى الجينات الصوديوم لقد وجد ان نسبة ٢ :١ من المادة اللبية الى المادة المغلفة كانت الافضل بمعدل تحميل ٧٠٪ ونتائج نهائية بلغ ٩٠٪ . كما اظهرت النتائج بتأثر تحرر العقار بشكل كبير من هذه الكبسولات المجهرية بطريقة التحضير ونسبة المادة اللبية الى المادة المغلفة اضافة الى الاس الهيدروجيني للوسط البيئي .

### Introduction

The principle of microencapsulation is formation of a thin coating of wall material around the substance, therefore making the particles more desirable in terms of physical and chemical properties<sup>(1,2)</sup>, the quantity of drug incorporation as core material vary from 20-95%<sup>(3)</sup> Naproxen is aryl acetic acid group derivative of non-steroidal anti inflammatory drugs widely used in rheumatoid arthritis and ankylosing spondylitis<sup>(4)</sup>. The main side effects of this drug are GIT disturbances and bitter taste .

The goals of this study are to mask the irritation effect of the active drug to the GIT, and improve physical properties of the drug like flowability and light sensitivity

### Experimental

#### Materials :

Naproxen powder supplied by Samarra" Drug Industry (SDI) ,acacia,gelatin,ethyl cellulose,sodium alginate,calcium chloride,formaldehyde,from Riedel De-Haen AG;Seelze,Hannover, Germany

All other reagents are of an analytical grade.

#### Instruments :

sartorius balance,type 1219 MP3 , electrical

stirrer Ike - Werk type Re- 16 , (Germany) , oven , mammert 854 Schwa Bach, (Germany) , microscope, Olympus CX21 Tokyo Japan,Cintra 5 GBC,UV-Vidible spectrometer, dissolution apparatus Erweka USP DT6 Hansen (Germany) , water bath pH- meter (W-Germany) .

#### Preparation of naproxen microcapsules (complex coacervation)

The microcapsules were prepared by incorporating naproxen powder in 50ml.of 2% w/w acacia solution previously heated to 40°C, then 50ml. of gelatin solution 2% w/w at 40°C was added and maintained at 250 rpm stirring speed for 50 minutes ,adjusting the pH of mixture to 4 with few drops of diluted HCL(0.1M),the formation of microcapsules can be watched microscopically ,then 10ml. of formaldehyde solution was added with continuous stirring for 10 minutes, cooling in ice bath , filtered the microcapsules formed using three portions of 100ml. isopropyl alcohol and then the wetted microcapsules were dried before the free flowing powdered microcapsules obtained<sup>(5)</sup> .

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**Preparation of naproxen microcapsules (ACPD method)**

The drug was dispersed in 50ml. of 2% w/w aqueous sodium alginate solution heated to 40°C, then 50ml. of 30% w/w ethyl cellulose prepared at room temperature was added with continuous stirring, (the weight of naproxen added depend on core:wall ratio of microcapsules prepared). The mixture was allowed to drop through modified separatory funnel into gently agitated calcium chloride (1% w/w), the gelled beads were separated after 2 minutes by vacuum filtration, rinsed with distilled water and allow to dry at 40°C over night<sup>(6)</sup>. All the microcapsules prepared by both two methods were of 1:2, 1:1 and 2:1 core : wall ratio which corresponds to 33.3%, 50% and 66.6% drug content respectively.

**Dissolution behaviour**

For all types of microcapsules prepared under sink conditions, the dissolution behaviour of

naproxen was carried out using 100mg. equivalent dose in 900ml. of different dissolution medium pH (1.2, 4.2 and 6.8) at 37 ± 0.5°C and constant stirring speed of 50 rpm. Then filtered samples were taken for analysis at different specified time intervals. The absorbance of each sample was determined spectrophotometrically at 272, 330, and 271 nm. respectively.

**Results and Discussions****Preparation of microcapsules:**

Table 1. (A and B) illustrates the yield percent and the encapsulation efficiency of naproxen by different preparation methods and core: wall ratios, it was found that coacervation method gave 75-85% yield compared with 86-93% given by ACPD method, while encapsulation efficiency was 48-82% and 27-70% for complex coacervation and ACPD method, respectively.

**Table (1) Effect of variation of core to wall ratio of naproxen microcapsules on the microencapsulation by:-A- Complex coacervation method**

Core To Wall ratio	Microencapsulation yield		% Yield	Drug loading %		Microencapsulation Efficiency
	Theoretical (gm)	Actual (gm)		Theoretical (gm)	Actual (gm)	
2:1	12	10.25	85.4	66.6	54.6	81.9
1:1	8	6.2	77.5	50	37.5	75
1:2	6	4.5	75	33.3	16.17	48.5

**B- Aqueous colloidal polymer dispersion method**

Core to wall ratio	Microencapsulation yield		% yield	Drug loading %		Microencapsulation efficiency (%)
	Theoretical (gm)	Actual (gm)		Theoretical (gm)	Actual (gm)	
2:1	70	46.6	66.6	93	14	15
1:1	60	30	50	85	8.5	10
1:2	27	9	33.3	86	6.5	7.5

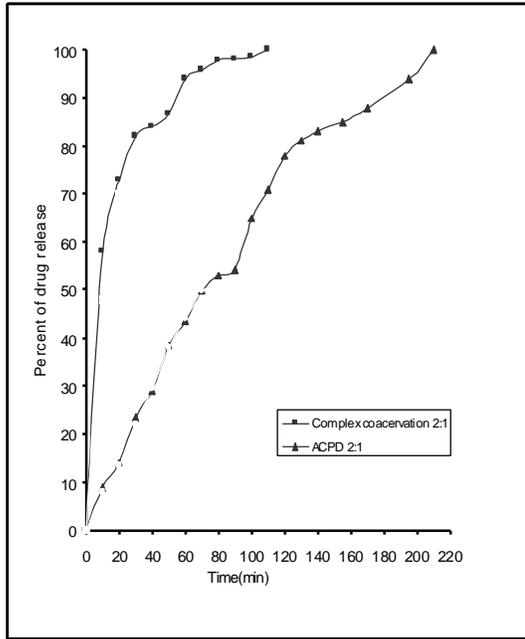
The results indicated that best encapsulation efficiency was in complex coacervation compared with ACPD method, which may be attributed to the ability of polymer used to encapsulate the drug<sup>(6)</sup>.

On the other hand the results revealed that encapsulation efficiency appeared to be core weight dependent, Higher percent of drug loading was shown with 2:1 core wall ratio. These results are consistent with the results obtained in case of metronidazole<sup>(7)</sup> and chloramphenicol microcapsules<sup>(8)</sup>. moreover

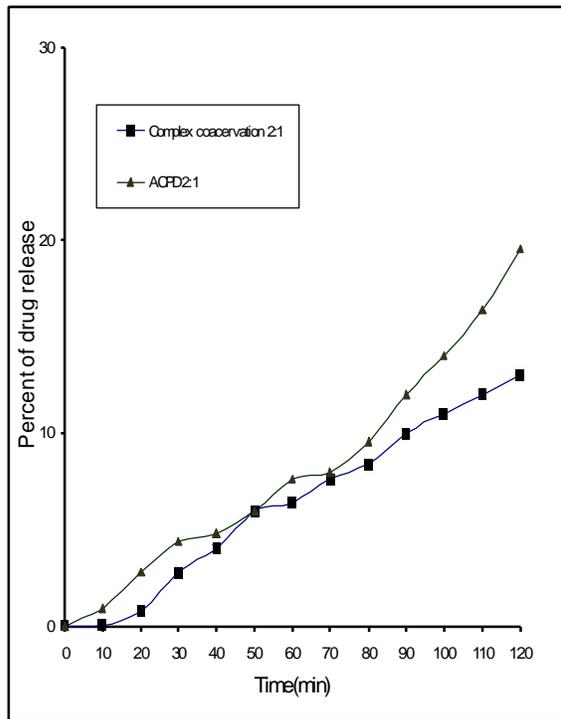
the appreciable amounts of microcapsule gained (86 - 93%) by ACPD method may be referred to the compatibility between naproxen and polymer used, since both of them are acidic in nature<sup>(9)</sup>.

**Dissolution behaviour of microcapsules:**

Figure 1 and 2 shows the release profiles of naproxen from 2:1 core wall ratio microcapsules for both methods of preparation at pH 6.8 and 1.2 respectively.



**Figure (1) : Effect of method of microencapsulation on the release of naproxen from microcapsules in phosphate buffer pH 6.8.**

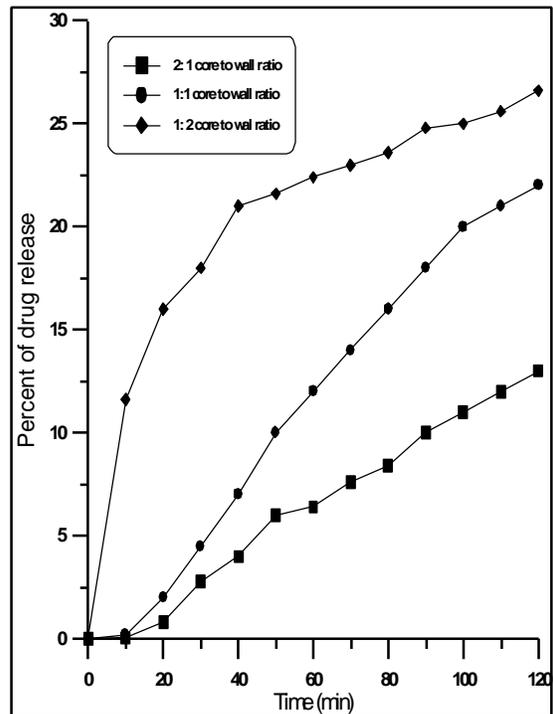


**Figure (2): Effect of method of microencapsulation on the release of naproxen from microcapsules in 0.1N HCl pH 1.2.**

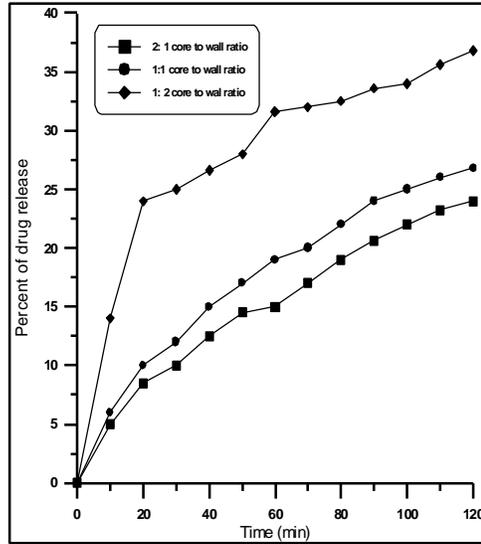
It was found that in complex coacervation method, the release was faster than in ACPD method at pH 6.8, since 50% of drug release took over 8 minutes for first method compared with 75 minutes for the later, these results are consistent with the results obtained by microencapsulation of diclofenac sodium (10) and protein (1).

The drug release at pH 1.2; decreased significantly for both method (not more than 30% at first two hours), this behaviour may be attributed to the nature of naproxen dissolution at low pH (12).

On the other hand the effect of core wall ratio on the release of naproxen from microcapsules was shown in figures 3 and 4, It was seen that high significant difference ( $p < 0.001$ ) in the percent drug release after 120 minutes between 2:1 and 1:2 core wall ratios (coacervation method), the cause is referred for both drug content and solvent penetration and this is consistent with the results obtained by the study of dissolution of diazepam microcapsules<sup>(13)</sup>.



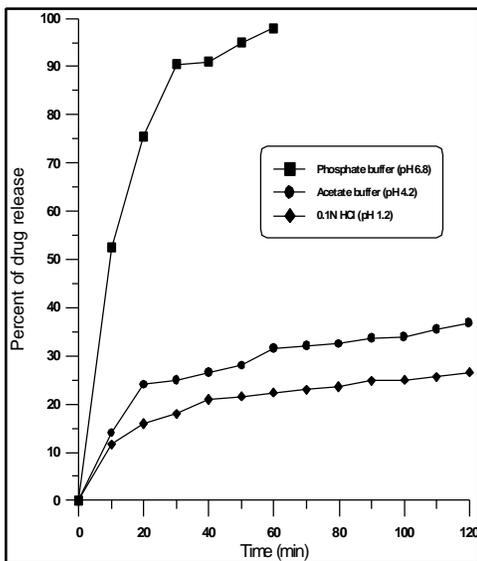
**Figure (3): Effect of varying core-wall ratios on the release of naproxen from microcapsules prepared by complex coacervation method in 0.1N HCl pH 1.2.**



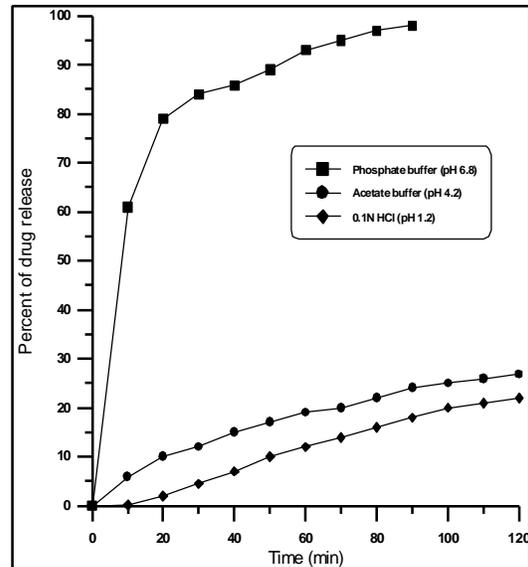
**Figure (4): Effect of varying core-wall ratios on the release of naproxen from microcapsules prepared by ACPD method in 0.1N HCl pH 1.2.**

The same results were obtained from microcapsules prepared by ACPD method, since 40,24 and 20% of drug released from microcapsules from 1:2, 1:1 and 2:1 core wall ratio respectively.

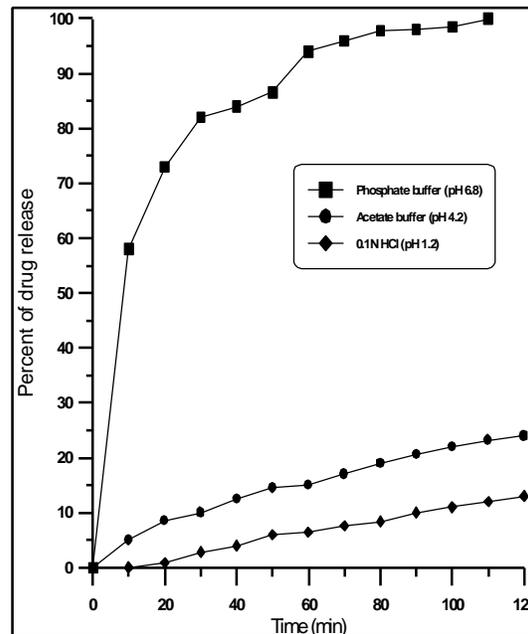
In an attempt to study the effect of different pH-medium on the release of naproxen from these microcapsules, figures 5 to 10 were constructed for both coacervation and ACPD methods.



**Figure (5): Effect of pH on the release of naproxen from 1:2 core-wall ratio microcapsules prepared by complex coacervation method.**



**Figure (6): Effect of pH on the release of naproxen from 1:1 core-wall ratio microcapsules prepared by complex coacervation method.**



**Figure (7): Effect of pH on the release of naproxen from 2:1 core-wall ratio microcapsules prepared by complex coacervation method.**

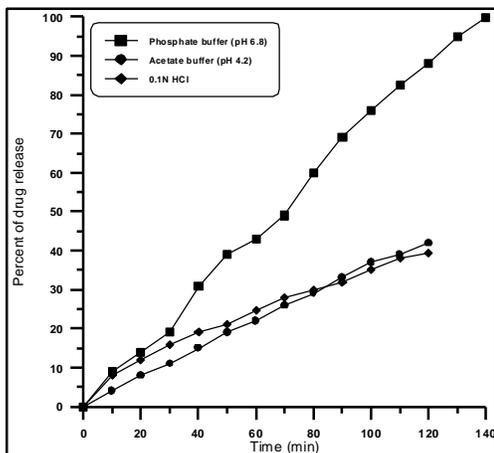


Figure (8): Effect of pH on the release of naproxen from 1:2 core-wall ratio microcapsules prepared by ACPD method

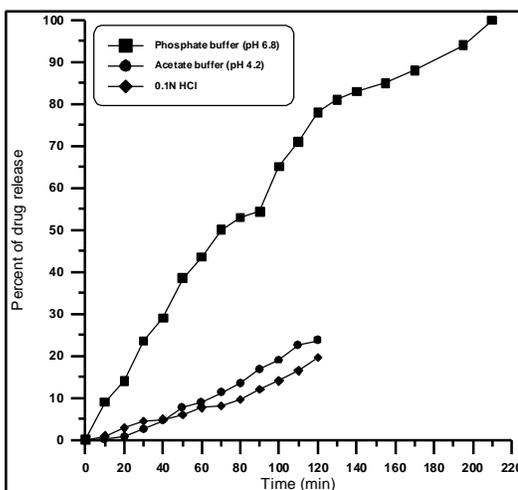


Figure (9): Effect of pH on the release of naproxen from 2:1 core-wall ratio microcapsules prepared by ACPD method.

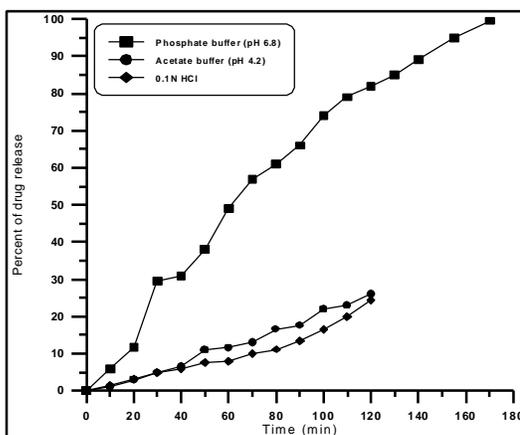


Figure (10): Effect of pH on the release of naproxen from 1:1 core-wall ratio microcapsules prepared by ACPD method

The results showed that there are high significant differences ( $p < 0.001$ ) in  $t_{50\%}$  drug release from different core wall ratios prepared by coacervation method at pH 1.2 and 4.2 in comparison with pH 6.8 (microcapsules prepared by coacervation method at pH 1.2 and 4.2)

The same results were recognized for the same core: wall ratios microcapsules prepared by ACPD method, these results are the same results obtained in the evaluation of sulfonamide, ibuprofen<sup>(14)</sup>, and mefenamic acid microcapsules<sup>(15)</sup>.

### Conclusion

Based on the results obtained, one may conclude the followings.

- Both complex coacervation and ACPD methods are valid for microencapsulation of naproxen.
- The dissolution behaviour of naproxen from microcapsules is affected by pH-medium, core:wall ratio and preparation methods.
- The results obtained in this study could be used to formulate naproxen in many microencapsulated dosage forms.

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