Effect of Temperature on the Stability and Release Profile of Ibuprofen Microcapsules

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Abstract

The stability and releasing profile of 2:1 core: wall ratio ibuprofen microcapsules prepared by aqueous coacervation (gelatin and acacia polymers coat) and an organic coacervation methods (ethyl cellulose and sodium alginate polymers coat) in weight equivalent to 300mg drug, were studied using different storage temperatures 40°C, 50°C ,60°C and refrigerator temperature 4°C in an opened and closed container for three months (releasing profile) and four months (stability study).It was found that, these ibuprofen microcapsules were stable with expiration dates of 4.1 and 3.1 years for aqueous and an organic method respectively.Aqueous prepared ibuprofen microcapsules were found more stable than those microcapsules prepared by organic method with activation energy (Ea) 4804.8 cal/mol and 5033.6 cal/mol of a drug respectively.The releasing percentage of ibuprofen for all microcapsules prepared by both methods was decreased as the storage temperatures increased, except for microcapsules prepared by aqueous method, which were found to be the same at 25-40°C as the standard one which stored at 25°C temperature, on the other hand , as the temperature decreased to 4°C (refrigerator) of an open and closed container ,the amount of drug detected in microparticles is increased. These differences in the amount of drug released may be referred to the change in physical properties in polymer coats or in the amount of drug detected in a whole microcapsules.

Keyword: Ibuprofen Microcapsules, Storage Temperature, Stability.

الخلاصة

تمت دراسة تأثير درجات الحرارة لكبسولات الايبوبروفين في درجات حرارة مختلفة (٦٠°م ,٥٠ °م، ٤٠ °م) واخرى بوضعها في درجة حرارة ٤°م(في وعائين مقتوح والأخر مغلق)على ثباتية وطريقة تحرر مادة الأيبوبروفين من النسبة(٢: ١) للكبسولات المجهرية المحضرة بالطريقتين المائية (المغلفة بمادتي الجلاتين والصمغ العربي)والطريقة العضوية (لسليلوز الأثيل والجينيت الصوديوم) بوزن يعادل ٣٠٠ ملغم من مادة الأيبوبروفين لمدة ثلاثة اشهر لدراسة تحرر الدواء واربعة اشهر لدراسة ثباتية الدواء .كان ثباتية تلك النسبة من الكبسولات المجهريه المحضرة بالطريقتين واضحا مع مدى صلاحية كل منهما٤.١ و ١,٣ سنوات للطريقتين المائية و العضوية على التوالي.ولقد وجد أن الكبسولات المجهرية المغلفة بالطريقة المائية أكثر ثباتية بسبب وجود المادة المصلبة للغلاف (الفورمالديهايد) التي تزيد من كفاءة التغليف وقابلية تحمله للحرارة العالية أو الرطوبة مع درجات حرارة منخفضة كان ذلك واضحا أيضا من خلال قلة طاقة تحفيز جزيئات الدواء.من جانب أخر وجد أن تحرر الدواء من تلك الكبسولات عند زيادة درجات حرارة الخزن تؤدي الى قلة في سرعة التحرر وعلى العكس بانخفاض درجات الحرارة ويعود ذلك الى التغيرات الفزياوية التي تحدث في المادة المغلفة للكبسولات المجهرية للأيبوبروفين والمشابهة لتحرر الأيبوبروفين من الكبسولات المجهرية المخزونة عند ٢٥°م عند خزنها في نفس تلك الدرجة ,كما لوحظ تحرر الدواء من الكبسولات المجهرية المحضرة بالطريقة المائية لا تتغير مقارنة للنسبة الأصلية عند الدرجة ٢٥-٤٠°م.

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Introduction:

Microencapsulation technique provides a good tool to protect the drug from environmental factors (temperature, humidity, light, oxygen) by improving its stability through enclosing of small drug particles of liquids, solids or gases by an intact shell[1,2]. Accelerated stability study at elevated temperatures is an important study which indicates the effect of temperature on chemical stability of microcapsules as well as their physical properties[3].

Chemically by predicting the rate of drug decomposition after experimentally evaluating the velocity constant of a particular reaction, the amount of active drug present at any time and expiration date could be determined the specific manor in which the rate of reaction varies with the concentration of the reactants [3,4].

The Arrhenius equation reveals the effect of temperature on an observed rate constant by affecting the molecular motion through determining the Arrhenius activation energy (Ea) , which is the minimum kinetic energy that a molecule must possess in order to undergo reaction [4] .

The physical effect of temperature, on microcapsules by altering the glass transition temperature (Tg) of microspheres polymers coat ; is a narrow temperature range over which microcapsules polymer reversibly change from phase to phase which occurs in amorphous polymers and in amorphous chains partly crystalline polymers, for example Tg of pure glycolide-L-lactide (PLGA) polymer of microcapsule wall was found to be 49^{o}C at which thermo-reversible gelation in which the long and flexible polymer chains tend to become entangled and attract each other by secondary side chain forces, this physical changes in microcapsules polymer cause an altering in the diffusion of the drug from microcapsules wall by affecting the driving forces of physico-chemical potential gradient and transport parameters[5,6].

On the other hand, protein microcapsules stored at 4^{o}C over the course of 28 days produced physical changes in shape or integrity of microcapsules that affected the releasing behavior of these spheres[7].

Aim of the work

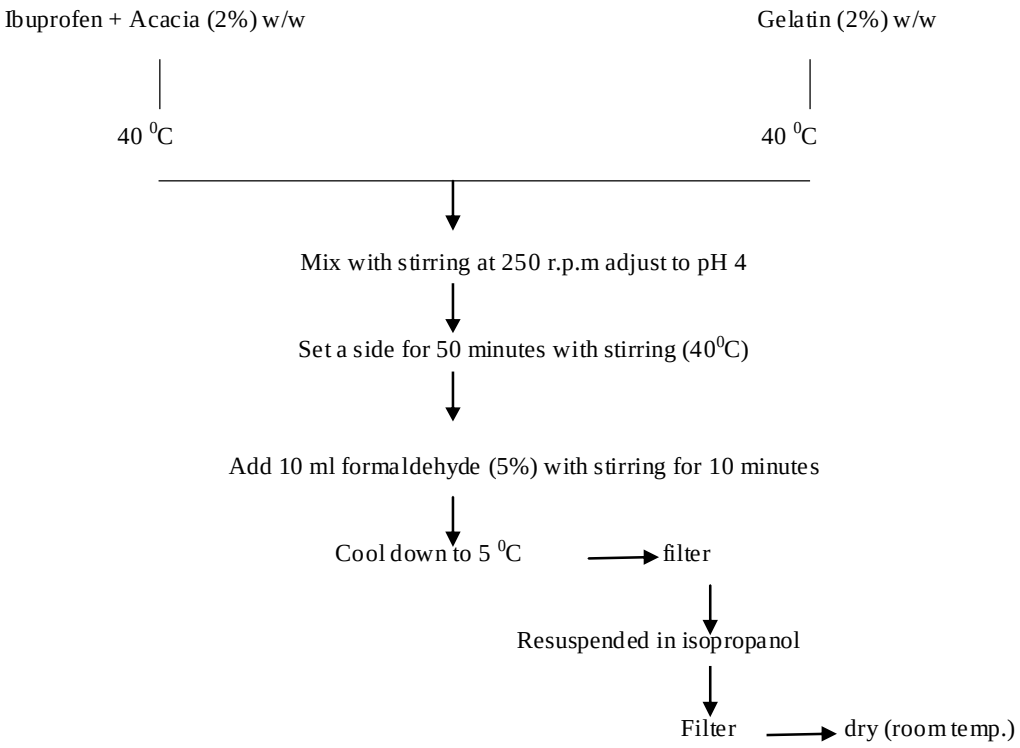
To study the effect of different storage temperatures on the stability (kinetic study) and releasing profile of 2:1 ibuprofen microcapsules prepared by aqueous (gelatin and acacia coat) and organic methods (sodium alginate and ethylcellulose polymer coat)[8].

Materials and Methods

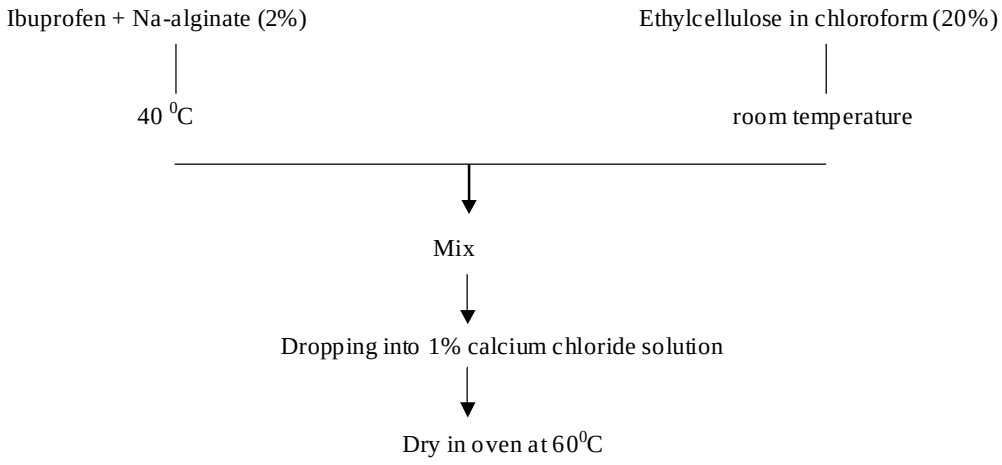
Ibuprofen powder SDI, Iraq. Gelatin granulated (Fluka A-G, CH-9470 Buchs, Switzerland). Ethylcellulose, Chloroform, Methanol and Ethanol 96%, (BDH Chemical Ltd, England). Phenophthaline Solution, Calcium Chloride, Sodium alginate (Judex laboratory regents, Sudbury, Middles, England). Sodium hydroxide, Potassium dihydrogen phosphate (E-Merk, Darmstadt, West Germany). Formaldehyde solution (Hopkin and Eilliams Essex, England). Acacia, Isopropanol (Riedel De- Haen AG, Seelze Hannover, Germany).

Preparation of Ibuprofen Microcapsules

Ibuprofen microcapsules were prepared freshly using aqueous method (complex coacervation phase separation) and organic method as shown in scheme 1 and 2 respectively [8]:



Scheme -1-
Preparation of ibuprofen microcapsules by aqueous method.



Scheme -2-
Preparation of ibuprofen microcapsules by organic method.

Assay of Microcapsules content

0.450gm of 2: 1 core : wall ibuprofen microcapsules prepared by aqueous and organic method (eq. to 207 mg (69%) and 261 mg (87%) ibuprofen receptively) was extracted in 50ml of methanol, 0.4ml of phenophthaline solution as indicator was added, then titrated against 0.1M sodium hydroxide until a red color was obtained, blank titration was carried out, and amount of drug content was determined ,each 1ml of 0.1M NaOH is equivalent to 20.63mg of $C_{13}H_{18}O_2$[9,10].

Determination of microcapsules properties

Microencapsulation yield and encapsulation efficiency of 2:1 core: wall ratio ibuprofen microcapsules prepared by aqueous and organic method were estimated using the following expressions.

$$\text{Microencapsulation yield (\%)} = \frac{\text{Actual wt. of microcapsules gained}}{\text{Theoretical wt. of microcapsules}} \times 100$$

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

Effect of temperature on stability of ibuprofen microcapsules :

The effect of different storage temperatures on the degradation rate of the selected formula 2: 1 core: wall ratio ibuprofen microcapsules prepared by aqueous and organic method was studied.

The study was done by incubated the prepared microcapsules in an amber colored glass containers at different temperatures (60^oC, 50^oC, 40^oC) and 4^oC of refrigerator in an opened and closed containers for 4 months. Samples of microcapsules of both preparation methods (aqueous and organic) in weight of 652mg and 517mg respectively equivalent to 300mg ibuprofen were taken at desired time intervals (every month) and assayed for the content of drug according to the procedure mentioned before for stability study.

The effect of temperature on the dissolution behavior of ibuprofen microcapsules:

In vitro drug release from 2:1 core: wall ratio ibuprofen microcapsules samples using basket method in weight equivalent to 300 mg drug of both preparation methods was studied using U. S. P dissolution apparatus with 900 ml of pH6.8 phosphate buffer at $37^oC \pm 1$ and stirring speed 150 r.p.m. At appropriate time intervals 5ml sample was withdrawn, filtered, and measured spectrophotometrically at λmax 264nm. This assay was repeated for three months, inorder, to study the effect of different storage temperature (40^oC, 50^oC, 60^oC), 4^oC opened container and closed one) on the release profile of ibuprofen from selected formula of both methods.

Results and Discussion

Microcapsules contents

Microencapsulation yield and encapsulation efficiency of 2:1 core: wall ratio ibuprofen microcapsules prepared by aqueous and organic method were calculated as shown in table 1.

Table (1)Microcapsules Contents of 2:1 Core to Wall Ratio Ibuprofen Microcapsules Prepared by Aqueous and Organic Method.

(2:1) core: wall ratio	Drug Amount (gm)	Coat (gm)				Microencapsulation yield		Percent yield	Drug loading (mg)		Encapsul - atin efficiency (%)
		Gel-atin	Aca-cia	Ethylcellu - lose	Na-Algina te	Theoretical (gm)	Actual (gm)		Theoretical (mg)	Actual (mg)	
Aqueously prepared ratio	8	2	2	-	-	12	8	67	300	207	69
Organicly prepared ratio	8	-	-	2	2	12	11.7	97.5	300	261	87

Effect of elevated temperature on stability of ibuprofen microcapsules

Figures (1) and (2) show the change in the log % remaining of ibuprofen versus time at different elevated temperature 40°C, 50°C, 60°C.The obtained profiles were linear for both 2: 1 core:wall ratio ibuprofen microcapsules prepared by aqueous and organic method indicating that ibuprofen degradation followed first order kinetics.

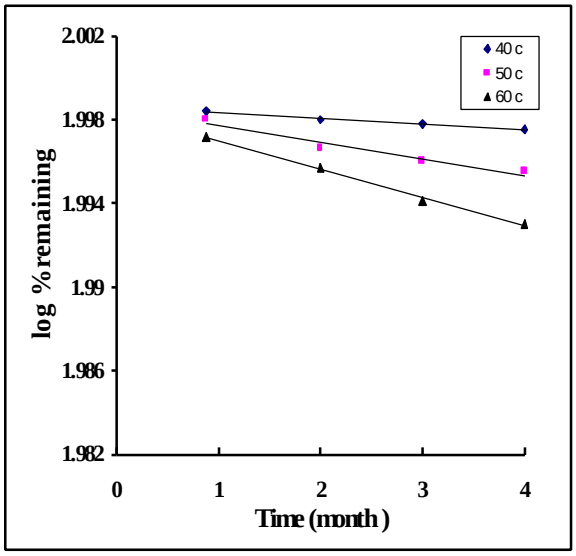


Figure (1): Accelerated breakdown of ibuprofen in 2:1 core: wall ratio microcapsules at different elevated temperatures using aqueous formula

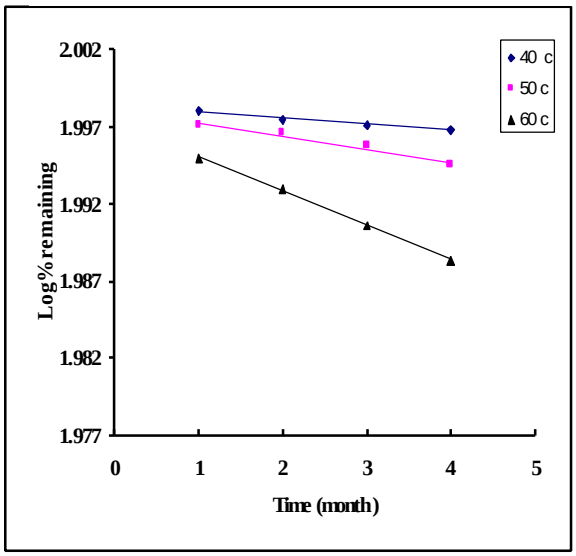


Figure (2): Accelerated breakdown of ibuprofen in 2:1 core: wall ratio microcapsules at different elevated temperatures using organic formula

The slope of this linearity was determined and the calculated rate constants are summarized in tables 2 and 3 for both methods, respectively. Arrhenius plots are shown in figures (3) and (4) .The rate constants (K) at 25°C obtained from the plot were 2.13 x 10^{-3} $month^{-1}$ and 2.81 x 10^{-3} $month^{-1}$ for aqueous and organic method respectively.

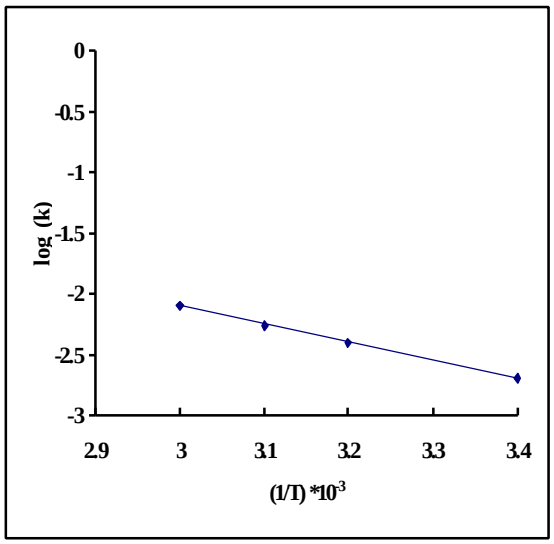


Figure (3): Arrhenius plot for estimation shelf life of ibuprofen microcapsules using 2:1 core : wall ratio prepared by (Aqueous method)

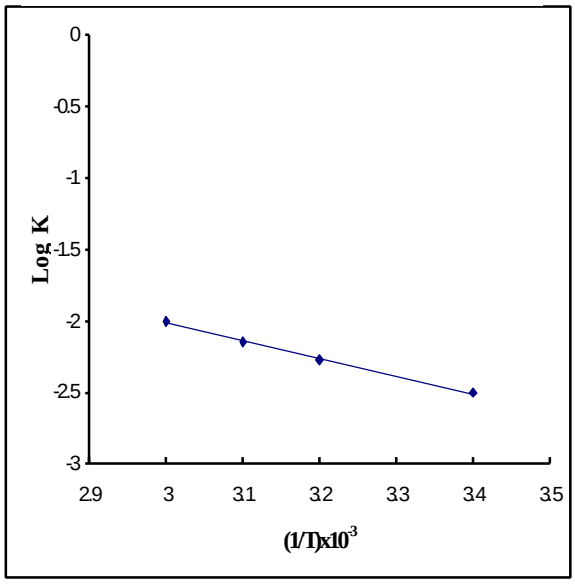


Figure (4): Arrhenius plot for estimation shelf life of ibuprofen microcapsules using 2:1 core: wall ratio prepared by (Organic method)

Table (2): Degradation Rate Constants (K) of Ibuprofen Microcapsules Using 2:1 Core: Wall Ratio at Different Temperatures (Aqueous Method)

Temperature	K ($Month^{-1}$)
40°C	3.96×10^{-3}
50°C	4.75×10^{-3}
60°C	6.45×10^{-3}

Table (3): Degradation Rate Constants (K) of Ibuprofen Microcapsules Using 2:1 Core: Wall Ratio at Different Temperatures (Organic Method).

Temperature	K ($Month^{-1}$)
40°C	4.67×10^{-3}
50°C	5.77×10^{-3}
60°C	7.59×10^{-3}

Since the degradation of the drug followed first order kinetic (straight line), the expiration date could be calculated by the following equation:-

$$t_{10\%} = \frac{0.104}{K_{25^\circ c}} \quad (4).$$

It was equal to 4.1 years (Aqueous) and 3.1 years (Organic).

While the Arrhenius activation energy (Ea) was calculated from the slope of Arrhenius plots .It was found to be 4804.8 cal/mol and 5033.6 cal/mol respectively.

The above results indicated that, the microspheric particles prepared from gelatin and acacia coat (aqueous method) were more stable because of presence of crosslinking agent (formaldehyde) [11], as well as, activation energy was less than that of organic method [12], which is in consistent with the results obtained by Sivakumar-PA who found that the stability of ibuprofen liposopmes increased by using a crosslinking agent[13].

The other manifestations of general appearance like color of microcapsules were not changed after 4 months for both formulas.

Effect of temperature on the dissolution behavior of ibuprofen microcapsules:

Figures 5 and 6 indicate that no largely difference was appeared in the releasing profile of all stored ibuprofen microcapsules of both methods at 60°C, 50°C, 40°C), 4°C in an opened and closed container (refrigerator) after one month in comparison with standard 2:1 core: wall ratio ibuprofen microspheres prepared by aqueous and organic method stored at room temperature[14] ,while after second and third months, the releasing behavior of microcapsules for both methods was clearly changed as shown in figures 7, 8 and 9,10 for aqueous and organic method, respectively.

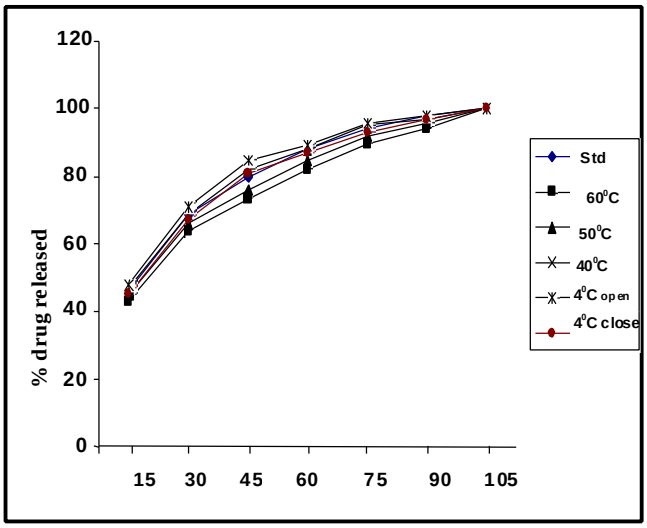


Figure (5): The releasing behavior of 2:1 core: wall ratio ibuprofen microcapsules prepared by aqueous method stored at different temperatures after one month using 6.8pH of phosphate buffer

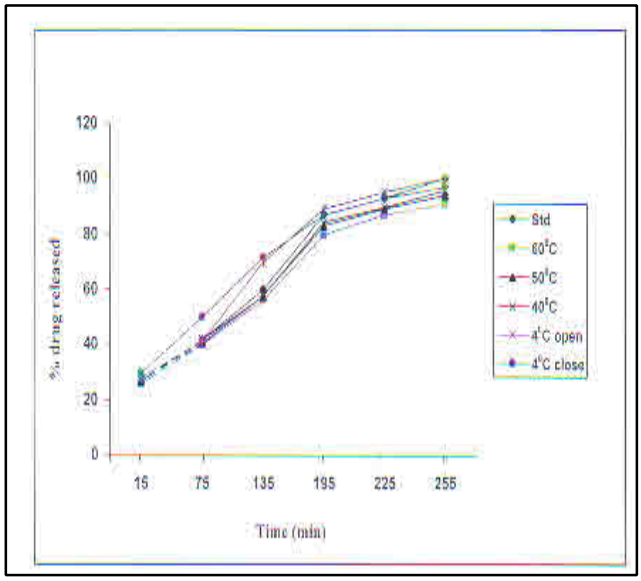


Figure (6): The releasing behavior of 2:1 core: wall ratio ibuprofen microcapsules prepared by organic method stored at different temperatures after one month using 6.8pH of phosphate buffer.

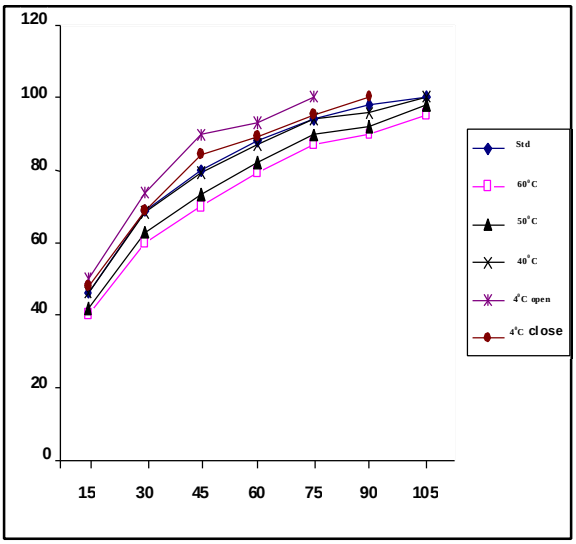


Figure (7): Dissolution behavior of ibuprofen microcapsules prepared by aqueous method stored at different temperatures using phosphate buffer pH 6.8 after 2nd month of storage.

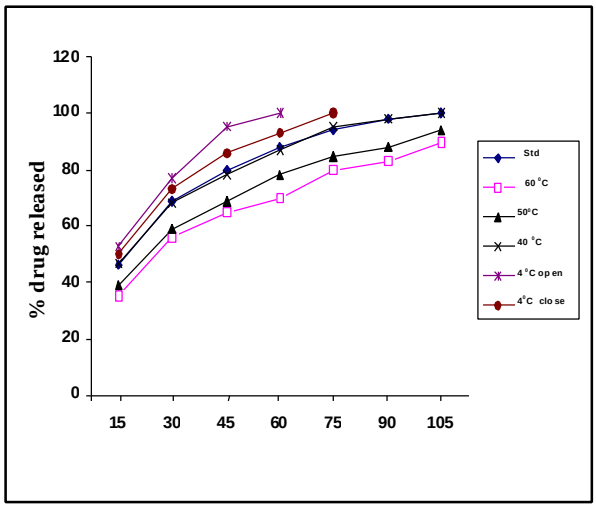


Figure (8): Dissolution behavior of ibuprofen microcapsules prepared by aqueous method stored at different temperatures after third month of storage using phosphate buffer pH 6.8

Figures 7 and 8, illustrate the releasing behavior of 2: 1 core: wall ratio ibuprofen microcapsules prepared by aqueous method stored at 40°C in which the release of the drug was the same as the standard one.

The same result was obtained by Carol-AS, he found that the release of tryptophan and theophylline from gel microcapsules stored at 25°C and 40°C remained unchanged[15].

On the other hand, microcapsules stored at 50°C and 60°C provided lower release of drug due to removal of solvent, denser periphery (viscous boundary) of microcapsules[16], but when the temperature of storage decreased to 4°C of refrigerator of an open and close container, the release of ibuprofen increased because of physically changes in the integrity of microcapsules shapes which became more spherical with smooth surface that provided larger surface area with porous surface after completion of stability study[17,18].

Also, microcapsules stored in an open container provided higher release of ibuprofen than closed one due to presence of humidity in the refrigerator environment that made the gelatin swell faster in the dissolution media with rapid diffusion of the drug from the texture of the gel[10].

The results obtained from figure 9 and 10 showed the delay in releasing profile of ibuprofen from microcapsules prepared by organic method when the temperature of storage increased from 40°C to 60°C due to tendency of microcapsules to sticking which was reversible after cooling to room temperature. The slightly decreased of dissolution rate and the sticking phenomena could be explained by change in the polymer film due to its low glass transition temperature, which could be additionally reduced by dissolved ibuprofen molecules in addition, storage at higher temperature allowed ethyl cellulose film to become more dense due to curing effect as it was reported for eudragit L100-55 polymer[19].

In spite of increasing the release of ibuprofen from microcapsules prepared by organic method when stored at refrigerator temperature in comparison with standard 2: 1 core: wall ratio stored at room temperature, the release of drug from microcapsules stored in an open container at 4°C showed lower release of drug at first 15-30 minutes because of some amorphous ibuprofen in the solid dispersion probably reacted with the polymer by catalytic action of water vapor during storage[20].

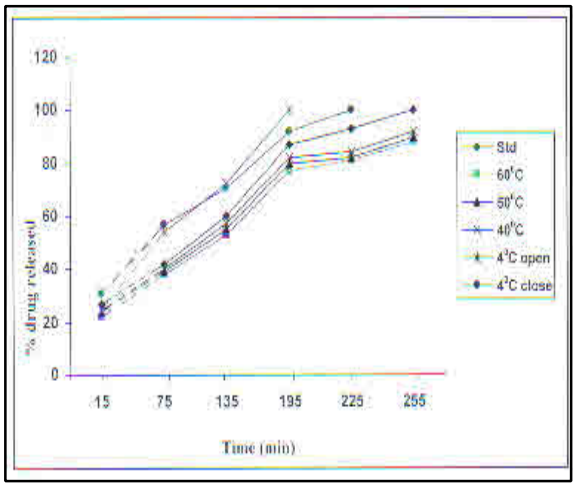


Figure (9): Dissolution behavior of ibuprofen microcapsules prepared by organic method stored at different temperatures after 2nd month of storage using 6.8 pH phosphate buffer.

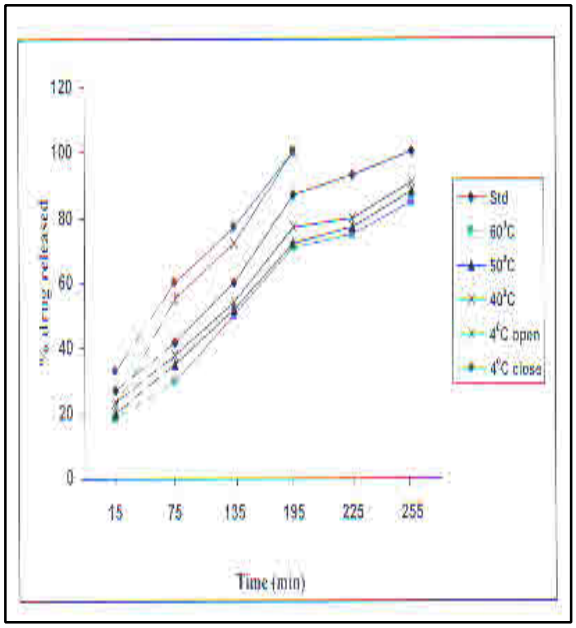


Figure (10): Dissolution behavior of ibuprofen microcapsules prepared by organic method stored at different temperatures after 3rd month of storage using 6.8 phosphate buffer.

Conclusion

2:1 core: wall ratio ibuprofen microcapsules prepared by both aqueous and organic method were stable with shelf life of 4.1 and 3.1 years.

All physical changes affected the releasing behavior of this ratio occurred at different storage temperature were reversible on leaving these formulas at 25°C in tightly closed container.

2:1 core: wall ratio ibuprofen microcapsules prepared by aqueous method can be stored at a temperature 25-40°C without altering its stability or the release profile.

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