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FORMULATION AND EVALUATION OF ORAL SUSTAINED RELEASE ETHYL CELLULOSE MICROPARTICLES INCORPORATED WITH FLURBIPROFEN

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A great effort has been devoted to develop a method for delivering an efficient potent analgesic drug flurbiprofen (FLB) into more absorbed and small polymeric microparticles ethyl cellulose (EC), moreover to avoid the absorption at the acidic pH of the stomach. EC microparticles loaded with FLB were prepared by emulsion-solvent evaporation. A complete study for the encapsulation efficiency percent (EE%), the size and weight of the microparticles incorporated with FLB were studied and optimized. The release profiles of FLB from EC microparticles were measured in Sorensen phosphate buffer (0.1 M, pH 7.4). The results showed that EE% for all forms of microparticles was decreased as drug : polymer ratios decreased. The microparticles had a mean diameter of 30-80 µm as showed by scanning electron microscopy, confirming that the structure was in micro-size, moreover the release rate of FLB from microparticles was strikingly lower than that from drug itself. The results allow for the conclusion that the formulated microparticles serve as promising platform to improve the solubility, absorption and sustained release of FLB.

INTRODUCTION

Most non-steroidal anti-inflammatory drugs (NSAIDs) currently used today show no selectivity to COX-1 and COX-2 lead to various side effects. Usually the excessive production of stomach acid caused by NSAIDs lead to gastrointestinal ulceration and bleeding, as the result of inhibiting of COX-1's housekeeping role and COX-2's inflammatory response[1]. A drugs usage selectivity to COX-2 and COX-1is an attempt to decrease the side effects of NSAIDs on the stomach otherwise develop an encapsulate drugs using a safe, cheap and available polymers such as ethyl cellulose (EC) moreover its releases required a pH above 7.0 away from the acid pH of the stomach[2&3].

Additionally, the processes of encapsulation reduce the gastrointestinal side effects of some active ingredients such as ferrous sulphate and potassium chloride solutions, and modify some drugs dissolution rates and hence their duration of action via sustained release system via encapsulation processes[4-6]. EC, as a type of cellulosic polymers, used in this study to prepare sustained release FLB microparticles in pH 7.4, is inert, hydrophobic polymer and has been extensively used as a release rate controlling material[7]. The process of encapsulation help also for enhancing the drug release and penetration, and can be used as targeting agent[8-12]. Flurbiprofen is a white to cream powder which is sparingly soluble in water at low pH values but readily soluble above pH 7, it is freely soluble in the common organic solvents at room temperature with the exception of light petroleum[13&14]. Solvent evaporation method is a simple method, from a

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numerous methods has been reported, and used to prepare the microparticles[15]. The aim of this study was to formulate EC microspheres loaded with FLB as a new method for releasing NSAIDs in small and large intestine and to avoid the release in stomach.

EXPERIMENTAL

Materials

FLB standard powder (Boots Co., Nottingham, UK) was kindly supplied by Al-Kahira pharmaceutical Co. (Cairo, Egypt). EC was obtained from Sigma Chemical Co., (California, USA). Methylcellulose (MC) was purchased from Dow Chemical Fluka (Greifensee, Swizerland). All other chemicals were of analytical grades and purchased from Elnasr pharmaceutical chemical Co. (Abu-Zaabal, Cairo, Egypt). Carrageenan and Urethane were purchased from Sigma Chem. Co. (St. Louis, USA). A male Albino rats (weight 120-200 g) were obtained from Assuit University Experimental Animal (Assuit, Egypt). The protocol of the study was approved by the research Ethics Committee in the Faculty of Medicine, Assiut University, Egypt.

Method

Preparation of ethyl cellulose microparticles incorporated with flurbiprofen using solvent evaporation method

Microparticles were prepared according to the previously reported method[16]. Briefly, the calculated amount of FLB were accurately weighed and dissolved into 70 mL of 2%, w/v solution of EC in ($CHCl_3$)/DCM. The weight of FLB was calculated as to produce the drug to polymer ratio as shown in table 1. The resulting solution was then emulsified into 250 mL of 1%, w/v aqueous solution of tween 80 in distilled water or HCl (0.1 M, pH 1.2). Stirring was continued at room temperature (25°C) to allow $CHCl_3$/DCM evaporation. The process was continued until the odor of $CHCl_3$/DCM disappears; then the microparticles produced were then separated by filtration using Whatman membrane filters nylon with pore size 1 µm, diam. 47 mm. The separated microparticles washed using distilled water and HCl (0.1 M, pH 1.2). The washed micro-particles were dried in a desiccator over $CaCl_2$ for 48 hours. EC microparticles could be prepared using DCM as the non- aqueous phase and using HCl (0.1 M, pH 1.2) as the aqueous phase (Fig. 1).

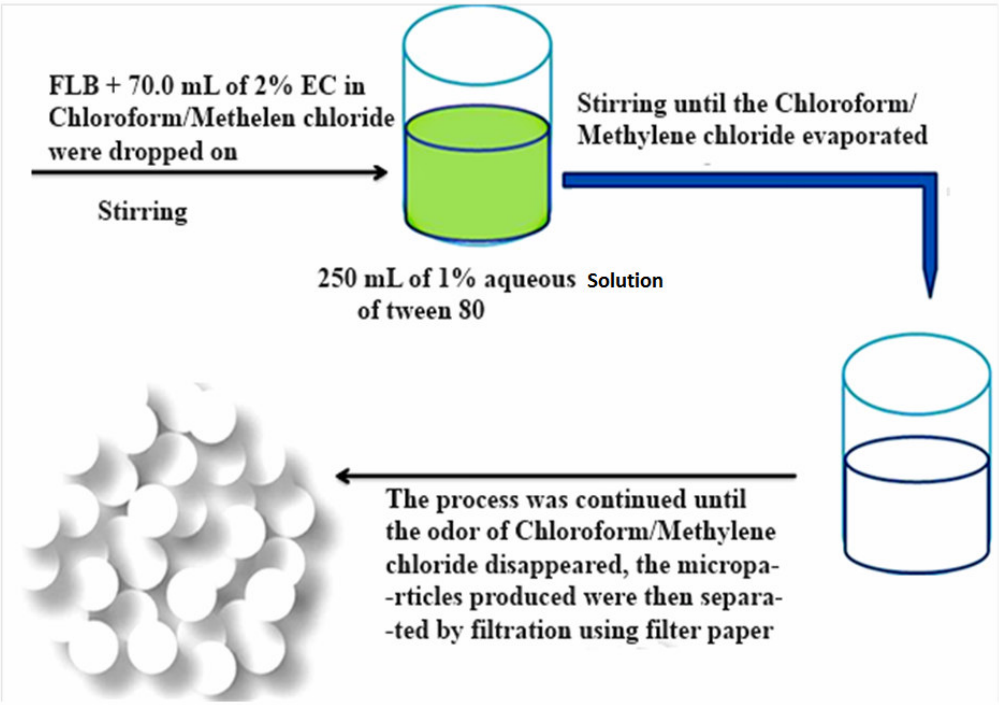

Fig. 1: Schematic diagram represent the process of EC microspheres formation.

Table 1: Different drug to polymer ratios for preparation of microparticles using different dispersion medium.

Microparticles prepared using distilled water (aqueous phase)		Microparticles prepared using acid buffer (pH 1.2) (aqueous phase)	
$CHCl_3$ (non-aqueous phase)	DCM (non-aqueous phase)	$CHCl_3$ (non-aqueous phase)	DCM (non-aqueous phase)
Drug : polymer	Drug : polymer	Drug : polymer	Drug : polymer
1:0.5	1:0.5	1:0.5	1:0.5
1:1	1:1	1:1	1:1
1:2	1:2	1:2	1:2
1:3	1:3	1:3	1:3

Drug content determination of ethyl cellulose microparticles incorporated with flurbiprofen

To determine the encapsulation efficiency (EE%) of FLB in EC microparticles, an amount equivalent to 20 mg of FLB entrapped microparticles was dissolved in 10 mL $CHCl_3$/DCM. After complete dissolution, 40 mL of phosphate buffer (0.1 M, pH 7.4) was added to the $CHCl_3$ solvent and the mixture was stirred on a magnetic stirrer at room temperature until the odor of $CHCl_3$completely evaporated. The solution was then filtered and diluted to 50 mL with phosphate buffer (0.1 M, pH 7.4)[17&18]. One mL of this solution was diluted with phosphate buffer to 25 mL in volumetric flask. Then the solution was analyzed for its FLB content spectrophotometrically at 247 nm against a blank solution prepared in the same manner using FLB-free microparticles[13].

Determination of surface drug content of ethyl cellulose microparticles

There are some of FLB precipitateson the surface of microparticles and didn´t entrap in the microparticles. To determine this amount, 20 mg equivalent to FLB of FLB microparticles was just washed with 10 mL $CHCl_3$/DCM without dissolution of microparticles to avoid the interference between the entrapped or precipitated on the surface of particles. 40 mL of phosphate buffer (0.1 M, pH 7.4)was added to the washing 10 mL of $CHCl_3$ solvent and the mixture was stirred on a magnetic stirrer at room temperature until the odor of $CHCl_3$ evaporates[19&20]. The solution was then filtered and diluted to 50 mL in volumetric flask with phosphate buffer. One mL of this solution was diluted with phosphate buffer to 25 mL in volumetric flask. The solution was then analyzed for its FLB content spectrophotometrically at 247 nm against a blank solution prepared in the same manner using FLB-free microparticles[13].

Size and weight of ethyl cellulose microspheres

EC microspheres incorporated with FLB before drying and the morphological examination of microspheres surface were examined by transmission electron microscope. The diameter of microspheres was determined, and the average weight of 10 of microspheres was determined. The mean of five determinations was considered as the weight of 10 microspheres.

***In-vitro* release study for ethyl cellulose microspheres incorporated flurbiprofen**

An accurately weighed quantity of EC microspheres equivalent to 50 mg of FLB was placed in the basket of USP dissolution tester (Validata-Hansen research Chatsworth, Ca, USA) rotating at 50 *rpm*. The dissolution medium was 500 mL of phosphate buffer (pH 7.4) at 37°C. One mL samples were withdrawn at predetermined intervals; the removed sample was replaced with one mL of phosphate buffer[21]. Each sample was diluted with appropriate volume of phosphate buffer so that absorbance values lie between 0.1 and 0.9 when measured spectrophotometrically at 247 nm using UV-1601 spectrophotometer (Shimadzu, Kyoto, Japan) with two matched quartz cells[13].

Analysis and computation of drug release data

The data obtained from the experiments were analyzed by means of computer to specify the mechanism of drug release[22&23]. The correlation coefficient was calculated for each release model to determine whether the release follows zero, first order or diffusion model.

Statistical analysis

Analysis of variance on SPSS software package (version 9) (SYSTAT statistical program) was used to test the present data. In the case of significant difference, in addition, means, summation, standard error, standard deviation, were applied in the present data. Probability values (P) $\leq$ 0.05 were defined as significant throughout the present study; however the values > 0.05 were defined as non-significant. *P*-values between 0.05 and 0.01 (both are included) were evaluated as significant, whereas that less than 0.01 were defined as highly significant[24].

Differential scanning calorimetry of ethyl cellulose microspheres

DSC studies were carried out for the previously prepared EC microspheres with a certain drug : polymer ratio, for the corresponding physical mixtures as well as for the untreated drug in order to determine the extent of crystalinity of the drug in presence of the used polymers[25].

Evaluation of the anti-inflammatory activity of flurbiprofen from selected ethyl cellulose microparticles

The anti-inflammatory activity of the selected formulations was evaluated applying the carrageenan-induced rat's paw edema method[26]. Thirty-six adult male albino rats weighing 120-200 g were used in this test. The rats were randomly allocated to six groups each of six rats. The animals were fasted overnight, and were given each 3 mL of water, before the administration of the test drugs to reduce variability to edema response. The selected sustained release formulations, as well as FLB powder were suspended in 1% carboxy-methylcellulose solution[27&28]. The rats were anaesthetized using urethane (dose 1 ml/kg intraperitoneal)[29]. Each group of animals received the specified drug product through a special gastric incubation into the esophagus in a dose equivalent to 20 mg/kg. Inflammation was induced by subcutaneous injection of 0.1 mL of 1% carrageenan solution in distilled water into the subplanator tissue of one hind paw. The anti-inflammatory effect was expressed as an inhibition % of edema thickness compared with control according to the following equation.

$$inhibation\ of\ edema, \% = \frac{T_0 - T_t}{T_0}\ x\ 100\%$$

Where, T_0 is the edema thickness in control group, T_t is the edema thickness in treated group. The obtained results were tested for a significantly difference by using one-way ANOVA test in SPSS software package (version 9).

RESULTS AND DISCUSSION

Size and weight of ethyl cellulose microspheres

Figure 2 shows the scanning electron microscope of EC 200 microspheres incorporated FLB prepared at 1:1 drug : polymer ratio using HCl (0.1 M, pH 1.2) as an aq. phase and DCM as a non-aq. phase. The microspheres were spherical in shape, and have a particle size of ≈30 - 80 µm.

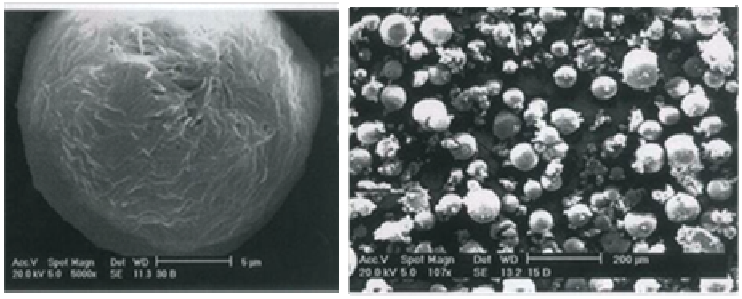

Fig. 2: Scanning electron micrographs of EC microspheres incorporated FLB prepared at 1:1 drug : polymer ratio using 0.1 M HCl (pH 1.2) and DCM.

Drug loading and surface content of ethyl cellulose microspheres incorporated flurbiprofen

Table 2 shows the FLB content of different types of EC microspheres; the drug loading for all forms of microspheres was decreased as the drug to polymer ratio decreased, while increased as the internal phase and external phase increased. The microspheres showed FLB precept on the surface of the microspheres. These amounts of non-entrapped FLB were recorded in table 3, indicating and confirming the amount of FLB incorporated. As FLB is slightly soluble at low pH values or in DCM, this system was used to minimize the drug solubility in aqueous phase (hence decrease the drug lost into this phase**.** Significantly, the drug amounts were not affected by using low pH, while was affected by using of DCM as non-aqueous phase. Drug incorporated microspheres prepared with $CHCl_3$, as the non-aqueous solvent was 29.9% in comparison to 25.1% of thoseprepared with DCM as the non-aqueous solvent. This might be attributed to the low boiling point of the later. On the other hand, drug incorporated microspheres which prepared with distilled water was 29.9% in comparison to 26.71% which prepared with acidic aq. solution. The slightly higher drug content in the former case is on the contrary to that was anticipated. This might be attributed to the presence of EC which was employed as emulsion stabilizer in the distilled water emulsion only.

EC, as a type of cellulosic polymers used in this study is an inert, hydrophobic polymer used as a release rate controlling material[30]. The emulsions formed using w/v tween 80 were not stable, and formed large aggregates. Stable emulsions and microspheres were prepared when methylcellulose in 0.05% w/v was used in order to avoid the excessive increase in aqueous phase viscosity which has a deleterious effect on the morphology of microspheres produced[31].

Table 2: FLB contents of different EC microspheres.

D : P ratio	FLB content* of EC microspheres prepared using different types of solvents (aqueous and non-aqueous solvents)			
	Distilled water/$CHCl_3$	Distilled water/DCM	0.1 M HCl/$CHCl_3$	0.1 M HCl/DCM
1:0.5	24.6%	26.7%	25.1%	29.9%
1:1	41.9%	42.9%	43.9%	49.9%
1:2	21. 9%	23.9%	21.9%	25.3%
1:3	11.9%	12.2%	13.2%	14.9%

Table 3: Surface content of different EC microspheres incorporated FLB**.**

D : P ratio	FLB content* of EC microspheres prepared using different types of solvents (aqueous and non-aqueous solvents)			
	Distilled water/$CHCl_3$	Distilled water/DCM	0.1 M HCl/$CHCl_3$	0.1 M HCl/DCM
1:0.5	7.4%	11.4%	8.8%	11.8%
1:1	18.6%	20.4%	18.9%	20.3%
1:2	5.4%	6.2%	4.5%	5.8%
1:3	2.4%	2.5%	2.9%	2.3%

$$^{*}FLB\ contents = \frac{Actual\ drug\ content}{theoretical\ drug\ content}\ x\ 100$$

In-vitro **release of flurbiprofen from ethyl cellulose microparticles**

The release of microspheres in HCl (0.1 M, pH 1.2) gives synergistic effect with polymer to retard the drug release by maintaining acidic environment in polymeric microspheres. The average gastric emptying time of drugs ranged from 15 minutes to 3 hrs, for that reason the microparticles were immersed in HCl (0.1 M, pH 1.2) for 2 hrs before dissolution in phosphate buffer (0.1 M, pH 7.4) which showed no release in that media (pH 1.2)[32&33]. The media of HCl (0.1 M, pH 1.2) was replaced by phosphate (0.1 M, pH 7.4) as a second medium of dissolution to confirm that FLB was release just in pH 7.4 media[34&35]. The release profile from EC microspheres prepared using the 1:0.5, drug : polymer ratio demonstrated the lowest efficiency in retarding FLB release, where 87.9% of the drug content of the microspheres was released after six hrs, while the release profile from EC microspheres prepared using the 1:2 drug : polymer ratio showed the highest retardation in release where only 27% of the drug content of the microspheres was released after six hrs (Figs. 3 and 4). These results of release indicated that, as the polymer ratio increased the release from microspheres decreased. EC polymer retards the release of FLB from the microspheres. The used organic solvents $CHCl_3$ and DCM in preparing of the drug-polymer solution did not exhibit any significant effect on drug entrapment, size, shape and release when compared against the microspheres prepared with same polymers.

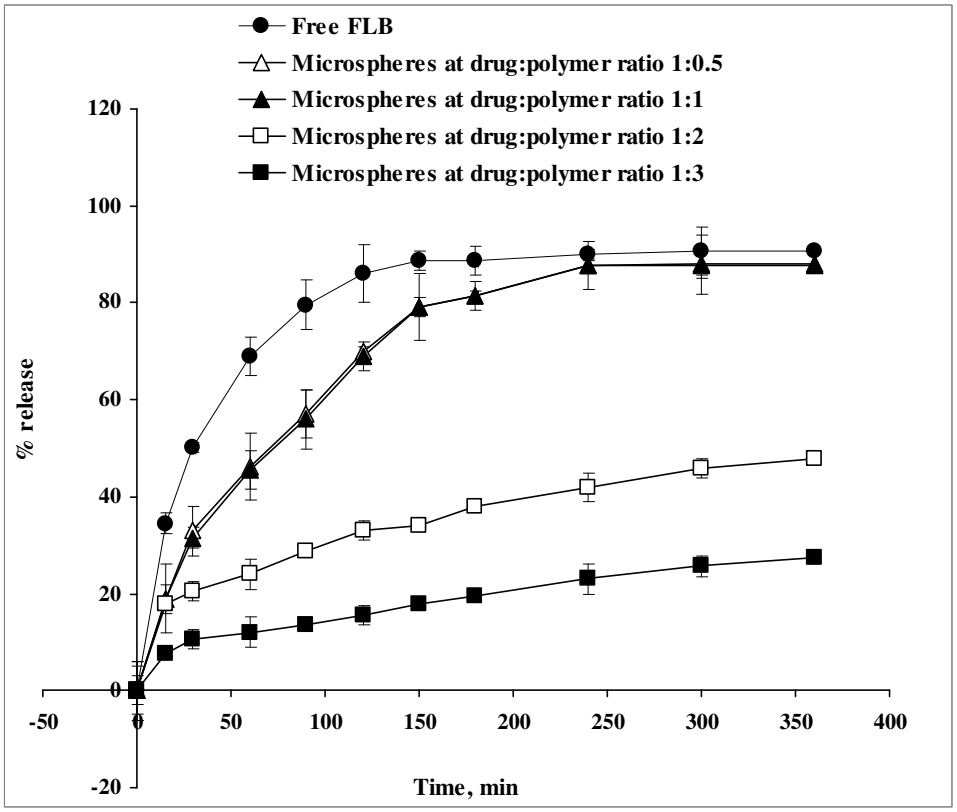

Fig. 3: Effect of different drug : polymer ratios on the release profile of EC microsphere, using distilled water as the aqueous phase and $CHCl_3$ as the non-aqueous phase, in phosphate buffer (pH 7.4) using the rotating basket apparatus methods, 50 *rpm*.

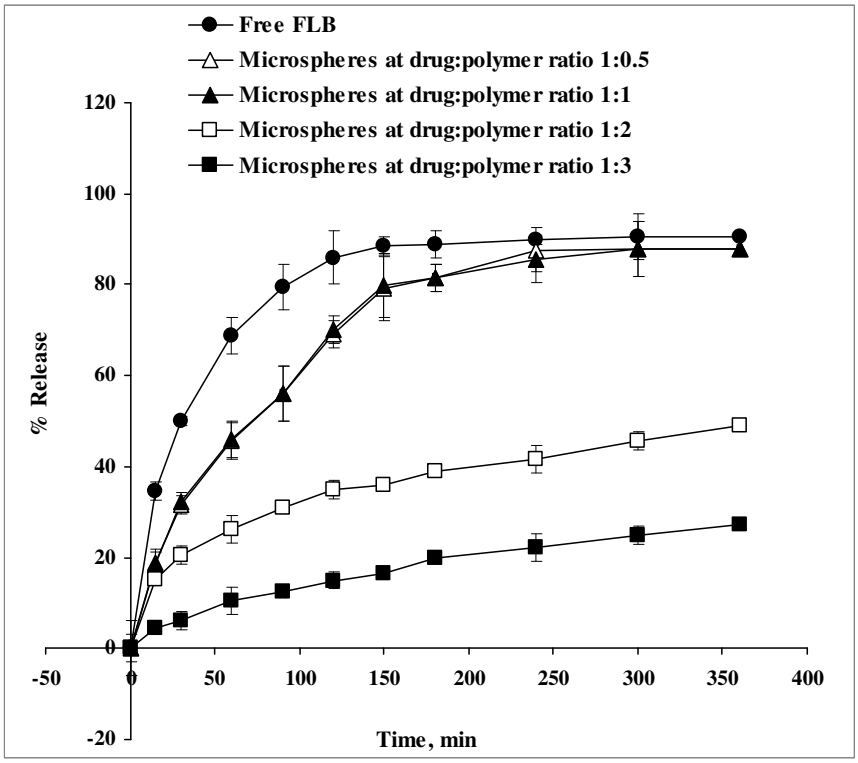

Fig. 4: Effect of different drug : polymer ratios on the release profile of FLB EC microsphere, when using distilled water as the aqueous phase and DCM as the non- aqueous phase, in second phosphate buffer (pH 7.4) using the rotating basket apparatus methods, 50 *rpm*.

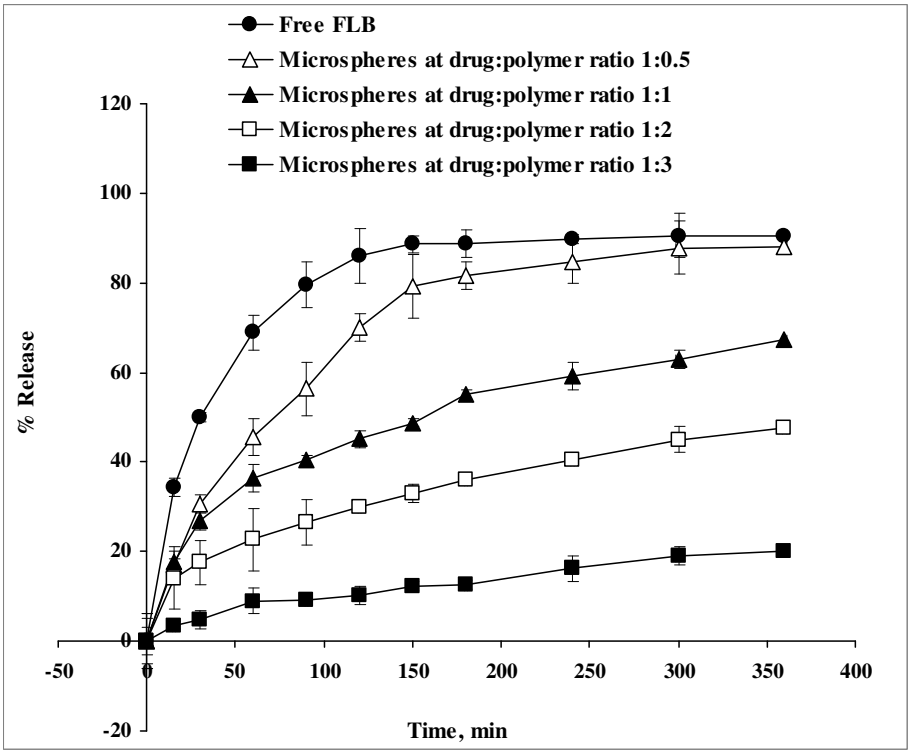

Fig. 5: Effect of different drug : polymer ratios on the release profile of FLB EC microsphere, when using acid buffer as the aq. phase and $CHCl_3$ as the non-aq. phase phosphate buffer (pH 7.4), at room temperature, using the rotating basket apparatus methods (50 *rpm*).

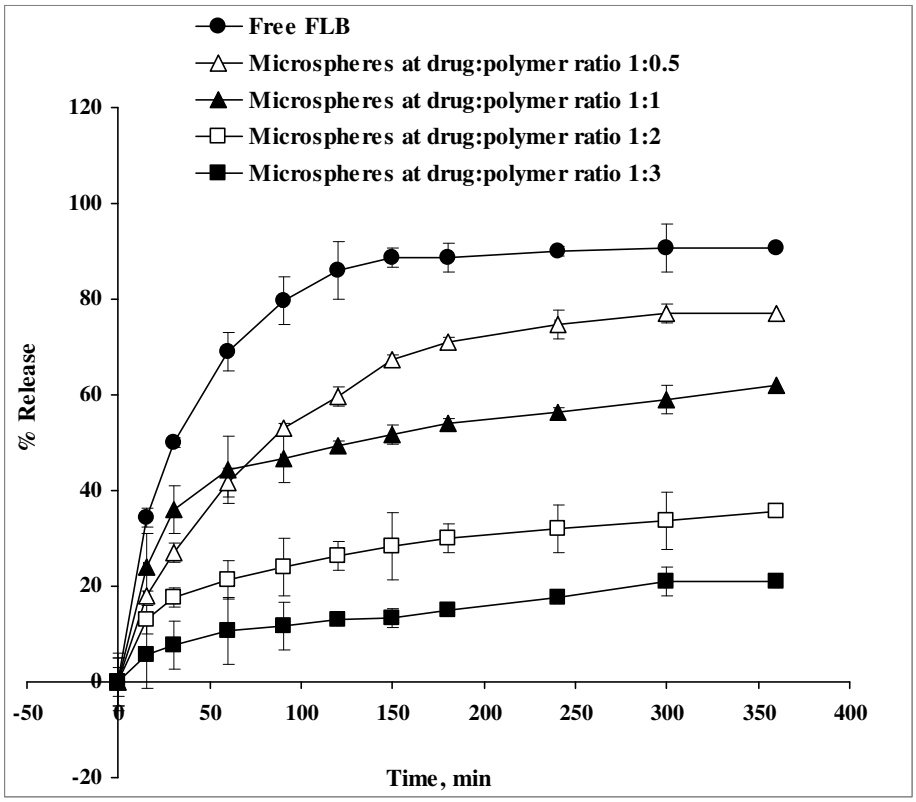

Fig. 6: Effect of different drug : polymer ratios on the release profile of FLB EC microsphere, when using acid buffer as the aqueous phase and DCM as the non-aqueous phase in phosphate buffer (pH 7.4) using the rotating basket apparatus methods, 50 *rpm*.

Kinetic analysis of the release data of flurbiprofen from ethyl cellulose microparticles

The diffusion matrix results are shown in table 4 for % of release data was obeyed the diffusion mechanism, these data were supported by previously results[36]. The results revealed that it can be concluded that the diffusion rate constant (K_h) of microparticles prepared at 1:0.5 drug to polymer ratio using distilled water as an aqueous phase and $CHCl_3$ as a non-aqueous phase was 1.321 $min^{-1.}$ Increasing the drug to polymer ratio to 1:1 and 1:2 ratios, have demonstrated an increase in the value of the K_h to 2.088 min^{-1} and 4.778 min^{-1}. Further increase in the drug to polymer ratio to 1:3 ratio, has demonstrated a slight decrease in the value of K_h to 4.588 min^{-1}.

The results in table 5 indicated that, that the K_h of microparticles prepared using distilled water as an aqueous phase and DCM as a non-aqueous phase increased as the drug to polymer ratios increased from 1:0.5 to 1:3 ratios. According the results in table 6 the K_h of microparticles prepared at 1:0.5 drug to polymer ratio using acidic media HCl (0.1 M, pH 1.2) as an aqueous phase and $CHCl_3$ as a non-aqueous phase was 3.199 min^{-1}. Increasing the drug to polymer ratio to 1:1 ratio, has demonstrated a decrease in the value of K_h to 1.106 min^{-1}. Further increase in the drug to polymer ratio to 1:2 ratio, increase in the value of K_h to 4.867 min^{-1}, while increase in the drug to polymer ratio to 1:3 ratio, has demonstrated a decrease in the value of K_h to 4.867 min^{-1}. Finally as in table 7 we can conclude that, K_h of microparticles prepared using acidic buffer as an aq. phase and DCM as a non-aqueous phase increased from 1.037 min^{-1} to 4.103 min^{-1} as the drug to polymer ratios increased from 1:0.5 to 1:3 ratios.

Table 4: Kinetic analysis of EC microspheres at different drug : polymer ratios using distilled water as aqueous phase and $CHCl_3$ as a non-aqueous phase in phosphate buffer (pH 7.4).

Mechanism of release		Drug : polymer ratios			
		1:1	1:0.5	1:2	1:3
First order	r*	-0.972	-0.992	-0.946	-0.951
	K_1** (min^{-1})	-0.0006	-0.001	-0.003	-0.003
Zero order	r	0.9776	0.989	0.878	0.811
	K_0*** (% released/min)	0.088	0.057	0.189	0.171
Higuchi's diffusion	r	0.996	0.993	0.952	0.911
	K_h**** (% released/min)	2.088	1.321	4.788	4.581
Log Q versus Log t	r	0.915	0.988	0.974	0.971
	Slope	0.348	0.398	0.488	0.491
Best fitted model		Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion

*r= Correlation coefficient.

**K_1= First order release rate constant.

***K_0= Zero order rate constant.

****Kh= Diffusion rate constant.

Table 5: Kinetic analysis of EC microspheres at different drug : polymer ratios using distilled water as aqueous phase and DME as a non-aqueous phase in phosphate buffer (pH 7.4).

Mechanism of release		Drug : polymer ratios			
		1:1	1:0.5	1:2	1:3
First order	r	-0.985	-0.947	-0.898	-0.948
	K_1 (min^{-1})	-0.001	-0.002	-0.001	-0.003
Zero order	r	0.979	0.968	0.954	0.876
	K_0 (% released/min)	0.065	0.036	0.089	0.189
Higuchi's diffusion	r	0.998	0.991	0.993	0.951
	K_h (% released/min)	1.541	0.869	2.159	4.789
Log Q versus Log t	r	0.998	0.666	0.977	0.971
	Slope	0.578	0.527	0.359	0.497
Best fitted model		Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion

Table 6: Kinetic analysis of EC microspheres at different drug : polymer ratios using 0.1 M HCl (pH 1.2) aqueous phase and $CHCl_3$ as a non-aqueous phase in phosphate buffer (pH 7.4).

Mechanism of release		Drug : polymer ratios			
		1:1	1:0.5	1:2	1:3
First order	r	-0.989	-0.981	-0.952	-0.996
	K_1 (min^{-1})	-0.0002	-0.001	-0.004	-0.0007
Zero order	r	0.983	0.951	0.875	0.979
	K_0 (% released/min)	0.047	0.132	0.192	0.096
Higuchi's diffusion	r	0.989	0.991	0.951	0.999
	K_h (% released/min)	1.106	3.199	4.867	2.271
Log Q versus Log t	r	0.991	0.992	0.972	0.998
	Slope	0.544	0.408	0.512	0.395
Best fitted model		Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion

Table 7: Kinetic analysis of EC microspheres at different drug : polymer ratios using 0.1 M HCl (pH 1.2) aqueous phase and DMC as a non-aqueous phase in phosphate buffer (pH 7.4).

Mechanism of release		Drug : polymer ratios			
		1:1	1:0.5	1:2	1:3
First order	r	-0.931	-0.982	-0.932	-0.939
	K_1 (min^{-1})	-0.001	-0.001	-0.001	-0.002
Zero order	r	0.925	0.978	0.888	0.883
	K_0 (% released/min)	0.057	0.044	0.087	0.163
Higuchi's diffusion	r	0.975	0.991	0.953	0.956
	K_h (% released/min)	1.401	1.037	2.185	4.105
Log Q versus Log t	r	0.991	0.991	0.965	0.975
	Slope	0.299	0.411	0.264	0.474
Best fitted model		Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion	Higuchi's diffusion

Differential scanning calorimetry (DSC)

Figures 7 and 8 show the DSC curve of the untreated FLB, plain EC, EC blank microparticles, EC microparticles incorporated with FLB prepared in the 1:1 ratio using distilled water as the aqueous phase and $CHCl_3$ as the non-aqueous phase, and EC microparticles loaded with FLB prepared in the 1:1 ratio using acidic media as the aqueous phase and $CHCl_3$ as the non-aqueous phase. Free FLB showed an endothermic peak at 113.3°C at a scanning rate of 5°C/min which corresponds to the melting of crystalline FLB. This peak disappeared in the DSC of EC microparticles prepared using distilled water or acidic solution as the aqueous phase. This indicates the absence of crystalline FLB within those microparticles. Thus, FLB is molecularly dispersed in the polymeric matrix of both types of microparticles and a solid solution of the drug in EC microparticles is therefore proposed.

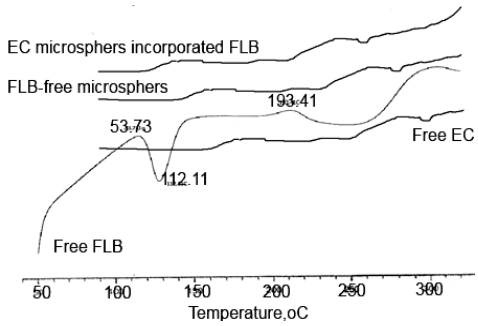

Fig. 7: DSC curves of free FLB, free EC, FLB-free EC microspheres blank, EC microspheres incorporated FLB prepared in the 1:1 ratio using distilled water as the aqueous phase and $CHCl_3$ as the non-aqueous phase.

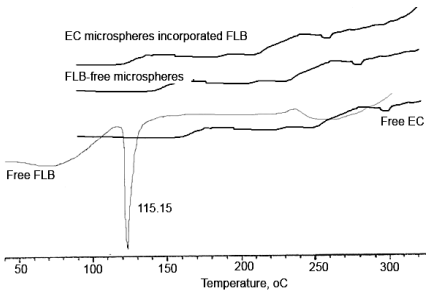

Fig. 8: DSC curves of FLB alone, EC, EC microspheres blank and EC microspheres loaded with FLB prepared in the 1:1 ratio using 0.1 M HCl (pH 1.2) as the aqueous phase and $CHCl_3$ as the non-aqueous phase.

Evaluation of the anti-inflammatory activity of ethyl cellulose microparticles incorporated with flurbiprofen on rat paw edema

All formulae were given two hrs after induction of edema. It is obvious that at 1hr post carrageenan injection, there is apparent reduction of swelling in groups treated with EC microparticles incorporated FLB (group 4), and free drug (group 3) compared with the control group (group 1), and there is no evident inhibition in edema swelling in groups that received free EC microparticles (group 2). The percentage inhibition in edema swelling in group 3 and group 4 was 12.3 and 14.1 respectively versus 1.56 percent inhibition for the groups 1 and 2. After 2 hrs post carrageenan injection the anti-edemal effect was higher when using the EC microparticles incorporated FLB and free drug (groups 3 and 4) respectively, where the percentage inhibition in edema swelling percentages were 23.1, and 33 versus 0 group 1. After 5 hr post carrageenan injection the anti-edemal effect was higher when using EC microparticles incorporated FLB, where the percentage inhibition in edema swelling was 53.21 versus 18.12 for the group that received the free drug (group 4 and 3) respectively. After 6 hr post carrageenan injection, the groups that received EC microparticles incorporated FLB still exhibited a significant inhibition of the carrageenan induced edema (group 4) which is numerically higher than that observed in the rats that received free drug, and free EC microparticles (groups 2), where the percentage inhibition in edema swelling was 46.74 versus 3.55 and 2.72 for the group 3 and 4 respectively (Table 8).

Table 9 shows the one way ANOVA test of the% of inhibition of rat paw edema of plain drug, free EC microparticles and EC microparticles incorporated FLB. The significant results are 0.240, 0.806, 0.857, and 0.966. The results obtained revealed that the selected EC microparticles incorporated FLB have an anti-inflammatory activity with long duration.

Table 8: The anti-inflammatory effect of the selected FLB incorporated EC on the carrageenan-induced edema in the hind paw of rats.

Dosage form	% of inhibition of edema					
	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Control (group1)	0.833	0.866	0.833	0.835	0.855	0.845
Plain EC microspheres (group 2)	0.820 1.561	0.866 0.011	0.812 2.522	0.834 0.122	0.850 0.584	0.815 3.553
Plain drug (group 3)	0.716 12.123	0.581 33.011	0.466 44.100	0.533 36.162	0.701 18.121	0.788 6.710
EC microspheres incorporated FLB (group 4)	0.716 14.234	0.666 23.122	0.544 34.691	0.445 46.725	0.411 53.204	0.450 46.7401

Table 9: One-way ANOVA test of the % of inhibition of rat paw edema of FLB incorporated EC microspheres on the carrageenan-induced edema in the hind paw of rats.

Dosage form			Summation of squares	Degree of freedom	Mean Square	F value	Significant limit
١	Control	Between groups	17.984	4	4.496	0.836	0.665
		Within groups	5.379	1	5.379		
		Total	23.363	5			
2	FLB-free microspheres	Between groups	1026.218	4	256.554	9.370	0.240
		Within groups	27.380	1	27.380		
		Total	1053.598	5			
3	Free drug	Between groups	702.232	4	175.558	0.412	0.806
		Within groups	426.320	1	426.320		
		Total	1128.552	5			
4	EC microspheres incorporated FLB	Between groups	5.000	4	1.250	0.100	0.966
		Within groups	12.500	1	12.500		
		Total	17.500	5			

Conclusion

EC microspheres incorporate FLB; a novel macro-encapsulation delivery system can be formulated not only for oral administration but also one of most advantageous delayed release that takes place far from the buccal region. Therefore it is a novel method to prepare efficient anti-inflammatory FLB microparticles which will be able to mask the drug taste and its burring effect in the oral cavity and stomach. The formulated microparticles serve as promising platform to modify the solubility, absorption and sustained release of FLB and as a coating micro-particle not affected in stomach by gastric juices.

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نشرة العلوم الصيدلية
جامعة أسيوط

تحضير وتقييم حويصلات دقيقة لعقار الفلوربايبروفين باستخدام بوليمر الإيثيل سيليولوز

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اشتملت الدراسة في هذا الجزء على تحضير حويصلات دقيقة لعقار الفلوربايبروفين باستخدام الإيثيل سيليولوز بطريقة تبخر المذيب في وجود أثنين من مواد الإستحلاب وهي الكلوروفورم وكلوريد المثيلين ، وقد أجريت تجارب تمهيدية لتحديد المدى الذي يمكن استخدامه عملياً لكل من حجم الطور الخارجي المائي، حجم الطور الداخلي العضوي ، تركيز مواد الإستحلاب ونسبة العقار مع البوليمر ، كما تم تقييم الحويصلات الدقيقة وذلك بدراسة الشكل الخارجي وخصائص السطح لها ، كما تم تعيين متوسط القطر ، وتقدير كمية المحصول الناتج ومحتوى العقار بالحويصلات بالإضافة إلى دراسة معدل ذوبان العقار من هذه الحويصلات.

أظهرت النتائج عدم تأثير كمية البوليمر على شكل الحويصلات المحضرة ، كما تم الحصول على حويصلات مستديرة منفصلة وذات سطح أملس ، بينما أدت زيادة كمية البوليمر إلى زيادة قطر الحويصلات ، بينما قل الناتج لزيادة لزوجة الطور العضوي ، وأظهر التحليل الإحصائي عدم تأثر محتوى العقار بتغيير نسبة العقار إلى البوليمر ، كما نقص إنطلاق الدواء من الحويصلات بزيادة محتوى البوليمر.أثبتت النتائج أن عملية إذابة الحويصلات المحملة بعقار الفلوربايبروفين تعتمد على قيمة الأسالهيدروجيني ، حيث أن العقار يذوب في الوسط القلوي بسرعة أكبر منها في الوسط الحامضي. الصيغة التي نسبة العقار فيها الي البوليمر ١:١ تم اختيارها لاستخدامها في دراسة الفاعلية ضد الإلتهابات حيث أنها أفضل الصيغ. كما تم قياس حجم الجسيمات الدقيقة باستخدام المجهر الاكتروني ليثبت أنه في حجم الميكروميتر من ٣٠ الي ٨٠ ميكروميتر.

في الخاتمة الحويصلات متناهية الصغر تعتبر نتائج واعدة في استهداف المناطق ذات الأس الهيدروجيني القلوي كما أنها تغير معدل إذابة العقار وزيادة إمتصاصه والتحكم في انطلاقه.