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Effect of polymer blends and evaluation from controlled release procaine hcl loaded poly(ε-caprolactone) microspheres

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ABSTRACT

The biodegradable poly(ε-caprolactone) (PCL) and ethylcellulose (EC) and blend polymers were tested for encapsulation of procaine hydrochloride (PR.HCl). The PCL and PCL blend EC microspheres were prepared by emulsion solvent evaporation method and the microcapsules were investigated using an image analyzer. The aim of this work is the evaluation of microencapsulation PCL and (PCL,EC) blend using the same weight to form the carrier polymer. It can be seen that the presence of ethylcellulose in formulation, decreases the rate of drug loaded percentage from microspheres but the higher molecular weight of PCL microparticles used for preparation of microspheres it led to rapid release. The drug release test of the (PCL,EC) and PCL microspheres in buffer solutions was characterized by UV-visible spectroscopy, the microsphers were characterized for drug content, percentage yield, particle size and by FTIR spectroscopy, DSC and DRX.

Keywords: *nanomaterials, biodegradable polymers, biocompatible polymers, poly(ε-caprolactone), drug release, ethylcellulose.*

1. INTRODUCTION

Biodegradable polymeric microcapsules have recently attracted some attention because of their potential applications in controlled drug delivery [1, 2, 3]. It has been shown that the polymeric microcapsules can be used, intravenously, to administer peptides and other drugs [4]. Using polymeric microcapsules could increase the availability, decrease possible associated adverse effects, and avoid surgical implantation in some cases [5, 6]. Synthetic aliphatic polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(ε-caprolactone) (PCL) [7], are often used in biomedical applications because they are biocompatible and non-toxic materials [8-9]. PCL is one of the currently available polymers used for Gastroretentive Floating and Mucoadhesive Drug Delivery [10]. The pharmacologically inactive biodegradation products, such as lactic acid from PLA and 6-hydroxycaproic acid from PCL, can be absorbed in the body and removed by metabolism, so that the removal of these polymer devices becomes unnecessary [11]. The successful use of these polymers in pharmaceutical applications has naturally led to the evaluation of other aliphatic polyesters such as poly (ε-caprolactone) (PCL), a biocompatible semi-crystalline polymer with a very low glass transition temperature [12]. The interest of PCL has been recently highlighted as platform for oral delivery of low molecular weight drugs [13]. This polymer has been also studied as a carrier for oral vaccines [14, 15], and also to entrap non-steroidal anti-inflammatory drugs [13] and estrogens [13]. Poly (ε-caprolactone) has also been blended with aliphatic polyesters [16, 17] to obtain microparticles of different biodegradability for the release of different drugs ;biodegradation of PCL is slow in comparison to other polymers, so it is suitable for long term delivery approaches, extending over a period of more than 1 year. PCL also has the ability to form compatible blends with other polymers, which can affect the degradation kinetics, facilitating tailoring to achieve the desired release profiles [18]. The advantages of PCL include its high permeability to small drug molecules, their failure to generate an acidic environment during degradation as compared to polylactides and glycolides, an exceptional ability to form blends with other polymers and degradation of PCL homopolymer being slow as compared to PLGA (polyglycolic acid-co-lactic acid) [19]/ making it more suitable for long term delivery systems extending to a period of more than one year [20]. Various categories of drugs have been encapsulated in PCL microparticles for their effective delivery. Microparticles can be prepared either by PCL [21] alone, or by using copolymers with PCL or ethyl cellulose because [22] Ethyl cellulose is biocompatible, nontoxic, non swellable and non-biodegradable polymer which releases the drug in sustained manner over an extended period of timeblends in order to obtain the desired release characteristics.

The fabrication of PCL microparticles from blends of PCL and ethylcellulose has also been studied. EC has extensively been used for microencapsulation due to its many versatile properties. Various techniques, mainly based on a one step emulsification process, have been used to prepare microparticulate sustained drug delivery systems [23]. Selection of the microencapsulation technique is primarily determined by the solubility of the drug and the polymer in various solvents systems [24].

Firstly the objectives of our work are to prepare PCL to entrap procaine HCl within PCL as a single (FIG1) polymer and as a blend ethylcellulose into microparticles, prepared by the oil/water (O/W) emulsion/solvent evaporation method; secondly to characterize the formulation in terms of a drug loading and release to compare the efficacy of polymers, morphology, size and physical state of both the drugs and the polymer.

2. EXPERIMENTAL SECTION

2.1. Materials and methods.

2.1.1. Materials.

Ethyl cellulose and gelatin from bovine skin (type B) emulsifying agent were obtained from (Sigma Aldrich), procaine HCl core material (Fluka chemika) and dichloromethane (DCM) was obtained from Aldrich.

2.2. Synthesis of polyester (PCL).

Synthesis of PCL: Poly (e-caprolactone) was produced by the ring opening polymersation of ε-caprolactone by adipic acidic (M_V= 16829,33 gr/mol) the conditions of reaction were reported in literature [19].

The PCL structure was shows in Figure 1, for all the text the procaine HCL was namely PR. HCl

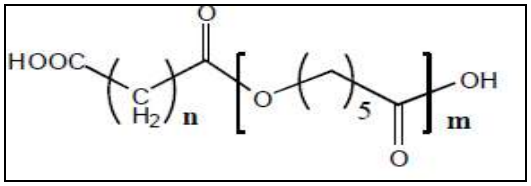

Figure 1. Structure of PCL (carboxyl end chains).

2.3. Preparation of Microparticles and tablets.

2.3.1.Microspheres.

The solvent evaporation technique which was used in this study is a simple process that is also inexpensive enough for scaling up to a commercial level [25] and many type of microspheres were developed [26], there are various methods used for the preparation of nanoparticles, including salting out method, solvent evaporation method, nanoprecipitation, and dialysis method, are widely used for lab scale as well as commercial purposes [27].

Microparticles of procaine HCl loaded PCL were prepared using modified Protocols [28, 29, 30] by a solvent evaporation method, firstly, 2g of PCL was dissolved in 20 mL of dichloromethane (DMC) and 0.5 g of procaine HCl was added to PCL solution (Table1). The PCL solution was mixed with 200 mL of 1 % (w/v) gelatin solution and stirred at 40 °C for 3H under continuous stirring at 645 rpm until the solvents were evaporated completely, and the prepared microcapsules were collected by filtering and watched 3 times with distilled water after microparticles were drying at room temperature(Figure2).

Table 1. Microspheres.

Formulations	**Ingredients**			
F1	PCL (2gr)	Dichloromethane 20ml	Gelatin(1%)	
F2	PCL(1gr) EC(1gr)	Dichloromethane 20ml	Gelatin(1%)	
	Tablets			
formulations	**Ingredients**			
	Mass of polymers	Mass of Discs	Mass of PR.HCl	pH
T1	PCL=140(mg)	143mg	60mg	1.2
	PCL=150(mg)	220mg	65mg	7.4
T2	PCL=73(mg) EC=72(mg)	178mg	61mg	1.2
	PCL=75(mg) EC=75 (mg)	199mg	63mg	7.4

Secondly a blend of polymers PCL (1gr) with EC (1gr) microcapsules were prepared by the same procedure the o/w emulsion /solvent (Figure 3).

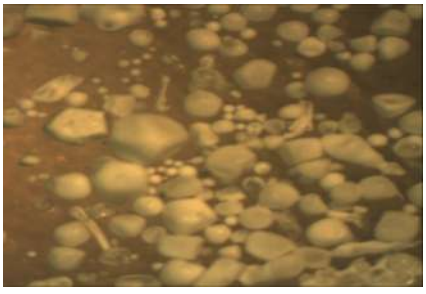

Figure 2. PCL microspheres.

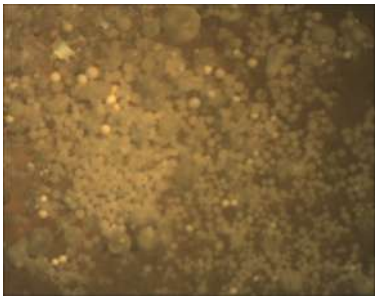

Figure 3. PCL/EC blend microspheres.

The discs were prepared by dispersion of the drug in matrix: PCL(2/3 ,1/3 ratio), or (PCL/EC (1/3,1/3,1,3 ratio), using

small amount of absolute ethanol; the discs were formed with a hydraulic press (Perkin–Elmer, Germany), and dried at room temperature to reach a constant weight.

2.3.2 Particles size analysis.

Particle size distribution of F_1 and F_2 microspheres were determined by using an image analyzer and the mean particles size was calculated by measuring 500 particles.

2.3.3. Determination of drug content.

The procaine hydrochloride content was determined by UV- spectrophotometer(JENWAY 7305) at a wavelength in 290 nm (pH=7.4) and 230 nm(pH=1.2),the molars extinction values were respectively (ε=17760, ε=11630 $Lmole^{-1}cm^{-1}$).

2.3.4. Percentage yield.

0,1 g of PR.HCl were dissolved in 100 mL of buffer solution pH=7.4;the solution was stirred from 24h, 1mL of the solution was transferred in flask and diluted with buffer solution ,and the absorbance of solution was measured with UV /vis spectrophotometer at 290 nm, using the buffer solution as a blank. The analysis was performed in triplicate.

The percentage of the production yield of microspheres percentage of drug (PR.HCl) content (equation 1) and , percentage of drug loaded (Equation 2) were calculated from the following formulas:

$$\%\text{Production yield}=\frac{total\,weight\,of\,drug\,in\,microspheres}{theoretical\,weight\,of\,drug\,in\,microspheres}\times 100 \quad (\text{Eq 1})$$

$$\%\ \text{PR.HCl loaded}=\frac{weight\,of\,PR.HCl\,in\,microspheres}{weight\,of\,microspheres}\times 100 \quad (\text{Eq2})$$

2.4. Microspheres characterisation.

2.4.1. Particle size particle size distribution of microparticles.

Size of the Microspheres Size distribution plays a very important role in determining the release characteristics of the microspheres. The size distributions in terms of average diameter of the microspheres were determined by the optical microscope method [32].

(F_1,F_2) were determined using an image analyzer (OPTICA 4083.B1).

2.5. PR.HCl-polymer interaction studies.

2.5.1.Infrared spectroscopy.

Interaction between drug-polymer was studied using ATR platinum Diamond spectrometer (the spectrum was scanned over a frequency range 4000-400cm^{-1}.

2.5.2.Differential scanning colorimetry [31].

DSC thermogram of microspheres was recorded using differential scanning calorimeter (NETZSCH DSC 204F1 PHOENIX) thermogram were obtained at scanning rate of 10°C/mn conducted over a temperature range of 0-400°C in the nitrogen environment.

2.5.3.X-ray powder diffractometry [31].

X-ray diffraction analysis was performed with an apparatus ,using nickel-filtered CuKα; data was collected in the continuous scan using step size 0,002°/23s ,the scanning rage was 0-70°C.

2.6. In vitro release studies.

The release rate of microspheres F_1,F_2, and discs T_1,T_2 were determined using dissolution testing apparatus ; the dissolution test were performed using 100ml for discs and 50 ml for microspheres of acidic solution (pH=1.2) and basic solution (pH=7.4) at 37°C±0,5 and at 500 rpm. Microspheres equivalent, to 100 mg of F_1,F_2 were used for the test .1mL of medium solutions were withdraw from dissolution apparatus at predetermined time points for 400 mn after appropriate dilution, after wards the released drugs were determined by UV spectroscopy at a wavelength in 290 nm ,for basic buffer solution and 230 nm for acidic buffer solution. The measurements were performed in triplicate and average values were considered for data analysis.

3. RESULTS SECTION

3.1. Encapsulation efficiency and particle diameter.

The production yield and encapsulation efficiency of PR.HCl loaded microparticles are shown in Table 2.

% yield of F1 formulation is low than F2, this mean that the quantity present of PCL was insufficient to cover the drug completely and we noted that the mean diameter size were increase when we introduced the ethyl cellulose in formulation F_2, this result was due to molecular weight of ethylcellulose and hydrophobicity of PCL. Viscosities of dispersion phase also play a role in determining particle size of the different formulations , the particles size were proportional with dispersed phase viscosities [33].

A bigger droplets were formed and mean particle size increased when the viscosity of dispersed phase present high viscosity. The formulations containing ethylcellulose matrix showed higher viscosity [33]. The F2 formulation present an increasing of mean size diameter, than F1 this result is consistent with NahlaS Barakat [34].

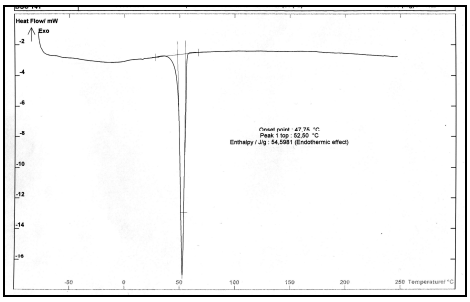

Figure 4. DSC thermogram of PCL

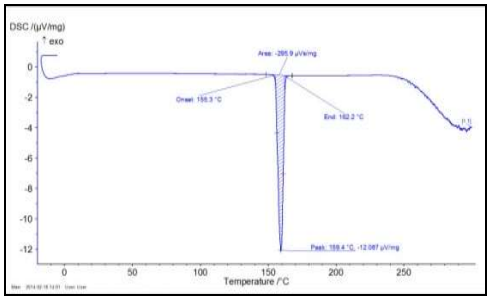

Figure 5. DSC thermogram of pure drug.

3.2. Diferential scanning calorimetric studies.

The thermograms of PCL (Figure 4) and of pure drug (PR.HCl) (Figure 5) loaded microspheres F_1 F_2 (Figures 6, 7) were taken.

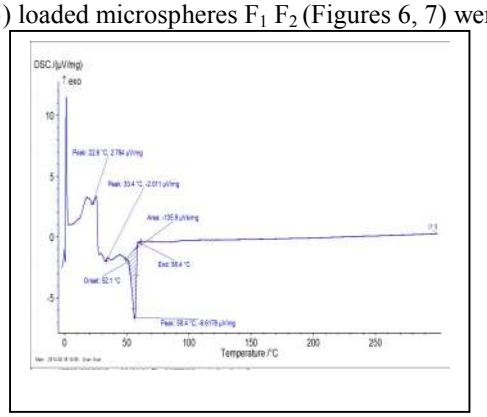

Figure 6. DSC thermogram of F1.

A large melting peak was observed for procaine hydrochloride at 159,4 °C ,corresponding for to its melting transition point. The melting peak was absent on the DSC thermogram of PCL microparticles F_1, and we noted the peak corresponding to PCL melting present in Figure 4 of pure polymer. The same observations were noted for F2 formulation, these results suggest that the presence of drug in formulations F1,F2 was in amorphous form. This phenomenon was confirmed by X-ray diffraction patterns (Figure 8).

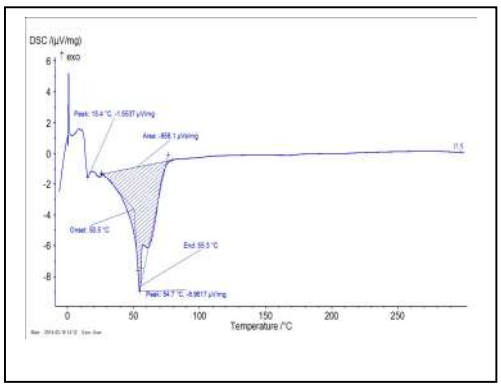

Figure 7. DSC thermogram of F2.

The figure 8 showed that the crystal peak of procaine hydrochloride is clearly observed in Figure 5 (PR.HCl) by X-ray data peak ,however , the diffraction patterns of pure PCL and the PCL microspheres containing PR.HCL (F1) and the PCL-EC blend microspheres were similar These microspheres did not contain any peaks associated at procaine hydrochloride crystals peaks, it's confirmed that the drug was in amorphous part in the PCL(F1) and PCL-EC (F2)blend ,not in the crystalline region.

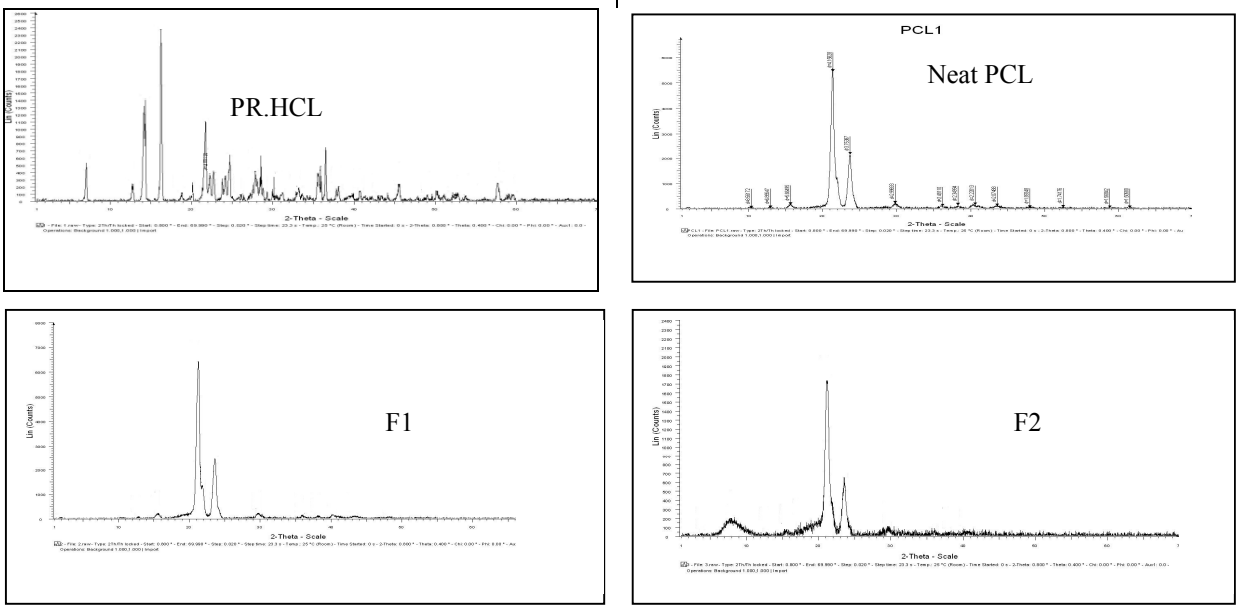

Figure 8. X-RAY diffraction patterns obtained from PR.HCl,neat PCL, F1, F2.

Table 2. Microspheres ,encapsulation and characteristics results.

	Polymers			Mean diameter (µm±SD)				Yield%	%Drug loaded
	PCL	EC	PR.HC	d10/ µm	d32/ µm	d43/ µm	Dispersion[m]		
F1	2/3	0	1/3	152,11 ±1.5	176,73 ±1.76	188 ±1.2	1.23	30%	3
F2	1/3	1/3	1/3	32.22	47.42	72.29	1.19	40%	1.3

3.3. IR spectrophotometry.

IR spectra were employed to confirm the compatibility and interaction of the matrix and active agent[35] in this purpose the interaction of procaine HCl with polycaprolactone and ethyl cellulose used to prepare the microspheres. The IR spectrum of pure drug showed characteristics peaks at 3200-3334 cm^{-1} due to the NH stretching bond ,aromatic CH stretching mode ,at 3100cm^{-1} ,C=C aromatic stretching at 1602 cm^{-1} , aromatic CH stretching mode (2950 cm^{-1}). We noted no difference between the spectra of procaine HCl loaded microspheres (F_1,F_2), a similar peak characterized the O=C-O-R at 1450 cm^{-1} was present in spectrum

of procaine HCl, $F_1$and F_2 formulations. In the short the microparticles prepared with different polymers blends had significant characters of PR.HCl in the IR spectra, suggesting there were no reactions between the drug and PCL, EC and had a good stability in formulations used (Figure 9).

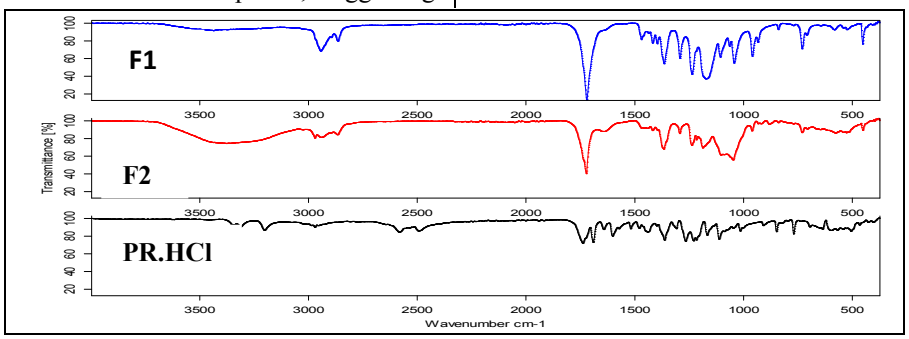

Figure 9. IR spectra of pure drug(PR.HCl) and microspheres PCL(F1) and F2(PCL-EC)blends.

3.4. *In vitro* release studies.

It well known that microspheres, prepared by single, emulsion evaporation, method present initial burst effect release [38] due to surface encapsulated substance. In vitro release of PR.HCl from F_1,and F_2 formulations were compared with disc T_1,T_2 in pH=2 and pH=7;4 buffer solutions; simulate the gastro intestinal tract conditions, the results obtained from dissolution studies of drug for 400 nm are shown in Figure 10 for F1 (PCL) in different pH.

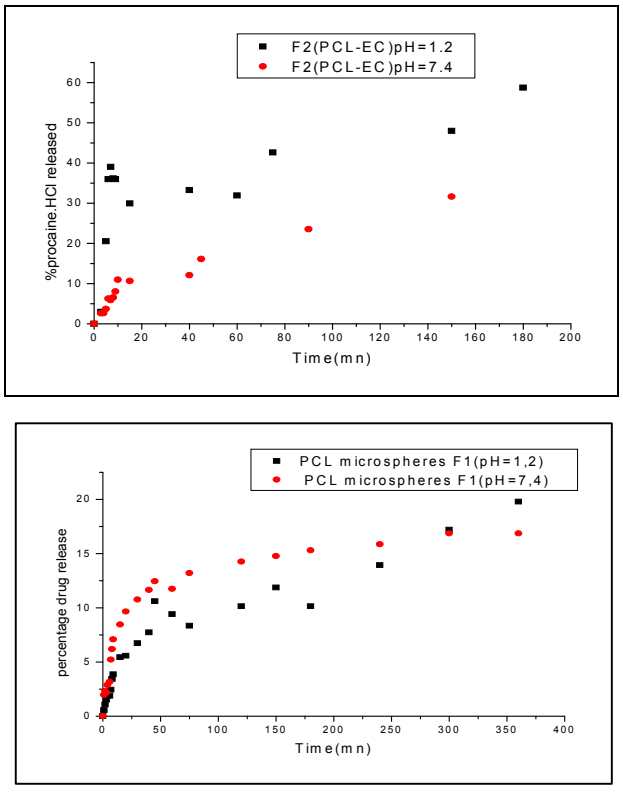

Figure 10. Release profile of PR.HCl from F_1,F_2,microspheres in pH=1.2 and pH=7.4.

For controlled release of drugs, the figures showed that the release of procaine HCl were faster in acid medium from F1,F2, and T1,T2 discs suggests the diffusion of procaine HCl from these systems may be favored by its solubility in acidic medium, at the initial stage the burst effect related to the procaine. HCl is very small in all release formulations, this phenomenon was due probably to the low permeability and hydrophobicity of PCL of the water, the crystallinity of polymers and a molar mass had an important effect in releasing the drug and the penetration of water into amorphous region.

In Figure 10, we showed that the result of introduction of EC in formulation (F2), the percentage of delivery of the drug was increased than F1 containing only PCL in formulation, it changes from 20% (F1) to 60% (F2), its due at the high crystallinity of PCL than EC was an important factor for diffusion and delivery systems of procaine HCl. The ethylcellulose facilitate the relaxation of polymers chain by, consequent an increased diffusional path, length and consequent retardation in drug release.

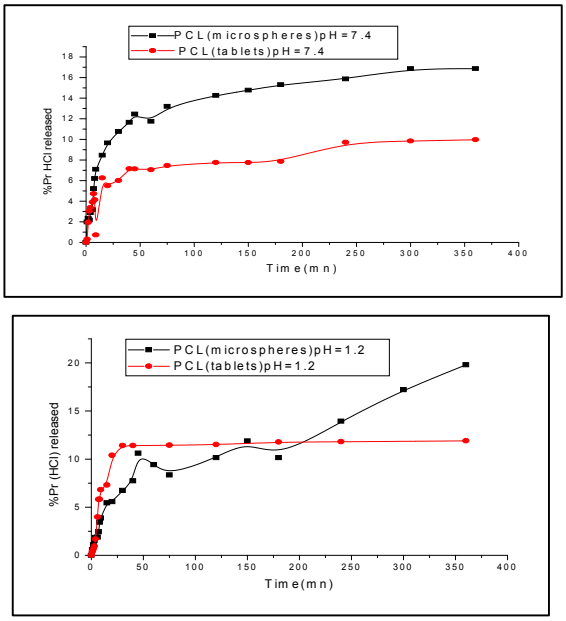

Figure 11. Release profile of PR.HCl from F1microsphere and discs T_1 in pH=1.2 and pH=7.4.

We noted in the Figure 11 and Figure 12 that the delivery systems of drug is very important, in the microspheres (F_1, F_2) than discs (T_1, T_2) its due to the surface of contact of microspheres with buffer solution is more pronounced than in tablets.

This property, favors the drug delivery systems, which indicate the release mechanism its diffusional system and not to a degradation, of PCL or EC [36, 37] polymers.

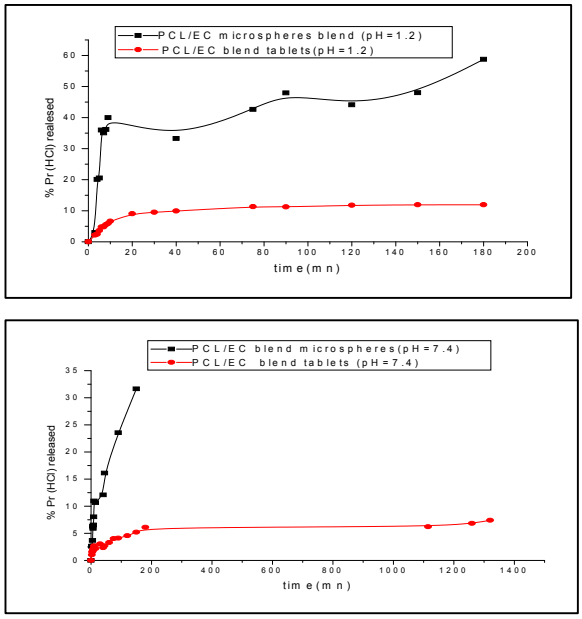

Figure 12. Release profile of PR.HCl from F_2microspheres and disc T_2 in pH=1.2 and pH=7.4.

3.5. Mathematical models of release kinetics.

For understanding the mechanism of kinetics of drug release, the results of in vitro drug release study were fitted with various kinetic equations like zero order (Eq 3), first order (Eq4), higuchi model:this model describes drug release as a diffusion process based on Fick's law: (Eq5); in order to define the appropriate model for different formulations and krosemeyer-Peppas model (eq 6) [39].

Zero order model: M_0-M_T=k_0t ……Eq 3

First order model: ln(M_0/M_t)=K_1t ……Eq4

Higuchi model: M_t=K_H $t^{1/2}$ ……Eq 5

Krosemeyer-Peppas model $M_t/M_\infty = Kt^n$

Were M_0, M_t correspond to drug amount taken at time equal at zero dissolved at particular time t respectively , the terms K_0, K_1, K_H refer to release kinetic constants obtained from linear curves of zero order, first order, and Higuchi model respectively.

After having tested 0, 1, 2 order release kinetics not correspond to any order used, this result shown that the diffusion kinetics the table below gives the results obtained from the equation of higuchi from F1, F2 (microspheres) and T1, T2 (tablets).

The release rate increases when PCL is used in all formulations, and it less than the EC matrix. The effect of acidic pH on the values of KH dissolution rate is important than values obtaining in pH=7.4 for tablets.

This result was observed in release rate of microspheres, the formulation containing PCL is the kinetic constant is considerable by comparing the kinetic constant of a formulation F2 (Figure 13,Table 4).

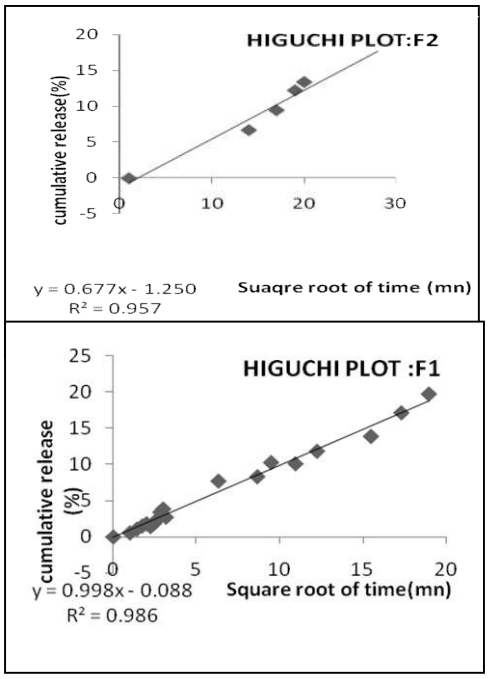

Figure 13. Higuchi plot of optimized batch (F1, F2).

Table 4. Comparison of coefficients of correlation and dissolution rate constants of procaine HCl from tablets (T1, T2).

Formulations	Higuchi plots		Krosmeyer Peppas plots	
	K_H	R^2	n	R^2
T1	0.375	0.993		0.831
T2	0.292	0.941		0.328

To determinate the mechanism of drug release, time profiles have been fitted with Ritger and Peppas $Mi/M\infty = Kt^n$, where $Mi/M\infty$ is the fraction of drug released at time, K is a kinetic rate constant and n is diffusional exponent characterizing the mechanism of drug release: (n=0;5, fickian diffusion, n>0.5: anomalous or non Fickian diffusion, n= 0.8 -1 release Kinetics is prevalent).

The Table 4 presented the n, and correlations coefficients, T1, T2 showed non fickian diffusion, the kinetics probably follows zero order type of release. (Table 4, Figure 14).

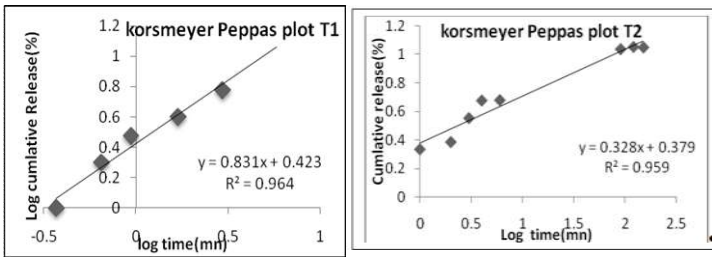

Figure 14. Krosmeter peppas plots of optimized batchs T1, T2.

4. CONCLUSIONS

Procaine HCl microspheres were successfully prepared by solvent evaporation method using polycaprolactone modified by chain carboxyl for more responsive, and ethyl cellulose, this investigation has provide an understanding of the effects of some parameters when EC was added in formulation with PCL on particle size, the drug loaded and yield of encapsulation.

For microspheres prepared with PCL are not spherical shape, but from formulation containing EC we noted a spherical shape and absence of aggregates, the yield was more important than PCL microsphers, this result suggest that the crystalline microstructure of PCL microsphers plays an important role in its drug release behavior. Finally the release drug used PCL matrix is very faster than PCL-EC blend matrix; it can reduce dosing frequency, decrease side effects and improve patient compliance.

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