Bull. Pharm. Sci., Assiut University
Vol. 16, Part 1, PP 63-72

SUSTAINED RELEASE FORMULATIONS OF PHENAZOPYRIDINE HYDROCHLORIDE WITH CELLULOSE ACETATE PHTHALATE

A.M. Aly, S.M. Ahmed, S.I. Abdel-Rahman, S.I. Saleh and A.E. Aboutaleb

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt.

ABSTRACT

Cellulose acetate phthalate (CAP) was utilized for the preparation of sustained release formulations of phenazopyridine hydrochloride (PHCl) by three different techniques: (a) solid dispersion (coprecipitation), (b) microencapsulation by phase separation coacervation using non-solvent addition technique and (c) pan coating. The three techniques studied resulted in different extents of sustaining the release of PHCl, in vitro, compared to the untreated drug. Pan coating proved to be the easiest and most convenient technique for the preparation of sustained release PHCl microcapsules. With regard to the release kinetics of PHCl from each of the formulations prepared, the first order model was found to be the most suitable mechanism describing the release of the drug.

INTRODUCTION

PHCl is is used mainly as urinary antiinflammatory. This drug is usually provided in very fine crystals which are quickly excreted into urine and a considerable proportion of the dose is metabolised to an inactive form[1]. Large doses are evidently required to exert the therapeutic effect. On the other hand large doses may cause gastrointestinal irritation and sometimes may give rise to renal stones of phenazopyridine[2]. Sustained release formulations may be the solution for these problems.

Among the diversed techniques usually used for sustaining the release of drugs is the solid dispersion of the drug in water insoluble carriers[3,4]. Microencapsulation in which small entities are wrapped in individual protective coatings may be designed to protect or aid in storage and handling in addition to prolonging the action of the encapsulated drug[5]. Phase-separation coacervation is one of the oldest and commonly used techniques for encapsulating water soluble or insoluble liquids, solids or suspensions[5]. Coacervation may be achieved by non-solvent addition[6,7], temperature change, salt addition or any other process. Moreover, pan coating technique may be utilized for the preparation of microcapsules[8]. The aim of this work was to sustain the release of PHCl using three different techniques including coprecipitation, microencapsulation and pan coating. In addition to presenting the solution for the above mentioned problems of PHCl conventional dosage forms, sustained release PHCl formulations could have other advantages such as producing more uniform action and reducing dose frequency which in turn improves patient compliance.

EXPERIMENTAL

Materials

-Phenzopyridine hydrochloride (United works of Pharmaceuticals and Diatetic Products, Budapest, Hungary).

-Cellulose acetate phthalate (Estman Chemicals Kodac, Rochester, New York, U S A).

-Chloroform, diethylether and acetone of analytical grades (El-Nasr Chem. Co., Cairo, Egypt).

Methods

Preparation of the matrices

The procedure followed was similar to that described by Ahmed *et al*[3]. PHCl (2 g) was completely dissolved in 100 ml of ethanol (95 %), and CAP (2, 4 or 6 g) was dissolved in 30 ml of acetone:ethyl alcohol mixed solvent (1:1 V/V). The two solutions were then mixed. A sheet consisting of the drug dispersed in the polymer matrix was obtained by evaporating the solvents at room temperature and milling the residue using a mortar and a pestle. The resulting particles were sieved and the 125 - 200 μ size fraction was collected.

Microencapsulation by non-solvent addition

The specified weight of CAP (6, 9 or 12 g) was dissolved in 100 ml of acetone:ethanol (1:1 V/V) mixture. An equal weight of PHCl, to that of the polymer, was suspended by stirring for 30 minutes using a magnetic stirrer. This suspension was then added dropwise (90 drop/min.) to diethylether (the non-solvent) in a beaker while stirring at 550-600 rpm. The microcapsules obtained were washed twice with diethylether, collected on a filter paper and dried at ambient temperature for 24 hrs. The microcapsules were then sieved to collect the 125 - 200 μ size fraction.

Pan coating technique

PHCl particles (20 g) were introduced into a stainless steel coating pan mounted on a shaft driven by an Erweka varying speed motor (Erweka Apparatebau, Frankfurt, Germany) rotating at 30 rpm. The coating solution, 20% CAP in acetone, was sprayed onto the rotating bed of PHCl powder from a spraying gun (Busch, PSP 260, Robert Bosch, GmbH, Germany). About 20 ml of the solution was delivered for each layer of coating which was followed by intermittent drying by hot air directed onto the pan, care has been taken to prevent loss of fine cores. The prepared microcapsules were fractionated into suitable size ranges: 80-125, 125-200, 200-250 and 315-400 μ.

Evaluation of the products

Scanning electron microscopy

Samples of PHCl-CAP microcapsules (125-200 μ) prepared by pan coating technique, as an example, were mounted onto stubs using double sided adhesive tape and vacuum-coated with a gold film (approximately 30 nm in thickness).

Determination of drug content

Acetone (10 ml) was added to an accurately weighed amount (25 mg) of each of the prepared formulations with shaking to dissolve CAP. 200 ml of distilled water was then added. The amount of PHCl was determined by measuring the absorbance of the filterate at 434 nm.

Dissolution studies

Samples (25 mg) of each product were introduced into the cups of USP dissolution apparatus (Erweka DT-6, Erweka Apparatabau, Frankfurt, Germany). The dissolution medium was 900 ml of 0.1 N HCl (pH 1.12), the temperature was kept at 37±0.2° and the stirring rate was 100 rpm. Samples of 5 ml were withdrawn at suitable time intervals using filtering pipettes and assayed spectrophotometrically at 434 nm.

RESULTS AND DISCUSSION

Physical properties and drug content

Scanning electron microscopic observations of the microcapsules prepared by pan coating technique revealed that these microcapsules were irrigularly shaped with round edeges and surrounded with a layer of the coating material (Fig. 1, A). Magnifying a part of the wall of a microcapsule showed some pores in the surface of these microcapsules (Fig. 1, B).

Table 1 shows the reproducibility of the solid dispersion method for preparing PHCl-CAP matrices. No or very little loss of drug was observed during the preparation. On the other hand, some loss was observed in case of the microcapsules prepared by coacervation technique which may be attributed to the solubility of some of the drug in the manufacturing vehicle. The drug content of the PHCl-CAP microcapsules prepared by pan coating was 49 % which indicated that 1:1 core:coat ratio was successfully obtained.

Release studies

Figs. 2-4 showed that all the tested formulations prolonged the release of PHCl at pH 1.12 compared to the release of PHCl powder. Pan coating technique gave rise to the most prolonged release PHCl microcapsules. Increasing the microcapsule particle size led to more delayed release of PHCl from these microcapsules (Fig. 4). This may be attributed to the accompanied decrease in the surface area[8]. Microcapsules prepared by coacervation technique (Fig. 3) showed faster release of PHCl than those prepared by the other two techniques. Increasing the proportion of CAP in these microcapsules resulted in a more prolonged release of the drug. This was also the same in the case of PHCl-CAP matrices which showed intermediate prolongation of PHCl release compared to the coacervated or the pan coated microcapsules. The extent in the prolongation of the release of PHCl and the effects of the different factors on this release could also be indicated from the T_{50} and T_{80} values given in Table 2.

Release kinetics

As shown in Figs. 2-4, all the tested formulations exhibited dissolution profiles of parabolic shape indicating that zero order release model is not applicable. On the other hand, upon plotting the logarithm of the percent of the drug remaining as a function of time, true linear relationships were obtained for all the tested formulations as shown in Figs. 5-7. This indicates that the release of PHCl from these formulations could follow first order release kinetics. This could be also confirmed by the correlation coefficient values listed in Table 2. The release data of the prepared formulations were also treated according to Hugchi[9] equation. Linear correlations were obtained for the matrices and the coacervated microcapsules only which was confirmed by the higher values of the correlation coefficients of these two types (Table 2).

CONCLUSIONS

From the results obtained throughout this study, it could be concluded that :

- CAP and the three techniques applied (solid dispersion, microencapsulation and pan coating) gave rise to a relative sustaining in the release of PHCl compared to the untreated drug. Pan coating technique was superior in this respet.

- The release profiles of the matrices or the microcapsules were

found to be affected by the proportion of the polymer (CAP) and the particle size of the product.

The first order release kinetics were found to be the most suitable model for explaining the release of PHCl from the prepared formulations.

Table 1: The percentage of drug loss during the preperation of PHCl-CAP formulations

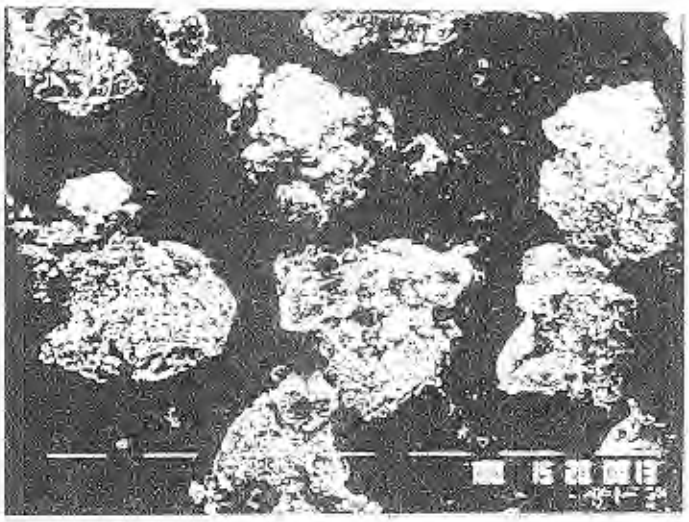
Formula			Theoretical % of drug	Actual % of drug	% of drug entrapped
Coprecipitated matruces of PHCl-CAP	Drug: Polymer ratio	1:1	50.0	48.3	96.6
		1:2	33.3	34.9	104.8
		1:3	25.0	24.0	96.0
Coacervated microcap. of PHCl-CAP	%of drug and polymer 1:1	6%	50.0	44.7	89.4
		9%	50.0	41.3	82.6
		12%	50.0	36.4	72.8
Pan-coated microcap. of PHCl-CAP	Drug Polymer ratio	1:1	50.0	49.3	98.6

Table 2: Kinetics of phenazopyridine HCl release from the prepared sustained release formulations.

Formula			Higucht: Initial phase r	Initial phase $k_H(h)^{-½}$	Initial phase A	Higucht: Terminal phase r	Terminal phase $k_H(h)^{-½}$	Terminal phase A	First-order r	First-order $K_F(h)^{-1}$	t_{50}	t_{80}
Coprecipitated matrices of PHCl-CAP	Drug: Polymer ratio	1:1	0.992	10.502	30.472	0.999	2.896	72.008	-0.995	3.974	10.463	24.308
		1:2	0.985	9.628	31.416	0.999	2.692	70.812	-0.986	3.508	11.853	27.537
		1:3	0.998	6.063	46.600	0.994	3.397	59.216	-0.993	2.984	13.934	32.373
Coacervated microcap. of PHCl-CAP	drug and polymer con.	6%	0.991	14.382	18.349				-0.993	5.901	7.026	16.323
		9%	0.976	12.067	18.343				-0.999	4.276	9.677	22.481
		12%	0.997	12.134	18.536	0.992	3.638	62.881	-0.985	3.588	11.589	26.923
Pan-coated microcap. of PHCl-CAP	micro cap. size	80-125 μm	0.958	9.016	12.733				-0.999	2.520	16.500	38.333
		125-200 μm	0.970	10.162	8.107				-0.999	2.346	17.724	41.176
		200-250 μm	0.981	9.123	-0.539				-0.997	1.382	30.087	69.899
		315-400 μm	0.989	9.571	-8.323				-0.996	1.209	34.392	79.901

k_H and k_F were the release rate contants of Higuchi and first order, respectively, t_{50} and t_{80} were time (min.) required for releasing 50 or 80% of the drug respectively, and was calculated from first order equation.

(A)



(B)

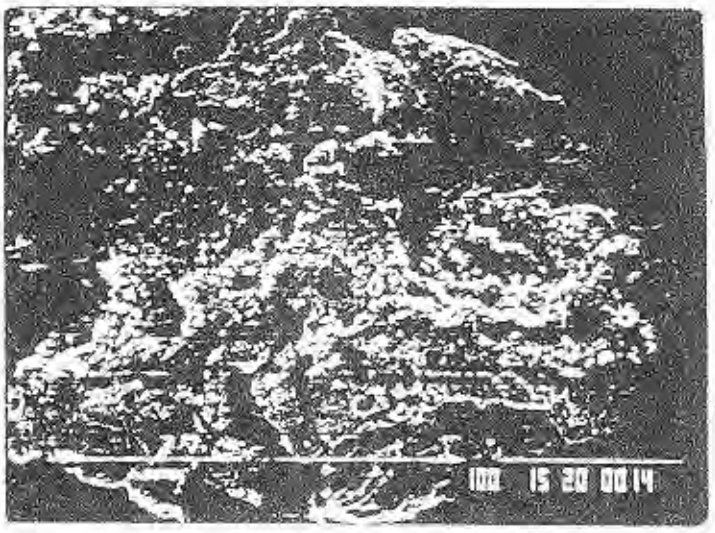


Fig. (1) : Scanning Electron Micrography of PHCl-CAP microcapsules (125-200 μm) prepared by pan-coating [A], and magnified part of the surface of microcapsule [B].

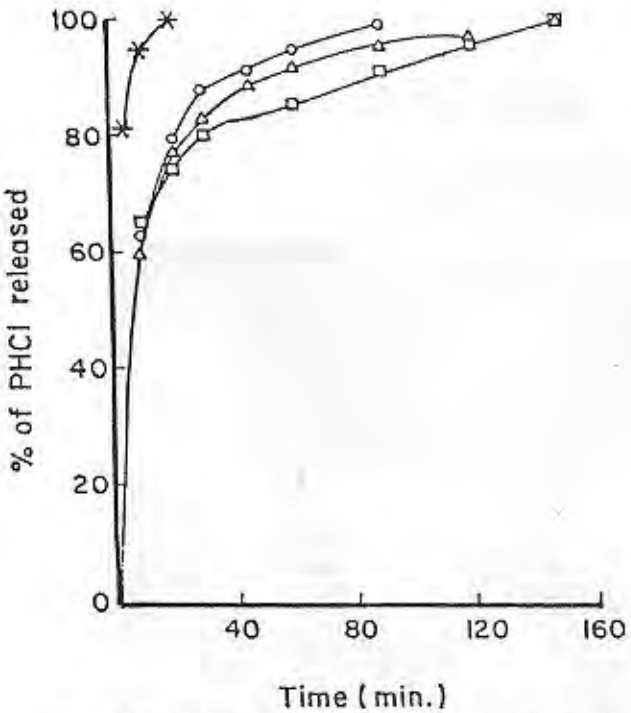


Fig. (2) : The release profiles of PHCl-CAP matrices at pH=1.12

key : (*) PHCl powder, PHCl : CAP ratios 1:1 (O), 1:2(Δ), 1:3 (□)

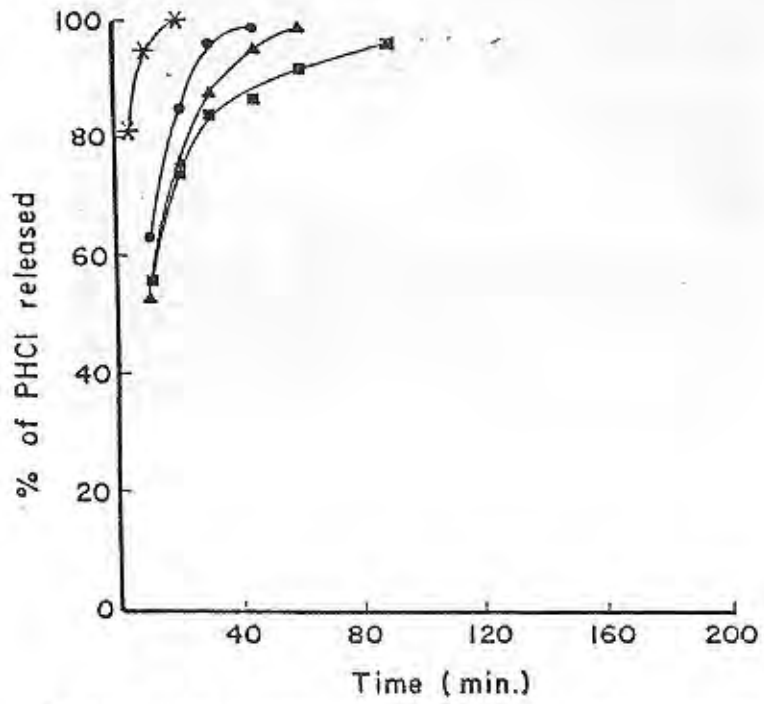


Fig. (3) : The release profiles of PHCl microcapsules. (at pH=1.12).

Key : PHCl powder (✳).

Each of PHCl and CAP : 6% (●), 9% (▲) and 12% (■)

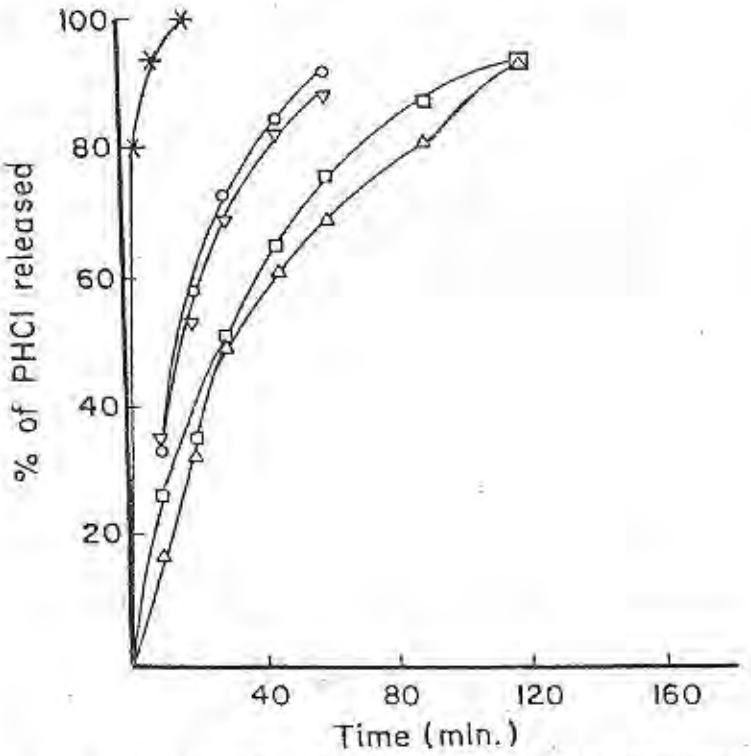


Fig. (4) : The release profiles of PHCl-CAP microcapsules of different sizes prepared by pan-coating (at pH=1.12). Key: PHCl powder (*),80-125 μm(o), 125-200 μm(▽), 200-250 μm(□), 315-400 μm (Δ).

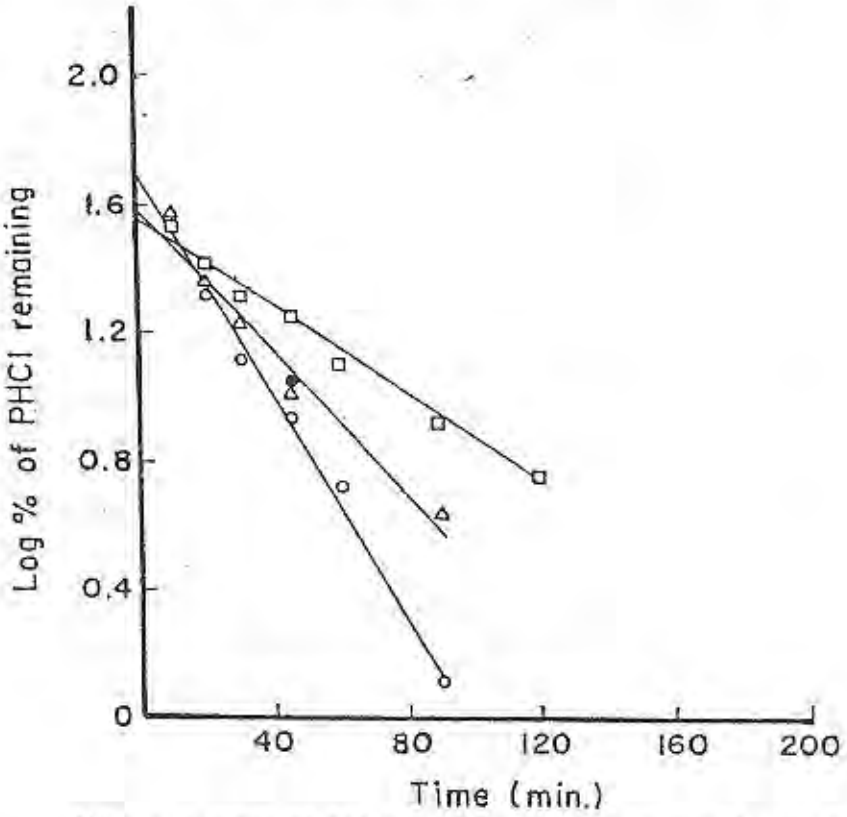


Fig.(5) : Plots of the logarithm of the percent of the drug remaining versus time for PHCl-CAP materices of 1:1(O),1:2(Δ), 1:3(□) , at pH=1.12.

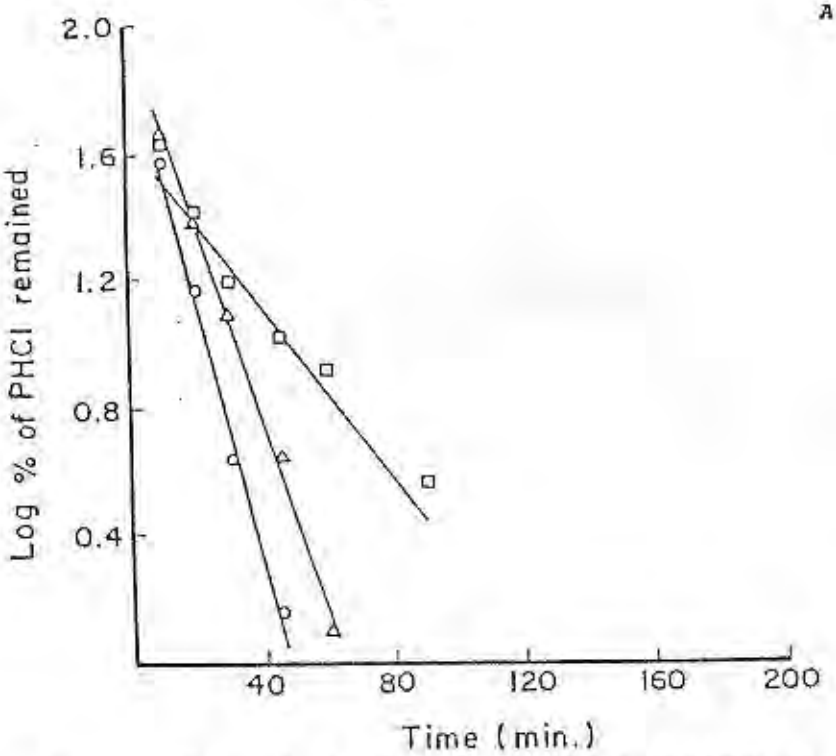


Fig.(6) : Plots of the logarithm of the percent of drug remaining versus time for PHCl microcapsules prepared with different concentrations of drug and polymer (PMM or CAP) in the solvent.
Key: Each of PHCl and CAP of 6% (o), 9%(Δ) and 12%(□)

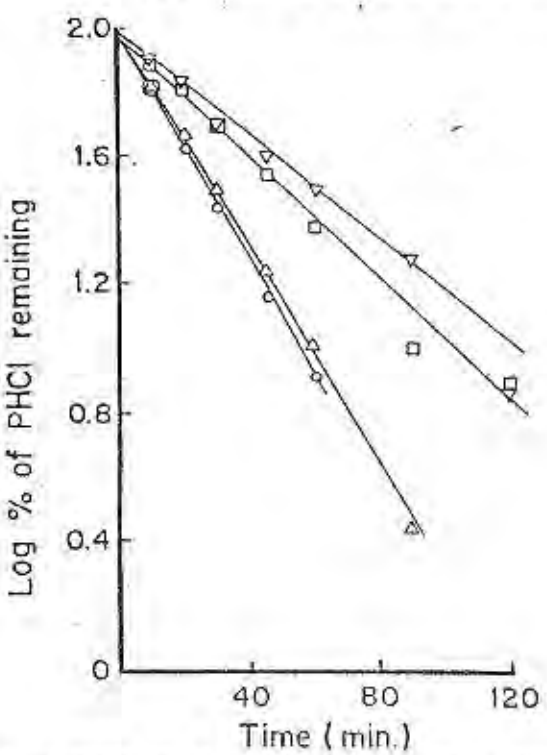


Fig.(7) : Plots of the logarithm of the percent remaining of the drug versus time for PHCl-CAP microcapsules of different sizes prepared by pan-coating (at pH=1.12).
Key: 80-125 μm (o), 125-200 μm (Δ), 200-250 μm(□), and 315-400 μm (▽).

REFERENCES

1-W.J.Johnson and A.J.Chartrand, Toxicol. Appl. Pharmacol. 37, 371 (1976).

2-S.C.Harvy, in Remingtons Pharmaceutical Science, 16th Ed., Mack Publishing Co., Easton (1980), p. 1099.

3-A.Hasegawa, A.Kawamura, H.Nakagawa, and I.Suginoto, Chem. Pharm. Bull., 34, 2183-2190 (1986).

4-S.M.Ahmed, S.I.Saleh, S.I.Abdel-Rahman, S.H.Khidr, A.E.Aboutaleb and A.M.Ali, S.T.P. Pharma Sciences, 2, 205-209 (1992).

5-L.A.Luzzi, J. Pharm. Sci., 59, 1367 (1970).

6-M.Donbrow, S.Benita and A.Hoffman, Israel, patent application 70431, (1984).

7-M.Donbrow, S.Benita and S.Benita, J. Pharm. Pharmacol.,40, 93-96 (1988).

8-S.C.Porter, C.H.Bruno and G.J. Jackson, in "Pharmaceutical dosage form tablets", Eds. Marcel Dekker, New York, (1982), p. 73.

9-T.Higuchi, J. Pharm. Sci., 52, 1145-1149 (1963).

تحضير تركيبات ممتدة المفعول من الفينازوبيريدين هيدروكلورايد باستخدام سليولوز اسيتات فيثالات

عادل محمد محمد على - سيد محمد احمد - سيد ابراهيم عبد الرحمن
صالح اسماعيل صالح - احمد السيد ابو طالب
قسم الصيدلية الصناعية - كلية الصيدلة - جامعة اسيوط

تم فى هذا البحث استخدام سليولوز اسيتات فيثالات لتحضير تركيبات ممتدة المفعول من عقار الفينازوبيريدين هيدروكلورايد.

وقد تم عمل ذلك باستخدام ثلاث طرق مختلفة وهى:-
أ- طريقة التشتت الصلب (الترسيب المتزامن).
ب- تحضير حويصلات العقار فى البوليمر (طريقة اضافة سائل غير مذيب).
ج- طريقة وعاء التغليف.

وقد نتج عن استخدام هذا البوليمر وبالطرق الثلاثة المذكورة تركيبات لها معدلات انطلاق بطيئة نسبيا مقارنة بالعقار الغير معامل وقد تباينت الطرق الثلاث فى قدرتها على إطالة زمن انطلاق العقار وعليه اظهرت طريقة وعاء التغليف تفوقا فى هذا المجال. وكذلك قد وجد ان معدل انطلاق العقار يتأثر بنسبة البوليمر المستخدم وكذا حجم الحويصلات المحضرة.

أما فيما يخص ميكانيكية انطلاق الدواء من التركيبات المحضرة فقد وجد أنها تخضع لمعادلة الدرجة الاولى بينما يمكن أن يخضع بعضها لمعادلة هيجوشى كذلك.

Received in 13/12/1992 & Accepted in 4/3/1993