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EFFECT OF CELLULOSIC POLYMERS ON THE PHYSICAL PROPERTIES AND DISSOLUTION OF IBUPROFEN GRANULES

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ABSTRACT

Ibuprofen sustained release granules were prepared using cellulosic polymers including, ethylcellulose 20, hydroxypropyl methyl cellulose (Pharmacoat 606) and hydroxypropyl methyl cellulose phthalate (HP 55 F). Polyvinyl pyrrolidone (PVP) was used also as a granulating agent for comparison.

Increasing the concentration of the granulating agents investigated lead to retardation of the drug release rate except for Pharmacoat 606. Ethyl cellulose 20 in 5% w/v concentration proved to be the best retardant for ibuprofen release rate from the prepared granules.

The physical properties of ibuprofen powder, ibuprofen granules as a control and ibuprofen granules granulated with 5% w/v ethyl cellulose 20 were examined and including the size range, the angle of repose, the flow rate, the bulk density, the Hausner factor, the compressibility, the friability and the parameters of Kawakita.

The effect of particle size of ibuprofen granules prepared by 5% w/v ethyl cellulose 20 as a granulating agent was checked. Increasing the particle size of the prepared granules lead to more prolongation in ibuprofen release rate.

INTRODUCTION

Beside the sustained release tablet and capsule preparations, newer drug delivery systems, like microcapsules, granules and micropellets are under extensive investigations. Tanaka *et al.*[1] first reported a gelatinised micropelleted dosage form for sulphanilamide and riboflavin in order to prolong the action of these drugs. Similar formulation for indomethacin[2] has been also reported. The development of micropelleted sustained release dosage form of theophylline has been accomplished using ethyl cellulose as a polymer[3]. The formulation of controlled release matrices of anhydrous theophylline maleate and acetaminophen using ethyl cellulose, surelease and colorcon as granulating agents has been investigated[4]. The dissolution behaviour of isoniazid, vitamin B_6, trimebutine maleate and theophylline from ethyl cellulose microcapsules has been reported[5]. The effect of molecular weight of ethyl cellulose on the drug release properties had been also demonstrated[6]. It was reported that microcapsulated formulation of indomethacin using gelatin acacia complex coacervation technique, significantly reduced the incidence and severity of GIT side effects[7].

Ibuprofen is a non-steroidal antiinflammatory analgesic and antipyretic drug. The present work represents the preparation of ibuprofen sustained release granules using ethyl cellulose 20, Pharmacoat 606, HP 55 F and PVP as granulating agents. The physical properties of the optimum sustained release granules, in terms of drug retardation, have been investigated. Furthermore, the effect of particle size of these granules on ibuprofen dissolution rate has been also demonstrated.

EXPERIMENTAL

Materials:

The following materials were used:

Ibuprofen (Francis S.P., Via origgio, (AV), Italy).

Cellulosic polymers used as granulating agents were ethyl cellulose 20, hydroxypropyl methyl cellulose 606 (Pharmacoat 606) and hydroxy propyl methyl cellulose phthlate (HP 55 F), (Laserson & Stabetay, 14 Rue Jean Ponal, Paris, France).

Polyvinyl pyrrolidone (PVP), (Prolabo, 12 Rue Peleé, F. 75011, Paris).

The following chemicals were of analytical grade and were used as received dibasic sodium hydrogen phosphate ($N_2HPO_4.12H_2O$), sodium chloride, hydrochloric acid (37%), ethanol (95%) and acetone (Prolabo Co., 12 Rue Peleé, F. 75011, Paris, France).

Equipment:

Dissolution apparatus according to the Second European Pharmacopoeia, Erweka FGS apparatus for making wet granulation (Erweka apparatebau GMbH, Germany).

UV/VIS spectrophotometer 550 (Perkin Elmer Co., Ltd).

Primax mixer (Kl. Kupper, Labor-und Elektronische Gerate, G 5357 Swisttal 3 (b. Bonn, Germany).

Mettler balance (Mettler H 35 AR, Germany).

Set of sieves.

Turbula mixer (Willy A. Bachoffen Maschinen Febrick, Basel, Switzerland).

Methods:

Preparation of ibuprofen sustained release granules:

The specific quantity of ibuprofen finely powdered was mixed with different concentrations (1, 3 and 5% w/v) of alcoholic solutions of ethyl cellulose 20, Pharmacoat 606, HP 55 F and PVP for five minutes. The mass was then granulated in the Erweka granulator through 2 mm mesh screen. The resulted granules were left in a desiccator for 24 hours and then passed through 1 mm mesh screen.

Dissolution rate studies:

The Erweka dissolution apparatus with a rotating paddle at 50 rpm was utilized. An amount of granules containing 100 mg of the drug was placed in 1000 ml of the dissolution medium which was previously degassed and warmed to 37°C. The water bath of the dissolution apparatus was also maintained at 37°C. At specific time intervals, 5 ml aliquots were withdrawn from the dissolution medium and were replaced by equal volume of fresh medium of the same pH. The withdrawn samples were filtered to remove any particulates and assayed for ibuprofen content at 222 nm using the UV/VIS spectrophotometer after doing suitable dilutions. This was normalized for the total ibuprofen content in the assayed granules. All assays were done in four replicates to determine the reproducibility of the method and the mean was considered in the calculations.

The pH of the dissolution medium was adjusted to pH 1.5 then 100 ml of the dissolution medium was taken every one hour and was replaced by the same volume of solutions of pH 7.5 "shift dissolution method". Thus the change in the pH of the dissolution medium during the dissolution experiment was: 1.5, 2.3, 5.9, 6.7, 7.1, 7.2 and 7.3.

Evaluation of the physical properties of the prepared granules:

1- Particle size: The mean particle size and the variation around this mean value "particle size distribution" was made by sieving according to the method described by Bolhuis and Lerk[8].

2- Bulk density: The bulk densities of the materials investigated were determined using measuring cylinders 100 ml capacity as follows: 50 g of powder or granules was allowed to flow freely into the measuring cylinder. Tapping was carried out on a hard wooden surface from a height of inch at 2 second intervals. Th bulk density was then obtained by dividing the weight in gm by the final volume in cm^3. The process was repeated at least 3 times and the average was taken in every case. A ratio between buk density and tapped density can be calculated. This ratio called "Hausner ratio", which gives an idea about the flow properties of the powder; the flow is better when the value of the ratio is close to 1.

3- The angle of repose: It was measured accoridng to the dynamic method using a locally made apparatus which consists of aluminium cup with 2.5 cm radius and a carton paper cylinder which can easily fit on the inverted cup and which can easily be moved and removed. The powder was allowed to flow freely into the cylinder which was then removed and a heap was formed. The height of the heap was measured and the angle of repose was obtained. The process was repeated 3 times in each case. When the angle of repose is high, it means that the particles do not have a smooth, round surface and that some frictions produed among these particles during flow. An irregular flow and some static charges occurred among the particles. On the contrary, a low value angle, is an indication of an excellent flow.

4- Flow rate: In order to get more quantitative results, the real flow of the powder and granules were measured by measuring the flow speed of the material through a hopper. The results are expressed in g/sec.

5- Granule friability: A modification of the method described by Marks and Sciarra[9] was carried out in order to assess the friability of the produced granules. 10 g of the prepared granules was taken from the part retained over 500 um sieve and was put in the Erweka friabilator, which was left to rotate at 25 rpm for 5 minutes. The granules were put over a preweighed 500 um sieve and were shaken for 15 seconds. The amount retained over was deduced. The friability of the granules under test was calculated as follows:

$$\text{Friability\%} = \frac{10 - \text{weight retained}}{10} \times 100$$

6- Compressibility of granules: This was computed from the powder density according to the following equation[10,11]:

$$\text{Compressibility \%} = \frac{P_t - P_b}{P_t} \times 100$$

Where P_t is the tapped bulk density and P_b is the initial bulk density.

7- Kawakita Parameter: The packing process of the powder or granules in a tapped graduated cylinder can be described by the following equation[12].

$$N/C = 1/ab + N/a \text{ and}$$

$$C = (Vo - Vn)/Vo$$

Where a and b are constants representing the proportion of consolida-

tion at the closest packing attained and packing velocity index respectively. N is the number of taps, Vo is the volume of powder in the measuring cylinder at the loosest packing and Vn is the volume after N th tapping.

Therefore a low value of (a) implies better flowability and packing of powder.

RESULTS AND DISCUSSION

The release characteristics of ibuprofen from the prepared sustained release granules granulated with ethyl cellulose 20, Pharmacoat 606, HP 55 F and PVP were examined in vitro. Fig. (1) shows the effect of different concentrations of ethyl cellulose 20 on the release of the drug from the prepared granules using the shift dissolution method at 37°C. Increasing the concentration of ethyl cellulose from 0 to 5% w/v lead to decrease in the release rate of ibuprofen. This may be due to the thicker insoluble ethyl cellulose film formed around the granules. Obviously, the release of ibuprofen was increased as the pH of the dissolution medium was increased from 1.5 to 7.1, which may be attributed to the insolubility of ethyl cellulose at lower pH values.

The effect of different concentrations of HP 55 F on the release rate of ibuprofen from the prepared granules is shown in Fig. (2). Increasing the concentration of the granulating agent from 0 to 5% w/v lead to plorongation of the drug release rate for the same reasons mentioned before. Higher release rates were obtained at higher pH values investigated, i.e., pH 7.1. That is because HP 55 F is insoluble at lower pH values but soluble at pH 5.5 or higher[13]. In such a medium, these granules would swell more easily than in an acidic one. The drug would be liberated from the hydrated polymer zone through a combination of diffusion and attrition process.

The effect of increasing the concentration of Pharmacoat 606 on the dissolution of ibuprofen from the prepared granules using shift dissolution method is shown in Fig. (3). Also, the effect of mixing 5 & 10% w/w of Pharmacoat 606 and ibuprofen in the granules which were granulated with 5% w/v Pharmacoat 606 is shown in Fig. (4). In both granules, the release rate of the drug was increased with increasing Pharmacoat in the outer layer or within the granule matrices. The mechanism of the drug release from both granules would involve the formation of a hydrated zone of Pharmacoat 606 on the surface of the granule matrix[14,15]. This would be the first step in the formation of a transport channel. Part of the drug would be diffused through the hydrated zone and would be released to the diffusion medium while the remainder would be liberated when the hydrated zone dissolved.

The observed release rate would be the function of the degree of the hydrophilic and hydrophobic polymers[14,16]. The above results clearly indicate that the release rate of ibuprofen granulated by Pharmacoat 606 was higher than the release rate of ibuprofen alone (control). This may be ascribed to the following[13]: (a) ibuprofen was dispersed as fine particles in the granules, since ibuprofen powder was dissolved in the solvent in the preparation of the granules, (b) ibuprofen was more easily wetted in the medium due to the addition of Pharmacoat 606 in the granule matrix and (c) crystalline ibuprofen was transformed to the amorphous form in the granules by using Pharmacoat 606 or HP 55 F[17,18].

The effect of different concentrations of PVP as a granulating

agent on the dissolution rate of ibuprofen from the prepared granules is shown in Fig. (5). It is clearly observed that the increase in PVP concentration lead to retardation of ibuprofen release rate. Dissolution rates do not show significant differences between PVP and HP 55 F specially at 1% w/v concentration, the respective T50% values are 142.5 and 146.5 minutes respectively, Table (1). The dissolution rate of ibuprofen from the prepared granules depend upon the type and concentration of the granulating agent used. Table (2) shows the T80% of the drug from the different prepared granules. The longest T80% of ibuprofen is shown in these grnaules granulated with 5% w/v ethyl cellulose 20 followed by PVP, HP 55 F and Pharmacoat 606 respectively. The same observation was noticed in the calculation of T50% of ibuprofen from different prepared granules Table (1) and Fig. (6). Thus ethyl cellulose 20 represent the ideal granulating agent for ibuprofen sustained release granules, so, the drug side effects would be minimized specially the highest release happened in higher pH values.

The different physical parameters of ibuprofen powder, ibuprofen granules granulated with ethyl alcohol alone as a control and ibuprofen granules granulated with 5% w/v ethyl cellulose as an optimum retardants for the drug, from granules, are shown in Table (3). These parameters include: particle size, particle size distribution, angle of repose, flow rate, bulk density, compressibility, friability and parameters of Kawakita. Wet granulation method gave rise to enlarged particle size than ibuprofen control. On comparing the physical properties of the granular form of the drug granulated with ethyl cellulose with that of crystalline ibuprofen, it could be seen that the wet granulation increased the average particle size which was confirmed by the size distribution shown in Table (3) and Fig. (7), as 90% of the granules lie between 750 and 375 um.

A wider angle of repose (56.7°) signifying less flowability than ibuprofen granules as a control and those granules grnaulated with 5% w/v ethyl cellulose 20. The latter granules showed lowered packed density as a result of the increase in particle size.

The Hausner factor of the prepared granules is shown in Table (3), which gives an idea about the flow properties of drug powder, control granules and ethyl cellulose granules. The flow is better when the value of Hausner ratio is close to 1. Thus ethyl cellulose granules is the best in terms of flowability.

Compressibility of the powder and granules as computed from the last mentioned equation is also related to the flowability of a free flowing powder. The more the flowability of the powder, the smaller the value of compressibility. A compressibility value smaller than 20% sugests excellent flowability of materials[10,11]. Table (3) shows that the compressibility value of ibuprofen powder (41.4%) is higher than that of the prepared granules (16.02 and 16.26 for control and ethyl cellulose granules respectively), indicating that the drug powder has very poor flowability due to the smaller particle size and vice versa the prepared granules.

The friability of the ethyl cellulose granules was found to be less than the control granules and the drug powder respectively, Table (3).

Kawakita parameter (a) in the last equation for ethyl cellulose granules was found to be smaller than control granules and the drug

powder respectively, Table (3). This result indicates that the particles of the drug powder might be packed more loosely than those of the control and ethyl cellulose granules. This might be due to the smaller particle of ibuprofen crystals which result in higher porosity and poor flowability.

Table (4) and Fig. (8) illustrate the influence of the particle size of ethyl cellulose granules on the dissolution rate of ibuprofen using the shift dissolution method. It is evident that the increase of the particle size of the granules resulted in a significant decrease in the release rate of the drug.

Table (1):Time for 50% of Ibuprofen Release from the Prepared Sustained Release Granules

Polymer Type	$T_{50\%}$ (min.)			
	Polymer Concentrations (%)			
	0	1	3	5
Ethylcellulose20	153.5	150.0	191.0	202.5
$HP_{55}f$	153.5	142.5	161.5	169.0
Pharmacoat 606	153.5	154.0	154.0	139.0
P.V.P	153.5	146.5	152.0	182.0

Table (2):Time for 80% of Ibuprofen Release from the Prepared Granules .

Polymer Type	$T_{80\%}$ (min.)			
	Polymer Concentrations (%)			
	0	1	3	5
Ethylcellulose20	202.5	214.0	265.0	285.0
$HP_{55}f$	202.5	174.0	211.0	211.0
Pharmacoat 606	202.5	202.5	196.0	187.5
P.V.P	202.5	202.5	203.0	229.0

Table (3):Physical Properties of the Prepared Ibuprofen Granules

Parameter	Ibuprofen powder	Ibuprofen[1] control	Ibuprofen[2] 5%Ethylcellulose
1-Size range(μm)			
1000-500	5.60	67.66	81.80
500 -250	27.00	20.77	15.60
250 -160	20.00	3.78	1.30
160 -125	16.00	2.13	0.38
< 125	31.40	5.67	0.92
2-Angle of repose	56.7°	49.2°	44.1°
3-Flow rate g/sec	very bad	1.34	1.50
4-Bulk density :			
before Tapping	0.32	0.41	0.36
after " g/cm^2	0.54	0.49	0.43
5-Hausner factor	1.69	1.20	1.19
6-Compressibility (%)	41.40	16.02	16.28
7-Friability (%)	> 8	7.75	3.35
8-Parameters of(a)	0.4199	0.1645	0.1503
Kawakita (b)	0.0117	0.0042	0.0038

(1) Ibuprofen Control: granulated with ethyl alcohol without polymer.
(2) Ibuprofen granulated with 5 %W/V Ethylscllulose 20.

Table (4):Effect of Particle Size on the Release of Ibuprofen (100 mg) Granulated With 5% Ethylcellulose 20 from Granules Using Shift Dissolution Method at 37°±0.5°C

Time (min.)	pH	Percentage Cumulative Release of Ibuprofen		
		5% Ethylcellulose 20		
		1000-500μm	500-250μm	250-160μm
5	1.5	6.6	6.6	6.6
30	1.5	12.7	14.0	15.6
60	1.5	14.0	18.1	19.8
90	2.6	17.1	23.2	30.8
120	6.6	17.6	28.7	39.1
180	6.9	33.3	67.2	95.5
240	7.1	64.5	97.7	107.9
300	7.2	93.0	111.1	114.6

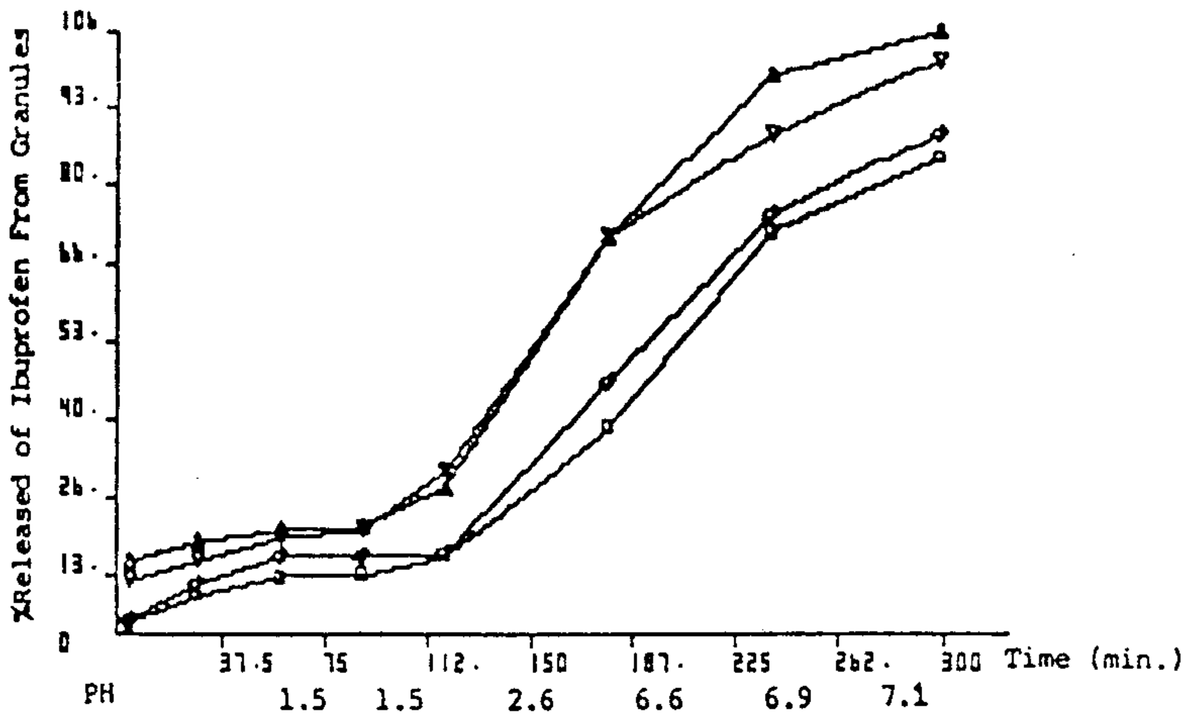


Fig.(1) :Release Profile of Ibuprofen Granules, Granulated With Different Concentrations of Ethylcellulose 20,Using Wet Granulation Technique and Shift Dissolution Method.

Key : ▲ 0%Ethylcellulose, ▼ 1%Ethylcellulose, ◆ 3%Ethylcellulose ◘ 5%Ethylcellulose.

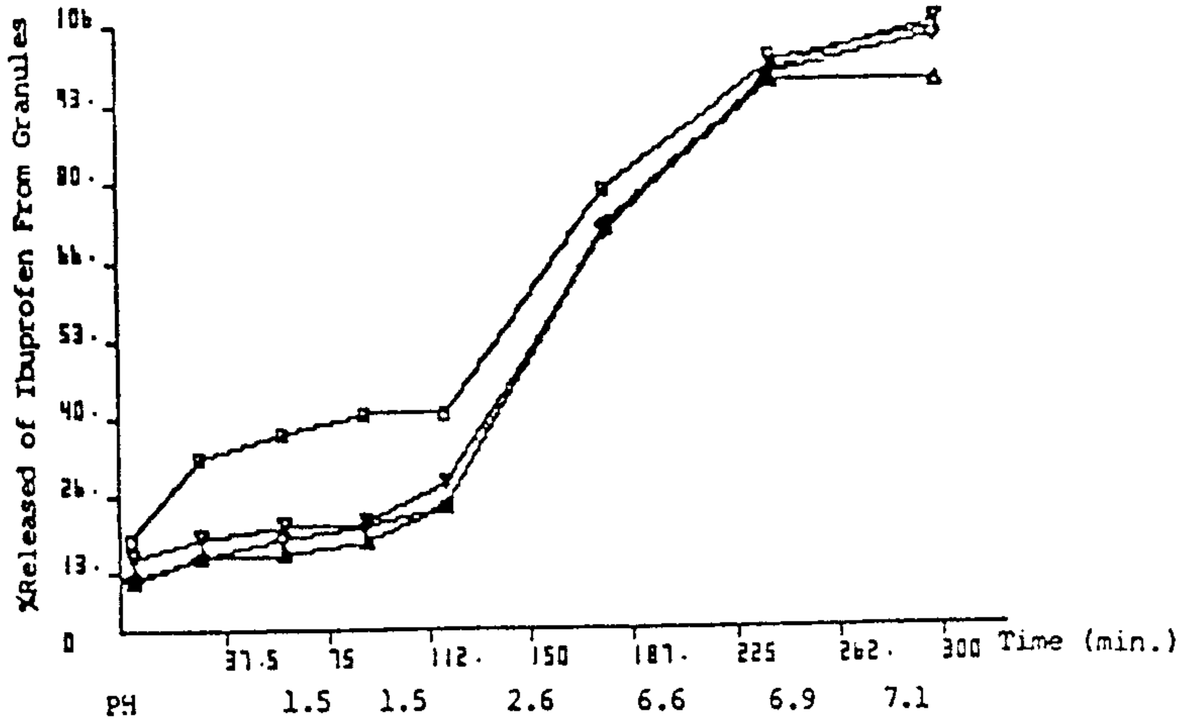


Fig.(3):Release Profile of Ibuprofen Granules, Granulated With Different Concentrations of HydroxypropylMethylcellulose, Using Wet Granulation Technique and Shift Dissolution Method.

KEy : ▼ 0% Pharmacoat 606 ▲ 1% Pharmacoat606, ◆ 3% PHarmacoat606. ◘ 5% Pharmacoat606.

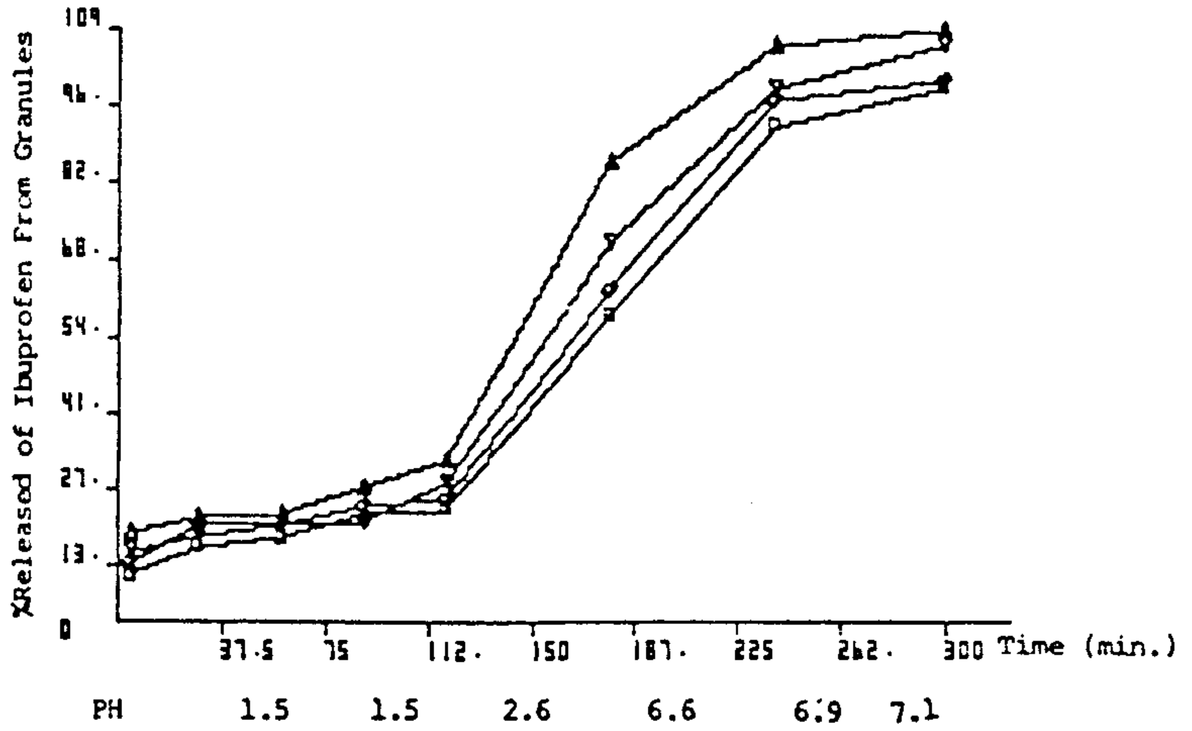


Fig.(2) :Release Profile of Ibuprofen Granules,Granulated With Different Concentrations of HydroxypropylMethylcellulose Phthalate, Using Wet Granulation Technique and Shift Dissolution Method.

Key : ▲ 0% HP_{55}, ▼ 1% HP_{55}, ◆ 3% HP_{55}, ◘ 5% HP_{55}.

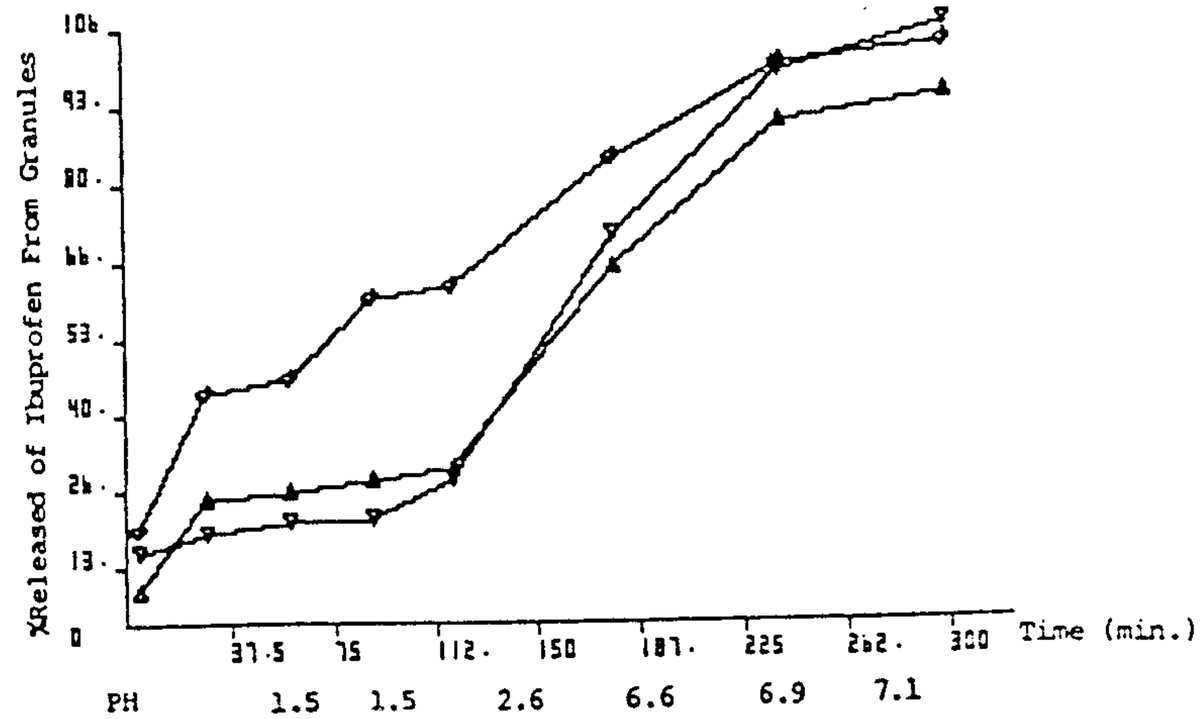


Fig.(4):Release Profile of Ibuprofen Granules Granulated With 5% Pharmacoat606, Containing Different Concentrations of Pharmacoat606 (5% & 10%) Using Wet Granulation Technique.

Key : ▲ 5%Pharmacoat , ◆ 10%Pharmacoat,, ▼ 0%Pharmacoat.

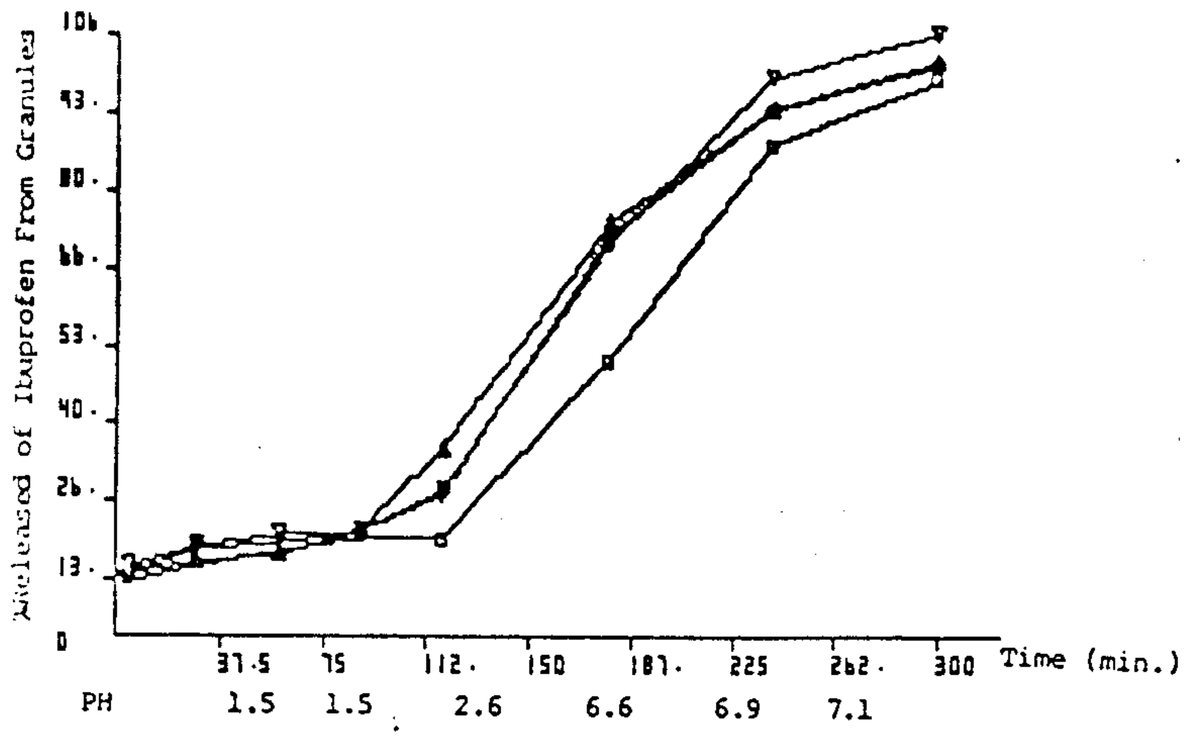


Fig.(5):Release Profile of Ibuprofen Granules, Granulated With Different Concentrations of Polyvinylpyrolidone, Using Wet Granulation Technique and Shift Dissolution Method.

Key : ▼ 0%P.VP, ▲ 1%P.V.P, ◆ 3%P.V.P, ■ 5%P.V.P.

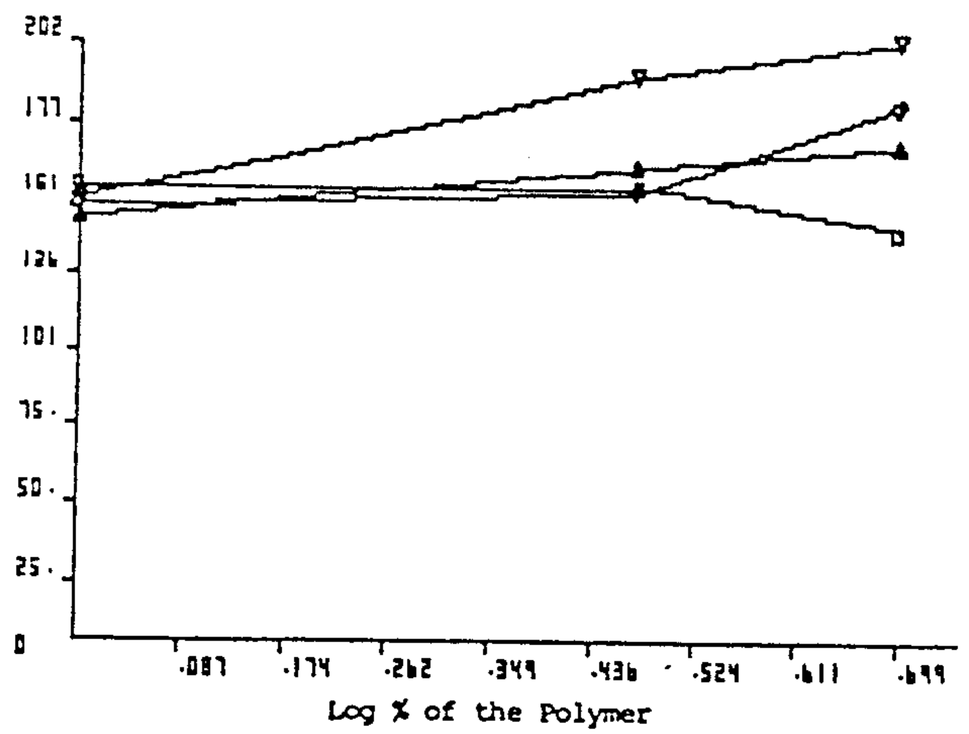
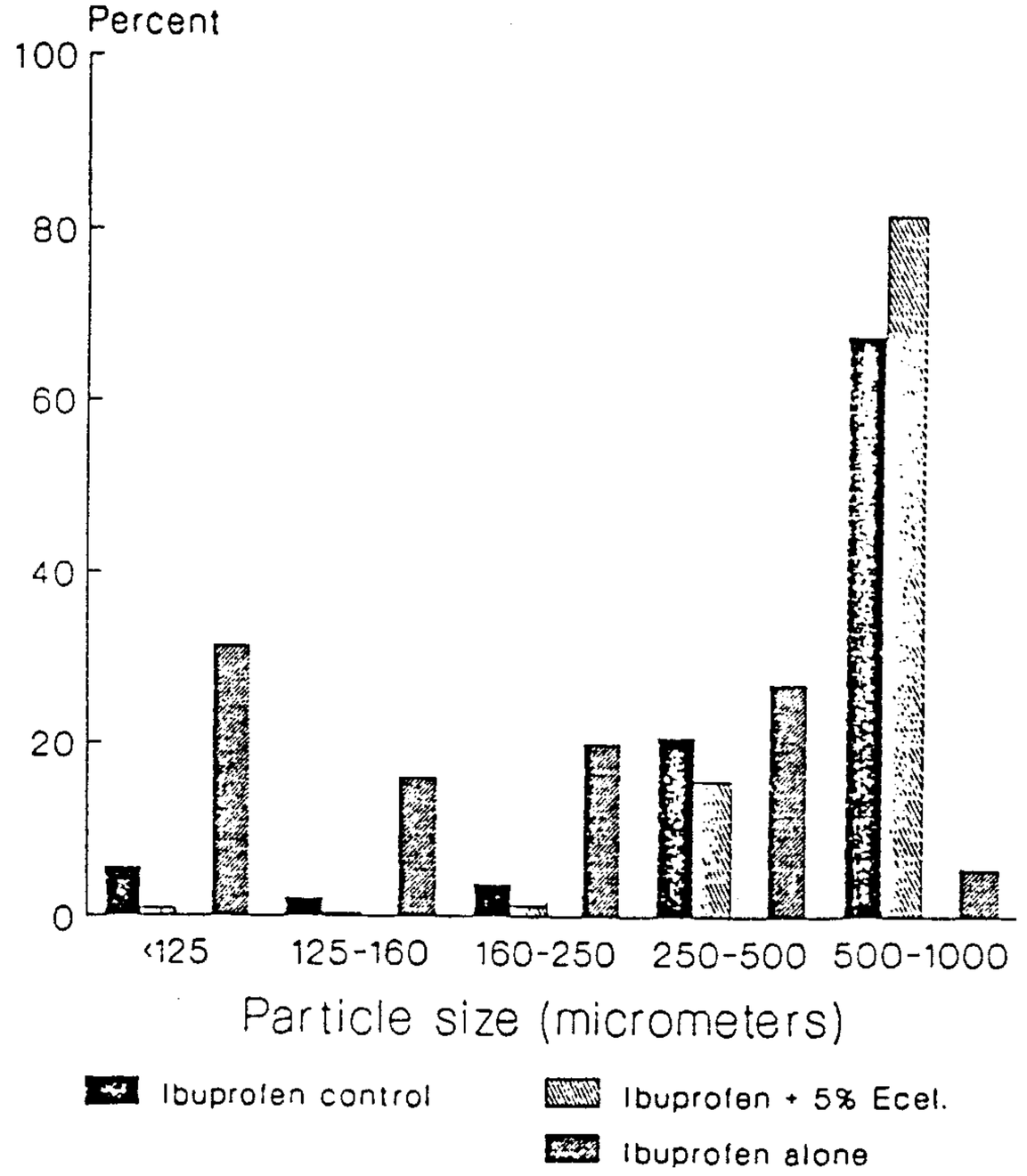


Fig.(6):Representation of Logarithmic Percentage of the Polymer Versus the T_{50} of the Ibuprofen.

Key : ▼ Ethylcellulose, □ Pharmacoat, ▲ HP_{55}, ◆ P.V.P.

Fig.(7): Histogram of particle size of Ibuprofen



Sieve analysis

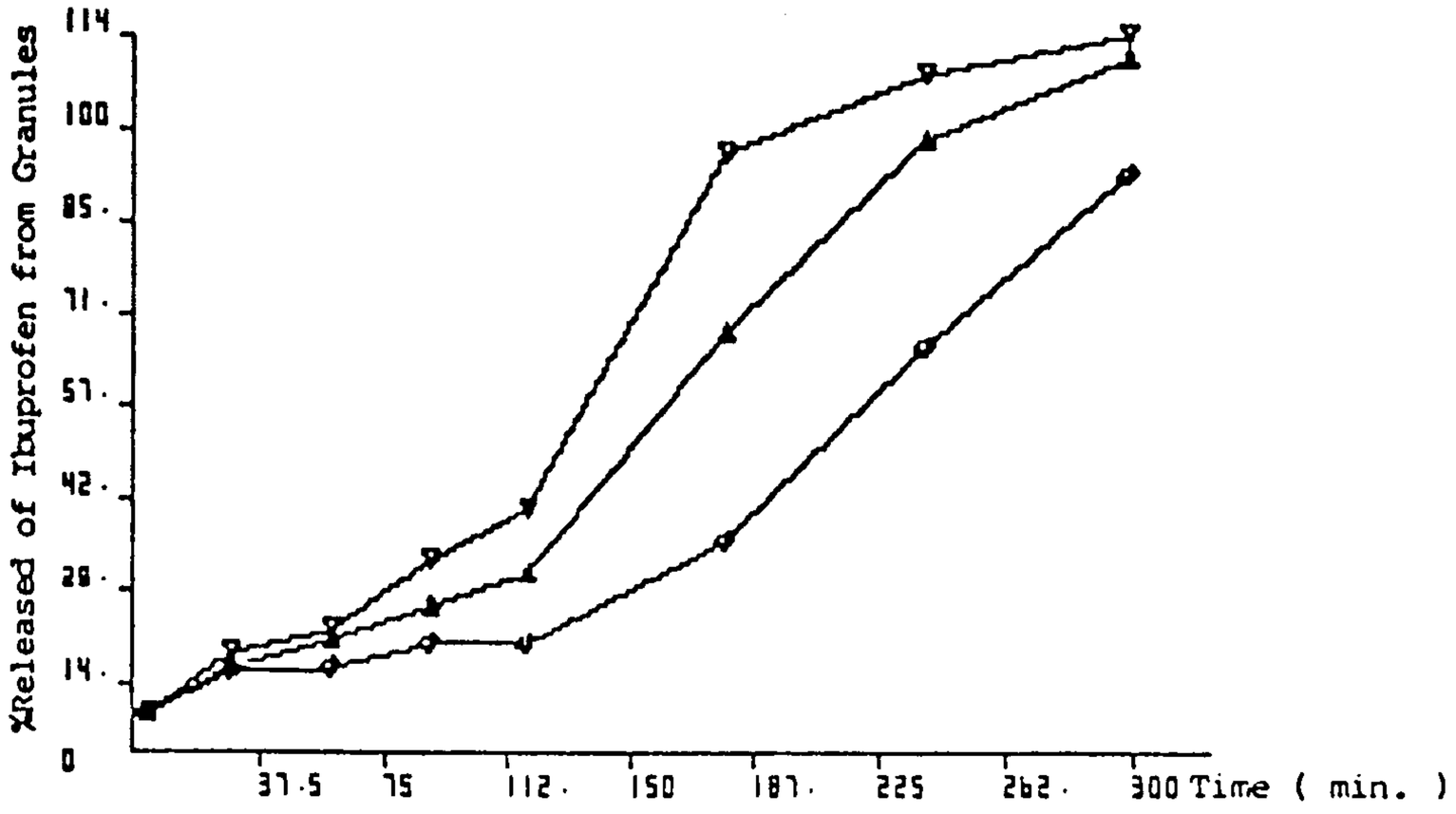


Fig.(8):Effect of Particle Size on the Release of Ibuprofen from Granules With 5% Ethylcellulose 20,Using Wet Granulation Technique and Shift Dissolution Method.

Key : ▼ 1000-500um , ▲ 500-250um , ▼ 250-160um.

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تأثير البوليمرات السليلوزية على الخواص الطبيعية ومعدل الإتاحة لعقار الأيبوبروفين من الحبيبات المحضـــرة

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حضرت حبيبات الايبوبروفين ممتدة المفعول باستخدام البويمرات السليلوزية وتشمل ايثيل سليلوز ٢٠ ، هيدروكسى بروبيل ميثيل سليلوز (فارماكوت ٦٠٦) وهيدروكسى بروبيل ميثيل سيلوز فيثالات.

وقد استخدم عديد الفينيل بيروليدون كعامل محبب للمقارنة. ولقد وجد أن زيادة تركيز المحبب أدت الى تأخير اتاحة العقار من الحبيبات المحضرة ما عدا الفارماكوت ٦٠٦. ولقد وجد الايثيل سليلوز ٢٠ فى ٥٪ وزنا/حجم قد حقق التأخير المطلوب فى اتاحة العقار من الحبيبات المحضرة.

ولقد فحصت الخواص الطبيعية لبودرة الأيبوبروفين ، حبيبات الايبوبروفين كمقارن ، حبيبات الايبوبروفين المحببة بواسطة ٥٪ وزنا حجم ايثيل سليلوز ٢٠ ولقد شملت هذه الخواص التوزيع الحجمى ، زاوية السكون ، معدل الانسياب ، الكثافة الكمية ، معامل هـــنر ، قابلية الانكباس ، الهشوشه ، معامل كواكيتا.

ولقد درس تأثير اختلاف حجم جزيئات الايبوبروفين المحبب بواسطة ٥٪ وزنا/حجم ايثيل سليلوز ٢٠. ولقد أدت الزيادة فى حجم الجزيئات الى اطالة اتاحة العقار من الحبيبات المحضرة.

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