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FORMULATION OF CONTROLLED-RELEASE IBUPROFEN GRANULES AND EVALUATION OF THE ANTIINFLAMMATORY ANALGESIC ACTIVITIES

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ABSTRACT

Two kinds of granules were prepared: one with pH-dependent release and the other with pH-independent release. The former was composed of ibuprofen, celluloseacetate phthalate, ethylcellulose and microcrystalline cellulose while the latter was composed of ibuprofen, hydroxypropyl methulcellulose, ethylcellulose and corn starch. The effects of mixing ratios of the polymers; pH of the release medium, and the drug content in the granules were examined *in-vitro* to investigate the release characteristics. In granules with pH-dependent, the release rate was decreased with the increment of ethylcellulose and as the pH of the release medium increased. While in granules with pH-independent, the release rate was decreased as the ratio of hydroxypropyl methylcellulose (HPMC) to ethylcellulose (EC) increased. Analgesic activity of four selected formulations of the controlled release was tested by two methods using p-benzoquinone (PBQ)-induced writhing and the hot-plate. Also the antiinflammatory activity of these formulations was examined after oral administration of the granules by using trypan-blue dye method. Results that the fomulation of ibuprofen granules pH-independent containing HPMC and EC revealed in ratio of 3:1 had a delayed onset of antiinflammatory and analgesic actions extended for four hours or more while granules of ibuprofen with pH-dependent containing 4 % ethylcellulose and 2 % cellulose acetate phthalate were capable of increasing analgesic against thermal stimuli for four hours whereas lower percentage protection against PBQ-induced writhing, was observed. Statistical analysis of the results were done using student's t-test.

The pH-independent release granules were superior to the pH-dependent release granules with respect to prolonging the effective antiinflammatory action when administered orally to rats.

INTRODUCTION

Ibuprofen is an orally administered, non-steroidal antiinflammatory drug having analgesic antipyretic activity, used extensively for treatment of rheumatoid arthritis[1-5], osteoarthritis[6], acute gouty arthritis[7] and more recently, in the treatment of dysmenorrhea[8].

It is important and desirable to prolong the effect by controlling the release of the drug and by maintaining the analgesic antiinflammatory effect. The use of pellets for pharmaceutical formulations is of interest for controlled release delivery systems. It has been demonstrated that modifying the polymer ratio in the formulation could alter the drug release[9]. The bioavailability of a drug formulated as pellets is influenced by the physicochemical properties of the drug, the composition of the non-active ingredients and the gastro-intestinal transit time[10-13].

The use of hydroxypropylmethylcellulose (HPMC) in the preparation of controlled release dosage forms has been well documented[14-23]. On exposure of such matrices to aqueous fluids the (HPMC) polymer hydrates and forms a gel layer at the granule periphery. Drug is liberated by a combination of diffunion through and attrition of thin gel layer[16]. The principal advantage of an HPMC matrix formulation is that drug release rates are generally independent of processing variables such as drug particle size and incorporation of a Lubricant[17].

However, there are few reports regarding prolongation of effective antiinflammatory analgesic activity of the drug.

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Takayoshi Hidaka et al [24] studied analgesic and antiinflammatory activities of indomethacin, naproxen and ibuprofen in rats. They found that analgesic activity using acetic acid-induced writhing in rats was 70%; 74% (inhibition %), respectively. Also, they found that antiinflammatory activity depended on the dose of the drug in the carrageenan paw edema-test and adjuvant arthritis[25] . One method to prolong the antiinflammatory effect is to employ a sustained-release formulation[26].

The purpose of the present study is to examine the effect of mixing ratios of different polymers in formulations; pH of the release medium, and the drug content in the prepared granules on the In-Vitro release rate of ibuprofen from controlled granules. Also,the purpose of this study extends to include examination of the relationship between the release rate of ibuprofen from controlled granules and the antiinflammatory analgesic activities of selected controlled formulations administered orally to experimental animals.

EXPERIMENTAL

Materials :

- Ethylcellulose-BDH-Chemicals Ltd. Poole England.
- Hydroxypropyl methylcellulose (50 CPS. Sigma Chemical Co.,U.S.A.)
- Celluloseacetate phthalate (40 CPS, Cid Co., U.A.R.)
- Avicel pH 101. Fluka AG, CH-9470 Buchs; Eingetragene Marke der FMc Co., Switzerland.
- Corn Starch. ADWIC. PROLABO. El-Nasr Co., for Chemicals, Egypt.
- Ibuprofen, Kahira Pharmaceutical Co., Egypt. U.A.R.) All other chemicals were of reagent grade.
- Histamine dihydrochloride; Aldrich Chemical Co., Ltd. England.
- PBQ-Tropane blue; Chemapan. Prag. Czechoslovakia.

Apparatus :

- Thermostatically controlled shaker Unitronic 320 OR (Selecta).
- Spectrophotometer-UV-150-20 Shimaldzu. Japan).
- pH-meter (U_qN Tacussel Electronique. Solea).
- Hot plate UGO-BASILE 21025 COMERIO-VARESE ITALY.

Methods :

Granules with pH-dependent release and pH-independent release were prepared according to the ratios of the components in Table 1. Selected formulations have been evaluated for their analgesic and antiinflammatory effects.

Preparation of Granules With pH-Dependent Release :

Ibuprofen, cellulose acetate phthalate, and ethylcellulose were dissolved in the mixed solvent (ethanol :acetone 1:1), and then microcrystalline cellulose was added with agitation by a magnetic stirring bar in a jacketed beaker connected to a thermostated water bath.

A slurry with suitable toughness was obtained by evaporating the solvent while maintaining the water bath at 70°C, and then resulting products were forced through 315 um-mesh sieve.

After drying the formed material at 50°C., a fraction of granules with a size between 220-315 um. were,obtained.

Preparation of Granules with pH-Independednt Release :

Ibuprofen, hydroxypropylmethylcellulose, and ethylcellulose were dissolved in the mixed solvent (ethanol: dichloromethane 1:1) and then corn starch was added. The granulation procedure was identical to the procedure used for granules with pH-dependent release.

Release Studies :

Release rate of ibuprofen granules was studied using 50 mg of the granules with pH-dependent release or 75 mg of granules with pH-independent release, each containing 25 mg of ibuprofen. These granules were dispersed in 250 ml of the medium at pH 2,6 and 7 and distilled water at 37 ± 0.5°C. The rate of stirring was at 50 rpm. Five milliliters of

each sample was removed at predetermined intervals, and 5 ml of each fresh medium was added to the flask to maintain the original volume. The drug concentration was analyzed spectrophotometrically at 268 nm. Triplicate runs were made on each batch.

Administration of Granules to Experimental animals :

Granules from formulations A and C with pH-dependent release,and formulations D and F with pH-independent relase and ibuprofen powder were administrated orally in the form of suspension in 5% aqueous solutions of gum acacia to rats or mice using gastric tubing in a dose of 200 mg/kg.

Evaluation of the Antiinflammatory Activity :

Antiinflammatory effect of pure ibuprofen and formulations A, C,D and F controlled granules was tested as described by the method of Golikov[27]. This method is based on the quantitative determination of the effects of the drug to be investigated on the rate of accelerated capillary permeability elicited by an intradermal injection of such a phlogogenic substance as histamine. A solution of a blue dye(trypan blue) was intravenously injected into rats in a dose of 2 ml/kg. This was followed by intradermal injection of histamine phosphate (0.02 ml of 1% solution). The rate of capillary permeability was calculated as the time taken for the appearance of the blue colour around the site of histamine injection. Suspensions of the tested drug (as well as 5% solution of gum acacia) were orally administered into different groups of rats in a dose level of 200 mg/kg and were tested for their antiinflammatory activity at 1,2,3 and 4 hours following their administration. One group of rats was used for each time interval.

Evaluation of the Analgesic Activity :

Analgesic activity of ibuprofen and controlled ibuprofen granule formulations A. C,D and F were studied in mice using two different methods :

1- Hot plate method :

The reaction time for mice to jumb within a plexiglass cylinder placed on a hot plate surface (55°C) was taken as the end point[28].

Responses were determined at different time intervals 1,2,3 and 4 hours following drug administration. Different groups of animals (consisting of 10 mice) were used for each time interval.

2- Writhing Method :

The analgesic activity of ibuprofen and its formulations were studied using p-benzoquinone (PBQ) writhing method[29]. Suspensions of the tested drug in 5% gum acacia were orally administered into mice and were allowed to act for different time intervals 1,2,3 and 4 hours. Following the specified period of time an i.p. injection of 0.25 ml of 0.02% solution of p-benzoquinone was given. Mice were watched for an elongation of the mouse's body development of tension of the abdominal region and an extent of the fore limbs.[30] Groups of 10 mice were used for each tested time interval. Control animals receving an oral dose of 5% gum acacia were included in this set of the experiment.

Statistical Analysis of the Results :

The degree of variability in results was expressed as mean ± standard error (X ± S.E). The significance of the differences between samples was determined using the student's L-test. The difference was regarded as significant when $p < 0.05$.

RESULTS AND DISCUSSION

Release of Ibuprofen from the Granules with pH-Dependent Release :

Granules were composed of ibuprofen and three components : celluloseacetate phtahlate and ethyl-cellulose as binders and microcrystalline cellulose as a filler. Figure 1. shows the effect of ethyl-cellulose on the relaease of ibuprofen from granules with pH-dependent formulations A,B and C. The release rate decreased with the increment of ethylcelullose and it followed diffusion-controlled mechanism. The effect of pH on

the release rate of ibuprofen from granules A,B and C was also examined and it was found that release rate of ibuprofen decreased at pH 7 and pH 2 release medium and increased at pH 6. From Figure 2, and Table 2, in-vitro data resulted in good correlation existed between pH value of the release medium and the release rate as diffusion controlled. Niazi[31] reported that the un-ionized form of a drug was the most suitable for gastrointcstinal absorption and the efficiency of absorption of weakly acidic compound would change as the dosage form passed through various pH conditions in the gastrointestinal tract and the ionization constant of ibuprofen pka equal 4.4. It was concluded that the release of ibuprofen from granules was pH-dependent in the medium, and was retarded by ethylcellulose content.

Release of Ibuprofen from Granules with pH-Independent Release:

Granules were composed of ibuprofen at three components : hydroxypropyl methylcellulose and ethylcellulose as binders and corn starch as filler. The effect of ratios of hydroxypropyl methylcellulose to ethylcellulose on the release of ibuprofen from controlled granules D,E and F in distilled water as the release medium was studied. As shown in Figure 3, the release rate increased with the increment of hydroxypropyl methylcellulose.

Figure 4 showed the profiles of ibuprofen release rate from the granules with different drug content, formulations G,H and E having the same ratio of HPMC to EC 1:1, respectively.

The release rate apparently increased with the increase of drug content. The release rate of ibuprofen from granules with pH-independent release followed apparencly first-order kinetic mechanism and diffusion controlled. It was found that a good correlation between drug content and the release rate at pH 6 and distilled water as seen from Table 3.

By inspection of the release data (using distilled water as release medium) showed a good correlation between the square root of the ratio HPMC to EC ($\sqrt{}$ ratio) and the release rate by diffusion-controlled mechanism of ibuprofen from granules D,E and F.

Figure 5- showed that release rate of ibuprofen decreased at pH 7 and distilled water than pH 6. Data indicated that there was no-correlation between release rate and pH of the medium.

Release of a drug from granules often occurs as a result of degradation of the granules as suggested by Hixson and Crowell[32]. Wagne[33] found that most sustained action dosage forms released their contained drug into fluids in the in-vitro test at pseudo (or apparent) first-order rates.

Generally, results clearly indicated that the release rate of ibuprofen from granules was less than that of pure drug powder. This may be ascribed to the following :(a): Ibuprofen was dispersed as fine particles in the granules, since ibuprofen powder was dissolved in the mixed solvent in the preparation of the granules; (b): Ibuprofen was more easily wetted in the medium due to the addition of corn starch, hydroxypropyl methylcellulose, or microcrystalline cellulose in the granules.

The mechanism of drug release from the granules with pH-independent release would involve the formation of a hydrated zone of hydroxypropyl methyl-cellulose on the surface of the granular matrix[34;35]. 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 medium while the remainder would be liberated when the hydrated zone dissolved. Altering the HPMC: EC ratio in the polymer composite mixture would affect the release rate markedly[34].

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In the case where there was less HPMC in the granular matrix, a comparatively slow release rate might be expected, due to the support provided by the hydrophobic ethylcellulose. The observed release rate would be the function of the balance of the hydrophilic and hydrophobic polymers[36].

The mechanism of drug release from granules with pH-dependent release would be almost the same as that of the granules with pH-independent release. As a binder, celluloseacetate phthalate was used to enhance the release at higher pH values. This is based on the fact that CAP is insoluble in an acidic enviroment but soluble in the medium at pH 5.5 or higher. In such a medium, these granules would swell such more easily than in an acidic enviroment. The drug would be liberated from the hydrated zone through a combination of diffusion and attrition processes. Schwartz et al[37] found that the release rate of drug from matrices occured by a diffusion-controlled process and this finding was in agreemdnt of our results.

1-Analgesic Activity as Measured by p-Benzoquinone (PBQ)-Induced Writhing :

In this experiment, the ability of ibuprofen and its controlled release formulations to protect mice from chemical pain induced by PBQ was calculated as percentage animals showing protection.

Control animals receiving gum acacia solution (5%) did not show any protection against writhing produced by PBQ i.e.they gave rise to 0.00% protection (Figure 6 and TAble 5).

Mice given non-formulated control (pure ibuprofen) displayed protection by a percentage of 80.70.40 and 20 at 1,2,3 and 4 hours; respectively, after oral administration of the drug.

Comparison of the analgesic activity of the ibuprofen formulations A.C.D and F with that of nonformulated control revealed that :

1- Formulation (A) exhibited its maximal analgesic activity at the first hour following administration and its analgesic activity was reduced progressively with time to reach a value 0.00% at four hours. At all tested time intervals, the magnitude of the analgesic activity produced by formulation (A) was less than that of control.

2- Formulation (C) did not prove to be advantageous over the control. The percentage protection afforded by this form was 30,40,20 at 1.2.3 and 4 hours following oral administration, respectively.

3- Formulation(D) demonstrated greater analgesia at 3 and 4 hours following its administration. However, its analgesic activity was lower at 1.2 hours after its administration.

4- Formulation (F) was able to elicit greater degree of protection against PBQ-induced writhing at 2,3 and 4 hours followitn its administration. At 4 hours after administration of the formulation (F) all mice were shown to be 100% protected from writhing produced by PBQ.

II- Analgesic Activity as Measured by the Hot Plate Method :

In this set of experiments, the time taken by mice to jump away from a hot plate (55°C) was taken as a measure of the analgesic activity of the tested formulations.

Control mice receiving a solution of 5% gum acacia were found to stay on the hot plate for a period of 4.7 to 5.9 seconds as shown in Table 6. Mice given non-formulated control were able to stay for longer periods on the hot plate at the various tested time intervals.

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Mice given formulations (A)and (F) were found to show a statistically different analgesic action 1 and 4 hours following their administration respectively. On the other hand, formulation (C) did not bring about any change in the duration of its analgesic effect except after four hours.

Antiinflammatory Effect :

In this test, the time taken until the appearance of the blue colour of the intravenously injected dye (trypan blue) around the site of intradermal injection of histamine was used as an expression of the antiinflammatory activity of ibuprofen and its controlled release granules. Antiinflammatory effect of the various tested formulations means a delay in the time of appearance of the blue colour. Table 7 shows that in animals that have been treated with 5% solution of gum acacia the appearance of the blue colour took place within 2.07 to 2.11 minutes at the various time intervals (1,2,3,4 hours). Oral adiministration of the non-formulated control into rats was found to increase significantly the time of appearance of the blue colour at one and two hours. Rats treated with the controlled-release granules formulation (A) of ibuprofen demonstrated an increase in the time of appearance of blue colour only after one hour if compared with the nonformulated control. The antiinflammatory activity of the formulation (C) of ibuprofen was the same as that of the non-formulated control. Formulation (D) of ibuprofen was able to show antiinflammatory activity after longer periods of time (at 3 and 4 hours). However, the onset of this action was delayed for more than two hours. Formulation (F) of ibuprofen was capable of eliciting an aniinflammatory response 2,3 and 4 hours following its administration.

Correlation Between In-Vitro and In-Vivo Results :

An exmination of the in-vitro-in-vivo data indicated that the a correlation existes between the ratio of HPMC to EC and the analgesic antiinflammatory activity in experimental animals.

As the ratio of HPMC to EC increases, the release rate decreases while the analgesic effect against chemical stimuli increases as it is evident from the higher percentage protection afforded by formulations D and F.

Besides, as the concentration of EC is increased, the release rate of ibuprofen is decreased and the analgesic effect against thermal stimuli is increased. This is shown by the significant difference (P 0.05) between formula C and the control drug. Furthermore, formulations D and F demonstrated a greater and more prolonged effect than the control drug.

According to our animal studies concerning the analgesic and antiinflammatory effects of ibuprofen, it is advisable that the drug can be formulated in different forms. Some forms D and F are used when ibuprofen is indicated for its antiinflammatory effect and all form(S) of ibuprofen are used it the drug is required as analgesic agent.

We suggest that, the formulations which are pH dependent or independent in their release must be throughly investigated in humans in order to find out whether similar results as those observed in animal studies can be obtained.

Table 1: Composition of ibuprofen controlled-release formulations.

Formulation	Ibuprofen %	Cellulose acetate phthalate.% CAP	Ethylcellulose EC.%	Microcrystalline cellulose %	Corn starch, ,%	Hydroxypropyl methylcellulose, HPMC ,%
A	10	20	0	70		
B	10	20	2	68		
C	10	20	4	66		
D	6.7		10		53.3	30
E	6.7		20		53.3	20
F	6.7		30		53.3	10
G	2		20		58.0	20
H	10		20		50.0	20

Table 2: Release characteristics of ibuprofen from granules with pH dependent release in different pH-release medium.

Formulation code	Correlation coefficient	Release rate (slope) $x10^{-3}$	Intercept
A	0.9986	0.4043	3.0623
B	0.9829	0.2025	1.6321
C	0.9261	0.2649	2.1359

Table 3: Correlation between ibupforen content and the release-rate in distilled water as first-order kinetic and diffusion controlled

Formulation code	Drug content %	Correlation* coefficient	Release rate* $k.hr^{-1} x10^{-3}$	Intercept*
G	0.20	0.9286	1.6430	1.1700
E	0.67			
H	1.00			

Table 4: Correlation between ratio of HPMC to EC and release-rate of ibuprofen from granules with pH-independent release in distilled water.

Formulation code	Polymer ratio	ratio	Correlation coefficient	Slope $x10^{-3}$	Intercept
D	3/1	0.574	0.9992	1.1351	3.0733
E	1/1	1.000			
F	1/3	1.73			

Table 5: Analgesic activity of ibuprofen and its controlled release formulations after p-benzoquinone-induced writhing in mice expressed as percentage protection.

Time following adiminstration (hrs)	Gum acacia control	Ibuprofen nonformulated(control)	A	C	D	F
1	0	80	70	30	60	50
2	0	70	30	40	60	80
3	0	40	10	30	60	90
4	0	20	0	20	80	100

Data represent the percentage of mice showing protection against p-benzoquinone-induced writhing(n=10).

Table 6: Analgesic activity of ibuprofen and its controlled release formulation as measured by hot-plate method in mice.

Time following administration (hrs)	Gum acacia control	Ibuprofen nonformulation(control)	A	C	D	F
1	5.6 ± 0.41	15.3±1.20^{o}	24 ±0.81*	17.5±0.31	15.8±1.72	25* ±0.082
2	4.7 ± 0.37	14.7±1.03^{o}	11.8 ±0.83	17 ±1.32	16.5±1.70	22.5* ±0.61
3	6.2 ± 0.53	16.5±1.2 ^{o}	17.5 ±1.49	16.2±1.12	13.3±1.42	18.7 ±1.02
4	5.9 ± 0.47	14.8±0.91^{oo}	15.2 ±1.13	25 ±1.03*	16 ±1.59	13.8 ±1.10

Data represent the mean reaction time(in seconds)taken by mice dropped on a hot plats(n=10).

* Significant different from ibuprofen($P < 0.05$).

o Significant different from gum acacia($P < 0.05$)

Table 7: Antiinflammatory activity of ibuprofen and its controlled release formulations in rats.

Time following administration (hrs)	Gum acacia control	Ibuprofen nonformulated control)	A	C	D	F
1	2.10±0.15	4.62±0.45^{o}	6.40±0.38*	0.98±0.28	0.96±0.25	0.30±0.40
2	2.07±0.16	4.40±0.32^{o}	4.22±0.40	4.64±0.33	3.96±0.36	6.28±0.54*
3	2.11±0.15	2.31±0.17	2.26±0.18	2.22±0.20	3.69±0.28*	6.94±0.05*
4	2.09± 14	2.16±0.13	2.06±0.19	2.32±0.18	5.28±0.43*	6.6 ±0.58*

Data represent the mean (n=5) reaction time(in min)taken for the appearance of blue colour [illegible] round the site of histamine injection ± S.E.

* Significant different from ibuprofen ($p < 0.05$)

o Significant different from Gum acacia ($p < 0.05$).

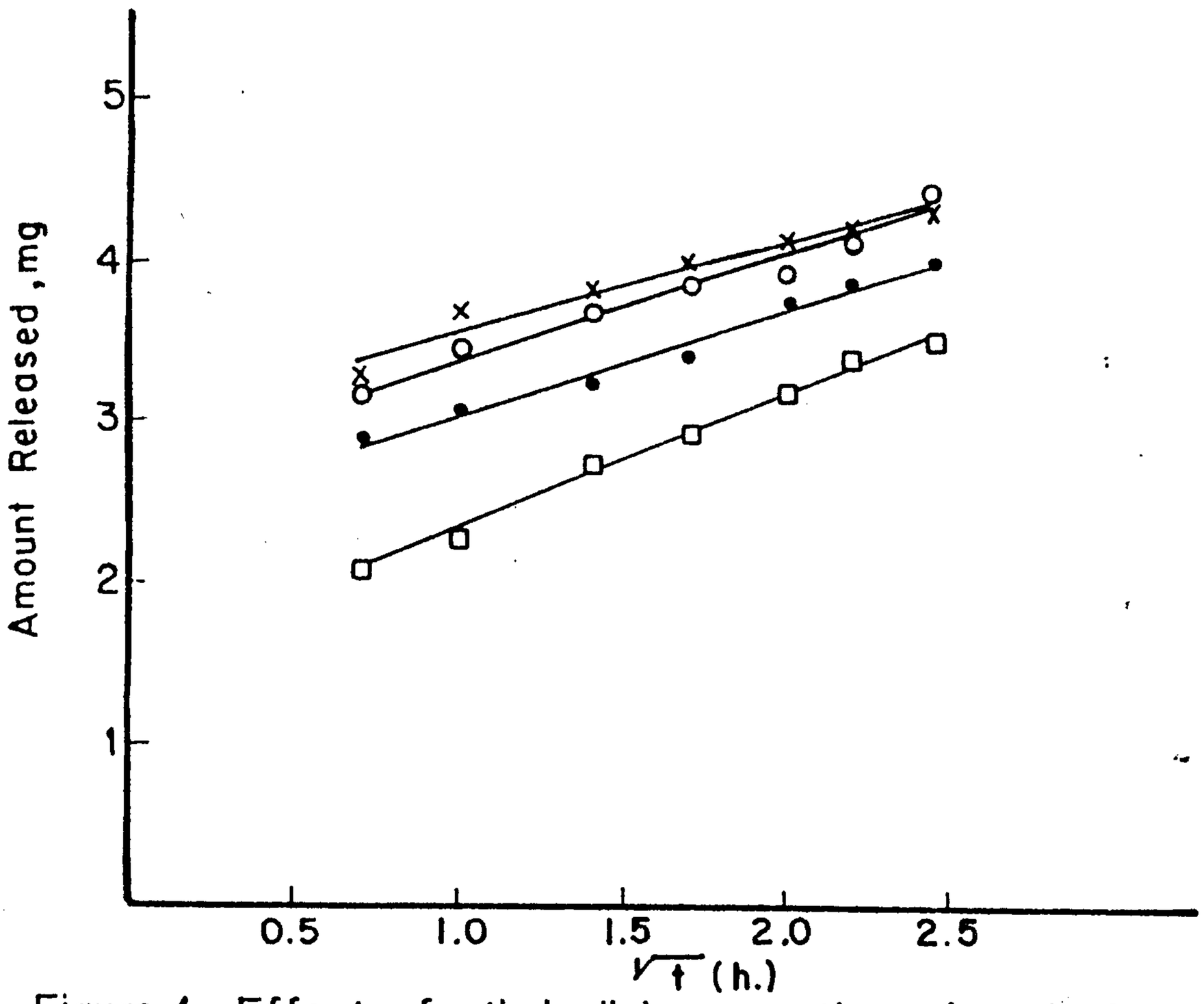

Figure 1– Effect of ethylcellulose on the release of Ibuprofen from granules with PH – dependent release in the medium at PH 6. (•) 0 % A; (○) 2 % B; (×) 4 % C; (□) drug powder.

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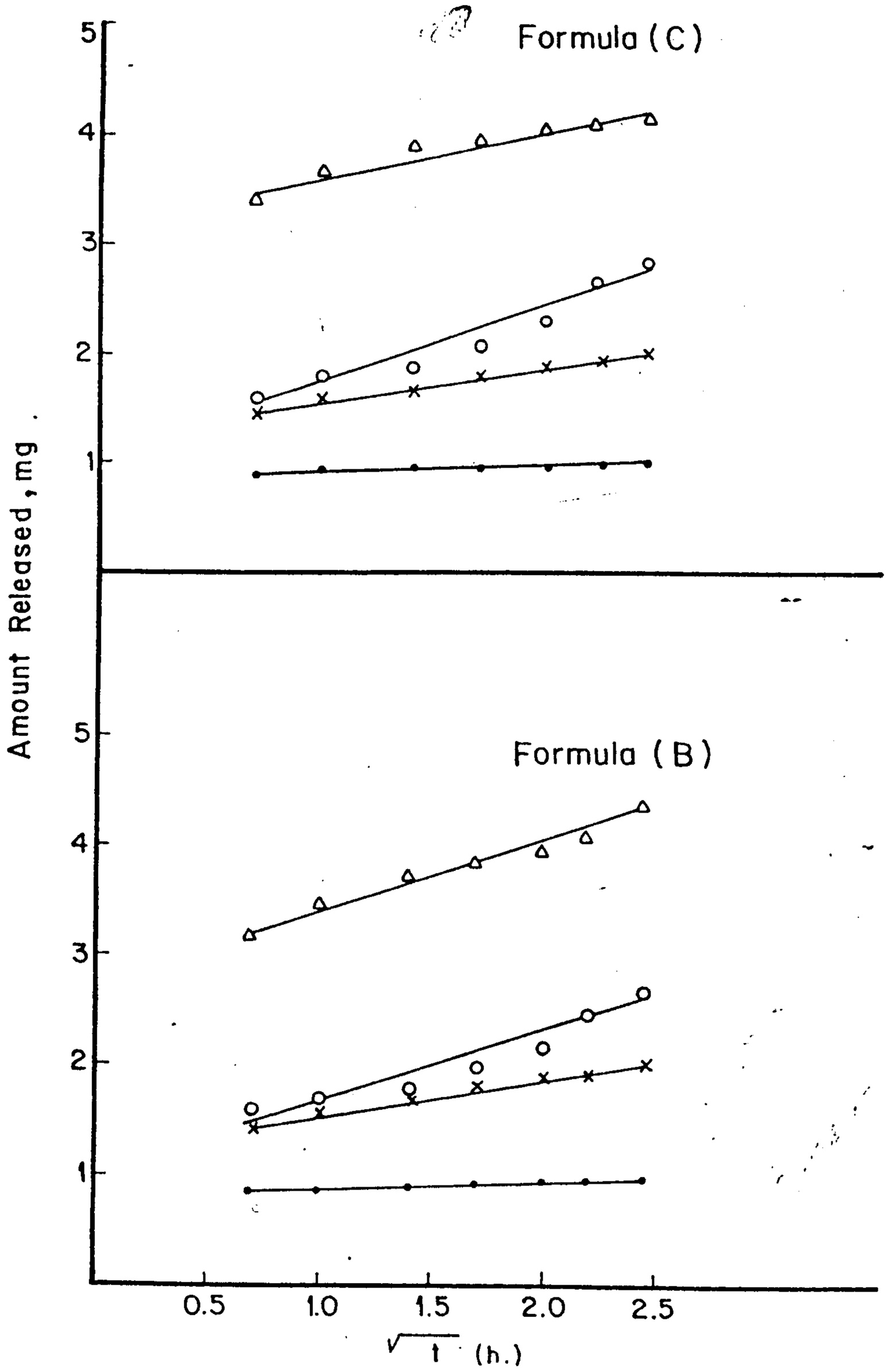

Figure 2–Effect of PH of the medium on the release of Ibuprofen from granules from formulation B and C with PH–dependent release.(•) PH 2 ; (△) PH6; (○) D.W; (×)PH 7 .

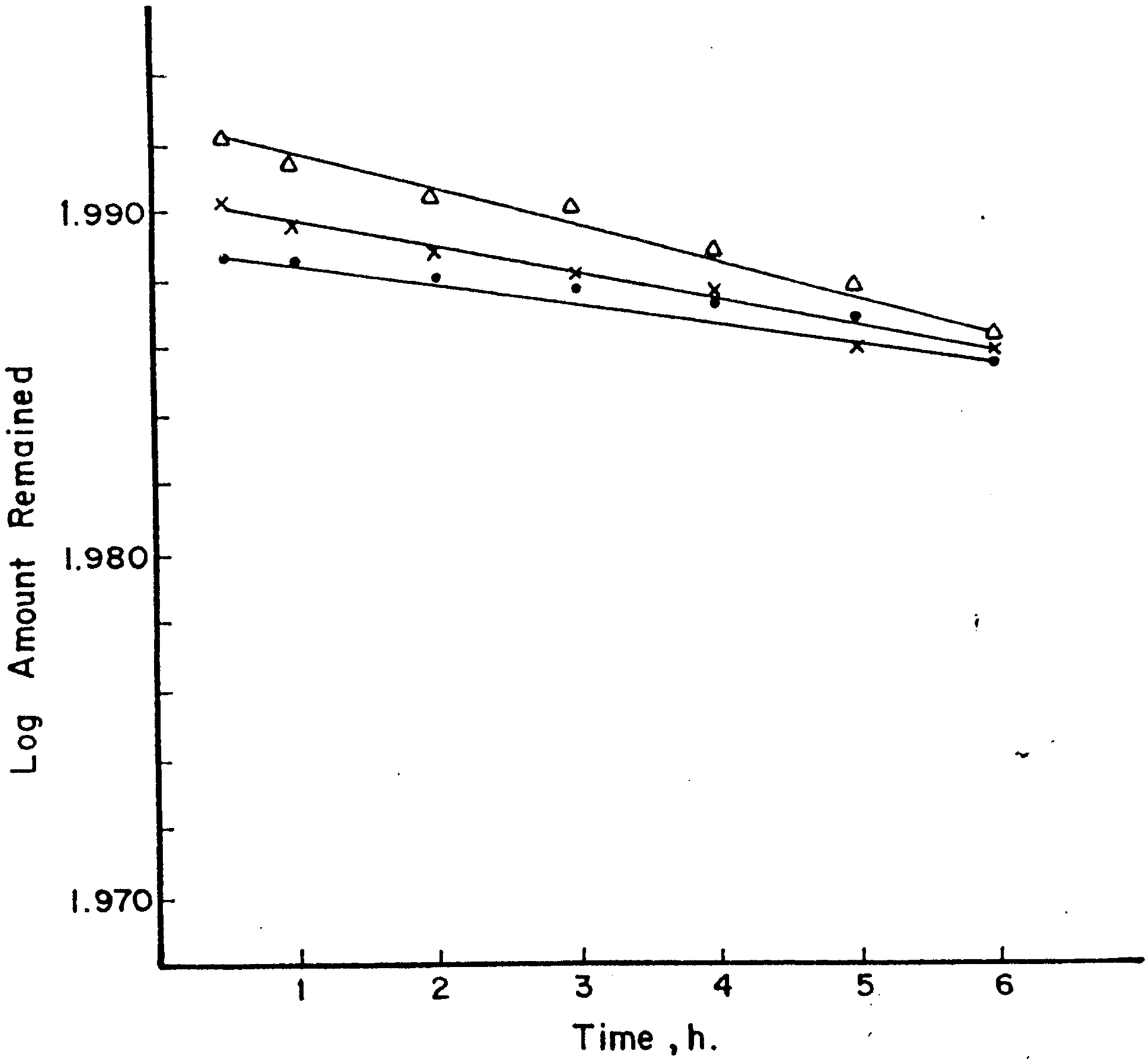

Figure 3-Effect of hydroxypropyl methylcellulose ethylcellulose ratio on the release of Ibuprofen from granules with PH- independent release in distilled water. (•) Formulation D(1 : ⅓) (x) Formulation E (1 : 1) (△) Formulation F(1 : 3).

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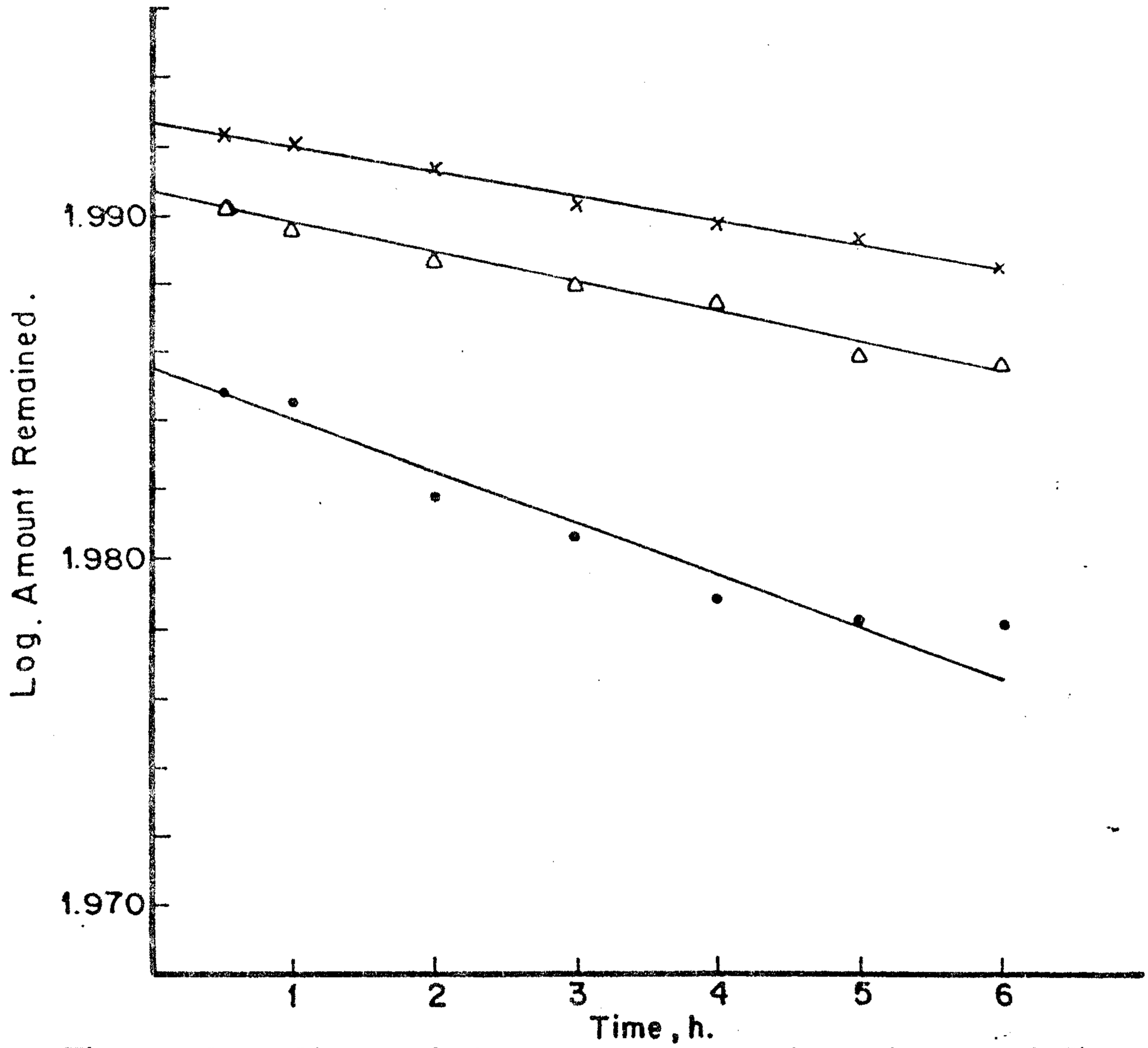

Figure 4 – Effect of drug content on the release of Ibuprofen from granules with PH – independent release in distilled water. (x) 0.2% formulation G, (△) 0.67% formulation E, (•) 1.00 % formulation H .

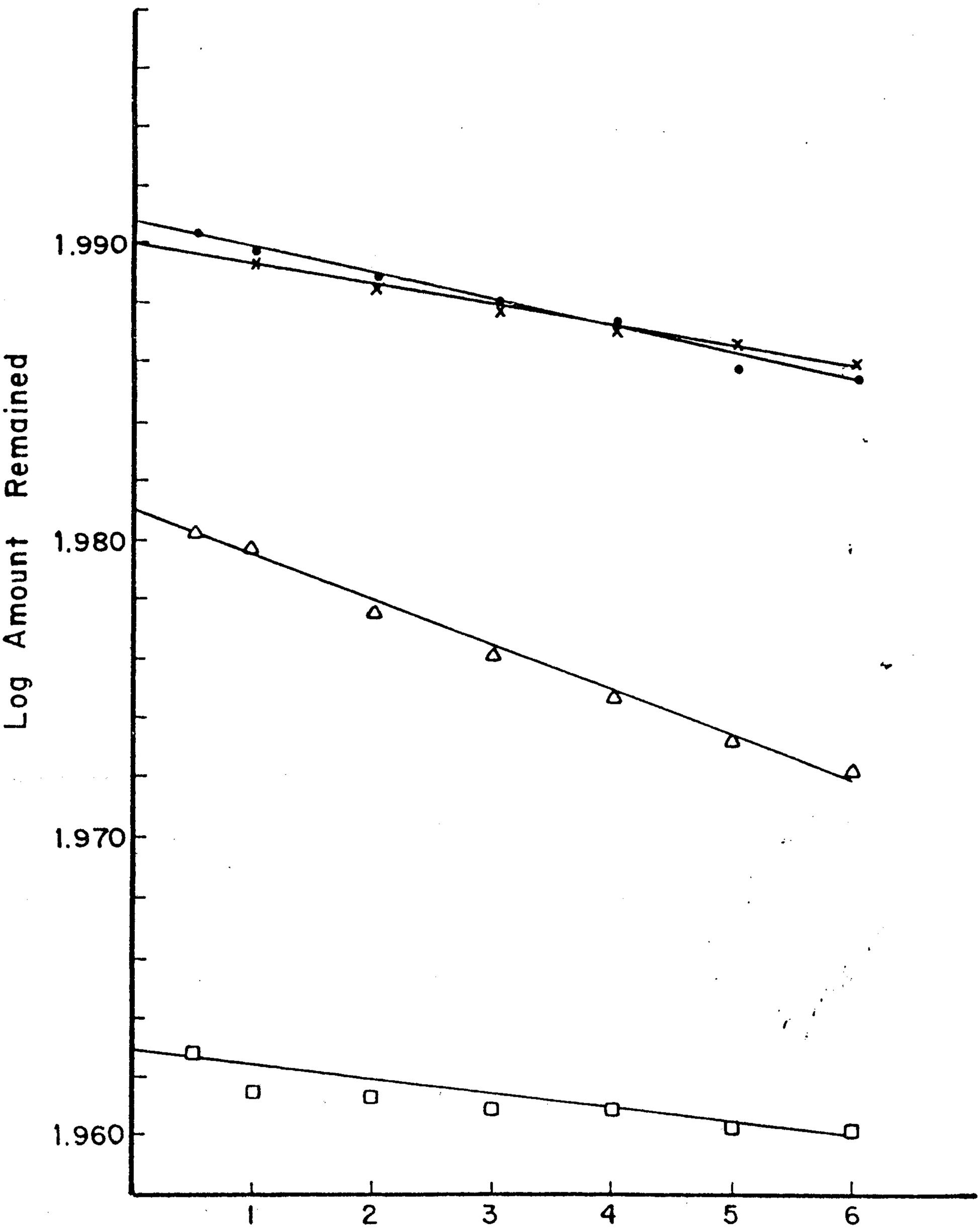

Figure 5-Effect of PH of the medium on the release of Ibuprofen from granules from formulation E with PH-independent release (•) Distilled water (×) PH 7; (△) PH6; (□) PH2 .

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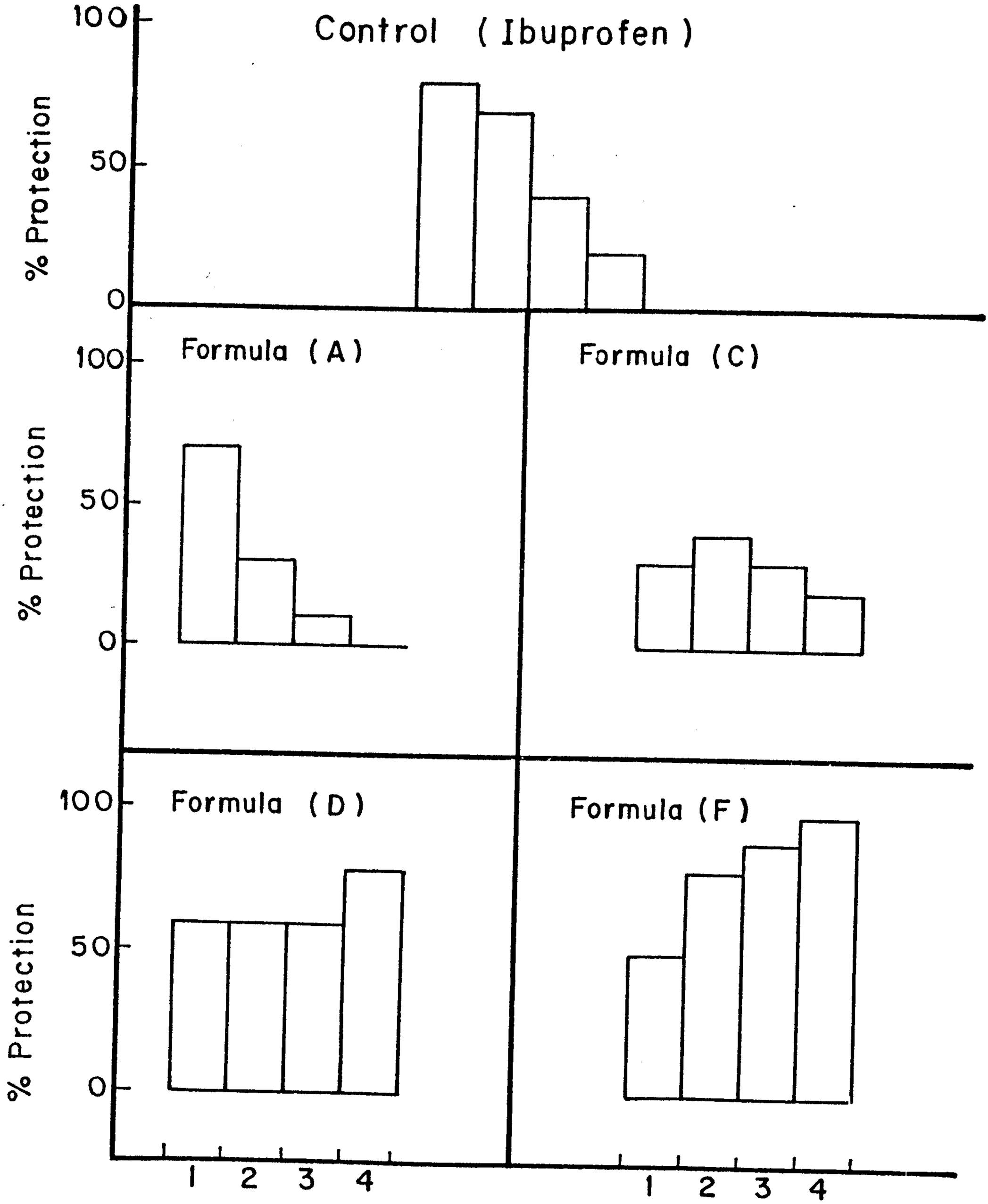

Figure 6- Percentage of animals showing protection against P-benzoquinone induced writhing.

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تحضير حبيبات الايبوبروفين ذات الأنطلاق المتحكم وتفييم التأثير المسكن والمضاد للالتهابات لها

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فى هذا البحث تم تحضير نوعين من حبيبات الايبربروفين : ـ النوع الأول يعتمد فى أنطلاق العقار على الاس الهيدروجينى لوسط الأنطلاق والنوع الثانى لايعتمد عليه فى الأنطلاق .

وقد كان تركيب النوع الأول يشمل العقار ومعه سيليلوز اسيتات فيثالات والاثيل سيليلوز الافيسيل بينما كان تركيب النوع الثانى يشمل العقار بنسبة مختلفة مع الهيدروكسى بروبيل ميثيل سيليلوز والاثيل سيليلوز أيضا بنسبة تتراوح من الثلث الى الثلاثة أجزاء وايضا مع أضافة نشا القمح .

وقد تمت دراسة تاثير العوامل الآتية : ـ

أ ـ نسبة خلط البولمرات فى التركيبه . ب ـ تأثير الاس الهيدروجينى لوسط الأنطلاق .

جـ ـ تركيز العقار فى الحبيبات على معدل أنطلاق العقار من هذه الحبيبات المحضره معمليا .

وقد أتضح من الدراسة مايأتى : ـ

١ ـ ان معدل انطلاق العقار من الحبيبات المعتمدة على الاس الهيدروجينى يقل بزيادة نسبة اثيل السيليلولوز فى الحبيبات والاس الهيدروجينى لوسط الأنطلاق .

٢ ـ ان معدل أنطلاق العقار من الحبيبات التى لاتعتمد على الاس الهيدروجينى يقل كلما زادت نسبة هيدروكسى بروبيل ميثيل سيليولوز الى نسبته الاثيل سيليولوز .

٣ ـ زيادة معدل أنطلاق العقار بزيادة تركيزه فى الحبيبات كما تمت دراسة التأثير المسكن لأربعة تركيبات مختلفة العقار بأستخدام طريقتين الأول بأستخدام مادة كيميائية (بارابنزوكينون) لاحداث الألم والأخرى بأستخدام طريقة السطح الساخن .

وكذلك تمت دراسة التأثير المضاد للألتهابات لهذه التركيبات بأستخدام طريقة حقن الهستامين تحت جلد الفئران البيضاء .

وقد أتضح من الدراسة أن الحبيبات التى لاتعتمد على الاس الهيدروجينى فى الأنطلاق ومحتويه على نسبة (٣:١) هيدروكسى بروبيل ميثيل سيليلوزالى اثيل سيليلولور) لها تأثير متحكم ضد الألتهابات وتسكين الألم لمدة أربعة ساعات أو أكثر . بينما الحبيبات التى تعتمد على الاس الهيدروجينى فى الأنطلاق والمحتوية على ٤ فى المائة اثيل سيليولوز و٢ فى المائة سيليلولوز اسيتات فيثالات لها القدرة على ريادة التأثير المسكن للالم وأقل نسبة لحماية الفأر ضد الألم الناتج من المادة الكيميائية .

كما أتضح أيضا من الدراسة أن الحبيبات التى لاتعتمد على الاس الهيدروجينى فى الأنطلاق أفضل من الحبيبات المعتمدة عليه فيما عدا تأثيرها المضاد للألتهاب عندما تعطى للفئران .

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