Bull. Pharm. Sci., Assiut University, Vol. 20, Part 1, June 1997, pp. 95-104.

IN VITRO RELEASE OF FREEZE-DRIED MEFENAMIC ACID-POLOXAMER FROM SUPPOSITORY BASES AND EVALUATION OF ITS ANTI-INFLAMMATORY EFFECT

S. A. El-Harras

Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

تضمن هذا البحث تحضير مركبات عقار حامض المفنمك مع البولوكسامير ٤٠٩ بنسب مختلفة [(١:٩) ، (١:١)] بطريقة التجفيد. وقد تم تحضير نوعين من اللبوسات ، النوع الأول هو اللبوس المحب للماء (بولى ايثلين جليكول) والنوع الثانى من اللبوسات المحبة للزيت (ويتبسول إتش ١٥) على أن يحتوى كل منهما كمية محسوبة من العقار بمفرده وكمية مساوية من التركيبات. كما تم تفسير النتائج فيزيائيا باستخدام طريقة الأشعة السينية والتفاضل السعرى الحرارى.

وقد تمت دراسة إنطلاق العقار من قواعد اللبوسات بنوعيها فى محلول منظم ذو أس أيدروجينى ٨ عند درجة حرارة ٣٧°. وقد قورنت النتائج مع نتائج معدل الانطلاق لنفس العقار بمفرده (دون معاملة) أو بعد تجفيده. وتمت هذه المقارنة عن طريق تعيين معدل نفاذية العقار.

أظهرت النتائج زيادة فى معدل انطلاق الدواء من التركيبات السابق ذكرها سواء من القاعدة المحبة للماء أو المحبة للزيت. غير أن معدل انطلاق الدواء من التركيبة (١:١) مع البولوكسامير من القاعدة المحبة للزيت أكبر من القاعدة المحبة للماء وذلك بدلالة معامل النفاذية (٨,٠٣٧٪ ، ١,٨٢٧٪ على التوالى).

وقد تم اختبار فاعلية قواعد اللبوسات التى تحتوى على تركيبة عقار المفنمك مع البولوكسامير (١:١) المجفدة فى كل من ويتبسول والبولى إيثيلين جليكول وذلك باستخدام اختبار (Carrageenin induced edema) فى الأرانب. وقد توصلت النتائج إلى أن التركيبة المجفدة مع البولوكسامير لها تأثير واضح كمضاد للالتهابات حيث أدت إلى تقليل حجم الإلتهاب بعد ساعة من إعطاء الدواء (٥٨,٦٪ ، ٤١,٤٪ على التوالى) بالمقارنة بتأثير الدواء الغير معامل (١٤,٧٪). ويتضح من ذلك أن البولوكسامير زاد من معدل انطلاق العقار من قواعد اللبوسات ولم يقلل من فاعليته كمضاد للإلتهابات.

The in vitro release of mefenamic acid (MFA) as well as its freeze-dried forms with poloxamer 409 (PF-127) in different ratios [(9:1), (1:1)] from suppository bases was investigated and confirmed with DSC and X-ray.

The release rate of MFA from lipophilic base (WH15) and hydrophilic base (3PEG 1000: 7 PEG 4000) in NaOH, KH_2PO_4 buffer at 37°C was performed. The release pattern of MFA:PF-127 freeze-dried samples from both selected bases was remarkably higher than that of pure untreated drug. However, the release of the drug as indicated by permeability rate constant was much more faster from WH15 compared to PEG using the same ratio of drug:PF-127 (8.037 vs 1.827, respectively).

MFA:PF-127 (1:1) freeze-dried formulated in WH15 and PEG suppository bases were evaluated by the carrageenin induced rabbit hindpaw edema. Both formulas resulted in inhibition of edema formation 1hr post medication (58.6%, and 41.4%, respectively) which was significantly greater than the rectal MFA as received in WH15 (14.7%).

INTRODUCTION

Mefenamic acid (ponstel) is N-(2,3 xylyl) anthranilic acid. It is a nonsteroidal agent with demonstrated anti-inflammatory, analgesic and antipyretic activity.[1] Following a single oral dose, peak plasma levels occurred in 2 to 4 hours with a half-life of 2-4 hours also.[2] Like

Received in 5/6/1997 & Accepted in 23/6/1997

other NSAIDs, the most common side effect of MFA acid in oral dosage forms is gastro-intestinal irritation.[3] Therefore, one of the alternative routes of administration to avoid the side effect of this drug is rectal suppository.[3] Besides, absorption of drugs from rectal mucosa directly into venous circulation may bring about faster onset of action than that observed of the oral administration.[4] Furthermore, drugs are administered rectally when the oral route is not convenient as in infants and elderly patients. It is well known that suppositories present a special dosage form which is suitable for several drugs.[4-11] However, literature reviews on MFA lack information concerning suppositories. In addition there is no rectal suppositories of MFA available on the market.

Poloxamer 409 (PF-127) one of many polyoxyethylene-polyoxypropylene-polyoxyethylene type block copolymers, is a nonionic surfactant with an average molecular weight of 12600.[3] Since it has many useful characteristics such as low toxicity, micelle formation, thermoreversibility and gelling property, PF-127 has been employed as a vehicle in various dosage forms such as semisolid dosage form for topical application,[12,13] injectable solutions[14] and ophthalmic use.[15]

Solid dispersions possess tremendous potential for improving physical, chemical and biopharmaceutical properties of drugs.[16-19] Quite recently, the use of solid dispersion to improve the release characteristic of different hydrophobic drugs from suppository bases has been studied by many authors.[20-22]

The aim of this study was to determine the impact of freeze-dried with PF-127 on the in vitro release of MFA from lipophilic WH15 and hydrophilic PEG 1000: PEG 4000 (3:7) suppository bases. The anti-inflammatory effect of MFA suppositories on the carrageenin induced edema in the hindpaw of rabbits was also evaluated.

EXPERIMENTAL

Materials

Mefenamic acid (MFA) [Upjohn U.S.A.], Carrageenin [Sigma U.S.A.], Carboxy methyl cellulose (CMC) [BDH Chemical, Ltd., Poole, England], Poloxamer 409 (PF-127) [BASF Wyandotte Corp., Parsippany NJ], Sodium hydroxide [El-Nasr, Egypt], Polyethylene glycol (PEG) 4000, 1000, 400, Potassium dihydrogen phosphate [May & Baker, U.K., Merck, Müchen, Germany], Propylene glycol (PG) [Sigma U.S.A.], Witepsol H15 (WH15) [Nobel Dynamite, Witten Werke, F.R.G.]., Dimethyl formamide (DMF) [Adwic Prolabs], Cellophane membrane [Spectrum Medical Industries, Inc., L.A., U.S.A.], Ammonium solution 33% [El Nasr, Egypt], Dimethyl sulfoxide (DMS) [Prolabo, France].

Apparatus

Double beam spectrophotometer [Shimadzu, Japan], Freeze-dryer: Model No. 500160 [Birchover Inst. Ltd., Herts, England], Water bath shaker [Gallenkamp EEC], Digital pH meter [MV870 NR (GDR)], TA-50I Differential scanning calorimeter [Shimadzu Co., Japan], X-ray diffractometer [Philips diffractometer PW 1710, Netherlands].

Methods

1- Solubility

Because of limited solubility of MFA in water,[23] different solvent buffer[24] mixtures (see Table 1) were attempted to determine the best one that may fulfill the pseudo sink condition solubility. Therefore, an excess amount of dry sample was added to 10 ml of one of the tested mixtures in 25 ml stoppered glass bottle which was placed in a mechanical shaking water bath at 37°C. After equilibrium, the aliquot was obtained by filtration and assayed spectrophotometrically at 287 nm.[23]

2- Preparation of freeze-dried samples

The freeze-dried samples were prepared according to Kurozumi *et al.*[18] PF-127 and MFA with different molecular ratios (PF-127:MFA 0:10, 1:9, 1:1 and 2:1) were dissolved in aqueous ammonium solutions (200 ml water + 35 drops of ammonium solution 28%) and then freeze-dried at -30°C under vacuum for 48

Table 1: Solubility of MFA in different media at 37°C.

Media composition	Solubility, mol/L x 10^5
Water	0.5880
KH_2PO_4/NaOH buffer (pH 7.4)	1.2828
KH_2PO_4/NaOH buffer (pH 8)	3.2654
KH_2PO_4/NaOH (pH 8) 5% DMF	9.2116
KH_2PO_4/NaOH (pH 8) 10% DMF	19.6264
KH_2PO_4/NaOH (pH 8) 5% DMS	4.9376
KH_2PO_4/NaOH (pH 8) 10% DMS	9.8584
KH_2PO_4/NaOH (pH 8) 5% PEG400	4.7302
KH_2PO_4/NaOH (pH 8) 10% PEG400	7.6040
KH_2PO_4/NaOH (pH 8) 5% PG	2.8782
KH_2PO_4/NaOH (pH 8) 10% PG	4.1762

hours. The dry powder was then stored in desiccator over silica gel at 25°C for D.S.C., X-ray examination and for the preparation of suppositories.

3- Differential scanning calorimetry (DSC)

Samples of about 5 mg were accurately weighed and encapsulated in flat-bottomed aluminum pans with crimped-on lids. The scanning speed of 10°C/min from 30°C to 300°C was used in nitrogen at flow rate of 40 ml/min. The instrument was initially calibrated with pure indium.

4- X-ray diffraction spectra

The x-ray diffraction patterns of the powder samples were obtained using a philips 1700 series diffractiometer which is equipped with curved graphite crystal monochromater, automatic divergence slit and automatic controller PW/1710. The target used was CuKα radiation operating at 40 KV and 30 mA ($\lambda_{K\alpha}$ = 1.5418 Å). The system was calibrated using silicon disc and/or powder (d_{111}= 3.1355 Å) as an external standard. The diffraction patterns were achieved using continuous scan mode with $2\theta°$ ranging from 2° to 80° or 70°. The output data achieved represented by 2θ, d Å, intensities is determined via the microprocessor of the PW/1710.

5- Preparation of suppositories

All suppositories, each containing 50 mg MFA, were prepared by fusion method.[25] Moulds of 1 g capacity were calibrated for each base. The amount of the respective bases required (WH15 and PEG) was calculated after determining the displacement value[26], then each base was melted on water bath at 70°C. In order to obtain uniform distribution of drug powder, the molten suppository base was allowed to cool until it almost reached 38-40°C. It was then blended with the drug (equivalent amount of 50 mg/suppository) by gradual addition of few milligrams at a time and stirred thoroughly till cloudiness developed. The mass was then poured into chilled moulds that previously kept at 5°C in fridge for 24 h. Before using in release studies, the filled moulds were allowed overnight to come slowly to room temperature.

6- *In vitro* release measurements

A simple assembly was used for release studies.[6] The suppository to be tested (Table 2) was placed in an open-ended glass tube over one end of which a standard cellophane membrane (soaked overnight in the release media) was stretched and securely fastened with a rubber band. The tube was hung in a vertical position into a 250-ml beaker containing 100 ml of release media at pH 8,[7] such that the lower end

Table 2: Composition of the different suppository formulas.

Formula	Composition
A	MFA as received incorporated with WH15
B	MFA freeze-dried incorporated with WH15
C	MFA:PF-127 (1:1) freeze-dried incorporated with WH15
D	MFA:PF-127 (1:1) freeze-dried incorporated with PEG blend (PEG/1000: PEG 4000 3:7)
E	MFA:PF-127 (9:1) freeze-dried incorporated with WH15
F	MFA:PF-127 (1:2)* freeze-dried

* It was difficult to be incorporated with the molten bases. Thus it was discarded from the study protocol.

of the tube was 3 cm from the bottom of the beaker. The beaker was then placed in a thermostatically controlled mechanical shaker bath (37±0.1°C). A 5 ml of 10% DMF in buffer placed inside the tube over the suppository at the beginning of the experiment. Samples of 5 ml each were withdrawn from the solution in the beaker (10% DMF in buffer) at specified time intervals (15, 30, 45, 60, 75, 90, 105, 120 minutes) and were replaced by fresh buffer. MFA concentrations of these samples were determined spectrophotometrically at 287 nm.

Calculations

The cumulative amount of MFA presented in the receptor compartment during the nth sampling (Q_n) was estimated by the following equation:[27]

$$Q_n = C_n \times V + V_s \times \sum_{i=1}^{n-1} C_i \quad (1)$$

where C is the measured concentration in the nth sample, V is the volume of receptor solution, and V_s is the volume of sampling. Fluxes (J) were determined from the slope of the cumulative amount of penetrated MFA versus time (t), and permeability coefficient (P) was estimated according to the following equation:

$$P = \frac{J}{C_d} \quad \ldots \quad (2)$$

where C_d is the concentration of the drug in the donor compartment.

7- Evaluation of anti-inflammatory effect of MFA

The anti-inflammatory effect of MFA was evaluated using the carrageenin induced rat or rabbit paw edema model.[28,29] The experiment was conducted on 20 male Bouscat rabbits weighing 1.6-2 kg fasted for 18 h with water available ad libitum. They were equally and randomly allocated into 5 groups. Paw edema was induced by subcutaneous injection into planter aponeurosis of the right hindpaw with 0.5 ml of 2.5% carrageenin physiologic solution whereas 0.5 ml saline solution was injected to the left hindpaw. A conical piece of suppository which contain 35 mg of MFA was cut and inserted to the rectum of the rabbit. The thickness of both right and left hindpaws was measured by thickness micrometer at a propriate time interval (1,2,4 and 6 hr) after treatment. The differences in thickness between each pair of hindpaws from each rabbit denoted the edema. The time course of anti-edemal effect

either oral or rectal of the following treatments was determined: control group or no medication (group 1), rectal drug as received incorporated with WH15 (group 2), rectal suppository of freeze-dried MFA:PF-127 (1:1) incorporated with WH15 (group 3), rectal suppository of freeze-dried MFA:PF-127 (1:1) incorporated with PEG (group 4) and Oral MFA suspension in 1% CMC by an oesophageal tube (group 5).

Statistical analysis

Statistical analysis was carried out by SAS computer program[30] using General Linear Models and Duncan's multiple range test for the differences between means.

RESULTS AND DISCUSSION

The aqueous solubility of MFA in different buffer solvent mixtures (Table 1) was determined at 37°C. The solubility of pure MFA was $0.58x10^5$ mol/L, $1.28x10^5$ mol/L and $3.26x10^5$ mol/L in water, at pH 7.4, and pH 8, respectively. Since the pH of rectum is 8, KH_2PO_4/NaOH buffer at pH 8 was used with other solvent to enhance the solubility of the drug to fulfill the pseudo sink condition solubility.

Based on the results displayed in Table (1) 10% DMF in KH_2PO_4/NaOH buffer increased the solubility of MFA almost 34 folds, compared to the solubility in water, therefore it was chosen as a media for suppository release study in vitro.

Differential scanning calorimetry (DSC)

The DSC tracing of MFA and PF-127 either alone or in binary system are displayed in Fig. 1. An endothermic peak (231.1°C) with a thaw melting point at 228.2°C and ΔH_f -349.29 joule/g was found at a scanning rate of 10°C/min for the untreated drug (Fig. 1: A). This endothermic peak ends with another broaden endothermic peak which may be attributed to melting the drug with effervescence.[23] This characteristic peak appeared again (228.2°C) on scanning the freeze-dried drug (Fig. 1: D) with thaw melting point at 210.8°C and ΔH_f -418.1 joule/g. On the other hand, PF-127 showed an endothermic transition peak at 54.2°C indicating the melting point of this polymer (Fig. 1: B). When MFA was either physically mixed or dispersed by freeze-drying with PF-127 (1:1) the characteristic peak of the drug almost disappeared (Fig. 1:C, Fig. 1: E) with ΔH -73.5 joule/g and -36 joule/g, respectively. The disappearance of the drug characteristic peak in freeze-dried sample indicates the lack of crystalinity of the freeze-dried drug as has been proved earlier by many author's.[17-19] However, the disappearance of the characteristic peak of the drug in physical mixture may be explained by the solubility of drug crystals in the molten PF-127 during the heating process. This agrees with the study of Khdr[31] who found that the characteristic endothermic peak of nifedipine PF-127 physical mixture disappeared on using DSC thermogram due to the solubility of this drug in the molten PF-127.

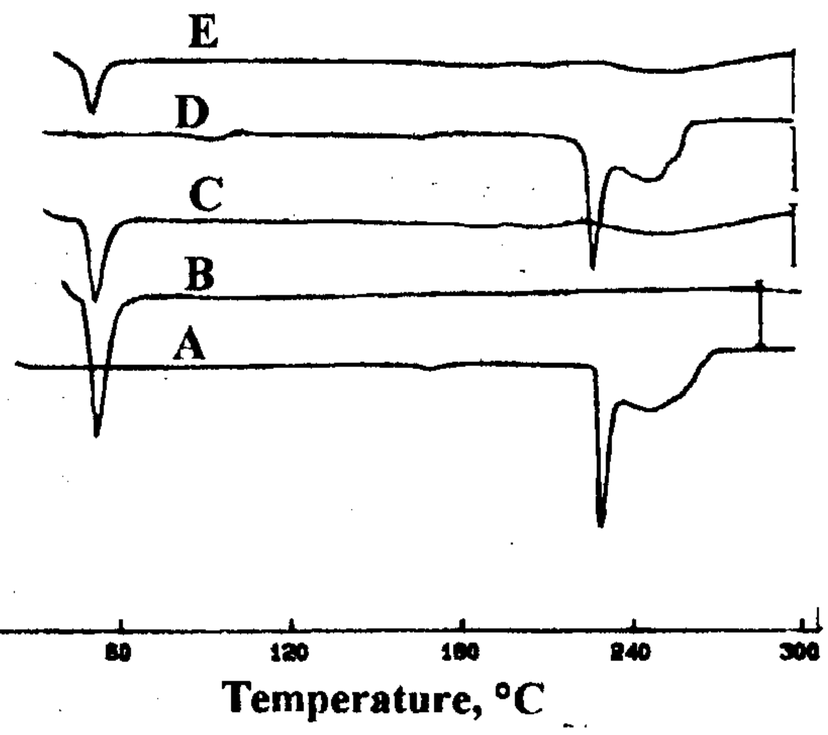

Fig. 1: DSC thermograms of (A) MFA, (B) PF-127, (C) 1:1 MFA:PF-127 physical mixture, (D) MFA freeze dried, (E) (1:1) MFA:PF-127 freeze-dried mixture.

X-ray diffraction spectra

Figure 2 shows the x-ray diffraction spectra of MFA, PF-127, MFA:PF-127 (1:1) physical mixtures, MFA:PF-127 (1:1) freeze-dried mixture. The spectrum of MFA (Fig. 2: A) exhibited characteristic peaks of MFA crystals at 13.92 Å, 4.15 Å, 3.39 Å, 3.2 Å (2 θ degree) with intensity of 6159, 8200, 10773, 3795, respectively. However, the spectrum of MFA:PF-127 (1:1) freeze-dried sample (Fig. 2: D) showed a reduction of intensity of these

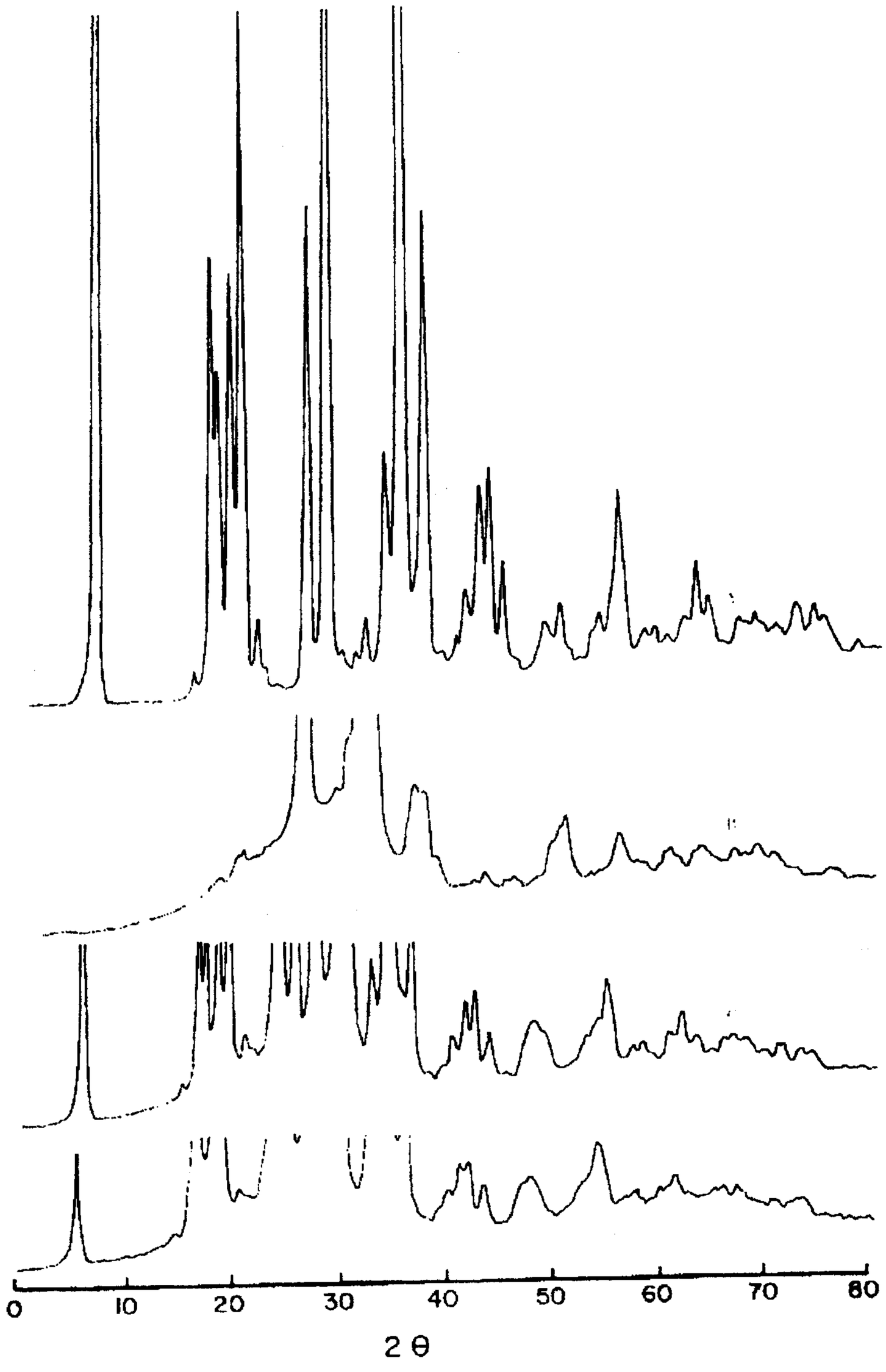

Fig. 2: X-ray diffraction patterns of (A) MFA, (B) PF-127, (C) MFA:PF-127 (1:1) physical mixture, (D) MFA:PF-127 freeze-dried form (1:1).

peaks (810, 3063, 4354, 1305, respectively). In case of the physical mixture of the same composition (1:1) (Fig. 2: C) these characteristic peaks were seen. These peaks though smaller than those of untreated drug due to the dilution factor, but still showed a larger intensity of peaks compared to freeze-dried drug (2187, 4321, 5207, 1855, respectively). On the other hand, PF-127 exhibited characteristic diffraction peaks (Fig. 2: B) which may interfere or overshadow the peaks of the drug. Thus, this finding indicates the presence of MFA freeze-dried sample in less crystalline form.

Release patterns

The release patterns of different formulations of MFA in two selected suppository bases were studied. Two bases were utilized in this study. Witepsol (lipophilic base) was selected since the base was found not to cause any apparent damage to rectal mucosa of rat.[5] The other base, PEG has been recommended for use as a suppository base for many drugs.[4,6,8,11] Plots of cumulative amount of MFA (Q) penetrated the cellophane membrane from different suppository formulations at different time periods are shown in Fig. 3.

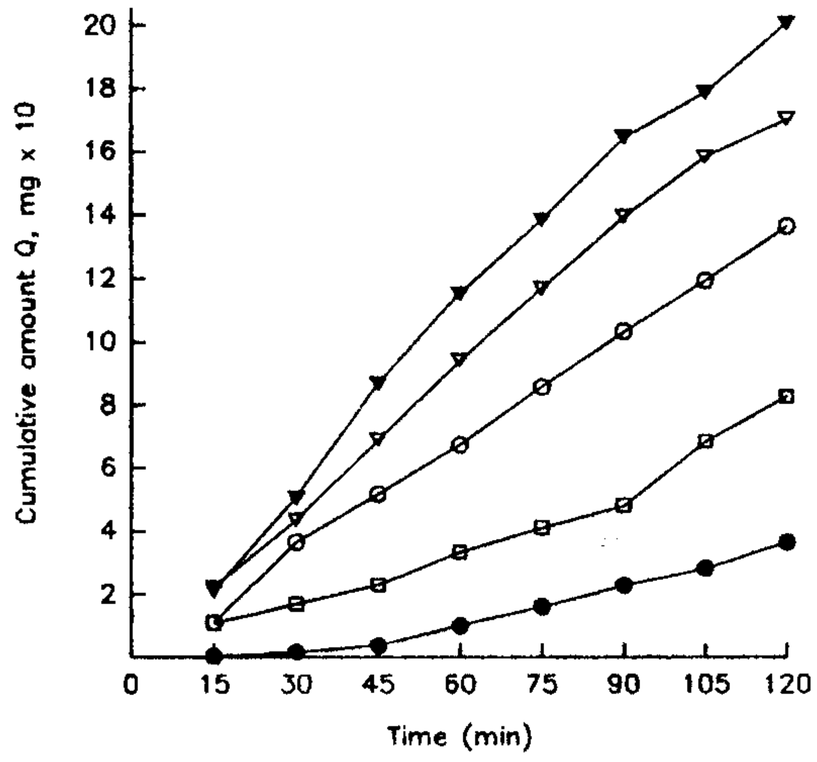

Fig. 3: Permeation patterns of MFA from WH15 and PEG suppository bases in pH 8 at 37°C.

- ● (A) MFA as received in WH15
- ○ (B) MFA freeze-dried with WH15
- ▼ (C) MFA:PF-127 (1:1) freeze-dried with WH15
- □ (D) MFA:PF-127 (1:1) freeze-dried with PEG
- ▽ (E) MFA:PF-127 (9:1) freeze-dried with WH15

As expected, the release of MFA:PF-127 freeze-dried samples from both lipophilic and hydrophilic bases through cellophane membrane was remarkably higher than that of pure untreated drug. This enhancement may be attributed to many factors such as surface activity of this polymer, increase the surface area of the drug due to freeze-drying process and/or the reduction in crystallinity of the drug as shown by DSC and X-ray. However, the release of the drug was much more faster from WH15 compared to PEG. This result is in a good agreement with that of Krasowska and Krowczynski[22] who stated that the release of ketoprofen from the lipophilic base was remarkably higher than that from the hydrophilic one. This can be explained by the suggestion of Ibrahim *et al.*[6] that the lipophilic base melted easily at 37°C (5 min), thus readily disperse the drug throughout the media. On the other hand, PEG base took about 40 minute to be completely dissolved as observed during the release study.

The release behavior was evaluated in terms of fluxes and permeability coefficients of MFA from these systems as summarized in Table 3.

It is clear that formula C [MFA:PF-127 (1:1) blended with WH15 base] permeated the cells membrane at higher rate (8 folds) compared to formula A (untreated drug blended with WH15 base). Furthermore, this formula permeated the cellophane at a rate 2 times higher compared to formula B (freeze-dried drug blended with WH15).

Analysis of the release data of MFA suppository was carried out according to zero order kinetics, first-order kinetic[32] and Higuchi model.[33] Table (4) shows that the data obtained followed zero order kinetics.

Evaluation of antiinflammatory effect

Table (5) and Figure (4) illustrate the anti-inflammatory effect of different formulations of MFA suppositories on the carrageenin-induced edema in the hindpaw of rabbits. From this table, it is obvious that at 1 hr post medication, the swelling was significantly reduced ($P < 0.05$) in all groups of rabbits treated with MFA suppositories as well as the group received oral suspension compared with the control group. The effect was more pronounced when using

MFA:PF-127 (1:1) freeze-dried in WH15 suppository where the average swelling percentage reached 38.8 vs 93.8 for the control group. While, upon using the same freeze-dried mixture in PEG suppository base the percentage of swelling was approximately equivalent to that of oral suspension (55% vs 50%, respectively). However, the least response was detected for the group treated with MFA as received where the swelling percentage was 80 (inhibition % = 14.7).

At 2 hr post treatment, rabbits of group 3 (drug:PF-127 freeze-dried in WH15) still showed the least swelling percentage which was significantly less than that of group 1 (control) or group 2 and numerically less than that of group 4 or group 5.

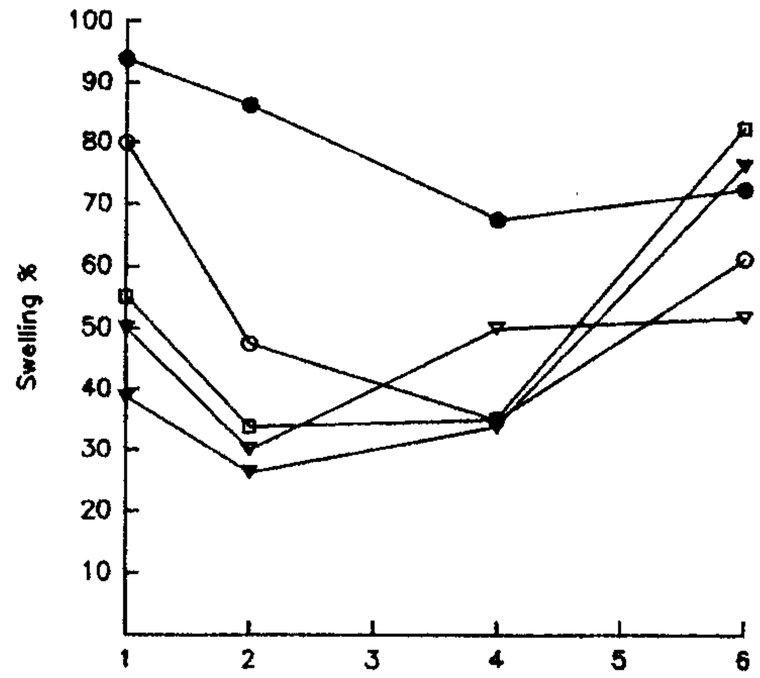

Fig. 4: Effect of MFA on swelling of rabbit hindpaw induced edema by carrageenin (Means of 4 rabbits).

- ● Control (no medication)
- ○ MFA with WH15
- ▼ MFA:PF-127 (1:1) freeze-dried with WH15
- □ MFA:PF-127 (1:1) freeze-dried with PEG
- ▽ MFA, oral suspension

Table 3: Permeation fluxes and permeability coefficient of MFA through cellophane membrane.

Suppository formulation	Flux (J) [$mg.cm^{-2}h^{-1}x10^{2}$]	Permeability coefficient (P) [$cm.h^{-1}x10^{3}$]	r
A	6.7196	1.3439	0.9825[a]
B	21.8973	4.3795	0.9990[a]
C	40.1884	8.0377	0.9989[b]
D	9.1372	1.8274	0.9897[b]
E	30.4203	6.0859	0.9990[b]

a Calculated for 2 hr. b Calculated for 1 hr.

Table 4: Kinetics assessment of release data from different formulations of MFA suppository.

Formula	Zero order		First order			Q vs $t^{0.5}$		Log Q vs log t	
	r	K_0 ($mg.h^{-1}$)	r	K_1 (h^{-1})	t½ h	r	K_H ($mg.h^{0.5}$)	r	slope
A	0.9826	0.4260	0.9825	0.0042752	162.09	0.9423	0.1252	0.8056	3.0520
B	0.9988	1.3883	0.9989	0.0140992	49.15	0.9937	0.4277	0.9923	1.1230
C	0.9932	2.0526	0.8716	0.0363627	19.06	0.9981	0.6388	0.9937	1.0820
D	0.9794	0.8021	0.9790	0.00809	85.66	0.9476	0.2404	0.9816	0.9666
E	0.9965	1.7546	0.9968	0.0179047	38.70	0.9951	0.5426	0.9988	1.0019

Table 5: The antiinflammatory effect of mefenamic acid (MFA) suppositories on the carrageenin-induced edema in the hindpaw of rabbits.

Group Treatment	Swelling % of edema[1,2]			
	1 hr	2 hr	4 hr	6 hr
1 no medication (control)	93.8±4.7[a]	86.3±0.5[a]	67.5±4.8[a]	72.5±4.8[a]
2 MFA rectal drug as received in WH15	80.0±4.0[b] (14.7)[3]	47.5±4.7[b] (49.9)[3]	35.0±7.9[b] (48.2)[3]	61.3±1.2[ab] (15.5)[3]
3 Drug:PF-127 (1:1) freeze-dried in WH15	38.8±6.3[d] (58.6)	26.3±4.2[c] (69.5)[3]	33.8±4.7[b] (49.9)[3]	76.3±1.3[a] (-5.2)[3]
4 Drug:PF-127 (1:1) freeze-dried in PEG	55.0±9.6[c] (41.4)[3]	33.8±4.5[c] (60.8)	35.0±5.0[b] (48.2)[3]	82.5±11.8[a] (-13.8)[3]
5 MFA oral suspension (drug as received)	50.0±4.6[c] (46.7)[3]	30.0±5.6[c] (65.2)[3]	50.0±4.2[b] (25.9)[3]	51.8±6.9[b] (28.6)[3]

[1] Mean ± SE
[2] Mean of the same column with the same superscripts are not significantly different ($P > 0.05$).
[3] The number between parenthesis indicates the inhibition % of edema =

$$\left[\frac{\text{Swelling \% of tested group - swelling \% of control group}}{\text{swelling \% of control group}} \times 100\right]$$

At 4 hr post treatment the antiinflammatory effect of MFA began to decrease as indicated by some increase in swelling percentage (i.e., decrease in inhibition% of edema) and by the insignificant differences in swelling % between the four groups received MFA. The increase in swelling percentage was more pronounced at 6 hr post treatment.

It seems that the duration of action of MFA is directly correlated with the $t^{1/2}$ of the drug ($t_{1/2}$= 2-4 hr). These results are in a good agreement with those of Miller[34] who stated that the duration of action of antiinflammatory drugs correlates with the half life of this group of the drug.

It can be concluded that the increase in release rate of MFA freeze-dried forms incorporated in suppository bases may be due to the reduction in crystallinity of the drug in this formation. Moreover, the surface activity of PF-127 polymer may enhance the affinity of MFA which is water insoluble drug to the aqueous release media. Consequently, the usage of PF-127 in preparing freeze-dried mixtures of the drugs is a useful technique for enhancing the release of the drug from different suppository bases, which is reflected in an improvement of the antiinflammatory effect of MFA from these formulations.

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