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RESEARCH PAPER

Effect of Chemical Structure on the Release of Certain Propionic Acid Derivatives from Their Dosage Forms

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ABSTRACT

The aim of this study was to investigate the relationship between the chemical structure and release properties of certain drug products. Propionic acid derivatives were used as a model. These include ibuprofen (I), ketoprofen (K), tiaprofenic acid (T), flurbiprofen (F), and naproxen (N). They are all aryl derivatives of propionic acid and differ only in the aryl group. Such an aryl group may be either isobutylphenyl, benzoylphenyl, benzoylthienyl, fluorobiphenyl, or methoxynaphthyl group in I, K, T, F, and N, respectively. Three dosage forms were selected for this study: capsules, suppositories, and creams. The release of propionic acid derivatives from the capsules and suppositories decreased in the order ibuprofen > tiaprofenic acid > ketoprofen > flurbiprofen > naproxen, and for the creams the release decreased in the order ibuprofen > tiaprofenic acid > flurbiprofen > ketoprofen > naproxen. The difference in drug release in the first case was attributed to the difference in the chain length, and in the creams which are composed of two phases, the partition coefficient was found to affect the drug release. The molecular weight of the drug had no effect on the release. The drug release from different dosage forms was not affected after 1 month storage.

INTRODUCTION

The importance of a drug's physicochemical properties in determining its biological and pharmaceutical characteristics has long been recognized. Of particular importance are the aqueous solubility and the partition coefficient, which are the major determinants of a drug's dissolution, distribution, and availability (1). Herman et al. (2) studied structure pharmacokinetic relationship for systemic drug distribution. Kim et al. (3) studied structure activity relationship of 5-lipoxygenase inhibitors. Flynn et al. (4) studied the correlation between alkyl chain length and mass transport across membranes. Literature review lacks any information concerning the relation between the structure and release of the drug.

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Release from dosage forms and subsequent bioabsorption are controlled by the physicochemical properties of drugs and delivery form, and the physiologic and physicochemical properties of the biological system. Drug concentration, aqueous solubility, molecular size, crystal form, protein binding, and pK_a are among the physicochemical factors that must be understood in order to design a delivery system that exhibits controlled- or sustained-release characteristics (5).

The aim of this research was to choose a group of drugs, for example, propionic acid drugs (nonsteroidal, anti-inflammatory), which have nearly the same physicochemical parameters and to investigate the effect of structure or some functional group on the release and stability properties from different dosage forms (capsules, creams, and suppositories). Propionic acid drugs used were naproxen (N), flurbiprofen (F), ketoprofen (K), tiaprofenic acid (T), and ibuprofen (I).

EXPERIMENTAL PROCEDURES

Materials

Ibuprofen and flurbiprofen (Boots Co., Nottingham, UK), were kindly supplied by El-Kahira Co. for Pharmaceutical and Chemical Industries, Egypt; ketoprofen (Rhône-Poulenc Rorer, France) was kindly supplied by Alexandria Co. for Pharmaceutical and Chemical Industries, Egypt; naproxen (Syntex Research) was kindly provided by Misr Drug Company, Egypt; tiaprofenic acid was kindly provided by Roussel-Uclaf, Egypt. Lactose (Meggle, Germany), maize starch, sodium lauryl sulfate (Prolabo, France), suppocire NA (Gattefosse, France), polyethylene glycols 600 and 6000 (PEG, Union Carbide, NY), white beeswax and propylene glycol (BDH, UK), cetyl alcohol (Henkel, UK), sodium borate, and liquid paraffin (of analytical grade purity) were used.

Equipment

A USP dissolution tester, Apparatus I and II (Pharma Test, Germany), double-beam spectrophotometer (Shimadzu UV 150-02, Kyoto, Japan), and thermostatically controlled shaking water bath (Gallenkamp, England) were used.

Preparation and In Vitro Release of Different Dosage Forms

Capsules

Two adjuvants were used: lactose and starch. These additives were used alone in concentrations of 100 mg drug and 30 mg adjuvant. The release of drugs from their capsule formulae (Table 1) was performed using the USP dissolution tester, Apparatus I. The basket was rotated at 50 rpm in 900 ml distilled water maintained at 37 ± 0.5°C. Drug content was determined by measuring the absorbance at λ_{max} 332 nm for naproxen (K = 156.89); λ_{max} 247 nm for flurbiprofen, (K = 12.66); λ_{max} 259 nm for ketoprofen (K = 15.15); λ_{max} 314 nm for tiaprofenic acid (K = 16.86), and λ_{max} 263 nm for ibuprofen (K = 648.5) in the withdrawn aliquots after suitable dilution using distilled water as a blank.

Suppositories

Suppositories of adult size, 2 gm each containing 100 mg of propionic acid drugs, were prepared adopting the cream melting technique. Two different bases were used in preparing the suppositories: water-soluble base (PEG) and emulsifying base (suppocire NA10). The components of these bases are shown in Table 1. The prepared suppositories were stored in a refrigerator, taken out 24 hr before investigation, and left at room temperature to attain equilibrium. The in vitro release of propionic acid drugs from the different suppository formulae was performed using the USP dissolution tester, Apparatus I. The basket was rotated at 100 rpm in 250 ml distilled water maintained at 37 ± 0.5°C. Drug content was determined as described.

Table 1

Composition of Dosage Forms Used

Dosage Form	Composition
Capsules	100 mg drug
	100 mg drug + 30 mg lactose
	100 mg drug + 30 mg starch
Suppository bases	
Water-soluble base	Polyethylene glycol 6000, 60 g
	Polyethylene glycol 600, 40 g
Emulsifying base	Suppocire NA 10
Cream bases	
o/w Base	Cetyl alcohol, 15 g
	Beeswax, 1 g
	Sodium lauryl sulfate, 2 g
	Propylene glycol, 10 g
	Water, 72 g
w/o Base	Spermaceti, 12.5 g
	White wax, 12.0 g
	Mineral oil, 56 g
	Sodium borate, 0.5 g
	Water, 19 g

Creams

Two creams were selected (o/w and w/o). The components of creams are shown in Table 1. The cream was prepared by hot fusion method (6), by melting the fatty ingredients on a water bath at a temperature not exceeding 70°C. The water-soluble ingredients were dissolved in water, heated to the same temperature and added to the melted ingredients. The base was left to cool with continuous levigation. Each 2 gm of cream base contained 100 mg of propionic acid drugs. The prepared cream was put in a watch glass of 8 cm diameter and covered with aluminum window screens (about 18 mesh) molded to fit a 9-cm diameter watch glass. The watch glass–cream–screen sandwich was held together by three equally spaced plastic clips (7). This assembly was placed at the bottom of a USP dissolution vessel containing 900 ml distilled water at 37 ± 0.5°C and the paddle speed was 50 rpm. The assembly was centered if needed with the aid of a glass rod. The distance between the paddle and the watch glass in the dissolution vessel was kept constant in all experiments. To avoid evaporation of receptor medium from the vessels, the vessels were kept covered except during sampling. Aliquots were withdrawn at each time interval and the amount of drug released was determined spectrophotometrically.

Effect of Storage on the Release of Propionic Acid Derivatives from Their Different Formulae

Propionic acid drugs in three dosage forms (capsules, creams, and suppositories) were stored in high-density polyethylene bottles at 40 and 40°C with 80% relative humidity for 1 month. After storage the samples were tested for drug release as described.

RESULTS AND DISCUSSION

Effect of Different Dosage Forms on the Release of Propionic Acid Derivatives

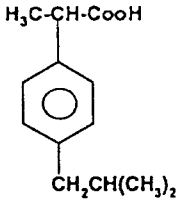
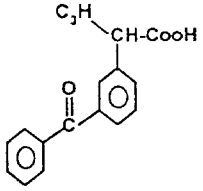
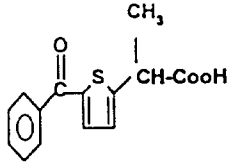
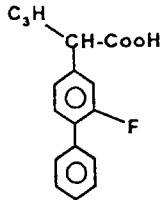
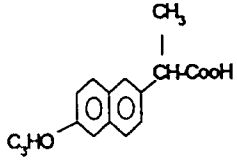
Table 2 shows the chemical structure and physical parameters of propionic acid derivatives (8,9). Figures 1 and 2 show the release of drugs from their different capsule formulations. It is clear that the presence of either lactose or starch as diluent increased the percentage of drug released. The release of propionic acid derivatives decreased in the order I > T > K > F > N in both the plain capsules and capsules containing lactose as a diluent. When starch was used as a diluent the release decreased in the order I > K > T > F > N. The increase in the release of propionic acid drugs using lactose as a diluent can be attributed to the fact that lactose is water soluble, thus the powder bed of drugs changes from a hydrophobic nature to a more hydrophilic nature (10). Starch, although water insoluble, increased the release of the drugs and the dissolution medium penetrated through the capsule content causing the starch to swell extensively, thus helping to break up the powder bed of drug and therefore facilitating its release (11). This finding is in accordance with that of Levy et al. (12) who studied the effect of starch on the rate of dissolution of salicylic acid tablets. The dissolution enhancing effect of starch was attributed to improved and more complete disintegration. Later, it was suggested that the fine starch particles form a layer on the outer surface of the hydrophobic drug particles. This association imparts a hydrophilic character to the granules and thus increases the effective surface area and the rate of dissolution. Similar results were obtained by Abd El-Bary et al. (13) for tenoxicam capsules using starch and lactose as diluents.

Figure 3 shows the release of propionic acid drugs from their different suppository bases. It is clear that the polyethylene glycol bases showed a higher medicament release in relation to suppocire NA10. This could be because the drugs, being water insoluble, had a higher affinity toward the fatty bases than the polyethylene glycol bases, which have great hydrophilic and solubilizing properties. The obtained results are in accordance with the results of Vidras et al. (14) for indomethacin release from polyethylene glycol, esterified fatty acids, and theobroma oil. They are also in agreement with the results obtained by Zein El-Din et al. (15), who found that the release of the insoluble Norfloxacin from polyethylene glycol suppositories was greater than its release from Witepsol suppositories. Similar results were also obtained by Abd El-Bary et al. (16) for tenoxicam release from polyethylene glycol and suppocire bases.

Figure 4 shows the release of drugs from their different cream bases. It is clear that the amount of propionic acid derivatives released from the o/w cream base was greater than that from the w/o cream base. This is because the drug is water insoluble and has a higher affinity toward the oil phase than the aqueous phase. The release of propionic acid derivatives decreased in the order I > T > F > K > N. The obtained results are in a good agreement with the work of Takamura et al. (17) for diclofenac sodium release from o/w emulsion hydrophilic and absorptive ointments. Similar results were also obtained by Akhter et al. (18) for ibuprofen and flurbiprofen. They found that flurbiprofen permeated to a lesser extent than ibuprofen. The results are also in agreement with the results of Berba et al.

Table 2

Structure and Physical Parameters of Propionic Acid Derivatives Used

	Ibuprofen	Ketoprofen	Tiaprofenic acid	Flurbiprofen	Naproxen
Structure					
Chemical formula	$C_{13}H_{18}O_2$	$C_{16}H_{14}O_3$	$C_{14}H_{12}O_3S$	$C_{15}H_{13}FO_2$	$C_{14}H_{14}O_3$
Mol. wt.	206.3	254.3	260.3	244.3	230.3
Melting point (°C)	75–78	93–96	95	110	156
pK_a	4.4	5.94	3	4.15	4.2

Ibuprofen: 2-(4-isobutylphenyl) propionic acid.
Ketoprofen: 2-(3 benzoylphenyl) propionic acid.
Tiaprofenic acid: 2-(5-benzoy-2-thienyl) propionic acid
Flurbiprofen: 2-(2-fluorobiphenyl-4-yl) propionic acid.
Naproxen: 2-(6-methoxy-2-naphtyl) propionic acid.

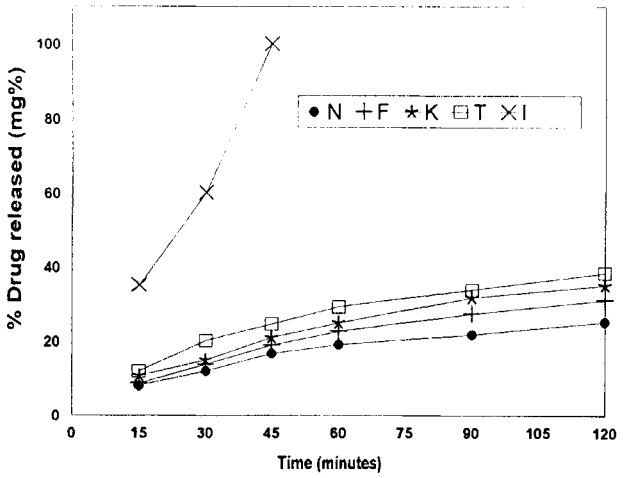


Figure 1. Release of propionic acid derivatives from their plain capsules in distilled water.

(19) for indomethacin, ketoprofen, and sulindac release from different ointment bases.

Effect of Structure on the Release Properties

The stereochemistry associated with the chiral center in the aryl propionic acid derivatives plays an important role in both in vivo and in vitro activities of these agents (9). All aryl propionic acid derivatives have been shown to possess the (S) absolute configuration (9). The release of drugs was in accordance with the melting point, i.e., as melting point increased (from I > T > K > F > N), the release of drug decreased, as for capsule and suppository dosage forms. For cream dosage form, the rank became different. This is because cream bases contain two phases (oil and aqueous) and according to the partition coefficient of each drug, the amount of drug released was different, therefore the partition coefficient was the controlling factor rather than the melting point. The effect of melting point on the drug release was in accordance with Yalkowsky et al. (1), who found that as chain length of alkyl *p*-aminobenzoate increased, the melting point decreased almost linearly to the butyl ester and then increased gradually and irregularly. This alteration in melting point toward aryl propionic acid drugs was in good agreement with Breusch (20), who showed that B-hydroxy, B-phenyl, and B-alkylpropionic acids exhibited a regular odd-even alteration in solubilities and in melting points above five carbons. Propionic acid derivatives consist mainly of aryl propionic acid, so that ibuprofen, which contains an

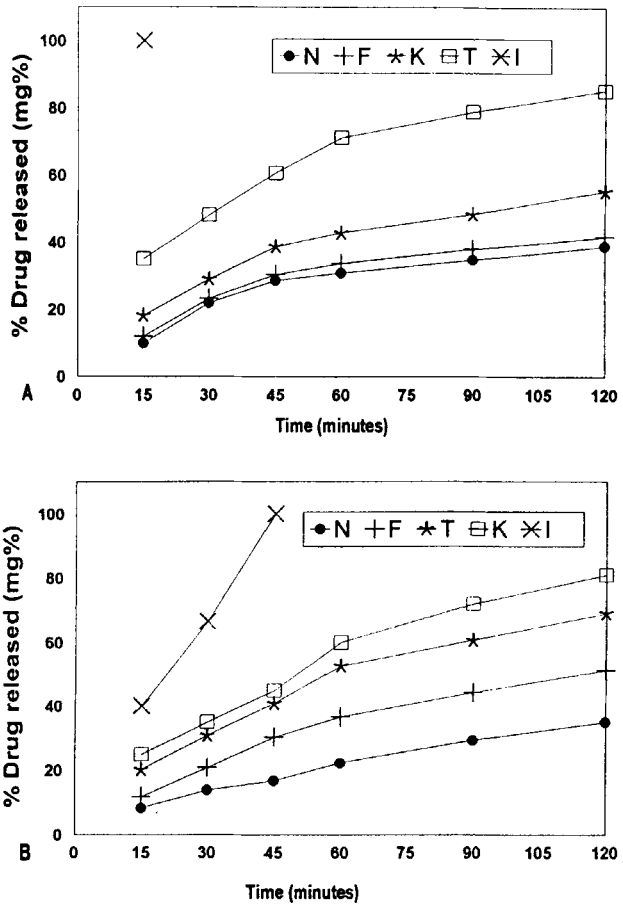


Figure 2. (a) Release of propionic acid derivatives from capsules containing lactose as a diluent in distilled water. (b) Release of propionic acid derivatives from capsules containing starch as a diluent in distilled water.

isobutyl group that is a small chain having low melting point, gave higher drug release in the three forementioned dosage forms. Replacement of isobutyl group by a benzoyl group (longer chain or aromatic ring) results in ketoprofen, which has a higher melting point with a moderate drug release. Replacement of the phenyl group in ketoprofen with thienyl group, as in case of tiaprofenic acid, does not affect either drug release or melting point. The obtained results are in accordance with the work of Flynn et al. (4) who found that the flux of alkyl *p*-aminobenzoate drops markedly at longer chain length. The results are also in agreement with those obtained by Flynn (21) who found that beyond the chain length (C_4 to C_6), further increase in chain length lead to incrementally higher melting points

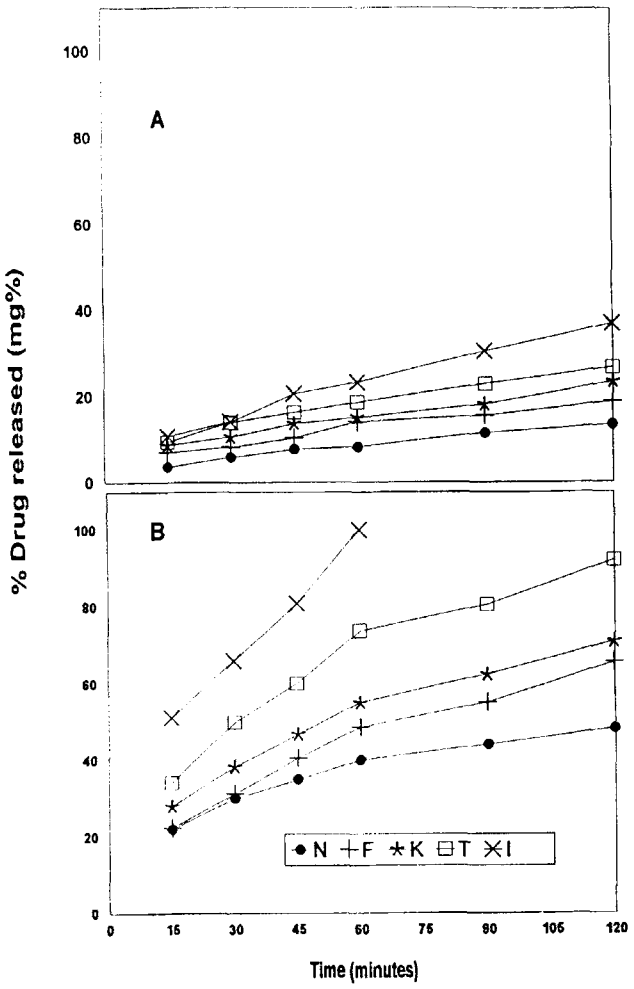


Figure 3. Release of propionic acid derivatives from their different suppository formulae in distilled water [suppocire NA10 (a) and PEG (b)].

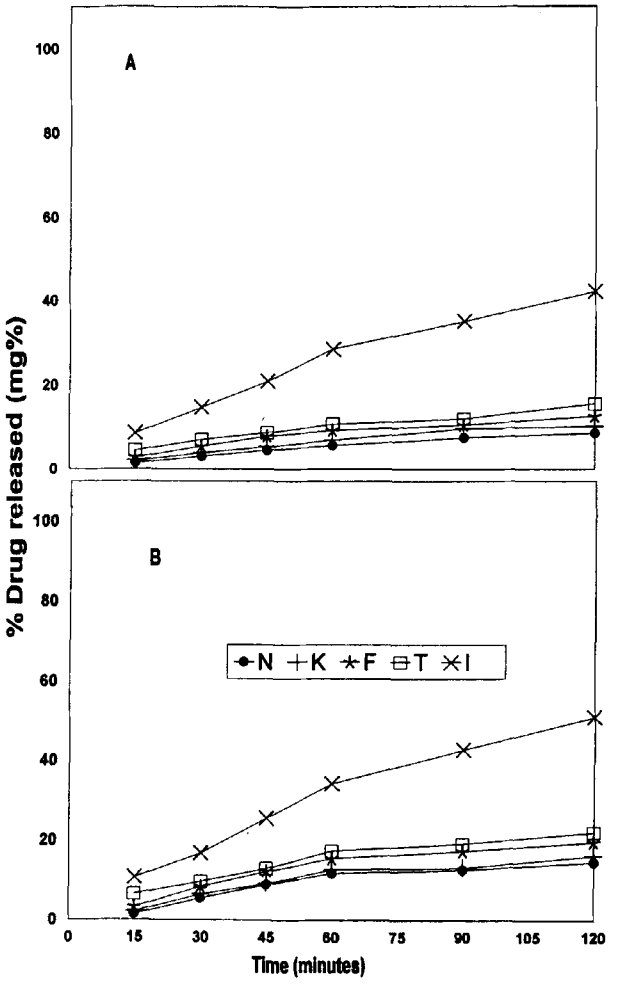


Figure 4. Release of propionic acid derivatives from their different cream formulae in distilled water [w/o (a) and o/w (b)].

and heats of fusion, both of which are unfavorable to solubility. Removal of carbonyl group in ketoprofen and addition of a fluorine atom produced flurbiprofen, which has a certain solubility in water; thus, it can partition itself between the oil and aqueous phases producing a higher drug release than ketoprofen, as in the case of cream bases.

Naproxen showed the lowest drug release from the three dosage forms used. This can be attributed to the presence of naphthyl group which increases aromaticity and hence lipophilicity of the compound.

These results were in a good agreement with Schmidt et al. (22), who showed that addition of another aromatic group in 2-alkoxybenzamide increased lipophilicity, whereas introducing a fluorine atom in the aromatic ring decreased lipophilicity by electrostatic influence of the fluorine atom. It is noteworthy that the molecular weight of the arylpropionic acid derivatives had no effect on the release of the drugs from their dosage forms.

Effect of Storage on the Release of Propionic Acid Derivatives from Their Different Dosage Forms

Storage for 1 month did not affect the amount of drug released from different dosage forms. The change in drug release did not exceed 5% after 1 month storage.

CONCLUSIONS

Chemical structure could affect the release properties of propionic acid derivatives from their dosage forms. As chain length and aromaticity increased, the drug release decreased. Melting point was another factor that affected the drug release; as melting point increased, a slower drug release was obtained. It is noteworthy that molecular weight had no effect on the drug release.

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