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Retardation of weakly basic drugs with diffusion tablets

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Summary

In the increasing pH milieu of the gastrointestinal fluid, the release of weakly basic drugs such as noscapine from diffusion dosage forms with polymethacrylate mixture film-coatings is problematical. Once their pK_a or the pH value at which precipitation occurs is exceeded by intestinal fluid, precipitation of the poorly soluble free bases takes place within the dosage form. Precipitated drug is no longer capable of diffusing through the film-coating. This problem of ensuring pharmaceutical availability could be solved, in the case of noscapine HCl, by the addition of organic acids such as succinic, adipic, tartaric or citric acids to the tabletting mass. By maintaining the pH value within the diffusion coating below the precipitating pH of noscapine, an improvement in release is achieved over the pH range 1.2 (first hour) to 7.5 (eighth hour), that depends on the type and amount of acid added.

Introduction

Many drugs for which sustained release is required are weak bases and can therefore experience problems on release from diffusion-controlled dosage forms in the small intestine because of their physicochemical properties. Due to the pH-dependent solubility of these drugs, the free base precipitates out after the pK_a has been exceeded, as is seen with noscapine, for example (Table 1).

The pH-dependency of the solubility is influenced by the ratio of more easily soluble, ionized drug to that of less soluble, unionized drug. The proportion of unionized drug present at a given pH value can be calculated from the Henderson-Hasselbalch equation (Ritschel, 1976). As shown in Table 2, if the pH and pK_a values lie close together, even minimal changes in the pH value can greatly reduce ionization and hence affect solubility.

Therefore, when sustained release dosage forms containing weak bases as the active ingredients are

TABLE 1

Relationships between pK_a values and the solubility of noscapine

Drug	pK_a	Turbidity pH in gastric/intestinal fluid mixtures	Solubility in water [a]	
			Hydrochloride	Free base
Noscapine	6.24 [b,c]	6.4	1+19	1+3300 (30 °C)

[a] Merck Index (1961).
[b] Herzfeldt (1980).
[c] Merck Index (1976).

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TABLE 2

Relationship between proportion of unionized noscapine α (%) and pH of the solution

pH	Noscapine $pK_a = 6.24$ unionized portion α (%)
1.2	9.1×10^{-4}
2.2	9.0×10^{-3}
3.0	5.7×10^{-2}
4.0	0.57
5.0	5.44
6.4	59.11
6.8	78.40
7.1	87.86
7.3	91.98
7.4	93.53
7.5	94.79
8.0	98.29

tested in vitro under the conditions of increasing pH of the Half-change method, release is not quantitative because of the reduced solubility of the unionized portion of the drug in water.

In the case of dosage forms with diffusion coatings, penetration of simulated gastric juice with pH above the precipitating pH of the incorporated drug causes a precipitation inside the coated tablets. This precipitated drug is no longer capable of diffusion through such a diffusion membrane, but remains as residual contents inside the tablet or the pellet and is not pharmaceutically available.

This could be demonstrated on testing coated tablets containing noscapine HCl as the active ingredient with the Half-change method. Depending on the thickness of the diffusion layer, some 15–85% of non-released drug remained inside the tablet. As shown in Fig. 1, 85% of the active ingredient was released from a hard gelatin capsule containing 5 tablets coated with a 16 μm thick polymethacrylate film after 3 h. As the pH of the test medium increases from the 4th hour onwards to 6.8, the precipitating pH of noscapine of 6.4 is exceeded and thereafter, virtually no more drug is released. With a thicker coating, correspondingly lower proportions of drug are released within the first 3 h. Since diffusion layers greater than 20 μm thick must generally be used to achieve delayed release over 6–8 h, low rates of overall release are particularly likely in such a case as noscapine.

Therefore, by adding suitable excipients to ensure the solubility of the drug inside the coated dosage form irrespective of the pH of the test medium, quantitative release ought to be guaranteed.

Present techniques for prolonging release of noscapine

As the clinical action of noscapine lasts only about 2–4 h (Jacobsen et al., 1976), its biological half-life is merely 8–9 min (Nayak et al., 1965; Gibaldi and Weiner, 1966; Loder, 1969; Ritschel, 1976) and its toxicity is relatively low, it represents a prime example of a drug for which a controlled release dosage form would be required. So far, the following means of retarding its release have been described:

(i) the binding of noscapine to an ion-exchange resin (British Patent No. 905 930; Jacobsen et al., 1976);

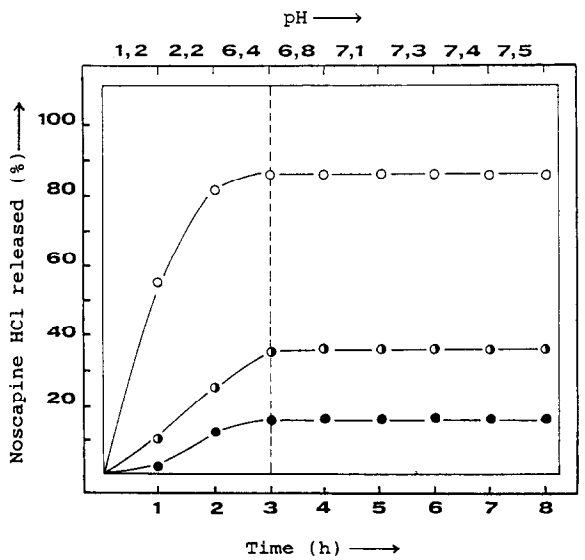


Fig. 1. Effects of pH and coating thickness on the release problems of noscapine HCl from diffusion tablets in the Half-change test (capsule contents: 5 tablets, each containing 10 mg drug). (○——○), 16 μm, (◑——◑), 20 μm, (●——●) 24 μm.

(ii) the binding to pamoic acid (= embonic acid; 4,4′-methylenebis(3-hydroxy-2-naphthoic acid) (Fontaine and Farriaux, 1972; French Patent No. 5 581 M; Saias et al., 1969);
(iii) the preparation of noscapine as coated sustained release granules in hard gelatin capsules (Appelt et al., 1972).

Materials and Methods

Materials

The ingredients and excipients used corresponded to pharmacopoeial (DAB, Ph. Eur., USP and DAC) requirements and were of commercial analytical grade quality.

The film-formers employed were Eudragit® Type RS 100, RL 100, (Röhm Pharma, Darmstadt, F.R.G.).

Methods

Preparation of diffusion tablets. To ensure satisfactory coatings, a 5 mm diameter concave punch was used. At a theoretical weight of 80 mg, up to 5 tablets can be combined in a hard gelatin capsule size 2 to form a single dosage unit.

Non-swellable excipients must be used to achieve suitable tablet formulations. Swelling leads to coarse-pored openings, collapse of the coating and hence to a rapid release of drug. The following formulation was chosen as a framework for tablets, each containing 10 mg noscapine HCl:

Noscapine HCl	10.00 g
Organic acid	67.40 g
Gelatin solution (2%)	q.s.
Talc	2.34 g
Magnesium stearate	0.26 g

The proportion of drug : acid is 1 : 6.74. In one tablet batch, mannitol instead of acids and in another, potassium phosphate were used for comparative purposes.

The mixture of drug and excipient was made into a sticky granulate with gelatin solution and then compressed into tablets on an excentric press after drying and addition of talc and magnesium stearate. The spray coating was applied in a fluid-bed apparatus (Aeromatic Type Ktre-1). A polymethacrylate mixture RS : RL in the ratio 8 : 2 as a 7.8% solution in acetone/isopropanol was used as the film-former. Dibutyl phthalate (10%) was added as plasticizer.

Noscapine release studies. When the release of weak bases from diffusion depot systems is tested in the increasing pH gradients of the Half-change method, precipitation of the released drug is likely at high pH values. Therefore, a modified flow-through cell was used for quantitative determination of released active ingredient (Thoma and Zimmer, 1989).

Results and Discussion

Effects of organic acids with diffusion tablets

Six organic acids (Table 3) were used to investigate the mechanism by which the release properties of noscapine HCl could be improved. Primary potassium phosphate and mannitol were used for comparative purposes.

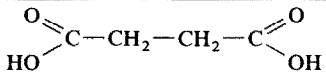
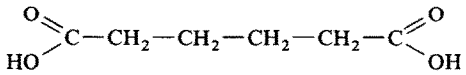
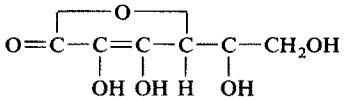
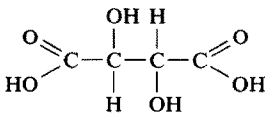
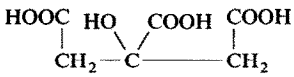
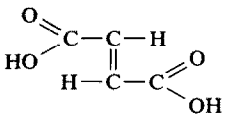
The results obtained on studying the release from 5 tablets are shown in Fig. 2. With succinic, adipic, tartaric and citric acids, pH-independent release profiles are achieved, in decreasing order of effectiveness. This refers particularly to the total release rate after 8 h, by which time succinic acid released practically 100% of the incorporated drug, with the corresponding values for adipic, tartaric and citric acids amounting to about 90, 78 and 69%. Depot tablets containing fumaric acid show the typical release curve of pH-dependent release, caused by the poor solubility of noscapine base in the tablet. Tablets containing ascorbic acid release their active ingredient after a relatively long delay of 1–3 h, release being independent of pH and a total of 87% is released after 8 h. Primary potassium phosphate and mannitol show no effect on improving release.

Effect of the proportion of succinic acid

To assess the effects of the amount of acid on the release properties of noscapine HCl from diffusion tablets, the proportion of succinic acid to

TABLE 3

Physicochemical properties of the organic acids used as excipients to improve the release of weakly basic drugs from diffusion pellets and tablets

Excipient	Structural formula and pK_a values [a,b]		Solubility in water [c]
Succinic acid (MWt = 118.0)		$pK_1 = 4.20$ $pK_2 = 5.63$	1 + 20 (15 °C)
Adipic acid (MWt = 146.1)		$pK_1 = 4.43$ $pK_2 = 5.41$	1 + 72 (45 °C)
Ascorbic acid (MWt = 176.1)		$pK_1 = 4.17$ $pK_2 = 11.56$	1 + 3
Tartaric acid (MWt = 150.0)		$pK_1 = 3.03$ $pK_2 = 4.36$	1 + 0.7 (20 °C)
Citric acid (MWt = 192.1)		$pK_1 = 3.12$ $pK_2 = 4.76$	1 + 1.7
Fumaric acid (MWt = 116.0)		$pK_1 = 3.01$ $pK_2 = 4.38$	1 + 150 (25 °C)

[a] Kortüm et al. (1961).
[b] Some of the pK_a values were calculated from the dissociation constants given in footnote a.
[c] Merck-Index (1961).

noscapine HCl was varied. As shown in Fig. 3, provided the thickness of the coating of all diffusion tablets was the same, the effect on release was dependent on the proportion of acid to active ingredient, as expected.

Effect of the coating thickness on release

Since the release of drugs through swellable, but insoluble polymethacrylic acid-copolymers is a process typifying the diffusion of a dissolved substance through a membrane, the relationships obey Fick's law of diffusion. Hence, the properties of the membrane, including its thickness, exert an effect on the rate of passage of noscapine (Fig. 4).

Possible tablet combinations

In order to obtain certain release profiles, non-coated and coated tablets can be combined in hard gelatin capsules to form dosage units. Such a technique can create particularly suitable initial rates of release (Fig. 5).

The ability to improve the release properties of weakly basic drugs by adding organic acids represents the sum of several, overlapping effects. These include the solubility of the acids, their acidic strength and buffer capacity together with the pK_a values and the solubility of the salts formed with the drug.

Effect of the solubility of the acid

The solubility of the acid used plays an important role in maintaining a pH value inside the coated dosage form. Acids without adequate solubility, as shown by the example of fumaric acid, only exert an effect that is of limited duration. Very easily soluble acids such as tartaric and citric

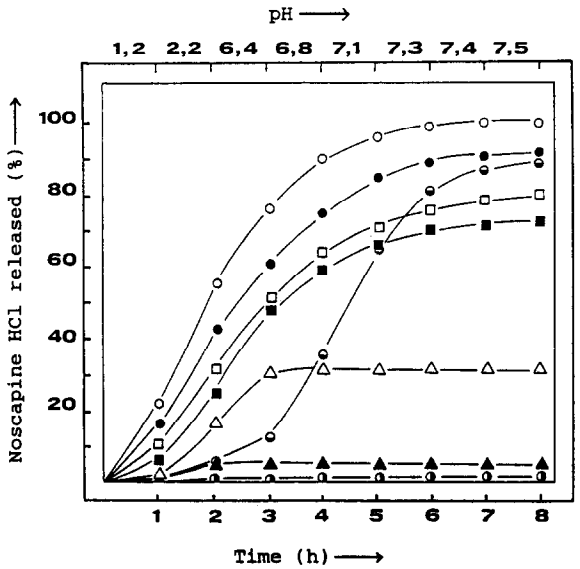


Fig. 2. Effects of organic acids and of primary potassium phosphate and mannitol on release of noscapine HCl from diffusion tablets in increasing pH milieu; 32 μm polymethacrylate mixture RS/RL 8:2 film-coating with 10% dibutylphthalate as plasticizer. (○——○) Succinic acid, (●——●) adipic acid, (◒——◒) ascorbic acid, (□——□) tartaric acid, (■——■) citric acid, (△——△) fumaric acid, (▲——▲) primary potassium phosphate, (◑——◑) mannitol (comparison).

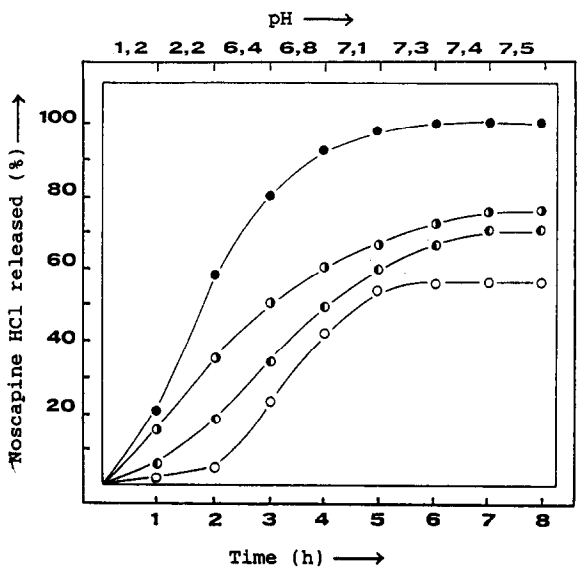


Fig. 3. Influence of ratio of noscapine HCl to succinic acid on release of drug from film-coated diffusion tablets; 32 μm polymethacrylate mixture RS/RL 8:2 film-coating with 10% dibutylphthalate as plasticizer. Ratio of amount of noscapine HCl: succinic acid: (●——●) 1:6.74, (◑——◑) 1:5.05, (◐——◐) 1:3.37, (○——○) 1:1.34.

acids diffuse too rapidly with the drug through the film-coating.

After completing the experiment, the coatings of citric and tartaric acid-containing tablets are almost completely empty and collapsed, whereas in the case of succinic acid, even after quantitative release of the drug, residual amounts of undissolved acid are still observed.

In other investigations, attempts were made to reduce the excessively rapid diffusion of the easily soluble acids from such systems by microencapsulation. These microcapsules are added to the tabletting ingredients (British Patent No. 2 025 227).

Another factor that must be taken into account is the solubility and rate of dissolution of the salts formed with the drug.

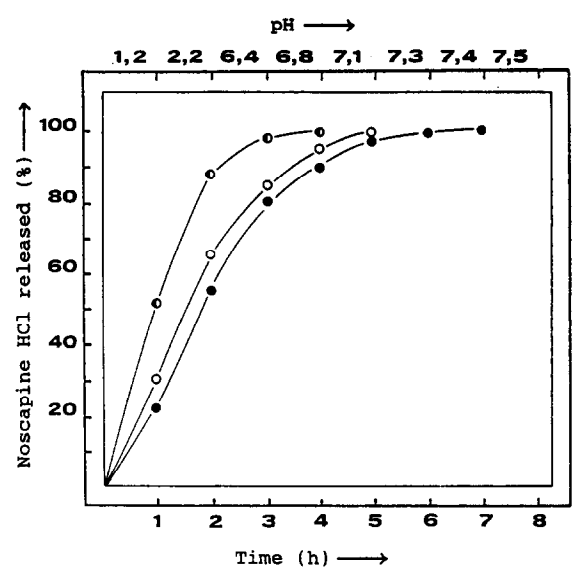


Fig. 4. Dependency of release of noscapine HCl from diffusion tablets on film thickness. Film-former: polymethacrylate mixture RS/RL 8:2 with 10% dibutylphthalate as plasticizer. (◐——◐) 16 μm, (○——○) 26 μm, (●——●) 32 μm.

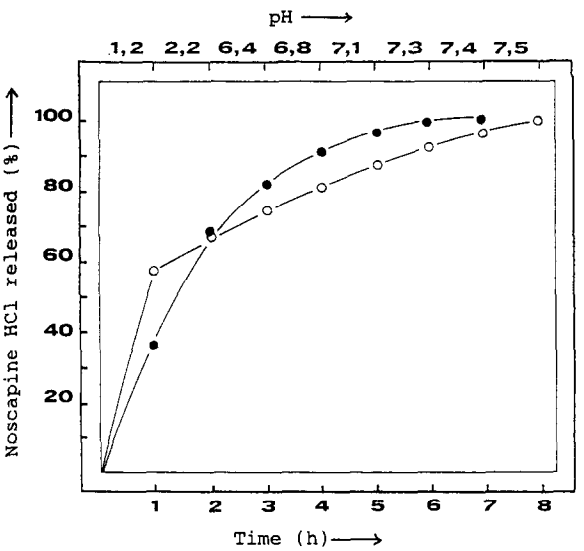


Fig. 5. Effect of different combinations of uncoated and coated diffusion tablets on the retardation of release of noscapine HCl. Film-former: polymethacrylate mixture RS/RL 8:2 with 10% dibutylphthalate as plasticizer. (●———●) Combination 1:1 uncoated tablet + 4 tablets with 28 μm coating; (○———○) combination 2:2 uncoated tablets + 3 tablets with 40 μm coating.

Effect of the buffer capacity and the pK_a value of the acid

The interaction between the strength and the buffer capacity of organic acids is reflected in their respective pK_a values. Thus, strong acids tend to dissociate completely and display lower buffer capacities, because their undissociated portion, as a necessary constituent of a buffer system, is smaller.

The pK_a values of the acids tested are listed in Table 3 in decreasing order of magnitude, that corresponds directly with their ability to improve the release of noscapine HCl. Succinic and adipic acids have higher pK_a values and lower dissociation constants (Kortüm et al., 1961):

Adipic acid	$K_1 = 3.70 \times 10^{-5}$
	$K_2 = 3.86 \times 10^{-6}$
Succinic acid	$K_1 = 6.21 \times 10^{-5}$
	$K_2 = 2.31 \times 10^{-6}$
Citric acid	$K_1 = 7.58 \times 10^{-4}$
	$K_2 = 1.74 \times 10^{-5}$
Tartaric acid	$K_1 = 9.20 \times 10^{-4}$
	$K_2 = 4.31 \times 10^{-5}$

These two acids are more suitable for maintaining an acid pH inside coated diffusion dosage forms than tartaric or citric acids, whose pK_a values are lower, together with dissociation constants in each case, 10-fold higher. Ascorbic acid cannot be drawn directly into the comparison, since its second pK_a value is very high. This also explains the different release curve from that of the active acids, shown in Fig. 2.

Acknowledgement

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