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INFLUENCE OF TECHNOLOGICAL VARIABLES ON RELEASE OF DRUGS FROM HYDROPHILIC MATRICES.

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NOMENCLATURE

CPM: Carboxypolymethylene; **DEAE**: Diethylaminoethyl; **EC**: Ethylcellulose; **HEC**: Hydroxyethylcellulose; **HPC**: Hydroxypropylcellulose; **HPMC**: Hydroxypropylmethylcellulose; **MC**: Methylcellulose; **NaCMC**: Sodium Carboxymethylcellulose; **PEG**: Polyethylene glycol; **PVA**: Polyvinyl alcohol; **SDDS**: Sodium Dodecylsulphate; **SHDS**: Sodium n-hexadecylsulphate; **SODS**: Sodium Octadecylsulphate; **SOS**: Sodium n-octylsulphate; **STDS**: Sodium n-Tetradecylsulphate.

SUMMARY

Hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. Entering the field of pharmaceutical technology almost 40 years ago, they have been steadily growing as regards applications, largely as a result of the increasing need for suitable polymers. Recently, the physico-chemical mechanisms implied in controlling release from such systems have been subjected to new studies, providing the basis for an interpretation of the many data concerning the dependence of the behaviour of these systems with respect to the technological variables involved in the processes used in their fabrication. It is from this viewpoint that this article analyzes bibliographic information and considers the possibilites for modulating release of drugs of high and low solubility through control of their physical properties, the correct choise of gelling agent and correctly setting up the conditions for fabrication.

INTRODUCTION

The formulation of active principles in rigid gelatinous capsules or, much more often, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of real interest in the field of controlled release. When these formulations meet water there is a rapid hydration of the macromolecules in the solid-liquid interface followed by formation of a viscous layer. The matrix system produced as a result of this process can pass along the gastrointestinal tract without breaking up, releasing the active principle progressively (1)(2)(3)(4)(5).

The interest awakened by hydrophilic matrices in the last few years (6)(7)(8)(9) is completely justified in view of the major advantages they have over other alternatives. Among these, the following stand out:

- With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is slightly less than that characterizing coated release forms (10)(11)(12)(13).
- Though the structure makes the immediate release of a small amount of active principle unavoidable (1)(2)(3)(14), their is no risk of "dumping" of a large part of the dose.
- Their capacity to incorporate active principles is large, which suits them to delivery of large doses.
- The manufacturing processes are notably straightforward. If the usual route of formulating as tablets is followed this can be done via direct compression or compression before granulation, either in the dry or in the wet.

Another reason for the success of hydrophilic matrices is the large variety of nonexpensive gelling agents approved for oral use by the competent official organizations (15)(16)(17)(18). All of them have a considerable viscous capacity and the barrier they form is enough to control the entry of water and the release of the active principle. Moreover, they must form this barrier quickly else a large part of the dosage is released prematurely (15)(19)(20). This assumes special importance for the tablets, which lack the gelatine coating that in the capsules functions as a barrier in the initial stages (15).

The polymers suggested for use can be arranged into three broad groups:

- **Non-cellulose natural or semisynthetic polymers.**- These are products of vegetable origin and are used as such -agar-agar (21)(22), alginates (23), molasses

(24)(25)(26), - or after being transformed via semisynthesis or physicals processes - Jaguar (21),.chitosan (27)(28)(29) -. Modified starches are being tried in this last respect (30)(31)(32)(33).

- **Polymers of acrylic acid.**- Arranged in the Carbomer group (16) and commercialized under the name of Carbopol (34). The most-used variety is termed 934 (35)(36)(37). The ionic nature of these polymers means that the gelling process is dependent on the pH of the medium (38)(39).

- **Cellulose ethers.**- This group of semisynthetic cellulose derivatives is, beyond doubt, the one which has found the most applications in hydrophilic matrices. The ones most used are non-ionic (gelling efficacy independent of pH of medium), in particular the most viscous varieties of hydroxypropylmethyl cellulose (4)(15)(19). The methylcelluloses (40)(41), in contrast, have not proved especially useful in this field. In the last few years a number of interesting applications of the ionic sodium carboxymethylcellulose have been found (40)(42)(43)(44)(45)(46).

In the large amount of literature on this theme, the influence exerted on active principle release by the prominent technological variables involved in the fabrication processes is well represented. To be able to extrapolate this information to specific cases which arise in practice, it is necessary to consider the available data, covering a large number of drugs and polymers of very different natures, in terms of the basic processes implied in release. In this respect it is important that the fundamental role that the physico-chemical properties of the active principles play in the release mechanism (46)(47) be taken firmly into account. Some recent publications, take this up (40)(44)(45).

To make an approximation like that suggested possible, the analysis of the information available concerning the influence of the principle technological variables on the properties of these matrix systems will be preceded by some considerations relative to the mechanisms implied in drug release from these systems.

PHYSICO-CHEMICAL ASPECTS OF THE RELEASE PROCESS.

When the dosage form comes in contact with water partial hydration of the polymer takes place resulting in the formation of a layer of gel. As the water penetrates the system at a rate which depends to a large extent on the nature of the polymer the gel layer expands by getting thicker. At the same time, the by now completely

hydrated outer layers start to disperse via an atrittion process which, furthermore, means the process of water penetration can continue until the system is completely dispersed (14)(15).

The release of an active principle by a matrix system is produced by two simultaneous mechanisms (48)(49)(15):

a) Erosion or attrition of the outermost, least consistent gel layers.

b) Dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed.

Which mechanism dominates is directly related to the hydrosolubility of the active principle. When this is very low the possibility of release by diffusion will be practically zero and release will be almost all by surface erosion, giving profiles characteristic of zero order kinetics. Or, if the drug is moderately or highly hydrosoluble, the mechanism governing release will be diffusion. Three stages can be discerned in the overall diffusion-ruled release process (17):

a) To begin, the water dissolves the active principle at the surface, causing its immediate release. The water penetrates the matrix through the pores and gives rise to the gelling of the polymer. The rate of penetration in the first stage depends on the porosity of the system and the gel formed does not necessarily constitute a continuous layer, particularly when the polymer particles are relatively large.

b) In the second stage, or stationary phase, occupying 60-70% of the process, the water is continuously penetrating the system, at the same time as the gel is expanding. During this phase release is controlled by the diffusion process and not by dissolution of the active principle or penetration of water.

c) The tailing-off period starts when the water reaches the centre of the system and the concentration of drug falls below the solubility value. This final stage is characterized by a reduction in the release rate.

Despite the great complexity of the process, data for the release of hydrosoluble active principles from hydrophilic matrixes is normally interpreted using the relatively simple models proposed by *T. Higuchi* (50) and *W. Higuchi* (51) adapted by *Lapidus and Lordi* (48)(52) for this type of systems and which apply to active principles of limited solubility and to highly hydrosoluble active principles, respectively. The equations derived from the two models, which assume active principle dissolution and diffusion through the water filling the pores in "sink" conditions, predict linear plots of quantity or percentage released against the square root of the time (square-root

type kinetics). These plots are actually obtained in practice in most experimental situations, at least in the intermediate stages of the process. The reasons for the frequent deviations observed in the initial and final stages have been discussed by *Lapidus and Lordi* (48). Other models developed since for active principles of similar characteristics (53)(54) lead to similar conclusions.

It follows from the comments made that the hydrosolubility of the active principle plays an important part in the release mechanism. Its importance is reforced by the repeated finding that in the case of soluble active principles the value of the Higuchi constant is directly related to the magnitude of its solubility (50)(51). The greater variability of release shown by formulations of very sparingly hydrosoluble active principles is certainly also of interest (17). Solubility is not the only physico-chemical characteristic that conditions a hydrosoluble active principle's capacity to diffuse through the gel barrier. Interesting in this respect are the results of *Korsmeyer et al.* (53) with potassium chloride, phenylpropanolamine hydrochloride and bovine albumin showing an inverse relation between molecular weight and release rate, and the large diversity of release rates, clearly correlated with the molecular size and form, observed in a large group of bronchodilators by *Baveja et al.* (46). The information currently available in relation to these points is summarized in Table 1.

In certain cases the usual linear dependence of the fraction of hydrosoluble active principle released on the square root of the time is not observed. To interpret these profiles it is necessary to look closely at the release process, taking into consideration the effects of the structural changes the polymer undergos as it swells, including alterations in the mobility of the polymer chains, macromolecular relaxations and changes in the porous structure regarding both the mean pore size and the pore size distribution (56). Hence, as the swelling process progresses, diffusion of the active principle will not only be via the water-filled pores, but also via the polymer chains, the incidence of the latter depending on the polymer's physical structure, its density of reticulation and its degree of crystallinity and also on the possible solute-polymer interactions.

Korsmeyer et al.(53) have proposed a semiempirical formula capable of revealing and identifying behaviours which are not usual or Ficklan:

$M_t/M = kt^n$

where:

TABLE 1
Summary of the literature available concerning the dependence of release on the physico-chemical properties of the active principle.

POLYMERS	NUMBER OF VARIETIES STUDIED	PRINCIPLES ACTIVES	REFERENCE
Carbomer	3	Furosemide	55
HPC	1	Aminophylline,Metropolol	40
HPMC	3	Atenolol	66
HPMC	4	Aminophylline,Promethazine	14
HPMC	1	Bronchodilators	46
HPMC	2	Differents Tracers	47
HPMC	1	Aminophylline,Diazepam Indomethacin,Promethazine Propranolol,Tetracycline Theophylline	56
HPMC	1	Potassium Chloride	60
HPMC	4	Aminophylline, Propranolol	64
HPMC	1	Potassium Chloride	63
HPMC	2	Potassium Chloride	62
HPMC	1	Clorpheniramine,Theophylline	94
HPMC	1	Aminophylline,Diazepam Indomethacin,Promethazine Propranolol,Tetracycline Theophylline	95
HPMC	3	Bronchodilators	96
HPMC	2	Salbutamol,Verapamil	97
MC	1	Alprenolol,Metroprolol	40
MC	1	Theophylline	79
MC	3	Hydrochlorothiazide	41
NaCMC	1	Alprenolol, Metoprolol	40
NaCMC	1	Bronchodilators	46
Natural Gum	1	Litium Sulphate	59
	2	Bovin Serum Albumin Phenylpropanolamine Potassium Chloride	53

TABLE 2.
Difussional exponents corresponding to different transport mechanism for systems with customary geometrical forms.

Slab	Cylinder	Sphere	Transport mechanism
0.50	0.45	0.43	Fickian A (case I)
>0.50 <1	>0.45 <0.89	>0.43 <0.85	Anomalous
1	0.89	0.85	Caseii

M_t/M is the fractional solute release, t is the release time and k is a kinetic constant characteristic of the drug/polymer system.

The value of the exponent is conditioned by the diffusion mechanism ruling the process (53)(54)(57)(58), enabling this to be identified according to the criteria shown in Table 2.

TECHNOLOGICAL VARIABLES AND RELEASE.

1. Properties of the active principle

Leaving to one side the physico-chemical properties which are not modifiable by technological processes, the only well described relation for the active principle is that between particle size and release. In general terms, the importance of this variable depends on the drug's hydrosolubility and becomes especially clear with sparingly soluble active principles (14)(59)(60). Nevertheless, the potential effects of changes in its magnitude on the consistency of the gel barrier (60) complicate matters and account for the apparently contradictory results that sometimes appear in the literature.

2. Properties of the gelling agent

The polymer is the element in the formulation that is most responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer. It is the

fundamental component of hydrophilic matrix systems. When selecting from the wide range of products nowadays available, the extensive bibliography on this subject mentions first and foremost the importance of the polymer's capacity to form sufficiently consistent gels (1)(5)(15). As far as highly soluble drugs are concerned, the rate at which this process occurs in the matrix systems prepared from the polymers is of added interest (19)(47)(61).

For each product with defined structure and chemical characteristics, varieties exist with different molecular weights and degrees of reticulation, which gives a range of viscous efficiencies. In practice, the importance of this variable, within the usual working ranges, is especially noticeable in the case of sparingly soluble active principles: release from these formulations is by erosion and directly depends on the gel consistency (55). With hydrosoluble drugs, its effects are only evident during the initial stages of release (4)(14)(62)(63)(64). *Doelker* (17) explains this in terms of the different gelling rates and the similar "continuum" viscosity (on which diffusion depends once the gel is formed) shown by dispersions of polymers with different viscous efficiencies. An interesting exception is the considerable differences in the bioavailability of theophillyne formulated in HPC matrices found by *Nakano et al.* (65), which they attributed to the different viscous efficiencies of the varieties used.

Regarding the polymer's physical properties, *Alderman* (15) has suggested particle size affects release through its incidence on the rate of formation of the gel.

The proportion of polymer is the usually employed control variable of release rate. With hydrosoluble active principles, this connection is directly deducible from *Higuchi*'s equation (50)(51). With sparingly soluble active principles it stems from the gel consistency being effected by the proportion of polymer (41)(55).

The similarity of the mechanisms by which the two variables mentioned condition release implies their effects frequently interact. This can be clearly shown if suitable experimental designs are initially chosen (41)(55)(66). The information on these points is summarized in Table 3.

A further point to consider relates to the possible effects of interactions between active principle and polymer on the gel's consistency, and hence, on release. Such interactions can reveal themselves as changes in the value of the thermal gelling temperature of the polymer. When the thermal gelling point is reached the consistency of the gel changes slightly due to the loss of water of hydration molecules and the strengthening of polymer-polymer interactions. The temperature at which this occurs

TABLE 3

Summary of the literature available concerning the dependence of characteristics of hydrophilic matrices on polymer properties and proportion.

POLYMERS	NUMBER OF VARIETIES STUDIED	ACTIVE PRINCIPLE	REFERENCE
Carbomer	3	Furosemide	55
CPM	1	Tartrazine	100
HEC	2	Ammonium Chloride	21
	1	Tracer	2
HPC	3	Theophylline	65
	1	Tracer	2
HPMC	1	Aminophylline	95
	4	Aminophylline	64
	3	Atenolol	66
	1	ß-Blockers	44
	1	Chlorpheniramine	52
	1	Diazepam	95
	3	Furosemide	5
	1	Indomethacin	95
	1	Isomazole	93
	1	Potassium Chloride	63
	2	Potassium Chloride	62
	1	Promethazine	95
	4	Promethazine	14
	1	Propranolol	95
	1	Propranolol	98
	4	Propranolol	64
	1	Quinidine	99
	3	Salbutamol	61
	3	Tartrazine	100
	1	Tetracycline	95
	1	Theophylline	95
	3	Tracer	2
	3	Tracer	4
Jaguar	5	Ammonium Chloride	21
MC	1	Theophylline	79

(continued)

TABLE 3 (Continuation).
Summary of the literature available concerning the dependence of characteristics of hydrophilic matrices on polymer properties and proportion.

POLYMERS	NUMBER OF VARIETIES STUDIED	ACTIVE PRINCIPLE	REFERENCE
NaCMC	1	Ammonium Chloride	21
	1	Doxylamine	99
	2	ß-Blockers	44
	1	Pheniramine Phyrilamine	99
	1	Tartrazine	100
	1	Salbutamol	61
Natural Gum	1	Sulphate Lithium	59
Natural Polymers	No indicated	Ammonium Chloride	21
PVA	2	Bovin Serum Albumin Phenylpropanolamine Potassium Chloride	53
Xanthan Gum	1	Potassium Chloride Theophylline	90

in the case of the cellulose ethers depends on the nature, type and amount of substituents in the cellulose, and is heavily affected by the presence of solutes in the medium (15)(17).The practical repercussions of the alterations in this parameter caused by the presence of active principles in solution can be gathered from work performed by *Toitou and Donbrow* (67) who observed large changes in gelling temperature with active principles that give rise to large ions, such as tetracaine hydrochloride, sodium salicylate or sodium benzoate. This shows the presence of this phenomenon is desirable when making a formulation because of its potential effects. Recently *Mitchell et al.* (68) have extended the analysis of interactions between cellulose ethers and ionic substances by looking at the cloud point. This parameter, not necessarily correlated with the thermal gelling point, is determined by measuring the transmission of light and corresponds to the temperature at which there is a 50% reduction in transmission in an aqueous dispersion of polymer (69). The results

TABLE 4
Summary of the literature concerning the use of mixtures of polymers in the formulation of hydrophilic matrix.

POLYMER	NUMBER OF VARIETIES STUDIED	ACTIVE PRINCIPLE	REFERENCE
HPMC (Two Varieties)	1,1	Propranolol	98
HPMC,NaCMC	1,1	Alprenolol	44
	1,1	Bronchodilators	46
	1,1	Metoclopramide	87
	1,1	Metoprolol	44
	1,1	Nicotinic Acid	87
	2,1	Oxprenolol	45
	1,1	Oxprenolol	44
	1,1	Tracers	49
HPMC,Carbomer 934	1,1	Brilliant Blue	70
HPMC,EC	1,1	Diclofenac	71
HPC,MC,NaCMC	1,1,1	Alprenolol	40
	1,1,1	Metoprolol	40

obtained indicate that the presence of electrolytes reduces the hydration of the polymer, which goes on to alter the value of the cloud point and leads to marked changes in dissolution rate.

The use of mixtures of polymers (Table 4) represents a potential way of achieving the required release properties. In addition to the possibilities offered by mixing polymers with different viscous efficiencies, for example different non-ionic cellulose ethers, to give gel barriers of varying consistency (19)(70)(71), mixing non-ionic and ionic varieties in the right proportions can lead to formulations of hydrosoluble active principles with zero-order release profiles (30)(40)(44)(46). The obtainment of constant release rates with mixtures of cellulose ethers of differing characteristics has its root in the formation of strong hydrogen bonds between the carboxyl groups of sodium carboxymethylcellulose, the ionic variety usually used, and the hydroxyl groups of the non-ionic cellulose ether (40).

The release mechanisms put forward (72)(73)(74)(75)(76)(77), and recently revised (13), have been in need of repeated adjustments to account for new data (45).

To conclude this discussion concerning swelling agents it must be realised that serious problems may be caused by replacing products with their equivalents nominals supplied by different sources or even belonging to different lots of the same supplier. The differences in behaviour observed with HPMC (20)(78) illustrate a need to revise and enlarge upon the specifications given in the official compendiums for these parameters.

3. Incorporation of additives

The obtainment of technologically acceptable formulations requires, in addition to the active principle and the gelling agent, the presence of other excipients, in particular diluents and lubricants, whose presence can markedly affect release.

The effects of adding diluents, both soluble and insoluble, are well documented. These products, if present in large enough quantities, bring about marked increases in the release rate of hydrosoluble active principles (48)(79). This effect has been attributed to an expansion of the gel layer, if the excipients swell and are insoluble, or the impossibility of a continuous gel barrier forming, if the matrix incorporates insoluble materials which do not swell. In general, diluent particle size does not affect the diluent's influence on release. Nevertheless, *Ford et al.* (56) indicate that adding finely divided calcium phosphate can cause formation of a complete barrier via accumulation at the matrix surface, lowering the area available for release and delaying it. The hydrophobic lubricants are known to slow release (17)(15).

The incorporation of additives as a means of modulating profiles of release from hydrophilic matrices has also been studied. *Feely and Davis'* work (49)(80) using different sorts of polymers, ion-exchange resins and tensoactive agents is relevant in this respect. The effects noted, which are considerable in certain cases, are almost always attributed to ionic interactions.

The addition of agents to modify the pH of the matrix's near environment has emerged as an means of adjusting the release rates of active principles with pH-dependent solubilities (2)(81)(82). Finally, the use of ionic additives which modify the thermal gelling temperature of the polymer forms a satisfactory way of modifying

TABLE 5
Summary of the literature available concerning the use of aditives in the formulation of hydrophilic matrices.

POLYMER	ACTIVE PRINCIPLE	ADITIVES	REFERENCE
HEC	Tracer	Lactose SD Phosphate di TAB^R Tartararic Acid	2
HPC	Tracer	Lactose SD Phosphate di TAB^R Tartaric Acid	2
HPMC	Aminophylline	Calcium Phosphate Lactose SD	56
	Benzocain	Lactose Tricalcium Phosphate	48
	Benzoic Acid	Lactose Tricalcium Phosphate	
	Chlorpheniramine	Lactose Tricalcium Phosphate	
	Chlorpheniramine	SDDS SHDS SODS SOS STDS	80
	Chlorpheniramine	Tricalcium Phosphate	48
	Diazepam	Calcium Phosphate Lactose SD	56
	Drotaverine	Oxalic Acid Succinic Acid Tartaric Acid	82
	Indomethacin	Calcium Phosphate Lactose SD	56
	Isomazole	Dextrose Lactose SD	93
	Promethazine	Calcium Phosphate Lactose SD	56
	Propranolol	Calcium Phosphate Lactose SD	
	Quinidine	Oxalic Acid Succinic Acid Tartaric Acid	82

(continued)

TABLE 5 (Continuation).
Summary of the literature available concerning the use of aditives in the formulation of hydrophilic matrices.

POLYMER	ACTIVE PRINCIPLE	ADITIVES	REFERENCE
HPMC	Sodium Salicylate	Lactose	48
	Sodium Salicylate	SDDS	80
		SHDS	
		SODS	
		SOS	
		STDS	
	Sodium Salicylate	Tricalcium Phosphate	48
	Tetracicline	Calcium Phosphate	56
		Lactose SD	
	Theophylline	Calcium Phosphate	
		Lactose SD	
	Tracer	DEAE	49
		EC	
		Ion exchange Resins	
	Tracer	Encompress	4
		Lactose Fast-Flo	
	Tracer	Lactose SD	2
	Tracer	PEG 6000	49
	Tracer	Phosphate di TAB^{R}	2
	Tracer	NaCMC	49
	Tracer	Tartaric Acid	2
	Vincamine	Oxalic Acid	82
		Succinic Acid	
		Tartaric Acid	
MC	Caffeine	Sodium Chloride	92
	Theophillyne	Lactose	79
Metolose^{R}	Paracetamol	Lactose	91
No specified	Vincamine	Succinic Acid	81

TABLE 6
Summary of the literature available concerning the dependence of compressed matrix properties with respect to the variables implied in the fabrication process.

POLYMER	TECHNOLOGICAL VARIABLE STUDIED	ACTIVES PRINCIPLE	REFERENCE
Carbomer	Compression Force	Furosemide	55
HEC	Compression Force Granules Shape	Ammonium Chloride	21
HPC	Compression Force Granulation Procedure	Theophylline Naproxen	65 86
HPMC	Compression Force	Atenolol Potassium Chloride Promethazine Sodium Diclofenac Potassium Chloride Tracers	66 60 14 89 88 56
	Crushing Strength Granulation Procedure Size and Shape of the tablets.	Furosemide Naproxen Potassium Chloride Tracers	5 86 60 62 56
Jaguar	Compression Force Granules Shape	Ammonium Chloride	21
Natural Gum	Compression Force Granules Size	Lithium Sulphate	59
Natural Polymers	Compression Force Granules Shape	Ammonium Chloride	21
NaCMC	Compression Force Granules Shape	Ammonium Chloride	21
Xanthan Gum	Compression Force	Potassium Chloride Theophylline	90

release in a controlled manner (17)(67)(83). In Table 5 the literature on the points commented upon in this section is summarized.

3. The preparation process

The more complex processes entailed in fabricating tablets, as against hard gelatine capsules, makes it opportune to discuss aspects related to them and point out that matrices obtained by compression have received most attention (Table 6). The possible effects of the fabrication technique used -direct compression or compression prior to granulation by different procedures- have been explored. However, the available data suggests that this variable is not very relevant and does not overlay affect release profiles (84)(85)(15) When granulation in the wet is used, the nature of the binder neither seems to be really of importance (86). Tablet shape, however, does significantly affect the rate of release. The results of a study by *Ford et al.* (56) with Prometazin tablets of equal weight and formula, show that the release rate, which follows the *Higuchi* kinetics, is inversely related to the surface area of the formulations. This leads to the conclusion that release is sustained best by spherical tablets.

Compression force has usually been thought to have little influence on release. Since the porosity of the hydrated matrix, which does affect release as in *Higuchi*'s model, is independent of the initial porosity, there seems to be a basis for this statement, at least in the case of matrices of hydrosoluble active principles. Most of the available data point along these lines (60)(65)(88), nevertheless, as indicated by *Korsmeyer et al.* (88), the initial porosity might be more important than it may at first seem. To explain their finding of an inverse relation between initial porosity or mean initial pore size and the release rate of potassium chloride in HPMC matrices they postulated that the air entrapped in the pores acts as a barrier to the transport of active principle, hence release would not be governed by diffusion through the pores. Finally, the significant effect of compression force detected in formulations of sparingly soluble active principles released by an erosion mechanism has been attributed to the effect of this variable on the gel consistency (41)(55).

CONCLUSION

This discussion has centred on the significant advantages and the large number of possibilities that hydrophilic matrices offer compared with other sustained-

release dosage forms usually used in the oral administration of drugs. The fact that their usage has persisted and increased over the almost 40 years since they were first described is doubtless a consequence of this.

It is possible to make the basis for their use firmer, however, for which the influence of different technological variables on release needs to be studied in greater detail. An essential aspect of this would be to consider the mechanisms implied in release and, consequently, the physico-chemical properties of the active principles and polymers.

Progress in this area requires not only new studies and more data, but the reinterpretation of already existing data in the light of current knowledge. The aim this article set itself was precisely the latter.

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