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Promoted rectal absorption of insulin: formulative parameters involved in the absorption from hydrophilic bases

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Summary

The profiles of the hypoglycaemic activity of rectally-administered insulin in hydrophilic bases containing various types of polyethoxylated non-ionic surfactants as promoters was measured as a function of important parameters involved in the formulation. Relatively high surfactant concentrations were used to minimize surfactant concentration membrane dependence. Screening revealed surfactant chain-length dependencies and also high activities in sorbitan esters similar to those found in some straight chain ethers; e.g. Myrj 45, a straight chain ester, was low in activity.

In the polysorbate series, a regular dependence of activity on surfactant lipophilic chain-length was found with EO 20 and EO 4, efficiency falling off on raising C from 12 to 18. Oleate was more active than stearate. In the PEG base dependence on carbon chain-length was not found for the EO 20 series but there was strong activity over the range. HLB change may be involved but is not the main factor.

Insulin absorption from promoting bases was strongly affected by pH, being minimal at pH 5.2. Without promoters, however, activity was low and pH-dependence absent.

A non-linear dose-dependence profile was found in the range 12–150 I.U./kg with maxima and minima in both bases, the polyacrylate base being somewhat more active than the PEG base.

The insulin activity was persistently high but the positions of the maxima and minima indicated clearly that the activity and formation of insulin aggregates is a significant factor.

The important parameter affecting insulin activity in rectal formulations are

promoter chemical structure, pH, carrier and insulin dose-level, all of which influence the chemical as well as the biological activity.

Introduction

In the long search for effective and practical alternatives to the parenteral administration of insulin, beset with well-known problems of patient compliance, several approaches have been used. Protection against enzymatic destruction has been combined with the use of highly dispersed emulsions for enteral administration (Shichiri et al., 1974, 1975). The work of Shichiri et al. (1978) and Touitou et al. (1978), showing that its rectal absorption could be promoted by non-ionic surfactants, opened new directions which have led to a considerable number of studies on related and new potential agents and also conditions for enhancing absorption (Ichikawa et al., 1980; Morimoto et al., 1980; Bar-On et al., 1981; Kamada et al., 1981; Mesiha et al. 1981; Nishihata et al., 1981, Ziv et al., 1981; Yamasaki et al., 1981a and b). Although the pronounced activity of some surfactants has been established, particularly in the work of Ichikawa et al. on corn oil suppositories, a number of gaps and contradictions are evident and there is a need for a systematic investigation of parameters involved in insulin absorption from rectal dosage forms with the object of obtaining a better understanding of the important elements of the process.

The purpose of the present study was to investigate the profiles of the rectal absorption of insulin in animals in the presence of various types of non-ionic surfactant and examine parameters involved, viz. pH, surfactant chain-length and insulin dose. Different carriers and formulations were employed, including polyacrylate and polyethylene glycols.

Materials and Methods

Materials

Neutral insulin[1], 80 I.U./ml, was used. The non-ionic surfactants selected were polysorbates (Tween[2] 20, 21, 40, 60, 65, 80, 81), polyoxyethylene esters (Myrj[2] 45, 52, 53) and polyoxyethylene ethers (Brij[2] 30, 35; Texofor[3] A6, A45; and Cetomacrogol[3] 1000). Carbomer (Carbopol[4] 934), a polyacrylate, and polyethylene glycols (PEG 400, 4000[5]) were used as carriers for the microenemas.

[1] Leo Neutral, Nordisk Insulin Laboratorium, Denmark.
[2] ICI, U.K.
[3] ABM, Cheshire, U.K.
[4] Goodrich, U.S.A.
[5] Sigma Chemicals, U.S.A.

TABLE 1

COMPOSITION OF MICROENEMAS

Ingredients	% w/w						
	Type A				Type B		
	1	2	3	4	1	2	3
Surfactant	–	10	33	54	–	10	33
PEG 4000	33	33	33	–	–	–	–
PEG 400	33	23	–	12	–	–	–
Carbopol gel 1%	–	–	–	–	64	56	33
Insulin soln. * 80 I.U./ml	33	33	33	33	33	33	33

* For dose-dependence studies, this solution was diluted with distilled water to obtain a wide range of concentrations.

Formulations

Two main types of formulation, one based on PEG (Type A) and the other on carbopol bases (Type B), were used containing different quantities of insulin, surfactant and carriers. The compositions are given in Table 1.

Methods

Preparation of microenemas

The PEG base ingredients were melted together and the insulin solution was added the mixture being maintained below 50°C, after which it was cooled to ambient temperature. Carbopol gel base was obtained by adjustment of 1% polymer solution with 1 N NaOH to pH 4 after which the remaining ingredients were added and the final pH adjusted to the required value with 1 N HCl.

Administration and testing

Normal rats and rabbits were used as the main animals and some work was done on rats in which diabetes was induced as described in a previous work (Touitou et al.,1978). One ml quantities of each product were administered as a semi-solid microenema by means of a short-mouth plastic injection syringe, without needle, the anus being clamped for 2 h to prevent possible loss of product. Blood samples were collected from the tails 1 h before and at intervals of 0, 1, 2 and 3 or 4 h after insulin application. The rats were ether anaesthesized during the administration. Plasma glucose concentration was determined at 610 nm by the glucose oxidase method (GOD period — Boehringer Kit) (Touitou et al., 1980).

Results and Discussion

In view of the reported high effectiveness on the rectal absorption of insulin of certain long-chain ethers, viz. Cetomacrogol 1000 (Touitou et al., 1978) and POE (9) lauryl ether (Shichiri et al., 1978; Ichikawa et al., 1980) and the absence of effect of polysorbate 80 (Ichikawa et al., 1980; Morimoto et al., 1980; Mesiha et al., 1981), it was considered necessary as a first step to screen chemical types of non-ionic surfactant.

The hypoglycaemic effect profile of 3 representative polyoxyethylene derivatives, viz. a straight chain ester (Myrj 45), a sorbitan ester (Polysorbate 20) and a straight chain ether (Texofor A6), compared with Cetomacrogol 1000, are shown in Fig. 1. The profiles of the sorbitan ester, the Cetomacrogol ether, and the Texofor are similar whereas the Myrj ester has insignificant activity. Notably, the time of the peak effect and the persistence for at least 4 h were common to all the active promoters.

Influence of surfactant chain-length

In view of the pronounced activity of polysorbate 20, the polyoxyethylene sorbitan ester series was subjected to a fuller investigation of the effect of the length of the component hydrophilic and lipophilic chains on activity.

The conventional hydrophilic rectal carrier, PEG 4000 (A3), was employed and also the Carbopol hydrogel (B3), widely-used pharmaceutically. All the surfactants were present at post-micellar concentrations. Results are presented in Table 2. It is evident that the hypoglycaemic effect is a property of a range of sorbitan esters but its magnitude varies. This is in contradiction to the widespread assumption that polysorbates are ineffective, which is based on results obtained with polysorbate 80.

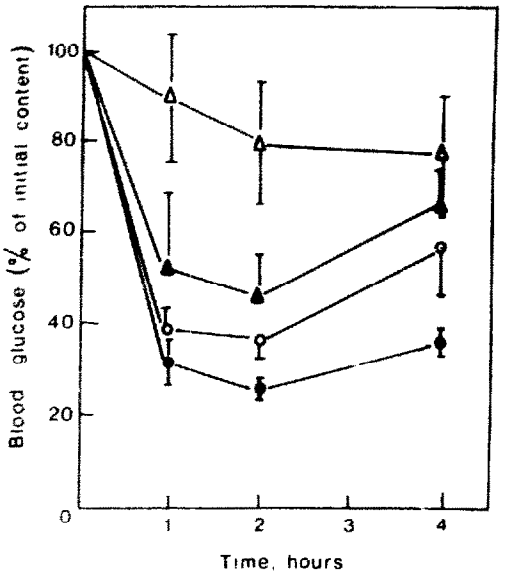

Fig. 1. Hypoglycaemic effect of insulin administered rectally to rats in PEG base containing; △, Myrj 45; ▲, Texofor A6; ○, Polysorbate 20; ●, Cetomacrogol 1000.

TABLE 2

EFFECTS OF POLYSORBATES (33% w/w) IN INSULIN MICROENEMAS ON BLOOD GLUCOSE LEVEL IN RATS

Microenemas contained 107 I.U. insulin in PEG base (A3) and in Carbopol base (B3)

Surfactant	Chemical name	HLB	Base	Blood glucose % of initial level ($\bar{X} \pm SE$) (n = 5)		
				1 h	2 h	4 h
Polysorbate 20	POE 20 sorbitan monolaurate	16.7	A3	59.9 ± 4.5	66.2 ± 27.3	71.2 ± 18.4
			B3	59.5 ± 2.4	42.4 ± 7.2	70.9 ± 43.8
Polysorbate 21	POE 4 sorbitan monolaurate	13.3	A3	84.4 ± 15.2	77.9 ± 24.0	82.4 ± 16.6
			B3	51.3 ± 4.5	47.1 ± 15.5	51.6 ± 23.0
Polysorbate 40	POE 20 sorbitan monopalmitate	15.6	A3	63.7 ± 14.6	65.0 ± 19.1	67.7 ± 22.9
			B3	66.7 ± 19.1	65.5 ± 20.4	60.3 ± 25.6
Polysorbate 60	POE 20 sorbitan monostearate	14.9	A3	58.3 ± 17.8	60.1 ± 23.0	68.1 ± 20.6
			B3	74.0 ± 11.0	97.9 ± 2.1	99.1 ± 6.6
Polysorbate 61	POE 4 sorbitan monostearate	9.6	A3	76.7 ± 19.1	82.9 ± 12.4	82.3 ± 3.7
			B3	102.9 ± 12.5	99.9 ± 8.7	99.5 ± 15.0
Polysorbate 80	POE 20 sorbitan monooleate	15.0	A3	55.5 ± 7.2	72.7 ± 12.5	89.6 ± 4.2
			B3	82.3 ± 16.4	96.5 ± 14.0	93.1 ± 8.1
Polysorbate 81	POE 4 sorbitan monooleate	10.0	A3	101.2 ± 31.8	96.3 ± 18.0	96.0 ± 21.4
			B3	89.1 ± 13.3	84.5 ± 20.8	85.2 ± 23.4

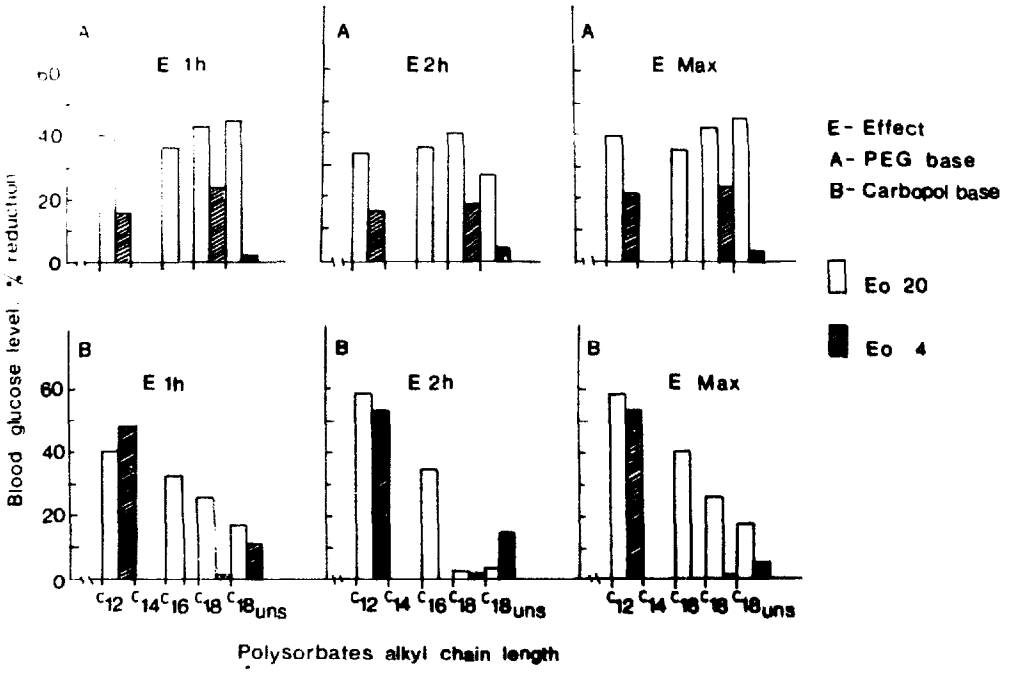

Fig. 2. Effects of polysorbates (33% w/w) in insulin microenemas on blood glucose level in rats. Microenemas contained 107 I.U. insulin in PEG base (A3) and in carbopol base (B3).

The chain-length effect is compared in Fig. 2 which presents the hypoglycaemic effect after 1 and 2 h and the maximum effect.

In carbopol base, a regular dependence on lipophilic chain-length was evident in the EO 20 and EO 4 series, efficiency falling off with increase of carbon chain-length towards 18; oleate was more active than stearate. The chain-length dependence is even more evident in the plot of maximum effect.

With the PEG base, the EO 20 chain series shows no dependence on carbon chain-length. The two C18 compounds are, however, more active in this base than in carbopol gel. On the other hand, the EO 4 compounds except for C18 have lower activities in PEG base. The profiles are the same in terms of the maximum effect.

If we consider the above observations in terms of HLB, the activities in carbopol base decrease somewhat with reduction of HLB (Table 2) but HLB is not the main factor, since the activities of the two lauryl compounds are quite similar. With regard to the PEG base, the lack of chain-length dependence may be connected with a possible contribution of the PEG moiety to the polysorbate HLB in the case of the EO 20 series. Such contributions of PEGs of different molecular weights to the HLB values of nonyl phenol ethoxylate derivatives have recently been reported by Marszall (1978), and from this work, it is also evident that the degree of such interaction and the effect depend on the EO content of the components. This could explain the absence of a PEG effect in the EO 4 series as compared to the EO 20 compounds.

Screening was also carried out on polyoxyethylene *n*-alkyl ethers of varying chain-length. Two PEG base formulations were used (A3, A4). The results given in

TABLE 3

EFFECTS OF NON-IONIC ETHER-TYPE SURFACTANTS IN INSULIN MICROENEMAS ON BLOOD GLUCOSE LEVEL IN RATS

Microenemas contained 107 I.U./kg insulin. Formulations A3 and A4 were used.

Surfactant	HLB	Base	Blood glucose % of initial level ($\bar{X} \pm SE$) (n = 5)		
			1 h	2 h	4 h
POE (22) cetostearyl ether [1]	16.1	A3	68.5 ± 19.9	70.2 ± 27.7	74.6 ± 17.6 *
POE (22) cetostearyl ether [1]	16.1	A4	33.2 ± 6.5	26.6 ± 1.4	37.4 ± 3.0
POE (6) stearyl ether [2]	10.6	A4	53.4 ± 15.9	46.4 ± 9.8	66.1 ± 9.2
POE (45) stearyl ether [3]	17.9	A4	50.5 ± 7.2	56.0 ± 8.0	76.7 ± 12.6
POE (23) lauryl ether [4]	16.9	A4	39.9 ± 5.1 *	D	D
POE (4) lauryl ether [5]	9.5	A3	59.8 ± 10.5	47.8 ± 12.5	63.3 ± 19.9

[1] Cetomacrogol 1000; [2] Texofor A6; [3] Texofor A45; [4] Brij 35; [5] Brij 30.

* n = 4, 1 rat died. D = all the rats died in hypoglycaemic coma.

Table 3 show that these ether-based non-ionic surfactants are generally effective as promoters. The lauryl ether (Brij 30) was slightly more effective than Cetomacrogol using the same base and concentration. This was unexpected in view of the lack of action of the short EO chain, Brij 30, at micellar concentrations in effecting transfer of paraquat across isolated gastric mucosa (Walters et al., 1981). Another short EO chain member, Texofor A6, was also active but less so than the longer chain Cetomacrogol and Brij 35 (EO 22–23) and the activity again fell with the large EO increase to 45 (Texofor A45). The structure EO 20–23 C12 has been found to be active in causing penetration in several systems, (Walters et al., 1981; Hirai et al., 1981) and confirms that the lauryl chain is a potent moiety in activity on the biological membrane, both in non-ionic surfactants such as Polysorbate 20 (Marsh and Maurice, 1971) and ionic surfactants such as sodium lauryl sulphate (Riegelman and Crowell, 1958).

pH-dependence of hypoglycaemic activity in PEG and carbopol bases

Hirai et al. (1978, 1981) showed that insulin absorption from the nasal cavity was influenced by pH, being minimal at pH 5.5 and 7.4, near to the isoelectric point, and rising sharply on either side. A similar pH effect was demonstrated by Ichikawa et al. (1980) using aqueous insulin solutions without additives administered rectally to rabbits. However, in rectal administration of insulin in polyacrylate base, Morimoto et al. (1980) obtained activity at pH 6.5 but observed no significant difference in the blood glucose levels at various other pH values investigated. This contradiction warranted study of the pH effect and in addition to a carbomer base similar to that used by Morimoto et al., a PEG base was examined in the present work.

The pH dependence in the presence and absence of surfactant is shown in Fig. 3.

With the simple aqueous PEG base (A1) in which no surfactant was present and

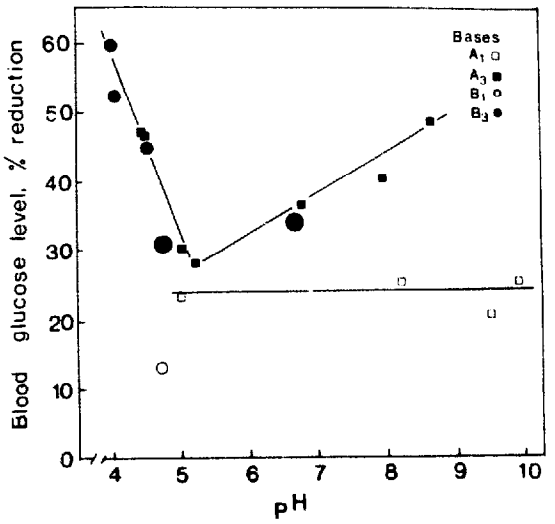

Fig. 3. Relationship between blood glucose level reduction in rats (□, ■, ○, ●) and rabbits (⬤) and the pH of microenemas containing 33% Polysorbate 20 in different bases and 107 I.U./kg.

at an insulin dosage of 107 I.U./kg, some hypoglycaemic activity was found (20–30% reduction on initial glucose level) but little or no pH effect could be discerned. However, when 33% of polysorbate 20 was present in PEG 4000 base (A3), the activity was strong (36–48% reduction) at all pH values and there was also a distinct biphasic pH-dependence, activity being lowest at pH 5.2, close to the isoelectric point of insulin, and increasing progressively at lower and higher pH values (Fig. 3).

The dilute carbomer base (1%) without surfactant (B1) showed no activity between pH 6 and 9 and very little at pH 4.3, in contrast to the work of Morimoto et al. with diabetic rats using a similar base but with the insulin (5 and 10 I.U./kg) in suspension, where activity was found between pH 4 and 8.

On the other hand, the presence of polysorbate 20 promoted hypoglycaemic activity to an extent which was related to the pH of the polyacrylate gel formulation. The pH-dependence fitted well into the pattern observed with the promoting polysorbate PEG bases (Fig. 3), irrespective of whether rats or rabbits were used as test animals, and in spite of some slight variation of gel viscosity with pH. However, with surfactants having little promotional activity, e.g. polysorbate 81, the pH dependence was virtually insignificant.

Dose-dependence of hypoglycaemic effect in different promoting bases

Though the hypoglycaemic activity is increased on raising the dosage of insulin, it is evident from experimental results published that there are unexplained deviations at higher dosages (Ichikawa et al., 1980; Mesiha et al., 1981). Again, absolute activities reported for rectal preparations containing similar levels of insulin dosage vary greatly and though this may be due, in part, to formulation variables or differences in experimental technique, major disagreements exist in the results

obtained using relatively simple bases containing little or no promoter. A series of studies was therefore made in the present work using medium and high insulin dosages to see whether there was a progressive change in activity, and whether a particular range offered special advantages in administration.

Change of dosage between 12 and 150 I.U./kg body weight was tested using PEG 400 (A2, A3) and polyacrylate bases (B2, B3) with two concentrations (10% and 33% w/w) of polysorbate 20 as promoter. The formulations were adjusted to be close to pH 4 (range 4.0–4.4) and the doses were obtained by using dilutions of the strongest insulin solution with water for injection. The blood glucose levels, measured for 3 h, show an unexpected dose-dependence (Fig. 4) which is, however, within a limited range of activity, much less than expected for such a large increase in insulin dosage. The differences in activity between the different bases and surfactant concentrations remain in the same limited range, which is itself significant. This indicates that the absorption kinetics are close to a steady-state condition, and that the state is not primarily a function of the surfactant concentration or the base used. It is therefore postulated that the transfer system has reached a state of saturation. The strong hypoglycaemic effect generally persisted for 2 h or more. At lower doses, the variation between animals increased greatly as the activity fell off, previous authors having worked in the lower ranges (Morimoto et al., 1980).

A secondary dose effect is nevertheless apparent from the activity–insulin concentration plots, from which it is clear that the dose-dependence is not linear. There is a maximum activity, followed by a depression at higher concentrations at both 10 and 33% surfactant concentrations, indicating that the formulation can have a significant influence. In fact, the results reported for rectal absorption from suppositories in rabbits by Ichikawa and Mesiha (loc. cit.) seem to indicate that the activity

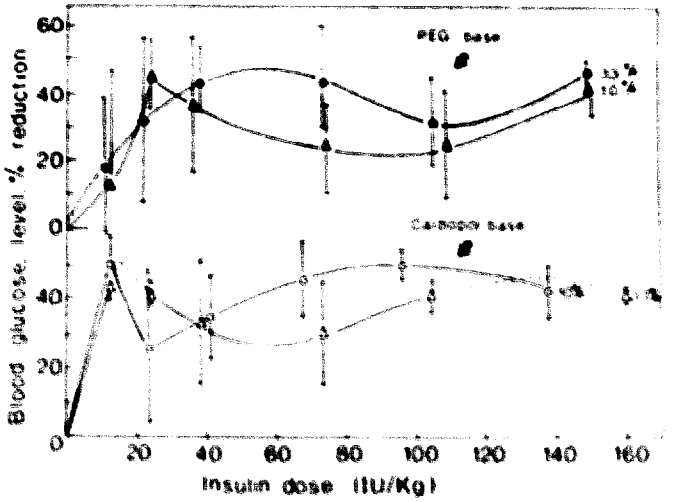

Fig. 4. Dose–response curves after rectal administration to rats of insulin in PEG base and Carbopol base containing 10% w/w and 33% w/w of Polysorbate 20. The data are expressed as mean ± S.E. (n = 5). For PEG base (A3): 38 I.U. versus 12 I.U., $P = 0.02$; 105 I.U. versus 150 I.U., $P = 0.02$; 150 I.U. versus 38 I.U., $P = 0.01$.

goes through a maximum and falls as the dose is raised. In the gel base the 10% polysorbate level is more effective than the 33% over most of the insulin dosage range but the activities approach a constant value at the highest dosage. However, towards the lower insulin values, there are two inversions, giving one dosage zone of direct and another of inverse activity relationship to concentration. In PEG base, similar anomalies occur; here, the higher dosage range is characterized by a direct activity–insulin concentration relation, again approaching a constant value, with two inversions at lower dosages. The values of the activities at the maxima and minima of the curves are significantly different ($P = 0.01–0.02$) as shown in Fig. 4.

Also notable is the closeness of the experimental values at the upper limits of activity for the two surfactant concentrations in the two bases; a similar closeness is found for the lower activity limits. The only exception is at the lowest dose in the PEG bases, which is in the region where activity decreases sharply with dose and animal variability is high (Fig. 4), (Morimoto et al., 1980; Shichiri et al., 1978).

These effects may be composite, and may be caused by parameters having opposing effects on the diffusion and absorption properties of insulin, such as the interplay between the aggregation state and the effective concentration gradients controlling the release rate from the base and the absorption rate.

The release rate, which is normally a direct function of dose for a single water-soluble species in an equilibrated hydrophilic system containing drug below saturation concentration (Touitou and Donbrow, 1982) will tend towards a constant value with concentration increase in aggregating systems where diffusion of the aggregate is relatively slow. The net effect expected would be a fall in the relative release rate with concentration rise towards a limiting plateau value. A similar argument is applicable to absorption rate of an aggregating system but on accumulation of high concentrations of aggregates in the lumen, the absorption rate may again increase as a consequence of transfer of higher aggregates or increased rate of deaggregation by the membrane.

A possible factor which may be considered is the chemical activity of the insulin in the base or, more simply, the effective concentration. Assuming the insulin to be in solution in the water present in the base, the fact that the water content is greater in the gel bases lowers the insulin concentrations relatively in this medium. Replotting the 4 curves on an insulin concentration scale based on water content, the gel curves are displaced to lower concentration ranges than the corresponding PEG curves, but the zones of direct and inverse relationship of effect to dose level are not correlated by concentration in the two bases.

Nevertheless, further treatment on the basis of insulin aggregation in the free water, i.e. the water unbound by the hydrophilic groups of the polymers and surfactants, led to a significant correlation (Donbrow and Touitou, unpublished data).

In the present study, high surfactant concentrations were used in order to ensure strong promotion of insulin absorption (Touitou et al., 1980), the intention being to enable comparison of potential promoters on a scale of relative activity. Furthermore, such concentrations were considered advisable to minimize the possibility of the surfactant concentration influencing the rate-determining step at the membrane

level in the insulin dose-dependence studies (Florence, 1981). The curves in Fig. 4 and the kinetic data over the full 3 h of the measurements do not reveal any effects which could be attributed to the two surfactant concentration levels used.

The general conclusion to be drawn is that the hypoglycaemic activity of rectally-administered insulin is strongly influenced by formulation factors affecting the aggregation state and hence the chemical activity of the insulin in the base. These include the nature of the base, the pH, the type and concentration of the surfactant and the insulin dose incorporated, all of which affect insulin aggregation and transfer through the rectal membrane. Not only do these parameters cause differences in the biological activity of insulin at similar dose levels from different bases but even from a single base in which all other factors are kept constant, the insulin dosage has an important and unexpected role where a plateau effect might have been anticipated at high dose levels. Formulation variables may thus dominate and obscure the effects of other parameters studied, explaining some of the contradictions cited earlier.

Acknowledgements

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