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FACTORS AFFECTING THE CHEMICAL STABILITY OF CARBOXYLIC ACID DRUGS IN ENHANCED SOLUBILITY SYSTEM (ESS) SOFTGEL FORMULATIONS BASED ON POLYETHYLENE GLYCOL (PEG).

M.S.Patel*, F.S.S.Morton, H.Seager and D.Howard

R.P.Scherer Ltd, Frankland Road, Swindon, England

ABSTRACT

Drug decomposition in ESS softgel formulations of three monocarboxylic acid drugs was measured after accelerated storage of solutions at 105 deg C for 3 or 7 days. Drug decompostion occured primarily by reaction between the unionised carboxylic acid function of the drug and the alcoholic groupings of the components in the solvent (e.g. PEG, glycerin) to form mainly the corresponding mono-esters. The ionised form of the drug was relatively unreactive. Different solvents were evaluated and the corresponding drug decomposition rates were explained in terms of the alcoholic group content of the solvent components. The presence of water in the formulation decreased the reaction rate. A rate equation was derived and utilised to compare chemical stabilities of related formulations. The

* Current address: Searle European Development Centre
Rue Grandbompre 11, 1348 Mont-St-Guibert, Belgium

stabilities of similar ESS formulations of the three drugs were greatly different due to differences in the intrinsic reactivities of the drugs. The findings of this study can be used to maximise chemical stability of ESS formulations of carboxylic acid drugs.

INTRODUCTION

The ESS system was discovered and developed in order to dissolve high concentrations of drugs in the fill liquids of softgel formulations. The principal characteristic of the ESS system is the enhancement of the solubility of a drug by the addition of alkali or acid for acidic or basic drugs respectively (1). The effect of the added excipient is to generate an ionised form of the drug which itself has a significant solubility in the softgel fill medium (1,2). The effect is to cause an enhancement of solubility which can be large enough to permit softgel fills to be formed which are composed of solutions rather than suspensions, with the potential advantage of improved bioavailability.

The patented ESS system has been widely applied and is particularly useful in PEG formulations since this medium generally provides the best solubility enhancements and additionally has the advantage of being soluble in the gastric fluids.

A major application of the ESS technology is to dissolve drugs which have a carboxylic acid group. This functional group, however, can potentially react with alcoholic groups of PEG and glycerin etc. to form esters (3). Since ESS formulations of such drugs modify the ionisation of the carboxylic acid group, the stability of such formulations may be altered.

The present study represents a systematic investigation into the factors affecting the chemical stability of carboxylic acid drugs in ESS formulations containing PEG and other alcoholic excipients under accelerated storage conditions.

EXPERIMENTAL

Materials

The three drugs, PEG 400, PEG 600, glycerin, sodium hydroxide and potassium hydroxide, were of pharmacopoeial quality. Tween 80, Tween 20, Synperonic L64, Triacetin and Tetraglycol were commercial grade materials. All materials were used as received.

Methods

Mixtures (8 g quantities) were prepared in glass vials (10 cm^3) by dispersing the drug in the solvent components followed by addition of aqueous solutions of the alkali and shaking until dissolution was complete. All mixtures were solutions at room temperature and at 105°C.

Aliquots (1 g) of the solutions were filled into amber glass ampoules (10 cm^3) which were then sealed. Ampoules were stored at 5°C or 105°C for the appropriate time period.

A storage condition of 105°C for 3 or 7 days was chosen from previous indications that it accelerated reaction rates without changing reaction mechanism or exhausting reactants.

The intact drug contents in the samples was determined by stability indicating analytical methods using high pressure liquid chromatography.

RESULTS AND DISCUSSION

Degradation of drug 1

Fig 1 shows a typical chromatogram from a degraded sample containing drug 1 as drug, PEG as solvent and glycerin as a formulation excipient. Apart from the intact drug, peaks corresponding to mono-ester products between the drug and PEG and between the drug and glycerin were identified, confirming the presupposed drug decomposition routes.

Effect of alkali levels

The effect of potassium hydroxide concentration on the chemical stability of mixtures containing 10 % drug 1, 8 % glycerin and 5 % water is shown in Table 1. The amount of added alkali in the formulations is expressed as the amount of drug converted to the ionic form. It is assumed that in the absence of added alkali, there is negligible drug ionisation and that there is complete drug ionisation in the presence of 1 mol equivalent of alkali, and a linear relationship exists between these limits (1,2).

The results show that drug degradation in an ESS formulation containing 0.5 m/e alkali was nearly half that in a classical formulation not containing added alkali where there was major drug degradation under accelerated conditions.

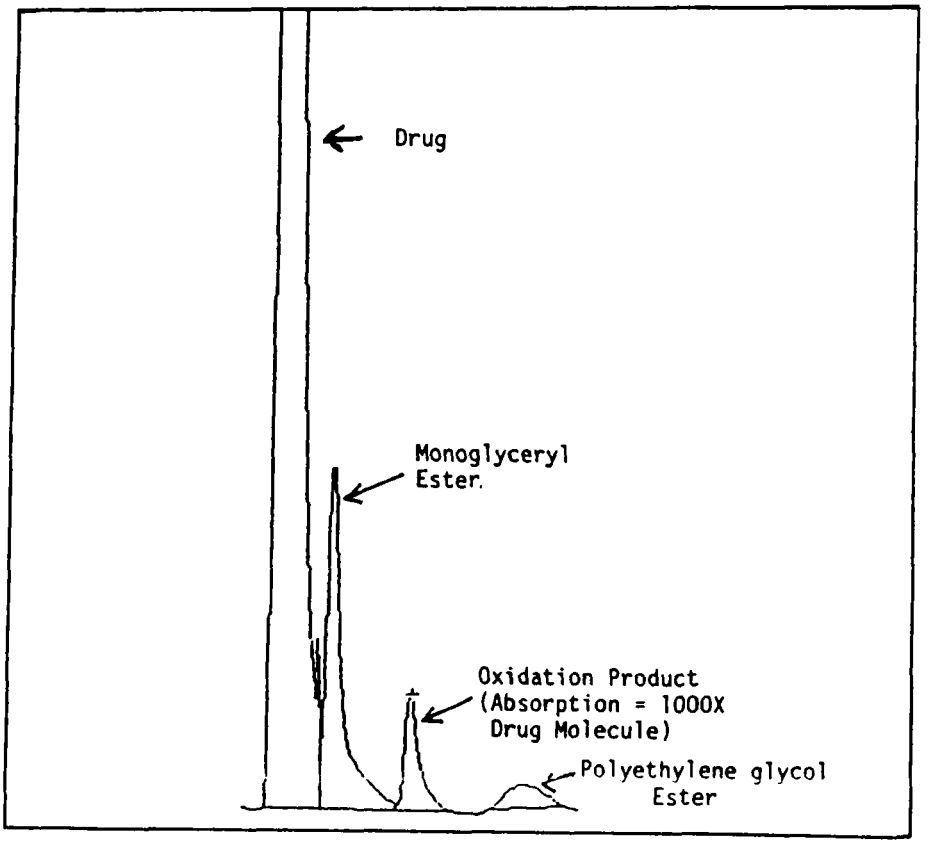

FIGURE 1

Typical hplc profile of a degraded sample of drug 1.

In Fig 2 the extent of drug degradation is plotted against the proportion of the drug unionised. It may be inferred that it is primarily the unionised form of the drug which is reactive, the ionised form being relatively inert to reaction. The esterification reaction between a carboxylic acid and an alcohol follows an $A_{AC}2$ reaction mechanism (4) in which a transition complex between the alcohol and the

TABLE 1

Effect of potassium hydroxide concentration on the chemical stability of formulations containing 10% drug 1 in PEG 600. Storage at 105 deg C / 7days.

KOH concn mol equiv	Drug ionised %	Drug unionised %	Drug decomp % of initial
0	0	100	24.6
0.1	10	90	21.7
0.3	30	70	19.3
0.5	50	50	14.9
0.7	70	30	7.5
0.9	90	10	5.6

protonated acid species is formed. An explanation of the above result may be that the ionised form of the drug can no longer be protonated to form the complex and hence does not effect reaction.

Effect of water

The effect of water concentration on the chemical stabilities of classical and ESS formulations of drug 1 is shown in Table 2. An increase in water concentration increased the chemical stability of the formulation, irrespective of the degree of drug ionization.

Since esterification and hydrolysis are generally reversible reactions (4), it would be expected from

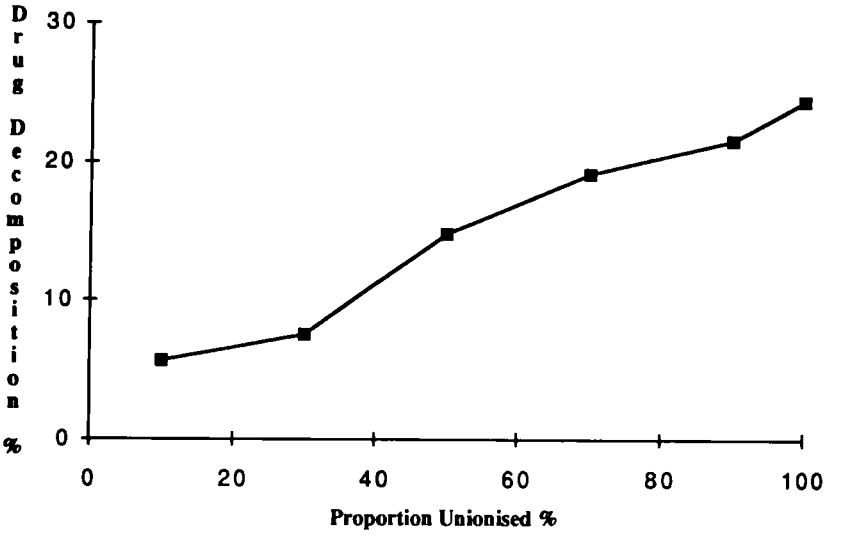

FIGURE 2

Effect of drug ionisation on the chemical stability of drug 1 formulations containing potassium hydroxide. Storage at 105 deg C / 7 days.

rate equations that an increase in water content would promote an increase in back-hydrolysis rate and hence a decrease in esterification rate. The observation corresponds with the expectations.

Effect of glycerin

The effect of glycerin concentration on the chemical stabilities of ESS drug 1 formulations is shown in Table 3. An increase in the glycerin concentration caused an increase in the rate of drug 1 degradation, confirming that the carboxylic group reacts with all solvent components possessing alcoholic groups.

TABLE 2

Effect of water content on the chemical stability of formulations containing 10 % drug 1 in PEG 600. Storage at 105 deg C / 7 days.

Drug ionisation %	Water content %	Drug decomposition % of initial
50	5.0	14.9
50	10.0	8.8
30	1.4	24.3
30	5.0	19.3
0	0.0	29.8
0	5.0	24.6

TABLE 3

Effect of glycerin content on the chemical stability of formulations containing 10 % drug 1 in PEG 600. Drug ionisation 50%, storage at 105 deg C / 7 days.

Glycerin concentration %	Drug decomposition % of initial
0	5.9
8	14.9
16	16.5

From the law of Mass Action, the reaction rate is proportional to the product of the concentrations of the reactants. In the formulations examined, reaction would occur between the unionized carboxylic acid group in the drug and the hydroxy groups in PEG 600 and in glycerin to form the appropriate esters.

For the purpose of establishing a rate equation, it may be assumed that at the low levels of drug degradation under consideration only the monoesters are formed. It is further assumed that the reactivities of PEG 600 and glycerin towards the drug are comparable.

The rate of the forward reaction may be estimated by :

$$-\frac{dc_f}{dt} \alpha [UD] \cdot ([P] + [G])$$

where $-\frac{dc_f}{dt}$ = rate of the forward reaction

[UD] = activity of unionized drug

[P] = activity of PEG

[G] = activity of glycerin

Since water reverses drug degradation, the overall drug degradation rate $-\frac{dc}{dt}$, may be approximated from

$$-\frac{dc}{dt} \alpha \frac{[UD] \cdot ([P] + [G])}{[W]} \qquad \text{Eq. 1}$$

where [W] = activity of water.

The relationship expressed by equation 1 is tested in the results shown in Fig 3, where reactant

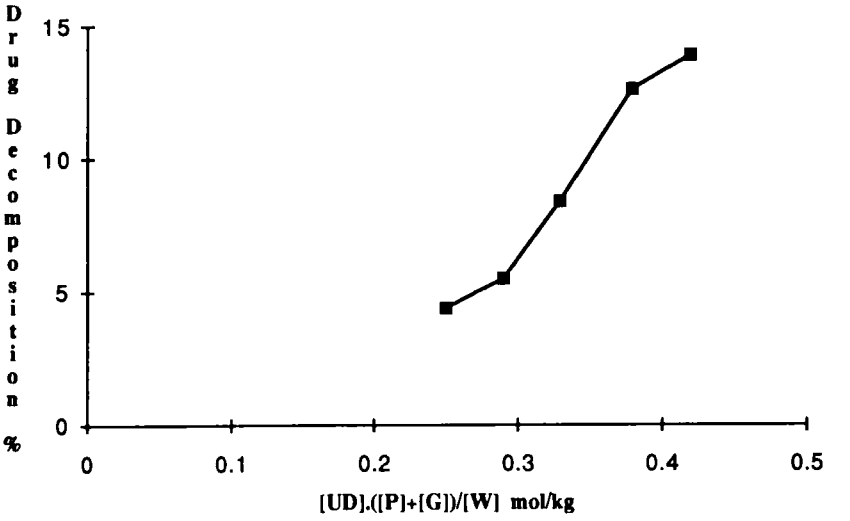

FIGURE 3

Relationship between calculated and observed reaction rates for drug 1 formulations at 50% drug ionisation.

activities are approximated by molar concentrations. The good corelation shows that such a relationship may be used to compare stabilities of related formulations.

Effect of drug concentration

The stability of ESS formulations containing drug concentrations ranging from 10% to 50% is shown in Table 4. There was an apparent decrease in drug degradation rate with an increase in drug concentration. However, formulations containing higher drug concentrations contain lower concentrations of PEG and higher concentrations of water which reverse the effect of drug concentration and cause a decrease in the drug degradation rate. The increasing water

TABLE 4

Effect of drug 1 concentration on the chemical stability of formulations at 50% drug ionisation. Storage at 105 deg C / 7 days.

Drug concn %	Reactant concn mol / kg [UD]	[P]	[G]	[W]	$\frac{[UD].([P]+[G])}{[W]}$ mol / kg	Drug decomp %
10	0.24	1.31	0.87	1.26	0.42	13.9
20	0.48	1.09	0.87	2.53	0.38	12.6
30	0.73	0.87	0.87	3.79	0.33	8.4
40	0.97	0.65	0.87	5.06	0.29	5.5
50	1.21	0.43	0.87	6.32	0.25	4.4

[UD], [P], [G], [W] are molar concentrations of unionised drug, PEG, glycerin and water respectively.

concentration is associated with an increasing amount of alkali solution added in proportion to the drug concentration.

Effect of type of alkali

The chemical stabilities of formulations containing either sodium hydroxide or potassium hydroxide are shown in Table 5. Comparable formulations contain different amounts of water due to the different concentrations of the aqueous alkaline solutions used. Fig 4 shows that for equimolar amounts of alkali, ESS

TABLE 5

Effect of type of alkali on the chemical stability of drug 1 formulations at 50% drug ionisation. Storage at 105 deg C / 7 days.

Alkali	Drug concn %	$\frac{[UD].([P]+[G])}{[W]}$ mol / kg	Drug decompsition % of initial
NaOH	20	0.50	14.7
NaOH	30	0.44	11.2
NaOH	40	0.39	9.1
KOH	20	0.38	12.6
KOH	30	0.33	8.4
KOH	40	0.29	5.5

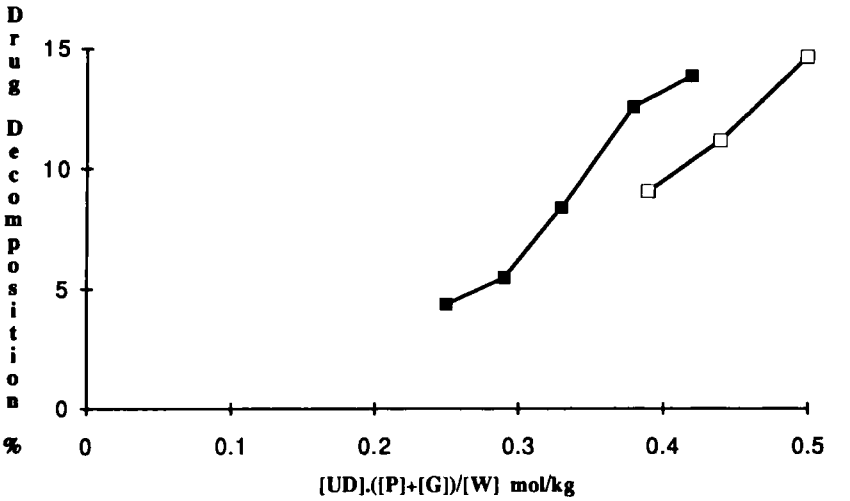

FIGURE 4

Rates of drug degradation in drug 1 formulations containing potassium hydroxide (■) or sodium hydroxide (□). Storage condition 105 deg C / 7 days.

TABLE 6

Effect of molecular weight of PEG on the chemical stability of drug 1 concentrations at 50% drug ionisation. Storage at 105 deg C / 7days.

Drug concn %	Molecular weight of PEG Daltons	[UD].([P]+[G]) / [W] mol / kg	Drug decomposition % of initial
20	400	0.48	14.1
20	600	0.38	12.6
40	400	0.35	10.0
40	600	0.29	5.5

formulations containing sodium hydroxide are more stable than those containing potassium hydroxide, at the alkali levels considered.

Effect of solvents

Formulations in which PEG 400 replaced PEG 600 on a weight basis gave a higher drug degradation rate (Table 6). Since PEG 400 has a lower molecular weight and a higher hydroxy group concentration than PEG 600, a higher reaction rate would be expected in the former solvent.

The effect of solvents having different hydroxy group concentrations is illustrated by accelerated stability data for drug 2 formulations (Fig. 5). Drug 2

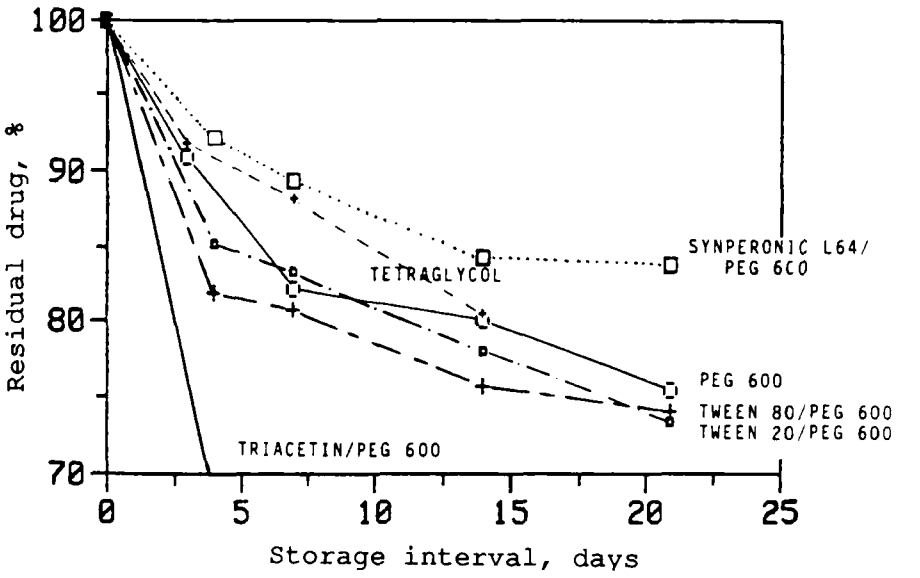

FIGURE 5

Chemical stabilities of drug 2 formulations in different solvents or solvent mixtures (1:1 w/w) stored at 105 deg C.

is a mono-carboxylic acid and is expected to react in the same way as drug 1 to form esters. Formulations either contained the pure solvent or equal weights of the solvent with the other solvents mentioned (Fig. 6).

Formulations containing the poloxamer 'Synperonic L64' were significantly more stable because of its higher molecular weight and hence a lower hydroxy group concentration. Formulations containing triacetin (glyceryl triacetate) were extremely unstable despite the fact that the molecule has no free hydroxy groupings.

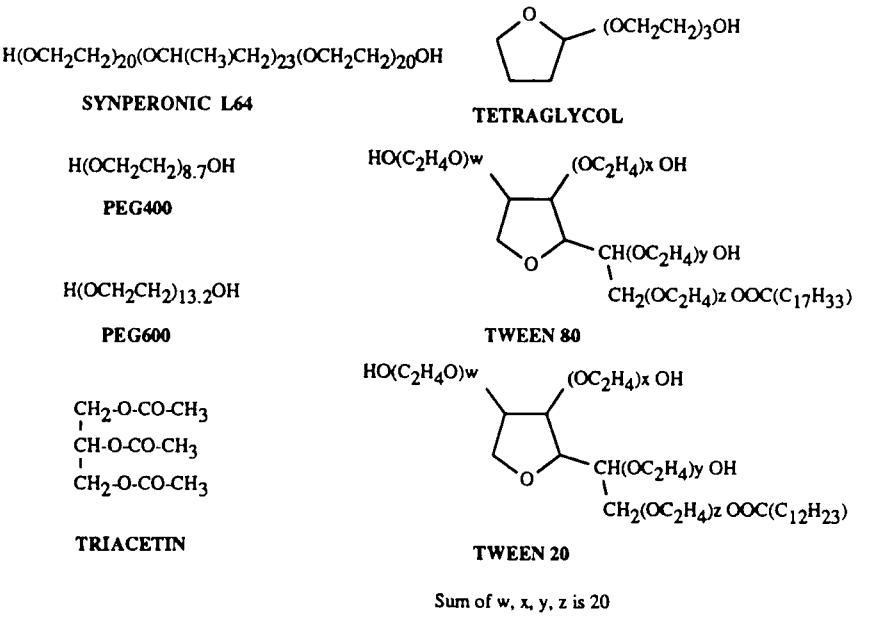

FIGURE 6

Chemical structures of solvents evaluated in this study.

The stabilities of formulations containing the polysorbates Tween 80 or Tween 20 and of PEG 600 were similar. While the molecular weights of the polysorbates are greater than that of PEG 600, they have poly-hydroxy functions capable of poly-esterification.

Formulations containing tetraglycol appear to be slightly more stable than those containing PEG 600 despite the fact that this molecule has a higher hydroxy group density.

TABLE 7

Chemical stabilities of ESS formulations of drugs 1,2 and 3. Storage at 105 deg C / 3 days.

Drug	Reactant concn mol / kg				$\frac{[UD].([P]+[G])}{[W]}$ mol / kg	Drug decomp %
	[UD]	[P]	[G]	[W]		
1	0.97	2.65	0.87	5.06	0.29	13.5
2	0.60	1.09	0.54	2.78	0.35	25.8
3	0.56	1.08	0.54	2.78	0.33	50.3

[UD], [P], [G], [W] are molar concentrations of unionised drug, PEG, glycerin and water respectively.

Effect of nature of drug

Drug degradation rates in ESS formulations containing drugs 1,2 and 3 are given in Table 7. The three drugs are common in having a mono-carboxylic acid group in the molecule.

The differences in the reactant concentrations do not account for the differences in reaction rates. From this it may be inferred that the three drugs have substantially different intrinsic reactivities. For equivalent reactant concentrations, it appears that drug 2 is nearly twice as reactive as drug 1 and that drug 3 is nearly four times as reactive as drug 1 in the ESS formulations under consideration.
The chemical stabilities of drug 3 ESS formulations containing varying amounts of reactants are given in

TABLE 8

Chemical stabilities of drug 3 formulations at 40% drug ionisation. Storage at 105 deg C / 3 days.

Reactant concentration mol / kg					$\frac{[UD].([P]+[G]+[S])}{[W]}$ mol / kg	Drug decomp %
[UD]	[P]	[G]	[S]	[W]		
0.40	1.20	0.54	0	2.78	0.25	14.2
0.56	0.54	0.54	0.11	2.78	0.24	14.4
0.56	1.08	0.54	0	2.78	0.33	16.5
0.51	0.97	1.30	0	3.88	0.30	16.8
0.72	0.96	0.55	0	2.79	0.39	17.1
0.56	1.00	1.09	0	2.78	0.42	20.6

[UD], [P], [G], [S], [W] are molar concentrations of unionised drug, PEG, glycerin, Symperonic L64 and water respectively.

Table 8. Due to the high intrinsic reactivity of drug 3, the extent of drug degradation is measured after 3 days of storage at 105°C compared with 7 days for previous studies.

The good relationship between the observed drug degradation rate and that calculated from Eq. 1 confirms that the theoretical relationship is applicable to carboxylic acid drugs generally. Drug degradation in a drug 3 formulation ceased after ca. 15 days storage at 105°C (Fig. 7), probably because

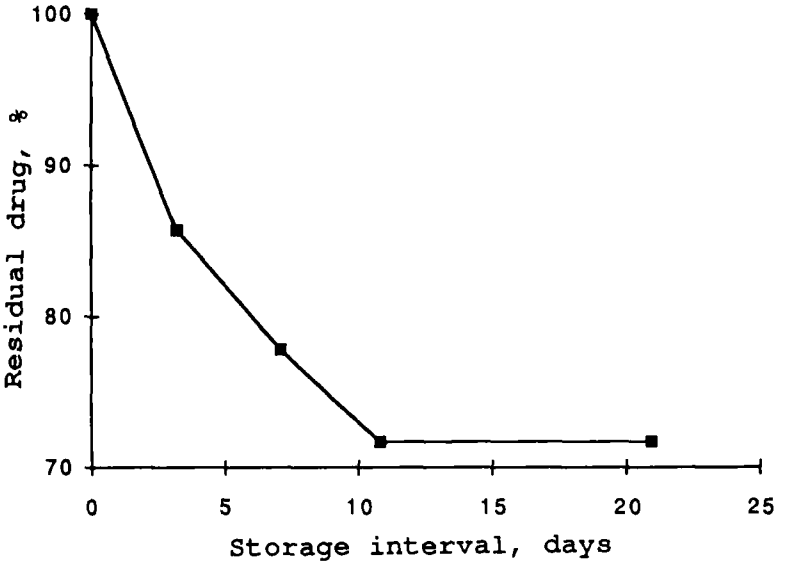

FIGURE 7

Rate of drug degradation in a drug 3 formulation stored at 105 deg C.

the rates of the forward (esterification) and reverse (hydrolysis) reactions are equal at this stage.

CONCLUSIONS

The degradation of carboxylic acid drugs in PEG as a solvent under accelerated conditions has been confirmed and related to the esterification of the drug. The chemical stability of such compounds in ESS softgel formulations is much greater than that in conventional softgel formulations due to the relative unreactivity of the carboxylate anion, compared with the unionized acid.

The factors which increase drug stability in ESS formulations are increase in drug ionization, decrease in the concentration of alcoholic hydroxy groups and an increase in the concentration of water which reverses the esterification process. Large differences in the intrinsic reactivities of drugs have been illustrated. The maximum chemical stability in an ESS formulation of a carboxylic acid drug can be achieved by optimizing the amount of alkali, choice of solvent(s) and excipients and their concentrations. A rate equation is described to compare relative stabilities in different formulations, and an accelerated stability testing condition has been described to screen ESS formulations. Using these techniques, optimised formulations with good long-term stability at ambient temperatures have been developed.

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