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Controlled release of radioprotective agents from matrix tablets—effect of preparative conditions on release rates

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Release rates of radioprotective agents from insoluble matrix tablets were measured as a function of ethylcellulose/stearic acid ratio and active ingredient concentration in the matrix. The influence of the compacting pressure applied during tablet formation on the release of these aminothiol compounds was also examined. The kinetic data conformed with the Higuchi square root equation and first order release. As both plots were linearly acceptable, a statistical method for release mechanism identification using the kinetic experimental results obtained without any further transformation was used. This non-linear regression search procedure accompanied by the χ^2-square test has shown that aminothiol release from the matrix tablets definitely follows the Higuchi square root equation. Increasing the ethylcellulose amount in the matrix consequently improves the degree of wettability and leads to a faster rate of solvent penetration. This tends to release the aminothiols more rapidly from the matrix tablets. Solvent penetration, which also follows a square root of time relationship, is probably the rate-limiting factor in the release process. The linear increase in release rates of the aminothiols observed with ethylcellulose concentration is explained by a parallel increase in the porosity of the matrix tablets. Increase in the drug concentration in the tablet increases the cysteine hydrochloride release rate and decreases the cysteamine hydrochloride release rate. A similar effect was also observed by applying increasing compacting pressure during matrix tablet formation. It was suggested that these two experimental factors differently affect the internal structure of the matrix during the preparation process. In the presence of cysteine hydrochloride larger porosities and smaller tortuosities are produced in the matrix leading to an increase in release rate. On the other hand, in the presence of cysteamine hydrochloride smaller porosities and larger tortuosities are formed in the matrix leading to a decrease in the release rate with increasing aminothiol concentration and compacting pressure respectively.

Cysteamine and cysteine are two of the most effective radioprotective agents tested in mammals (Doull et al 1962). They protect against radiation as a result of their ability to trap primary free radicals formed via degradation radiolysis of water (Bacq 1975). Their practical use is limited by their rapid excretion and degradation. The objective of this research has been to improve the efficacy and bioavailability of these radioprotectants by development of a controlled drug delivery system based on an insoluble matrix tablet. Release rates of the thiol compounds from the insoluble tablet have been studied as a function of ethylcellulose/stearic acid ratio and active ingredient concentration in the matrix. The influence of the compression force applied during tablet formation on the release of the radioprotectants has also been examined.

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THEORETICAL

Previous investigations (Desai et al 1965; Roseman & Higuchi 1970; Roseman 1975; Cobby et al 1974) have shown that the Higuchi square root equation can be used to describe drug release from inert matrices. Higuchi (1963) suggested that the amount of active ingredient, Q, liberated per unit exposed area into the external medium in time t, from a planar single surface of a heterogeneous matrix tablet containing a dispersed drug, should follow the relationship:

$$Q = \left[\frac{D.\varepsilon}{\tau} (2A - \varepsilon.C_s) C_s.t \right]^{\frac{1}{2}} \quad (1)$$

where ε is the porosity of the matrix, τ is the tortuosity of the matrix, D is the diffusion coefficient of the drug in the extracting medium, A is the total amount of drug present in the matrix and C_s is the solubility of the drug in the extracting medium. Equation 1 would be essentially valid for systems in

which A is much greater than εC_s, indicating that dispersed solid drug particles are in equilibrium with dissolved drug in the matrix. However, in cases where all the drug has been completely dissolved in the heterogeneous matrix, assuming then that the matrix is saturated with the drug solution, release rate would obey the following equation (Desai et al 1966b):

$$Q = 2C_o\varepsilon\left(\frac{D.t}{\tau.\pi}\right)^{\frac{1}{2}} \quad (2)$$

where C_o is the concentration of the solution in the matrix. Equation 2, which is an approximation, is in good agreement with the experimental results only during the first 30% release from the initial dose as stated by Higuchi (1962). It is not the purpose of the present work to provide further confirmation for the Higuchi model, but to measure drug release profiles and to design a sustained release delivery system that will improve the bioavailability of the thiol compounds and reduce their toxicity.

Higuchi (1963) had also studied the release kinetics of drugs from a spherical pellet. According to his evaluation, initial release of the drug should follow the square root of time relationship (up to 50% release) but significant deviations would occur toward the end of the leaching process. An initial drug release rate from a total matrix tablet can be described by a similar mathematical expression:

$$Q = k \cdot t^{\frac{1}{2}} \quad (3)$$

where k is the release rate constant. The dependence of k on the kinetic parameters already mentioned in equations 1 and 2 is not clear. An attempt to derive an exact solution with regard to drug release from a whole heterogeneous matrix tablet appears impossible. This would require an accurate knowledge of the release kinetic pattern followed by the dispersed particles in the entire matrix tablet. It should be noted that various workers have investigated the release mechanism of drugs having moderate water solubility from insoluble and inert matrices. However, little is known concerning the release of highly water soluble compounds from insoluble matrices such as in the present case.

MATERIALS AND METHODS

Ethylcellulose (N-type) had an ethoxyl content of 47.5–49%. The viscosity of a 5% w/w solution in toluene–ethanol (80 : 20 w/w) was 100 cP (Hercules, Wilmington, Delaware). Stearic acid conformed to U.S.P. XVI. Cysteine and cysteamine hydrochloride were supplied by Sigma (St Louis, Missouri).

Methods

Matrix tablet preparations

Cysteamine and cysteine hydrochloride, having the same particle size distribution during the entire investigation, were dried and suspended in the melted stearic acid into a Pyrex 100 ml glass container. The mixture was then continuously stirred even after heat removal until complete solidification to prevent the separation of the active ingredients from the wax. To facilitate compression and mixing, the solid mixture was granulated by means of a 20-mesh screen and mixed with various proportions of ethylcellulose in a mortar. Various concentrations of the active material, not exceeding 50%, were prepared in defined ratios of stearic acid and ethylcellulose matrix mixture. The mixture was then compressed into cylindrical tablets of 13.1 mm in diameter and a mean surface area of 400 mm^2 (500 mg, weight) in a vacuum KBr die, using a laboratory press, at various compacting pressures. Each batch of matrix tablet formulation has been triplicated.

Release kinetics experiments

Release of the drug was measured spectrophotometrically (Unicam, model SP-1805) at 240 nm, using a rotating basket dissolution apparatus as described in U.S.P. XIX. The dissolution medium, phosphate buffer pH 7·4, was kept under nitrogen except in the work on pH effects, in which McIlvaine buffers were used. Exactly 500 ml of the buffer, previously heated and maintained at 37 ± 0·3 °C, was used for each experiment. The basket was immersed in the buffer and rotated at 150 rev min^{-1}. Experiments were carried out for 8–16 h, and the concentration of the unoxidized drug was monitored continuously, using a 10 mm flow-cell fed by a peristaltic pump (Buchler, model 2-6100), at a flow rate of 25 ml min^{-1}. Pure cysteine and cysteamine hydrochloride were determined in the release system under identical experimental conditions to ensure that the thiol compounds remain intact during the entire in-vitro release experiments. The constant optical density registered on the uv recorder, during 24 h for both compounds, confirmed that no oxidation occurred in the sink solution.

The solubilities of cysteine and cysteamine hydrochloride at 37 °C were determined by exposing an excess of solid to phosphate buffer solution and assaying the supernatant, after equilibrium was reached, according to the experimental conditions already described.

The applicability of the Higuchi equation and of

the first order release model were considered using different computer programs which analysed the experimental kinetic results obtained.

RESULTS AND DISCUSSION

During all the drug release experiments the matrix tablets were examined and remained intact even after complete exhaustion of the active ingredient. However, a mild erosion was observed in some tablet formulations such as matrix tablets containing 50% active ingredient or tablets compacted at a pressure of 1500 kgf cm^{-2}. This erosion was confirmed by the presence of small insoluble particles in the sink solutions but, in any case, this erosion did significantly change the surface area available for drug release.

Kinetic results obtained from the computer release data analysis show that a linear relationship exists between the cumulative amount of drug released and the square root of time up to 80% release indicating that drug release from the whole tablets follow a square root time equation 3. To avoid any ambiguity concerning the release mechanism the applicability of the classical first order equation was also examined:

$$\log W = \log W_0 - \frac{k_1 t}{2{\cdot}303} \qquad (4)$$

where W is the quantity of drug remaining in the tablet at time t, k_1 is the first order release constant and W_0 is the initial quantity of drug in the matrix tablet. In the present case the data also fit the first order release pattern. This release behaviour, which conformed with both release kinetic models, was observed for all the matrix tablets analysed without any exception. A linear dependence of the total amount of drug released as a function of square root of time is unexpected from the whole matrix tablet because of geometrical shape limitations. However, some authors have already reported that drug release from insoluble whole matrix tablets follows the Higuchi square root equation (Farhadieh et al 1971; Fessi et al 1978). Apparently, the flat cylindrical shape of the tablet gives more prolonged linearity than a sphere (up to 75% release). This probably indicates that for a given matrix tablet, τ and ε remain practically constant during the overall release of the active ingredients. Moreover, Schwartz et al (1968a) have reported that the kinetic data from an inert whole matrix tablet conformed both with first order release and Higuchi matrix model. A more stringent mathematical treatment was needed to distinguish between the two release mechanisms. They applied the differential rate mathematical treatments (Schwartz et al 1968a). Although this is mathematically legitimate it will be preferable to use a more valid test for drug release from matrices. The differential rate test suffers from a lack of accuracy due to the transformation performed on the initial kinetic parameters by linearization and differentiation of the original curve Q′ versus time. Sometimes, when a clear distinction is possible, the release rate treatment could lead to distinct differentiation between the two models. However, a normal examination of the release mechanism identification should be carried out using the experimental results obtained without any further transformation. Since two kinetic models are expected the χ^2-test should be used which is useful for comparison purposes. Therefore, the resultant values of χ^2 for the first order expected equation having the following expression:

$$Q = W_0(1 - e^{-k_1 t}) \qquad (5)$$

and the square root of time expected function represented by equation 3 can be compared to determine which of the two models better describes the experimental kinetic data.

The smallest χ^2 value obtained during the comparison will designate the correct release model. χ^2 therefore, is an evaluation of the goodness of fit to the experimental data. The computer program used is based on the method of non-linear least squares which is a technique for fitting the data with a function which is not linear in its parameters. According to this method the optimal parameter values are obtained by minimizing χ^2 with respect to each of the parameters simultaneously. This search leads to the best fit curve expressed by the appropriate minimum value of χ^2 for each of the two expected kinetic models taking into consideration the experimental data obtained. The two expected curves, as are predicted by first order kinetic pattern and Higuchi equation, are shown in Fig. 1 and compared with the observed kinetic data of cysteamine hydrochloride release from a specific matrix formulation. It can be seen from Fig. 1 that the best fit is unequivocally given by the square root equation model which best describes the experimental data reported. This result is also confirmed by the χ^2 value calculated for both kinetic models. The first order equation yields a value of 24·3 which is much higher than the value of 0·66 yielded by the Higuchi square root equation. The apparent inconsistency between the compliance of the data with first order kinetics and the least squares fitted line in Fig. 1

arises from equations 3 and 5 which describe the different release patterns. These equations depend on one kinetic constant only, k_1 or k which govern the overall release reaction. Since the χ^2 value has been correctly minimized, any attempt to improve the fit of the dotted curve in Fig. 1 will increase the χ^2 value. All the different matrix formulations examined show similar kinetic behaviour. These results indicate that the aminothiol release from the whole tablet follows definitely a linear square root of time relationship.

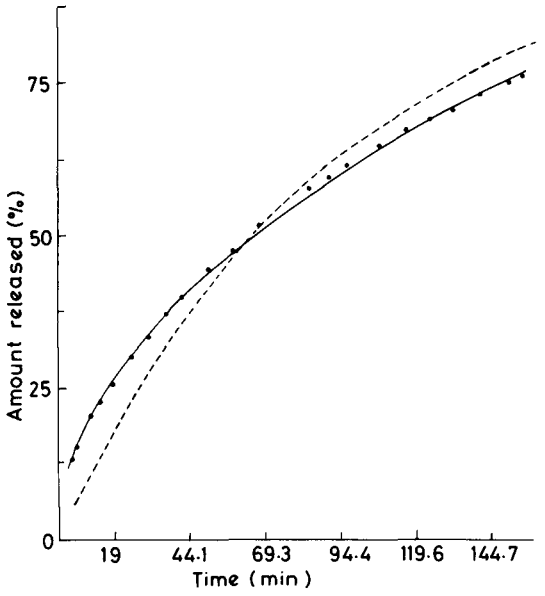

FIG. 1. Fitting and comparison of predicted release curves as were reported by the computer according to the square root equation (——, continuous line) and first order equation (– – – –) to observed kinetic data (●) as were extracted from the whole experimental release curve.

The water solubility of the aminothiols was measured and found to be 4·5 g ml^{-1} for cysteamine hydrochloride and 1·26 g ml^{-1} for cysteine hydrochloride while their concentration in various tablets was varied from 0·02 to 0 3 g ml^{-1} and from 0·20 to 0·5 g ml^{-1}, respectively. Obviously, $\varepsilon C_s \gtrsim 2A$ and one of the most fundamental conditions of the Higuchi diffusion-controlled model does not exist in our present study. Therefore, equation 1 cannot be valid. Less than 5% of the tablet volume of water is needed in order to dissolve the entire amount of cysteamine present in the tablet (at a 20% concentration). It is then assumed that the solvent penetrating the matrix completely dissolves the thiols upon contact. Release of the active ingredient from a single planar surface of such a tablet would probably follow equation 2, which should be used for a better comprehension concerning the influence of the different experimental factors on the release of the aminothiols from the whole tablets.

Effect of ethylcellulose concentration

The weight of the matrix base, which is composed of ethylcellulose and stearic acid, was kept constant in the different formulations prepared. The variable increase of ethylcellulose concentration in the matrix was, therefore, accompanied by a parallel decrease of the stearic acid concentration while the active ingredient concentration and the compacting pressure applied to form the tablets remained unchanged.

The experimental results obtained for the two radioprotectants show that release rate increases with increasing ratio of ethylcellulose in the matrix tablet.

An unexpected linear relationship was observed when the release rate was plotted against the concentration of ethylcellulose (Fig. 2). The increase in release rates was expected since it reduces the stearic acid concentration in the matrix tablet and it is well accepted in the literature (Schwartz et al 1968b; Doelker & Buri 1981) that diffusion is most difficult in the wax regions of a heterogeneous matrix, especially for freely water-soluble compounds such as cysteine and cysteamine hydrochlorides. Moreover, it has been shown by Boymond et al (1981) that ethylcellulose in matrices has good wetting properties which were confirmed by the lack of influence of surfactant solutions as release media on drug release rates from ethylcellulose matrix tablets. In this work, increasing the ethylcellulose amount in the matrix improved the degree of wettability and led to a larger rate of solvent penetration which tended to dissolve the active material more rapidly and this then diffused out through the matrix. This result suggests that the aminothiols' release may be controlled by the rate of solvent penetration and this will explain the linear square root of time relationship obtained for the overall release from the whole tablet. The penetration rate of a fluid through powdered systems was studied by Washburn (1921) who found that the volume of penetrated liquid is linear with the square

root of time. Groves & Alkan (1979) demonstrated the apparent validity of the Washburn equation when applied to compressed tablets. In the present study a similar kinetic process could occur: solvent penetration may be visualized as a front moving into the tablet, according to a linear square root of time relationship, dissolving the aminothiols which then diffuse out. The solvent penetration, being the slowest step in the kinetic pattern, determines the release mechanism. However, the linear relationship observed with increasing ethylcellulose concentration (Fig. 2) cannot be explained by the change of solvent penetration rate. It should be assumed that ethylcellulose variation affects also the porosity and

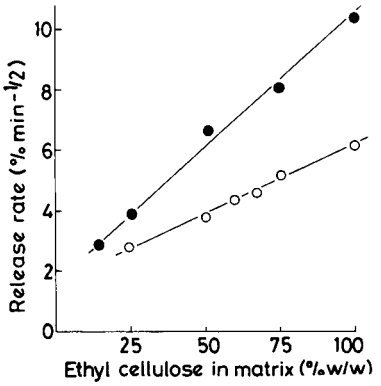

FIG. 2. Influence of ethyl cellulose concentration on release rate* of cysteamine hydrochloride (—●—) and cysteine hydrochloride (—○—) from matrix tablets having the following composition (20% aminothiol concentration and compacted at a pressure of 3000 kgf cm^{-2}).
* k, calculated from equation 3.

tortuosity of the matrix. This is suggested by the increasing difference in release constant values between cysteamine and cysteine hydrochloride for an identical matrix formulation in the higher ethylcellulose concentrations. According to Desai et al (1966a) the porosity of a matrix refers to the volume fraction that is permeated by the solvent and available for diffusion in the already leached portion of the matrix. It appears that this volume fraction is directly proportional to the ethylcellulose concentration which, in turn, probably little alters the tortuosity factor. Nevertheless, the effect of τ is less pronounced than that of ε on release rate in accordance with equation 2. The resulting combined effect, whch in fact reflects mainly the influence of the porosity, leads to a linear increase of the aminothiols' release rate as is also suggested by equation 2.

Effect of active ingredient concentration

It is desirable to produce several tablet concentrations of the same drug to provide a variety of dosage schedules. Therefore the dependency of the aminothiol concentration on release rate has been investigated. Increase of the drug concentration in the tablet should increase the release rate as indicated by the square root equations previously described. However, opposite kinetic results have been observed during the release experiments of the two aminothiols. Increasing the active ingredient concentration enhances the release rate of cysteine hydrochloride from the tablets while the same effect reduces the release rate of cysteamine hydrochloride from the tablets (Table 1). Since no linear dependence was observed, it can be concluded that not

Table 1. Release rates of cysteine and cysteamine hydrochloride from matrix tablets prepared using different active ingredient concentrations (matrix base was composed of 25% ethylcellulose, 75% stearic acid and compacted at a pressure of 3000 kgf cm^{-2}).

Cysteine Hydrochloride		Cysteamine Hydrochloride	
Concn % w/w	Release rate* % min$^{-½}$	Concn % w/w	Release rate* % min$^{-½}$
20	2·89 (0·999)**	5	4·72 (0·999)**
25	3·26 (0·999)	10	4·51 (0·999)
30	4·71 (0·999)	20	3·87 (0·999)
50	5·22 (0·999)	25	3·01 (0·999)

* Release rate value reported is the mean of 6 different values (each release experiment was duplicated and performed on 3 different batches of the same matrix tablet formulation). Release rates were calculated from equation 3. In all the cases deviation from the mean release value was within 3–7% range; ** correlation coefficients.

only A and ε were affected but also other factors such as τ. The drug particles are isolated in a sea of wax during the matrix preparation and probably opposite interactions occur between the two aminothiols and stearic acid during fusion and congelation. The cysteine hydrochloride increasing concentration would produce larger porosities and smaller tortuosities in the wax portion of the matrix leading to an enhancement of the release rate as was expected (Table 1). The cysteamine hydrochloride increasing concentration would produce smaller porosities and

larger tortuosities in the wax portion of the matrix and account for release rate reduction (Table 1).

Effect of compacting pressure

The compacting pressure applied to produce the matrix pellet has little effect on drug release from tablets prepared using lipid material such as stearic acid by fusion and congelation method (Doelker & Buri 1981). However, compacting pressure variation should affect drug release from matrix tablets prepared by direct compression since it will reduce the void porosity of the tablet. The matrix formulations used in this study are a combination of the two methods and it might be expected that increasing the pressure force should reduce the release rate of drugs incorporated in the matrix. The experimental results in Table 2 show an opposite effect: cysteamine hydrochloride release was reduced while cysteine hydrochloride release was enhanced by increasing the applied compacting pressure. Since most waxes flow around the drug particles during compression (Schwartz et al 1968b) it could be assumed that an interaction occurs between the embedded aminothiols and the stearic acid and also between the wax

Table 2. Release rates of cysteine and cysteamine hydrochloride from matrix tablets compressed using different compacting pressures. (Matrix base was composed of 25% ethylcellulose and 75% stearic acid; cysteine hydrochloride was incorporated at 25% concentration and cysteamine hydrochloride at 20% concentration).

Cysteine hydrochloride		Cysteamine hydrochloride	
Compacting pressure kgf cm^{-2} × 10^3	Release rate* % min$^{-\frac{1}{2}}$	Compacting pressure kgf cm^{-2} × 10^3	Release rate* % min$^{-\frac{1}{2}}$
1·5	2·37 (0·999)**	1·5	4·80 (0·999)**
3	3·26 (0·999)	3	3·87 (0·999)
4·5	3·98 (0·999)	4·5	2·30 (0·999)
6	4·77 (0·999)		

*; ** see Table 1.

portion and the ethylcellulose polymer during the compression process. Depending which amino acid is present, a different internal structure of the matrix is formed by increasing compacting pressure. In the presence of cysteine hydrochloride larger porosities and smaller tortuosities are produced in the matrix and hence release rate increases with increasing applied compacting presure (Table 2). In the presence of cysteamine hydrochloride smaller porosities and larger tortuosities are produced in the matrix leading to a decrease in the release rate with increasing compacting pressure (Table 2). The magnitude of the effect on porosity and tortuosity cannot be clearly evaluated. It could be that the influence of the compacting pressure applied on porosity is negligible and only the tortuosity of the wax portion is affected and, inversely, the porosity can be more influenced than the tortuosity. The resulting combined effect on release rate of the aminothiols remains unchanged. This possible explanation also supports the experimental findings previously reported.

Effect of pH of the sink solution

The release of the aminothiols in different pH sink solutions was expected to remain almost unchanged since the water solubility of cysteine and cysteamine are not markedly affected by pH. However, this factor should be examined so as to allow predictions of a certain kinetic release behaviour in in-vivo experiments. For a specific formulation (cysteine hydrochloride 50% compacted at a pressure of 3000 kgf cm^{-2} in a matrix base containing stearic acid 75%, ethylcellulose 25%), the release rates observed were 5.17, 4.86, 4.73, 5.22, 4.91, 5.14 (percent min$^{-\frac{1}{2}}$) at the following pH releasing media, 1, 4, 5, 7·4, 8, 9, respectively. It is then concluded that no marked effect is produced by different pH sink solutions.

CONCLUSION

Controlled release of the highly water soluble aminothiols was achieved by incorporating the cysteine hydrochloride or cysteamine hydrochloride in a matrix system based on two insoluble components: stearic acid and ethylcellulose. Increasing the ethylcellulose concentration in the matrix tablet improved the degree of wettability and led to a faster rate of solvent penetration and drug release. Solvent penetration, which followed a square root of time relationship, was probably the rate-limiting factor and therefore governed the overall drug release process from the whole tablet. Drug release rate from the tablets was also influenced by variation of drug concentration and compacting pressure applied to produce the matrix pellets. It was concluded that the different experimental factors affected the internal structure of the matrix tablet. Change in the rate of drug release was dependent on the combined effect produced by these factors on the porosity and tortuosity of the matrix tablet.

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