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The kinetics of drug release from ethylcellulose solid dispersions.

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Abstract:

Sulphadiazine - ethylcellulose (EC) solid dispersions with different drug: carrier ratios were prepared and fractionated. In vitro drug release followed an apparent zero-order kinetics rate constant being dependent on the thickness of the coat which was the rate controlling step in the process. Drug release was found to increase as the granule size was decreased. The amount of drug released was found to be pH dependent thus showing the existence of pores in the coat surrounding the drug particles. Inclusion of polyethylene glycol or sodium lauryl sulphate in the coat material or dissolution medium resulted in increased dissolution, an effect which was attributed to increase in porosity, reduction of interfacial tension and increase in wettability which was associated with the presence of these compounds.

Introduction

Solid dispersions are used either to enhance or reduce the dissolution rate of drugs. Enhancement of drug dissolution is normally achieved by incorporating a water insoluble drug in a soluble phase or carrier such as polyethylene glycol (1-5), urea (6) and dextrose (7). Methods of preparations and mechanisms of action

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of this type of dispersions have been extensively reviewed by chiou and Riegelman (8) and Corrigan (9).

Reduction of the dissolution rate is normally achieved by incorporating the drug in an insoluble carrier such as ethylcellulose (10) polyethylene (11) and wax (12). This type of solid dispersions is sometimes considered as a matrix system. The release from which has been considered by Higuchi (13) and Chanderasekran and Paul (14). These matrix systems result in prolonging the duration of time over which the drug is released and hence are suitable for formulating a sustained release dosage form. Such formulations are reported to have several advantages which include reduction of the frequency of dosing and improved patient compliance (15).

The purpose of this work is to investigate the kinetics of the in vitro release of sulphadiazine incorporated in an inert water insoluble carrier such as ethylcellulose. The effect of incorporating surfactant or hydrophilic polymers molecules in the matrix structure is also studied.

Materials and methods

Materials:

Anhydrous citric acid was purchased from Aldrich Chemical Co. Ltd. Gillingham, Dorset, England. Dimethylsulphoxide (DMSO), ethyl alcohol, ethyl - cellulose and polyethylene glycol were obtained from Sigma Chemical Company U.S.A. Disodium phosphate and sodium lauryl sulphate were obtained from B.D.H. Chemical Company, Poole. England. The water used was triple distilled of a surface tension 71-72 mNm^{-1} at $25^{o}C$ obtained from an all glass still .

Methods:

Preparation of the solid dispersions

Solid dispersions of sulphadiazine in ethylecllulose were prepared by dispersing the required amount of the drug in a given volume of ethylcellulose alcoholic solution of the required concentration. The dispersion was then evaporated to dryness and the resulting mass was then dried to a constant weight by storing in a desiccator under vacuum. The mass was then pulverised and separated into different size fractions using a nest of sieves. The sample retained over

500 µm aperture size sieve and of drug: carrier ratio 1:5 was used to sudy the effect of the core thickness, pH and incorporation of water soluble macromolecules or surfactant molecules in the core structure or dissolution medium.

Preparation of the physical mixtures

The required amount of drug was mixed with the corresponding amount of ethylcellulose to give a drug to carrier ratio 1:5 in a glass morter in a geometric dilution technique till the two powders were homogeneously distributed within each other .

Preparation of solid dispersions containing macromolecules or surfactants molecules in the core structure.

This was carried out by dissolving the required amount of polyethylene glycol or sodium lauryl sulphate in the alcoholic ethylcellulose solutions. The drug was then dispersed in the solution which was then evaporated to dryness. The dried mass was then treated as previously described.

Dissolution studies:

The dissolution experiments were carried out in a USP dissolution apparatus (Erweka, DT-D6, F.R. Germany) maintained at 37°C. 250 mls of the dissolution medium were placed in the one litre flask. A stirring rate of 60 r.p.m was maintained throughout the experiment 5-ml samples were withdrawn at the designated time intervals and replaced with a simlar volume of dissolution medium. The sample was transferred to a syringe and rapidly filtered through a 0.22 µm membrane filter unit. (Millipore U.K. Ltd., London). The drug concentration was determined spectrophotometricaly against the appropriate blank at a wavelength of 241 nm. Absorbance values were then converted to the corresponding concentration by reference to a suitable calibration curve.

Determination of the wall integrity

This was done by studying the dissolution of the dispersions as a function of pH. A series of McILVAIN buffer solutions to span the pH range of 2.2-7.6 were used as the disslution medium. Dissolution was then carried out as previously described.

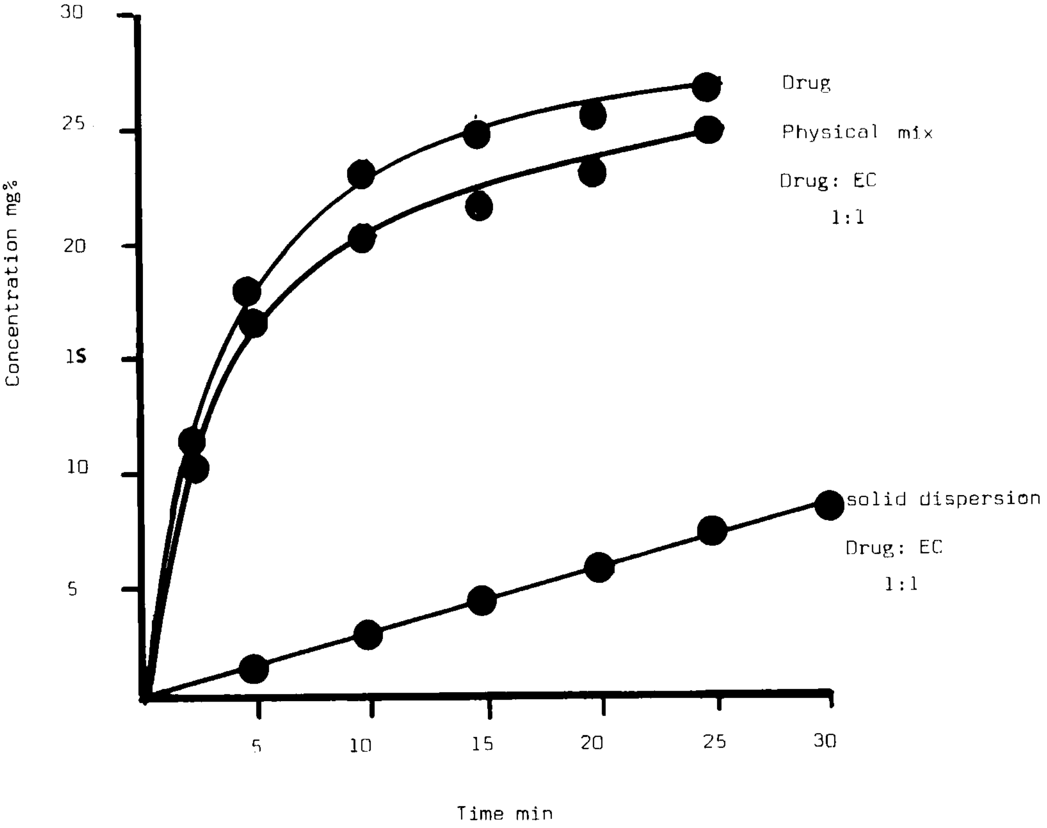

Fig. 1. The release of sulphadiazine from uncoated drug particles, from drug - ethylcellulose physical mixture and from drug ethylcellulose solid dispersion .

Content uniformity

0.1g of grounded solid dispersion was dissolved in 5 mls DMSO 1ml of this solution was then appropriatly diluted with water and the amount of drug present was determined spectrophptometrically by reference to a suitable calibration curve. This was repeated three times for every sample. The three determinations resulted in 98.8-100.1% of the theoretical determination.

Results and discussion:

Figure 1 compares the release of sulphadiazine from uncoated drug particles with the release from drug-ethylcellulose physical mixture and with the release

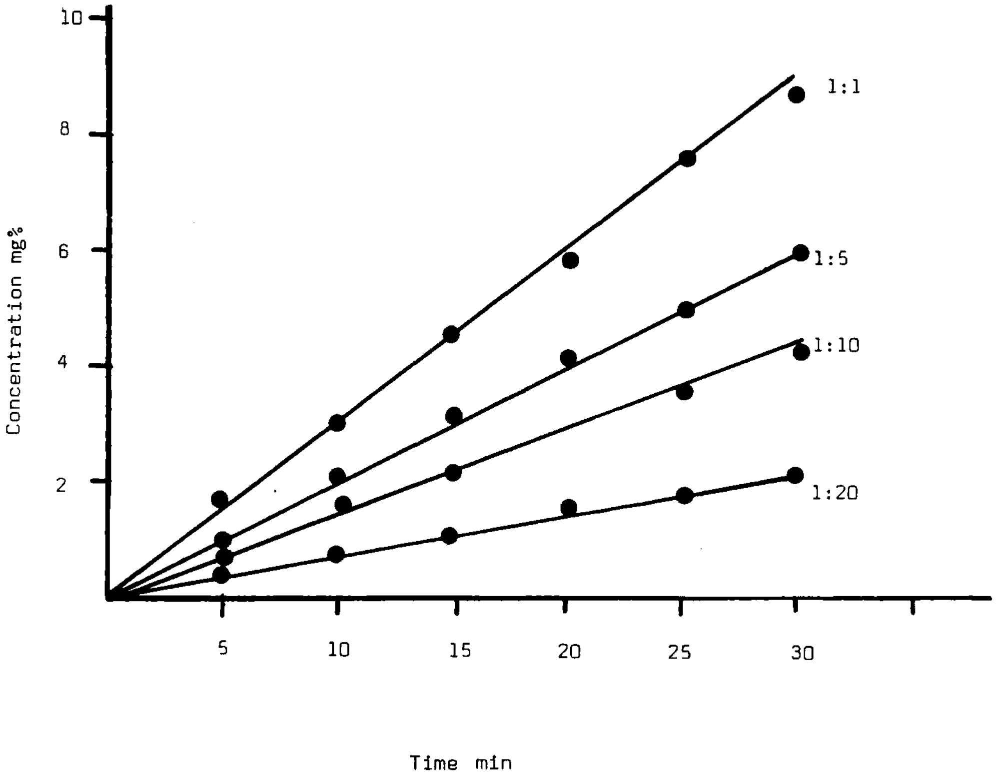

Fig. 2. Release of sulphadiazine from ethylcellulose solid dispersions of different drug: polymer ratio.

from drug-ethylcellulose solid dispersions in distilled water. As can be noted from the figure, a small difference exists between the release of the drug from the uncoated drug particles and from the physical mixture which could be due to the formation of aggregates between the drug and the ethylcellulose particles. This reduces the accessability of the dissolution medium to the drug particls and hence dissolution rate reduced . In contrast a pronounced reduction in the dissolution rate was obtained when the release was studied from drug-ethylcelluinse solid dispersions as compared to the release from the uncoated drug particles. This was attributed to the coating of the drug particles with a water insoluble ethylcellulose coat through which the drug has to diffuse before reaching the dissolution medium, and as the dissolution rate is inversly related to the diffusion path length (20) a reduction in the dissolution rate resulted.

Table 1. The values of K_o for different compositions of drug: ethylcellulose (EC) solid dispersions.

Drug	:	EC	K_o Conc. min^{-1}	r	n
1	:	0	3.5000	0.9960	3
1	:	1	0.2984	0.9991	6
1	:	5	0.1911	0.9960	6
1	:	10	0.1351	0.9963	6
1	:	20	0.0757	0.9982	6

The release of the drug matrices containing the same amount of drug but different carrier contents is shown in figure 2. It can be seen that as the amount of carrier used increases the release rate decreases. This was attributed to the increase in the coat thickness and the path overwhich the drug is diffusing and consequently the dissolution rate is reduced.

In order to describe the kinetics of the release process of drugs incorporated within an insoluble carrier various equations are normally used such as the zero-order rate equation (16),the first order rate equation (12) and the Higuchi square root equation (13). In figures 1 and 2 the results obtained in this work are plotted in accordance with the zero - order rate equation i.e amount released as a function of time. A linear relationship was obtained in all cases for the coated particles and an initial linear relationship for the uncoated drug particles and the physical mixture. This suggests that the release from drug-ethylcellulose solid dispersions is concentration independent, a situation desirable in sustained release formulation (16). The zero-order constants (K_o) which were obtained from the slopes of these linear plots are shown in table 1. It can be noted from the table that K_o descreased as the amount of carrier increased suggesting a slower release rate. In figure 3 the results are plotted in accordance with the first order rate equation i.e the logarithm of the amount released as a function of time. A non linear relationship is obtained suggesting that the release process cannot be described by the first order rate equation.

In figure 4 the results are plotted in accordance with the Higuchi square root equation i.e amount released as a function of the square root of time. It can be seen that a linear relationship is obtained after an initial lag time has lapsed.

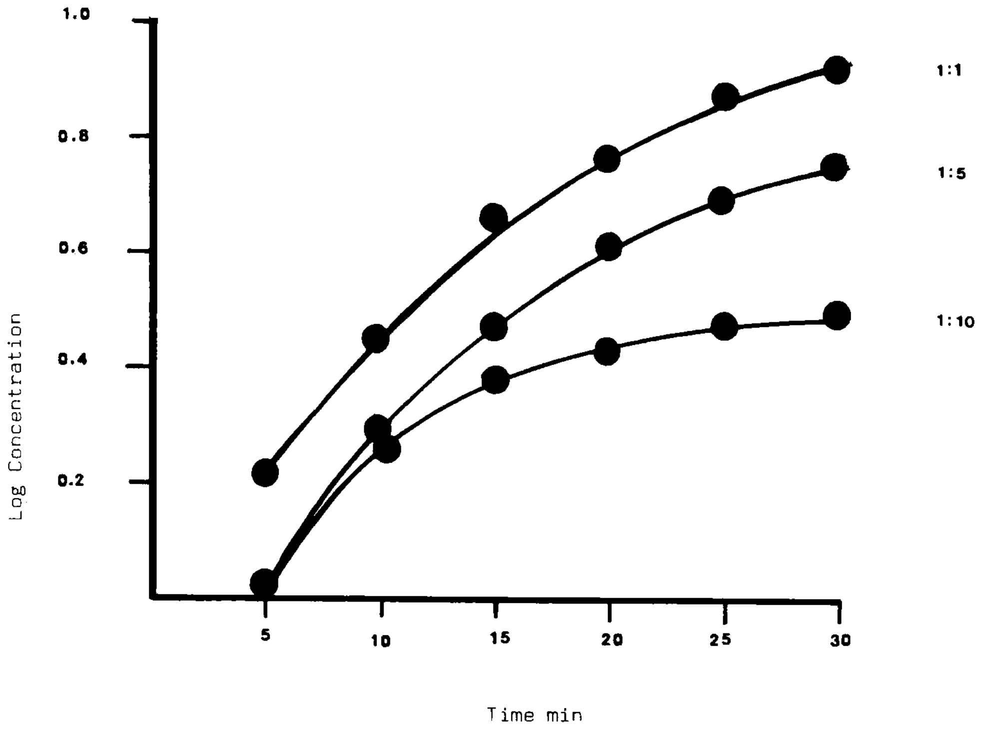

Fig. 3. The logaritm of the amount of drug released as a function of time (First order equation plot).

This indicates that the release process is diffusion controlled and hence is dependent on the drug matrix load.

Form figures 1,2,3, and 4 one can conclude that the kinetics of the release process is of the apparent zero order type and diffusion controlled. The matrix system under investigation seems to comprise a reservoir of drug which gives a steady release rate for as long a time as the drug reservoir is able to maintain the concentration gradient a cross the boundary through which diffusion is taking place. Hence an apparent zero order kinetics seems to apply to this system in that the diffusion of the drug becomes concentration dependent only when the drug reservoir is unable to maintain a constant supply of the drug. Similar findings have been reported by Dunbrow and Samulov (16).

The effect of granule size on the amount of drug released is shown in figure 5 for granules containing 1:10 drug to polymer ratio. It can be noted that

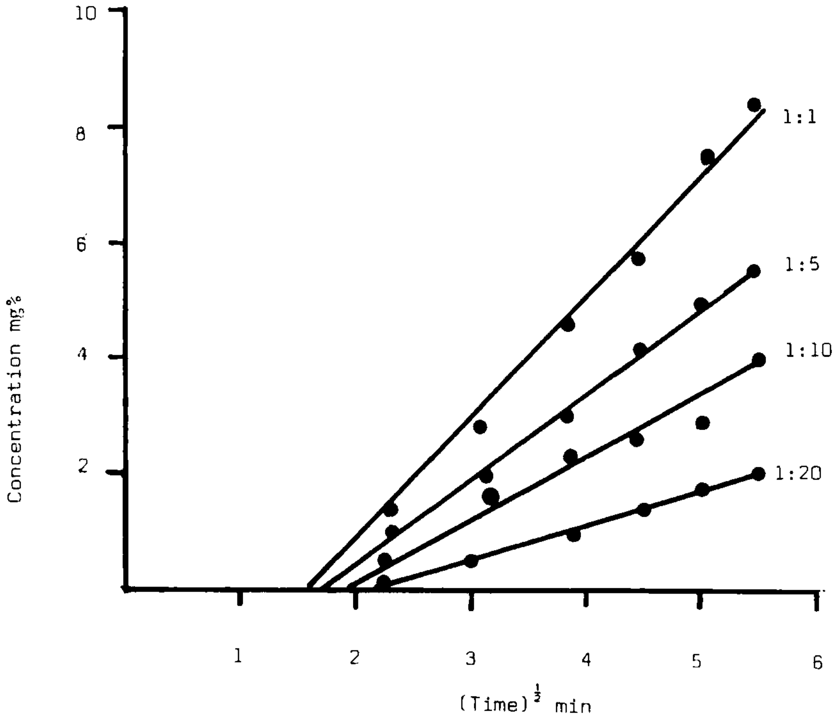

Fig. 4. The amount of drug released as a function of the sqaure root of time (Higuchi square root plot).

the smaller the granule size the greater is the dissolution rate. This could be due to the larger surface area of the smaller granules over which dissolution is taking place.

The integrity of the ethylcellulose film was checked by studying the release from the coated particles as a function of pH, a technique used by Dunbrow and Benita (17). The results obtained are shown in figure 7. It can be seen from the figure that the release was pH dependent, in that, higher release was obtained at low and high pHs. This suggests that the buffer components have penetrated through the ethylcellulose film and changed the pH in the vicinity of the drug particles. This indicates the existence of pores within the film (10,17). The increased release at the low pH i.e pH 2.2 is due to the increased solubility of the drug resulting from the ionisation of the strongly basic amino and imino groups whereas the

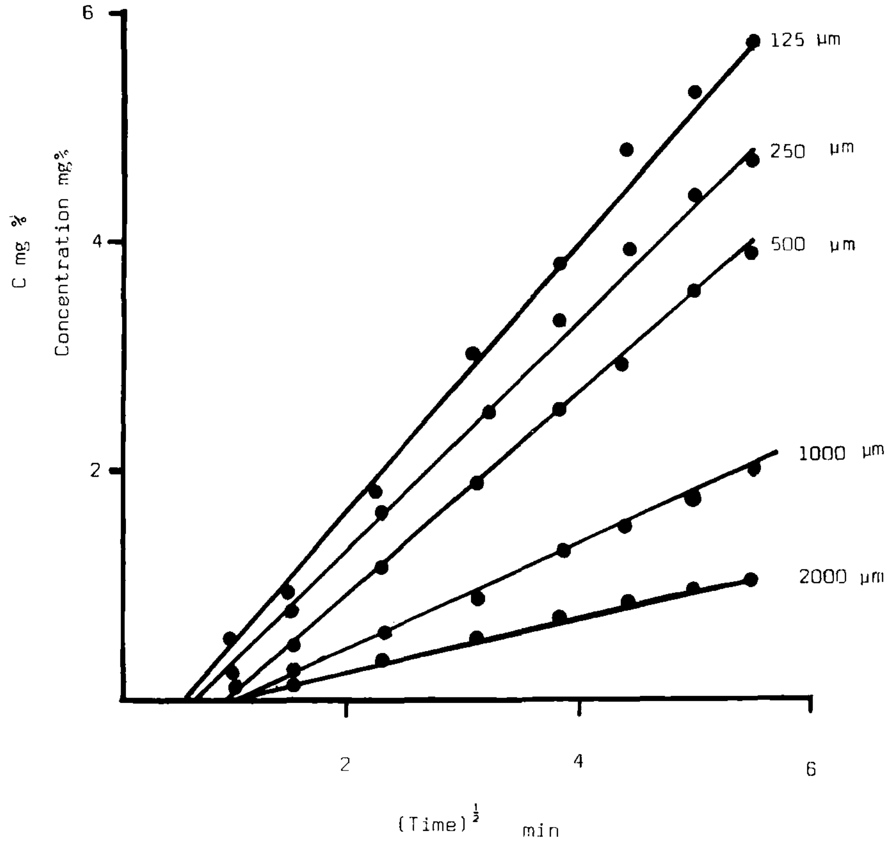

Fig. 5. The effect of the matrix granule size on the amount of drug released. Drug to polymer ratio 1:10.

increased release at pH 7.6 is due to the increased solubility resulting from the ionisation of the sulphonic acid group. Minimum release was obtained at pHs ranging from 4-6.

The effect of incorporating water soluble macromolecules such as PEG 6000 and surfactant molecules such as SLS was investigated. Incorporation of PEG molecules in the coating material or its addition to the dissolution medium resulted in an increase in the dissolution rate (figure7). It can be seen however that incorporating the PEG in the coat resulted in a greater release than when the polymer was

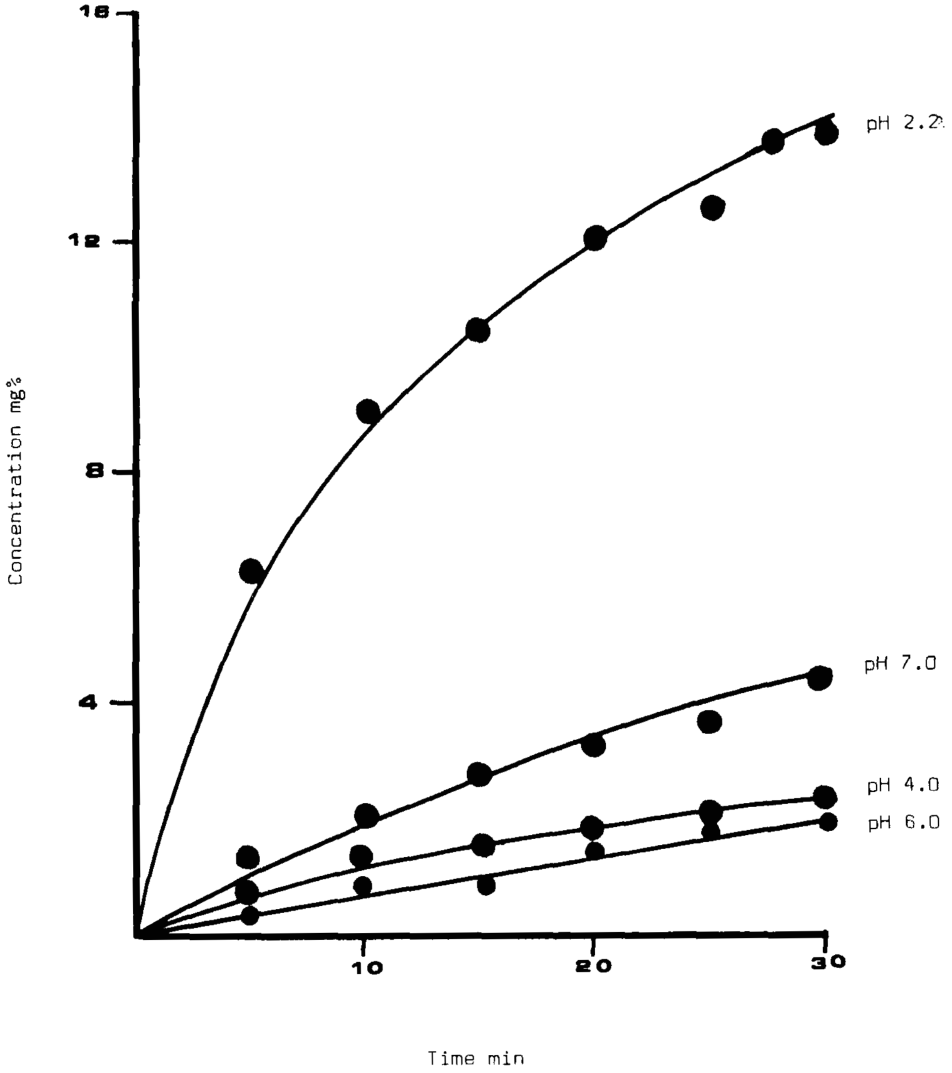

Fig. 6. The effect of pH on the amount of drug released.

present in the dissolution medium. The higher release obtained in the former case could be attributed to the creation of additional pores resulting from the dissolution of the PEG molecules which results in an increase in the porosity of the granules. Similar findings have been previously reported (18). When the PEG was included in the dissolution medium the increase in the release was less than that obtained when the polymer molecules were incorporated in the

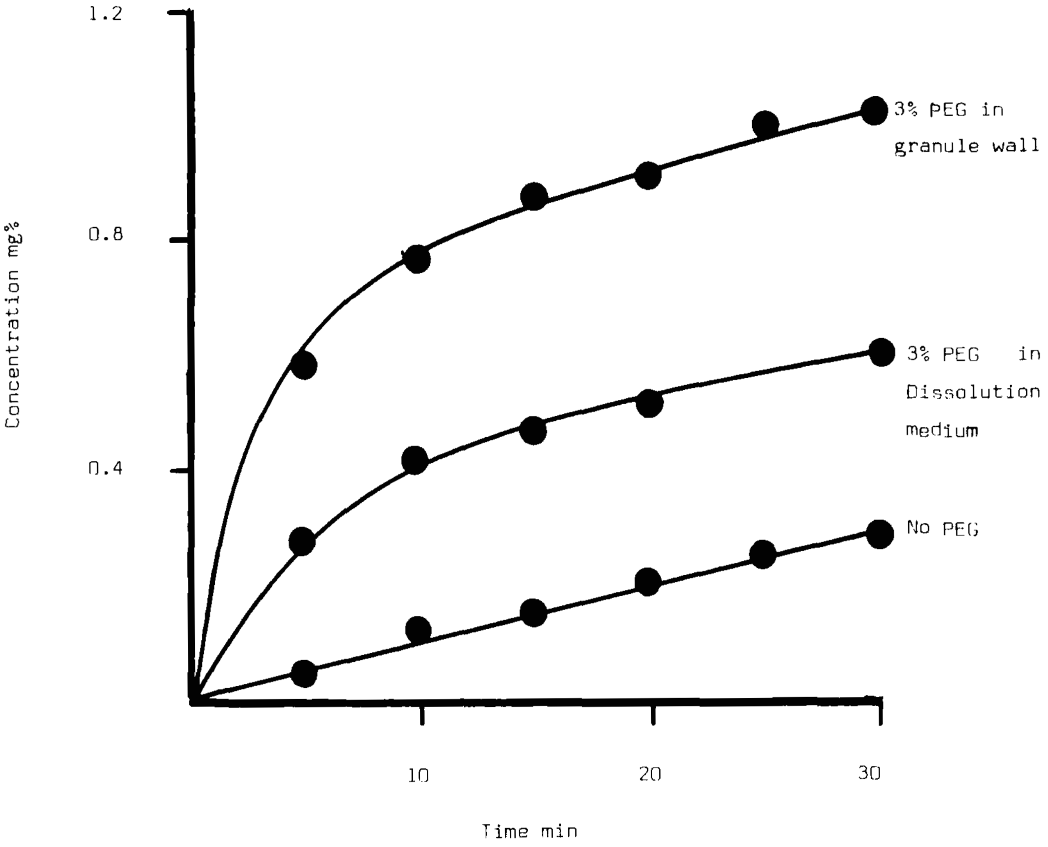

Fig. 7. The effect of PEG 6000 on the release of sulphadiazine.

wall. This could be due to the negligible effect PEG had on the porosity of the granule in this case and to its poor surface properties.

The effect of incorporating SLS in the solid dispersion or adding it to the dissolution medium is shown in figure 8. It is clear from the figure that in both cases an increase in the release was obtained as compared to the solid dispersion granules containing no SLS . This was attributed to the surface tension lowering and to the wetting effect of SLS molecules. The greater increase in the release obtained when the SLS molecules were incorporated in the wall could be due to the increase in the porosity of the matrix resulting from the dissolution of SLS molecules which provided additional channels for the diffusion of the drug molecules. Similar findings have been previusly reported by Desai et al (11,19).

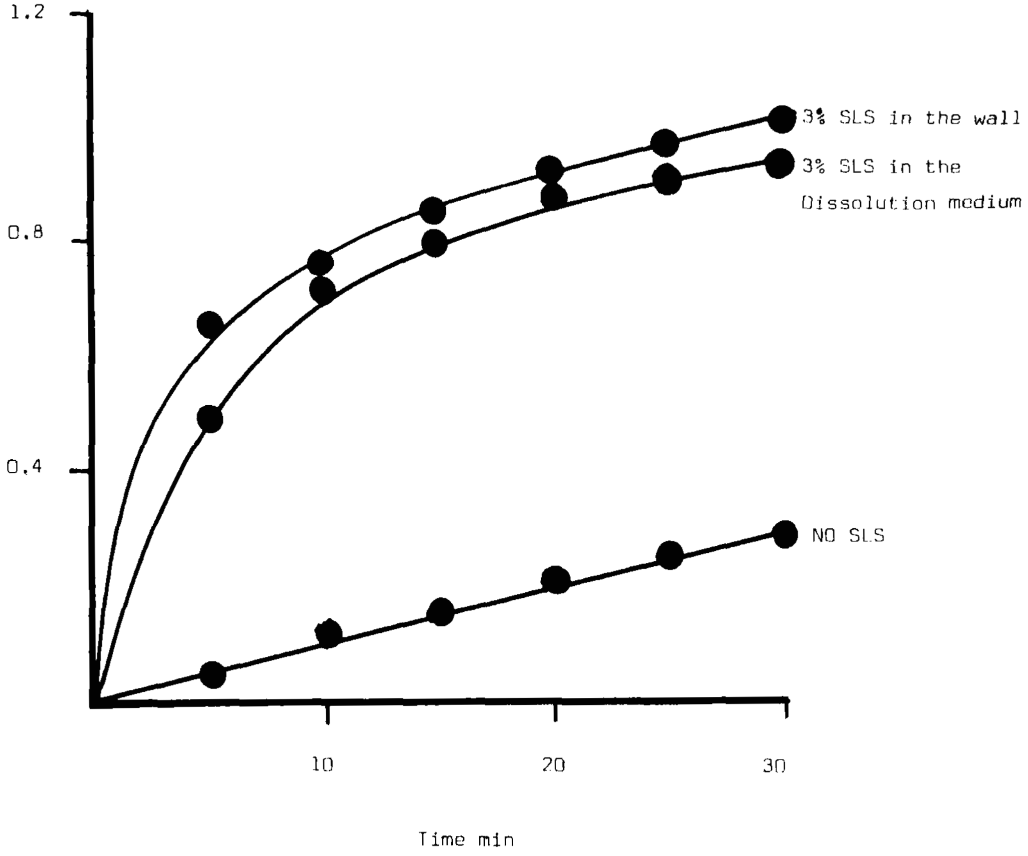

Fig. 8. The effect of SLS on the release of sulphadiazine .

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