DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(2&3), 697-724 (1985)

MECHANISMS OF DISSOLUTION OF FAST RELEASE SOLID DISPERSIONS

Owen I. Corrigan, Department of Pharmaceutics, School of Pharmacy, Trinity College, 18 Shrewsbury Road, Dublin 4, Ireland.

ABSTRACT

Drug dissolution from a solid dispersion is dependent on the technology employed to prepare the dispersion and on the proportion and properties of the carrier used. The diffusion models describing dissolution from multicomponent solids seem to adequately describe drug release from non-disintegrating systems in the weight fraction range where the drug phase is expected to control dissolution. When solid dispersions have higher dissolution rates than corresponding mechanical mixtures, solid state changes during the formation of the dispersion are indicated. These increases in rate may result from the formation of higher energy phases of either component or from interactions between the components. The carrier may play an important role in the formation of these phases and in stabilizing them during subsequent dissolution. When a large relative solubility difference exists between the carrier and the drug, deviations from theory can be expected to occur at high carrier weight fractions. The model fails because insufficient drug phase is present to form a viable surface drug layer. Drug release then becomes controlled by dissolution of the carrier. In polymer based systems

0363-9045/85/1102-0697$3.50/0

the presence of drug retards dissolution of the carrier, possibly through effects on binding and polymer swelling. These effects need to be quantified in order to allow prediction of drug release from high carrier weight fraction systems.

INTRODUCTION

The method of enhancing drug dissolution by incorporating a poorly water soluble drug in a soluble phase or carrier was first proposed by Sekiguchi and Obi in 1962[1]. Urea was used as the soluble carrier phase and melt formation as the method of incorporating the drug. The concept was broadened by Tachibana and Nakamura who used the water soluble polymer polyvinylpyrrolidone (PVP) and the solvent method to prepare aqueous dispersions of poorly soluble organic materials[2]. This concept was subsequently applied in attempts to improve the biopharmaceutical properties of many drugs of low aqueous solubility. The pharmaceutical applications of solid dispersion systems were extensively reviewed[3] in 1971 and to date two solid dispersion systems, Grispeg (Sandoz-Wander) a griseofulvin-polyethylene glycol solid dispersion and Cesamet (Lilly) a nabilone-PVP solid dispersion, are known to have reached the market place.

The enhancement in drug release reported as a result of solid dispersion formation relative to pure drug vary from as high as four hundred fold[4] to less than two fold. An understanding of the mechanisms of release from solid dispersions would allow the formulator to predict the potential gain in dissolution resulting from a given solid dispersion. In this paper current understanding of the mechanisms

involved in the release from solid dispersions will be reviewed.

SCOPE OF REVIEW

Over thirty different materials have been examined as potential carrier substances (Table 1). These carriers vary widely in chemical and physicochemical properties. A large proportion however are classifiable as either sugars, soluble polymers, surfactants or soluble acids. The techniques employed to combine the drug and carrier have also diversified. Originally these techniques were employed to improve the dissolution and solubility characteristics of drugs and utilized soluble materials as carriers. More recently the term solid dispersion has also been applied to systems containing insoluble carrier materials.[3,20] The current review will be confined to release mechanisms from soluble solid dispersions. Drug release from systems fabricated with an insoluble carrier may be considered as matrix systems, the release from which has been considered elsewhere.[21,22]

In its broadest sense the term solid dispersion, as used in this review, refers to the product formed by converting a fluid drug-carrier combination to the solid state. This classification includes systems prepared by coprecipitation, melting or fusion, spray drying, freeze drying and by the melting-solvent method[3], but not the products of traditional mixing or comminution operations.

Because of the diversity of materials used and methods of preparation employed, the physical characteristics of solid dispersions vary widely, ranging from simple eutectic mixtures to drug carrier complexes.

TABLE 1

Materials Tested as Carriers for Solid Dispersions.

Sugars	Polymeric Materials	Surfactants
Dextrose[5]	Polyvinylpyrrolidone[2]	Polyoxyethylene Stearate[14]
Sucrose[5]	Polyvinylpolypyrrolidone[9]	Renex 650[15]
Galactose[5]	Polyethylene glycols[10]	Poloxamer 188[16]
Sorbitol[6]	Hydroxypropylmethyl-cellulose[11]	Texafor AIP[8]
Maltose[6]	Methylcellulose[11]	Deoxycholic Acid[17]
Xylitol[6]	Pectin[12]	Tweens[19]
Mannitol[6]	Hydroxyethylcellulose[8]	Spans[19]
Lactose[8]	Hydroxypropylcellulose[8]	
	Cyclodextrins[13]	
	Galactomannan[7]	

Acids	Miscellaneous
Citric Acid[10]	Pentaerythritol[10]
Succinic Acid	Pentaerythrityltetraacetate[10]
	Urea[1]
	Hydroxyalkylxanthins[18]
	Urethane[8]

DISSOLUTION OF MULTICOMPONENT SOLIDS

Non-Interacting Systems

In practice solid dispersions consist of more than one component and drug release involves the simultaneous dissolution of more than one phase. Physical models involving simultaneous diffusion and rapid equilibria have been developed and tested for two[23,24] and three component systems.[25-27] They represent a good first approximation of

the release from solid dispersions. The models assume that dissolution of each component is diffusion controlled and that the dissolution surface is non-disintegrating. The properties of a component which influence dissolution rate are its solubility (C_s) diffusion coefficient (D) and, if the component becomes depleted from the outer solid-liquid interface, the amount of the component in the system. In a two component system, three different situations are possible at the solid-liquid interface during dissolution, depending on the relative amounts of the components present (Fig. 1). At the critical mixture ratio, i.e. when $N_d/N_c = D_d \cdot C_{sd}/D_c \cdot C_{sc}$, both components (drug, d, and carrier, c) coexist at all times at the solid-liquid interface and dissolution profiles are linear under sink conditions. At all other weight ratios, one or other component forms a porous layer at the surface which represents an additional barrier retarding dissolution of the receding phase, and resulting in a curved dissolution profile for the receding component. Three component systems are more complicated, there being thirteen different possibilities at the solid-liquid interface[26] (Fig. 1). In two component solid dispersions, except when the carrier weight fraction is very high, the less soluble drug will be the phase at the surface controlling dissolution. The dissolution rate of the drug per unit surface area, G_d, is given by

$$G_d = \frac{D_d \cdot C_{sd}}{h} \qquad (1)$$

where h is the diffusion layer thickness. The limiting dissolution rate of the carrier is given by

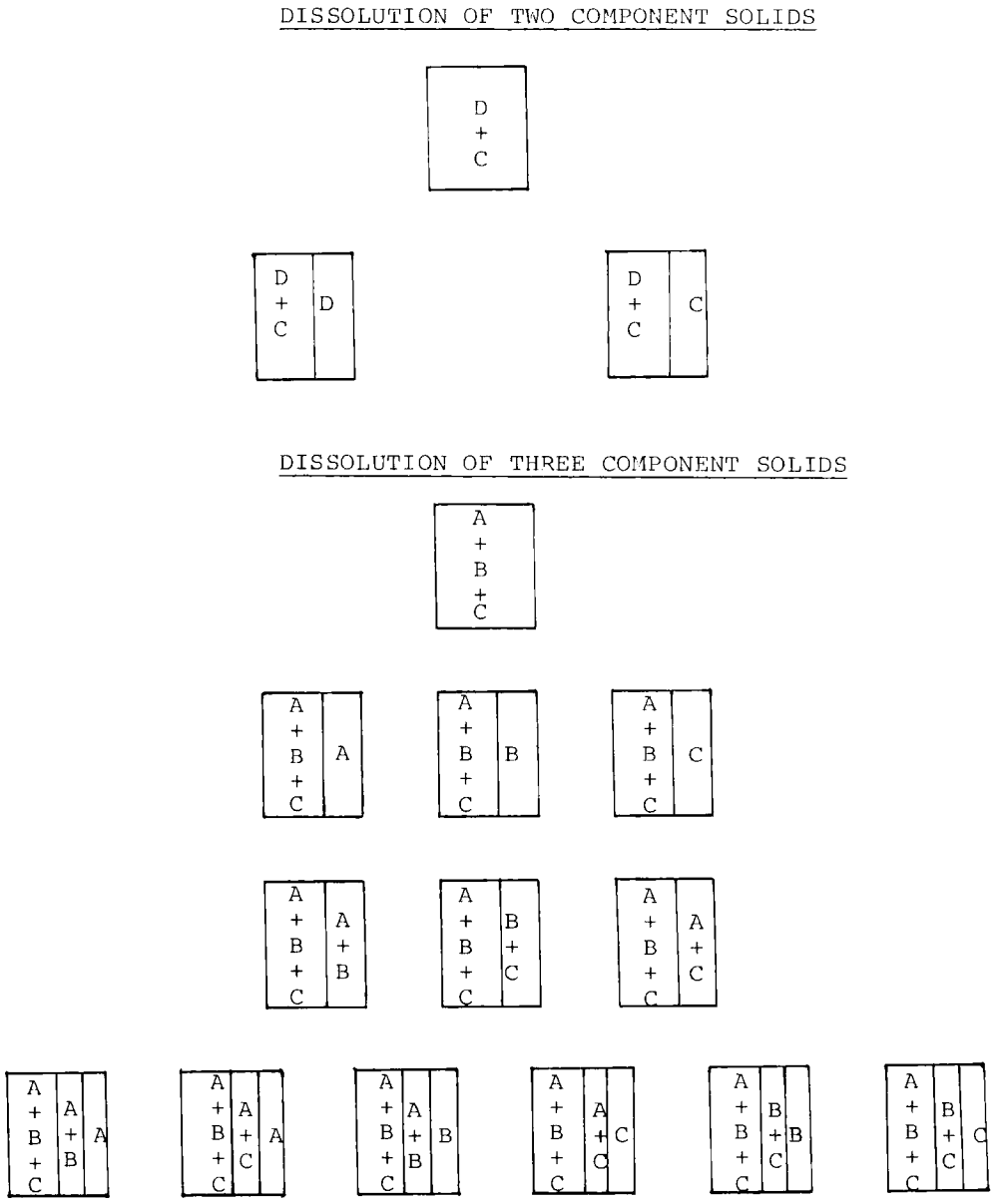

FIGURE 1

The possible dissolution behaviours of two and three component systems.

$$G_c = \frac{N_c \cdot G_d}{N_d} \qquad (2)$$

According to the model, if a large difference exists between the solubilities of the carrier and the drug, the range of weight fractions over which dissolution is controlled by the carrier is very small and occurs only at the higher carrier weight fractions (Fig. 2). The model also predicts that the release rate of either component in the dispersion is never greater than that of the pure component alone. In addition, no dissolution advantage is predicted for eutectic mixtures, a conclusion also arrived at by Goldberg et al.[28] Therefore where increases in rate are observed, disintegration or complex formation are likely to be involved.

Interacting Systems

Soluble Complex Formation: The models for non-interacting systems were extended to situations where the components interact in solution to form a soluble complex.[23,25] Many carrier materials readily form soluble complexes with drugs thereby enhancing the drugs apparent solubility.[3,29] When two such components are present in a solid dispersion, dissolution of each component is enhanced by the contribution from the diffusing complex. Dissolution rates above those of the individual pure components are observed (Fig. 3). The maximum rates occur at the critical mixture ratio given by[30]:-

$$\frac{N_d}{N_c} = \frac{D_d \cdot C_{sd} + D_{cd} \cdot K \cdot C_{sd} \cdot C_{sc}}{D_c \cdot C_{sc} + D_{cd}\, K \cdot C_{sd} \cdot C_{sc}} \qquad (3)$$

where K is the binding constant and D_{cd} the diffusion coefficient of the complex.

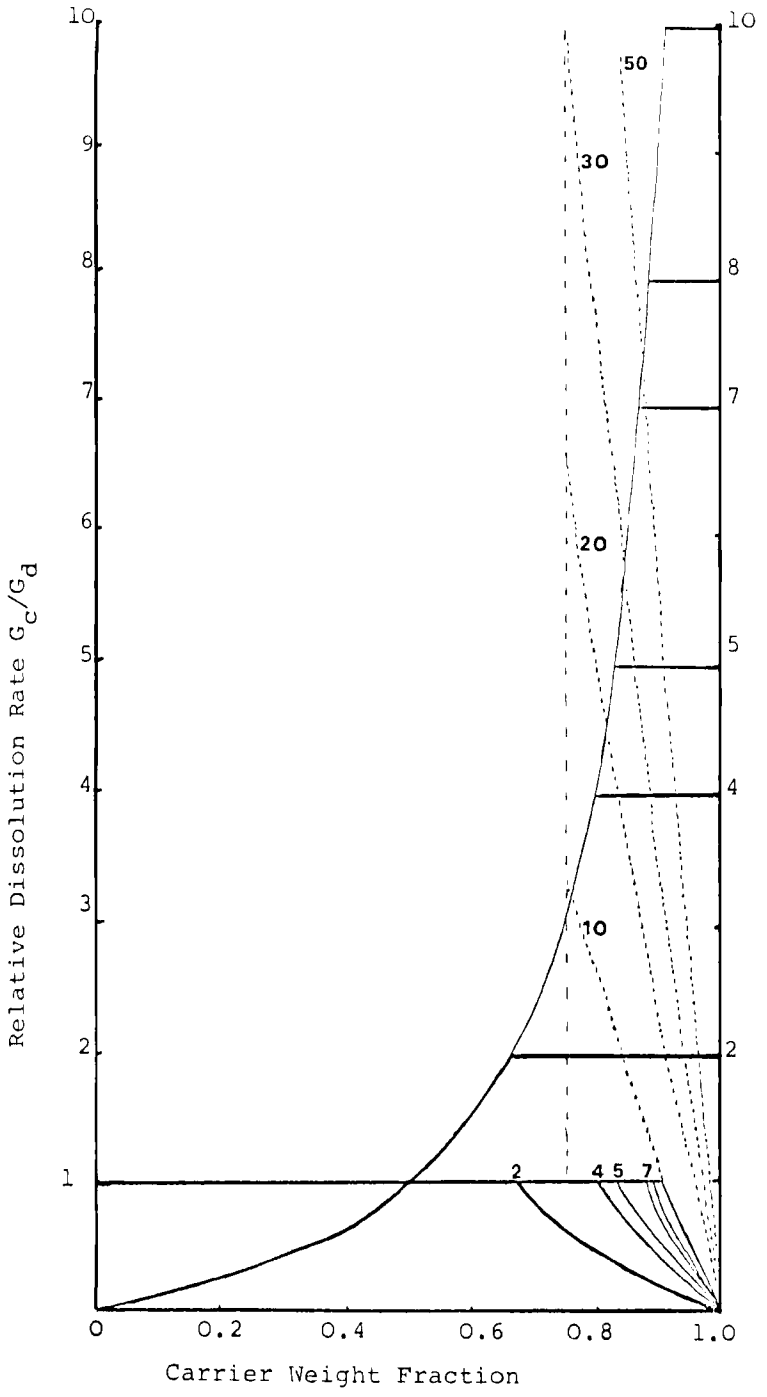

FIGURE 2

Theoretical changes in relative dissolution rates of drug and carrier with increasing carrier weight fraction for two non-interacting components. Dashed lines illustrate the effect on drug dissolution rate of an extension of carrier control dissolution to systems containing up to 25% drug, for relative dissolution rates of 10, 20, 30 and 50 fold.

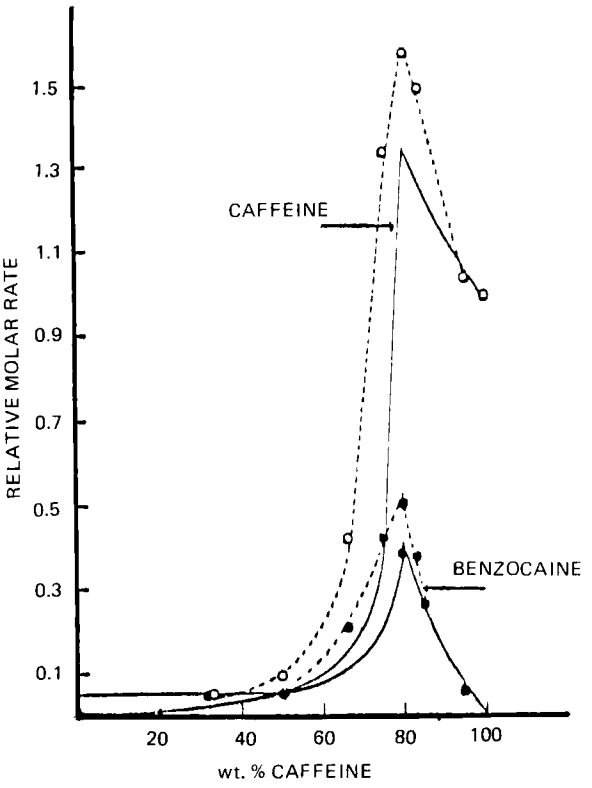

FIGURE 3

Comparison of benzocaine-caffeine mixture dissolution data with the soluble complex model.
From : Higuchi et al J. Pharm. Sci., 54, 1405 (1965).

The magniture of the dissolution rates of each component (G^{max}) at the critical mixture ratio are[23]

$$G_d^{max} = (D_d \cdot C_{sd} + D_{cd} \cdot K\, C_{sd} \cdot C_{sc})/h \quad (4)$$

$$G_c^{max} = (D_c \cdot C_{sc} + D_{cd} \cdot K \cdot C_{sd} \cdot C_{sc})/h$$

Equations for the limiting rates at other weight fractions have also been derived.[23] It is worth noting from Eq. 4 that the absolute magnitude of the increase in rate at the critical mixture ratio is the same for each component ($D_{cd} \cdot K \cdot C_{sd} C_{sc}$). Therefore the relative maximum increase

in rate is greatest for the less soluble component. The relative increase in drug dissolution rate is given by[30]:-

$$\frac{G_d^{max}}{G_o} = 1 + \frac{D_{cd} \cdot C_{sc} \cdot K}{D_d} \qquad (5)$$

Where G_o is the intrinsic dissolution rate of the drug. Dissolution rates of each component decline rapidly as the weight fraction deviates from the critical mixture ratio. Rigorous tests of this "soluble complex" model, involving examination of the release rates of both dissolving species, have been reported and good agreement with theory obtained (Fig. 3). The dissolution rates of β-cyclodextrin-phenobarbitone freeze dried dispersions and physical mixtures were also well described by this model[31] (Fig.4). In other dispersion systems, where the release of one component, the drug, had been monitored over a range of weight fractions, qualitative agreement with theory was evident[32]. In these hydroflumethiazide-polyethylene glycol (PEG) systems, little difference in rate between coprecipitates, melts and physical mixtures of similar weight fraction was observed, at the lower carrier weight fractions [32] (Fig.5). If solid state changes do not occur in either the drug or carrier during formation of the solid dispersion, then in theory the dissolution rates of the solid dispersion and physical mixtures of similar composition should not differ. In practice dispersed systems tend to give more reproducible results, due to more intimate contact between the components. Where significant differences occur they suggest solid state changes during formation of the dispersion.

Solid State Changes. During the process of forming a solid dispersion the individual components may precipitate in

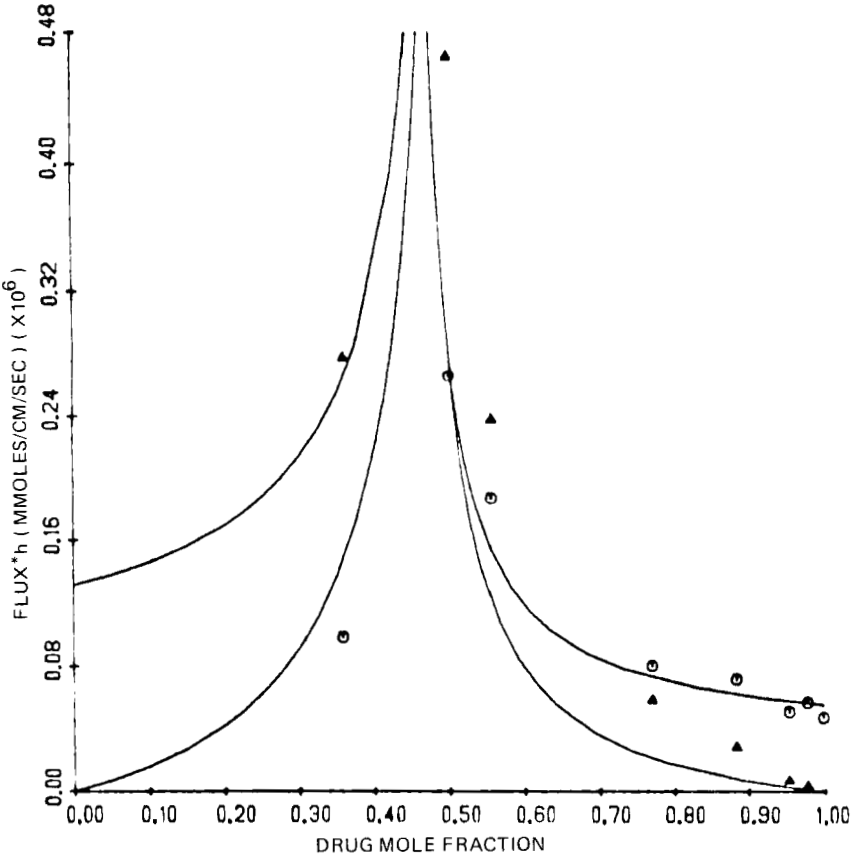

FIGURE 4

Comparison of theory with data for dissolution rate of phenobarbitone- β-cyclodextrin freeze dried systems. Key: ○ phenobarbitone; ▲ β-cyclodextrin.

different solid phases from those present in a similar physical mixture i.e. as polymorphic, solvated or amorphous phases. The physical forms produced are a function of the solidification technique, the solvent medium, the specific drug carrier system and the relative proportion of the components present. Thus griseofulvin -PVP coprecipitates prepared from chloroform result in the precipitation of the drug as the crystalline chloroform solvate. However, when

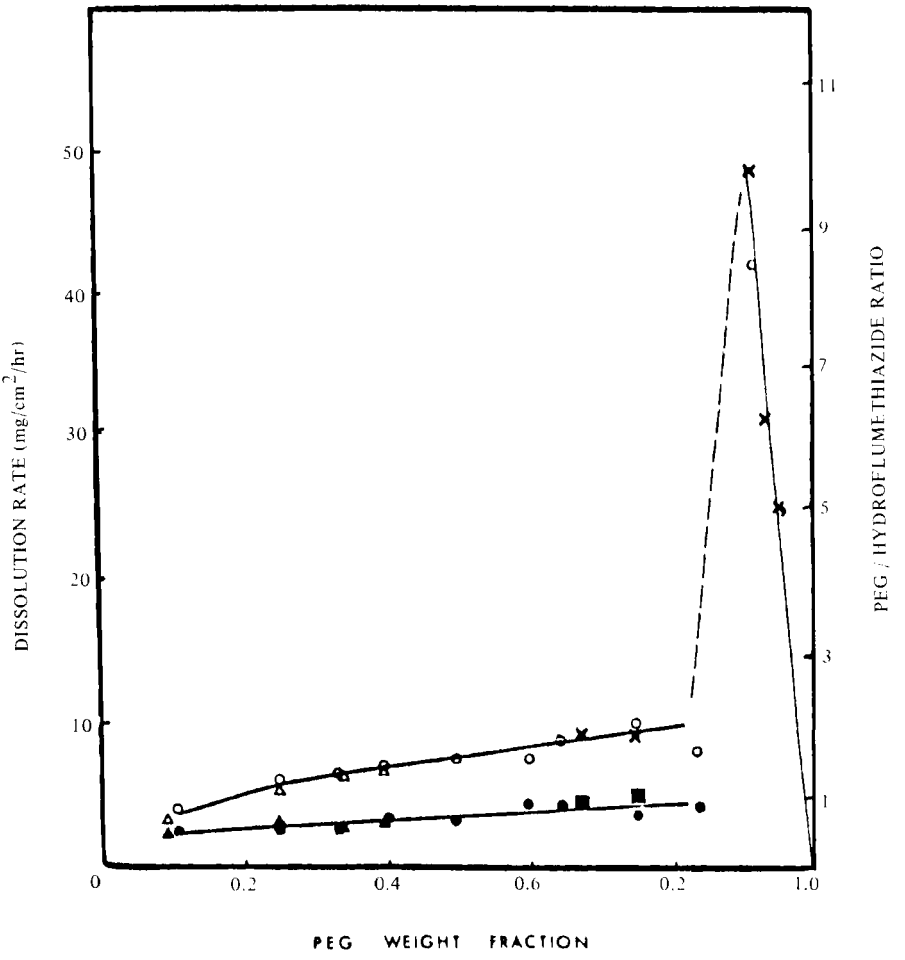

FIGURE 5

Relationship between PEG weight fraction and the initial and limiting dissolution rates of hydroflumethiazide from PEG 4,000 systems.
Key; initial rates: mechanical mix systems △, solvent systems ○, melt systems × . Limiting rates: mechanical mix systems ▲, solvent systems ● and melt systems ■.

the same systems are spray dried, amorphous dispersions are formed.[33,34] In sulphathiazole-PVP coprecipitate systems, the weight fractions of PVP and the method of precipitation determines the proportions of form 1, form 2 and amorphous phase of drug produced.[35] Although rapid precipitation of hydroflumethiazide from ethanol resulted in the ethanol

solvate[36], coprecipitation of this drug with PVP from ethanolic solution yielded the nonsolvated crystalline form at low PVP weight fractions and an amorphous system at higher weight fractions.[37] However, when these components were spray dried, all systems were amorphous.[38,39] Solid state changes may also be induced in the carrier. Citric acid is present in griseofulvin-citric acid dispersions in the form of a glass.[10] If the new phases produced in the solid dispersion have a higher solubility, remain stable in the dispersion and do not rapidly revert to the less soluble form on contact with the dissolution medium, then enhanced dissolution from the dispersion over the mechanical mixture can be expected. The nature of the carrier plays an important role in maintaining the stability of many high energy drug phases.

In the classical study of sulphathiazole-PVP coprecipitates, Simonelli et al[35] found the dissolution rates in qualitative agreement with the soluble complex model (Fig. 6). The enhanced dissolution rates, above those observed for mechanical mixtures, in the weight fraction range where drug is expected to be the surface layer controlling dissolution, were attributed to the formation of a high energy amorphous phase of drug. The existence of this phase was supported by X-ray diffraction,[35] dissolution[35] and extensive solubility data.[40]

The theoretical analysis also highlighted the considerable enhancement in dissolution rate obtainable in the region of the critical mixture ratio when the formation of a high energy drug form is coupled with complexation. The study also emphasised the important role played by PVP in inhibiting

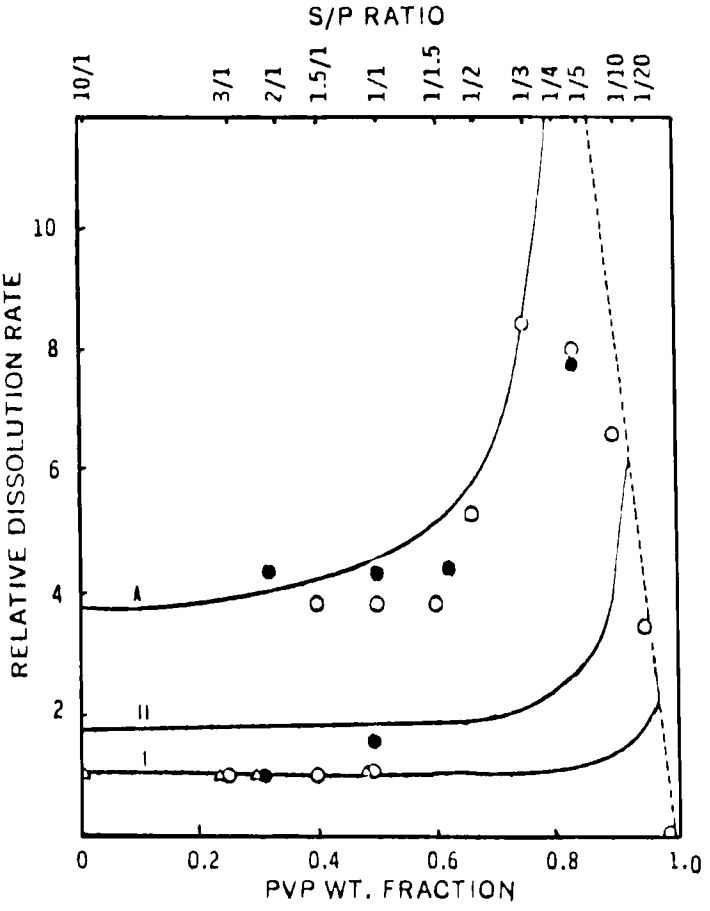

FIGURE 6

Comparison of Theoretical and Experimental Relative Release Ratesof sulfathiazole as a function of PVP weight fraction. Theoretical curves for controlling layers: I, sulfathiazole Form 1; II, sulfathiazole Form II; A, amorphous sulfathiazole.
From : Simonelli et al, J. Pharm. Sci. 58, 538 (1969).

nucleation and crystal growth thereby promoting fast release from PVP based solid dispersions. The inhibiting effect of PVP on crystallization, crystal growth and phase transformation[43] has been demonstrated for many drugs in both organic[41] and aqueous media.[42] The magnitude of this effect for a given drug has been linked with the ability to form an amorphous coprecipitate. The molecular weight of the polymer[44] and

the structure of the drug[42] are also determinants. Evidence that the formation of high energy amorphous systems in PVP-solid dispersions was not unique to sulphathiazole was subsequently presented by other workers.[37,46,47] An investigation of the effects of steroidal structure on the activity of drug-PVP coprecipitates suggested the involvement of both hydrogen bonding and van der Waals type interactions as well as spatial factors.[48]

In order to explore the generality of high energy drug phases to other carrier systems, Simonelli et al investigated polyethylene glycol (PEG)-drug coprecipitates[49] and reported some success with benzoic acid and sulphathiazole. A high energy phase was also observed with griseofulvin; however rapid conversion to crystalline drug occurred.[49] Rapid crystallization has also been reported in indomethacin-PEG systems[50], while no evidence was obtained for the formation of a high energy form of hydroflumethiazide in PEG dispersions.[32] Therefore the most successful carrier to date for promoting amorphous phase formation is PVP, and this appears to be related to the polymer's potent capacity to inhibit crystal growth.[41-44]

The nature of the high energy drug phases present in coprecipitates is the subject of some debate. It has been possible to separate the contributions from free drug and soluble complex formed using dissolution, solubility and membrane transport[51,52] methodologies; all three methods yielded similar activities for a given drug. Other membrane transport studies have also demonstrated that drug is substantially in a free form in PVP-stabilized supersaturated solutions.[53-55] Shefter & Cheng measured drug solubility in PVP by the DSC

method and related molecular dispersibility in the polymer to hydrogen bonding with the pyrrolidone moiety [56] They suggested that molecularly dispersed drug in the polymer probably accounts for the observed higher intrinsic dissolution rate of dispersions over physical mixtures. Evidence for the formation of a discrete amorphous drug phase as well as molecularly bound drug in spray dried PVP-hydroflumethiazide systems was recently reported.[39] A better understanding of the nature of these high energy drug forms is necessary to enable prediction of their activity and stability.

In solid dispersions, the formation of discrete drug carrier complexes of low solubility may also occur. The low dissolution rate of a phenobarbitone-PEG complex was correlated with reduced absorption.[57] Interactions, between sulfamethoxazole and sugars having carbonyl groups, have also been reported in solid dispersions made by the fusion method.[6] Anomalous reductions in dissolution rate and apparent solubility of a number of drugs in the presence of low concentrations of PVP have been observed.[37,58,59] These effects may be related to the ability of bound drug to form reversible cross links, possibly by hydrogen bonding, between polymer molecules, which if sufficiently extensive lead to polymer precipitation.

The diffusion models describing dissolution from multicomponent solids seem to adequately describe drug dissolution from solid dispersions at the lower weight fractions where the drug is expected to control dissolution.

Coacervate Formation. An alternative dissolution model has been proposed by Sekikawa et al for drug-PVP coprecipitates, which envisages formation of a coacervate at the coprecipitate-solvent interface.[60] These authors suggest that the faster drug release observed from lower molecular weight PVP coprecipitates supports their view. Coacervate formation has also been implicated in the release from PVP-sulfathiazole systems.[61]

CARRIER CONTROLLED DISSOLUTION

While the interpretation of drug release from solid dispersions by the models for the dissolution of multi-component systems is satisfactory for many drug carrier combinations at low carrier weight fractions, application of these models to high carrier weight fractions is less tenable. Chiou and Riegelman[3] challenged the view that at high carrier weight ratios PVP forms a controlling external layer in PVP-sulfathiazole coprecipitates. Their analysis of the original data showed that the relative boundary movements of both species present were close to unity in the 20:1, 10:1 and 5:1 PVP-drug systems. They suggested that this finding conflicted with the original model, which predicted boundaries continuously moving together only at the critical mixture ratio. They interpreted the results in terms of molecular and/or colloidal dispersion of drug in the carrier. An examination of both polymer and drug release rates from PEG-drug dispersions of high carrier composition, also revealed simultaneous recession of the solid-liquid boundaries of both components.[62] Furthermore the observed maximum enhancements in drug dissolution were orders of magnitude greater than the theoretical values assuming enhancement was solely due to soluble complex formation.

Thus at high carrier weight fractions the drug dissolves simultaneously with the carrier.

Examination of equations 2 and 3 reveals that the greater the difference in solubility between the drug and carrier and

the smaller the value of K, the smaller will be the proportion of the less soluble component (i.e. drug) present at the critical mixture ratio. Therefore in dispersions of low drug content, theory predicts a controlling drug layer at the outer solid liquid interface. Formation of this layer however is physically dependent on their being enough drug present, with the necessary cohesive properties, to form and support a porous surface layer. In practice there is insufficient drug to maintain an intact surface. In effect the drug is dispersed in the carrier either as fine particles or in solid solution. Dissolution of the carrier ceases to be hindered by a surface drug layer and drug release becomes carrier phase controlled at higher drug weight fractions than predicted by theory. This effect is illustrated by the dotted line in Fig. 2.

In the situation where the carrier dissolves bringing dispersed drug into the dissolution medium, drug release is dependent on the product of the carrier dissolution rate and the ratio of drug present[30]

$$G_d = \frac{G_c \cdot A_d}{A_c} \qquad (6).$$

where A is the component concentration in the system.

Dissolution from high carrier weight fraction systems of PVP-sulfathiazole[35] and PEG-drug[62] is consistent with equation 6. Further confirmation of carried controlled dissolution from PVP dispersions was obtained for hydrocortisone, prednisone and clonazepam systems.[63,64] The energies of activation of drug release and polymer dissolution were identical. It is apparent from equation 6 that if the presence of drug does not interfere with dissolution of the carrier, the absolute release rate of

different drugs at a given weight fraction should be the same. The relative change in drug dissolution rate becomes[30]

$$\frac{G_d}{G_o} = \frac{C_c A_d}{G_o A_c} \quad (7)$$

Thus the relative rate of release from a given carrier is inversly proportional to the intrinsic dissolution rate (or solubility) of the drug. In this context it is noteworthy that dissolution of hydroflumethiazide and endrofluazide from PEG: drug 10:1 solid dispersions were of a similar order of magnitude (Fig. 7) while the relative increases in rate were 13 and 180 fold respectively.

The enhancement in drug dissolution rate, above that predicted by the classical multicomponent models, is due to an extension of carrier phase dissolution control to higher drug weight fractions than predicted by these models and is a consequence of the disparate solubilities of carrier and drug. In the absence of this effect, both models would predict similar limiting drug release rates at low drug weight fractions, since in the classical models, above the critical mixture ratio, a carrier layer will also control drug release. The studies of β-cyclodextrin-phenobarbitone freeze dried dispersions (Fig. 4) and mechanical mixtures both showed reasonable agreement with the soluble complex model even though a solid state inclusion complex[45] forms on freeze drying. In contrast thiazide diuretics, which have lower solubilities than phenobarbitone and interact less strongly with β-cyclodextrin deviated from the soluble complex model and gave higher than predicted dissolution rates. If drug is present in solid dispersions as fine particles and dissolution

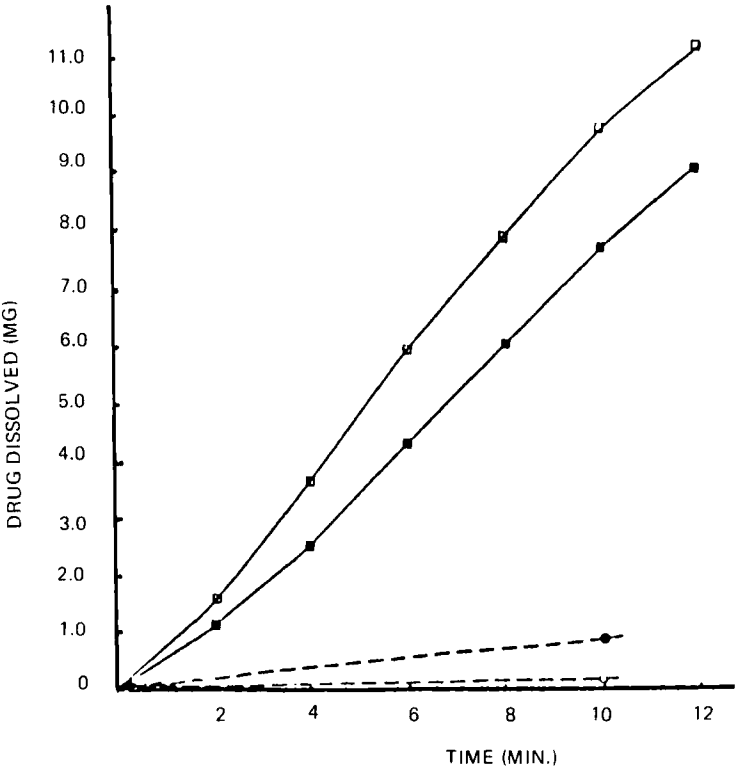

FIGURE 7

Drug release profiles of □ PEG-bendrofluazide 10:1 melt systems, ■ PEG-hydroflumethiazide 10:1 melt systems, o pure bendrofluazide and ● pure hydroflumethiazide, from constant surface area discs.

is carrier controlled, the ultimate dissolution rate of the drug will depend on the particle size of drug released into the dissolution medium with the dissolving carrier. Therefore, solid dispersions may give higher release rates than corresponding mechanical mixtures, even when solid state interactions have not occurred, provided there has been a reduction in drug particle size. Differences of this nature have been reported.[30,32,65,66]

Inhibition of Polymer Dissolution

Further deviations from the multicomponent models become apparent when dissolution of the carrier component of solid dispersions is examined. Above the critical mixture ratio carrier dissolution rate should be equal to that of the pure carrier in non-interacting systems and greater than that of the pure carrier if soluble complexes are formed. However, studies with the following carriers, PVP[35], PEG[62], Renix[15] and β-cyclodextrin[30] show a decline in carrier dissolution rate. The presence of dispersed drug retards dissolution. The effect tends to increase with increasing concentration of dispersed drug and is related to drug carrier interactions[64]. Marked inhibition of carrier dissolution has been observed in salicylic acid-PVP dispersions[64] and phenobarbitone-PEG[69] dispersions, systems in which strong interactions are known to occur.[57,59]

Intrinsic dissolution rate profiles of low molecular weight crystalline solids are linear under sink conditions and follow the Nernst-Brunner model[70]. However, many carrier materials are polymeric in nature and significant permeation of solvent into the dissolving carrier occurs. In the case of amorphous polymers, dissolution involves transition from a hard glassy substance to an elastic swollen mass and finally to a low viscosity solution. Dissolution profiles of carriers such as PVP[67] and PEG[62] have a positive curvature; swelling is evident and the curvature tends to increase with molecular weight[62,68](Fig. 8). Contributions from polymer swelling to drug release from solid dispersions have been reported, particularly initial positive

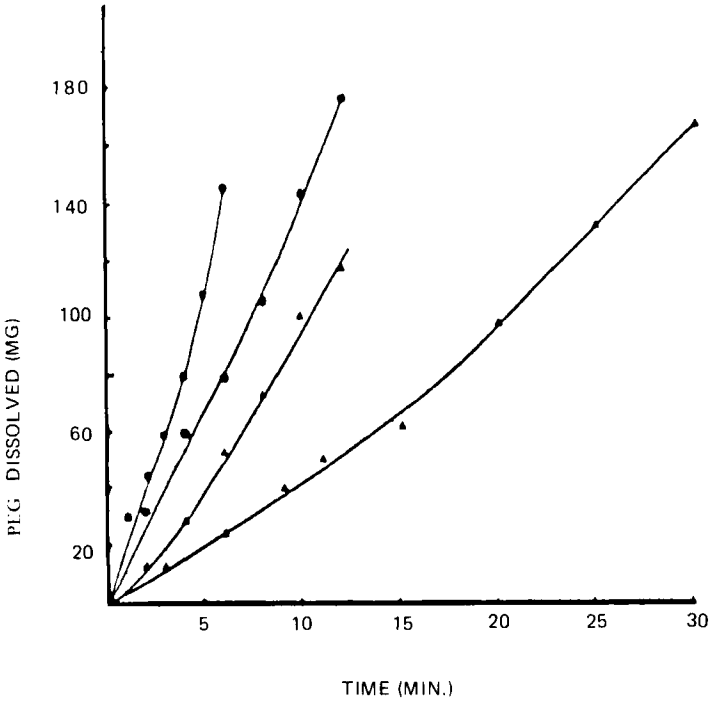

FIGURE 8

Effect of molecular weight on the release profile of PEG in water at 37°C using the beaker method. Key : ● PEG 1000; o PEG 4000; ▲ PEG 6,000 and △ PEG 20,000.

curvatures[37,62]. The early literature on dissolution of polymers was reviewed by Ueberreiter[71]. More recently the dissolution of glassy polymers was described by a model involving the motion of two boundaries: the liquid-gel and gel-glass boundaries[72]. Contrasting dissolution characteristics were predicted for the effect of different types of polymer-solvent pairs as well as for the effects of molecular weight. There is an obvious need to quantify the dissolution of pharmaceutically relevant polymeric materials and particularly the influence exerted by dispersed drugs on such dissolution, in order to advance our understanding of the mechanisms of release from soluble solid dispersions.

CONCLUDING REMARKS

The above interpretation of the mechanism of dissolution from soluble carrier systems rests heavily on the results of studies undertaken using constant surface area methods. Many solid dispersion systems are difficult to examine by these methods because of disintegration of the total system soon after contact with the dissolution medium. In practice when such disintegration occurs, with the ensuing increase in surface area, it contributes substantially to the enhancement in dissolution and may constitute the dominant factor controlling drug release.

While the formation of both high energy drug phases and soluble complexes can enhance drug dissolution, opposing effects on drug absorption may result. High energy drug phases may produce supersaturated solutions and thus enhance membrane transport, while soluble complex formation with an unabsorable carrier may retard the rate of drug absorption.[55] Consideration of these effects and also physical stability aspects of solid dispersions are beyond the scope of this review.

REFERENCES

1. K. Sekiguchi and N. Obi, Chem. Pharm. Bull., 9,866 (1961).
2. T. Tachibana and A. Nakamura, Kolloid-Z. Polym., 203, 130 (1965).
3. W.L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1281, (1971).
4. S.A. Said, H.M. Fatatry and A.S. Geneidi, Aust. J. Pharm. Sci., 53, 42, (1974)
5. L.V. Allen, V.A. Yanchick and D.D. Maness, J. Pharm. Sci., 66, 494 (1977).

6. A. Ganem, M. Meshali and Y. Ibraheem, J. Pharm. Pharmacol., 32, 675 (1980).

7. E. Nurnberg, Progr. Colloid, Polym. Sci., 59, 55, (1976).

8. A. Hoelgaard and N. Moller, Arch. Pharm. Chemi Sci. Ed., 3, 34 (1975).

9. H. Imaizumi, N. Nambu and T. Nagai, Chem. Pharm. Bull., 31, 2510 (1983).

10. W.L. Chiou and S. Riegelman, J. Pharm. Sci., 58, 1505 (1969).

11. E. Nurnberg and B. Dolle, Pharm.Ind., 42, 1020 (1980).

12. Y. Takahashi, N. Nambu and T. Nagai, Chem. Pharm. Bull., 26, 3836 (1978).

13. K.H. Fromming and I. Weyermann, Arch. Pharm., 303, 290, (1972).

14. R. Kaur, D.J.W. Grant and T. Eaves, J. Pharm. Pharmac., 31, 48p (1979).

15. J.L. Ford and M.M. Rubinstein, J. Pharm. Pharmac., 30, 512 (1978).

16. R.K. Reddy, S.A. Khalil and M.W. Gouda, J. Pharm. Sci., 65, 1753 (1976).

17. R.G. Stoll, T.R. Bates and J. Swarbrick, J. Pharm. Sci., 62, 65 (1973).

18. G. Ollenschlager and T. Eckert, Pharm. Ind., 39, 388 (1977).

19. H. Junginger, Pharm. Ind., 36, 333 (1974)

20. J. Kreuter, in "Topics in Pharmaceutical Sciences 1983" D.D.Breimer and P. Speiser, eds., Elsevier, Amsterdam (1983) p.359

21. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963)

22. S. K. Chandrasekaran and D.R. Paul, J. Pharm. Sci., 71, 1399 (1982)

23. W. I. Higuchi, N. A. Mir and S. J. Desai, J. Pharm Sci., 54, 1405 (1965)

24. S. A. Shah and E. L. Parrott, J. Pharm. Sci., 65, 1784 (1976)

25. G. R. Carmichael, S. A. Shah and E. L. Parrott, J. Pharm., Sci., 70 1331 (1981)

26. M. Simpson and E. L. Parrott, J. Pharm. Sci., 72, 757 (1983)

27. E. L. Parrott, M. Simpson and D. R. Flanagan, J. Pharm. Sci., 72, 765 (1983)

28. A. H. Goldberg, M. Gibaldi and J.L. Kanig, J. Pharm. Sci., 55, 482 (1966)

29. T. Higuchi and K. A. Connors, Adv. Anal, Chem. Instr., 4, 117 (1965)

30. O.I. Corrigan and C. T. Stanley, J. Pharm. Pharmacol. 34, 621 (1982)

31. O. I. Corrigan and C.T. Stanley, Pharm. Acta Helv., 56, 204 (1981)

32. O. I. Corrigan and R. F. Timoney, Pharm. Acta Helv., 51, 268 (1976)

33. H. Junginger, Pharm. Ind., 39, 383 (1977).

34. H. Junginger, Pharm. Ind., 39, 498 (1977).

35. A.P. Simonelli, S.C. Mehta and W.I. Higuchi, J. Pharm. Sci., 58, 538 (1969).

36. O.I. Corrigan and R.F. Timoney, J. Pharm. Pharmac., 26, 838 (1974).

37. O.I. Corrigan and R.F. Timoney, J. Pharm. Pharmac., 27, 759 (1975).

38. O.I. Corrigan, K. Sabra and E.M. Holohan, Drug. Devel. Ind. Pharm., 9, 1 (1983).

39. O.I. Corrigan and E.M. Holohan, J. Pharm. Pharmac. 1984. In press.

40. A.P. Simonelli, S.C. Mehta and W.I. Higuchi, J. Pharm. Sci., 65, 355 (1976).

41. H. Sekikawa, M. Nakano and T. Arita, Chem. Pharm. Bull. 26, 118 (1978).

42. H. Sekikawa, R. Hori, T. Arita, K. Ito and M. Nakano, Chem. Pharm. Bull., 26, 2489 (1978).

43. A.R. Ebian, M.A. Moustafa, S.A. Khalil and M.M. Motawi, J. Pharm. Pharmac., 25, 13 (1973).

44. A.P. Simonelli, S.C. Mehta and W.I. Higuchi, J. Pharm. Sci., 59, 633 (1970).

45. S.G. Frank, J. Pharm. Sci., 64, 1535 (1975).

46. E.I. Stupak, H.A. Rosenberg and T.R. Bates, J. Pharmacokin. and Biopharm. 2, 525 (1974).

47. H. Junginger, Pharm. Ind., 38, 461 (1976).

48. S.C. Mehta, A.P. Simonelli and W.I. Higuchi, A. Ph.A. Meeting Abstract 67 (1971).

49. A.P. Simonelli, S.C. Mehta, A.B. Bikhazi and W.I. Higuchi, A. Ph. A. Meeting Abstract 66, (1971).

50. D.J. Allen and K.C. Kwan, J. Pharm. Sci., 58, 1190 (1969).

51. O.I. Corrigan, M.A. Farvar and W.I. Higuchi, Int. J. Pharm., 5, 229 (1980).

52. W.I. Higuchi and M.A. Farvar in "Proceedings of the International Symposium on Povidone". G.A. Digenis and J. Ansell, eds., University of Kentucky, 1983 p.71.

53. H.P. Merkle, Pharm. Ind., 42, 1009 (1980).

54. H.P. Merkle, Pharm. Ind., 43, 183 (1981).

55. K.M. O'Driscoll and O.I. Corrigan, Drug. Devel. Ind. Pharm., 8, 547 (1982).

56. E. Shefter and K.C. Cheng, Int. J. Pharm. 6, 179 (1980).

57. P. Singh, J.K. Guillory, T.D. Sokoloski, L.Z. Benet and V.N. Bhatia, J. Pharm. Sci., 55, 63 (1966).

58. W.B. Breuninger and R.W. Goettsch, J. Pharm. Sci., 54, 1487 (1965).

59. M. Gibaldi and H. Weintraub, J. Pharm. Sci., 57, 832 (1968).

60. H. Sekikawa, M. Nakano and T. Arita, Chem. Pharm. Bull., 27, 1223 (1979).

61. A.A. Badawi and A.A. El-Sayed, J. Pharm. Sci., 69, 492 (1980).

62. O.I. Corrigan, C.A. Murphy and R.F. Timoney, Int. J. Pharm., 4, 67 (1979).

63. H.P. Merkle, Acta Pharm. Tech. 27, 193 (1981).

64. H.P. Merkle in "Proceedings of the International Symposium on Povidone". G.A. Digenis and J. Ansell, eds., University of Kentucky, 1983, p202.

65. J.A. Rogers and A.J. Anderson, Pharm. Acta Helv., 57, 276 (1982).

66. M.P. Summers and R.P. Enever, J. Pharm. Sci., 65, 1613 (1976).

67. H. Nogami, T. Nagai and A. Kondo, Chem. Pharm. Bull. 16, 1185 (1970).

68. A. Heyd, D.O. Kildsig and G.S. Banker, J. Pharm. Sci., 58, 586 (1969).

69. O.I. Corrigan and M. Murtagh unpublished results.

70. W. Nernst and E. Brunner, Z. Phys. Chem. 47, 52 (1904).

71. K. Ueberreiter in "Diffusion in Polymers" eds. J. Crank and B.G.S. Park, \cademic Press, N.Y. 1968 p. 219.

72. Y.O. Tu and A.C. Ouano, IBM Journal of Res. and Devel. 21, 131 (1977).