International Journal of Pharmaceutics, 92 (1993) 211–218

IJP 03157

Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronisation

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(Received 29 October 1992)
(Modified version received 9 December 1992)
(Accepted 15 December 1991)

Key words: Extrusion/spheronisation; Sustained release; Dissolution; Chitosan; Diclofenac; Compensation analysis; Thermodynamics

Summary

Spheres have been prepared from a wet mass by extrusion and spheronisation. Chitosan was included as a solution in the powder mix. Four formulations were considered, containing two different concentrations of chitosan, each prepared at two different sizes of sphere; either approx. 1 or 2 mm. The release of a model drug (diclofenac sodium) from the spheres was found to be considerably slower than formulations without added chitosan (i.e. ca. 100% in 6 h, rather than 30 min). Thus it is possible to retard drug release from a sphere, without the need for polymer coating, by use of a hydrophilic gel. The drug release profiles followed first order kinetics (for all four systems), and produced a straight line when plotted as a function of the square root of time. A straight line was also obtained when a double logarithmic plot of release as a function of time was prepared, the gradient of which was in the order of 0.5, this would indicate Fickian diffusion, if from a thin slab, but as the release was from a sphere, the process was described as fitting a non-Fickian diffusion model. Dissolution testing at different stirring speeds did not alter the rate of drug release, demonstrating that the diffusion process was controlled within, rather than in the layer of fluid around, the sphere. Thermodynamic activation parameters were calculated and the four formulations were compared by compensation analysis. It was apparent that there was no common mechanism for drug release, but that the concentration of the Chitosan related to the enthalpy change, and the Gibbs free energy change correlated with the dissolution rate.

Introduction

Sustained release pellets can be prepared by extrusion and spheronisation. It is conventional to achieve sustained release from such pellets by polymeric coating. If control of drug release could be achieved by matrix formulation, the film coating stage could be removed from the production process.

Several types of matrix system are used in order to achieve sustained release, these include various hydrophobic systems, release from which is controlled by either diffusion or erosion, and hydrophilic matrices which swell in water to form a gel, from which drug is liberated primarily by diffusion. The systems that are currently employed are reviewed in many standard texts, in-

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cluding those of Lee and Robinson (1978) and Kydanieus (1980a,b).

Multiparticulate systems are thought to have numerous advantages over single unit dose devices. These include: (i) the possibility of dispersion in the stomach, with a consequent reduction in local drug concentrations (as would be formed around a tablet), and thus less of a tendency to cause gastric irritation (Wilson and Washington (1989) have reviewed data on this subject which suggests that dispersion of the pellets will be dependent upon gastric contents); (ii) the possibility of retaining pellets in the stomach (by using either high or low density systems), and consequently to further extend the duration of action of a sustained release dosage form (see, for example, Wilson and Washington (1989)); and (iii) the disruption of certain matrix sustained release tablets could occur (e.g., due to chewing, or due to abrasion with food in the stomach) leading to serious problems with dose dumping, however, it is considerably less likely that small pellets will be disrupted, and even if some are disrupted, it is very unlikely that all pellets will be affected, thus there is a reduced risk of dose dumping.

Hydrophilic systems are more amenable to the process of extrusion spheronisation; such hydrogel matrix systems have been reported by O'Connor and Schwartz (1989), although not for the production of sustained drug release.

Certain natural polysaccharides swell in aqueous environments forming hydrogel systems. Chitosan is obtained from the natural polysaccharide chitin, by *N*-deacetylation. Chitosan has been demonstrated to have considerable potential as a pharmaceutical excipient with numerous applications; these include the slowing of drug release by gel formation (e.g., Miyazaki et al., 1981) or by floating on gastric contents (Miyazaki et al., 1988), or by bioadhesion to gastro-intestinal mucosa (in combination with other bioadhesives) (Takayama et al., 1990), and the enhancement of dissolution rates of poorly soluble drugs, if low molecular weight chitosan grades are used (Shiraishi et al., 1990).

Directly compressed mixes of chitosan, lactose and diclofenac sodium have been shown to produce sustained release (Acarturk, 1989). The kinetics of the release at pH 6.8, showed a gradual change from first to zero order as the chitosan/drug ratio was increased (Acarturk, 1989). Acarturk (1989) argues the value of chitosan as a method of slowing the release of diclofenac, and thus reducing gastric irritation; if chitosan is bioadhesive (as suggested by Takayama et al., 1990), then it would not be a suitable dosage form by which to administer a gastric irritant. However, in light of published work on this tabletted product, it was decided that diclofenac would be used as a model drug in the preparation of pellets containing chitosan.

Materials and Methods

Materials

The following materials were used to prepare the pellets:-diclofenac sodium (Profarmaco Nobel), chitosan (Sea Cure 242, Protan), lactose (Pharmatose 450 M), Avicel PH-101 (FMC Corporation) and glacial acetic acid (Analar, BDH).

Methods

Preparation of the pellets

The powder mixes were prepared as 800 g batches, containing 10 g (1.25%) diclofenac sodium, 340 g (42.5%) Avicel PH-101, 150 g (18.75%) lactose, and 300 g (37.5%) chitosan solution (all % w/w). The chitosan solution was prepared in glacial acetic acid, and two different strengths were used; 2 and 3% w/w. The formulations will be designated chitosan 2% and chitosan 3% (although this does not represent the % composition of chitosan in the final preparation). A formulation with no added chitosan was also prepared (i.e., water replaces the chitosan solution in the formula above). Chitosan solutions of higher concentrations resulted in a gel like structure for the extrudate, which could not be spheronised.

The powders were mixed with the solution (Kenwood Chef), and forced through a die at the base of a ram extruder, using a Lloyd press

(MX50). The ram was moved at 100 mm/min. Two different dies were used, one of 1 mm diameter and 4 mm length and the other of 2 mm diameter and 2 mm length. The extrudate was spheronised for either 10 min (2%, 2 mm × 2 mm sample), 15 min (2%, 1 mm × 4 mm sample) or 30 min (3% samples), this representing the time needed to produce uniform spherical particles. The spheres were dried in a fluid bed drier (PRL Engineering) for 30 min.

Dissolution tests

Dissolution was undertaken using the USP paddle method (Pharma Test), using 1000 cm^3 of pH 7.4 phosphate buffer (USP), which had a measured pH of 7.5. The low equilibrium solubility of the drug at acidic pH values made it impossible to obtain sink conditions at gastric pH, using official batch dissolution tests, consequently such experiments are not reported (diclofenac has a pK_a of 3.8, and a solubility of 1.5×10^{-5} M at pH 2 and 25°C; Fini et al., 1985).

Dissolution experiments were undertaken at four different temperature (25, 30, 35 * and 43°C) using a stirring speed of 100 rpm. At 35°C three different stirring speeds were used (50, 100 and 120 rpm).

Filtered samples were taken automatically (Pharma Test, PTFC sample collector) at various time intervals over a 6 h period, and assayed using a UV spectrophotometer at 275 nm (Perkin Elmer, 554). Results are averages of three determinations.

Sizing of the pellets

The pellets were sieved into size fractions, and the distribution was presented as cumulative % oversize as a function of weight.

Results

The median size of the pellets was: 2% chitosan (1 mm × 4 mm die), 1.1 mm; 2% chitosan (2 mm × 2 mm die), 1.75 mm; 3% chitosan (1 mm × 4 mm die), 1.1. mm; and 3% chitosan (2 mm × 2 mm die), 2.1 mm.

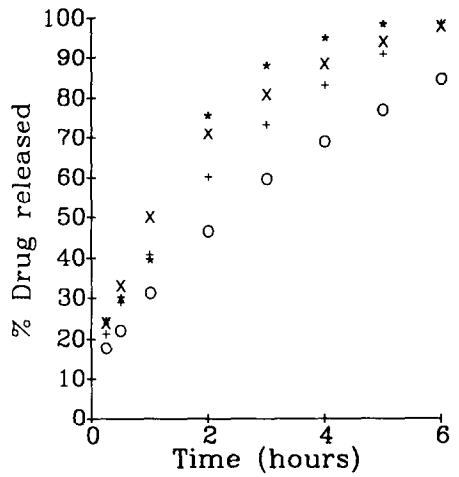

Fig. 1. Dissolution profiles from the four different products at 35°C. (×) 2%, 1.1 mm; (+) 2%, 1.75 mm; (*) 3%, 1.1 mm; (○) 3%, 2.1 mm.

The dissolution profiles of the four products at 35°C are presented in Fig. 1. The release profile of the product with no added chitosan (not shown) was such that 99% release was obtained in 30 min. The addition of chitosan had a significant retardant effect on the drug release. The size of the pellets appears to be of importance in determining the release rate; both the approx. 1 mm pellets (from 2 and 3% chitosan solutions) have very similar release profiles, which were not as sustained as the approx. 2 mm pellets. The slowest release is observed with the 3%, 2.1 mm sample, which was the product with the largest size (Fig. 1).

Discussion

The reason why drug release rate from a product is reduced in the presence of chitosan is reported to be due to the formation of a gel, through which the drug must diffuse (Miyazaki et al., 1981). If the mechanism of drug release from the pellets is by formation of, and then by slow diffusion through, a gel, it is not surprising that size is a significant factor in the dissolution pro-

* The dissolution bath was set to 37°C, but the true measured temperature was in fact found to be 35°C.

cess, this will be discussed in more detail below. During the dissolution experiment there was no visible increase in the size of the pellets, this is probably due to the fact that chitosan was present in a relatively small proportion (compared to the work of Acarturk (1989), for example).

Higuchi (1963) reported that a linear relationship between drug release and the square root of time demonstrates that a diffusional process is occurring. The Higuchi plots for the four products are presented in Fig. 2, good relationships were obtained in each case, with linear regression correlation coefficients of 0.995 or better. Korsmeyer and Peppas (1981) have advocated the use of a double logarithmic plot of drug release as a function of time, for which a linear relationship with a gradient of 0.5 would demonstrate Fickian diffusion. For the period between 30 min and 4 h, the release profiles for all four pelleted chitosan samples produced a linear fit to a double logarithmic plot (not shown); correlation coefficients and gradients were as follows: 2%, 1.1 mm, $r = 0.993$, gradient = 0.48; 2%, 1.75 mm, $r = 0.999$, gradient = 0.50; 3%, 1.1 mm, $r = 0.999$, gradient = 0.45; and 3%, 2.1 mm, $r = 0.999$, gradient = 0.55. It might be deemed reasonable to assume that the drug release from each product followed a Fickian diffusion process, as all the gradients were close to 0.5, however, Ritger and Peppas (1987a,b) have demonstrated that this model is only acceptable for thin films, and the correct interpretation for a spherical system is that gradients of 0.43 will result if Fickian diffusion occurs. Thus, the approx. 1 mm samples are close to Fickian diffusion, but all the products are in fact releasing by 'anomalous (non-Fickian) transport'.

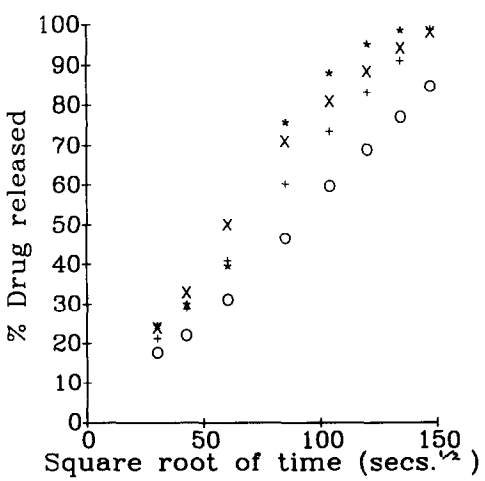

Fig. 2. Higuchi plot showing % drug released, at 35°C, as a function of the square root of time. Symbols as Fig. 1.

TABLE 1

The release of drug from the spheres at 35°C, at stirring speeds of 50, 100 and 120 rpm (time intervals quoted are 1, 3, and 5 h; these are representative of the entire dissolution process from 0 to 6 h

Formulation	Speed (rpm)	% released at (h)		
		1	3	5
2%, 1.1 mm	50	52.0	84.3	98.0
2%, 1.1 mm	100	51.1	82.6	96.1
2%, 1.1 mm	120	55.9	84.6	97.3
2%, 1.75 mm	50	46.8	78.7	95.4
2%, 1.75 mm	100	41.3	74.5	92.2
2%, 1.75 mm	120	47.4	78.3	94.1
3%, 1.1 mm	50	51.8	84.7	97.7
3%, 1.1 mm	100	53.9	87.8	98.3
3%, 1.1 mm	120	50.0	85.8	97.7
3%, 2.1 mm	50	32.6	58.2	82.0
3%, 2.1 mm	100	31.2	59.7	77.1
3%, 2.1 mm	120	26.8	53.3	70.2

As no visible swelling of the pellets was observed, it is interesting to explore the extent of the diffusion region. If the diffusion process is internalised, i.e., entirely within the sphere, it should not be altered significantly by changes in the stirring speed during the dissolution experiment, however, if the diffusion is occurring in a static layer of fluid surrounding the spheres, then changes in stirring speed will drastically alter the release profile. The release profiles at different stirring speeds are presented in Table 1, from which it is apparent that the drug release rate is not dependent upon stirring speed. The diffusion process(es) that control the drug release rate must be occurring within the sphere. This could explain why there is a high initial release of drug; i.e., ranging from 17% (for formulation 3%, 2.1 mm) to over 30% at 15 min (for formulation 3%,

1.1 mm), as the drug on the edges of the sphere will be comparatively free from the gel structure, and thus tend to dissolve rapidly.

The fact that the spheres are of different particle sizes, and therefore have different surface areas, should also be considered, as larger surface areas should result in faster dissolution rates, if the release mechanisms are the same. There is a degree of correlation between median size and the release rate constant for the spheres, as the approx. 2 mm spheres have slower release rates than the approx. 1 mm spheres. To investigate the reason for this difference, the surface areas of each sample have been determined by counting the number of spheres present in the dissolution experiment, and calculating the total surface area, based on the median radius. The available surface areas (in mm^2) were: 2%, 1.1 mm, 376; 2%, 1.75 mm, 499; 3%, 1.1 mm, 285; 3%, 2.1 mm, 333. The surface areas are not simply related to the particle size, as the 2% chitosan formulations clearly have a different density to the 3% (i.e., in the weighed sample, there were less of the 2% pellets than there were 3% chitosan pellets). On the basis of surface area alone, the rank order of dissolution rate would have been 2%, 1.75 mm, followed by 2%, 1.1 mm and then 3%, 2.1 mm with 3%, 1.1 mm being the slowest; this in no way correlates with the observed dissolution rates (Table 2), demonstrating that although size is of importance, this does not seem to be due to a surface area effect, thus the mechanism and release rates are significantly influenced by other factors. Although the four chitosan pelleted formulations all release by a non-Fickian diffusion process, the mechanism by which this is achieved may not be common; for example, either one or both of the two variables may control the release mechanism, i.e., the size of the pellets and/or the concentration of the chitosan in the pellet may be important. It has already been shown (above) that the release rate is not a simple function of surface area, but it may be related to the size of the pellet, perhaps due to the existence of a larger volume for diffusion; and the concentration of chitosan influences the physical properties of the product (e.g., it has been shown above that the 2 and 3% spheres are of different densities), and it can therefore be assumed that it will influence the diffusion pathways during the dissolution process.

TABLE 2

Apparent first order release constants (all in $s^{-1} \times 10^{3}$) for the dissolution from the four products at four different temperatures

Temperature (°C)	2%		3%	
	1.1 mm	1.75 mm	1.1 mm	2.1 mm
25	4.90	3.02	6.04	2.29
30	6.08	3.94	6.50	2.66
35	9.97	5.42	9.45	3.90
43	12.64	8.54	13.29	4.99

In recent publications (Buckton, 1990, 1992; Buckton and Efentakis, 1990; Efentakis and Buckton, 1990), it has been demonstrated that it is possible to describe drug release from controlled release dosage forms by use of thermodynamic activation parameters. Furthermore, it is possible to compare common mechanisms, and outliers to common mechanisms, by use of compensation analysis (Buckton, 1990; Buckton and Efentakis, 1990). Compensation analysis looks for relationships between two thermodynamic parameters, usually enthalpy is plotted as a function of entropy, but as such a plot can be subject to statistical artifacts the more exacting test is to plot enthalpy as a function of free energy (see Krug et al., 1976a,b; Tomlinson, 1983; Buckton, 1990). A correlation between enthalpy and free energy, at the harmonic mean experimental temperature (T_{hm}), will indicate a common mechanism for any given process.

Apparent first order rate constants (k) have been calculated for dissolution profiles for each formulation, obtained at each of four temperatures (Table 2). Plots of ln k as a function of $(1/T) - (1/T_{hm})$ (Fig. 3), where T is the absolute temperature, have been used to calculate the thermodynamic functions of activation using the method of Krug et al. (1976a,b). The values for the thermodynamic parameters are presented in Table 3. As with previous data on slow release dosage forms, the results are indicative of a disfavoured process (Efentakis and Buckton, 1990). The numerical values of the free energy and thus

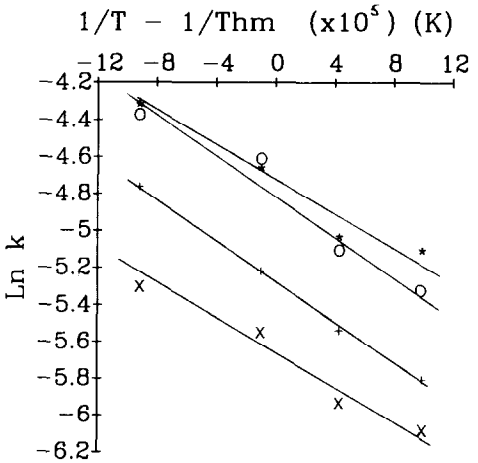

Fig. 3. Ln k as a function of $(1/T) - (1/T_{hm})$; the gradient is used to calculate the enthalpy, and the y-axis intercept is used to calculate the free energy of activation. (×) 3%, 2.1 mm; (+) 2%, 1.75 mm; (○) 2%, 1.1 mm; (*) 3%, 1.1 mm.

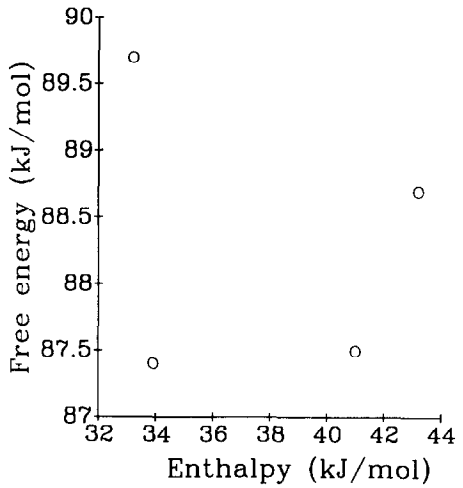

Fig. 4. Enthalpy-free energy compensation plot for the four formulations, revealing the absence of any common mechanism.

the entropy terms are dependent upon the choice of units for the rate constant, but nonetheless still provide a suitable ranking system for the products. From Fig. 4, it can be seen that the thermodynamic parameters do not form a single linear plot, thus there is not a common mechanism associated with the release from the four products. From Fig. 3, it can be seen that the gradients are similar for the formulations made with the same strength chitosan solutions, i.e., the products from 2% solutions have very similar gradients (and thus enthalpies, see Table 3), which are different from the gradients for the 3% formulations, and vice versa. The ranking of free energies (Table 3) again causes the formulations to be paired, in this case, however, the size of the spheres (and not the strength of the chitosan solution) is the linking factor.

In previous studies (e.g., Buckton and Efentakis, 1990), the release rate of drug from a matrix tablet was found to correlate reasonably well with the entropy term; in this study, however, neither the entropy or the enthalpy term correlates with the rate constant, but the overall process (as reflected by the Gibbs free energy change) does correlate with release rate (Fig. 5). It can be postulated that two mechanisms are

TABLE 3

The values of the thermodynamic parameters of activation for the dissolution of the pellets at T_{hm}

Formulation	ΔH (kJ/mol)	ΔG (kJ/mol)	ΔS (J/mol per K^{-1})
2%, 1.1 mm	41.0	87.5	−151.6
2%, 1.75 mm	43.2	88.7	−148.2
3%, 1.1 mm	33.9	87.4	−174.1
3%, 2.1 mm	33.2	89.7	−184.0

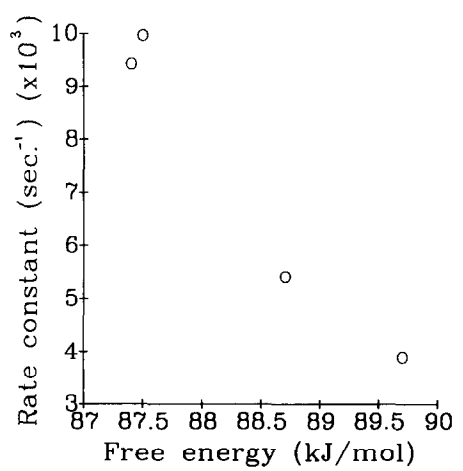

Fig. 5. The Gibbs free energy of activation as a function of the apparent first order dissolution rate constant (at 35°C).

responsible for controlling the diffusion process. Firstly, the amount of chitosan present alters the enthalpy of activation, the higher concentration seems to decrease the enthalpic barrier to dissolution, this is probably due to the hydrophilic properties of the chitosan gel. Secondly, increasing the size of the spheres results in an increased free energy change.

Conclusions

It is possible to prepare pellets by extrusion and spheronisation which form hydrophilic gels during dissolution, resulting in sustained release of drug over a number of hours. This sustained action can be achieved without the need to coat the pellets.

The release from the hydrophilic matrices follows a non-Fickian diffusion process. The diffusion front is internal to the sphere, as it is not affected by stirring rate during the dissolution process.

The values obtained for the thermodynamic activation parameters revealed that the release process is proportional to the Gibbs free energy change, but not directly proportional to either the enthalpy or the entropy change. Compensation analysis proved that there was more than one mechanism of release from the four formulations. The enthalpy of activation can be strongly linked to the composition of chitosan, but the Gibbs free energy is more closely linked to the size (but not the available surface area) of the pellet.

Compensation analysis has once again been proved to be a valuable approach to the study of drug release from controlled release dosage forms.

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