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Novel method to evaluate diffusion controlled release of drug from resinate

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Summary

A novel method is presented to evaluate diffusion-controlled release of a drug from a resinate. The method is direct, simple, involves no trial and error, and is applicable to any drug–resin complex. Experimental data are reported on the release of metoclopramide from Amberlite 1R-120 resinate which adequately confirm the validity of the method. The method is also shown to work well for available published data of other investigators.

Introduction

Many drugs require to be released at a controlled rate so that sustained or prolonged action is obtained. Out of the many methods for the preparation of sustained release formulations (Hoover, 1975), use of ion exchange resins has occupied an important place due to its well controllable properties like particle size and its distribution, particle shape and internal pore structure. Morphological characterization of particles and the various measurement techniques have been discussed in great detail in earlier reports (Viswanathan, 1984, 1985).

The release of drug from a resinate particle can be controlled by the pore diffusion resistance (also called 'particle diffusion control') or by the resistance of the film surrounding the particle. In order to be able to finally produce a good formulation, it is essential to determine the controlling mechanism of release. While diffusivity is the pertinent parameter in case of particle diffusion control, film thickness (or the mass transfer coefficient) is relevant for film diffusion control. Normally, particle diffusion control is expected for drug release from a resinate and hence the data is tested for particle diffusion control.

The precise expression for particle diffusion control is obtained by solving the basic partial differential equation and the standard solution is (Boyd et al., 1947):

$$F = 1 - \frac{Q}{Q_0} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-n^2 Bt) \qquad (1)$$

$$B = 4\pi^2 D / d_p^2 \qquad (2)$$

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where the various symbols are explained in the Nomenclature.

Obviously it is not possible to estimate the B-values from measured F using Eqn. 1 because infinite terms are involved. Many workers have therefore sought simpler approximate expressions for Eqn. 1. Reichenberg (1953) obtained the following approximation

$$Bt = \begin{cases} 2\pi - \pi^2 F/3 - 2\pi(1 - \pi F/3)^{1/2} \\ \quad \text{for } F \leqslant 0.85 \\ -\ln(1 - F) - 0.04977 \text{ for } F > 0.85 \end{cases} \quad (3)$$

He used Eqn. 3 to estimate the Bt-values from the measured F-values. He calculated the values of Bt at different values of F ranging from 0.01 to 0.99 using Eqn. 3. This standard table has been used by Chaudhary et al. (1956), Gyselinck et al. (1981) and Schacht et al. (1982) to calculate the Bt-values at different experimentally obtained F-values (at different times). By plotting Bt versus t and passing a straight line, they obtained the B-value and hence the diffusivity. The main disadvantage with this method of determining diffusivity is that every time one has to consult the standard table developed by Reichenberg (1953) and the procedure becomes cumbersome and lacks elegance.

Gyselinck et al. (1982) proposed another approximate equation to determine the diffusivity value.

$$F = P_1 + P_2 \exp(P_3 t^2 + P_4 t) \quad (4)$$

where $P - P_4$ are different parameters. It was shown that parameter P_2 is related to diffusivity. The drawback with this technique is that a computer is required to determine these parameters. Moreover, the parameters P_1–P_4 vary with the drug and hence have to be determined for every drug–resin complex.

An attempt is made in the present paper to develop a new elegant method to test for the particle diffusion-controlled release of drug. A method is then presented to determine diffusivity directly. Extensive experimental results are used to validate the method developed. The method is also shown to explain the data of other investigators extremely well.

Theoretical

Using the monotonic transform method of Viswanathan (1984b) it has been shown by Viswanathan (1984a) and Viswanathan et al. (1984a) that an alternative simpler relation to Eqn. 1 is

$$1\text{-}F = Q/Q_0 = \exp(-1.59x^{1.3}) \quad (5)$$

$$x = \frac{6}{d_p} \cdot \sqrt{Dt} \quad (6)$$

and Eqn. 5 was used for the data of drying of agricultural grains. It can be used for the release of drug from resinate as well. Using Eqns. 5 and 6, we get

$$-\ln(1 - F) = \ln(Q_0/Q) = 1.59\left(\frac{6}{d_p}\right)^{1.3} D^{0.65} t^{0.65} \quad (7)$$

This suggests that particle diffusion control can be tested by simply testing for linearity between $\ln(Q_0/Q)$ and $t^{0.65}$. The slope of the resulting straight line is related to the diffusivity according to

$$D = \frac{d_p^2}{36}(\text{slope}/1.59)^{1/0.65} \quad (8)$$

The main advantages of the proposed method over other methods are: (i) the method is simple and elegant; (ii) the diffusivity is simply obtainable from Eqn. 8; and (iii) the constants 1.59 and 0.65 in Eqns. 7 and 8 are applicable for all drug–resin complexes and need not be re-estimated.

Materials and Methods

Materials

Metoclopramide hydrochloride (sample gifts obtained from IPCA Laboratories, Bombay, Carter Wallace, Goa and Shalak Chemicals, Delhi) was used as model drug Amberlite IL-120 with 8% cross-linking (Loba Chemie, Austranal) was used

as the model resin. 0.1 N hydrochloric acid (IDPL Hyderabad) was used as the gastric dissolution medium and 0.1 N sodium chloride (BDH Glaxo, Bombay) was used as the intestinal dissolution media.

Drug–resin complex

The drug–resin complex was prepared by adsorption in a packed bed, the details of which are reported elsewhere (Bhaskar, 1985). The drug content of the resinate was determined by the graphical integration method which is essentially a material balancing technique. This technique was originally used by Viswanathan (1983) and Viswanathan and Rao (1984) for adsorption/desorption of moisture on silica gel in a fluidized bed. The drug content calculated by this technique compared well with the chemical method of analysis as can be seen in Table 1.

Apparatus

The assembly for continuous dissolution is shown in Fig. 1. A 2 litre and 5 litre flask were

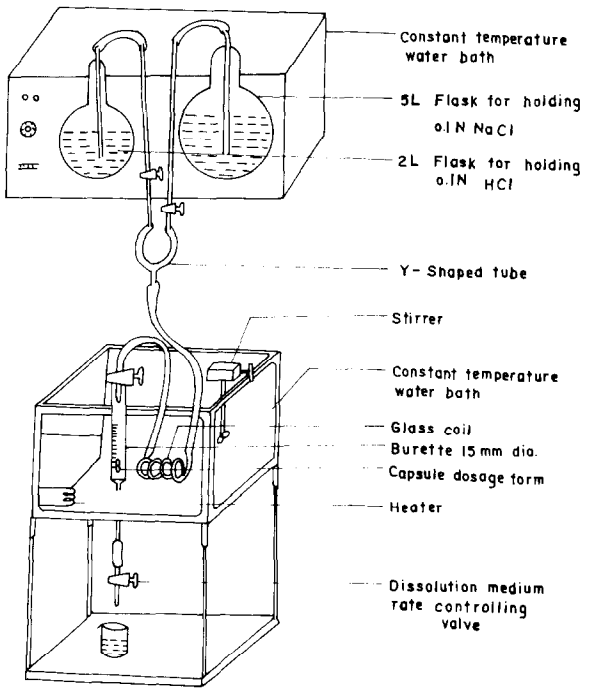

Fig. 1. Apparatus for continuous method of dissolution.

TABLE 1

OPERATING CONDITIONS CORRESPONDING TO DESORPTION RUNS

Run no.	Resin particle size (mm)	Drug content, Q_0 (g/g)		Flow rate of dissolution media, F_t (ml/min)	Temperature T (°C)
		Graphical integration	Chemical analysis		
D1	1.242	0.714	0.702	5	23
D2		0.714	0.702	10	23
D3		0.714	0.702	5	37
D4		0.714	0.702	10	37
D5		0.729	0.706	10	40
D6	0.652	0.650	0.640	5	23
D7		0.650	0.640	10	23
D8		0.650	0.640	20	23
D9		0.650	0.640	5	37
D10		0.650	0.640	10	37
D11		0.650	0.640	10	40
D12	0.371	0.704	0.695	5	23
D13		0.649	0.631	10	23
D14		0.632	0.614	5	37
D15		0.632	0.614	10	37
D16		0.632	0.614	5	40
D17		0.632	0.614	10	40

The amount of resin particles in all the runs was 3.2 g which corresponded to a bed height of 5 cm.

used as a reservoir for gastric and intestinal dissolution media, respectively. Two organ baths to conduct dissolution at constant temperature were employed. Two siphons one each for gastric and intestinal dissolution media were employed so as to maintain the flow of these over the bed of resin. A sintered disc of 00 porosity placed at the bottom of burette was used to hold the resin bed. The operating conditions corresponding to various experiments performed are listed in Table 1.

Procedure

Before the start of dissolution, the temperature in both the organ baths were brought to the required value. A sintered disc was placed inside the burette. The dissolution media were sucked into both the siphons and their stopcocks closed. An accurately weighed amount of the resinate was first transferred into a beaker containing some water. The resinate was then transferred into the burette taking care that no wastage occurred during transfer. The flow of 0.1 N hydrochloric acid was started by opening the stopcock of the siphon connected to flask containing 0.1 N hydrochloric acid. The flow rate of dissolution medium was adjusted with the stopcock of the burette. Dissolution studies with 0.1 N hydrochloric acid were carried out for 2 h after which the flow of 0.1 N sodium chloride was started. The amount of drug desorbing from the drug–resin complex was estimated at definite time intervals by withdrawing the sample from the effluent and measuring the drug concentration by the colorimetric method developed by Shingbal and Sawant (1982). More details of the experimental procedure are reported elsewhere (Bhaskar, 1985).

Results and Discussion

The present experiments are tested for particle diffusion-controlled release as suggested by Eqn. 7. Typical plots of $\ln(Q_0/Q)$ vs $t^{0.65}$ for both HCl and NaCl desorption are shown in Figs. 2 and 3. It can be seen that the data fall on good straight lines confirming particle diffusion-controlled release of the drug. The estimated diffusivity values from Eqn. 8 are summarized in Table 2. The following conclusions follow.

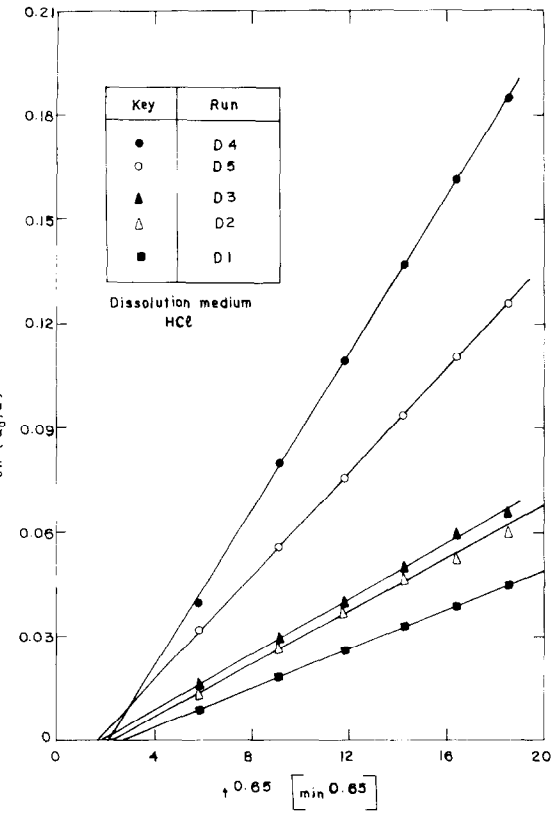

Fig. 2. Plot to check particle diffusion-controlled drug release.

(1) From runs D1 and D3; D6 and D9; D12, D14 and D16, it is clear that diffusivity increases with temperature.

(2) Diffusivity decreases with decrease of the resin particle size. It is probable that smaller resin particles have smaller pores which offer greater resistance to the release of drug from the resin interior to the surface.

(3) According to Eqn. (7), the straight lines obtained by plotting $\ln(Q_0/Q)$ versus $t^{0.65}$ should pass through the origin. However, this is not observed in the present work. At the start of dissolution a definite quantity of drug–resin complex was transferred into the burette. The burette was then filled with water. The dissolution was started by allowing the dissolution medium to flow over the drug–resin complex. Since the drug–resin complex was already covered with water, it was very difficult to know the exact time at which the dissolution commenced. The points on which these

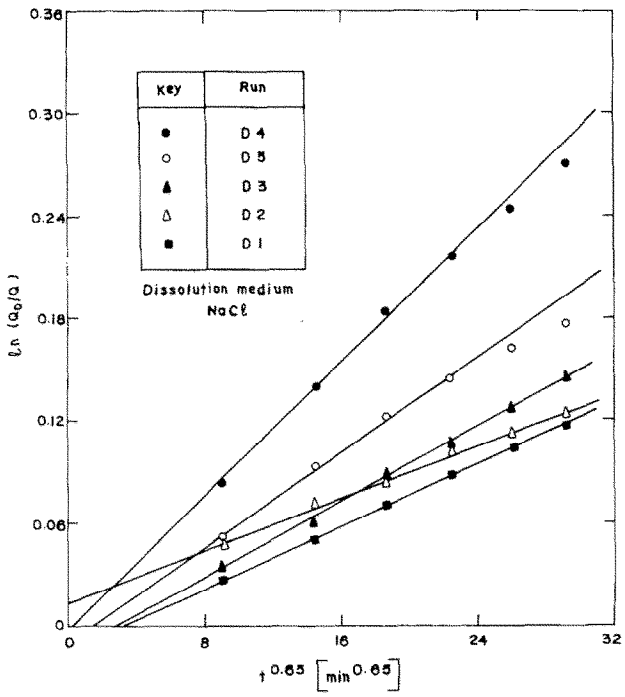

Fig. 3. Plot to check particle diffusion-controlled drug release.

straight lines meet the x-axis represent the time at which the dissolution medium might have taken to come in contact with the resin bed which is approximately 5 min. This tallies with the value estimated from the x-intercept in Figs. 2 and 3. In any case, this value is considerably smaller than the total desorption time and can, for all practical purposes, be neglected.

The plots of ln D versus $1/T_k$ are shown in Fig. 4 for determining the Arrhenius relationship.

$$D = D_0 \exp(-E/RT_k) \tag{9}$$

It can be seen that the straight lines obtained for the three particle sizes are parallel to each other, i.e. same E of 76 kJ/g mole. The preexponential factors are obtained as:

$$D_0 = \begin{cases} 52\ m^2/min \text{ for } d_p = 1.242\ mm \\ 36\ m^2/min \text{ for } dp = 0.653\ mm \\ 10\ m^2/min \text{ for } d_p = 0.371\ mm \end{cases} \tag{10}$$

The results show that D_0 and energy of activation E are independent of flow rate of dissolution medium. The obtained Arrhenius relationship coupled with the model presented can be used for predicting drug release rate, drug content etc. for different particle sizes, temperature, flow rate, etc. for the present drug–resin complex. This will help

TABLE 2

SUMMARY OF DIFFUSIVITY VALUES

Run no.	Slope × 10^2 ($min^{-0.65}$)		Diffusivity values × 10^6 (mm^2/min)	
	HCl	NaCl	HCl	NaCl
D1	0.28	0.45	2.46	5.09
D2	0.36	0.43	3.61	4.70
D3	0.38	0.55	3.97	6.90
D4	0.11	1.00	20.10	17.41
D5	0.72	0.68	10.60	9.62
D6	0.38	0.55	1.06	1.90
D7	0.43	0.45	1.32	1.45
D8	0.60	0.41	2.19	1.23
D9	0.76	0.89	3.17	3.99
D10	1.00	1.27	4.80	7.01
D11	1.27	2.33	6.97	17.30
D12	0.28	0.34	0.21	0.31
D13	0.71	0.65	0.92	0.79
D14	0.81	1.08	1.13	1.75
D15	1.38	1.23	2.53	2.12
D16	0.96	1.00	1.46	1.55
D17	1.17	1.00	1.99	1.54

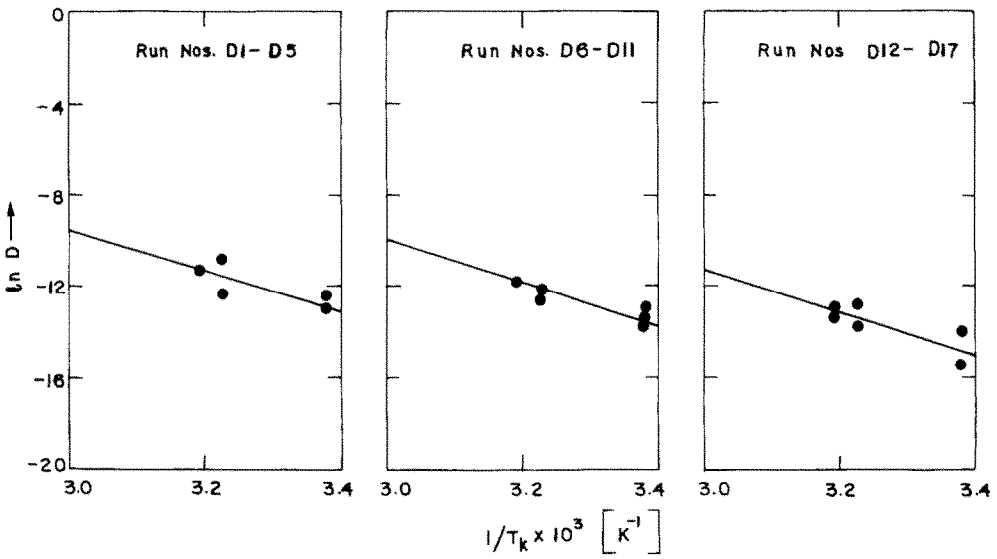

Fig. 4. Plot of ln D versus $1/T_k$ to determine the Arrhenius parameters, E and D_0.

in obtaining the final formulation as well as in the manufacture of drug–resin complex by adsorption assuming that the diffusivity remains the same for adsorption and desorption under otherwise identical conditions.

The proposed method is now tested with available published data of Chaudhary and Saunders (1956) Gyselinck et al. (1981) and Schacht et al. (1982). The data of Gyselinck et al. (1981) and Schacht et al. (1982) were in the form of plots of

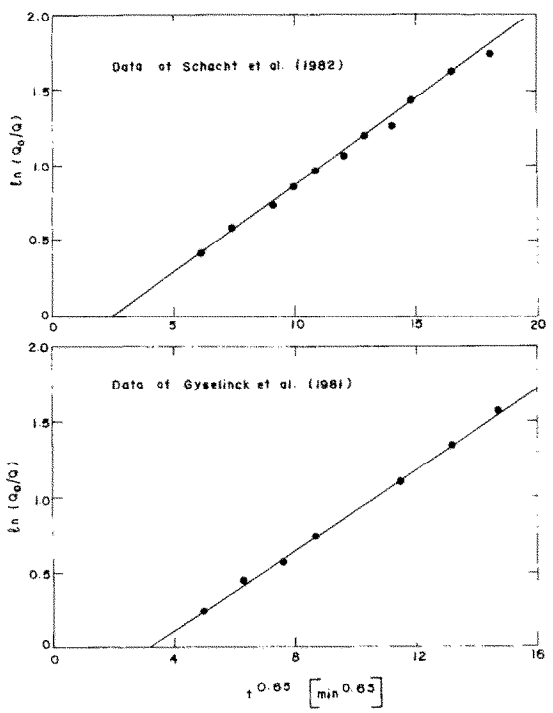

Fig. 5. Testing for particle diffusion control by the new technique.

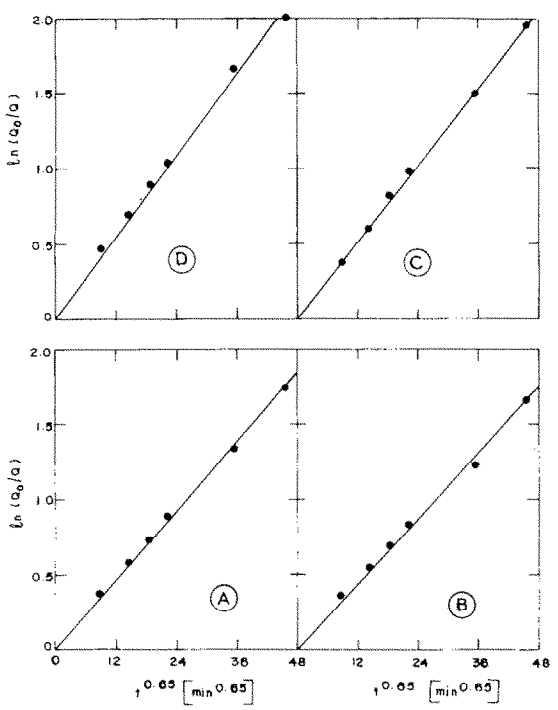

Fig. 6. Testing for particle diffusion control by the new technique (data of Chaudhary and Saunders, 1956).

TABLE 3

SUMMARY OF DIFFUSIVITY VALUES FOR AVAILABLE PUBLISHED DATA

Data from		Slope × 10^2 ($min^{-0.65}$)	Diffusivity × 10^6 (mm^2/min)		Lag time (min)
			Present method	Reported	
Chaudhary et al. (1956)	A	3.85	45.1	66.1	0
	B	3.63	41.3		0
	C	4.28	53.1		0
	D	4.39	55.2		0
Gyselinck et al. (1981)		13.3	6.8	6.2	6.0
Schacht et al. (1982)		11.3	5.3	4.7	4.1

Bt versus t. Values of Bt at different times were obtained from these plots and were then used to calculate fractional dissolution values F with the help of the following equation which follows from Eqn. 3.

$$1 - Q/Q_0 = F = \frac{6}{\pi^{3/2}} Bt - \tfrac{3}{2}(Bt) \qquad (11)$$

The F-values thus obtained at different times are used to obtain the plots of $\ln(Q_0/Q)$ versus $t^{0.65}$ These plots are shown in Fig. 5. These plots also show good straight lines which confirm the validity of Eqn. 7. The experimental data of Chaudhary and Saunders (1956) is plotted in Fig. 6. Interestingly, all the straight lines obtained from the data of Chaudhary et al. (1956) pass through the origin while those obtained with the data of Gyselinck et al. (1981) and Schacht et al. (1982) show about 5 min lag time as also obtained with the present experimental data. The diffusivity values obtained from the experimental data of other workers calculated by the use of present technique and also by the following equation

$$B = 4\pi^2 D/d_p^2 \qquad (12)$$

using the B-values reported by them are summarized in Table 3. The diffusivity values obtained by the two techniques are quite close to each other substantiating the validity of Eqn. 7.

Conclusions

A novel method was presented to evaluate particle diffusion-controlled release of the drug from the resinate. The method is direct, elegant, involves no trial and error and is applicable to any drug–resin complex. Experimental data were reported on metoclopramide–Amberlite system. The method developed was found to be applicable for the present data as well as the data of other drug–resin complexes published by different investigators.

The diffusivity values obtained in the present study were correlated in the form of Arrhenius relation. This can be useful in predicting the behaviour of the drug release as well as in the manufacture of drug–resin complex.

Nomenclature

B	Intermediate variable, min^{-1}
d_p	Resin particle diameter, mm
D_0	Pre-exponential factor, mm^2/min
D	Diffusivity, mm^2/min
E	Energy of activation, J/g mole
F	Fractional dissolution value, dimensionless
n	Integer
P_1-P_4	Parameters in equation developed by Gyselinck et al (1982)

Q_0 Drug content of resinate at time $t = 0$, g/g
Q Drug content of resinate at any time, g/g
R Gas constant, J/g mole k
t Time, min
T_k Temperature on Kelvin scale, K.

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Note

The three technical reports referred above (PTC:84-6, 7 and 85-1) are available from Dr. K. Viswanathan.