Factors influencing drug release from stearic acid based compacts

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Abstract

Fatty acids are potentially suitable carriers for use in the design of drug delivery systems, being biocompatible, biodegradable inexpensive and of low toxicity. The release of the model compound benzoic acid from fatty acid compacts of stearic acid was evaluated using the USP Apparatus 2 dissolution assembly in phosphate buffer pH 7.4. Matrix controlled drug release was expected. Release profiles were approximated by square root of time kinetics. Release rate was independent of stirring speed in the rpm range 50–150, however, at 200 rpm a significant increase in release rate was observed particularly at later times, the amount released versus square root of time plots becoming non-linear. Release was independent of compression pressure in the range 1–7 tons. The particle size of the benzoic acid and stearic acid used had a significant influence on release. The use of particles in the range 250–500 μm gave release rate constants (k, g/cm² per min⁻⁰.⁵) ~ 1.5 greater than those of smaller particle size (63–125 μm). The formation factor (F) tended to increase exponentially with drug loading, the increase being steeper for compacts prepared from the larger particle sizes. At 80% drug loading for large sized systems the matrix appeared to offer little resistance to drug release and F approached one. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Fatty acid carriers; Stearic acid; Benzoic acid; Release mechanism

1. Introduction

Fatty acids have been used previously in the development of drug delivery systems as they are considered to be inert, inexpensive, biocompatible as well as being of a low toxicity. While stearic acid is widely used as a lubricant (Phadke et al., 1994), such excipients have also been employed to produced fatty acid implants containing insulin and shown in diabetic rats to reduce resting blood glucose levels (Wang, 1987). However, in vitro data was not presented in the course of this work, nor was the mechanism of release discussed.

Kaewvichit and Tucker (1994) assessed the in vitro release of the protein bovine serum albumin (BSA) from fatty acid compacts. The amount of drug released was shown to be affected by the particle size of both the drug and fatty acid, the greatest release achieved when both components...
were of a large particle size. Release was anomalous in that it deviated from the expected square root of time diffusion mechanism.

Robson et al. (1999, 2000a) produced stearic acid microspheres containing Cefuroxime axetil, which were found to mask the bitter taste of the drug. While the resultant product is a marketed brand, the release mechanism is still not fully understood. SEM studies revealed changes in the integrity of the microspheres following dissolution in different media. These changes were more pronounced at high pH and were also affected by the composition of the dissolution medium.

In order to clarify the mechanism of release from fatty acid matrices we have systematically investigated the release of the model acidic drug benzoic acid (Ramtoola and Corrigan, 1987; Hastedt and Wright, 1990). Stearic acid is a suitable inert base for forming matrices, showing a low aqueous solubility and a melting point above body temperature.

Higuchi (1963) developed a model to describe drug release from solid matrices where the drug is randomly dispersed throughout the matrix (Eq. 1). In such systems drug is leached by dissolution medium which penetrates the matrix through pores, cracks and intergranular spaces, dissolving the solid drug and then releasing it by diffusion through these solvent-filled pores.

$$Q = \frac{D_0 e}{\tau} (2A - eC_s) C_s t$$ (1)

where $Q$ is the amount of drug released per unit surface area, $D_0$ is the diffusion coefficient of the drug in the dissolution media, $e$ is the porosity of the matrix, $\tau$ is a tortuosity factor, $A$ the content of drug in the insoluble matrix, $C_s$ is the solubility of the drug in the dissolution media and time is $t$.

When $A \gg C_s$ then:

$$Q = k t^{0.5}$$ (2)

where $k = 2AD_0C_s e/\tau$. Thus, drug release from an inert matrix is linearly related to square root of time. The tortuosity factor ($\tau$) accounts for a reduction in the release rate due to increased path length for diffusion, that is, it accounts for the internal pore geometry, in terms of branching and bending of pores.

Siegel et al. (1989) proposed that the terms $e$ and $\tau$, in Eq. (1) be combined producing a single term, the formation factor ($F$) which corresponds to $e/\tau$. The authors define $F$ as a factor, which accounts for the effects of pore geometry and topology on diffusion. The formation factor will be $\leq 1$. A value close to 0 implies that the matrix system has a large retardation effect on drug release. In contrast, a value of $F$ close to 1 suggests that the matrix provides little resistance to drug release. Eq. (2) may, therefore, also be written as:

$$Q = \sqrt{2AC_sD_0Ft}$$ (3)

where $F$ is the ratio of $e/\tau$, and all other parameters are as previously described.

2. Material and methods

2.1. Disc manufacture

Benzoic acid (May & Baker, Dagenham, England) and stearic acid reagent grade, (containing a minimum of 97% stearic/palmitic acid, m.p.: 67–69°C, grade 800673, Merck, Germany) were sieved before use to control the particle size. Unless otherwise stated compacts were prepared from sieve fraction 63–125 μm. Appropriate amounts of drug and carrier material were weighed and placed into amber jars. Mixing was achieved using a Turbula mixer (Glen Creston Ltd, England) at speed 2 for 10 min. Approximately, 200 mg was weighed into a 13 mm punch and die set (Perkin Elmer, England) and compressed at 7 tons for 2 min.

2.2. Dissolution testing

Release studies were performed using the USP apparatus 2 (Sotax AT6 dissolution bath) linked to a UV (Cecil 2020) spectrophotometer fitted with flow through cells, via an Ismatec IPC multi-channel peristaltic pump. An online standard enabled the determination of drug levels by way of Cecil dissolution software. The spectrophotometer was fitted with either 2 or 10 mm Spectrosil® Far UV Quartz window cells. For the majority of
dissolution studies, filtered phosphate buffer pH 7.4 was maintained at 37 °C and agitated at 100 rpm Di-sodium hydrogen phosphate-12-hydrate, sodium dihydrogen phosphate-2-hydrate and sodium chloride (Merck, Germany) were used in appropriate quantities to prepare isotonic phosphate buffer pH 7.4 (Pharmaceutical Handbook, 1980).

Non-linear curve fitting of release data to various mathematical models was achieved using MicroMath® Scientist™ for Windows™. Parameter estimates were generated by the software, the suitability of the model was assessed by the values of the associated statistics, model selection criterion (MSC) and coefficient of determination ($r^2$). The MSC value is a modification of the Akaike Information Criterion (AIC), that is normalised such that it is independent of the scaling of the data points (Scientist User Handbook, 1993).

2.3. Surface texture analysis

Surface texture analysis employed the use of a UBM microfocus measurement system (UBM, Germany). This system comprises a non contact laser profilometer linked to a computer. An area was analysed with a $x$-resolution of 250 parts per mm and a $y$-resolution of 20 parts per mm. Data was levelled and roughness parameters were calculated using specific DOS software. Profiles were obtained before and after dissolution to monitor surface changes as previously described (Healy et al., 1995; Healy and Corrigan, 1996). $R_a$ is the parameter chosen to compare the changes in surface texture with dissolution. It is called the roughness average and is the arithmetic average of the absolute values of all points of the measured surface (Dagnall, 1980).

3. Results and discussion

3.1. Effect of stirring speed

The effect of stirring speed on the release of benzoic acid from stearic acid matrices is shown in Fig. 1, where the quantity released per unit area is plotted versus the square root of time, for 1:1 ratio compacts of benzoic acid and stearic acid. The linearity of the profiles is consistent with matrix controlled release. No significant difference in drug release was observed over the stirring speed range 50–150 rpm, commonly employed in dissolution testing. However, when the medium was agitated at 200 rpm the amount of drug released was higher, especially after $\approx 140$ min where the plot became non linear and there was an obvious increase in slope. After 5 h dissolution

![Fig. 1. Release data for 50% w/w benzoic acid–stearic acid compacts at 50 (●), 100 (■), 150 (▲) and 200 (●) rpm plotted against $t^{0.5}$.](image)
Table 1
IR_\text{a} \text{ values for stearic acid compacts of 50\% w/w benzoic acid loading, agitated at 50, 100, 150 and 200 rpm in phosphate buffer pH 7.4.}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50 rpm</th>
<th>100 rpm</th>
<th>150 rpm</th>
<th>200 rpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR_\text{a} (\mu m)</td>
<td>1.17</td>
<td>1.37</td>
<td>1.73</td>
<td>2.47</td>
</tr>
<tr>
<td>CV (%)</td>
<td>2.56</td>
<td>23.3</td>
<td>39.8</td>
<td>48.2</td>
</tr>
<tr>
<td>AR_\text{a} (\mu m)</td>
<td>10.4</td>
<td>9.47</td>
<td>11.97</td>
<td>13.03</td>
</tr>
<tr>
<td>CV (%)</td>
<td>10.19</td>
<td>3.69</td>
<td>5.4</td>
<td>17.26</td>
</tr>
</tbody>
</table>

at 200 rpm the amount of drug released was \approx 40\% greater than from systems agitated at a lower stirring speed.

Values of surface roughness of compacts are listed in Table 1. IR_\text{a} \text{ values refer to initial measurement recorded before dissolution and AR_\text{a} \text{ values reflect surface roughness after dissolution. Although IR_\text{a} estimates for 100–200 rpm compacts were high, relative to 50 rpm systems, the spread of the data, as reflected by high estimates of coefficient of variation (CV) suggested that surfaces were equally smooth. After dissolution, the surface roughness of all compacts had increased approximately seven-fold reflecting dissolution of benzoic acid from the surface. While higher estimates of AR_\text{a} were obtained for compacts agitated at 150–200 rpm, relative to the lower stirring speeds employed, the differences were not statistically significant.}

3.2. Effect of compaction pressure

The effect of compaction pressures of 1, 3 and 7 tons on drug release was investigated. Fig. 2 shows the average rate of release versus time for compacts prepared at each compaction pressure. The overlapping profiles indicate that the release rate did not vary significantly with compaction pressure.

3.3. Effect of particle size

Initially three particle size ranges were employed (a) 0–63 \mu m, (b) 63–125 \mu m and (c) 125–250 \mu m. Compacts were prepared from drug and stearic acid of equivalent particle size at 20 and 80\% w/w drug loading. Release from compacts of equivalent drug loading was affected by particle size of the components (Fig. 3). The effect of particle size on release was most evident at the 80\% loading as shown by large differences in the amount of drug released after 3 h. The amount released was shown to increase by a factor of

![Fig. 2. Average rate of release from 20\% w/w benzoic acid–stearic acid systems prepared at 1 (.), 3 (■) or 7 (▲) tons compaction pressure versus time (n = 6).](image-url)
approximately 1.3 and 2.1 on increasing particle size from \( a \) to \( b \) and to \( c \), respectively. At the 20% loading, drug release from systems of particle size \( a \) and \( b \) overlapped at time points up to 100 min, marginally greater release resulting from systems of particle size \( b \) beyond this time. In this study the greatest release was achieved from the larger particle size system \( c \). The amount released, per unit exposed surface area \( (Q) \), from compacts of 20% drug loading increased by a factor of approximately 1.2 or 1.5 on changing from systems of particle size range \( a \), to \( b \) or \( c \). These differences are reflected in the values of \( k \) obtained on fitting the profiles to Eq. (2) (Table 2). The values of \( k \) increased systematically with increase in particle size at both loadings. Release from compacts of 80% loading was better described by Eq. (2) than release data at the 20% loading, based on values of MSC and \( r^2 \). With respect to \( k \), the differences seen indicate changes in the ratio of \( e \) to \( \tau \). The data shows that with increasing particle size of the pure components, higher amounts of drug are released, consistent with decreasing \( \tau \). These particle size related trends are consistent with previous reports (Kaewvichit and Tucker, 1994; Millán et al., 1998) which found that particle size, though not a parameter in the Higuchi equation, has a significant effect on drug release.

Since the effect of particle size was dependent on drug loading the study was extended to assess drug release over a greater range of drug loading, using powders of particle size 63–125 \( \mu \)m (small, \( s \)) and 250–500 \( \mu \)m (large, \( l \)). Compacts were prepared with drug and carrier material of equiva-
lent particle size. The amount of drug released increased with increasing drug loading and was in good agreement with $\sqrt{t}$ release (Figs. 4 and 5). Estimates of $k$ and related statistics, for systems of small and large particle size, are summarised in Tables 3 and 4, respectively.

Figs. 4 and 5 show a similar trend in release profiles. For both particle size ranges, release profiles, for systems of 5, 10 and 20% benzoic acid loadings, were low and lay close together while at 80% loading significantly higher amounts of drug were released at a given time. At all drug loadings the amount released, after 3 h, was approximately 1.3 times higher with the larger particle size systems, relative to small particle sized compacts.

A linear relationship was observed between the release rate constants for systems of large and small particle size (Fig. 6). The values of $k$ for large particle sized systems was $\approx 1.5$ times higher than that for small particle sized systems of equivalent drug loading [$y = 1.51x, r^2 = 0.9813$].

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**Fig. 4.** Release data for stearic acid compacts of 5% (○), 10% (■), 20% (▲), 40% (●), 50% (＊), 60% (×) and 80% w/w (+) benzoic acid loading, with both components of particle size 63–125 μm (small) fitted to Eq. (2).

**Fig. 5.** Release data for stearic acid compacts of 5% (○), 10% (■), 20% (▲), 40% (●), 50% (＊), 60% (×) and 80% w/w (+) benzoic acid loading, with both components of particle size 250–500 μm (large) fitted to Eq. (2).
Table 3
Estimates of $k$ (g/cm² per min⁰.⁵) and statistics obtained for benzoic acid release from stearic acid compacts of 5–80% w/w benzoic acid loading, with both components of particle size 63–125 μm (s), fitted to Eq. (2)

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>40% s</th>
<th>50% s</th>
<th>60% s</th>
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<tbody>
<tr>
<td>$K$</td>
<td>$0.817 \times 10^{-4}$</td>
<td>$1.3 \times 10^{-4}$</td>
<td>$6.9 \times 10^{-4}$</td>
<td>$9.6 \times 10^{-4}$</td>
<td>$9.4 \times 10^{-4}$</td>
</tr>
<tr>
<td>S.D.</td>
<td>$9.39E^{-7}$</td>
<td>$1.05E^{-6}$</td>
<td>$4.84E^{-6}$</td>
<td>$5.98E^{-6}$</td>
<td>$8.3E^{-6}$</td>
</tr>
<tr>
<td>SS</td>
<td>$2.71E^{-8}$</td>
<td>$3.39E^{-8}$</td>
<td>$7.22E^{-7}$</td>
<td>$1.1E^{-6}$</td>
<td>$2.12E^{-6}$</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.986</td>
<td>0.994</td>
<td>0.995</td>
<td>0.996</td>
<td>0.994</td>
</tr>
<tr>
<td>MSC</td>
<td>4.08</td>
<td>4.61</td>
<td>4.95</td>
<td>5.23</td>
<td>4.64</td>
</tr>
</tbody>
</table>

Table 4
Estimates of $k$ (g/cm² per min⁰.⁵) and statistics obtained for data from stearic acid compacts of 5–60% w/w benzoic acid loading, with both components of particle size 250–500 μm (l), fitted to Eq. (2)

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>10% l</th>
<th>40% l</th>
<th>50% l</th>
<th>60% l</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K$</td>
<td>$0.88 \times 10^{-4}$</td>
<td>$1.7 \times 10^{-4}$</td>
<td>$8.8 \times 10^{-4}$</td>
<td>$11 \times 10^{-4}$</td>
<td>$16 \times 10^{-4}$</td>
</tr>
<tr>
<td>S.D.</td>
<td>$7.64E^{-7}$</td>
<td>$1.33E^{-6}$</td>
<td>$1.64E^{-5}$</td>
<td>$1.52E^{-5}$</td>
<td>$1.74E^{-6}$</td>
</tr>
<tr>
<td>SS</td>
<td>$1.79E^{-8}$</td>
<td>$5.4E^{-8}$</td>
<td>$8.28E^{-6}$</td>
<td>$7.09E^{-6}$</td>
<td>$9.32E^{-6}$</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.990</td>
<td>0.994</td>
<td>0.954</td>
<td>0.976</td>
<td>0.986</td>
</tr>
<tr>
<td>MSC</td>
<td>4.37</td>
<td>4.71</td>
<td>2.75</td>
<td>3.46</td>
<td>3.91</td>
</tr>
</tbody>
</table>

Fig. 6. The release rate constant, $k$, (g/cm² per min⁰.⁵) for large particle sized systems (250–500 μm) versus $k$ (g/cm² per min⁰.⁵) for small particle sized systems (63–125 μm), of stearic acid compacts containing 5–80% w/w benzoic acid.

Using known values for $D_0$ ($7.42 \times 10^{-4}$ cm²/min Ramtoola and Corrigan, 1987), $C_s$ (0.01204 g/cm³) and $A$, estimates of $F$ were determined by fitting data to Eq. (3) and these are summarised in Table 5. The trend for $F$ versus drug loading and particle size is depicted in Fig. 7. Estimates of $F$ tended to increase nonlinearly with increased drug loading. At 5% drug loading, $F$ was practically identical for systems of small and large particle size. However, at all other drug loadings, $F$ for large sized systems was consistently higher than for the respective small sized systems, ranging from 1.3 to 2.9 times greater. At 80% drug loading for large sized systems the matrix appeared to
offer little resistance to drug release and \( F \) was close in value to 1.

The non-linear profiles illustrated in Fig. 7 indicated that changes in \( \tau \) were not proportional to changes in \( \varepsilon \). The relationship between \( F \) and drug loading, for both particle sized systems was fitted by an exponential equation.

Siegel and Langer (1990) observed that drug release from a matrix occurs primarily through a network of pores created by soluble drug particles. At higher drug loading the connective network spans a greater area of the matrix, thereby lowering the tortuosity. High porosity estimates result with increasing loading, as the soluble fraction of the matrix is increased. The values of \( F \), therefore, tend towards 1, as high porosity is coupled with low tortuosity.

Percolation thresholds were calculated for small and large systems in accordance with the method defined by Bonny and Leuenberger (1991). Estimates of \( p_{c1} \) were determined from the linear portion of plots of \( \beta \) versus \( \varepsilon \). For small systems, \( p_{c1} \) was 0.34 and for large systems the value was 0.32. In terms of drug loading, these critical porosities correspond to a drug loading of slightly greater than 40% w/w for small systems, and just below 40% w/w for large systems. Identification of the percolation threshold is an important preformulation tool as above \( p_{c1} \) release from a system is in agreement with Higuchi \( \sqrt{t} \) kinetics (Leuenberger et al., 1990). The values of \( p_{c1} \) determined, are reflected in the changes in \( F \) with drug loading, where at loadings below \( p_{c1} \), increasing the drug loading yields minimal increases in \( F \) (Fig. 7). At drug loadings above \( \approx 40\% \) w/w, in which the critical porosity has been exceeded, the values of \( F \) rise exponentially with increasing drug loading.

In conclusion solid fatty acids may be used as matrix carriers in the preparation of extended

<table>
<thead>
<tr>
<th>Parameters</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A ) (g/cm(^3))</td>
<td>0.052</td>
<td>0.104</td>
<td>0.215</td>
<td>0.446</td>
<td>0.602</td>
<td>0.723</td>
<td>1.004</td>
</tr>
<tr>
<td>( F ) (Small)</td>
<td>0.007</td>
<td>0.009</td>
<td>0.018</td>
<td>0.059</td>
<td>0.086</td>
<td>0.068</td>
<td>0.348</td>
</tr>
<tr>
<td>( F ) (Large)</td>
<td>0.008</td>
<td>0.016</td>
<td>0.032</td>
<td>0.097</td>
<td>0.112</td>
<td>0.199</td>
<td>0.838</td>
</tr>
</tbody>
</table>

Fig. 7. Estimates of \( F \) as determined from Eq. (3), plotted against drug loading for stearic acid compacts of 5–80\% w/w benzoic acid loading, with both components of particle size 63–125 \( \mu \mathrm{m} \) (small) (●) and 250–500 \( \mu \mathrm{m} \) (large) (■).
release dosage forms. Dissolution profiles were approximated by square root of time kinetics, consistent with matrix controlled release. Release rate was independent of stirring speed in the rpm range 50–150, however, at 200 rpm a significant increase in release rate was observed particularly at later times, the amount released versus square root of time plots becoming non-linear. This increase in release rate suggests an alteration to the physicochemical properties of the matrix material, possibly leading to some erosion at later times. Interestingly Robson et al., (2000a,b) observed buffer dependent changes in stearic acid based cefuroxime axetil microspheres following dissolution and suggested the generation of a new physical or chemical species. Fatty acid soap formation is a possibility and may be contributing to the anomalous release observed at the higher stirring speed. Release was also independent of compression pressure in the range 1–7 tons. The particle size of the benzoic acid and stearic acid used had a significant influence on release and compacts prepared from particles in the range 250–500 μm gave release rate constants (k, g/cm² per min⁰.⁵) ~1.5 greater than those of smaller particle size (63–125 μm). The formation factor (F) tended to increase exponentially with drug loading, the increase being steeper for compacts prepared from the larger particle sizes.

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