Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 316 (2006) 47–51
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Effect of soluble filler on drug release from stearic acid based compacts

Bronagh U. Killen [a,b], Owen I. Corrigan [a,*]

[a] School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland
[b] Servier Laboratories, West Pier Business Campus, Old Dunleary Rd, Dun Laoghaire Co., Dublin, Ireland

Received 29 June 2005; received in revised form 27 January 2006; accepted 17 February 2006
Available online 5 April 2006

Abstract

Fatty acids are potentially suitable carriers for use in the design of drug delivery systems, being biocompatible, biodegradable, of low toxicity inexpensive, with drug release being approximately proportional to the square root of time. However, at low drug loadings, below the critical percolation threshold, release is likely to be extremely slow and incomplete. To overcome these problems, we have investigated the use of increasing amounts of the soluble filler lactose on drug release. Benzoic acid and insulin were used as model low and high molecular weight drugs, respectively. At a 10% loading, benzoic acid was an order of magnitude higher than that observed for insulin. Using lactose as soluble filler, it was possible to effect greater release with increasing lactose content in the range 10–50%. Values of F, the formation factor, increased, but not to the same extent as for increased drug loading. The Higuchi release rate constant, k, was similar at lactose loadings of 5–20%, but increased rapidly at higher lactose loadings. Quantitatively, the addition of lactose yielded release rate constants 1.2–3.6 times greater than the value for lactose-free compacts in the case of benzoic acid and two- to five-fold in the case of insulin. A linear relationship was demonstrated between k, and the percentage soluble fraction of the matrix above the percolation threshold.

Keywords: Drug release; Insulin; Benzoic acid; Stearic acid; Lactose filler

1. Introduction

Fatty acids have been investigated as carriers for the development of delivery systems as they are considered to be inert, inexpensive and biocompatible. Traditionally, stearic acid is widely used as a lubricant (Phadke et al., 1994). More recently, such excipients have been employed to produce solid fatty acid implants containing insulin and shown in diabetic rats to reduce resting blood glucose levels (Wang, 1987, 1989, 1991). Kaewvichit and Tucker (1994) assessed the in vitro release of the protein bovine serum albumin from fatty acid compacts. The amount of drug released was shown to be affected by the particle size of drug and fatty acid, the greatest levels 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) 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 (Robson et al., 2000a,b).

Under sink conditions drug release (Q) from an inert matrix is linearly related to square root of time, i.e. $Q = kt^{0.5}$ (Higuchi, 1963). Siegel et al. (1989) defined the formation factor (F) as a parameter, which accounts for the effects of pore geometry and topology on diffusion. F will be ≤ 1 and the closer the value is to 0, the greater the retardation effect on drug release. In contrast, a value of F close to 1 suggests that the matrix provides little resistance to drug release. F will increase with drug loading and particle size (Killen and Corrigan, 2001). When the loading (A) is $\gg$ solubility (C_s), drug release will be described by Eq. (1):

$$Q = \sqrt{2AC_sD_0Ft} \quad (1)$$

A more general form of Eq. (1) is

$$Q = kt^n \quad (2)$$

Values of n greater than 0.5 reflect anomalous non-Fickian diffusion (Ritger and Peppas, 1987). Previously, we examined the mechanism of release from stearic acid compacts using the

* Corresponding author. Tel.: +353 1 6082782; fax: +353 1 6082783.
E-mail address: ocorrign@tcd.ie (O.I. Corrigan).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.02.048

model drug benzoic acid. Release profiles were approximated by square root of time kinetics, independent of the dissolution apparatus stirring speed, the compression pressure above 75 MPa, but dependent on particle size, larger values of F being observed using the larger size particles.

At drug loadings below the percolation threshold (pc_1) (~40% benzoic acid loading), a significant amount of drug may be entrapped within the insoluble matrix, resulting in incomplete drug release (Killen and Corrigan, 2001). Thus, at low drug loadings release is greatly retarded and incomplete. This limits the potential use of these matrices for the delivery of low doses of potent drugs, often a feature of biotechnology products. The purpose of this work was to explore the potential use of a soluble filler to enhance the rate and extent of drug release at low drug loading. Lactose was used as the soluble filler and benzoic acid and insulin as model drugs.

2. Experimental

2.1. Disc manufacture

Appropriate amounts of benzoic acid (May and Baker, Dagenham, England) and carrier material (stearic acid reagent grade, Merck, Germany) were weighed and placed in amber jars with lactose monohydrate (Riedel de Haën, Germany) where appropriate. These systems were prepared with all components of particle size 63–125 μm. Mixing was achieved using a Turbula mixer (Glen Creston Ltd., England) at speed 2 for 10 min as previously described (Killen and Corrigan, 2001). Approximately, 200 mg was weighed into a 1.3 cm punch and die set (Perkin-Elmer, England) and compressed at 517 MPa for 2 min.

In the case of insulin (bovine insulin, Sigma), discs of 0.3 cm diameter were prepared using a 0.3 cm punch and die set at compression force of 1387 MPa. Discs produced weighed approximately 10 mg. It was necessary to scale down batch production for the systems containing insulin and a Whirlimixer, rather than the Turbula mixer (42 rpm) was employed in the mixing stage. The average particle size of the insulin was 9.83 μm as determined by light microscopy. The stearic acid (grade 1, Sigma Chemical Co., USA) as received had an average particle size of 300 μm and was size reduced to ≈15 μm using a Retsch ball mill. Lactose of average particle size 19.1 μm, was used.

2.2. Dissolution testing

Drug release was measured, under sink conditions, in phosphate buffer pH 7.4 at 37 °C.

2.2.1. Benzoic acid

Studies were performed in a Sotax AT6 dissolution bath linked to a Cecil 2020 UV 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 0.2 or 1 cm Spectrosil® Far UV Quartz window cells depending on the absorbance values being measured. The dissolution medium (1000 ml) was phosphate buffer pH 7.4 at 37 °C and agitated at 100 rpm (Killen and Corrigan, 2001).

Non-linear curve fitting of release data was achieved using MicroMath® Scientist™ for Windows™. Parameters estimates, standard deviation were generated by the software, the suitability of the model represented by the values of the associated statistics, i.e. the model selection criterion (MSC) and coefficient of determination (r^2) (Killen and Corrigan, 2001).

2.2.2. Insulin method

Because of the low dose and the large volume of dissolution medium used in the above method, this conventional dissolution apparatus was not appropriate for the smaller matrices of insulin and stearic acid.

A volume (5 ml) of phosphate buffer was accurately pipetted into glass vials. Sealed vials were placed in a Precision reciprocal shaking water bath (M25) set at 37 °C (Precision Scientific, USA). Flasks were shaken horizontally at 100 cycles per minute. At regular intervals, the individual compacts were removed using tweezers and placed into fresh buffer. Samples were assayed by HPLC.

The HPLC assay was based on a method reported by Soriano et al. (1996) and Khaska et al. (1998). Beckman System Gold equipment was used, consisting of a programmable 126 solvent module and 166 detector module, with samples injected via a Shimadzu SIL-9A automated sampler. A Vydac 218TP C_{18} reversed-phase column (5 μm, 15 cm × 0.46 cm) was used, which is specific for identification of polypeptides. The column was eluted with mobile phase consisting of a mixture of 74 parts of 0.2 M sodium sulphate anhydrous adjusted to pH 2.3 with phosphoric acid and 26 parts of acetonitrile. The mobile phase and all cleaning solutions were filtered under vacuum through 0.2 μm nylon membranes. The flow rate was set at 1 ml/min and the UV detector monitored the response at $\lambda = 214$ nm. The retention time of insulin in phosphate buffer pH 7.4 was approximately 5 min. Standard solutions were freshly prepared in triplicate and appropriate dilutions made. The relationship between AUC and insulin concentration was linear in the concentration range employed.

3. Results and discussion

3.1. Effect of soluble filler on benzoic acid release

At drug loadings below the percolation threshold (pc_1) a significant amount of drug may be entrapped within the insoluble matrix, resulting in incomplete drug release. In preliminary studies using stearic acid matrices of 20% benzoic acid loading, only ~50% of the drug load was released after 15 h. The incorporation of lactose, as a soluble filler was investigated in order to alter the effective porosity of low loadings, thereby increasing the rate of release and encouraging more complete release. Matrices were composed of 10% drug and a lactose content ranging from 5% to 50%. The release profiles (Fig. 1) indicate that as expected, the inclusion of increasing amounts of lactose brings about increased release. Systems of 50% lactose showed a change in release profile around 140 min, where the rate of

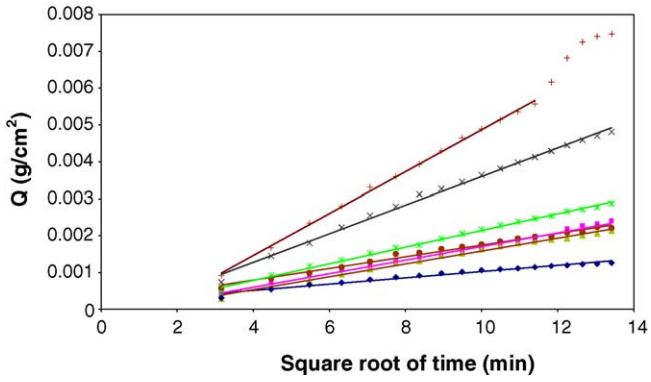

Fig. 1. Release data for benzoic acid from stearic acid compacts of 10% (w/w) benzoic acid loading, with a lactose content of 0% (♦), 5% (■), 10% (▲), 20% (●), 30% (*), 40% (×) and 50% (w/w) (+), plotted vs. the square root of time.

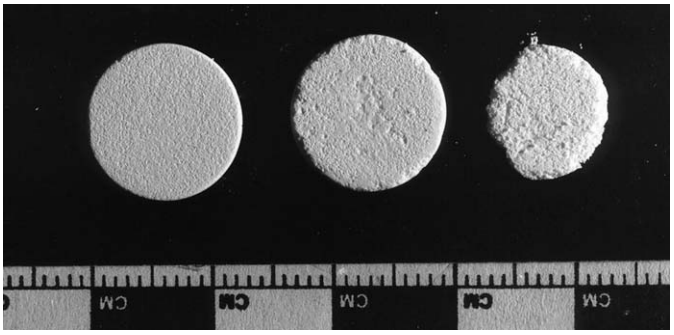

Fig. 2. Photographs of stearic acid compacts containing 10% (w/w) benzoic acid and a lactose content of 5%, 30% and 50% (w/w), after 3 h dissolution in phosphate buffer pH 7.4 (left to right).

drug release increased significantly. This may relate to matrix erosion, which was evident following dissolution. Photographs of 5%, 30% and 50% lactose containing discs following 3 h of drug release are shown in Fig. 2. An increase in surface roughness occurred with increased lactose content. Also a change in disc diameter, reflecting erosion, was evident for systems containing 50% lactose, relative to discs containing 5% or 30% lactose. Release data was fitted to Eq. (2), with n fixed at 0.5. It was evident that the presence of lactose increased release in all systems even at 5% loading. Estimates of k, the Higuchi release rate constant, and statistics relating to the fit are listed in Table 1. The value of k was very similar at lactose contents of 5–20%. Beyond this loading, however, the release rate became increasingly large. At lactose loadings of 30%, 40% and 50%, k was approximately 1.6, 2.8 and 3.6 times greater, respectively, than for lactose-free systems.

In Fig. 3, the relationship between k and soluble fraction (%, w/w), i.e. drug plus lactose is shown. Above the percolation threshold (pc_1), as the lactose content increases k increases, reflecting the increase in F (Eq. (1)). Dissolution of lactose encourages pore formation and enables faster penetration of medium and release from a more porous matrix.

Release of theophylline from a Precirol® (glycerol palmitostearate) matrix containing varying amounts of mannitol was studied (Parab et al., 1986). The quantity of drug released was linear with $\sqrt{t}$, suggesting that drug release was in agreement with the *Higuchi* model. The inclusion of mannitol, a soluble excipient, increased the amount of drug released, relative to mannitol-free compacts. The fraction of mannitol contained was proportional to increases in the $\sqrt{t}$ release rate constant. Values of the $\sqrt{t}$ release rate constant are also plotted versus soluble fraction in (Fig. 3). A similar trend of a linear increase in the release rate constant with the inclusion of mannitol in Precirol® matrices, is evident.

Also shown in Fig. 3 is the corresponding change in k with drug loading (taken from Killen and Corrigan, 2001). The slope of the release rate constant (k, g/min$^{0.5}$) versus % soluble fraction is approximately two to three times steeper with increasing drug loading than with increasing lactose content. This can be explained in terms of changes in both F and A (Eq. (1)), both of which increase with benzoic acid loading, but only the former with increasing lactose. The critical porosity for benzoic acid/stearic acid systems was close to a drug loading of 40% (w/w) (Killen and Corrigan, 2001). Therefore, at drug loadings

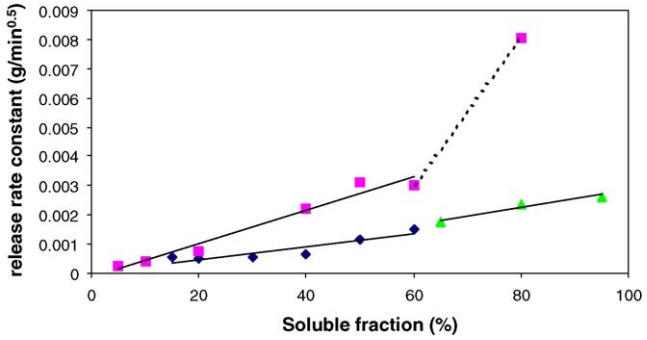

Fig. 3. The $\sqrt{t}$ release rate constant, plotted against % soluble fraction for stearic acid compacts of 10% (w/w) benzoic acid loading and lactose content of 0–50% (w/w) (♦) and lactose-free systems of 5–80% (w/w) benzoic acid loading (■), and Precirol® (glycerol palmito-stearate) matrices containing 50% theophylline and 15–45% (w/w) mannitol (▲) (Parab et al., 1986).

Table 1
Estimates of the Higuchi release rate constant (k) (g/cm^2/min$^{0.5}$) and statistics obtained for release data from stearic acid compacts of 10% (w/w) benzoic acid loading and a lactose content of 0–50% (w/w)

Parameters	0%	5%	10%	20%	30%	40%	50%[a]
k	1.3×10^{-4}	1.7×10^{-4}	1.6×10^{-4}	1.7×10^{-4}	2.1×10^{-4}	3.6×10^{-4}	4.7×10^{-4}
S.D.	1.05×10^{-6}	1.02×10^{-6}	1.59×10^{-6}	1.72×10^{-6}	1.39×10^{-6}	2.77×10^{-6}	8.98×10^{-6}
SS	9.12×10^{-8}	3.23×10^{-8}	7.74×10^{-8}	9.12×10^{-8}	5.99×10^{-8}	2.35×10^{-7}	7.55×10^{-7}
r^2	0.991	0.996	0.990	0.988	0.995	0.994	0.976
MSC	4.62	5.31	4.38	4.17	5.19	4.88	3.65

[a] For systems of 50% lactose, k was based on release data up to 120 min.

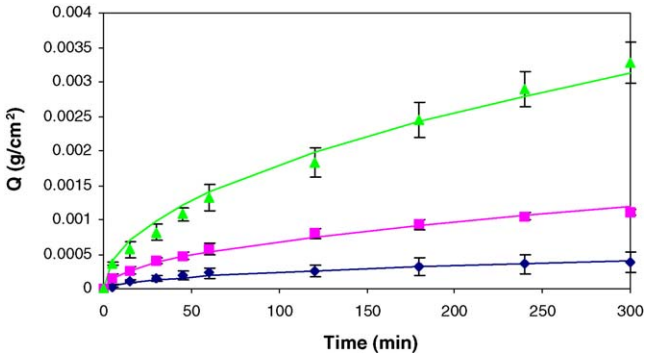

Fig. 4. Insulin release vs. time profiles from 0.3 cm stearic acid-insulin compacts of 10% (♦), 20% (■) and 30% (w/w) (▲) insulin loading.

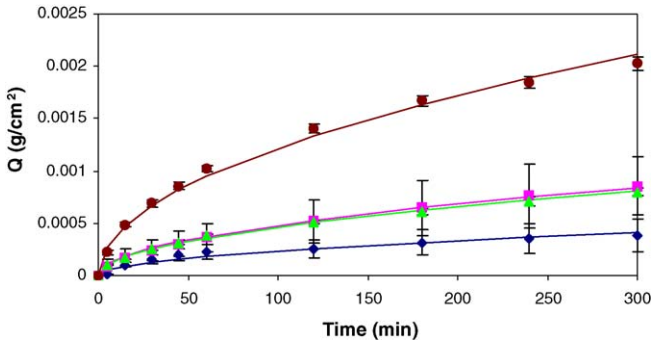

Fig. 5. Insulin release from stearic acid compacts of 10% (w/w) insulin loading and a lactose content of 0% (♦), 10% (■), 20% (▲) and 50% (w/w) (●).

greater than 40% (w/w) complete drug release was possible. The effect of overcoming the percolation threshold is demonstrated in Fig. 3, where at low drug loading the difference in k between drug and drug/lactose systems is minimal but sharply increases from 40% drug loading upwards.

The value of F was estimated for these systems, substituting known parameter values into Eq. (1). The trend in F-values was similar to the trend for k-values whereby values for systems of 5–20% lactose content were similar and steadily increased for higher lactose loadings. Lactose was therefore affecting pore formation such that greater drug release was facilitated.

Data was also fitted to Eq. (2) and yielded values of the exponent, n, which were higher for compacts containing lactose, than for lactose-free compacts. In systems of 50% lactose loading, n was 0.63, in contrast to 0.46, as determined for lactose-free systems. Release from compacts containing lactose was therefore tending towards a zero order profile.

3.2. Effect of soluble filler on Insulin release

Compacts of 3 mm diameter were produced from bovine insulin and stearic acid. The discs obtained weighed 10 mg on average and contained 10%, 20% or 30% drug. Release studies showed increasing release with increasing drug load (Fig. 4). At a loading of 10%, the release of insulin per unit surface area was much less than that observed for benzoic acid at the same loading, the differences reflecting the different diffusivities and solubilities of the two compounds. The amount of drug released after 5 h, increased by a factor of approximately 3 on increasing drug loading from 10% to 20%, and was nine times higher for systems of 30%, relative to 10% systems. The release rate constant increased by a factor of 2.8 on increasing drug loading from 10% to 20% and by a factor of ≈8 when the loading was increased from 10% to 30%, consistent with three- and nine-fold differences in the amount of drug released after 5 h, respectively.

The effect of adding lactose, at 10%, 20% and 50% loading, was investigated and the release profiles are shown in Fig. 5. As with the benzoic acid systems, the inclusion of lactose promoted greater release. For compacts of 10% insulin, the addition of 10–20% lactose yielded a similar increase in the amount of drug released, while at 50% lactose much greater release was seen. The release rate constant, k, increased by a factor of ≈2 or 5 on adding 10–20% or 50% lactose, respectively (Table 2). Comparable enhancements in the release rate constant, on the addition of lactose, were seen with the compacts of benzoic acid and stearic acid, as shown previously. These findings are consistent with those of, Kaewvichit and Tucker (1994) who, using sodium chloride as filler, observed a linear relationship between the soluble filler loading and the amount of bovine serum albumin released from stearic acid matrices. More recently, Pongjanyakul et al. (2004) showed that the inclusion of the soluble fillers PEG 4000 and Gelucire 50/13 in melted glyceryl palmitostearate (GPS) pellets increased lysozyme release and ascribed the effect to the achievement of interconnecting hydrophilic channels throughout the GPS matrix. The in vivo performance of insulin containing lactose-stearic acid implants is under evaluation.

Table 2
Estimates of k and statistics for release data from stearic acid compacts of 10% (w/w) insulin and a lactose content from 0% to 50% (w/w)

Parameters	0%	10%	20%	50%
k (g/cm^2/min$^{0.5}$)	2.38×10^{-5}	4.84×10^{-5}	4.64×10^{-5}	12.0×10^{-5}
S.D. for k	8.86×10^{-7}	5.03×10^{-7}	2.66×10^{-7}	17.3×10^{-7}
SS	7.03×10^{-9}	2.27×10^{-9}	6.34×10^{-10}	2.66×10^{-8}
r^2	0.987	0.999	0.999	0.998
MSC	2.94	5.62	6.72	4.89

4. Conclusions

Using lactose as a soluble filler, it was possible to effect greater release from drug-fatty acid systems with increasing filler content. Values of F were increased, but not to the same extent as for increased drug loading. The release rate constant, k, was similar in the lactose loading range of 5–20%, but increased rapidly at higher lactose loadings. Quantitatively, the addition of lactose yielded release rate constants 1.3–3.6 times greater than the value for lactose-free compacts. A linear relationship was demonstrated between k, and the percentage soluble fraction of the matrix.

References

Higuchi, T., 1963. Mechanism of sustained-action medication, theoretical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Kaewvichit, S., Tucker, I.G., 1994. The release of macromolecules from fatty acid matrices: complete factorial study of factors affecting release. J. Pharm. Pharmacol. 46, 708–713.

Khaska, G., Nalini, K., Bhat, M., Udupa, N., 1998. High-performance liquid chromatographic determination of insulin in rat and human plasma. Anal. Biochem. 260, 92–95.

Killen, B.U, Corrigan, O.I., 2001. Factors influencing drug release from stearic acid based compacts. Int. J. Pharm. 228, 189–198.

Parab, P.V., Oh, C.K., Ritschel, W.A., 1986. Sustained release from Precirol® (glycerol palmito-stearate) matrix. Effect of mannitol and hydroxypropyl methylcellulose on the release of theophylline. Drug Dev. Ind. Pharm. 12, 1309–1327.

Phadke, D.S., Keeney, M.P., Norris, D.A., 1994. Evaluation of batch-to-batch and manfacturer-to-manufacturer variability in the physical properties of talc and stearic acid. Drug Dev. Ind. Pharm. 20, 859–871.

Pongjanyakul, T., Medlicott, N.J., Tucker, I.G., 2004. Melted glyceryl palmitosterate (GPS) pellets for protein delivery. Int. J. Pharm. 271, 53–62.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release I., Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinder or discs. J. Control. Release 5, 23–36.

Robson, H.J., Craig, D.Q.M., Deutsch, D., 1999. An investigation into the release of cefuroxime axetil from taste-masked stearic acid microspheres, part 1, the influence of the dissolution medium on the drug release profile and the physical integrity of the microspheres. Int. J. Pharm. 190, 183–192.

Robson, H.J., Craig, D.Q.M., Deutsch, D., 2000a. An investigation into the release of cefuroxime axetil from taste-masked stearic acid microspheres, part 11. The effect of buffer composition on drug release. Int. J. Pharm. 195, 137–145.

Robson, H., Craig, D.Q.M., Deutsch, D., 2000b. An investigation into the release of cefuroxime axetil from taste-masked stearic acid microspheres part 111. The use of DSC and HSDSC as means of characterising the interaction of the microspheres with buffered media. Int. J. Pharm. 201, 211–219.

Siegel, R.A., Kost, J., Langer, R., 1989. Mechanistic studies of macromolecular drug release from macroporous polymers I, experiments and preliminary theory concerning completeness of drug release. J. Control. Release 8, 223–236.

Soriano, I., Evora, C., Llabrés, M., 1996. Preparation and evaluation of insulin-loaded poly(DL-lactide) microspheres using an experimental design. Int. J. Pharm. 142, 135–142.

Wang, P., 1989. Lipids as excipient in sustained release insulin implants. Int. J. Pharm. 54, 223–230.

Wang, P., 1991. Palmitic acid as an excipient in implants for sustained release of insulin. Biomaterials 12, 57–62.

Wang, P., 1987. The reliability of a compressed mixture of insulin and palmitic acid to sustain a reduction in hyperglycaemia in rodents. Trans. Am. Soc. Artif. Intern. Organs 33, 319–322.