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CONTROLLED RELEASE FROM GLYCEROL PALMITO-STEARATE MATRICES PREPARED BY DRY-HEAT GRANULATION AND COMPRESSION AT ELEVATED TEMPERATURE

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ABSTRACT

Diprophylline release from glycerol palmito-stearate "precirol" matrices containing different direct compression (DC) excipients, with variable dissolving/disintegrating ability, is investigated. The matrices are formed by employing dry-heat granulation and compression at elevated temperature.

Greater drug release prolongation is achieved with the dissolving DC excipients than with the swelling ones. The release is described on the basis of two bi-exponential first order models and the Weibull function as well.

The effect of compression conditions (temperature and pressure) on the drug release is found to be related to the compaction behaviour of the DC excipients, i.e. plastic deformation or fragmentation.

INTRODUCTION

Glycerol palmito-stearate "precirol" is a low melting point material which has been used for the preparation of sustained release dosage forms, both inert and erodible matrices, for oral administration. For the preparation of these matrices compaction of mixtures containing drugs, precirol and other excipients is usually employed.The release

of the drugs from such matrices is controlled through both diffusion and erosion mechanisms and has been found to be greatly modified by the added excipients and the processing conditions[1 - 6], especially the temperature[7].

The added excipients either produce a wetting action by displacing the air present in the pores of the matrix or interrupt the matrix due to dissolution or disintegration and increase the release. The direct compression (DC) excipients provide the simplest possible approach to compact manufacture. During compression heat generation at points of contact[8] possibly results in the melting and subsequent resolidification of particle asperities at temperatures below the conventional melting point of the materials concerned[9]. Furthermore, temperature changes during compression may cause great changes in tablet properties, especially when low m.p. or thermoplastic excipients are involved[10,11]. Therefore it was considered appropriate to examine the effect of some processing conditions, in particular dry-heat granulation and compression at elevated temperature, on the drug release from precirol-/DC excipient matrices in relation to the dissolving/disintegrating ability of the excipients. For this purpose precirol, diprophylline and some DC excipients are physically mixed and the resulting mixtures are slugged and tableted either directly or after dry-heat granulation (fusion) by massing at 65°C (10°C above the m.p. of precirol). Tableting is performed either at room (25°C) or at elevated temperature (45°C or 10°C below the m.p. of precirol) at two levels of compression pressure.

MATERIALS AND METHODS

Materials

Diprophylline (Rorer, East Sussex, G.B.) was selected as the model drug entity. Glycerol palmito-stearate (Precirol ATO 5, m.p. 52-55°C, Gattefossé, St. Priest, France) was the main matrix forming material. Both these materials were utilized at a 33.3% level. At the same level (33.3% by weight) the following DC excipients were added: spray dried hydrous lactose, SDL, (DMV, Veghel, The Netherlands); Emdex, which is dextrates in hydrated form (Edward Mendell,

TABLE 1

Dissolution/Disintegration time, in distilled water 36°C, of DC excipients tableted at 140 MPa pressure.

D.C. Excipient	Dissolution/Disintegration time (min)
Spray Dried Lactose (SDL)	0.1
Emdex	3
SDL and Avicel	15
Emdex and Avicel	30
Avicel	>240

N. York, U.S.A.) and microcrystalline cellulose (Avicel pH 101, Vanderbilt, RT Co, Norwalk, Connecticut, U.S.A.). Combinations of Avicel with spray dried lactose (SDL) and Emdex, in equal quantities (15,15% w/w) were also used. The dissolving/disintegrating ability of DC excipients tableted at 140 MPa is given in Table 1.

Powder mixing and granulation

100 g batches of Diprophylline, Precirol and D C excipients (3X100 g) were mixed together in a turbula mixer for 30 min at 50 rpm. The degrees of mixedness[12] were determined spectrophotometrically at 263 nm and were >0.96. Half the amount of each powder mixture (150 g) was stored at 55% RH and the other half was granulated by transferring and stirring thoroughly in a round-bottomed stainless steel bowl on a water bath, thermostated at 65°C to melt the precirol. The plastic powder mass was passed through a 1.6 mm stainless steel sieve and the resulting granules were stored at 55% RH until used.

Powder Compaction

Slugs and tablets were prepared from the simple (physical) mixtures and the dry-heat granulations as well. Slugs were formed at room temperature by placing 300 mg of powder in a 7 mm diameter flat faced punch and die set and applying 40 N load on the upper

punch. Tablets were compressed in a hydraulic press using 12 mm diameter flat faced punches and a die which were lubricated with a suspension of magnesium stearate in chloroform. For the compression at 45°C, 300 mg samples of the powder mixtures were placed in 5 ml sealed glass vials and were heated in an oven until they reached the required temperature. The punches and the die were also preheated in the oven. The powder mixtures were quickly emptied into the die with the lower punch prefixed and the upper punch then was inserted. The filled punch and die set was kept in the oven for 10 minutes more and afterwards transferred quickly in the hydraulic press. Compression pressures of 50 and 140 Mpa were applied for 10 seconds to the upper punch by lowering the hydraulic ram at a rate of 1.5 mm/sec. All the resulting slugs and tablets were subjected to a drug release test after 24 hour storage at room temperature and 55% RH.

In vitro drug release testing

A standard USP (Method II) dissolution apparatus (Pharmatest type - PTW/SII, Haiburg, F.G.R) was employed. The dissolution medium was 900 ml of distilled water. It was stirred at 50 rpm. Aliquots were withdrawn at 15, 30, 60, 90, 120 min and then at 1h intervals up to 12 hours. Diprophylline content was measured spectrophotometrically at 263 nm after filtration. Each release determination was carried in quadruplicate.

RESULTS AND DISCUSSION

The slugs and tablets which were prepared from the physical (simple) mixtures did not show satisfactory release prolongation. From all the formulations 80% of diprophylline was released in less than 4 hours, while it is known that for a 12 hour dosage form the release could be characterized as optimum if it is in the range of 60-80% by 8 hours. Also, the uncompacted dry-heat granulations gave, in general, fast drug release. It was always faster than that obtained from tablets or corresponding simple mixtures depicted in Fig 1a.

The cumulative percent diprophylline release vs time from slugged dry-heat granulations is shown in Fig 1b. It is seen that incorporation

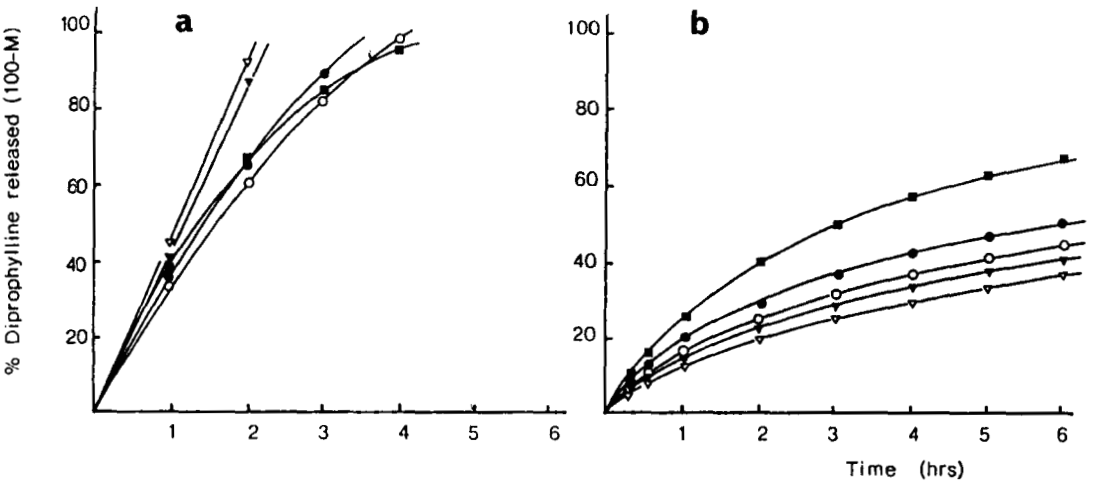

FIGURE 1 (a,b)

Release of diprophylline from: a) Simple (physical) mixtures tableted at 45°C and 140 Mpa pressure, b)Dry-heat granulations slugged at 25°C. (DC excipients contained: ▽ -Spray Dried Lactose (SDL), ○ -Emdex, ▼ -SDL and Avicel, ● -Emdex and Avicel, ■ -Avicel)

of spray dried lactose and Emdex, which have great dissolving ability (Table 1), gives the greater release prolongation. On the contrary, Avicel which has low solubility but some ability to swell and draw up water into a compact (wicking process)[13] gives faster drug release.

The above observation constitutes evidence that interruption of drug masking by the precirol, which might be caused by Avicel swelling, has more significant effect on the drug release than the creation of pores due to the dissolution of the other added excipients.

The release of diprophylline from tableted dry-heat granulations is shown in Figs 2(a-d). It is seen that at higher pressure and temperature the release is becoming slower mainly for matrices containing Avicel. In general, the compression conditions (pressure and temperature) affect differently the drug release from the matrices containing different excipients. These differences are probably related to the compaction mechanism of the excipients (plastic deformation or

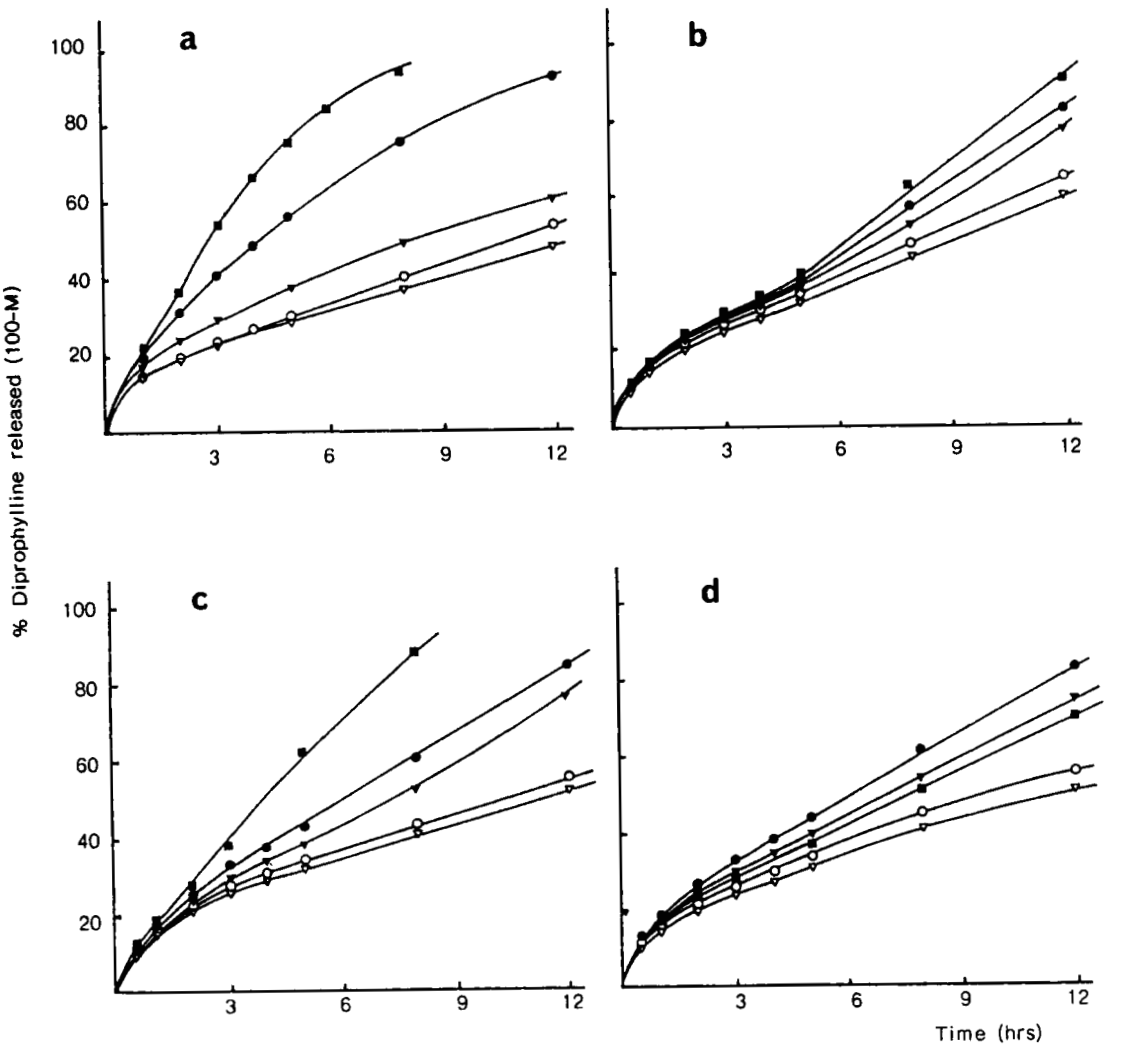

FIGURE 2 (a-d)

Release of diprophylline from dry-heat granulations tableted at: a) 25°C and 50 MPa, b) 45°C and 50 MPa, c) 25°C and 140 MPa, d) 45°C and 140 MPa. (Symbols as in Fig. 1).

fragmentation) and to their dissolving/disintegrating ability as well. In order to evaluate in detail such effects the drug release mechanism from the matrix system under investigation has first to be elucitated.

The precirol/DC excipient matrices may have variable porosity due to the incorporation of different DC excipients. Also, pores are developed to a variable extent during the dissolution process since the dissolution liquid penetrating into the matrices can create pores by hydrating and swelling or dissolving the constituents (drug, precirol and DC excipients). Therefore, since the drug release involves: a) penetration of the dissolving liquid into the matrix b) dissolution of the drug and c) diffusion of the dissolved drug out of the matrix into the bulk solution, the release mechanism could be described by a two-phase process. One phase involving penetration and diffusion through the preexisting pores and another through the pores which are developed by the dissolution or swelling of the matrix forming materials and particularly of the DC excipients in the present system.

In order to elucidate the possible operation of a two-phase drug concentration dependent release mechanism, the dissolution results are expressed on the basis of two bi-exponential first order models[14] corresponding to the following equations:

$$M = A\exp(-k_a t) + B\exp(-k_b t) \quad (1)$$

$$100 - M = m_1\exp(-a/t) + m_2\exp(-b/t) \quad (2)$$

Equation 1 is analogous to that generally used to describe pharmacokinetics after rapid intravenous injection of drug. M is the percentage of undissolved drug. k_a and k_b are the release rate constants corresponding to the two release phases. Equation 2 takes into account two independent probabilistic release phases. m_1 and m_2 indicate the percent release that would be achieved at infinite time by each particular phase. The total ($m_1 + m_2$) equals 100 when release can be completely described in terms of the two separate phases. The parameters a and b, having dimen-

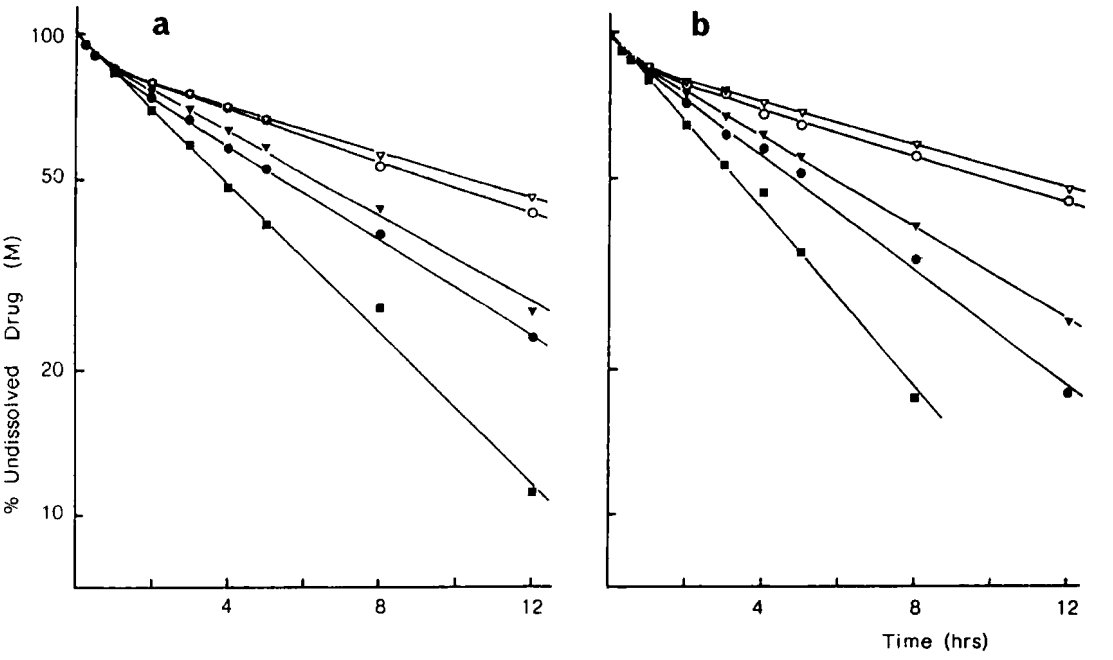

FIGURE 3 (a,b)

Percentage of undissolved diprophylline vs time for dry-heat granulations tableted at: a) 45°C and 50 MPa, b) 25°C and 140 MPa. (Symbols as in Fig. 1).

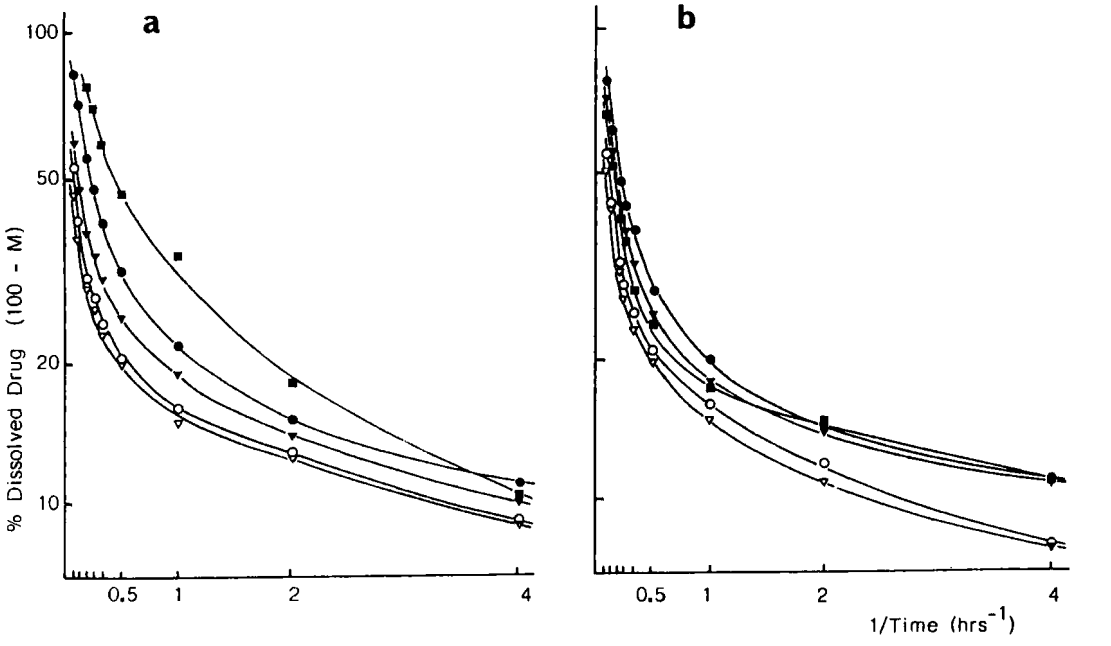

FIGURE 4 (a,b)

Percentage of dissolved diprophylline vs reciprocal time for dry-heat granulations tableted at a) 25°C and 50 MPa, b) 45°C and 140 MPa. (Symbols as in Fig. 1).

TABLE 2

Parameters for the release of diprophylline on the basis of equation: $M = Aexp(-k_a t) + Bexp(-k_b t)$

Compression conditions Temp (°C)	Pres. (MPa)	DC excipient incorporated	k_a (h^{-1})	k_b (h^{-1})	A	B
25	50	SDL	1.60	0.04	7.9	86.3
"	140	"	0.77	0.05	10.0	84.1
45	50	"	2.28	0.06	13.1	88.4
"	140	"	2.20	0.05	8.2	88.4
25	50	Emdex	1.60	0.11	7.8	92.4
"	140	"	3.33	0.05	6.8	89.8
45	50	"	4.08	0.06	15.4	90.9
"	140	"	4.30	0.06	12.3	89.0
25	50	SDL/Avicel	1.45	0.06	9.9	83.7
"	140	"	-	0.11	-	97.9
45	50	"	-	0.11	-	98.5
"	140	"	-	0.09	-	90.6
25	50	Emdex/Avicel	1.72	0.13	6.3	87.9
"	140	"	-	0.13	-	95.7
45	50	"	-	0.10	-	96.3
"	140	"	-	0.12	-	98.4
25	50	Avicel	-	0.28	-	94.0
"	140	"	-	0.21	-	98.5
45	50	"	-	0.18	-	99.5
"	140	"	-	0.10	-	98.2

Correlation coefficient values $r>0.95$ for at least 4 points

sions of time, would indicate the magnitude of time when the particular phases are taking place with the greater probability.

Representative plots of the percentage of undissolved drug vs time and of dissolved drug (100-M) vs reciprocal time 1/t are shown in Figs 3 and 4 respectively, and the values of the release parameters A, B, k_a, k_b, m_1, m_2, a and b for the tableted dry heat granulations are given in Tables 2 and 3.

The sums A+B and m_1+m_2 are not always close to 100. Also, in some cases the dissolution data do not fit to the bi-exponential model, giving B values greater than 100. The zero order release model

TABLE 3

Parameters for the release of diprophylline on the basis of equation: $M=100-m_1\exp(-a/t)-m_2\exp(-b/t)$

Compression conditions		DC excipient				
Temp. (°C)	Pres. (MPa)	incorporated	a (h)	b (h)	m_1	m_2
25	50	SDL	0.17	6.96	17.7	49.9
"	140	"	0.19	4.49	17.8	45.9
45	50	"	0.36	6.89	21.2	66.0
"	140	"	0.20	5.12	17.0	43.4
25	50	Emdex	0.19	5.75	18.9	43.7
"	140	"	0.19	4.95	17.8	42.4
45	50	"	0.36	5.85	21.2	51.1
"	140	"	0.23	5.46	19.6	46.1
25	50	SDL/Avicel	0.21	4.80	22.5	46.5
"	140	"	0.24	5.20	21.4	73.5
45	50	"	0.36	5.02	21.2	66.7
"	140	"	0.16	4.92	20.3	67.6
25	50	Emdex/Avicel	0.22	4.59	25.6	78.5
"	140	"	0.23	4.33	20.8	76.4
45	50	"	0.36	4.54	21.2	73.0
"	140	"	0.19	4.62	22.6	73.3
25	50	Avicel	0.39	4.79	45.6	92.9
"	140	"	0.27	3.79	23.7	90.8
45	50	"	0.40	4.30	24.0	88.7
"	140	"	0.16	5.54	21.0	63.3

Correlation coefficient values $r>0.95$ for at least 4 points

provide a better fit to these release data. A possible explanation for the later could be the faster release due to extensive erosion of the matrix or the accelerating development of pores that seems to be related to the presence of Avicel (see Table 2).

On the basis of the release parameters given in Tables 2 and 3 it can be realized what kind of effects any preparation variable has separately had on the release mechanism.

In order to express the effect of the compression conditions (temperature and pressure) in a simpler way by using only two parame-

TABLE 4

Weibull function analysis data for tableted dry-heat granulations

Compression conditions Temp. (°C)	Press. (MPa)	DC excipient incorporated	T_d (h)	β	(r)
25	50	SDL	35.3	0.50	0.884
"	140	"	25.3	0.56	0.993
45	50	"	16.9	0.68	0.953
"	140	"	25.7	0.56	0.930
25	50	Emdex	29.8	0.52	0.909
"	140	"	20.4	0.59	0.942
45	50	"	14.4	0.71	0.960
"	140	"	22.0	0.57	0.985
25	50	SDL/Avicel	18.3	0.54	0.955
"	140	"	10.0	0.72	0.970
45	50	"	11.2	0.72	0.969
"	140	"	11.8	0.61	0.958
25	50	Emdex/Avicel	5.5	0.78	0.991
"	140	"	7.9	0.78	0.981
45	50	"	9.3	0.84	0.975
"	140	"	9.1	0.67	0.968
25	50	Avicel	3.2	0.93	0.998
"	140	"	4.3	0.94	0.987
45	50	"	7.7	0.91	0.975
"	140	"	14.0	0.58	0.949

ters the Weibull function drug-release model[15] is applied. This model has also been chosen because is capable in dealing with S shaped dissolution curves corresponding to an initial release phase followed either by a faster (e.g. for disintegrating tablets) or by a slower one (e.g. for sustained release tablets). The Weibull function is:

$$F = F_\infty (1-\exp -((t-T_o)/T_d)^\beta) \quad (3)$$

where F is the amount of drug dissolved at time t, F_∞ is the amount dissolved after infinite time, T_o is the time lag before the actual onset of the dissolution process which in most cases will be equal

to zero, β is the shape parameter and T_d is a parameter which represents the time for release of 63.2% of total dose.

Provided that the $T_o = 0$ and $F_\infty = 1$, the parameters T_d and β were calculated according to Langenbucher[15] and are given in Table 4, together with the correlation coefficients (r).

From Table 4 and the above discussion it may be concluded that: **a)** The diprophylline release is lower from matrices containing spray dried lactose and faster from those containing Avicel. **b)** The increase in compression pressure and temperature is decreasing the release but only from tablets containing Avicel. The release from tablets containing lactose and Emdex is increasing with pressure but only at room temperature.(25°C). Also it is increasing with temperature but only at low compression pressure (50 Mpa). **c)** For the combinations of lactose and Emdex with Avicel the effect due to lactose is predominant in the first case but in the later one the effect due to Avicel.

All the above changes in drug release due to compression pressure and temperature may be attributed to fragmentation of lactose and the plastic deformation of Avicel during compression.

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