International Journal of Pharmaceutics, 26 (1985) 165–174
Elsevier

IJP 00881

The effects of aging on the dissolution of phenytoin sodium capsule formulations

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(Received November 19th, 1984)
(Modified version received April 17th, 1985)
(Accepted May 17th, 1985)

Key words: phenytoin – capsule – dissolution – aging – Weibull function—excipient

Summary

The effects of formulation and storage conditions on the dissolution of sodium phenytoin capsules have been evaluated. Capsule formulations were prepared containing lactose or $CaSO_4 \cdot 2H_2O$ as the excipient at a low (1 : 1) and high (3 : 1) excipient to drug ratio. The capsules were stored for 2 or 8 weeks at 11% and 67% relative humidity. The dissolution data were analyzed using a non-linear least-squares regression program and the Weibull function. An analysis of variance (ANOVA) performed on each of the Weibull function parameters revealed that the formulation and storage conditions had different effects on each of these parameters. A specific interaction between $CaSO_4 \cdot 2H_2O$ and phenytoin sodium was not evident from the data; however, significant effects on the deaggregation process could be detected from changes in the β parameter. Several interaction effects between storage conditions and formulation factors were also evident from the ANOVA results. This study illustrates the utility of the Weibull function analysis of dissolution data for detecting drug–excipient interactions and storage-related changes in solid dosage forms.

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Introduction

The importance of formulation factors on the rate and extent of release of medication from a dosage form has been recognized for some time. Phenytoin is a compound whose bioavailability has been found to be greatly affected by formulation (Glazko and Chang, 1972). The variability in the bioavailability of phenytoin has been attributed to a number of factors. These are primarily associated with the poor solubility of the drug which can be partially attributed to its high melting point, 298°C (Windholz et al., 1976) and high lipophilic character as evidenced by the octanol–water partition coefficient, log PC = 1.98 (Hafkensheid, 1983). Various techniques, including salt formation, micronization (Glazko and Chang, 1972) and the use of solid dispersions (Stavchansky and Gowan, 1984) have been applied to the formulation of phenytoin in order to improve its bioavailability. The sodium salt of phenytoin is used in capsule formulations to enhance its dissolution rate. Despite this modification, problems have occurred with the absorption of the drug.

An additional factor which has been found to affect the bioavailability of phenytoin became apparent after a number of reports concerning an outbreak of phenytoin intoxication in Australia in 1968 (Tyrer et al., 1970). It was found that the intoxication was apparently caused by a change in the excipient used in the capsule formulation (Tyrer et al., 1970, 1971a and b). The original capsule formulation contained calcium sulfate dihydrate as an excipient which was changed to lactose by the manufacturer. Patients who were stabilized on the formulation containing calcium sulfate developed symptoms of phenytoin toxicity when given the formulation containing lactose. It was proposed that phenytoin was less available when formulated with calcium sulfate than with lactose since an increased fecal excretion of phenytoin was observed from capsules containing calcium sulfate than from capsules containing lactose (Bochner et al., 1972, 1973).

The mechanism behind the reduced bioavailability of phenytoin in the presence of calcium sulfate has not yet been fully elucidated. A number of studies have dealt with the effect of concomitant administration of calcium-containing antacids (Chapron et al., 1979; O'Brien et al., 1978; Kulshrestha et al., 1978) or dietary calcium (Herishanu et al., 1976) on phenytoin absorption. However, the results of these studies are conflicting. Bochner et al. (1972, 1973) suggested that a non-absorbable salt or complex is formed between calcium and phenytoin, while Chapron et al. (1979) found no evidence for such an interaction. Bastami and Groves (1978) found that the dissolution characteristics of phenytoin capsules containing calcium sulfate were different from those containing lactose. The present study was undertaken to determine the effects of the type and amount of diluent as well as humidity and storage time on the dissolution characteristics of phenytoin capsules.

Methods and Materials

Preparation and filling of experimental capsule formulations

Four types of capsule formulations were used in the experiments: (1) phenytoin (100 mg):$CaSO_4 \cdot 2H_2O$ (130 mg); (2) phenytoin (100 mg):lactose (130 mg) (mimick-

ing the drug to excipient ratio found in the commercial Dilantin product); (3) phenytoin (100 mg):$CaSO_4 \cdot 2H_2O$ (300 mg); and (4) phenytoin (100 mg): lactose (300 mg). These latter two formulations were used in an attempt to exaggerate any possible effects due to the excipients.

The proper amounts of sodium phenytoin (Sigma, lot no. D-4505) and lactose anhydrous U.S.P. (Amend Drug & Chemicals, lot no. G19731H16) or $CaSO_4 \cdot 2H_2O$ (J.T. Baker, lot no. 910271) were mixed in a mortar and pestle and tumbled manually for 5 min. The powder mixture was then sifted through a 10-mesh screen twice. The capsules were filled using a capsule-filling machine (Chemical and Pharmaceutical Industry). Size 2 hard gelatin capsules (Lilly, lot no. 4DU12A) were used for the 1.3 : 1 excipient to drug ratio capsules [1] and size 0 capsules (Lilly, lot no. E7GP16) were used for the 3 : 1 ratio capsules.

The weight variation (Anon, 1980, p. 989) and content uniformity (Anon, 1980, p. 955) tests were performed to ensure that the filled capsules conformed to U.S.P. standards.

Calibration of the dissolution apparatus

The Apparatus Suitability Test (as required in U.S.P. XX-NF XV, p. 959) was performed on the Dissolution Test Unit (Hanson Research, Model 500-115). U.S.P. dissolution calibrator non-disintegrating salicyclic acid tablets (U.S.P., lot G) and disintegrating prednisone tablets (U.S.P., lot F) were used.

Capsule storage conditions

The capsules were stored in clear glass vacuum desiccators at room temperature (24 ± 1°C). Relative humidities of 11% and 67% were maintained in each desiccator using saturated solutions of LiCl and $CuCl_2 \cdot 2H_2O$, respectively (Meites, 1963). Capsules were stored for either 2 or 8 weeks.

Dissolution test

The dissolution tests were performed on the unit previously described according to the specifications in the U.S.P.-NF monograph for phenytoin sodium capsules (Anon, 1980). Samples were taken at 5, 10, 20, 30, 40, 50 and 60 min using a 5-ml plastic syringe to which a short piece of polyethylene tubing had been attached. A 5 μm filter was connected to the tubing to remove undissolved solids from the sample. To sample, the first 3 ml were withdrawn and returned to the flask and a second 3-ml sample was saved. Exactly 2 ml were measured using a Finn Pipette and this aliquot was stored in a disposable culture tube. The remaining sample was returned to the flask and the 2 ml removed were replaced by exactly 2 ml of 37°C deaerated water from a previously calibrated pipette.

Assay of dissolution media

The 2-ml samples were placed in 1 cm quartz cuvettes. The absorbance of each sample was then measured at 258 nm on a Beckman DU-8 spectrophotometer

[1] Referred to as 1 : 1 ratio capsules for the rest of the discussion.

promptly after each dissolution test. It was determined previously that lactose and $CaSO_4 \cdot 2H_2O$ did not interfere with the absorbance of phenytoin at this wavelength. These data were converted to concentrations using a previously prepared calibration curve.

Treatment of data

The Weibull function (Weibull, 1951) of the form shown in Eqn. 1 was fitted to the concentration dissolved vs time data using a non-linear least-squares regression program (Anon, 1979):

$$C = C_\infty(1 - e^{-(t-t_L)/T_d)^\beta}) \quad (1)$$

This expression was first applied to drug dissolution data by Langenbucher (1972). In the present study, t_L (the lag time) was held constant and the other three parameters, i.e., C_∞ (the concentration in solution to time t_∞), T_d (the time scale parameter or the time for 63.2% of the solid to dissolve) and β (the shape parameter) were estimated by the regression procedure. Initial estimates for these parameters were obtained by the linearization procedure described by Langenbucher (1972).

The T_{diss} parameter described by von Hattingberg et al. (1980) was calculated as:

$$T_{diss} = T_d\left[\Gamma\left(\frac{\beta+1}{\beta}\right)\right] + t_L \quad (2)$$

where Γ represents the gamma function (Hastings and Peacock, 1975). Eqn. 2 provides an exact calculation of the mean value of the Weibull distribution function since tables of gamma function values are readily available (Weast, 1967) which provide values to solve equations of this general type. T_{diss} is an estimate of the mean dissolution time (MDT) of the individual dissolving solid particles. Since t_L could not be estimated reliably due to the lack of early time points (caused by the unexpectedly rapid dissolution of phenytoin) the fixing of t_L at 0 was justified since the t_L for capsules is usually extremely short, i.e. less than 1–2 min (Ludwig and Van Ooteghem, 1980) and merely represents the time for the capsule shell to rupture.

A four-way, two-level analysis of variance (ANOVA) was then applied to the data to determine whether there were any statisically significant differences between the four parameters tested (i.e. MDT, C_∞, T_d and β) for each of the storage conditions employed. In all comparisons tested, $P < 0.05$ was taken as the minimum level of significance.

Results

Fig. 1 illustrates two representative sets of dissolution data which were fit using non-linear regression and the Weibull function. The capsule containing lactose as a diluent was found to dissolve more rapidly than the capsule containing calcium sulfate. This is evident by visual inspection and by comparison of the T_d values. The

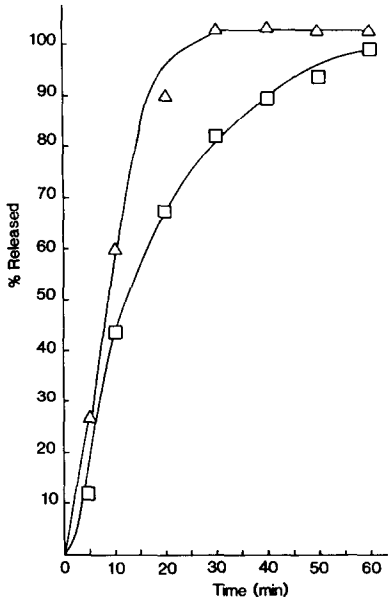

Fig. 1. Representative dissolution curves. △, lactose diluent 300 mg; 67% humidity for 2 weeks; $T_d = 11.3$, $\beta = 1.94$. □, $CaSO_4 \cdot 2H_2O$ 130 mg; 67% humidity for 2 weeks; $T_d = 17.8$, $\beta = 0.96$.

general shapes of the curves are markedly different, illustrating the differences in the β values of the fitted curves.

The results of the analysis of variance performed on the dissolution parameters are present in Table 1. The individual cell means used in the ANOVA, number of replications and standard deviations are presented for each parameter in Table 2. It can be seen from Table 1 that the various parameters were affected by different external variables. For example, T_{diss} was only affected by the excipient to drug ratio with the higher amount of excipient resulting in the larger value of T_{diss} for both lactose and calcium sulfate (Table 2).

C_∞ was significantly affected by the excipient to drug ratio (E/D), humidity and storage time. In addition, an interaction occurred between humidity and storage time. This indicates that these two variables may not work independently of each other. Higher excipient to drug ratios and humidity resulted in a slightly lower value of C_∞ (Table 2). When considered alone, a longer storage time resulted in a slightly lower value of C_∞; however, the interaction between time and humidity results in a greater reduction in C_∞ from 2–8 weeks storage at 67% humidity than for 2–8 weeks storage at 11% humidity.

The value of T_d was significantly affected by the excipient to drug ratio with the higher excipient ratio resulting in a larger value of T_d. This parameter was also influenced by an interaction between the type of excipient and the storage time. The capsules containing calcium sulfate were found to dissolve more rapidly after aging while capsules containing lactose dissolved more slowly with aging.

TABLE 1
SIGNIFICANCE OF EFFECTS BY PARAMETER

Source of variation	Significance			
	C_∞	T_d	β	T_{diss}
Excipient	0.737	0.768	0.000 *	0.147
E/D ratio **	0.018 *	0.000 *	0.868	0.000 *
Humidity	0.013 *	0.941	0.630	0.771
Time	0.012 *	0.630	0.131	0.361
2-Way Interactions				
Excipient–E/D ratio	0.266	0.806	0.079	0.638
Excipient–humidity	0.880	0.343	0.033 *	0.685
Excipient–time	0.986	0.016 *	0.920	0.054
E/D ratio–humidity	0.303	0.176	0.666	0.064
E/D ratio–time	0.268	0.225	0.172	0.581
Humidity–time	0.047 *	0.837	0.216	0.324
3-Way Interactions	None Significant			
4-Way Interactions	None Significant			

* Significant at the 0.05 level.
**Excipient/drug.

TABLE 2
SUMMARY OF AGING EFFECTS ON WEIBULL FUNCTION PARAMETERS

	T_{diss} E/D ratio			C_∞ E/D ratio *			
	1.1	3.1	Humidity	1.1		3.1	
				2 wks	8 wks	2 wks	8 wks
$\bar{X}$	8.79	12.29	11%	104.2	104.9	103.3	100.1
n	57	60		15	13	18	13
S.D.	4.99	5.37		14.7	8.3	9.8	14.3
			67%	104.5	97.8	99.7	88.2
				17	12	17	12
				7.2	9.5	7.6	12.7

Excipient	β Humidity			T_d E/D ratio			
		11%	67%	1:1		3:1	
				2 wks	8 wks	2 wks	8 wks
Lactose	$\bar{X}$	1.32	1.55	8.54	9.02	10.3	14.9
	N	31	29	16	11	18	15
	S.D.	0.38	0.50	4.58	5.20	3.10	5.33
$CaSO_4$	$\bar{X}$	1.15	1.01	9.30	6.95	12.9	11.4
	N	28	29	16	14	17	10
	S.D.	0.41	0.60	5.63	4.38	5.77	6.15

$\bar{X}$ = individual cell means; n = number of replications; S.D. = standard deviation
* E/D = Excipient-to-drug ratio

The value of β was affected by the type of excipient with the capsules containing lactose resulting in a significantly higher value of β. The β value was also influenced by an interaction between the type of excipient and humidity. Opposite effects are again seen between 11% and 67% humidity for calcium sulfate and lactose. In the case of calcium sulfate, the higher humidity results in a lower value of β while in the case of lactose, the higher humidity results in a higher value of β.

Discussion

The use of the single parameter approach to analyzing dissolution data has been criticized as not always providing enough information to adequately judge the efficiency of release of a drug from a dosage form. It has been suggested (Langenbucher, 1976) that the analysis of the entire dissolution profile is necessary to obtain a complete view of the dissolution characteristics of a dosage form.

The Weibull function was first suggested as a model for analyzing dissolution data by Langenbucher (1972). The parameters comprising the Weibull function have been suggested to reflect different characteristics associated with the release of drug from a dosage form. The C_∞ parameter is a measure of the total amount of drug released from the dosage form. The value of this parameter should ideally be equal to the amount of drug in the dosage form divided by the total volume of dissolution medium. If the solubility of the drug is changed or if the drug is sequestered or bound in the dosage form matrix material, it would be expected that C_∞ would be reduced. Although C_∞ was significantly affected by the excipient-to-drug ratio, humidity and time, the changes were generally small. Thus, the overall effect of the formulation and storage factors on the total amount of drug released from the dosage form is probably minimal in this case.

T_{diss} is a measure of the average time required for the drug molecules to be released from the dosage form (Brockmeier and von Hattingberg, 1982). It can be thought of as the mean residence time of the dissolving particles in the solid state before they enter into solution. It can be seen in Table 1 that this parameter was only affected by the excipient-to-drug ratio. Higher amounts of either lactose or calcium sulfate cause a more prolonged release of phenytoin from the dosage form. Since no specific effect on dissolution rate was seen with respect to the type of excipient used, the changes in T_{diss} do not support the theory that a specific interaction occurs between calcium sulfate and phenytoin.

The T_d parameter is a measure of the rate of dissolution and can be thought of as the time required for 63.2% of the drug in the dosage form to dissolve (Langenbucher, 1976). This is comparable to other single parameter measures of dissolution rate such as t_{50}, the time required for 50% of the drug in the dosage form to dissolve. It can be seen that T_d was significantly affected by the excipient-to-drug ratio. This result agrees qualitatively with the changes seen in T_{diss}, i.e. a larger amount of excipient results in a slower release of drug from the dosage form. A significant interaction effect between the type of excipient and storage time was not evident from an examination of T_{diss} or C_∞. The effect of aging on drug release was

dependent upon the type of excipient used. Longer storage times resulted in a faster release of drug when calcium sulfate was used as an excipient but a slower release was seen with longer storage times when lactose was used as an excipient.

The β parameter was significantly affected by the type of excipient with a larger value resulting when lactose was used as an excipient than with calcium sulfate. A significant interaction between the type of excipient and the humidity was also observed to affect β. Higher humidity was found to decrease β when calcium sulfate was used as an excipient but increased the value of β when lactose was used as an excipient. The β parameter has been stated to provide useful qualitative information on the effects of disintegration and diffusion processes on the dissolution rate (Langenbucher, 1976). It can be seen from Eqn. 1 that when $\beta = 1$ a first-order dissolution rate results. When $\beta > 1$ the dissolution rate profile takes on a sigmoidal appearance. This may occur when a prolonged disintegration or deaggregation process causes a slower initial dissolution rate. As the disintegration process continues, the surface area of the powder increases and reaches a maximum. The maximum surface area results in a maximum dissolution rate. A value of $\beta < 1$ may be indicative of a disintegration or deaggregation process which remains constant with time, i.e. is very fast or near zero.

The lower β values seen with the calcium sulfate formulations indicate an approximate first-order release of phenytoin, possibly due to a more constant deaggregation process. In contrast, the lactose formulations deaggregate to produce a powder mass which attains a maximum surface area and dissolution rate. This is exemplified in Fig. 1. The constant deaggregation of the calcium sulfate capsules is also substantiated by the observation that a powder mass remained in the basket at the end of the dissolution test more frequently when calcium sulfate was used as an excipient. Similar observations were reported by Arnold et al. (1970) for a commercial phenytoin capsule preparation.

It has been suggested previously that a specific interaction between phenytoin and calcium sulfate may result in the decreased bioavailability of the drug (Bochner et al., 1972, 1973). In vitro studies in these laboratories involving partitioning and solubility measurements of phenytoin in the presence and absence of calcium ion failed to uncover any significant effects. Chapron et al. (1979) also found no evidence of a specific interaction between calcium and phenytoin. In the light of these findings it is probable that the reduced bioavailability of phenytoin in the presence of calcium sulfate may be due at least in part to the effects of the excipient on the deaggregation of the dosage form. This phenomenon has been shown in the present study to be influenced by such factors as humidity and storage time as well as the amount of excipient used.

It has also been shown that the analysis of dissolution data using the Weibull function can provide useful qualitative information on the effects of formulation and storage conditions on the dissolution properties of a dosage form. The use of the Weibull function in analyzing dissolution data may therefore be a convenient method for evaluating formulations in the developmental stage of production.

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