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RESEARCH PAPER

Influence of Dissolution Medium Agitation on Release Profiles of Sustained-Release Tablets

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ABSTRACT

Reaching nearly perfect sink conditions is very important in the determination of drug dissolution rates. Many times, the only factor that is taken into consideration in achieving sink conditions is the relation between the drug concentration and its solubility. The analytical conditions of the dissolution assay, as well as the dissolution apparatus, stirring speed, and nature and volume of the dissolution fluid may also influence the dissolution results. The main objective of this work was to study the influence of the stirring rate conditions and of the dissolution apparatus in the diltiazem hydrochloride release from tablets. Diltiazem hydrochloride sustained-release (SR) tablets were tested and the following dissolution parameters were evaluated: $t_{10\%}$, $t_{25\%}$, $t_{50\%}$, *dissolution time, mean dissolution time (MDT), and dissolution efficiency (DE) at* t_{120}, *and at* t_{360}. *To analyze the release mechanism, several release models were tested, such as Higuchi, zero order, first order, Baker-Lonsdale, Hixson-Crowell, Weibull, and Korsmeyer-Peppas. The similarities between two in vitro dissolution profiles were assessed by the similarity factor* f_2. *The in vitro release kinetics of diltiazem hydrochloride sustained-release tablets were evaluated using the USP 2 (paddle) and USP 4 (flow-through) apparatus.*

Key Words: *Diltiazem hydrochloride; Dissolution assay; Sink conditions*

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INTRODUCTION

Dissolution is the process by which a solid of only fair solubility characteristics enters into solution (1). The earliest reference to dissolution was made by Noyes-Whitney (1817), and it was suggested that the dissolution rate of solid substances was determined by the diffusion rate of a very thin layer of saturated solution that forms instantaneously around the solid particle.

To explain the mechanism of dissolution, Nernst proposed the film-model theory. A solid particle immersed in a liquid undergoes two consecutive steps. In the first step, the dissolution of the solid at the interface occurs, forming a thin stagnant layer (or film) with thickness h around the particle. The second step consists of the diffusion of the solute molecules from this layer to the bulk of the dissolution fluid. The first step is almost instantaneous, but the second is much slower and becomes the rate-limiting step. The drug flux across this film dC/dt can be described by the equation proposed by Noyes-Whitney and modified by Brunner (1904):

$$\frac{dC}{dt} = k\frac{DS}{vh}(C_s - C_t)$$

where k is the intrinsic dissolution rate of the drug, D is the diffusion coefficient, S is the surface area, C_s is the saturation concentration (maximum solubility), C_t is the concentration at time t, and v is the volume of the dissolution medium.

To simulate the in vivo sink conditions, in vitro dissolution testing is conducted using either a large volume of dissolution medium or a mechanism by which the dissolution medium is replenished constantly with fresh solvent. In these conditions, $C_s \gg C_t$, and the previous equation becomes

$$\frac{dC}{dt} = k\frac{DS}{vh}C_s$$

In these conditions, usually known as *sink conditions*, the driving force of the whole dissolution process is the drug solubility in the dissolution medium. In this way, it is not or should not be affected by operational conditions. To be considered as sink conditions, the C_t value, or the drug concentration limit, should be lower than 10%–20% or even 30% (2) of its maximum solubility. This theory states that the dissolution rate is directly proportional to the diffusion coefficient and inversely proportional to the film thickness h.

One of the main principles of in vitro dissolution testing is that it should be conducted under sink conditions (3). Consequently, a main priority is to know the maximum drug solubility, especially if it is slightly or very slightly soluble in the dissolution media. In these cases, concentration at the boundary layer can get close to the maximum solubility, delaying or even stopping drug dissolution. The analytical conditions of the dissolution assay, as well as the dissolution apparatus used, and the stirring speed of the dissolution liquid may influence the results. If the liquid is not well stirred, the boundary layer will increase, and drug dissolution and diffusion will become slower and slower. So, in this case, the measured drug release rate of that pharmaceutical dosage form will vary with different stirring rates or with different dissolution apparatus.

The main advantage of a sustained-release (SR) dosage form is the maintenance of the drug blood concentration at therapeutic levels by means of controlled release of the drug during a long period of time and using only one administration. The knowledge of the drug release rate of a SR dosage form is a very important parameter as its variation could lead to a lack of therapeutic effect or to toxicity levels within the body. If perfect sink conditions are not maintained, the determination of this release rate will be compromised.

The SR dosage forms studied were polymeric matrix tablets. The drug release with different stirring speeds (USP apparatus 2) and with different dissolution apparatus (USP apparatus 2 and 4) were compared to verify if they were identical using the following dissolution parameters: $t_{10\%}$ dissolution time, $t_{25\%}$ dissolution time, $t_{50\%}$ dissolution time, mean dissolution time (MDT), and dissolution efficiency (DE) (4,5) at t_{120} and at t_{360} (also dissolution efficiency at t_{1440}, but only for USP dissolution apparatus 2). To analyze the release mechanism, several release models (Table 1) were tested such as Higuchi (6–8), zero order, first order (9,10), Baker-Lonsdale (11), Hixson-Crowell (12), Weibull (13–16) and Korsmeyer-Peppas (17–19). The differences for $t_{10\%}$, $t_{25\%}$, and $t_{50\%}$ dissolution times were statistically examined by a one-way analysis of variance (ANOVA). The similarity factor (20) was evaluated to compare diltiazem release profiles.

$$f_2 = 50 \times \log\left\{\left[1 + \left(1/n\right)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

Table 1

Release Models Tested

Higuchi	$Q_t = K_H\sqrt{t}$
Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 e + K_1 t$
Baker-Lonsdale	$(3/2)\left[1-(1-(Q_t/Q_\infty))^{2/3}\right]-(Q_t/Q_\infty) = Kt$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Weibull	$\log[-\ln(1-(Q_t/Q_\infty))] = \beta \times \log t - \log\alpha$
Korsmeyer-Peppas	$Q_t/Q_\infty = K_k t^n$

This similarity factor is a logarithmic reciprocal square root transformation of one plus the average mean squared differences in percentage dissolved between the test T_j and reference R_j products over all time points n. The FDA suggests that two dissolution profiles are declared similar if f_2 is between 50 and 100 (21).

The objective of this work was to study the influence of the stirring conditions and of the dissolution apparatus in the drug release of SR tablets. Diltiazem (hydrochloride) is a calcium channel blocker used as an antianginal and antihypertensive drug. Its classical oral adult dose is initially 30 mg four times a day before meals and at bedtime, which can be increased to 360 mg/day when necessary (22).

EXPERIMENTAL

Diltiazem hydrochloride SR tablets were from a commercial formulation marketed in Portugal. Diltiazem hydrochloride was obtained from Sigma (Germany); acetonitrile Lichrosolv and disodium phosphate were obtained from Merck (Germany); and triethanolamine was obtained from JMVP (Portugal). The weight of the tablets was determined using a Mettler AG 245. We weighed 20 tablets, and the mean value was determined (23). The hardness of the tablets was determined using an Erweka TBH 28. The friability was determined using an Erweka TAP. The hardness friabrasion ratio (HFR), as described by Mendes (24), was determined. The dissolution testing of diltiazem hydrochloride SR tablets was performed on USP apparatus 2 ($n = 6$) (Sotax AT 7) and USP apparatus 4 ($n = 3$) (Sotax CE 1). Although there is a monograph of diltiazem hydrochloride extended-release capsules in the USP 23 (25), it does not make reference to the release assay.

With USP apparatus 2 experiments, 1000 ml of dissolution fluid (water) were used with a stirring speed of 50, 100, or 150 rpm. The dissolution fluid used was the one indicated in the USP monograph for diltiazem hydrochloride tablets at $37^\circ C \pm 0.5^\circ C$ (26). At predetermined time intervals, the dissolution fluid was collected for analysis and replaced by an equal volume of fresh dissolution fluid. With USP apparatus 4, the same dissolution fluid was used; it was maintained at $37^\circ C \pm 0.5^\circ C$ and with a flow rate of 10 ml/min.

The high-performance liquid chromatography (HPLC) system consisted of a pump (Varian model 9012), a 20 µl loop, a variable-wavelength detector (Varian model 9050) set to 235 nm, and a C8 column (LiChrospher 100 RP8 5 µm 100 × 4 mm). The mobile phase was acetonitrile/disodium phosphate 0.01 M solution (Na_2HPO_4) (50 : 50) with triethanolamine 0.01% with a flow rate of 2.0 ml/min.

RESULTS

The hardness and friability of the tablets were 10 kp and 0.23% (HFR 10.8), respectively. After contacting with the dissolution fluids, the diltiazem matrix tablets swelled, forming a jelly mass that practically did not change for more than 4–6 h. The dimensions of the diltiazem tablets increased after swelling. The influence of the stirring speed (USP apparatus 2) and of the type of dissolution apparatus in the release profile of the tablets can be seen in Figs. 1 and 2, respectively. A large influence of

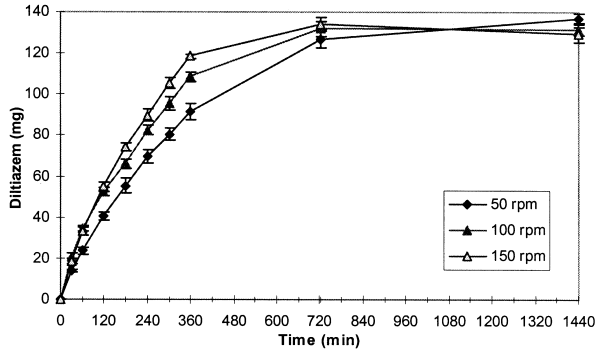

Figure 1. Influence of the stirring speed on the diltiazem release profile.

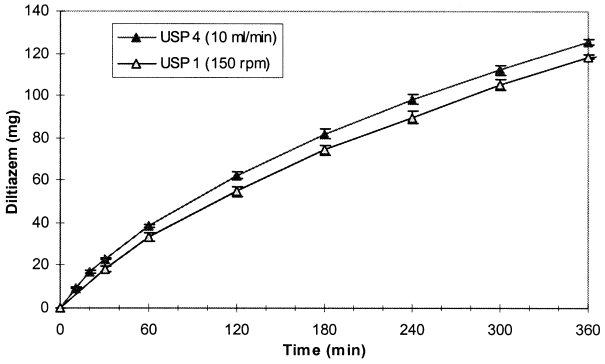

Figure 2. Influence of dissolution apparatus on the diltiazem release profile.

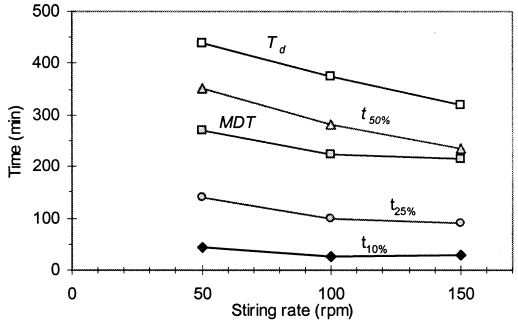

Figure 3. Influence of stirring rate on the diltiazem release from sustained-release tablets.

the stirring speed and of the type dissolution apparatus in the release profiles was noticed. It can be concluded that USP apparatus 2, mainly with lower stirring speeds, does not follow sink conditions; the real release profile hardly can be determined this way.

Table 2

Comparison of the Dissolution Parameters

	50 rpm	100 rpm	150 rpm	USP 4
$t_{10\%}$	42.8	26.9	28.7	22.0
$t_{25\%}$	139.1	97.8	90.7	77.2
$t_{50\%}$	353.0	282.8	234.7	213.0
MDT	318.2	215.6	193.7	140.8
DE t_{120}	12.5	17.0	17.4	19.9
DE t_{360}	29.3	35.2	39.3	41.9
DE t_{1440}	54.7	57.8	62.3	—

There were differences among the dissolution parameters used in the four dissolution conditions studied, especially for the 50-rpm stirring rate (Fig. 3 and Table 2). The $t_{10\%}$, $t_{25\%}$, and $t_{50\%}$ dissolution times and the mean dissolution time decreased as the stirring speed increase. The dissolution efficiencies increased as long as the stirring rates increased. Using one-way ANOVA ($\alpha = 0.05$), statistically significant differences were found for $t_{10\%}$, $t_{25\%}$, and $t_{50\%}$ dissolution times between the 50 rpm stirring rate and the other stirring conditions. Between 100 rpm and 150 rpm, the differences were statistically significant only for the $t_{50\%}$ dissolution time. The differences between USP apparatus 2 (150 rpm) and USP apparatus 4 were statistically significant for $t_{10\%}$, $t_{25\%}$, and $t_{50\%}$ dissolution times.

Table 3 summarizes release rate constants K calculated by the above-mentioned mathematical release models and determination coefficients R^2 of the observed release data and the simulated profiles. The results show that rate constant values are significantly smaller in the case of the 50-rpm stirring rate. For each of the examined samples, the best fit was achieved with the application of Higuchi, Weibull, and Korsmeyer-Peppas ($n \approx 0.6$) models for both USP apparatus 2 and USP apparatus 4. The Weibull shape parameter (13) β characterizes the dissolution profile as exponential ($\beta = 1$); as sigmoid, S shaped, with upward curvature followed by a turning point ($\beta > 1$); or as parabolic, with steeper initial slope than consistent with the exponential ($\beta < 1$). This shape parameter showed no significant variation ($\beta < 1$).

T_d represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form. The T_d values were tendencially smaller (fast dissolution process) when

Table 3

Linearization of the Diltiazem Release Profiles (Q Expressed in mg)

Release Models	50 rpm	100 rpm	150 rpm	USP 4
Higuchi				
K	5.8250	6.4435	7.4424	7.3687
R^2	0.9954	0.9951	0.9980	0.9988
Zero order				
K	0.2487	0.2603	0.2603	0.3282
R^2	0.9854	0.9910	0.9910	0.9782
First order				
K	0.0054	0.0046	0.0052	0.0064
R^2	0.8934	0.8980	0.8807	0.8199
Baker-Lonsdale				
K	0.0002	0.0002	0.0003	0.0003
R^2	0.9760	0.9707	0.9724	0.9787
Hixson-Crowell				
K	0.0061	0.0058	0.0065	0.0076
R^2	0.9389	0.9409	0.9294	0.8923
Weibull				
β	0.8837	0.8023	0.9145	0.8505
R^2	0.9990	0.9955	0.9987	0.9993
T_d	440.1647	376.8107	320.9218	302.1661
Korsmeyer-Peppas				
K	0.1519	0.1688	0.2233	0.2765
n	0.697	0.695	0.638	0.560
R^2	0.9994	0.9989	0.9999	0.9999

K, release rate constants; n, exponent release; β, shape parameter.

the stirring rate was increased following a linear relation, as shown by the 0.999 determination coefficient obtained for the USP apparatus 2 (Fig. 3).

The diltiazem release rate from this pharmaceutical system was not constant and diminished with the square root of time, indicating that diffusion occurring inside the matrix was the rate-limiting step in the control of the drug release. This fact can best be seen for analytical conditions in which the dissolution medium is more rapidly replenished with fresh solvent (higher stirring rates or USP apparatus 4).

DISCUSSION

When the dissolution assay, described in any monograph of any pharmacopoeia, is performed, it should occur under perfect sink conditions. Many times, the only factor taken into consideration in achieving sink conditions is the relation between the drug concentration and its solubility, with a limit of 30%. Under sink conditions, no influence of the concentration gradient should occur; then, it is necessary also to study the dissolution liquid stirring rate, which in many cases is disregarded and empirically chosen. With low stirring rates, small differences in the drug release may not be verified, leading to a similar release profile of pharmaceutical formulas with different release characteristics. Higher stirring rates, or better dissolution liquid renewal conditions, allow distinguishing those, even small, differences. With very high stirring rates, turbulent fluxes can appear inside the dissolution cell, originating a large variation in the amount of the drug released.

The f_2 similarity factor among the stirring speeds of 50–100 rpm, 50–150 rpm, and 100–150 rpm were

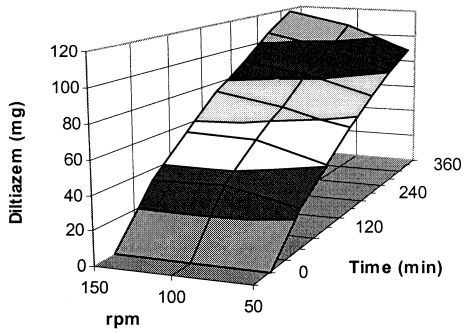

Figure 4. Topographical dissolution characterization of diltiazem.

61.8, 49.7, and 65.3, respectively. The diltiazem dissolution profiles obtained with the 50–150-rpm stirring rate were not considered similar ($f_2 < 50$). The differences between 50–100 and 100–150 rpm were smaller, and the diltiazem dissolution profile could be considered similar ($f_2 > 50$). The f_2 similarity factor between USP 4 and USP 2 at stirring speeds of 50, 100, and 150 rpm were 43.2, 55.9, and 76.9, respectively. Again, the diltiazem dissolution profiles obtained with USP 2 at 50 rpm were not considered similar ($f_2 < 50$), this time when compared with the USP 4 dissolution profile. The f_2 value was the highest for the comparison of the 150 rpm and USP 4 dissolution results, confirming the similarity of these two profiles (Fig. 4). This similarity factor is a sample statistic that cannot be used to formulate a statistical hypothesis for assessment of dissolution similarity. It is, therefore, impossible to evaluate false-positive and false-negative rates of decisions for approval of drug products based on f_2. Simulation results also indicate that the similarity factor is too liberal in concluding similarity between dissolution profiles (27,28).

Shah et al. (29) used a three-dimensional topographical plotting technique to characterize immediate-release preparations. This procedure was useful in delineating the properties of drug release rates associated with the agitation rate of the dissolution assay. An increase in the dissolution rate following an increase in the agitation rate from 50 to 100 rpm was observed. This result supports the idea that paddle speed for SR dosage forms should be 100 rpm or higher for normal characterization of the dissolution profile and for drug quality assurance.

The results obtained with these tablets permit us to conclude that the stirring rate and the dissolution apparatus chosen affected the dissolution characteristics, as can be seen by the dissolution parameters used. It can be concluded that USP apparatus 2, mainly with lower stirring rates, does not follow sink conditions, and the real release profile can hardly be evaluated in this way. The choice of the type of dissolution apparatus and of the stirring conditions must be made with care to allow the correct determination of the real release profile from the pharmaceuticals forms. With USP apparatus 2 using low stirring rates, the drug release profiles of pharmaceutical formulas with different release characteristics may be misunderstood.

The diltiazem release rate from this pharmaceutical system was not constant and diminished with the square root of time (as stated by the Higuchi model). It is possible to conclude that the phenomenon controlling drug release was the diffusion occurring inside the swelled polymeric matrix.

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