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EVALUATION OF THE FLOW-THROUGH CELL DISSOLUTION APPARATUS: EFFECTS OF FLOW RATE, GLASS BEADS AND TABLET POSITION ON DRUG RELEASE FROM DIFFERENT TYPE OF TABLETS

G.H. Zhang*#, W.A. Vadino, T.T. Yang, W.P. Cho and I.A. Chaudry
Formulation R&D, Schering-Plough Research Institute
Kenilworth, NJ 07033.

*Present Address: Pharmaceutical R&D, Hoffmann-La Roche
Nutley, NJ 07110.
#To whom correspondence should be addressed.

ABSTRACT

Several factors affecting the dissolution performance of various solid dosage forms tested using the flow-through cell method have been evaluated in this study. These factors include the flow rate, the position of tablets in the flow through cell and the glass beads, as well as the physical properties of the dosage forms. The experimental results indicated that the flow rate through the cell greatly affects drug release from disintegrating tablets. Drug release increases with increasing the flow rate of the dissolution medium, as expected. However, the flow rate does not significantly influence drug release from tablets which are not disintegratable, for example, an erodible tablet. The position of the tablets in the flow cell without glass beads is also of importance. Drug release from horizontally positioned tablets is different from vertically positioned tablets in the flow-through cell. It was also observed that the use of glass beads in the flow cell can make the flow pattern

more laminar. This may help avoid a turbulent agitation within the cell, which could impact on drug dissolution.

INTRODUCTION

As an alternative USP dissolution method, the flow-through cell approach has received some attention in recent years. Specially, the flow-through cell dissolution method has been found wide acceptance in pharmaceutical research(1-6). The advantages of the flow-through cell dissolution method for characterization of drug release from pharmaceutical dosage forms have been repeatedly emphasized(7-8). For example, an important advantage is that the sink conditions in a flow-through cell could be reached, which is independent of the solubility of the dissolving species. Therefore, this method has been particularly suggested for dissolution tests of drugs with low solubilities. Other advantages include (a) changing pH conditions during the dissolution tests, for example, for enteric coated dosage forms; (b) positioning the specimen in the small-size dissolution chamber for floating or other special preparations; and so on. With these properties the flow-through cell dissolution method presents an useful alternative to the other existing official compendia dissolution methods. Some investigators demonstrated that a good correlation could be established between in vitro drug release and in vivo drug absorption using the flow-through cell dissolution method(9-10).

Langenbucher, Tingstad and other researchers investigated some factors affecting drug dissolution using the flow-through cell dissolution method(1-6, 11-14). It is reported that the linear flow velocity of the dissolution medium is a major parameter which defines the hydrodynamic "agitation" of the dissolution fluid. In general, the higher the flow rate of the dissolution medium through the chamber, the faster the drug release, which is expected

in most cases. It is reported that the mass of drug released at a given time was a direct function of the flow rate for a film coated product, but an inverse function for a sugar coated tablet(13).

The current study aims at evaluation of other factors affecting drug release in the flow-through cell. An emphasis is focus on the flow rate, tablet position in the chamber and the glass beads in the flow-through cell.

EXPERIMENTAL

Materials: A water soluble drug (Drug A) and a water sparingly soluble drug (Drug B) were utilized as model actives. Hydroxypropyl methylcellulose (Methocel E5 and Methocel K4M, Dow Chemical Co. MI), microcrystalline cellulose (Avicel PH 101, FMC, PA), lactose and corn starch were selected as fillers in the tablet formulations. An ethylcellulose based aqueous dispersion (Surelease) was supplied by Colorcon, PA.

Preparation of Different Type of Tablets: Three types of tablets, including erodible, disintegrating and coated matrix tablets, were prepared using the following procedures:

A. Erodible tablets mainly containing drug A and HPMC (Methocel E5) were made using a direct compression technique by means of Carver Press. Methocel E5 was used as an erodible polymer, as demonstrated in the previous study(15). The tablet shape is round with a flat surface.

B. Disintegrating tablets were made from drug B, microcrystalline cellulose (Avicel PH 101) and corn starch. The wet granulation was used in the process. The tablets were compressed using an F-press. A set of round tooling with a flat surface was used in compaction.

C. Coated matrix tablets were prepared by applying an aqueous ethylcellulose based dispersion (Surelease) on matrix tablets at a 5% coating level. The coating process was performed in Accela-Cota. The matrix tablet cores were formulated with drug A, lactose and hydroxypropyl methylcellulose (Methocel K4M) and tableted by means of an F-press. The tablets were long capsule shaped.

Dissolution Study: A flow-through cell dissolution apparatus (Erweka) with cells of an internal diameter of 22.6 mm was used in all experiments. Six tablets were tested for each experiment at the flow rates ranging from 7 mL/min to 21 mL/mim. During testing, the dissolution medium (1000 mL distilled water) was circulated by pumping it through each cell. Tablets were vertically or horizontally positioned in the cells with or without 6 g of glass beads (1 mm in diameter) filling up the conical part at the bottom of each cell. Glass microfibre filters (GF/D grade) were used in the filter-head in each experiment.

RESULTS AND DISCUSSION

In general, drug dissolution from solids can be described using Noyes-Whitney equation, as shown in the following:

$$\frac{dM}{dt} = \frac{DS(C_s - C)}{h} \quad (1)$$

where M is the amount of drug dissolved in time t, D is the diffusion coefficient of the solute in the dissolution medium, S is the surface area of the exposed tablets, h is the thickness of the diffusion layer, C_s is the solubility of the solute and C is the concentration of the solute in the medium at time t. Theoretically, it is assumed that an aqueous diffusion layer or stagnant liquid film of thickness h exists at the surface of the solid undergoing dissolution.

This thickness h represents a stationary layer of solvent in which the solute molecules exist in concentration from C_s to C. The static dissolution layer thickness is altered by the force of agitation at the surface of the dissolving tablets. Therefore, the flow rate in dissolution testing should impact the force of agitation, resulting in changing the aqueous diffusion layer thickness. The higher the flow rate applied through the cell, the thinner the diffusion layer thickness, hence the faster the dissolution rate in terms of Equation 1.

Figure 1-3 demonstrate the dissolution profiles of drug from disintegrating, erodible and coated matrix tablets using the flow-through cell dissolution apparatus with glass beads, respectively. As expected, the amount of drug released at a given time is a direct function of the flow rate for disintegrating tablets. With an increase in the flow rate, the aqueous diffusion layer thickness should be decreased, resulting in an acceleration of drug release based on Equation 1. Interestingly, the flow rate does not influence drug release from erodible and coated matrix tablets. A possible interpretation is that drug release from both erodible tablets and coated matrix tablets is more complicated than from disintegrating tablets in terms of the drug release mechanisms. Drug release from both erodible and coated matrix tablets is not only related to drug transport through the static diffusion layer at the surface, but also associated with the drug delivery mechanism from dosage forms. For the erodible tablets, the amount of drug released depends on the erosion rate of the device. Therefore, the intrinsic erosion rate of the device dominates the drug release. In this study, especially in the case where glass beads are filled in each cell, the erosion rate of the tablets possibly was not significantly affected by the given range of the flow rate, so that no significant change in the dissolution rate was observed. For the coated matrix tablets, the coating breaks after polymer swelling. Drug release is mainly contributed by the matrix diffusion mechanism. The drug molecules have to travel through the depletion zone in the matrix and the aqueous diffusion layer at

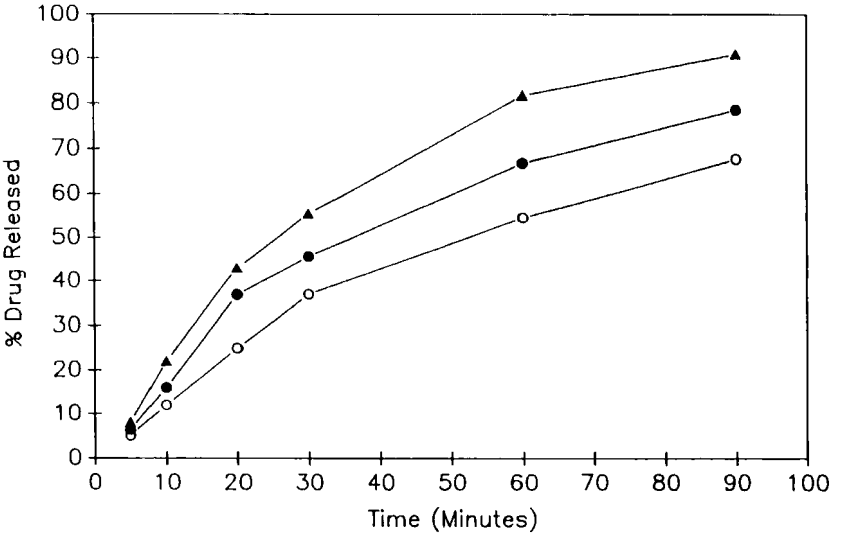

FIGURE 1

Effect of flow rate on drug release from disintegrating tablets in flow-through cell with glass beads at the flow rate of (○) 7.0 mL/min, (●) 14.0 mL/min and (▲) 21.0 mL/min.

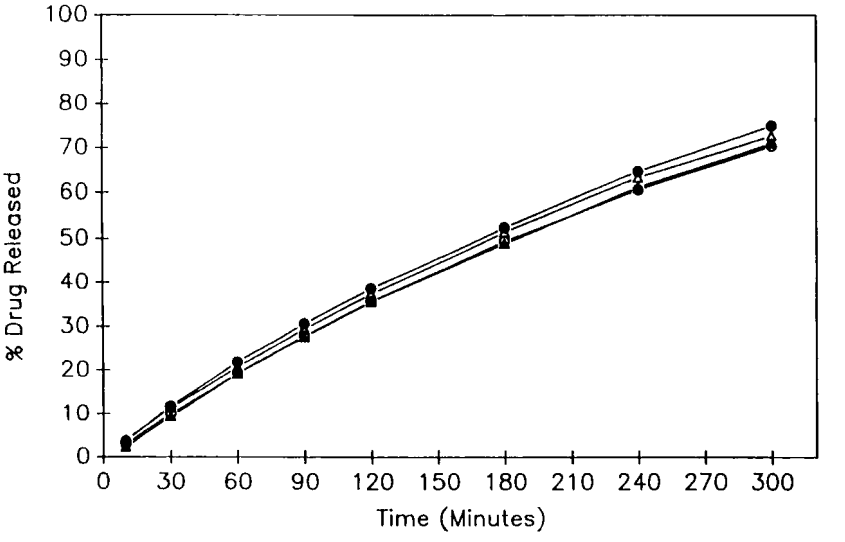

FIGURE 2

Effect of flow rate on drug release from erodible tablets in flow-through cell with glass beads at the flow rate of (○) 7.0 mL/min, (●) 10.5 mL/min, (△) 17.5 mL/min and (▲) 21.0 mL/min.

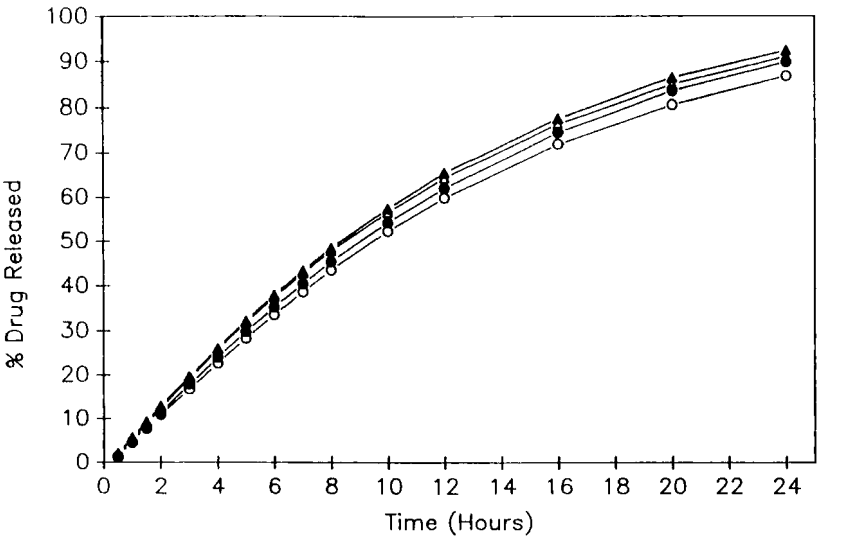

FIGURE 3

Effect of flow rate on drug release from coated matrix tablets in flow-through cell with glass beads at the flow rate of (○) 7.0 mL/min, (●) 10.5 mL/min, (△) 17.5 mL/min and (▲) 21.0 mL/min.

the surface to be released. Therefore, the static diffusion layer involves not only the aqueous diffusion layer at the tablet surface, but also in the matrix depletion zone. In this case, drug release is predominately governed by drug diffusion through the matrix depletion zone because the distance of the matrix depletion zone is much greater than the aqueous diffusion layer at the surface. In general, the force of agitation could not be a factor affecting the diffusion distance in the matrix depletion zone. Consequently, drug release from the coated matrix tablets is not affected by changing the flow rate which only influences the thickness of the diffusion layer at the tablet surface, which is ignored in comparison with the depletion zone of the matrix.

The effect of the flow rate on drug release is also shown in Figures 4-6 when a bed of glass beads was not used in each cell. Drug release profiles

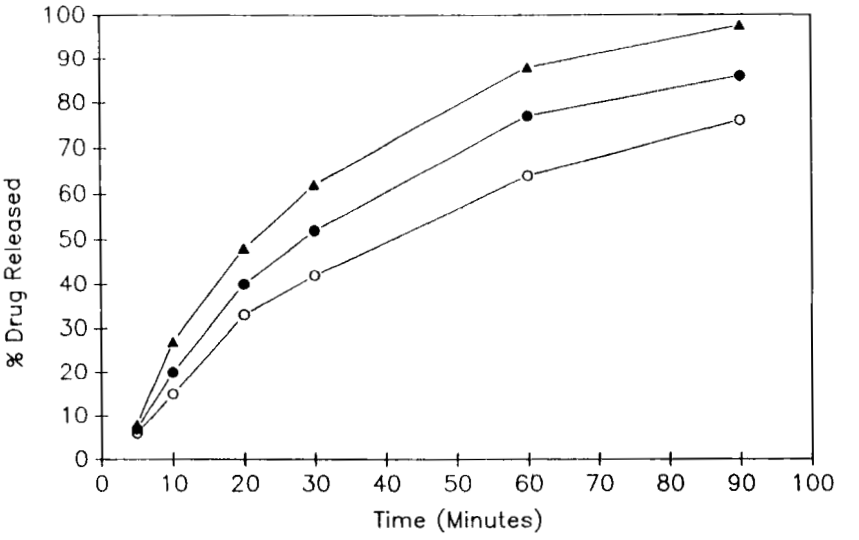

FIGURE 4

Effect of flow rate on drug release from disintegrating tablets in flow-through cell without glass beads at the flow rate of (○) 7.0 mL/min, (●) 14.0 mL/min and (▲) 21.0 mL/min.

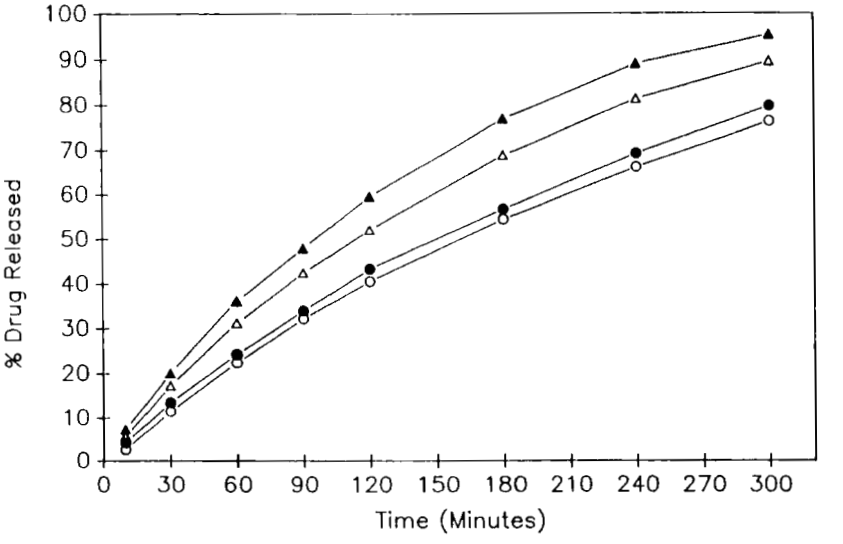

FIGURE 5

Effect of flow rate on drug release from erodible tablets in flow-through cell without glass beads at the flow rate of (○) 7.0 mL/min, (●) 10.5 mL/min, (△) 17.5 mL/min and (▲) 21.0 mL/min.

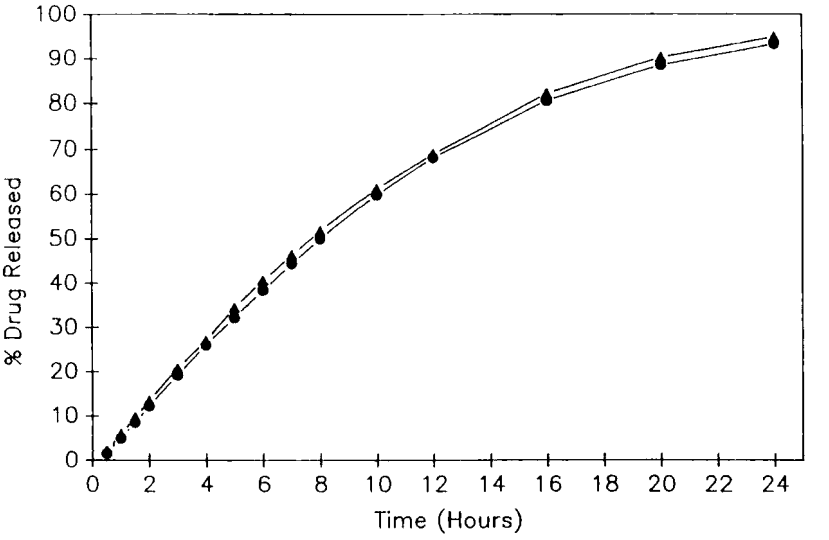

FIGURE 6

Effect of flow rate on drug release from coated matrix tablets in flow-through cell without glass beads at the flow rate of 14.0 mL/min and (▲) 21.0 mL/min.

indicate a significant change for erodible tablets due to various flow rates, which is different from the case where glass beads are filled in each cell. A possible interpretation is that a sharp jet of liquid enters and achieves rather heavy and turbulent agitation which is enough to result in a change in the erosion rate. To avoid this problem, a bed of glass beads is used to equalize liquid entrance to achieve a "laminar" flow. Drug release increases with increasing the flow rate for disintegrating tablets, while drug release from the coated matrix tablets is not significantly affected by changing the flow rate in the case where a bed of glass beads is used in each cell. Therefore, it could be concluded that the effect of the flow rate on drug release is dependent on the characteristics of the dosage forms tested using the flow-through cell dissolution apparatus.

The effect of a bed of glass beads in the flow-through cell during dissolution testing at a 21 mL/min of the flow rate is demonstrated in Figures 7 and 8. Drug release from erodible tablets is significantly influenced by using glass beads in the cell at the same flow rate due to the different flow pattern, "laminar" or "turbulent", as discussed above. Theoretically, drug release from the coated matrix tablets should not be significantly affected by the glass beads in the cells, because the flow pattern does not change drug diffusion through the matrix depletion zone. However, a minor difference of drug release from the coated matrix tablets was observed when glass beads are not used in the cell, as indicated in Figure 8. A phenomenon was observed in dissolution testing that the tablets were sticky to the cell wall in a small portion reducing the surface area to release drug when glass beads are not used in the cell. As a result, drug release shows an unexpected decrease.

The effect of the tablet position in the flow-through cell on drug release was determined for both erodible and coated matrix tablets. No significant change in drug dissolution was observed when erodible tablets and coated matrix tablets were horizontally or vertically positioned in the flow-through cell with glass beads, as expected (Figures 9 and 10). This is because a laminar flow pattern does not affect the drug dissolution conditions in these cases, as mentioned previously. Without glass beads in the flow-through cell, drug release from horizontally positioned erodible tablets is faster than vertically positioned tablets, as shown in Figure 11. It is observed that the surface of horizontally positioned tablets, undergoing a turbulent flow, is greater than the surface area of vertically positioned tablets, facing to the water entrance from the conical part at the bottom of each cell. Therefore, the tablets erode faster due to exposure of more surface area to the turbulent flow, which makes drug release from horizontally positioned tablets accelerated. For the coated matrix tablets, as observed in Figure 12, drug

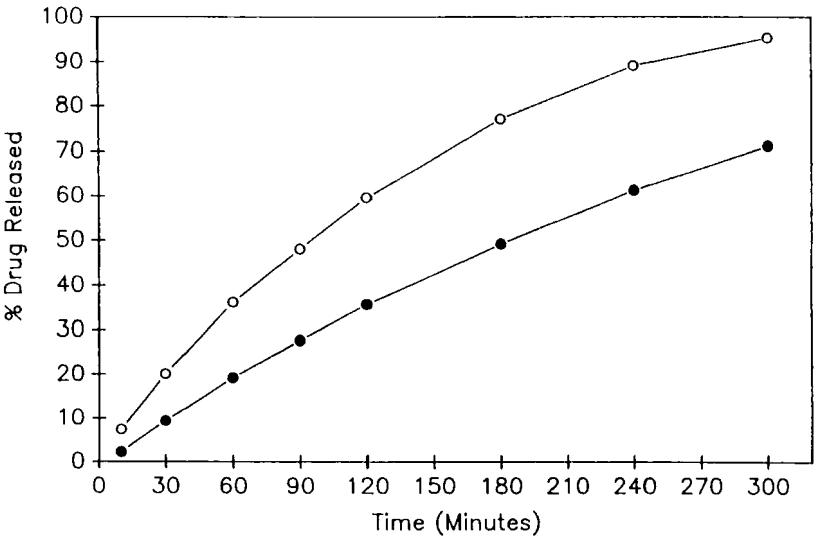

FIGURE 7

Effect of glass beads in the flow-through cell on drug release from erodible tablets at the flow rate of 21.0 mL/min. (○) Without glass beads and (●) with glass beads.

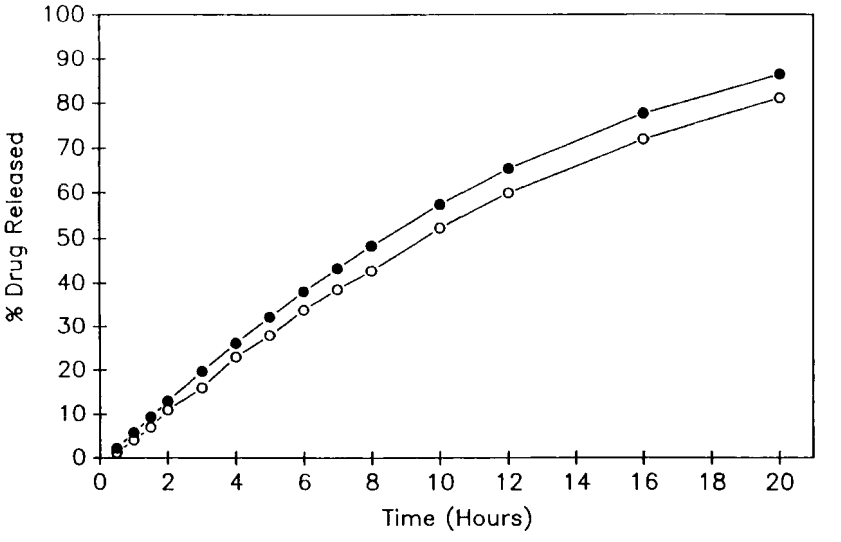

FIGURE 8

Effect of glass beads in the flow-through cell on drug release from coated matrix tablets at the flow rate of 21.0 mL/min. (○) Without glass beads and (●) with glass beads.

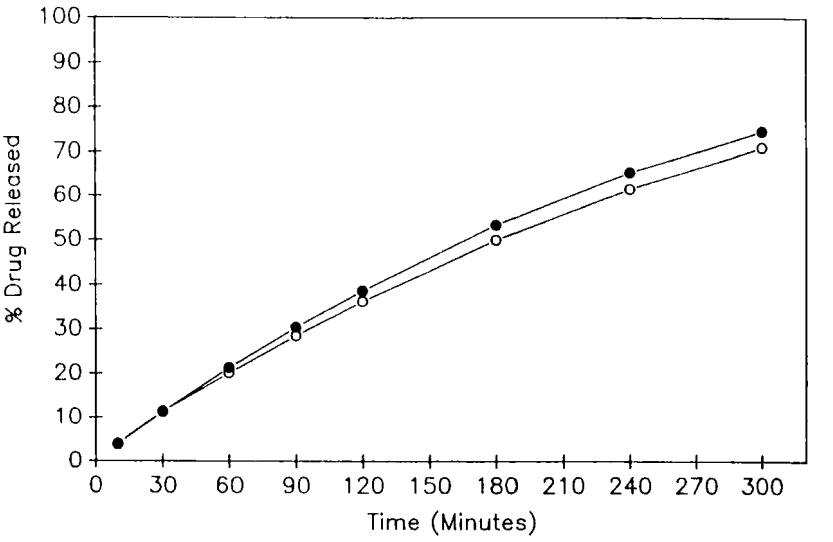

FIGURE 9

Effect of tablet position in the flow-through cell with glass beads on drug release from erodible tablets at the flow rate of 17.5 mL/min. (○) Horizontal position and (●) vertical position.

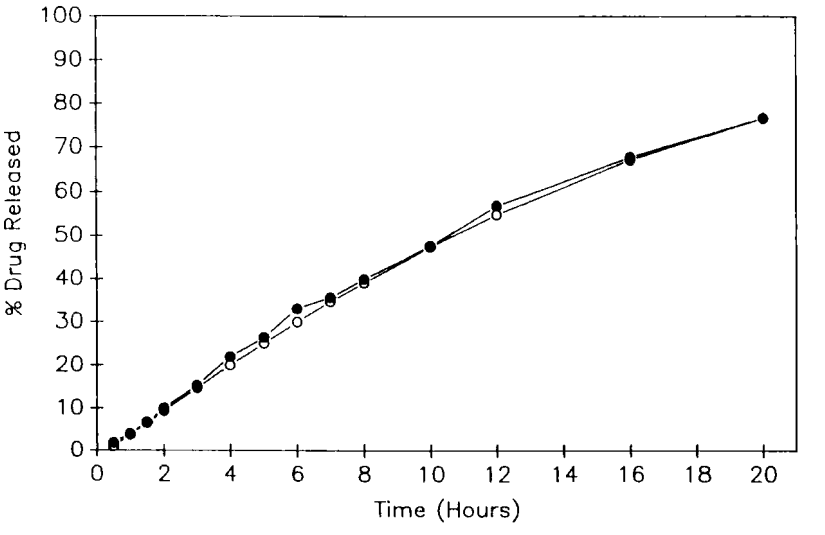

FIGURE 10

Effect of tablet position in the flow-through cell with glass beads on drug release from coated matrix tablets at the flow rate of 10.5 mL/min. (○) Horizontal position and (●) vertical position.

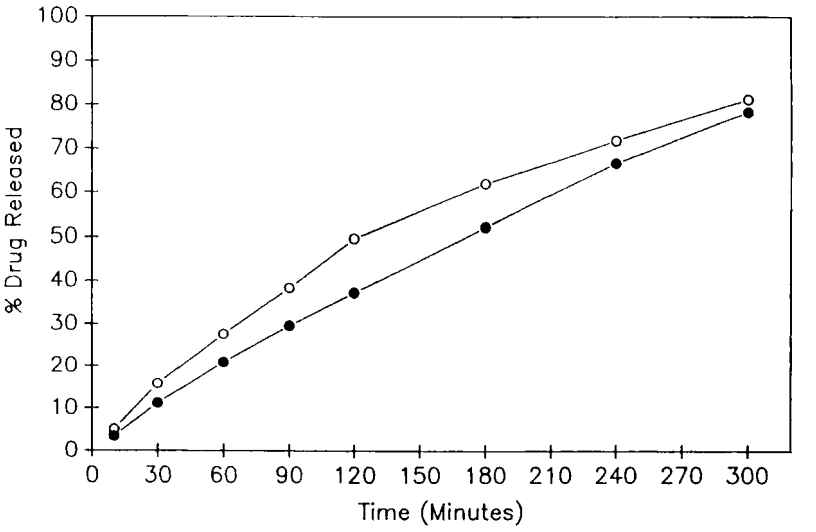

FIGURE 11

Effect of tablet position in the flow-through cell without glass beads on drug release from erodible tablets at the flow rate of 10.5 mL/min. (○) Horizontal position and (●) vertical position.

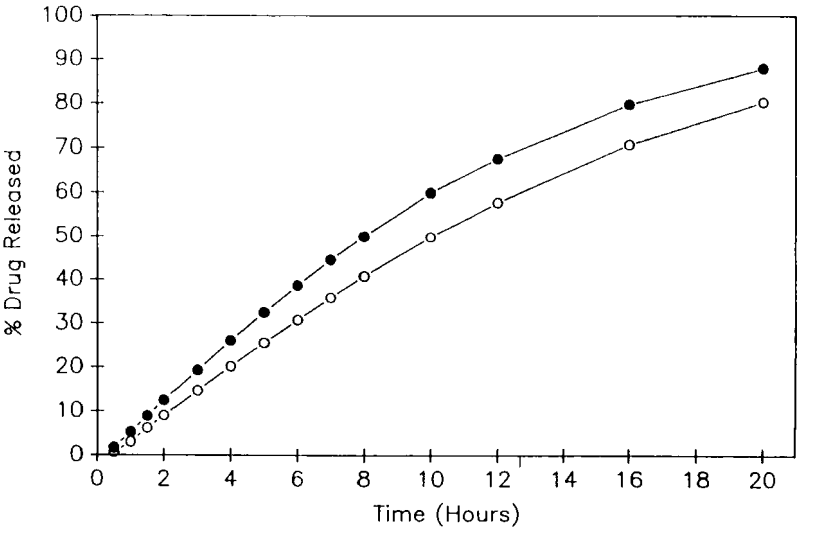

FIGURE 12

Effect of tablet position in the flow-through cell without glass beads on drug release from coated matrix tablets at the flow rate of 17.5 mL/min. (○) Horizontal position and (●) vertical position.

release is faster from vertical positioned tablets than from the horizontally positioned tablets. This results from the coating breakage rate. Because of the long capsule shape, the tablets were inserted into the conical part of the bottom of each cell when vertically positioned, while the tablets were above the conical part in the cell when horizontally positioned. Therefore, the tablets vertically positioned underwent a more turbulent flow than the tablets horizontally positioned. The more the turbulent flow, the faster the coating breakage, leading to a faster drug release profile.

CONCLUSION

The experimental results reveal that the effect of the flow rate of the dissolution medium on drug release is associated with the type of dosage forms and the force of agitation. The flow rate through the cell greatly affects drug release from disintegrating tablets. Drug release increases with increasing the flow rate of the dissolution medium. The flow rate did not significantly influence drug release from coated matrix tablets in both cases where glass beads are or are not used in the cells, because the static diffusion distance in the matrix depletion zone is less affecter by the force of agitation. The flow rate appreciably impacts drug release from erodible tablets when glass beads are not utilized in the cells because of the turbulent flow causing the erosion rate to change. The flow rate insignificantly affects drug release from erodible tablets as glass beads are used in the cell.

The tablet position in the flow-through cell containing glass beads does not seem to be important for both erodible and coated matrix tablets, which could not change the dissolution conditions in terms of the drug release mechanisms. When glass beads are not used in the cells, the tablet position affects drug release from both erodible and coated matrix tablets in different ways. For the erodible tablets, the horizontal position makes drug release

faster possible due to more surface area exposed to the turbulent flow in this case. For the coated matrix tablets, the vertical position causes drug release to be faster because of the change of the coating breakage rate under the turbulent flow condition. The use of glass beads in the flow-through cell is more crucial during dissolution testing, which serves as an equalizer to maintain the flow pattern laminar.

REFERENCES

1. D.C. Baun and G.C. Walker, J. Pharm. Sci., 58, 611, (1969).
2. F. Langenbucher, J. Pharm. Sci., 58, 1265, (1969).
3. J.E. Tingstad and S. Riegelman, J.Pharm. Sci., 59, 692, (1970).
4. H.G. Kwee and G.A. Ulex, Pharm. Ind., 36, 576, (1974).
5. C. Cakiryildiz, P.J. Mehta, W. Rahmen and D. Schönleber, J. Pharm. Sci., 64, 1692, (1975).
6. F. Langenbucher and H. Rettig, Drug Dev. Ind. Pharm., 3, 241, (1977).
7. J. Posti and P.P. Speiser, Int. J. Pharm., 5, 101, (1980).
8. F. Langenbucher, D. Benz, W. Kürth, H. Möller and M. Otz, Pharm. Ind., 51, 1276, (1989).
9. J.M. Aiache, M. Islasse, E. Beyssac, S. Aiache, R. Renoux and J.P. Kantelip, Int. J. Pharm., 39, 235, (1987).
10. J.G. Phillips, Y. Chen and I.N. Wakeling, Drug Dev. Ind. Pharm., 15, 2177, (1989).
11. E.G. Rippie and J.R. Johnson, J.Pharm. Sci., 58, 428, (1969).
12. P.V. Pedersen and K.F. Brown, J. Pharm. Sci., 65, 1442, (1976).
13. M.J. Groves, M.H. Alkan and M.A. Deer, J. Pharm. Pharmac., 27, 400, (1975).
14. M. Nicklasson, B. Wennergren, J. Lindberg, C. Person, R. Ahlgren, B. Palm, A. Petterson and L. Wennergren, Int. J. Pharm., 37, 195, (1987).

15. G.H. Zhang, W.A. Vadino and I.A. Chaudry, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 17, 333, (1990).

16. A. Martin, J. Swarbrick and A. Cammarata, Physical Pharmacy, 3rd Ed., Chap.15, Lea & Febiger, Philadelphia, 1983.