Drug Development and Industrial Pharmacy, 32:669–675, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600683485

Taylor & Francis

High-Throughput Evaluation of Non-Swellable Controlled Release Matrix Tablets

R. Panchagnula, A. Gupta, S. Kandavilli, and M. V. S. Varma
Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER) Sector 67, S.A.S. Nagar (Punjab), India

ABSTRACT Drug release from controlled-release (CR) matrix tablets involves the permeation and diffusion of water through the system. In this study, a new methodology is proposed for the measurement of water permeation and simultaneous drug release from the inert, non-swellable CR matrix tablet of diltiazem (DLT) and a correlation is made between these two processes. Cylindrical matrices were readily prepared by direct compression of pellets obtained by extrusion-spheronization. Water transport was studied using tritiated water (HTO) as a permeant in a Franz-diffusion cell and simultaneously drug release was measured. Further, dissolution was performed on USP XXI/XXII dissolution apparatus I using demineralized water. Matrices showed a steady water-uptake up to 6 h and the steady state for HTO permeation lasting from 6-h to 24-h Flux of water permeated and flux of drug released correlated well. Thus, HTO permeation through the matrix tablet and the proposed methodology can be used as a tool and/or surrogate marker for evaluation of controlled release matrix tablets. This methodology can be coined as "high-throughput" in terms of amount of labor and resources required in comparison to that of dissolution.

KEYWORDS Controlled release, Dissolution, High throughput, Permeation, Diltiazem

INTRODUCTION

Interest in controlled-release (CR) systems and its release mechanism have continued for more than six decades in pharmaceutical arena and are being pursued. CR matrix systems have been divided into porous and nonporous matrices (Colombo, 1993). Nonporous matrices are true swelling-controlled systems in which the drug is essentially immobile when the polymer is glassy (dry), but relatively mobile when the polymer goes to rubbery state on hydration.

Per oral controlled-release matrix formulations containing inert matrices release their drug through either diffusion and/or dissolution-controlled mechanism. In such systems, water uptake/transport is an important prerequisite for subsequent release of the drug from the inert matrix and therefore an

Address correspondence to Dr. R. Panchagnula, Pharmacy School of Biomedical Sciences University of Ulster, Cromore Road, Coleraine BT52 1SA; Tel: +44 (0)28 7032 4128; Fax: +44 (0)28 7032 4965; E-mail: r.panchagnula@ulster.ac.uk

insight into its relationship to drug release can be valuable for the development and evaluation of CR systems (Varma et al., 2004). Moreover, dissolution testing is the fundamental and functional method for evaluation of the performance of the CR release systems, which is used as a surrogate for in vivo performance (Sood & Panchagnula, 1999). However, it is laborious and cumbersome in case of controlled-release system, as the study goes up to a few days, which includes sample collection, preparation, and its analysis (in case of nonautomated dissolution apparatuses). Hence, a "high-throughput" method for evaluating CR system is desired, wherein not only water ingress/transport but also drug release can be measured simultaneously. This water ingress/transport measurement once correlated with the drug release can act as a surrogate marker for drug release. Water transport and its behavior have been studied extensively in case of swellable matrices with the help of scanning electron microscopy (Melia, 1991), nuclear magnetic resonance imaging (Asraf et al., 1994), optical imaging technique (Gao & Meury, 1996), ultrasound (Konrad et al., 1998), rheology (Talucder et al., 1996), and texture analysis (Pillay & Fassihi, 2000; Varma et al., 2005). Similarly, water diffusion and permeation in polymeric films (reservoir systems) have been studied by radio-scintillation-based method, fluorescent probes/color dyes, and infrared absorption. However, similar studies in case of inert, non-swellable porous matrix system have not been reported. The major objective of this investigation is to evaluate the water diffusion across matrix tablet as a possible tool and/or surrogate for evaluation of CR formulations, which may be used in lieu of dissolution testing. Further, we intend to provide a simple methodology to study the water ingress into inert, non-swellable porous matrix system and simultaneously evaluate drug release.

MATERIALS AND METHODS

Materials

Diltiazem (DLT) was received as *gratis* sample from Global Bulk Drugs & Fine Chemicals Ltd., India, glyceryl mono-stearate, microcrystalline cellulose, and polyvinyl pyrolidone (all used as excipients) were procured from Allwell Pharmaceutical Company, India; aerosil from Panacea Biotech Ltd., India, and tritiated water (HTO) (1Ci/gm) from Sigma Co., USA. All other chemicals and reagents used were of laboratory grade.

METHODS

Formulation

DLT pellets were first prepared using extrusion-spheronization (ES) having the rotating roller extruder (Model 10, Caleva) with standard screen (1 mm diameter aperture, 150 mm diameter, and 1 mm thick) and spheronizer (Model 120, Caleva) with 120 mm diameter plate (3 × 3 mm squared pitch, 1 mm depth) according to the optimized master formula given in Table 1 (Sood et al., 2004). Prior weighted 330 mg of DLT pellets (109 mg drug content) of desired size range, i.e., 355–710 μm (passed through mesh no. 16 and retained on 22, 30, and 44), premixed with 0.2% w/w aerosil in a cone mixer (Erweka, Germany) was manually filled and compressed using a single punch tablet machine (Cadmach, India) fitted with standard 9.0 mm circular flat-faced punches to give DLT tablets (DLT-TAB). Hardness of the tablets was kept between 14–16 kiloPascals. Optimized batch prepared was coded as DLT-TAB B11, and subsequent three reproduced batches (batch size ~150 tablets each) were coded as DLT-TAB B11A, B, and C respectively (Sood et al. 2004).

Dissolution Studies

Dissolution of DLT-TAB was performed on USP XXI/XXII dissolution apparatus I (basket) (Electrolab, India) rotating at 100 rpm and maintained at 37 ± 0.5°C and demineralized water was used as media. Samples were withdrawn at different time intervals over a 24 h period and the volume withdrawn was immediately replaced with fresh medium. Samples were filtered through 0.45 μm pore-size hydrophilic filter (Minisart, Sartorius) and analyzed at 236 nm (Sood et al., 2004).

TABLE 1 **Master Formula of the Selected Model Tablet**

	DLT- TAB
1. DLT HCl	33% w/w
2. MCC	50% w/w
3. GMS	17% w/w
4. PVP (20% w/w in water)	q.s.

Key: DLT HCl – Diltiazem hydrochloride; MCC – Microcrystalline cellulose; GMS – Glyceryl mono-stearate; PVP – Polyvinyl pyrolidone. Complete details about formulation development and evaluation is described elsewhere (Sood et al. 2004)

Water Uptake and Permeation Studies

To study HTO permeation, DLT-TAB was fixed in the donor compartment of Franz-diffusion cells having an internal diameter of approximately 9 mm, with molten beeswax and then contact with the receptor fluid was ensured (Fig. 1). Care was taken to prevent any wax being adhering to the tablet surface facing both the donor and receptor compartment. The tablet-fixed-donor chamber was then mounted on the receptor cell platform filled with demineralized water and maintained at 37 ± 0.5 °C. Either 200 µl or 400 µl of HTO (60 nCi/mL) was filled in the donor compartment and then covered with Parafilm™ to prevent any evaporation. Samples of 200 µl from the receptor chamber were withdrawn at predetermined time points and replaced by fresh receptor medium. Both DLT and HTO in samples were quantified by UV spectrometry and liquid scintillation counting, respectively. Further, water uptake studies were also done in shaker water-bath (Heto-Holton, Denmark), maintained at 37 ± 0.5°C and 50 rpm to quantify the amount of HTO permeated within the tablets. Tablets were kept in a petri dish having 25 mL of water spiked with 1 mL of HTO (60 nCi/mL), and kept in the shaker water-bath. At predetermined time points, tablets were taken out, carefully blotted dry, and HTO in tablets were quantified by liquid scintillation counting.

Amount of HTO permeated into and through the tablets in mg/cm^2 was plotted as a function of time. The permeation parameters; flux (J, in mg/cm^2/hr), the lag time ($T_{lag,}$ in hr) and diffusion coefficient (D in cm^2/sec) were calculated as described earlier (Jain et al., 2002)

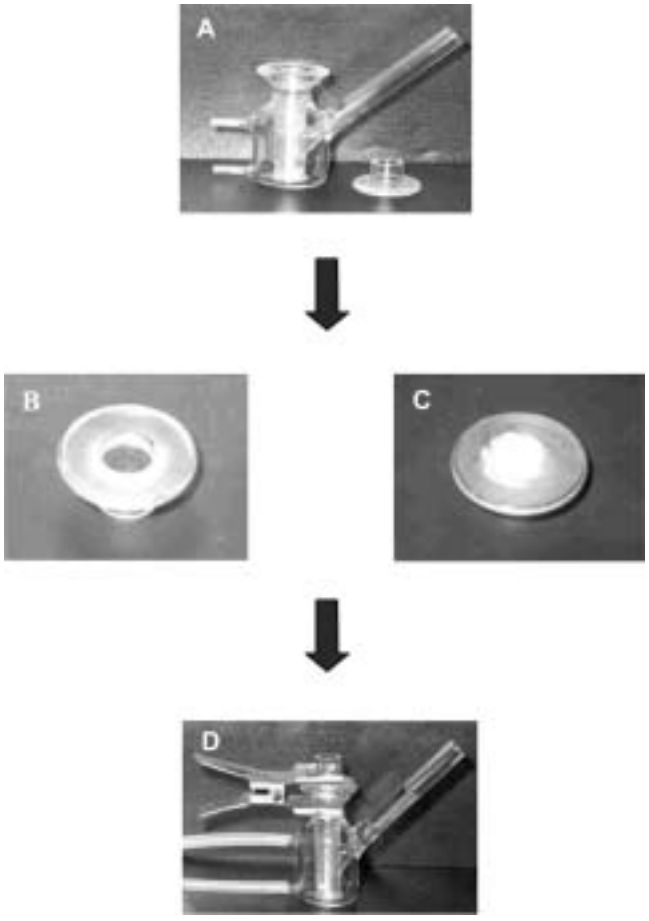

FIGURE 1 **Experimental Setup for HTO Permeation Study Through the Matrix Tablets Using Franz-Diffusion Cells.**

Key: A – Empty Franz-diffusion cell; B – Donor cell; C – Tablet fixed in the donor cell with wax; D – Donor cell is mounted onto the receptor cell platform coated with silicone grease along the circumference of the platform and held in position by a metallic clamp. The set up is then placed on magnetic stirring platform for agitation. Water (37 ± 0.5°C) is circulated through the inlet and outlet of the diffusion cell.

Analytical Methods

DLT samples from assay, dissolution and permeation studies were analyzed using UV spectrophotometer (Beckman, USA) at 236 nm. Radioactivity of HTO within the formulations and in the samples was determined by liquid scintillation counting (Wallac 1409, Finland) and converted into milligrams of HTO permeated.

RESULTS AND DISCUSSION

Biopharmaceutics classification system (BCS) class I drug, DLT was selected for this study because it is highly soluble and permeable and thus its absorption and bioavailability are not influenced by the environmental factors like fluid volume, pH, and other GI contents. Drug release from DLT-TAB was 20–25% release within 1 h, while about 60% of the drug is released in 6 h (Fig. 2). Figure 3 shows the permeation profile/parameters of the same through the matrix tablet at two different label volumes in the donor compartment (i.e., 200 µl and 400 µl). It was observed that as the volume of the donor compartment is increased, flux of HTO also increased through the matrix tablet. However, lag time obtained in both cases were the same, which indicates uniformity in the porosity of the matrix tablets wherein a definite period of time is needed in order to fill the pores within the matrix, then allowing the labeled water to appear in the receptor

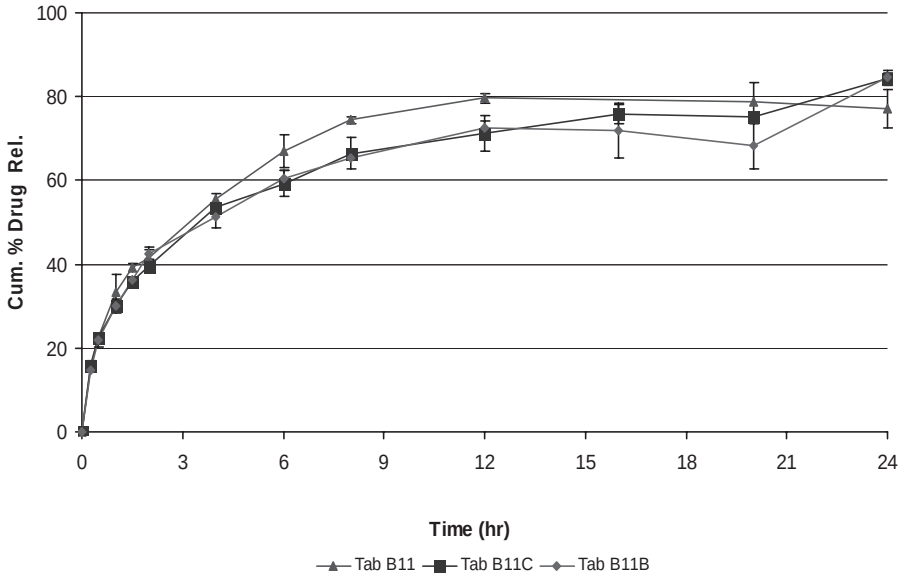

FIGURE 2 **Drug Release Profile from DLT-TAB.**

TAB B11 is tablet compressed out of DLT B11 pellets with flat-faced punches having a diameter of 9.03mm, thickness of 3.81 mm and hardness of 14–16 kp. B11B and B11C is the reproduced batch for DLT B11. Dissolutions were done in USP 1 (rotating basket) at 100 rpm, maintained at 37 ± 0.5°C, with three (n = 3) replicates, using demineralized water (900 ml) as dissolution media.

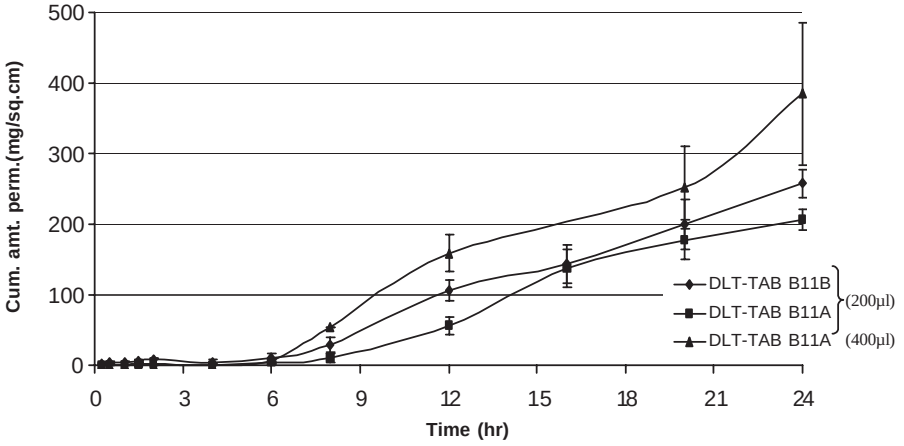

FIGURE 3 **Permeation Profile of HTO Through Various DLT-TAB. Permeation Profile Shown Here Corresponds to Two Different Label Volumes of 200 µl and 400 µl in the Donor Compartment of the Franz-Diffusion Cell. Data Represents Mean of Three Readings ± S.E.M.**

Permeation parameters for various DLT-TAB formulations obtained from above data[1]

Batch	Lag time (hr)[4]	Flux (mg/cm^2/hr)[4]	Diffusion coefficient (cm^2/sec)
1) DLT-TAB B11A[2]	7.51 (±0.20)	14.48 (±3.48)	8.57×10^{-7}
2) DLT-TAB B11B[2]	5.78 (±0.53)	14.56 (±3.36)	11.10×10^{-7}
3) DLT-TAB B11A[3]	5.80 (±0.10)	25.62 (±5.87)	11.00×10^{-7}

[1]Data represents mean of three readings ± S.E.M.

[2]Permeation data obtained with 200 µl of tritiated water (60 nCi/mL) as donor fluid.

[3]Data obtained with 400 µl of tritiated water. Permeation was done in Franz-diffusion cell set up as shown in Figure 1 with demineralized water as the receptor fluid maintained at 37 ± 0.5°C and stirred at 850 rpm with the help of magnetic beads (1 cm in length).

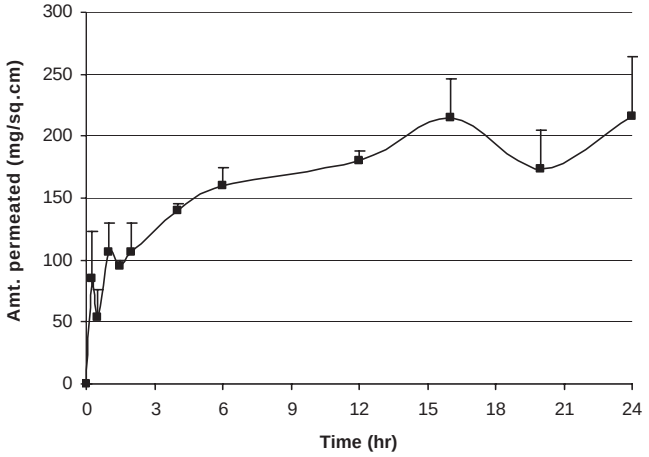

FIGURE 4 **HTO Uptake within the DLT-TAB B11A. Study Was Done in Petri Dishes Containing Tritiated Water That was Kept in Shaker Water-bath Set at 37 ± 0.5°C and 50 rpm. Water Uptake Was Seen up to 6 h, after Which There Was a Plateau Phase Indicating No More Water Uptake and Starting of Permeation Phase, Which Was Consistent with the Permeation Profile. Data Represents Mean of Three Readings ±S.E.M.**

compartment. This is further substantiated by HTO uptake by the tablets (Fig. 4), which showed a steady water-uptake up to 6 h and then reached a plateau. The steady state for HTO permeation lasting from 6-h till the end of experiment (24-h) indicated continuous formation of pores within the tablets, with function of time that allowed consistent mobility of water within the tablets (Fig. 3). For an inert matrix, this could be possible only when there is simultaneous release of drug from the dosage form, thus creating additional pores and channels for HTO permeation.

Drug release from DLT-TAB into the receptor compartment of the Franz-diffusion cell as well as USP I dissolution vessel is shown in Fig. 5. About 65% of drug was released in 12 h, which is consistent with the drug release obtained from the dissolution apparatus. However, the release rate was lesser in case of Franz-diffusion cell. This could be due to difference in surface area of tablet available for drug diffusion in two different setups. Moreover, the hydrodynamic stress within the Franz-diffusion cell is less as compared to that of the dissolution apparatus, which has a direct influence on the drug release. However, as DLT is a highly water-soluble drug, the release behavior is generally unaffected by the apparatus design. The release behavior obtained within the Franz-diffusion cell may not be applicable to drugs having medium or lower solubility due to the constraint of maintaining the sink conditions within the available volume of 5–6 mL of receptor phase.

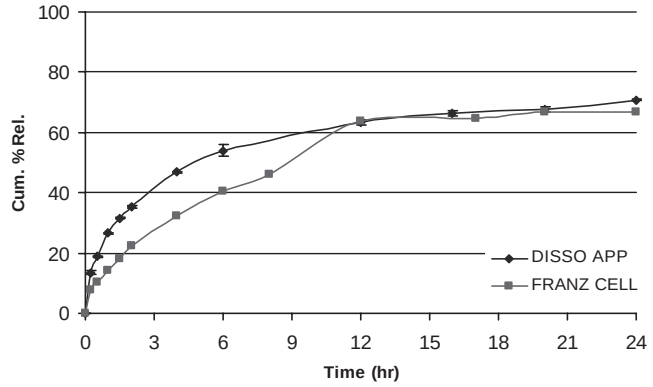

FIGURE 5 **Drug Release Profile from DLT-TAB B11A in Franz-diffusion Cell in Comparison to Drug Released from Dissolution Vessel (USP1). Drug Release Was Done in Demineralized Water As the Receptor Fluid Maintained at 37 ± 0.5°C and Stirring Was Provided By Magnetic Beads (1 cm Length) Rotated at 850 rpm.**

In order to correlate water transport and simultaneous drug release from the matrix tablet in the Franz-diffusion cell, the events occurring in the system are shown schematically in Fig. 6. The water transport across the matrix tablet follows a sequence of events *viz*. penetration into and permeation across the tablet, characterized by diffusion constants K_1 and K_2, respectively. Time required for water to penetrate the tablet core is designated as the first lag time (T_{lag1}), and a second lag time (T_{lag2}) is required wherein the penetrated water permeates out of the matrix tablet into the receptor compartment. During these events, drug release occurs consistently and uniformly, and is characterized by zero-order release rate constant given by K_3. To quantify and correlate water flux through the matrix tablet with the amount of drug released per unit surface area, lag time corrections (for both T_{lag1} and T_{lag2}) were performed. HTO uptake studies revealed that

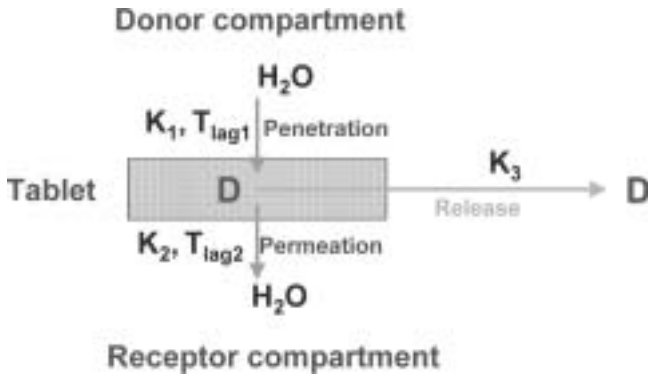

FIGURE 6 **Kinetic Model for Simultaneous Water Transport and Drug Release from DLT Matrix Tablet in Franz-diffusion Cell.**

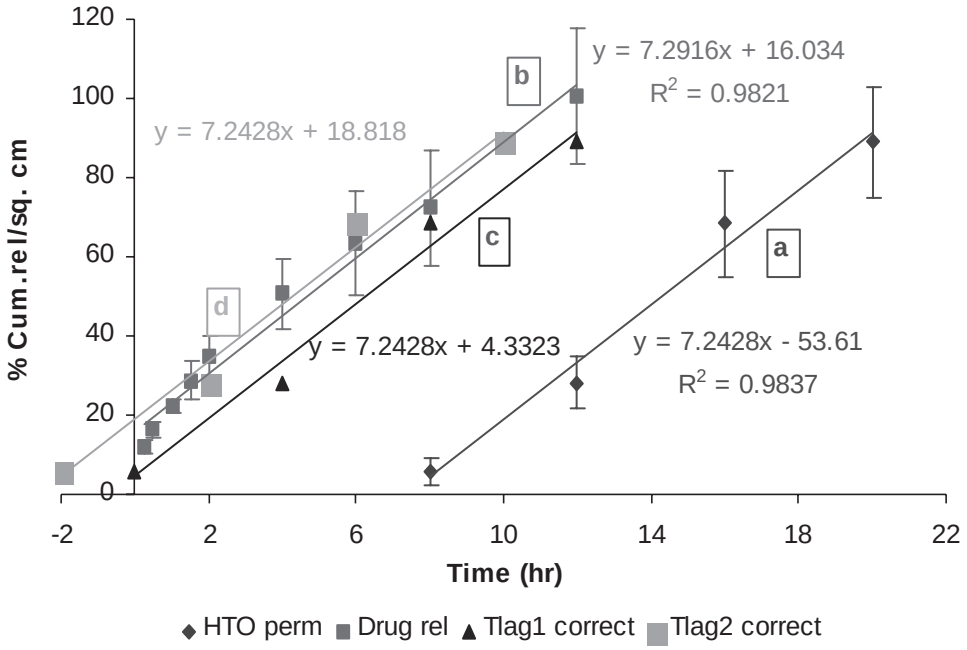

FIGURE 7 **Plot Showing Correlation Between Water Permeation and Drug Release from Matrix Tablets Using Franz-diffusion Cells.**
Key: a. HTO permeation. b. DLT release from matrix. c. Water permeation corrected for T_{lag1}. d. Water permeation corrected for T_{lag2}

T_{lag1} was about 6 h. Further, permeation experiment using the Franz-diffusion cell showed that total lag time before the steady-state diffusion attained was around 7–8 h and thus the T_{lag2} should be about 2 h.

A plot of cumulative percentage HTO permeated and drug released per unit cross section area (calculated from πr^2) with respect to time gives profiles having same slope (Fig. 7). As mentioned earlier, due to the lag time involved, HTO permeation profile is displaced toward the right. Hence, this profile was corrected for first lag time, T_{lag1} to get a point-to-point correlation as shown in Fig. 7C; however, due to the involvement of the second lag time T_{lag2}, exact overlap could not be obtained. Therefore, correction for the second lag time was performed in order to get a point-to-point correlation with super imposable profiles (Figure 7b and d). Similarity in flux value for HTO permeation and drug release rate constant indicates that the interaction of both solutes with the matrix is similar; moreover although there is a difference in molecular weight, high solubility of DLT (400–600 mg/mL) might have offset its influence on diffusion coefficient. Since the flux values obtained in both cases were similar, the water flux through the matrix system can act as a surrogate marker to drug release for at least highly soluble and low molecular weight drugs such as DLT for routine quality control once a similarity between the drug release and water permeation pattern is established.

Since drug release profiles from both apparatuses (USP I dissolution vessel and Franz-diffusion cell) were nearly equal, one would expect to have the same correlation as obtained previously. However, no correlation between drug release from dissolution testing and water permeation in the Franz diffusion-cell could be established, as surface area of tablet releasing drug in the case of dissolution vessel is more, as compared to that of Franz-diffusion cell, wherein drug release occurs from only one surface. In addition, the release in Franz-diffusion cell is unidirectional rather than being multidirectional as in the case of standard dissolution apparatus.

Drug release from inert matrices is controlled by the volume fraction of water and the porosity in matrix. Due to high solubility of BCS class I and III drugs, water permeation is the rate-limiting step that determines the rate and extent of drug release. With dynamic water uptake, a drug volume fraction gradient is established in the region between moving and the erosion fronts resulting in altered porosity of the matrix. As the drug starts dissolving, water volume fraction in the matrix increases constantly until water soluble components diffuse out of the matrix into the surrounding medium. Hence water permeation across

the inert matrix started only after about 7-h where the water volume fraction of matrix reached its maximum as observed in water uptake studies (Fig. 4). For insoluble drugs, more time is required for achieving maximum water volume fraction of the matrix and thus the lag time will be long. Formulation factors like matrix former type, proportion, and hardness of matrix determine the porosity of the matrix and thus the dynamics of water within it during dissolution.

On normalizing the drug release to the total surface area in case of dissolution, the effective percent cumulative drug released falls well below the required release profile (data not shown) and thus making correlation was not possible. This needs further investigation so that water permeation could act as a surrogate for drug release (studies under progress and shall be reported separately). Correlating the water flux (corrected for lag time) and drug released, we propose to devise water flux as an indicator for drug release which can be used in routine evaluation of CR matrix formulation, thus making it a tool and/or surrogate marker, wherein the need for dissolution testing is avoided once a correlation is made between drug released and water flux. These results indicate rapid screening of CR formulations in the developmental phase (BCS class I drugs). Further validation of this methodology shall provide high-throughput surrogate marker for performance evaluation of oral CR matrices.

CONCLUSIONS

A simple methodology for evaluation of controlled-release matrix tablet of DLT, through the use of Franz-diffusion cell setup, was successful as water permeation and drug release could be correlated after correcting for the lag time involved for water transport. The major advantages of this technique over other reported methods are (1) its use to study the water ingress into inert, non-swellable porous matrix system; and (2) estimate the drug release (performance) and water ingress (mechanism) simultaneously. Further, establishing correlation between in vivo drug release and water permeation could provide high-throughput surrogate marker for performance evaluation of oral CR matrices.

REFERENCES

Ashraf, M., Iuorno, V. L., Coffin-Beach, D., Evans, A., & Augsburger, L. L. (1994). A novel nuclear magnetic resonance (NMR) imaging method for measuring the water front penetration rate in hydrophilic polymer matrix capsule plugs and its role in drug release. *Pharm. Res. 11*, 733–737.

Colombo, P. (1993). Swelling-controlled release in hydrogel matrices for oral route. *Adv. Drug. Del. Rev. 11*, 37–57.

Gao, P., & Meury, R. H. (1996). Swelling of hydroxypropylmethylcellulose matrix tablets. I. Characterisation of swelling using a novel optical imaging method. *J. Pharm. Sci. 85*, 725–731.

Jain, A. K., Thomas, N. S., & Panchagnula, R. (2002). Transdermal delivery of imipramine hydrochloride: effect of terpenes. *J. Cont. Release 79*: 93–101.

Konrad, R., Christ, A., Zessin, G., & Cobet, U. (1998). The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC tablets using NMR imaging. Int. *J. Pharm. 163*, 123–131.

Melia, C. D. (1991). Hydrophilic matrix sustained release systems based on polysaccharide carriers. *Crit. Rev. Ther. Drug Carr. Sys. 8*, 395–421.

Pillay, V., & Fassihi, R. (2000). A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. *J. Control. Release. 67*, 67–78.

Sood, A., & Panchagnula, R. (1999). Role of dissolution studies in controlled release drug delivery system. *S.T.P. Pharm. Sci. 9*, 157–168.

Sood, A., Ashokraj, Y., & Panchagnula, R. (2004) Use of extrusion-spheronization to develop controlled release dosage forms for diltiazem hydrochloride. *Pharm. Tech*. 62–85.

Talucdar, M. M., Vinckier, I., Moldenaers, P., & Kinget, R. (1996). Rheological characterization of xanthan gum and hydroxypropylmethyl cellulose with respect to controlled-release drug delivery. *J. Pharm. Sci. 85*, 537–540.

Varma, M. V. S., Kaushal, A. M., Garg, A., & Garg, S. (2004). Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. *Am. J. Drug Deliv. 2*, 43–57.

Varma, M. V. S., Kaushal, A. M., & Garg, S. (2005). Influence of micro-environmental pH on the gel layer behavior and release of a basic drug from various hydrophilic matrices. *J. Control. Release. 103*, 499–510.