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Release performance of a poorly soluble drug from a novel, Eudragit®-based multi-unit erosion matrix

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Abstract

Mechanisms governing the release of drugs from controlled delivery systems are mainly diffusion, osmosis and erosion. For poorly soluble drugs, the existing mechanisms are limited to osmosis and matrix erosion, that are commonly observed in single unit matrix dosage forms. This study reports formulation and dissolution performance of Eudragit® L 100 55 and Eudragit® S 100 based multi-unit controlled release system of a poorly soluble thiazole based leukotriene D_4 antagonist, that was obtained by an extrusion/spheronization technique. Effect of triethyl citrate, that was incorporated in the matrix, on the dissolution performance of the drug was also evaluated. In vitro matrix erosion and drug release from the pellets were determined by the use of USP Dissolution Apparatus I, pH 6.8 phosphate buffer, gravimetry and UV spectrophotometry, respectively. Results obtained demonstrated that matrix erosion and drug release occurred simultaneously from the pellets. Pellets eroded with a consequent reduction in size without any change in the pellet geometry for over 12 h. Matrix erosion and drug release followed zero order kinetics. Data obtained strongly suggested a polymer controlled, surface erosion mechanism.

Keywords: Extrusion/spheronization; Eudragit® L 100-55; Eudragit® S 100; Surface erosion; Effect of plasticizer; Pellets; Controlled release

1. Introduction

Release of poorly soluble drugs from controlled delivery systems is a challenging task for the pharmaceutical scientist. Alza Corporation has developed a gastrointestinal therapeutic system (GITS) for the release of nifedipine, a poorly soluble drug, over a period of 24 h. The system is an 'Oros' tablet that releases the drug under osmotic pressure differences between the GI fluids and the osmotic agents in the semi-permeable membrane surrounding the tablet. Release of a

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drug from this system occurs as a fine suspension from the laser drilled GITS device (Chien, 1992). Other approaches for the release of poorly soluble drugs from the controlled release erosion matrix tablets employing hydrophilic cellulosic polymers are reported (Giunchedi et al., 1993; Emara, 1994). Existing mechanisms controlling the release of poorly soluble drugs are limited to osmosis and erosion. Due to their negligible aqueous solubility, diffusion has practically very little or no contribution in the release of insoluble drugs from the controlled delivery systems.

More recently, multi-unit dosage forms have gained considerable popularity over conventional single units for controlled release technology. Due to their rapid dispersion in the gastrointestinal tract, they maximize drug absorption, reduce peak plasma fluctuations, minimize potential side effects without lowering drug bioavailability. They also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter-subject variability of plasma profiles, which are common with single-unit regimens, are minimized. They are also less susceptible to dose dumping than the reservoir or matrix type, single-unit dosage forms (Ghebre-Sellassie, 1989).

Controlled release of poorly soluble drugs such as nifedipine, ampicillin and isosorbide dinitrate via pellets have been reported (Yang et al., 1989; Chandy and Sharma, 1992, 1993; Lalla and Bhat, 1993a,b). All these studies primarily employed microcrystalline cellulose as a pellet forming agent. Microcrystalline cellulose provides good pellet forming properties and thus offers potential advantage in pellet manufacturing by extrusion/spheronization technology. Release from such pellets were extensively studied (O'Connor, 1987). It was concluded that drug release from these pellets followed Higuchi's square root of time equation suggesting a diffusion controlled release mechanism.

In this paper, effects of two different Eudragit® polymers and triethyl citrate on the formulation and release performance of the matrix pellets of a poorly soluble leucotriene D_4 antagonist were reported. It was hypothesized that, zero order drug release from such as system would occur, if the matrix pellet erodes slowly from the pellet surface as a function of time. As erosion progresses from the pellet surface towards the core, the drug which is homogenously dispersed in the matrix, will be released in constant increments. Eudragit® L 100 55 and Eudragit® S 100 polymers were tested in this study to obtain surface erosion. These are anionic polymers based on methacrylic acid and methacrylic acid esters. The ratio of carboxyl groups to ester units is about 1:1 in Eudragit® L 100 55 and about 1:2 in Eudragit® S 100. These polymers dissolve above pH 5.5 and 7.0 respectively by salt formation.

2. Materials and methods

The poorly soluble drug used as a model was a thiazole based leukotriene D_4 antagonist with a solubility less than 1.3 μg/ml at pH 6.8 (Hoffmann-La Roche Inc., Nutley, NJ). Eudragit® L 100 55 and Eudragit® S 100 (Röhm America Inc., Piscataway, NJ) were used as rate controlling polymers and pellet matrix forming agents. Kollidon® 90 F (BASF Inc., Parsipanny, NJ) was used as a binder. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was employed to prevent inter-pellet sticking during the spheronization stage. Triethyl citrate (Morflex, Inc., Greensboro, NC), is a hydrophilic plasticizer that was recommended for use in Eudragits® for coating purposes. During preliminary studies, addition of triethyl citrate increased the drug released from the pellets. Therefore, its effect on the release performances of the Eudragit® pellets was also studied.

2.1. Formulation of pellets

Eudragit®L 100 55 and Eudragit®S 100 powders were mixed in a turbula mixer (Turbula Mixer, Impandex Inc., Maywood, NJ, USA) for 30 min. Triethyl citrate was added to some formulations (Table 1) as a plasticizer and the resultant mixture was triturated in a mortar for 5 min. The drug and polyvinyl pyrrolidone (Kollidon®K90F), used as the binder, were added and mixed for 30 min in the turbula mixer. This mixture was then granulated with 70% w/w deionized water in a

mortar and later extruded through a LCI Xtruder (Model DG-L1, Fuji Paudal Co., Ltd., Japan) with a screen size of either 1.2 or 2.0 mm diameter at 40 rpm screw speed. The extrudates were immediately transferred into a rotating plate in the spheronizer (G.B. Caleva Ltd, Model 120, Dorset, UK, consisting of a stationary vertical cylinder with a friction plate (diameter 32 cm) of 2-mm cross-hatched pattern and a rotation speed of 200–3000 rpm).

Spheronization was carried out for 5 min at 500 rpm followed by 15 min at 1000 rpm. During the first 5-min period, 5% w/w of total batch size Avicel® PH 101 was sprinkled over the rotating extrudates to prevent the pellets from sticking. Pellets obtained were dried on trays at 50°C for 12 h (Hotpack Oven, Model # 212 539-10, Hotpack Corp., Philadelphia, PA). Dried pellets were later sieved to obtain 1.2-mm pellets to study the effect of the plasticizer on drug release only. However for all other studies 2.0-mm pellets were used (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, fitted with sieve # 8, 10, 12, 14, 16, 18 and 20). The pellets consisted of the drug (10.0% w/w), Eudragit®L 100 55 and Eudragit® S 100 (88.0% w/w) and Kollidon®K90F (2.0% w/w). The composition of formulations with different polymer ratios is given in Table 1.

2.2. Characterization of pellets

2.2.1. Determination of glass transition temperature (T_g)

Polymer blends (Eudragit® L 100-55: Eudragit® S 100 in ratio of 1:3) in the presence and absence of triethyl citrate, were weighed (approximately between 10 and 15 mg) in a DSC aluminium pan. The DSC (Differential Scanning Calorimeter, Seiko Instruments Inc., Japan, Model SSC5200) was programmed to perform a heat-cool-heat cycle from 0 to 200°C. Heating and cooling rates of 10°C/min was used. The T_g was measured at the midpoint of the transition.

2.2.2. Determination of matrix erosion

Matrix erosion was monitored by using a standard USP dissolution apparatus with baskets (Distek, Dissolution System 2100A, USP Apparatus I). Dissolution medium used was 500 ml pH 6.8 phosphate buffer with the ionic strength of 0.05 M. Three stirring speeds of 25, 50 and 100 rpm were tested at 37.0 ± 0.5°C respectively. Matrix erosion was determined by removing the baskets containing pellets at 2-, 4-, 6-, 8-, 10-, 12-h intervals and drying them for 12 h at 50°C to constant weight. The difference between the initial and final weight was calculated as percent matrix erosion.

2.2.3. Determination of erosion volume reduction

Pellets were visually inspected. Their diameters were measured and they were photographed under an optical microscope after drying (Optical Microscope, Nikon HFX, IIA, Japan). Ten pellets per time interval were evaluated.

Volume reduction due to erosion of pellets was calculated by using Eq. (1).

$$V_s = 1/6\pi D^3 \quad (1)$$

Where, V_s is the volume (mm^3) and, D is the diameter (mm) of a sphere.

Cumulative percent erosion volume was calculated by using Eq. (2).

$$V = 100\,\Delta V_t / V_0 \quad (2)$$

Table 1
Formulation of 1.2 and 2.0 mm pellets with different polymer ratios

Drug (% w/w)	PVP (% w/w)	Eudragit® L 100 55:Eudragit® S 100 ratio	Triethyl citrate (% w/w of total Eudragits®)	Granulation water (% w/w)
10.0	2.0	1.0:1.0	15.0	70.0
10.0	2.0	1.0:1.0	–	70.0
10.0	2.0	1.0:3.0	15.0	70.0
10.0	2.0	1.0:3.0	–	70.0

where V is cumulative percent erosion volume, ΔV_t is the change in volume at time t and V_0 is the initial volume at time zero.

Rate of erosion volume (K) was calculated by using Eq. (3).

$$K = \Delta V/\Delta t \quad (3)$$

where ΔV is the change in volume over the time interval Δt.

2.2.4. Dissolution studies

In vitro dissolution was performed using USP XXII Apparatus I, in 500 ml of pH 6.8 phosphate buffer at 50 rpm and 37.0 ± 0.5°C (Distek Inc., NJ, USA). Since the drug is poorly soluble, drug release from the pellets was determined by an indirect procedure, which involved determination of drug left in the pellets after dissolution by UV analysis. The difference between initial and final amount of drug present in the pellets after dissolution was calculated as percent drug release.

3. Results and discussion

3.1. Effect of the plasticizer on release properties

Release profiles of the pellets (1.2 mm) that were formulated in the presence and absence of triethyl citrate (plasticizer) are shown in Fig. 1. It was observed that 70–100% drug release was obtained from these pellets within 6 h. To study the effect of plasticizer on the rate of drug release, pellets with 1:1 and 1:3 ratios of Eudragit® L 100 55: Eudragit® S 100 were formulated. Regardless of the polymer ratios used, the pellets that were obtained with the plasticizer demonstrated enhanced release rates of the drug compared with the batches lacking the plasticizer. The plasticizer effect was consistent when the polymer ratio of the pellets was increased. The enhanced drug release from the pellets containing the plasticizer may be due to the increased dissolution rate of the plasticized polymers. Plasticization of Eudragit® polymers with triethyl citrate was confirmed by determining the effect of triethyl citrate on the glass transition temperature of the polymer, Table 2. In the presence of ethyl citrate it was reduced from 93.2 to 54.5 in Eudragit® L 100 55 and, from 166.4 to 109.4 in Eudragit®S 100 blends. Heat capacities (C_p) were also reduced from 0.112 to 0.05 mJ/°C for Eudragit® L 100 55 and from 0.189 to 0.083 mJ/°C for Eudragit®S 100 blend indicating that, the polymer blends processed with the plasticizer were subjected to a significant reduction in the glass transition temperature and heat capacity.

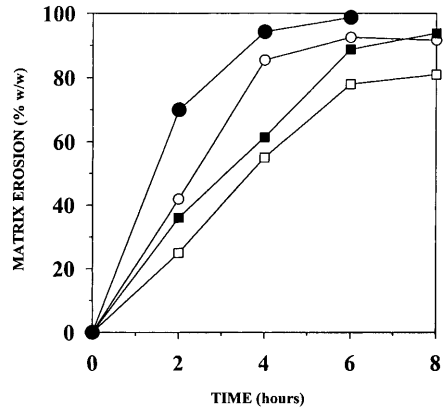

Fig. 1. Effect of plasticizer on matrix erosion (%w/w) from pellets: (pellet size 1.2 mm, drug load: 10% w/w, Eudragit L 100 55 to Eudragit S 100 ratio of 1:1 and 1:3). Closed circles: 1:1, plasticized formulation, open circles: 1:1, unplasticized formulation, closed squares: 1:3, plasticized formulation and open squares 1:3 unplasticized formulation.

Table 2
Effect of plasticizer (triethyl citrate) on T_g and C_p of Eudragit® L 100 55 and Eudragit® S 100 polymers

Polymer	T_g (°C)	C_p (mJ/°C mg)
Eudragit® L 100 55	103.0	0.221
Eudragit® S 100	169.1	0.057
Eudragit® L 100 55[a]	93.2	0.112
Eudragit® S 100[a]	166.4	0.189
Eudragit® L 100 55[b]	54.5	0.050
Eudragit® S 100[b]	109.4	0.083

[a] Ratio of 1:3 Eudragit® L 100 55 and Eudragit® S 100 unplasticized polymer blend.

[b] Ratio of 1:3 Eudragit® L 100 55 and Eudragit® S 100 plasticized with 15% w/w of triethyl citrate.

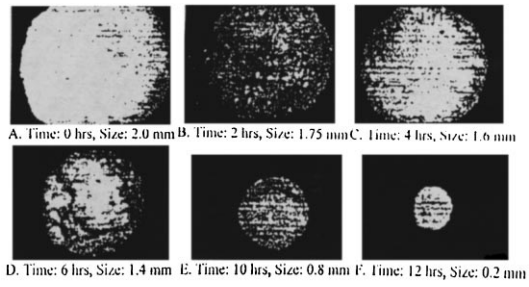

Fig. 2. Microscopical evaluation of matrix erosion and size reduction of 2.0 mm pellets (magnification 5 ×).

3.2. Characterization of matrix erosion and mechanism of drug release

Microscopic studies showed that, during dissolution studies, the pellets were gradually reduced in size as a function of time, while maintaining a constant surface geometry (Fig. 2A–F). The particular formulation shown in Fig. 2A–F contained 10% w/w drug, 2% w/w PVP and 88% w/w Eudragit® L 100 55 and Eudragit® S 100 mixture (in the ratio of 1:3), plasticized with 15% w/w triethyl citrate relative to the polymer. Pellet size used was 2.0 mm. Fig. 3 demonstrates the extent of matrix erosion and drug release from the pellets. Matrix erosion and drug release occurred simultaneously (Fig. 3). It was not influenced by the stirring rates of 25, 50 and 100 rpm as demonstrated by Fig. 4. This study further demonstrated that the drug release was directly related to volume reduction by erosion.

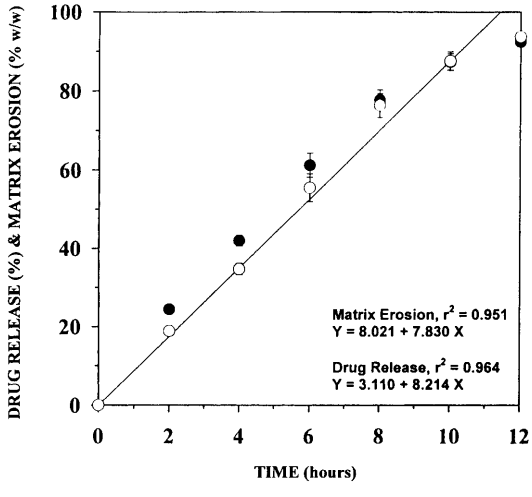

Fig. 3. Correlation of matrix erosion (%w/w) with drug release (%) from pellets: (pellet size: 2.0 mm, drug load: 10% w/w, Eudragit L 100 55 to Eudragit S 100 ratio of 1:3 n = 5 ± SE). Closed circles represent matrix erosion and open circles represent drug release.

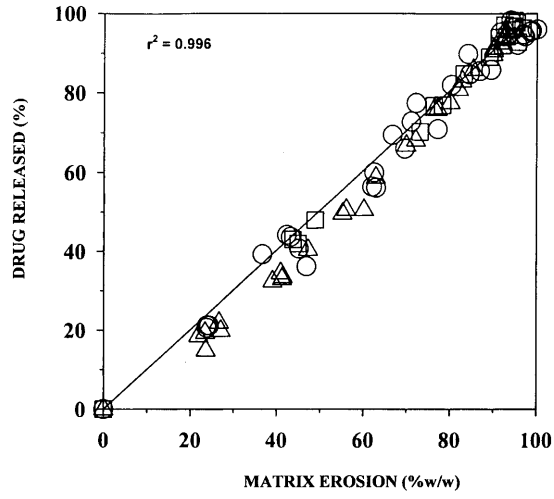

Fig. 4. Correlation of matrix erosion (%w/w) with drug release (%) at different dissolution stirring speeds: (pellet size: 2.0 mm, drug load: 10% w/w, Eudragit L 100 55 to Eudragit S 100 ratio of 1:3, $n = 4 \pm$ S.E.). Circles: 25 rpm, triangles: 50 rpm and squares: 100 rpm.

Table 3 contains data that explain the release mechanism. Data presented are the changes in the pellet volume, cumulative% erosion volume and rate of erosion volume as a function of dissolution time (Fig. 5). The volume reduction depends on the diameter of the pellets. As a pellet erodes with time, the pellet diameter is reduced with simultaneous reduction of the surface area. To compensate the loss of surface area, the erosion volume is increased to maintain a constant rate of drug release. In this case, the rate of erosion volume reduction remained constant up to 10 h. This finding indicated that the pellets were eroded from the surface causing size reduction without significantly affecting the erosion volume. As a consequence, a zero order release pattern was obtained. However, some deviations from the constant erosion rate may be expected of this size of beads at a point, where the surface area to volume ratio begins to increase very rapidly.

Table 3
Determination of the rate of erosion volume reduction from 2.0 mm pellets ($n = 10$)

Time (h)	Pellet diameter (mm)	Pellet volume (mm^3)	Volume change (mm^3)	Cumulative percent erosion volume (mm^3)	Rate of erosion volume reduction (%/h)
0.0	2.08	4.7118	–	0.0000	0.0000
2.0	1.94	3.8229	0.8889	18.8654	9.4327
4.0	1.76	2.8545	1.8573	39.4180	9.8545
6.0	1.26	1.0473	3.6645	77.7728	12.9621
8.0	1.03	0.5721	4.1392	87.8581	10.9822
10.0	0.40	0.0335	4.6783	99.2890	9.9289

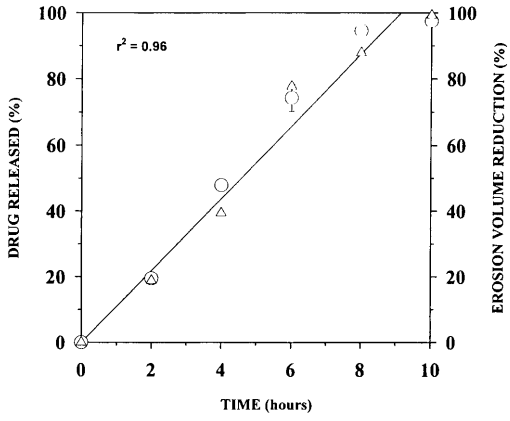

Fig. 5. Correlation of drug release (%) with erosion volume reduction (%) of pellets: (pellet size: 2.0 mm, drug load: 10%w/w, Eudragit L 100 55 to Eudragit S 100 ratio of 1:3 $n = 4 \pm$ S.E. for drug released and $n = 10 \pm$ S.E. for erosion volume reduction). Circles represent drug release and triangles represent erosion volume reducion.

4. Conclusions

Using Eudragit® polymers, multi-unit pellet systems were formulated. They demonstrated zero order release pattern for a thiazole based leukotriene D_4 antagonist. Addition of triethyl citrate to the pellet core modified release properties. In dissolution testing, the pellets obtained were reduced in size as a function of time for 12 h. The cumulative percent erosion volume calculated was increased while the rate of erosion of volume reduction remained constant. Findings indicated a surface erosion-based release pattern of the Eudragit spheres.

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References

Chandy, T., Sharma, C.P., 1992. Chitosan beads and granules for oral sustained delivery of nifedipine: in vitro studies. Biomaterials 13 (13), 949–952.

Chandy, T., Sharma, C.P., 1993. Chitosan matrix for oral sustained delivery of ampicillin. Biomaterials 14 (12), 939–944.

Chien, Y.W., 1992. Novel Drug Delivery Systems, second ed. Dekker, New York.

Emara, L.H., 1994. Sustained niclosamide release from biodegradable gelatin compositions: a study of matrix degradation. Proc. Int. Symp. Control. Release Bioactive Mater. Control. Release Soc. 21, 827–828.

Ghebre-Sellassie, I., 1989. Pharmaceutical Pelletization Technology. Dekker, New York.

Giunchedi, P., Maggi, L., Conte, U., La Manna, 1993. Linear extended release of a water-insoluble drug, carbamazepine, from erodible matrices. Int. J. Pharm. 94, 15–22.

Lalla, J.K., Bhat, S.U., 1993a. Controlled-release isosorbide dinitrate pellets. Part I: Design and evaluation of controlled release caspsule dosage form. J. Pharm. Sci 82 (12), 1288–1291.

Lalla, J.K., Bhat, S.U., 1993b. Controlled release isosorbide dinitrate pellets. Part II: In vivo studies. J. Pharm. Sci. 82 (12), 1292–1295.

O'Connor, R.E., 1987. The drug release mechanism and optimization of a microcrystalline cellulose pellet system. Philadelphia College of Pharmacy and Science, Pennsylvania, PA Ph.D Thesis.

Yang, T.H., Zhang, J.S., Liu, G.J., Chen, G., 1989. Studies on the controlled-release pellets of nifedipine. Yao-Hsueh-Hsueh-Pao 24 (8), 622–628.