Compressed Donut-Shaped Tablets with Zero-Order Release Kinetics

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Purpose. Simple uncoated compressed tablets with a central hole (donut-shape) are proposed to provide a constant drug release over a long period of time (>20 hrs). The effect of hole size and drug solubility on the release kinetics is investigated. ***Methods.*** The donut-shaped polyethylene oxide (PEO, Mw = 4×10^6) tablets (600 mg and 12 mm diameter) are bored with a drill bit (3/32", 7/64", 1/8", and 5/32"). ***Results.*** The release of theophylline from the donut-shaped tablets is zero order (80–90% release) before rapidly decreasing. As the hole size is increased from 7/64" to 5/32", the release rate increases and the release time is shortened. However, the release of theophylline from the donut-shaped tablet with a hole size of 3/32" follows the same anomalous release profile from a tablet without a hole. As drug solubility increases, the duration of linear drug release is shortened to 65 – 70% release followed by a severe tailing at the later stage of the release. ***Conclusions.*** Donut-shaped PEO tablets with a hole provide zero-order release kinetics because the effect of the releasing surface area on the release kinetics is reduced.

KEY WORDS: zero-order release kinetics; swelling; erosion; constant surface area; donut-shape; diffusion.

INTRODUCTION

Simple monolithic tablets for extended release dosage forms fabricated by compressing a mixture of hydrophobic polymer, a drug and excipients yield first-order release kinetics or square root of time kinetics [1,2]. A main interest is to develop extended release tablets which prolong drug release (i.e. > 20 hrs) and follow zero order release kinetics. It has been reported that the incorporation of hydrophilic polymer into tablet matrices provides non-Fickian (or anomalous) release kinetics [3,4]. The release of drugs from tablets having a constant surface area, controlled by the swelling/erosion processes of the polymer, follows a zero-order rate via synchronization of front velocities at the swelling and erosion interfaces [5–7]. For most common geometrical shapes (i.e. tablets), the total surface area accommodating drug release decreases with time even though hydrophilic polymers (swellable/erodible) are employed. This results in the square root of time kinetics or deviation from zero-order kinetics. Attempts have been made to obtain zero-order release kinetics via coating a porous membrane or employing osmotic pumps [8,9]. Recently multi-layer tablets have been developed to provide a constant drug release by geometrically modifying tablets to minimize the effect of the releasing surface area [10,11]. A swellable/erodible barrier layer coated by compression modifies the swelling behavior of tablets and furnishes zero order release kinetics. This results from the zero-order release through the swellable/erodible layer which acts as a membrane and anomalous release from the radial direction [3,4,12]. However, the production of multi-layer tablets requires advanced tablet manufacturing technology (three-step operation).

The inherent limitation of a monolithic matrix, which is the increase of diffusional length resistance with time, can be compensated with the increase of the inwardly releasing surface area with time. This led to pie shaped [13], semi-hemisphere [14], multi-holed [15], and frustum-shaped devices [16], where all the surfaces of the matrix were coated with a water-impermeable polymer except for an opening through which water and drugs are transported in and out. However, those designs are not suitable for large scale manufacturing processes. A tablet with holes, which provides a constant releasing surface area, was proposed in theory [17]. Others developed perforated coated tablets with a central hole which meets the mass production requirement [18,19]. In the perforated coated tablets consisting of hydrophobic polymer, drug is released only from the central hole, resulting in a constant release rate because the inwardly increasing releasing surface area counterbalances the increase of the diffusional length resistance with time. During the coating operation, however, the inner surface of the central hole may be coated to form a film [19].

In this study, a simple "donut" (or ring) geometry [20] is proposed to obtain zero-order release kinetics from uncoated compressed hydrophilic tablets. In this design, the swelling and/or erosion controlled principles of the hydrophilic polymer are exercised with a reduced effect of releasing surface area over time.

MATERIALS AND METHODS

Materials

POLYOX®-WSR (poly(ethylene oxide) (PEO) NFs of average molecular weight of 2×10^6, and 4×10^6 were supplied by Union Carbide Corporation (Danbury, CT.). Theophylline anhydrous U.S.P. and magnesium stearate U.S.P. were purchased from Amend Co. (Irving, NJ.) and Mallinckrodt Chemical (Jersey City, NJ.), respectively. Propranolol HCl and was purchased from Sigma Chemical Co. (St. Louis, Mo.). The materials were used as received.

Preparation of Donut-Shaped Tablets

The ingredients (PEO, drug, and magnesium stearate) were mixed and then tableted using a Carver press machine (Model C, Wabash, IN.). A set of tablet punches with flat surfaces were used to prepare tablets with a 12 mm diameter. They were charged with the formulation (600 mg), and the compression of 4000 lb and 8000 lb was exerted by hand for theophylline and propranolol HCl, respectively. A central hole was bored with a high speed drill bit (3/32", 7/64", 1/8", and 5/32").

Testing of Tablets

In vitro release of drugs from the different formulation tablets was carried out by using the USP bracket procedure

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(DISTEK Model 2000, Somerset, NJ.) in distilled/deionized water at a stirring rate of 100 rpm and 37°C, if not otherwise stated. Theophylline and propranolol HCl were chosen as model drugs. The release of theophylline and propranolol HCl was assayed by a HP8252A diode-array spectrophotometer at 244 nm and 270 nm, respectively.

RESULTS AND DISCUSSION

Even well designed polymeric drug delivery systems, such as swelling/erosion controlled systems exhibiting front synchronization, rarely furnish zero-order release kinetics in the form of a simple monolithic matrix. Drug release from a tablet occurs from all surfaces (circular faces and lateral area). During drug release, the releasing surface area decreases with time regardless of the system's modulating release mechanisms. The donut-shaped tablet proposed herein at least reduces the effect of the releasing surface area laterally. Typically, during dissolution, drug release takes place through a central hole, a lateral area, and circular faces. By using the donut-shaped tablet, laterally one can maintain a constant releasing surface area with time. Due to usage of hydrophilc polymer (swellable/erodible), drug release from the tablet without a hole yields anomalous kinetics [11,21,22], showing $0.6<n<0.8$ of $M_t/M_\infty = kt^n$ where M_t, M_∞, k, and n are the amount of drug released at time t, the total amount of drug in the dosage form, the constant, and the exponent, respectively.

Figure 1 illustrates the effect of the hole size on the release of theophylline from donut-shaped PEO tablets ($MW = 4\times10^6$). Release profiles show good reproducibility. The 95% confidence value to the slope of the release profile (⅛″) and 95% value of the exponent n for the tablet with no hole were determined. The percent values of the 95% confidence to the slope and the exponent n are 1.95% and 4.11% for the tablets with ⅛″ hole and no hole, respectively. The drug release from the donut-shaped tablets is rapid initially due to the burst-effect from the surface, followed by a linear release region for a long period of time (up to 80 – 90% release) before rapidly decreasing. In comparison, drug release from a tablet without a hole displays anomalous release kinetics ($n = 0.74$) due to the swelling of the polymer and the decreasing releasing surface area with time. The tailing of drug release from the donut-shaped tablets at the later stage of time is short compared to that from the tablet without a hole. The extension of linearity depends upon the hole size. The larger the hole size the longer the linear release (percent release) will be. However, the release of theophylline from the donut-shaped tablet with a 3⁄32″ hole size closely follows the release profile from a regular shaped tablet without a hole. The general behavior of observed erosion boundaries and diffusion fronts during drug release from the donut-shaped tablets is presented in Figure 2. It is evident that the decrease of releasing surface area from the outer lateral area is compensated by the increase of releasing surface area from the central hole. This results in a constant releasing surface area laterally. At the later stage of drug release, the swollen gel thickness of the donut-shaped tablet is thin enough to be broken by a fast rotation of the paddle. However, if the hole size is too small, the hole collapses during drug release because the inward swelling of polymer from the inner surface is so high that the inner space cannot accomodate the swelling volume of the polymer. As a result, drug release from a donut-shaped tablet with a small hole (3⁄32″) tends to follow the drug release from the tablet without a hole. The minimum hole size to provide a constant releasing surface area is dependent upon the molecular weight of poly(ethylene oxide). As the molecular weight of the polymer decreases, the degree of polymer swelling decreases as reported earlier [21,22]. This provision allows a small hole size for the donut-shaped tablet to be used for the lower molecular weight of PEO ($MW = 2\times10^6$) as shown in Figure 3. The linear drug release from the donut-shaped tablet with a 3⁄32″ hole size retains up to 80% release before tailing off to exhaustion. The higher the molecular weight of PEO the larger the minimum hole size of the donut-shaped tablet.

The increasing hydrodynamic condition of dissolution testing influences the dissolution of the swollen polymer so that the release of drugs from the hydrophilic matrices are facilitated. The effect of the stirring rate on the release of theophylline from the donut-shaped tablets ($MW = 4\times10^6$) with a ⅛″ hole size is presented in Figure 4. As the stirring rate increases from 50 rpm to 100 rpm, the release rate of the

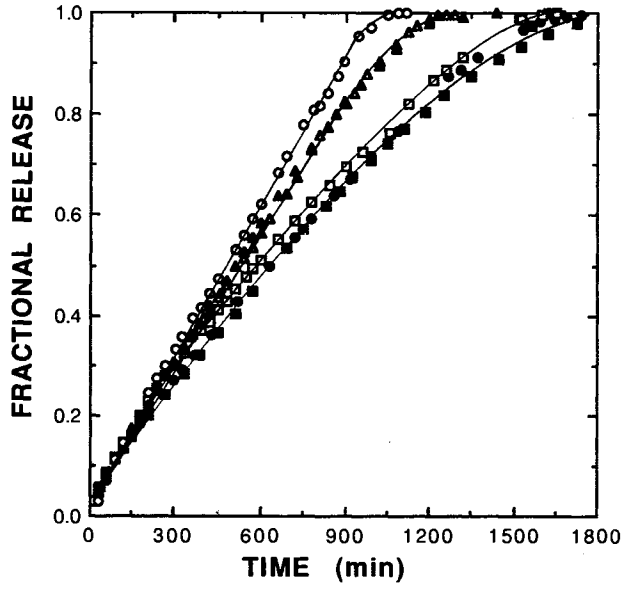

Fig. 1. Effect of hole size on the release of theophylline from donut-shaped tablets: (●, ■) no hole; (□) 3⁄32″; (△, ▲) ⅛″; (○) 5⁄32″.

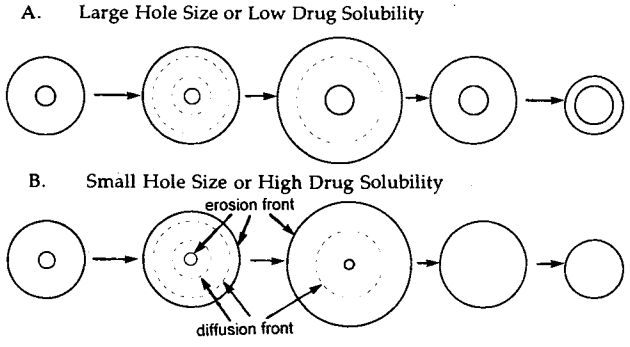

Fig. 2. Schematic diagram of releasing surface area boundaries and overall size changes with respect to the hole size.

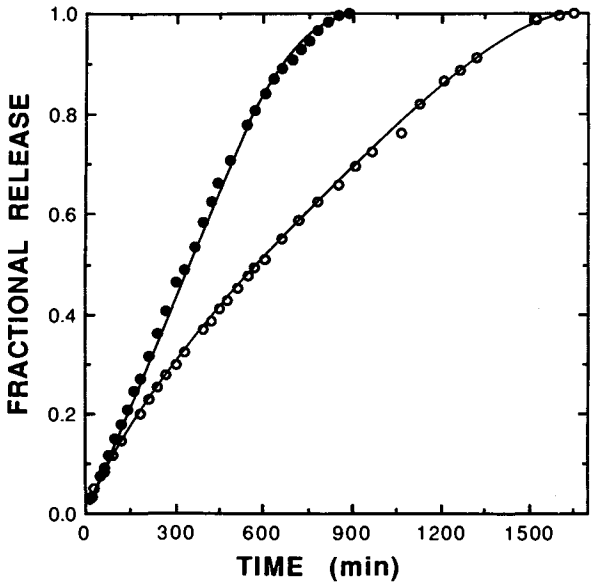

Fig. 3. Effect of molecular weight on the release of theophylline from donut-shaped tablets with a 3/32" hole size: (○) MW = 4×10^6; (●) MW = 2×10^6.

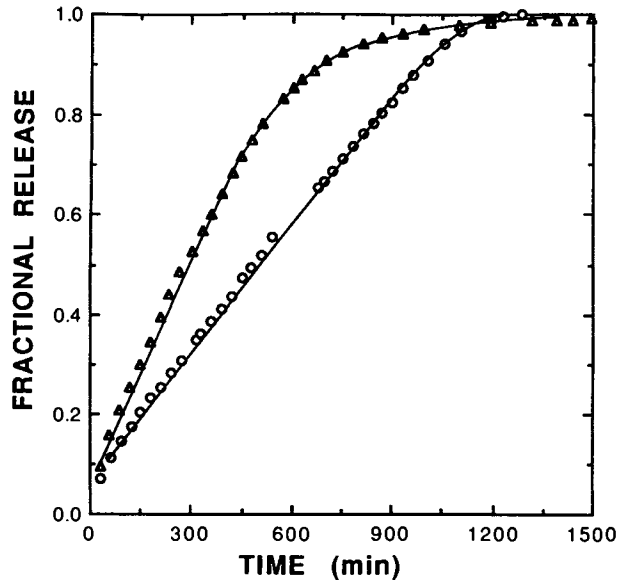

Fig. 5. Effect of drug solubility on the release of drugs from donut-shaped tablets with a 7/64" hole size: (△) propranolol HCl (solubility, 5%); (○) theophylline (solubility < 1%).

drug is faster. However, even though the stirring rate is further increased to 150 rpm, indistinguishable release profiles are obtained for 100 rpm and 150 rpm. The same observation was reported earlier with the PEO tablets (no holes) consisting of MWs = 0.9×10^6 and 2×10^6 [21]. Insensitivity of the tablets to the stirring rate was not found in other erodible polymer systems [5,6]. Others showed that the drug release from coated perforated tablets was not affected by the hydrodymamic conditions [19]. This suggests that the hydrodynamic environment in the inner hole does not significantly influence the erosion of the polymer nor the drug release.

Figure 5 shows the effect of drug solubility on the release of drugs from donut-shaped tablets with a 7/64" hole size. As drug solubility increases from < 1% (theophylline) to 5% (propranolol HCl), the release rate of drugs increases. Drug release from PEO tablets of MW = 4×10^6 is not governed by the swelling/erosion processes of the polymer [21], but is controlled by the swelling of the polymer at the early stage of time followed by the erosion of the swollen polymer at the late stage of time. As drug solubility increases, the water penetration is enhanced by the osmotic force generated by the high concentration of highly water soluble drug within the tablet. This results in the increasing release rate of drugs with increasing drug solubility. It is interesting to point out that the duration of linear drug release is shortened to 65–70% release as the drug solubility increases compared to 80–90% release for a drug of low solubility (theophylline). However, we found that even though diltiazem HCl (solubility > 50%) was used the drug release from the donut-shaped tablet (7/64" hole) was not hastened but superimposed with the release of propranolol HCl (not shown). As drug solubility increases, the swelling of the polymer increases due to the osmotic forces generated by the dissolved drug. This leads to the collapse of the centrol hole (7/64") at about 60–70% release time. As a result, a severe tailing of drug release at the late stage of time is observed in the case of highly soluble drugs (propranolol HCl). This is attributed to the collapse of the constant releasing surface area and the decrease in drug concentration in the matrix after the drug content falls below its solubility. It was observed, however, that the increase in the hole size of the donut-shaped tablets and the increase in the molecular weight of PEO from 4×10^6 to 7×10^6 did not extend the linearity of the release of highly water soluble drug beyond 70% with a shortened release time. This explains that the release of highly water soluble drug from PEO tablets is controlled by the diffusion of the drug in the swollen gel. Modification of the donut-shaped tablets is necessary to extend the linear release up to 80% for a longer time (>20 hrs) and will be reported elsewhere.

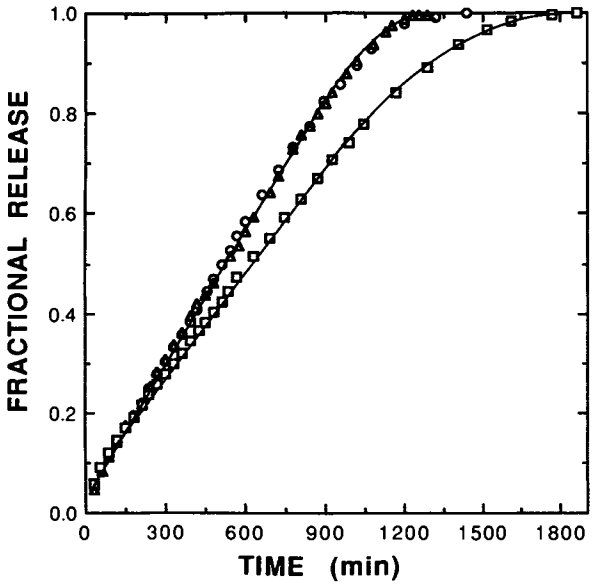

Fig. 4. Effect of stirring rate on the release of theophylline from donut-shaped tablets with a 1/8" hole size: (□) 50 rpm; (△) 100 rpm; (○) 150 rpm.

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