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Estimation of the percolation thresholds in ternary lobenzarit disodium–dextran–HPMC hydrophilic matrices tablets: Effects of initial porosity

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ABSTRACT

The aim of this work is to estimate the excipient percolation threshold for a new combined matrix native dextran (DT), series B110-1-2 (Mw 2×10^6): HPMC K4M CR: lobenzarit disodium (LBD) system and demonstrate the advantages of this ternary system with respect to previously reported binary dextran:LBD and HPMC:LBD tablets. The formulations studied were prepared with different amounts of excipient (DT:HPMC, 4:1 (wt/wt) for all tablets and relative polymer/drug particle size of 4.17) in the range of 10–70% (wt/wt). Dissolution studies were carried out using the paddle method (100 rpm) and one face water uptake measurements were performed using a modified Enslin apparatus. The Higuchi's models as well as the non-linear regression were employed as empiric methods to study the released data. Values of diffusion exponent $0.588 < n < 0.784$ (Korsmeyer equation) for dissolution profile and water uptake mechanism $0.715 < n < 0.960$ (Davidson and Peppas equation) suggests anomalous or complex mechanisms in all cases. The critical points in ternary tablets were reduced from 44.75% (v/v) of excipient (correspond to purely native dextran) to 22.34% (v/v) (corresponding to mixture native dextran:HPMC, 4:1, wt/wt). The initial porosity (IP) of hydrophilic matrices above the values of 20% has an important influence on the percolation threshold as well as on establishment of the gel barrier responsible for the controlled release from the DT:HPMC:LBD tablets.

1. Introduction

Percolation theory is a statistical theory that studies disordered or chaotic systems where the components are randomly distributed in a lattice. It has wide application in many scientific disciplines and was introduced in the pharmaceutical field by Leuenberger et al. (1987) to improve the characterization of solid dosage forms. In this first definition, through the compaction process to form a pharmaceutical tablet, a site-percolation and a bond-percolation may be observed.

The sites can be occupied by particles or pores and bonds can exist between neighbouring particles. This theory assumes that at a specific solid/pores composition in the tablet, i.e., when particles or pores form a continuous network in the system, a sudden change in the tablet properties (release rate, mechanical properties, etc.) is observed. This particular ratio corresponds to the percolation threshold (Holman and Leuenberger, 1991).

In a binary pharmaceutical tablet, two percolation thresholds are expected: the drug and the excipient percolation threshold. A cluster is defined as a group of neighbour-occupied sites in a lattice (Stauffer and Aharony, 1992). When this cluster extends from one side to the rest of the sides of the lattice – percolates the whole lattice – it is considered as infinite or percolating cluster. It has to be emphasized that the infinite cluster of excipient responsible for the drug release control must be present before the matrix is placed in the dissolution medium, i.e., before the swelling process starts (Miranda et al., 2006a,b; Fuertes et al., 2006).

The factors influencing the release of drugs from hydrophilic matrices include, viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle size, pH of the matrix, entrapped air in the tablet, solubility of the drug, the presence of excipients or additives and the mode of the incorporation of these substances (Castellanos Gil

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et al., 2006a; Campos Aldrete and Villafuerte Robles, 1997; Tahara et al., 1995).

Dextrans can be defined as glucose homopolysaccharides that feature a substantial number of consecutive α-(1 → 6) linkages in their major chains, usually more than 50% of the total linkages. These α-D-glucans possess also side chains stemming from α-(1 → 2), α-(1 → 3), or α-(1 → 4) branch linkages. Coming from renewable sources, polysaccharides have frequently also economical advantages over synthetic polymers. Polysaccharides are usually non-toxic, biocompatible and show a number of peculiar physico-chemical properties that make them suitable for different applications in drug delivery systems (Coviello et al., 2007; Robyt, 1986).

Hydroxypropyl methylcellulose has been employed extensively as hydrophilic matrix former in oral controlled release dosage forms for different drugs. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading (Bettini et al., 1994).

The percolation theory has been applied to describe controlled release inert matrix systems (Caraballo et al., 1993). Recently we started to apply the percolation theory to the study of HPMC hydrophilic matrix systems. Miranda et al. demonstrated experimentally the influence of the particle size of the components on the percolation threshold in HPMC hydrophilic matrices (Miranda et al., 2006a,b, 2007c; Fuertes et al., 2006) and some evidence of the influence of the initial porosity in the formation of the gel layer (sample-spanning cluster of excipient) were achieved.

Lobenzarit disodium (LBD) is a drug conceived for the treatment of rheumatoid arthritis. This drug produces an improvement of immunologic abnormalities and has a regulatory effect upon the antibody producing system. It is administered orally in the form of tablets and its daily dosage is 240 mg (80 mg three doses per day) (Ohsugi et al., 1985).

The objective of the present work was to estimate the excipient percolation threshold for a new combined matrix native dextran (DT), series B110-1-2 (Mw 2×10^6): HPMC K4M CR: LBD system, to characterize its release kinetics and to demonstrate the advantages of this ternary system with respect to previously reported binary dextran:LBD tablets (Castellanos Gil et al., 2008b). At the same time the influence of the initial porosity (IP) of hydrophilic matrices in the range 0–30% on the release and percolation behaviour was analyzed.

2. Materials and methods

2.1. Materials

Commercial native Dextran B512-F (Mw 5 000 000–40 000 000, according to manufacturer's data and Mw 22 000 000, according to viscometer analysis (Castellanos Gil et al., 2008c)) was obtained from Sigma (Saint Louis, USA) and used as reference polymer. High molecular weight native dextran (B110-1-2, Mw 2 000 000 (Castellanos Gil et al., 2008c)) was obtained from the Center of Studies of Sugar Cane (Havana, Cuba). Lobenzarit disodium (LBD) was prepared in the Synthesis Laboratory at the Center of Pharmaceutical Chemistry (Cuba). Hydroxypropyl methylcellulose (HPMC) with a viscosity grade 4000 cps (Methocel K4M CR) was obtained from Colorcon (Kent, England). Other chemicals and reagents were of analytical grade.

2.2. Preparation of matrix tablets

The polymers were sieved (Retsch type Vibro, Germany), the granulometric fractions 150–200 μm were employed and Carr's index (CI) was calculated. The drug was not sieved but its mean particle size was measured as 42 ± 0.61 μm using a He–Ne laser diffraction system (Malvern Instr., type Matersize x, 1.2 b, UK). The apparent particle density of LBD (2.159 g/cm^3) and polymers (1.330 g/cm^3 for DT and 1.285 for HPMC K4M CR) has been calculated using an air pycnometer (Quantachrome type Stereopycnometer spy-3, USA) and not very different values to those reported in the literature were achieved (Novoa et al., 1996; Fuertes et al., 2006).

Ternary mixtures DT:HPMC:LBD keeping ratio DT:HPMC always as 4:1 (wt/wt), were prepared with varying polymer's mixture contents (10%, 15%, 20%, 30%, 40%, 50%, 60% and 70%, wt/wt) (for volumetric fraction see Table 1) and with a constant amount of the drug (150 mg dosage) without any further excipient. Binary system DT:LBD was prepared with the same polymer amount (range 10–70%, wt/wt) with respect to LBD according to previously reported data (Castellanos Gil et al., 2008b). Table 1 also shows the composition of the studied batches as well as the tablet thicknesses (n = 12). Tablet components were mixed for 3 min (optimal mixing time) using a Turbula mixer (Basel, Switzerland).

Tapped density and bulk density of polymers and mixtures were determined according to European Pharmacopoeia (PhEur 4, 2002). Approximately 100 ml of powder is gently poured into a tare graduated cylinder and the initial volume and weight of the material is recorded. The graduated cylinder is placed on a tapped density tester and the final volume is recorded after 500 taps (SBS model. VOL-1 tap density tester) and Carr's index was obtained (Eq. (1)).

$$\text{Percent compressibility index} = 100 \times \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \quad (1)$$

The mixtures were compressed with a F. RASSANT (France) hydraulic press fitted with a 10 mm diameter flat punch. After some time (around 10 s) the formed tablets were ejected from the punch. Based on previous studies where the influence of compression force was studied as a function of the reduction in volume of dextran placebo tablets, compression force 14 kN was applied for all experiments in order to minimize initial porosity of tablets (Castellanos

Table 1
Properties of LBD tablets (dosage 150 mg) at various amounts of polymers mixture DT:HPMC (4:1, wt/wt).

Batch (total excipients %, v/v)	DT (%, v/v)	HPMC (%, v/v)	[a]Tablet weight (mg)	[a]Tablet thickness (mm)
DT:HPMC-10 (10.81)	8.59	2.22	166.1 ± 0.9	1.480 ± 0.031
DT:HPMC-15 (15.89)	12.63	3.26	176.2 ± 2.1	1.600 ± 0.025
DT:HPMC-20 (22.34)	17.75	4.59	187.5 ± 1.1	1.618 ± 0.060
DT:HPMC-30 (33.10)	26.30	6.80	214.2 ± 0.9	1.878 ± 0.063
DT:HPMC-40 (43.55)	34.60	8.95	250.0 ± 1.4	2.213 ± 0.065
DT:HPMC-50 (53.89)	42.81	11.09	300.0 ± 1.3	2.683 ± 0.056
DT:HPMC-60 (63.65)	50.57	13.08	375.2 ± 1.3	3.407 ± 0.047
DT:HPMC-70 (68.62)	54.52	14.10	500.1 ± 1.9	4.916 ± 0.078

[a] Values expressed the mean of experimental ± RSD values for 12 samples.