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*Original Article*

# Effect of Polyox™ Molecular Weight on Drug Release and Physicochemical Properties of Liquisolid and Physical Mixture Formulations

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## Abstract

The liquisolid (LS) technique is a relatively recent approach for developing sustained-release dosage forms. This study investigated the effect of Polyox™ molecular weight (MW) on the physicochemical properties and drug-release behavior of LS formulations containing the highly water-soluble model drug diltiazem (DTZ) HCl, using corresponding physical mixture (PM) formulations for comparison. LS formulations were prepared using polysorbate 80 as the liquid vehicle and different grades of Polyox™. Higher-MW Polyox™ grades generally produced slower drug-release profiles than lower-MW grades in both LS and PM matrixes. Based on the release exponent (*n*), LS formulations containing Polyox™ grades up to and including WSRN1105 (MW = $9 \times 10^5$) exhibited Case-II or Super Case-II-type transport, whereas formulations containing WSR301 (MW = $40 \times 10^5$) and WSR303 (MW = $70 \times 10^5$) exhibited anomalous transport. Thus, the observed transition in release mechanism occurred between Polyox™ MWs of $9 \times 10^5$ and $40 \times 10^5$. Similarity-factor analysis indicated that LS formulations containing Polyox™ with MWs $\leq 3 \times 10^5$ had release profiles similar to their PM counterparts, whereas formulations containing Polyox™ with MWs $\geq 9 \times 10^5$ showed greater release retardation and dissimilar release profiles. Physicochemical analysis showed that LS formulations containing Polyox™ with MWs below $9 \times 10^5$ generally had larger particle size distributions, more irregular particle morphology, and lower bulk and tapped densities than their PM counterparts. LS formulations containing Polyox™ with MWs $\geq 9 \times 10^5$ also exhibited lower net electrostatic charge than the corresponding PM formulations, which may influence powder-handling behavior. Solid-state analyses revealed no detectable drug–Polyox™ interactions. Overall, higher-MW Polyox™ grades, particularly those with MWs $\geq 9 \times 10^5$, provided greater retardation of DTZ release from LS tablets, while the transition in the n-based release mechanism occurred between $9 \times 10^5$ and $40 \times 10^5$.

## Keywords

Diltiazem HCl, dissolution rate, molecular weight, polyethylene oxide, physicochemical properties

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## Introduction

Diltiazem (DTZ) is a calcium channel blocker employed in the treatment of angina pectoris and hypertension. DTZ is largely metabolized by the liver and excreted by the kidneys. Although DTZ is well absorbed from the gastrointestinal tract (approximately 80–90%), it is subjected to relatively low absolute oral bioavailability of approximately 40% due to extensive first-pass metabolism in the liver.[1] Additionally, the plasma elimination half-life resulting from single or multiple administrations is relatively short (~3–5 h). Therefore, DTZ is a good candidate for a sustained-release dosage form, which is useful for maintaining therapeutically effective plasma concentrations over an extended period.[2] One of the

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main goals of designing a sustained-release form is to achieve a steady-state blood level of the drug that is non-toxic and therapeutically effective for an extended time while reducing dosing frequency and minimizing fluctuations in plasma drug concentrations.[3]

Polymers are long-chain molecules formed from smaller molecules called monomers. Numerous studies have reported the influence of polymer-related factors, particularly molecular weight (MW),[4] concentration,[5] and particle size distribution (PSD),[6] on drug release from hydrophilic matrix systems, especially those based on hypromellose. However, data are scarce on the influence of factors associated with polyethylene oxide (Polyox™). Polyox™ is an attractive hydrophilic polymer for use in the preparation of pharmaceutical formulations because of its non-toxicity, ease of production, high water solubility, high swellability, and insensitivity to the pH of the biological medium.[7] Its physicochemical and gel-forming properties vary considerably with MW, which may significantly influence matrix integrity, swelling behavior, and drug-release performance. Despite this, the systematic effect of Polyox™ MW on physicochemical characteristics and drug release in liquisolid (LS) systems remains insufficiently investigated.

LS formulations were initially designed to improve the solubility and dissolution rate of poorly soluble drugs.[8] More recently, the LS approach has been explored for sustaining the release of highly water-soluble drugs through polymer-controlled mechanisms.[9]

The influence of Polyox™ MW on the physicochemical and pharmaceutical properties of LS formulations has not been systematically investigated. To this end, LS formulations containing various grades of Polyox™ having MWs ranging from $1 \times 10^5$ to $70 \times 10^5$ were prepared and studied for their physicochemical and drug-release properties in comparison to their physical mixture (PM) counterparts. While the work of Kaialy et al.[10] focused on evaluating the effect of solvent type on drug release from sustained-release Polyox™-based LS tablets, that study did not investigate the impact of a wide range of Polyox™ MWs on sustained-release performance, nor did it examine correlations between MW, PSD, electrostatic properties, and drug-release mechanism. Therefore, the present study provides a systematic investigation of Polyox™ MWs and correlates MW with transitions in drug-release mechanism. Moreover, PSD, electrostatic properties, swelling behavior, and dissolution kinetics are analyzed to provide mechanistic insights into sustained drug release from Polyox™-based LS systems containing a highly water-soluble model drug.

## Materials and Methods

### Materials

Diltiazem HCl (DTZ) was purchased from TCI Chemicals, UK. Various grades of polyethylene oxide (Polyox™), that is, WSRN10 ($MW = 1 \times 10^5$), WSRN80 ($MW = 2 \times 10^5$), WSRN750 ($MW = 3 \times 10^5$), WSRN110[5] ($MW = 9 \times 10^5$), WSR301 ($MW = 40 \times 10^5$) and WSR303 ($MW = 70 \times 10^5$) were obtained from Colorcon (Dartford, Kent, UK). Polysorbate 80 (PS 80) was purchased from Sigma-Aldrich, USA.

### Preparation of LS and PM Formulations

Diltiazem HCl (DTZ; 1.2 g) was gradually incorporated into polysorbate 80 (PS80; 1.2 g) at 60°C under stirring at 200 rpm to produce a visually homogeneous drug–vehicle dispersion at a fixed DTZ ratio of 1:1 (w/w). Because the amount of DTZ used exceeded its previously reported equilibrium solubility in polysorbate 80, the resulting system should not be interpreted as containing the entire drug dose in a molecularly dissolved state. Rather, polysorbate 80 served as a non-volatile liquid vehicle in which DTZ was dispersed before incorporation into the Polyox™ carrier matrix.[10]

Each grade of Polyox™ powder under investigation (3.6 g, solid phase) was introduced to a mortar, then the liquid medication phase (drug:solvent) was slowly added to the solid phase over approximately 5–7 minutes, under continuous and thorough mixing using a pestle repeatedly until the liquid medication phase was absorbed into the solid phase and an apparently homogeneous powder mixture was obtained.

For comparison purposes, conventional PM formulations (without a solvent) were also produced. Each PM formulation contained a mixture of DTZ (1.2 g) and Polyox™ (3.6 g). The mixing was performed using a V-shaped powder mixer (GHP72, Zhejiang Wisely Machinery, Jiangsu, China) at a rotation speed of 100 rpm (10 rotations clockwise followed by 10 rotations anticlockwise repetitively) for 5 minutes under laboratory conditions (22°C, RH = 50%). A DTZ:Polyox™ ratio of 1:3 (w:w) was kept constant during the preparation of all formulations. The formulations prepared were stored in sealed glass vials for at least 7 days in laboratory conditions (22°C, RH = 50%) before further investigation.

The DTZ:PS80 ratio, 1:1 w/w, was selected based on previous optimization studies that ensured drug solubilization and good powder handling without exudation. This DTZ:Polyox™ (1:3 w:w) ratio was applied consistently across all Polyox™ grades to allow a systematic evaluation of MW effects. This is to ensure that the observed changes in physicochemical and release properties are caused by Polyox™ MW rather than variations in formulation composition. For each formulation condition (LS and PM across all Polyox™ MWs), a single, homogeneous master batch was prepared. All subsequent physical, powder, and dissolution evaluations were performed using technical replicates sampled directly from these individual master batches.

### Laser Diffraction

Volume-weighted particle size analyses of LS and PM formulation powders were conducted using a Malvern Mastersizer

2000 laser diffraction particle size analyzer equipped with a dry sampling system (Malvern Instruments Ltd, Malvern, UK), as the particle size range covered by this laser diffractometer is from 0.1 to 3500 µm. Before measurement, a background reading was taken. The dispersion of air pressure was adjusted to 2.0 bar, and a feed rate of 30% was applied. The measurement time was 5 s. The particle sizes at 10% ($d_{10}$%), 50% ($d_{50}$%, median diameter), and 90% ($d_{90}$%) of the volume distribution, and the volume mean diameter (VMD, the average diameter based on the unit volume of a particle) were calculated automatically using the Malvern Software (Version 2.20**,** UK) using a refractive index within the typical range for organic polymers (1.4–1.6) and an absorption index of 0.01. The span (calculated using Equation (1)) of the volume distribution was used as a measure of the width of the distribution of size relative to the median diameter.

$$\text{Span} = \frac{d_{90\%} - d_{10\%}}{d_{50\%}} \quad (1)$$

Three samples were measured for each product, and results were averaged.

## Powder Density

Formulation samples were gently poured into a 100 mL graduated measuring cylinder through a glass funnel at a fixed height above the cylinder and then weighed accurately. The bulk volume of each powder was recorded. Then, the cylinder was tapped 500 times using an automatic Tap Density Tester (JV 1000, Copley Scientific, UK) under laboratory conditions (20°C, RH = 50%) and the tap volume after each tapping of each powder was recorded. The tapper operated with a 3.2 mm vertical travel at a tapping speed of 200 taps/min. Tap density was calculated as powder weight over powder tap volume. The CI (Equation (2)) was calculated as the percentage change in the volume of a constant mass of powder because of tapping.

$$Carr's\ index\left(CI\right) = \frac{Tap\ density - Bulk\ density}{Tap\ density} \times 100 \quad (2)$$

Five technical replicates were sampled from each powder batch for each measurement, and the results were expressed as mean ± standard deviation.

## Scanning Electron Microscopy

A specimen of each sample was gently mounted on an aluminum stub (G301, Agar Scientific Ltd, Essex, England) with a double-sided adhesive carbon tab (G3347N, Agar Scientific Ltd). To increase the electrical conductivity of the surface of the samples, a sputter coater (Emscope SC500, Quorum Technologies, Laughton, UK) was used to coat the samples with gold (15 nm layer thickness) in an argon atmosphere before observation. Morphological properties of commercial DTZ as well as LS and PM formulation samples were investigated using a field emission scanning electron microscope (SEM, Zeiss EVO050, Germany) operating at an acceleration voltage of 10 kV and a beam current of 10 µA. SEM images were obtained with maximum care to ascertain their representativeness.

## Electrostatic Charging Analysis

The charge properties of commercial DTZ, PM, and LS formulation powders were analyzed using a custom-built electrostatic charge measurement system, as described in detail elsewhere.[11] The system was developed for the detection of bipolar electrostatic charge distributions in particulate materials. The experimental apparatus comprises a single non-contact electrostatic inductive sensor (probe), a charge amplifier unit, National Instruments data acquisition equipment, and a computer for data recording and processing. This method allows the detection and measurement of charge distribution on the basis of charge sign in a population of particles. The positive charge is the sum of all positive charges, whereas the negative charge is the sum of all negative charges. The net charge is the sum of positive and negative charges. The charge-to-mass ratio (CMR) is the charge (negative charge for N–CMR, positive charge for P–CMR) per unit mass, expressed in nC/g.

## Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) structural patterns of all formulations were collected using a Panalytical Empyrean diffractometer (PANanalyical, Almelo, The Netherlands) powder diffractometer with Cu Kα radiation (1.54056 Å) operated at laboratory conditions (22°C, RH = 50%). Data acquisition and processing were performed using PANalytical HighScore Plus software (version 3.0 or later, PANalytical BV, The Netherlands). Each sample was placed in a sample holder, surface-smoothed with a glass slide, and scanned between 5° and 40° in 2θ with a step-by-step increase of 0.01° 2θ/1 s. The sample stage was spun at 30 rpm. The instrument was calibrated using a silicon standard.

## Fourier Transform Infrared Spectroscopy

All formulations were analyzed using an Alpha Platinum–ATR Fourier transform infrared (FT–IR) spectrometer (Bruker, USA) to investigate whether DTZ was chemically altered or whether DTZ–Polyox™ interaction occurred during the preparation of LS formulations. A few milligrams of each powder were placed in the middle of the sample stage and then compressed by clicking the top of the arm of the

sample stage. The samples were scanned between 650 $cm^{-1}$ and 4,000 $cm^{-1}$ with a 1 $cm^{-1}$ resolution. The spectrum produced for each sample was a consequence of averaging 15 scans. The acquired spectra were processed using Opus software (version 7.5.18, Massachusetts, USA).

## In Vitro Dissolution Studies

The release of DTZ from both LS and PM formulation tablets containing a 60 mg unit dose of DTZ was monitored using a USP dissolution apparatus 2 (paddle method) at a rotational speed of 75 rpm. The tablets were compressed at a fixed pressure of 693 MPa using a single-punch Specac press KBR 25.011 (Gemini BV, The Netherlands), which was calibrated prior to use with standard calibration weights according to the manufacturer's instructions to ensure consistent applied compression force, fitted with 6 mm diameter flat–faced punches. The dissolution testing was performed using a Varian VK 705 DS Dissolution Apparatus (Varian Inc., USA) operated via the manufacturer's integrated control module. The dissolution media consisted of 900 mL distilled water equilibrated to 37°C ± 0.5°C. Samples were withdrawn from the dissolution vessels at predetermined time intervals for up to 10 h (600 min): every 5 min during the first 30 min, every 15 min thereafter up to 2 h, and every 30 min from 2 h to 10 h. The absorbances were recorded using a Biochrom WPA Lightwave II UV/Visible spectrophotometer (Biochrom Ltd., Cambridge, UK) at 235 nm. Three individual tablets compressed from the same batch were evaluated per formulation as technical replicates to assess intra-batch dissolution consistency. Distilled water was selected as a discriminatory medium to isolate polymer-controlled release mechanisms; however, this limits direct physiological extrapolation.

## Swelling Behavior

To evaluate the effect of Polyox™ dissolution on DTZ release kinetics, Polyox™ tablets were separately weighed ($W_0$) and then placed in small containers with a metal mesh underneath them. Another mesh was placed on top of each container to make sure the tablets were held inside the chamber. To simulate the in vitro dissolution conditions, the small containers carrying the tablets were placed in the bottom of dissolution vessels containing distilled water equilibrated to 37°C ± 0.5°C. Paddles were used to stir the dissolution medium at a rate of 100 rpm at 37°C ± 0.5°C. At various time intervals (0, 2, 5, 15, and 30 min), the tablets were withdrawn using a small basket and soaked on tissue paper (to remove excess water). The percentage increase in weight of each tablet due to water uptake was calculated using the following equation.

$$Swelling\,(\%) = \frac{M_t - M_0}{M_0} \times 100 \quad (3)$$

where $M_t$ is the tablet's weight at time "$t$," and $M_0$ is the tablet's weight at time 0. The experiment was performed in triplicate for each time point. Fresh samples were used for each time point.

## Dissolution Parameters

Independent models, including the (DE, Equation (4)),[12] the mean dissolution time (MDT, Equation (5)), and the mean dissolution rate (MDR, Equation (6)) were employed to quantify DTZ release profiles from different LS tablets compared to conventional tablets. Such mathematical analyses enable the statistical comparison between different formulations and the evaluation of how each formulation factor affects the dissolution rate of DTZ. The DE is the area under the dissolution curve produced up to a certain time, $t$, expressed as a percentage of the area of the rectangle.

$$DE_t = \frac{\int_u^t y \times d_t}{y_{100}} \times 100 \quad (4)$$

where $t$ is the total time of drug release, $y$ is the percentage of drug release at time $t$, and $Y_{100}$ is 100% drug release. The MDT is a model-independent method that is suitable for dosage forms having different mechanisms of drug release. The MDT (Equation (5)) is the time at which 50% of the drug is dissolved from its solid state under dissolution conditions.

$$MDT = \frac{\sum_{j=1}^{n} t_j \times \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (5)$$

The MDR is the percent release of the drug per minute.

$$MDR = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n} \quad (6)$$

where $j$ is the sample number, $n$ is the number of dissolution samples, $t_j$ is the time at the midpoint between t and $t^{-1}$ (which can be calculated using $(t + (t^{-1}))/2$), and $M_j$ is the additional amount of drug dissolved between $t$ and $t^{-1}$.

## Similarity Factor

The similarity factor ($f^2$, Equation (7))[13] was used to compare the in vitro release profiles of LS tablets in comparison to conventional tablets.

$$f^2 = 50 \times Log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]\right\}^{-0.5} \times 100 \quad (7)$$

where $n$ is the number of test points for the samples, $R_t$ is the reference assay at time point $t$; and $T_t$ is the test assay at time

point $t$. An $f^2$ value between 50 and 100 suggests a similarity between the two release profiles, and the closer the value is to 100, the more similar or identical the profiles are. Dissimilarity occurs with decreasing values below 50. The similarity factor ($f^2$) was used as a comparative metric to assess differences between LS and PM dissolution profiles rather than for regulatory demonstration of dissolution profile equivalence.

### Release Kinetics

The kinetics of DTZ release from all formulations under investigation were determined to obtain information on the mechanism of drug release from LS matrix tablets in comparison to conventional tablets. The release data obtained were analyzed using the power law proposed by Peppas and Korsmeyer, known as the Peppas model.[14] In this method, the log cumulative percentage of the drug release is plotted against the log of time. As the model assumes a uniform distribution of drugs through a polymeric matrix (diffusion model), the release kinetics are evaluated by using drug release from 5% to 60% and fitting it into Equation (8) as proposed by Ritger and Peppas.

$$Q = K t^n \quad (8)$$

where $Q$ is the fraction of drug released at time $t$, $k$ is the release constant incorporating characteristics of the macromolecular network system, and n is the diffusional release exponent, which is indicative of the operating release mechanism of the drug. Since the tablet matrixes prepared in this investigation had a cylindrical shape, Fickian diffusion is suggested for n values up to 0.45, whereas Case-II transport is suggested when values are above 0.89. Values of n between these two suggest anomalous transport occurring.[15]

### Statistical Analysis

Statistical analyses were performed using one-way analysis of variance (ANOVA) using Microsoft Excel 365 (Data Analysis ToolPak; Microsoft, Redmond, WA, USA), with statistical significance considered at $p < .05$. Separate one-way ANOVA analyses were conducted according to the specific comparison being investigated. For comparisons between formulation types, LS and PM formulations containing the same Polyox™ MW were compared, whereas the effect of Polyox™ MW was evaluated separately within LS formulations or PM formulations. When a significant difference was detected by ANOVA, Tukey's honestly significant difference (HSD) post-hoc test was applied to identify specific pairwise differences between groups.

Because all experimental measurements ($n = 3$ or $n = 5$) represent technical replicates derived from a single homogeneous formulation batch per composition, statistical analyses primarily reflect intra-batch consistency and comparative formulation trends rather than true inter-batch population variability. Therefore, the reported statistical differences should be interpreted as screening-level comparisons, and confirmation using independently prepared batches would be required to establish formulation robustness.

## Results and Discussion

### Particle Size and Shape Distributions

LS formulations, in the case of Polyox™ grades with MW $< 9 \times 10^5$, showed larger PSDs compared to their PM counterparts (Table 1). This could be attributed to increased particle aggregation in LS formulations, as confirmed by SEM images (Figure 1). The smaller DTZ particles were generally not present as distinct particles in the case of LS formulations but as aggregates (Figure 1).

LS formulations showed relatively narrower size distributions compared to their PM counterparts, as indicated by their lower span values (Table 1). Statistical analysis (one-way ANOVA with Tukey's HSD) showed that LS formulations of DTZ–WSRN80 and DTZ–WSRN1105 had significantly lower span values ($p < .05$), while differences for the other MW grades were not significant. A significant reduction in fine particulate content was recorded for LS formulations compared to their PM counterparts, as indicated by the higher $d_{10}$% values (Table 1), suggesting improved size homogeneity. This could be attributed to the adhesion of such fines on the surfaces of larger particles in the case of LS formulations, as confirmed by SEM observations (Figure 1).

Two different populations of particles could be observed in the PMs, accounting for the morphologies of both DTZ (slabby) and Polyox™ (botryoidal) particles, whereas no distinct DTZ or Polyox™ particles were observed in LS formulations (Figure 1). The improved mass distribution for LS formulations is of importance because it relates to content uniformity. In contrast to LS formulations, the different-sized particles in the case of PM formulations could lead to a different amount of drug per unit mass. When the various-sized particles segregate (e.g., by percolation segregation), drug-rich areas may result where the small particles congregate.[16]

SEM analysis was qualitatively employed in this study to support the trends observed regarding particle morphology and agglomerates; quantitative image analysis, for example, surface roughness or aggregation indices, was not conducted but will be the focus of future work.

### Powder Density

LS formulations showed significantly ($p < .05$) lower bulk densities compared to PM formulations (Table 2), indicating that there are fewer average points of physical contact

**Table 1**. Particle Size Distribution (i.e., Particle Size at 10% (*d*10%), 50% (*d*50%), 90% (*d*90%), Volume Mean Diameter (VMD), and Span; Mean ± SD, *n* = 3, Technical Replicates) of DTZ–Polyox™ Liquisolid (LS) Formulation Powders and Their Physical Mixture (PM) Counterparts.

| Product | | *d*10% (μm) | | *d* 50% (μm) | | *d* 90% (μm) | | VMD (μm) | | Span | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Polyox™ | 8.2 ± 0.1 | | 29.2 ± 0.3 | | 147.3 ± 8.0 | | 67.0 ± 4.5 | | 4.0 ± 1.5 | |
| DTZ (alone) | MW | PM | LS | PM | LS | PM | LS | PM | LS | PM | LS |
| DTZ–WSRN10 | $1 \times 10^5$ | 23.0 ± 4.7 | 59.5 ± 0.0 | 119.0 ± 9.2 | 163.1 ± 0.1 | 337.0 ± 49.0 | 486.0 ± 0.0 | 167.7 ± 38.1 | 273.0 ± 0.0 | 2.6 ± 0.2 | 2.5± 0.0 |
| DTZ–WSRN80 | $2 \times 10^5$ | 21.2 ± 0.3 | 52.8 ± 0.4 | 114.7 ± 9.3 | 143.2 ± 1.1 | 346.3 ± 44.8 | 343.7 ± 5.0 | 156.3 ± 19.1 | 174.3 ± 1.5 | 2.8 ± 0.2 | 2.0 ± 0.0 |
| DTZ–WSRN750 | $3 \times 10^5$ | 27.7 ± 3.5 | 56.6 ± 0.6 | 144.3 ± 20.8 | 159.0 ± 4.6 | 387.7 ± 42.8 | 421.0 ± 50.1 | 188.0 ± 18.1 | 230.7 ± 38.0 | 2.5 ± 0.1 | 2.3 ± 0.2 |
| DTZ–WSRN1105 | $9 \times 10^5$ | 24.9 ± 2.6 | 60.0 ± 0.4 | 139.7 ± 20.6 | 155.0 ± 0.6 | 389.3 ± 47.5 | 378.7 ± 9.0 | 184.7 ± 26.6 | 195.3 ± 8.5 | 2.6 ± 0.1 | 2.1 ± 0.0 |
| DTZ–WSR301 | $40 \times 10^5$ | 36.1 ± 3.5 | 58.0 ± 0.3 | 167.7 ± 9.3 | 166.1 ± 1.7 | 439.3 ± 19.6 | 439.7 ± 11.5 | 211.7 ± 10.0 | 218.3 ± 9.2 | 2.4 ± 0.1 | 2.3 ± 0.0 |
| DTZ–WSR303 | $70 \times 10^5$ | 35.0 ± 1.1 | 51.6 ± 13.4 | 152.0 ± 11.3 | 163.2 ± 1.2 | 390.5 ± 31.8 | 395.7 ± 1.1 | 190.0 ± 14.1 | 199.7 ± 2.3 | 2.3 ± 0.0 | 2.1 ± 0.1 |

**Table 2**. Bulk Density, Tap Density and Carr's Index (CI) (Mean ± SD, *n* = 5, Technical Replicates) for DTZ–Polyox™ Liquisolid (LS) Formulation Powders and Their Physical Mixture (PM) Counterparts.

| | | Bulk Density (g/cm$^3$) | | Tap Density (g/cm$^3$) | | CI (%) | |
|---|---|---|---|---|---|---|---|
| Product | Polyox™ MW | PM | LS | PM | LS | PM | LS |
| DTZ–WSRN10 | $1 \times 10^5$ | 0.42 ± 0.01 | 0.35 ± 0.01 | 0.57 ± 0.00 | 0.55 ± 0.01 | 25.7 ± 0.9 | 36.5 ± 1.2 |
| DTZ–WSRN80 | $2 \times 10^5$ | 0.41 ± 0.01 | 0.34 ± 0.01 | 0.54 ± 0.01 | 0.52 ± 0.02 | 23.7 ± 1.1 | 34.1 ± 2.8 |
| DTZ–WSRN750 | $3 \times 10^5$ | 0.36 ± 0.01 | 0.33 ± 0.01 | 0.50 ± 0.01 | 0.49 ± 0.03 | 23.0 ± 0.4 | 33.3 ± 3.1 |
| DTZ–WSRN1105 | $9 \times 10^5$ | 0.40 ± 0.01 | 0.34 ± 0.01 | 0.52 ± 0.02 | 0.50 ± 0.02 | 23.0 ± 1.2 | 32.1 ± 5.4 |
| DTZ–WSR301 | $40 \times 10^5$ | 0.38 ± 0.01 | 0.34 ± 0.01 | 0.48 ± 0.01 | 0.50 ± 0.01 | 20.0 ± 1.3 | 31.7 ± 1.7 |
| DTZ–WSR303 | $70 \times 10^5$ | 0.40 ± 0.01 | 0.36 ± 0.02 | 0.51 ± 0.00 | 0.51 ± 0.03 | 21.4 ± 1.5 | 30.0 ± 1.0 |

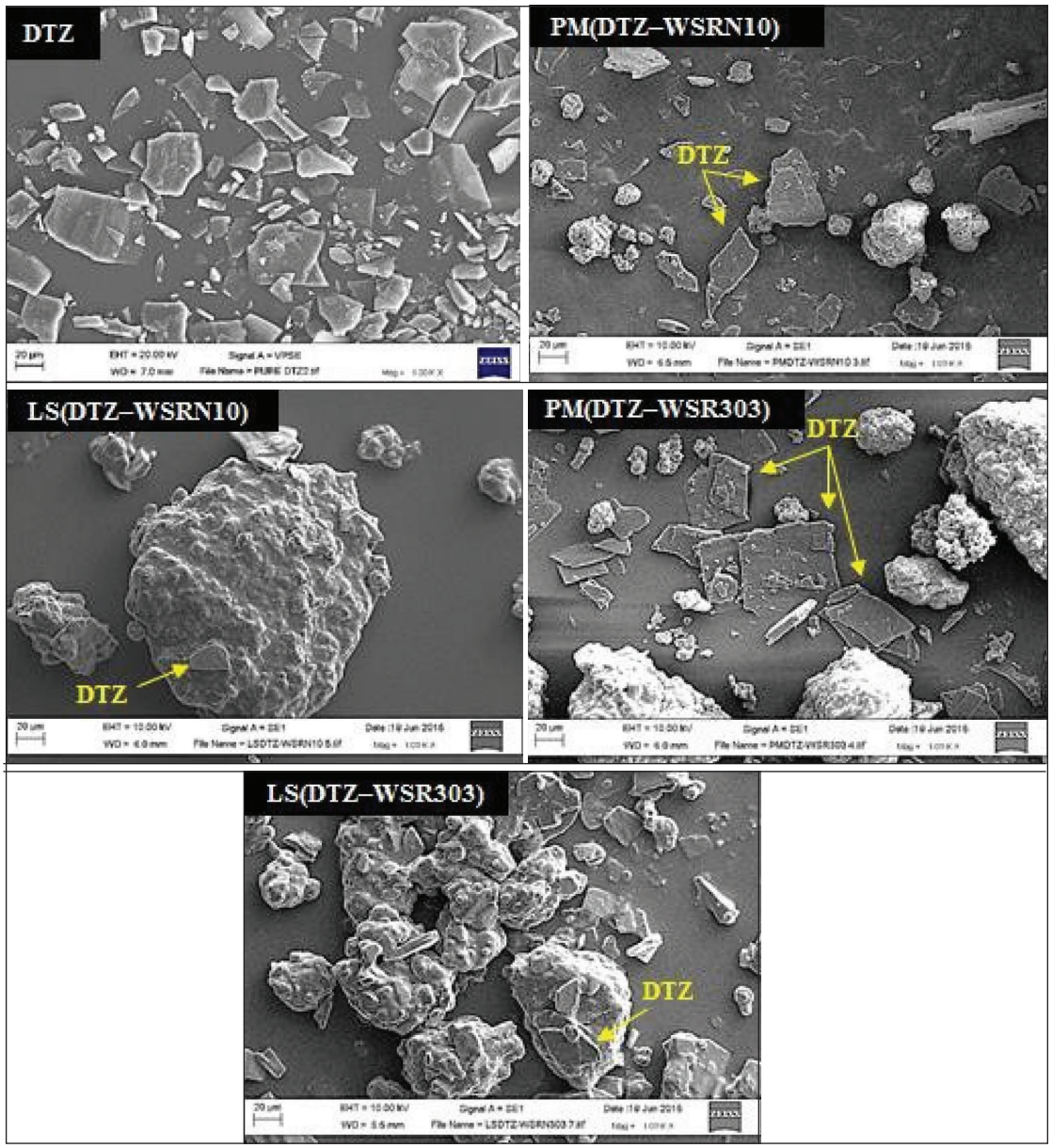


**Figure 1**. Representative Scanning Electron Microscopy (SEM) Photographs of Commercial Diltiazem HCl (DTZ) and Liquisolid (LS) Formulations Containing DTZ and Formulated with Polyox™ WSRN10 or Polyox™ WSR303 in Comparison to Their Physical Mixture (PM) Counterparts.

between particles within LS powders compared to PM powders. The wider polydispersity of particle size for PM formulations compared to LS formulations (Table 1) could account for their higher bulk and tapped densities because polydispersed particles pack more efficiently (i.e., smaller particles occupy the voids between larger particles).

Undoubtedly, the nature and extent of interparticle forces provide a major influence on powder flowability. The high viscosity of PS 80 increases the cohesive properties of the LS powders. SEM photographs confirmed that LS powders are composed of irregular, deformed particles with rough/uneven surfaces and increased particle aggregation due to increased interparticle cohesion (Figure 1). Therefore, LS powders may have a higher propensity for geometrical interlocking upon packing, resulting in higher frictional resistance. The tap density and CI of both LS and PM formulations showed generally decreasing trends with increasing MW of Polyox™ (Table 2), indicating that powders containing Polyox™ grades with higher MWs have slightly better flow properties.

The physicochemical changes during the physicochemical transformations of the LS systems, such as increased particle size (Table 1), irregular particle shape (Figure 1), reduced bulk density, and low flowability (Table 1), have a direct relationship to the drug-release behavior from the

prepared tablets. For one, these transformations affect particle packing and porosity, thus making way for faster permeation of the aqueous dissolution medium and polymer hydration and subsequently polymer swelling. Moreover, the reduced density and low flowability indicate a system packed more within the void volume, which is an indication of enhanced medium permeation and an accelerated rate for swelling-controlled drug delivery systems involving hydrophilic polymers, such as those systems containing water and involving polymer hydration and swelling processes. Moreover, irregular particle shape and liquid distribution irregularity could create areas for enhanced polymer chain flexibility and polymer plasticization, especially for systems involving a mixture containing polysorbate 80.

## Electrostatic Charge

Triboelectrostatic charging is a complex phenomenon that depends on several factors such as contact surface resistivity, particle surface roughness, PSD, particle surface resistivity, and environmental relative humidity.[17]

Commercial DTZ, LS, and PM formulation powders showed strong bipolar charging behaviors (Figure 2), a phenomenon that has been particularly recognized in polydispersed powder mixtures with either similar or dissimilar compositions. Commercial DTZ showed an electronegative net charge (Figure 2). Compared to their PM counterparts, LS formulations containing Polyox™ grades with MWs below $9 \times 10^5$ showed significantly higher net charge, whereas the reverse trend could be observed for LS formulations containing Polyox™ grades with MWs $\geq 9 \times 10^5$ (Figure 2). This suggests that LS formulations containing higher-MW Polyox™ may provide improved handling compared to PM formulations. The differences in electrostatic behavior between LS and PM powders arise because particles can roll, slide, and collide during LS formulation preparation; all these actions can induce electrostatic charge development at the level of the particle surfaces. Although PM formulations containing Polyox™ with MWs below $9 \times 10^5$ showed a negligible absolute magnitude of net charge (≤0.3 nC/g), these formulations showed considerable levels of bipolar positive charging and negative charging (Figure 2). This confirms that measuring only the net charge for powders exhibiting bipolar charge behavior is not a good indicator of charging behavior as it can produce misleading conclusions. Thus, it is necessary to characterize particulate materials for their bipolar electrical distribution

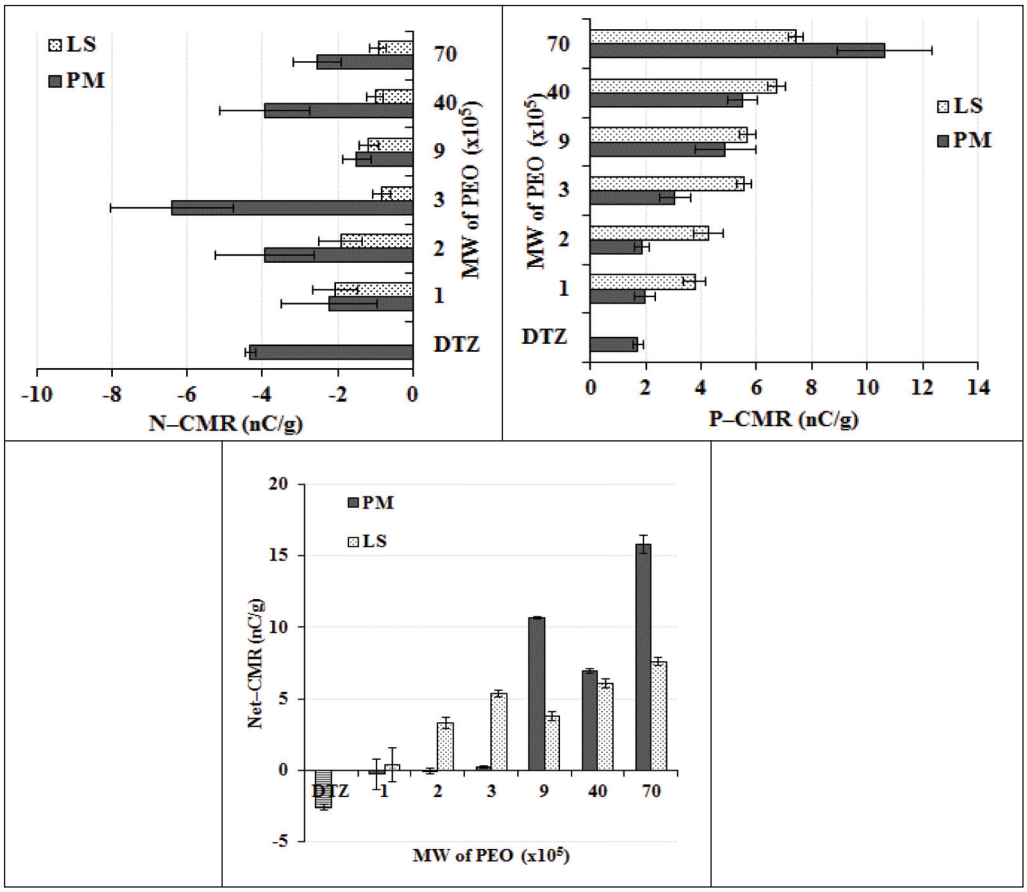


**Figure 2**. Positive–charge-to-mass Ratio (P–CMR), Negative–charge-to-mass Ratio (N–CMR) and Net Charge (Mean ± SD, $n$ = 3) for Commercial Diltiazem HCl (DTZ), Liquisolid (LS) Formulations Containing Various Grades of Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303) in Comparison to Their Physical Mixture (PM) Counterparts.

to recognize the underlying phenomenon of tribocharging and its implications for handling, flow, and tabletting performance.

Our findings indicate that LS and PM powders exhibit different bipolar charging behavior (Figure 2), because LS preparation involves wetting and intensive mixing that promotes particle collisions and triboelectric charge separation. Electrostatic charge accumulation during powder handling correlates with enhanced inter-particle cohesion and changed flow properties, which can adversely affect feed frame consistency, die filling, and content uniformity in large-scale manufacturing, as triboelectric charging affects flow and feeder performance.[18] High charge levels can also result in enhanced adhesion of particles to equipment surfaces and contribute to segregation, therefore increasing the risk of non-uniform dosing of powder upon tabletting.[17,18] These considerations emphasize the importance of electrostatic behavior during the scale-up of LS formulation, particularly for cohesive drug–excipient blends.

## Solid State

DTZ displayed sharp peaks at 8.10°, 10.12°, 18.30°, 19.53°, 20.10°, 21.66°, 24.77°, 28.10°, 30.01°, 32.10°, 40.23°, and 42.10° 2θ. A previous crystallographic study reported the same powder pattern for diltiazem hydrochloride samples prepared under different crystallization conditions, suggesting a typical crystalline pattern.[19] The same peaks were observed in both LS and PM formulations (SM-1). No significant changes were observed in the FT-IR spectra of LS formulations in comparison to their PM counterparts (SM-2). Such observations confirmed that there was no significant change in the solid state of the drug during the preparation of LS formulations. These results also indicate the absence of significant drug–excipient interactions in both LS and PM formulations. Although no changes were detected by PXRD or FT-IR, the presence of weak molecular interactions or non-crystalline associations cannot be fully ruled out using these techniques alone.

## Drug Release

The release profiles of DTZ from various PM and LS formulations under investigation are shown in Figure 3. No tablet exhibited any initial burst drug release (Figure 3). This is because Polyox™ forms a viscous gel layer when it is exposed to aqueous media, allowing the retardation of the release of highly water-soluble drugs (Figure 4).[20]

Polysorbate 80 (PS80) served as a non-volatile liquid vehicle enabling DTZ dispersed/partially solubilised in the liquid vehicle within the LS system, consistent with established LS formulation principles.[21] In addition, polysorbate 80 may potentially influence Polyox™ matrix behavior through interactions with polymer chains, which could affect polymer hydration, gel formation, and drug diffusion pathways. However, this effect was not directly investigated in the present study and remains a viable contributing mechanism. Although this effect was not experimentally measured in the present study, it should be considered a potential factor influencing release kinetics.

The high compression pressure (693 MPa) was necessary to ensure adequate integrity of tablets. Such pressure can reduce initial porosity and induce polymer deformation, which may influence dissolution behavior and flow properties. However, Polyox™ was one such polymer that, upon immediate hydration, rapidly swelled into a gel that subsequently controlled drug release. Although tablet hardness, friability, thickness, and porosity were not assessed, all formulated tablets have been compressed under uniform conditions. This standardization ensures that observed

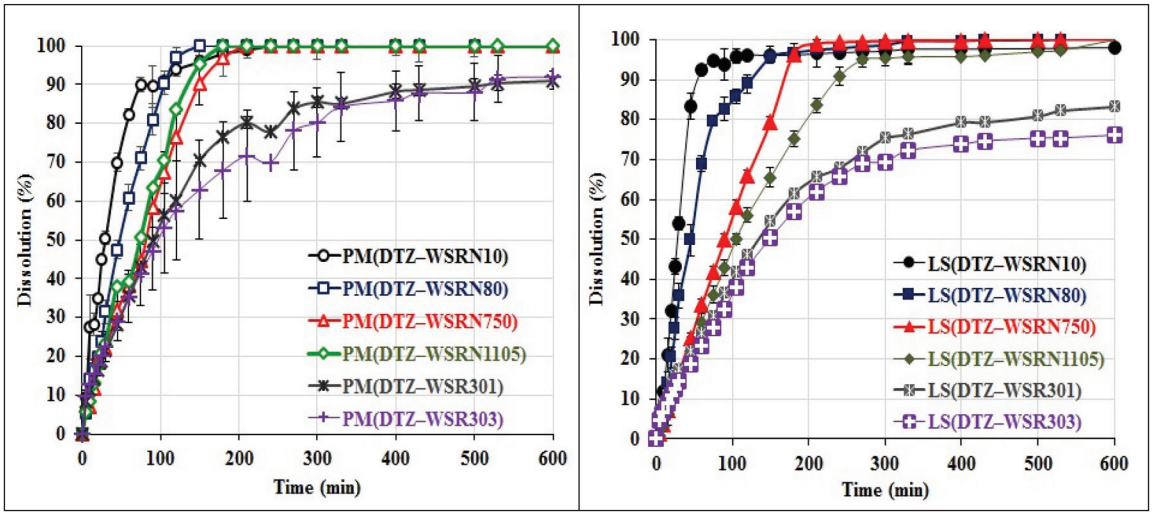


**Figure 3.** Release Patterns (Mean ± SD, *n* = 3) of Diltiazem HCl (DTZ) from Physical Mixture (PM) and Liquisolid (LS) Formulations Containing Various Grades or Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303).

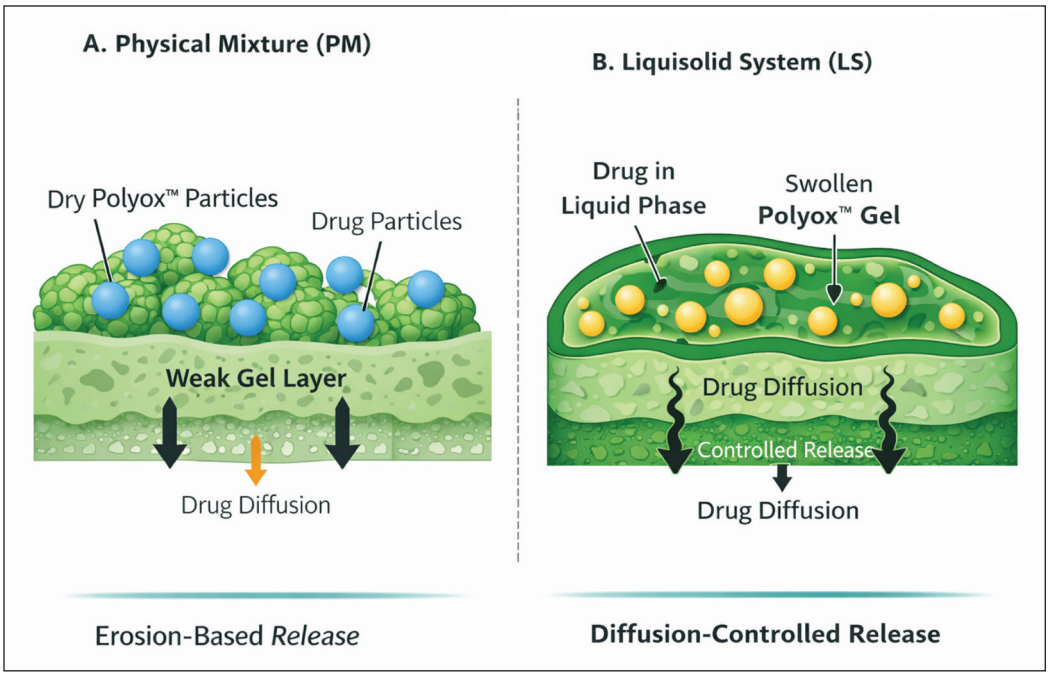


**Figure 4**. Schematic representation of structural and mechanistic differences between liquisolid (LS) and physical mixture (PM) tablets, illustrating DTZ dispersion/partial solubilization in the liquid vehicle, gel formation, diffusion pathways, and polymer-chain interactions.

differences in dissolution or drug-release mechanisms are mainly due to the inherent properties of the formulations rather than compaction variability, although future work should quantify these parameters.

The dissolution rate of DTZ from both LS and PM tablets decreased as the MW of Polyox™ increased (Figure 3). This was confirmed by dissolution parameters analyses that showed both LS and PM tablets containing Polyox™ grades with higher MWs to produce lower DEs, higher MDTs, and lower MDRs compared to those containing lower MWs (Table 3). However, it should be noted that all dissolution experiments were conducted in triplicate, which represents a limitation regarding statistical power. Future studies will include more replicates to improve reliability.

The delayed DTZ release could be related to the rate and extent of hydrogel formation on the tablet surface. Soluble drugs such as DTZ are predominantly released by diffusion through the gel layer. Upon immersion in an aqueous medium, the hydrophilic Polyox™ matrix physically swells to form a hydrogel layer around the tablet. The quick formation of such a gel layer is vital, as it contributes to retaining structural integrity, slows down water entering the interior of the matrix tablet, and prevents tablet disintegration (Figure 4).[22] It could be assumed that the solvent penetrates the free spaces between the macromolecular chains of Polyox™, and the Polyox™ chains become flexible, enhancing the thickness of the gel layer and allowing drug release through the gel's outer surface.[23] This could also be described as water plasticizing the Polyox™ and transforming it from a glassy state to a rubbery state. When it is highly hydrated, the outer layer ultimately reaches a dilution point, leading to Polyox™ disentanglement from the surface of the matrix. The gel layer is then constantly replaced with the hydrated Polyox™ from inside the core.

Polysorbate 80 possesses flexible polyoxyethylene chains that may interact with and become incorporated within the Polyox™ macromolecular network.[24] This effect could influence polymer deformation, hydration, and drug diffusion within the matrix. The plasticizing effect of non-ionic surfactants on polymeric matrixes has been reported to impact release characteristics, by lowering the polymer glass-transition temperature, reducing matrix stiffness, and increasing polymer-chain mobility.[25] Although this effect was not quantitatively measured in this work, it may have been relevant to the release profiles and should be further explored.

In comparison to matrixes containing a Polyox™ grade with a lower-MW, matrixes containing a Polyox™ grade with a higher-MW could produce more coherent (thicker, more viscous) hydrogel layers, acting as a barrier against the release of drug and thereby resulting in a slower drug release since it takes more time for DTZ molecules to travel across the gel layer and reach the dissolution medium. In contrast, Polyox™ grades with low MWs are more susceptible to erosion due to the formation of thinner (softer) hydrogel layers.[26] Higher-MW polymers may also require more energy to disentangle the longer polymer chains, contributing to slower drug release. This was confirmed by swellability studies, which showed the water uptake of both LS and PM tablets to increase as the MW of Polyox™ increased (Figure 5). LS tablets showed lower swellabilities than their

**Table 3.** Dissolution Efficiency (DE), Mean Dissolution Time (MDT), Mean Dissolution Rate (MDR), Similarity Factor ($f_2$) and In Vitro Release Kinetic Parameters (r2, Correlation Coefficient Squared; *n* Value, and MPE, Mean Percentage Error Based on Korsmeyer-Peppas Equation, $Q = k\ tn$ (Equation (8)) of Diltiazem HCl Obtained for Liquisolid (LS) Formulations Containing Various Grades or Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303) in Comparison to Their Physical Mixture (PM) Counterparts.

| | | DE (%) | | MDT (min) | | MDR ($min^{-1}$) | | $f^2$ | $r^2$ | | n | | MPE (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Formulation | Polyox™ MW | PM | LS | PM | LS | PM | LS | LS vs PM | LS | PM | LS | PM | LS | PM |
| DTZ–WSRN10 | $1 \times 10^5$ | 90.6 ± 2.4 | 91.6 ± 1.2 | 31.5 ± 10.0 | 34.0 ± 4.5 | 0.60 ± 0.01 | 0.59 ± 0.01 | 62.7 | 0.997 | 0.931 | 1.301 | 0.871 | 3.51 | 9.63 |
| DTZ–WSRN80 | $2 \times 10^5$ | 90.3 ± 1.3 | 89.0 ± 0.9 | 48.4 ± 6.6 | 57.8 ± 5.7* | 0.49 ± 0.02* | 0.48 ± 0.01* | 70.2 | 0.989 | 0.975 | 1.150 | 0.812 | 6.98 | 7.72 |
| DTZ–WSRN750 | $3 \times 10^5$ | 86.7 ± 3.0 | 82.3 ± 1.4* | 79.9 ± 12.1 | 93.5 ± 3.5* | 0.37 ± 0.02* | 0.34 ± 0.01* | 64.0 | 0.989 | 0.952 | 1.169 | 0.771 | 10.11 | 11.69 |
| DTZ–WSRN1105 | $9 \times 10^5$ | 87.9 ± 0.4 | 78.4 ± 2.1* | 72.7 ± 2.4 | 101.4 ± 16.0* | 0.38 ± 0.01* | 0.38 ± 0.05* | 43.7 | 0.972 | 0.990 | 1.239 | 0.828 | 16.82 | 5.51 |
| DTZ–WSR301 | $40 \times 10^5$ | 74.4 ± 2.5 | 64.4 ± 0.7* | 109.4 ± 6.2 | 136.5 ± 0.4* | 0.32 ± 0.01* | 0.27 ± 0.01* | 49.0 | 0.989 | 0.987 | 0.726 | 0.650 | 5.39 | 5.96 |
| DTZ–WSR303 | $70 \times 10^5$ | 69.4 ± 8.7 | 58.0 ± 2.5* | 131.3 ± 24.4 | 119.4 ± 5.9* | 0.35 ± 0.05* | 0.25 ± 0.01* | 47.5 | 0.994 | 0.998 | 0.712 | 0.580 | 4.84 | 5.10 |

**Note:** The counterpart physical mixture was chosen as the standard for each liquisolid formulation when calculating $f^2$ values. The results are expressed as the mean ± SD, $n = 3$, technical replicates. (*indicates significant difference, $p < .05$ between LS and corresponding PM formulations containing the same Polyox™ molecular weight).

PM tablet counterparts, likely due to restricted expansion of the glassy matrix core.

Better retardation properties were observed for LS tablets containing Polyox™ with MWs $\geq 9 \times 10^5$ (i.e., WSR1105, WSR301 and WSR303) in comparison to the conventional tablets (Figure 3), as substantiated by $f^2$ values below 50 (Table 3). The similarity factor ($f^2$) values were computed to evaluate the similarity of LS and PM formulation dissolution profiles. It has been stated that when $f^2$ values are between 50 and 100, the dissolution profiles are similar. According to the European Medicines Agency guideline on bioequivalence, $f^2$ values between 50 and 100 indicate similar dissolution profiles, whereas values below 50 indicate dissimilar profiles.[27,28] In the present investigation, the formulations containing Polyox™ MW $\leq 3 \times 10^5$ have $f^2 > 60$, suggesting similar release profiles compared to their PM formulations (Table 3). On the contrary, formulations containing MW $\geq 9 \times 10^5$ have $f^2 < 50$ (Table 3), suggesting considerable differences in the release profiles. These changes are in accordance with the observed differences in the mechanisms, where gel strength, polymer mobility, and matrix relaxation are altered. The present calculations should be interpreted as comparative indices because only three tablets per formulation were tested and the study was designed to investigate formulation behavior rather than demonstrate regulatory equivalence.

Similar conclusions could, in general, be obtained when considering MDT, MDR, and DE values. For example, LS tablets produced lower DEs than conventional tablets in the case of Polyox™ with MWs $\geq 9 \times 10^5$ (Table 3). An interesting trend was obtained when plotting the difference in the dissolution efficiency of DTZ obtained from PM and LS formulations ($\Delta DE = DEPM - DELS$) against the MW of Polyox™. ΔDE increased with increasing Polyox™ MW, supporting the role of polymer chain entanglement in release retardation (Figure 6).

The dissolution data were fitted to Equation (8), and the in vitro release kinetic parameters are listed in Table 3. All profiles were well fitted as indicated by the excellent $r^2$ values obtained. In comparison to PM formulations, all LS formulations showed higher *n* values regardless of Polyox™ MW (Table 3), indicating a greater contribution of polymer relaxation and erosion mechanisms. For cylindrical matrixes, n values above 0.89 are consistent with Case-II or Super Case-II transport; however, the release exponent alone does not establish zero-order release. The release of DTZ from all PM formulations followed the anomalous transport mechanism ($0.45 < n < 0.89$) regardless of Polyox™ MW (Table 3). In contrast, the mechanism by which DTZ was released from LS formulations was dependent on Polyox™ MW. LS formulations containing Polyox™ grades up to and including WSRN1105 ($MW = 9 \times 10^5$) exhibited Case-II transport ($n > 0.89$), whereas formulations prepared with the higher MW grades WSR301 ($40 \times 10^5$) and WSR303 ($70 \times 10^5$) exhibited anomalous transport ($0.45 < n < 0.89$). These findings indicate that the transition in release mechanism occurred between $9 \times 10^5$ and $40 \times 10^5$ under the experimental conditions investigated.

More efficient encapsulation of the drug particles by the Polyox™ particles could be a mechanism of drug-release prolongation in the case of LS tablets. The solvent incorporated in the LS formulation may also alter Polyox™ swelling and diffusion behavior, potentially through plasticisation of the hydrated polymer matrix. This interpretation is supported indirectly by previous evidence that triethyl citrate/polysorbate 80 mixtures lower the glass-transition temperature of Eudragit® RS films.[29] Polysorbate was shown to

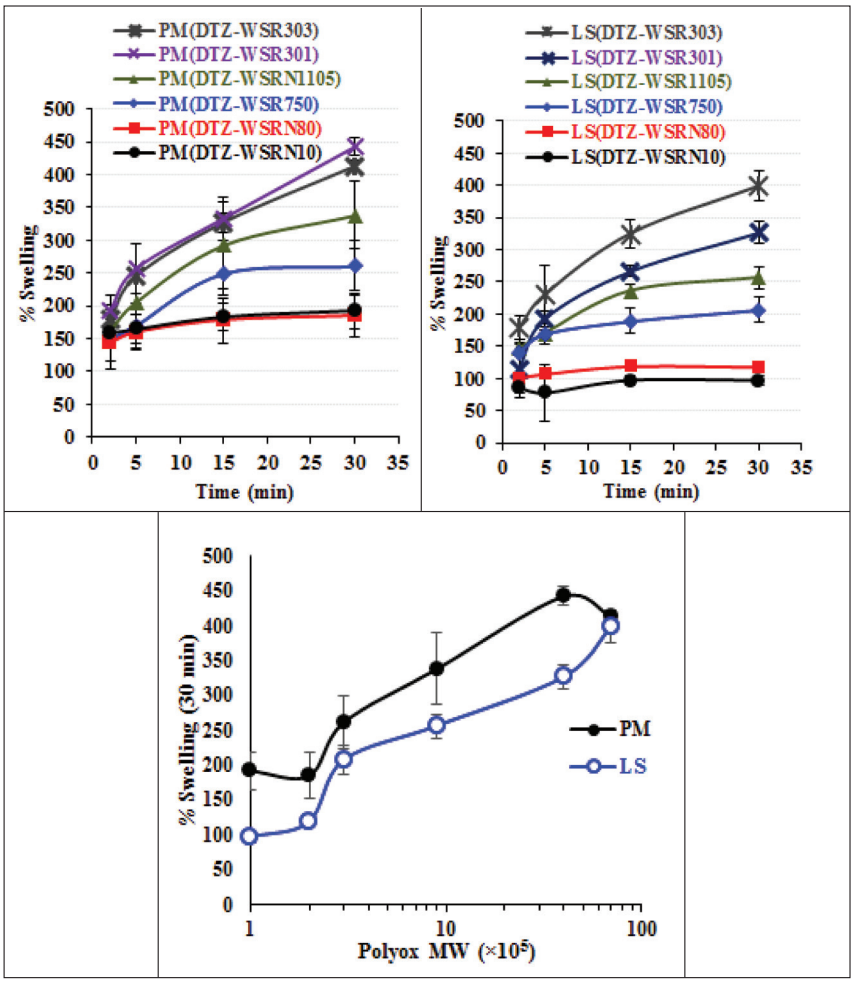


**Figure 5**. Percent Swelling of Physical Mixture (PM) and Liquisolid (LS) Formulation Tablets Containing Various Grades of Polyox™ (WSRN10, WSRN80, WSRN750, WSRN1105, WSR301 and WSR303); and the Effect of Molecular Weight (MW) on % Swelling (Mean ± SD, $n$ = 3).

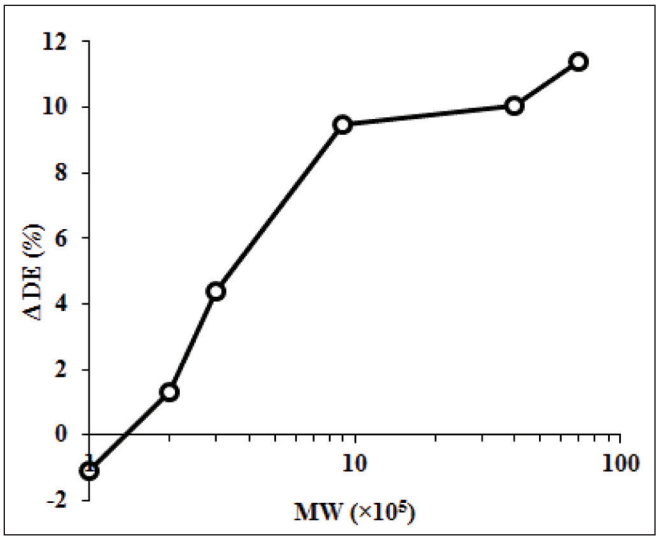


**Figure 6.** Difference in Dissolution Efficiency (ΔDE, %) of Diltiazem HCl (DTZ) Between Liquisolid (LS) and (PM) Formulations in Relation to Polyox™ Molecular Weight (MW).

reduce the glass transition temperature (Tg) of polymers such as Polyox™, and thus it could slow the release rate of DTZ from LS tablets compared to the PM tablets by affecting the intermolecular bonds between Polyox™ chains. While the modulation of release rate has been found by Kaialy et al.,[10] as solvent-dependent, the current results provide new insights into the release mechanisms by indicating that the MW of Polyox™ is an important factor in the release mechanisms. High MW polymers $\geq 9 \times 10^5$ cause diffusion-controlled release because of gel strength and increased polymer chain entanglements.

While the release exponent ($n$ value) gives information on the release mechanism, the release of drugs from Polyox™ matrixes is a complex process involving the interrelated processes of polymer swelling, relaxation, and erosion. The initial step in the process is the rapid swelling of the polymer chains upon hydration, followed by relaxation and gel layer formation, which gradually controls the release of the drug. At higher MWs of Polyox™, the process is diffusion-controlled, whereas matrix erosion is more important for lower MWs.

The present results suggest that the transition in release mechanism occurred between Polyox™ MWs of $9 \times 10^5$ and $40 \times 10^5$. These mechanisms can be justified by an enhanced level of polymer chain entanglements that improves the hydrogel's viscosity and the rate of relaxation and/or disentanglement of the polymers, all of which contribute to an enhanced gel strength that ensures the release of the drug by impeding the mobility of the gel matrix.[30] Statistical analyses were performed in triplicate ($n = 3$), which is typical for preliminary formulation screening. Although this allows valid comparative insights, it limits statistical power, and future studies should include larger replicates to strengthen the analysis.

The use of distilled water was adopted as a discriminatory dissolution medium to separate polymer-controlled gel formation and release without the influence of ionic strength on Polyox hydration and swelling. Though this ensured clarity from a mechanistic viewpoint, extrapolation to a physiological environment is certainly limited and hence calls for more experimentation on how easily a drug dissolves in physiological fluids. Swelling was assessed over the first 30 min to capture the early hydration and gel layer formation; however, assessing swelling over longer time periods would offer a better correlation with the 10-hour dissolution profiles and will be explored in future studies.

Although the Polyox™ grades with an MW $\geq 9 \times 10^5$ had slower, diffusion-controlled release, they had higher bulk cohesivity and changed electrostatic properties, which might cause difficulties in large-scale production. Lower flowability, higher tablet compression pressures, and the possibility of segregation during mixing might necessitate optimization of powder handling, humidity, and even the addition of glidants. These factors are significant when it comes to the large-scale production of tablets.

It should be noted that the experimental design employed single formulation batches per condition with repeated technical measurements ($n = 3$ or $n = 5$). While this approach is well-suited for initial screening and establishing mechanistic trends across Polyox™ MWs, it carries an intrinsic risk of pseudoreplication. Therefore, statistical significance reported herein demonstrates intra-batch precision and comparative differences between technical samples rather than true inter-batch variability. Future formulation scale-up studies should incorporate multiple independent production batches ($N \geq 3$) to reinforce process robustness and batch-to-batch reproducibility.

## Conclusion

The potential of Polyox™-based LS tablets in modulating the release of the highly water-soluble drug substance DTZ HCl was successfully demonstrated, and more sustained-release profiles were achieved if the right grades of polymer were selected for use in the formulation. Higher MW Polyox™ grades generally produced slower drug release. Based on the release exponent (n), the transition from Case-II to anomalous transport occurred between WSRN1105 ($9 \times 10^5$) and WSR301 ($40 \times 10^5$), suggesting a transition region rather than a single critical MW. It was also established that the selection of the MW of Polyox™ played an important role in the formulation design, and only formulations that utilized high MW Polyox™ with a MW greater than or equal to $9 \times 10^5$ exhibited slower release profiles compared to the conventional PM tablets.

Although the LS method is a simple and potentially easy-to-scale-up drug delivery system, it should be noted that the results obtained from this current study only involve a highly water-soluble drug substance, and thus caution should be exercised when generalizing the results for other drug substances that may have different physicochemical properties. In particular, drugs with low water solubility, poor polymer compatibility, high MW, or a tendency to interact with excipients may exhibit different release behaviors and gel-matrix interactions.

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### Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

### Consent to Participate

Not applicable.

### Consent for Publication

Not applicable.

### Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical Approval

This study does not involve experiments on animals or human subjects.

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## Informed Consent

Not applicable.

## Use of Artificial Intelligence (AI)-assisted Tools

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

## Supplemental Material

Supplemental material for this article is available online.

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## References

1. Chaffman M and Brogden RN. Diltiazem: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1985; 29: 387–454.
2. Costa P and Sousa Lobo JM. Divisibility of diltiazem matrix sustained-release tablets. *Pharm Dev Technol* 2001; 6: 343–351.
3. Drapińska P, Skulmowska-Polok K, Chałupka J, et al. Sustained-release oral delivery of NSAIDs and acetaminophen: Advances and recent formulation strategies—a systematic review. *Pharmaceutics*. 2025; 17(10): 1264 DOI: 10.3390/pharmaceutics 17101264.
4. Gao P, Skoug JW, Nixon PR, et al. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. *J Pharm Sci* 1996; 85: 732–740.
5. Mitchell K, Ford JL, Armstrong DJ, et al. The influence of concentration on the release of drugs from gels and matrices containing Methocel®. *Int J Pharm* 1993; 100: 155–163.
6. Velasco MV, Ford JL, Rowe P, et al. Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *J Control Release* 1999; 57: 75–85.
7. Shojaee S, Kaialy W, Cumming KI, et al. Comparative evaluation of drug release from aged prolonged polyethylene oxide tablet matrices: Effect of excipient and drug type. *Pharm Dev Technol* 2016; 21: 189–195.
8. Ezegbe AC, Ezegbe GA, Ogbonna JI, et al. A review on liquisolid: A novel technique for enhancement of solubility and bioavailability of poorly water-insoluble drugs. *Science Frontiers* 2023; 4: 17–24.
9. Javadzadeh Y, Musaalrezaei L and Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrixes. *Int J Pharm* 2008; 362: 102–108.
10. Kaialy W, Bello H, Asare-Addo K, et al. Effect of solvent on retarding the release of diltiazem HCl from Polyox-based liquisolid tablets. *J Pharm Pharmacol* 2016; 68: 1396–1402.
11. Hussain T, Kaialy W, Deng T, et al. A novel sensing technique for measurement of magnitude and polarity of electrostatic charge distribution across individual particles. *Int J Pharm* 2013; 441: 781–789.
12. Khan KA. The concept of dissolution efficiency. *J Pharm Pharmacol* 1975; 27: 48–49.
13. Moore JW and Flanner HH. Mathematical comparison of dissolution profiles. *Pharm Technol* 1996; 20: 64–74.
14. Talevi A and Ruiz ME. Korsmeyer–Peppas, Peppas–Sahlin, and Brazel–Peppas: Models of drug release. In: *The ADME Encyclopedia*. 2022, pp.613–621.
15. Siepmann J and Peppas NA. Mathematical modeling of controlled drug delivery. *Adv Drug Deliv Rev* 2001; 48: 137–138.
16. Kaialy W. On the effects of blending, physicochemical properties, and their interactions on the performance of carrier-based dry powders for inhalation—a review. *Adv Colloid Interface Sci* 2016; 235: 70–89.
17. Kaialy W. A review of factors affecting electrostatic charging of pharmaceuticals and adhesive mixtures for inhalation. *Int J Pharm* 2016; 503: 262–276.
18. Liu Z, Muzzio FJ and Callegari G. Powder property change after passing through a feeder: The effect of electrostatics on powder flow. *Powder Technol* 2023; 425: 118532.
19. Mayer I, Cohen S, Tsamir L. Crystal data of diltiazem hydrochloride C22H26N2O4S. HCl. *Powder Diffr*. 1990; 5(3): 160–161.
20. Shojaee S, Emami P, Mahmood A, et al. An investigation on the effect of polyethylene oxide concentration and particle size in modulating theophylline release from tablet matrices. *AAPS PharmSciTech* 2015; 16: 1281–1289.
21. Sharma V and Pathak K. Liquisolid system of paclitaxel using modified polysaccharides: In vitro cytotoxicity, apoptosis study, cell cycle analysis, in vitro mitochondrial membrane potential assessment, and pharmacokinetics. *Int J Biol Macromol* 2019; 137: 20–31.
22. Khan MA, Karnachi AA, Singh SK, et al. Controlled release coprecipitates: Formulation considerations. *J Control Release* 1995; 37: 131–141.
23. Colombo P, Bettini R, Massimo G, et al. Drug diffusion front movement is important in drug release control from swellable matrix tablets. *J Pharm Sci* 1995; 84: 991–997.
24. Lind TK, Nilsson EJ, Wyler B, et al. Effects of ethylene oxide chain length on crystallization of polysorbate 80

and its related compounds. *J Colloid Interface Sci* 2021; 592: 468–484.

25. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer–surfactant combinations using solubility parameters and testing the processability. *Int J Pharm*. 2007; 328(2): 119–129.
26. Wu N, Wang LS, Tan DCW, et al. Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: Polyethylene oxide with high molecular weights. *J Control Release* 2005; 102: 569–581.
27. US Food and Drug Administration. Guidance for industry: Dissolution testing of immediate release solid oral dosage forms. Center for Drug Evaluation and Research (CDER), https://www.fda.gov/media/70936/download (1997, accessed 27 January 2026).
28. European Medicines Agency. Guideline on the investigation of bioequivalence (Rev. 1). Committee for Medicinal Products for Human Use (CHMP), CPMP/EWP/QWP/1401/98 Rev. 1, https://www.ema.europa.eu/en/investigation-bioequivalence-scientific-guideline (2010, accessed 27 January 2026).
29. Gruetzmann R and Wagner KG. Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from Eudragit® RS films by differential scanning calorimetry. *Eur J Pharm Biopharm* 2005; 60: 159–162.
30. Maggi L, Segale L, Torre ML, Machiste EO, Conte U. Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug: dimensionality study. *Biomaterials*. 2002; 23(4): 1113–1119.