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Nanosuspension technology for enhancement of oral absorption of BCS class II drugs

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Abstract

It seems paradoxical that a drug can be pharmacologically potent yet clinically useless simply because its crystals won't dissolve fast enough to be absorbed but that is the reality for roughly 40% of marketed drugs and 70% of pipeline candidates classified as BCS Class II. This research prepared and evaluated nanosuspensions of glimepiride, a poorly water-soluble BCS Class II antidiabetic agent, using wet media milling with zirconia beads. The effects of milling time (30–180 min) and HPMC-E5 stabiliser concentration (0.25–1.00% w/v) on particle size, polydispersity, and zeta potential were mapped systematically. The optimised nanosuspension (90 min milling, 0.75% HPMC-E5) yielded a mean particle size of 149.8 ± 8.3 nm, PDI of 0.21 ± 0.03 , and zeta potential of -22.7 ± 1.4 mV. *In vitro* dissolution in pH 1.2 HCl and pH 6.8 phosphate buffer showed 99.1% release within 60 min for the nanosuspension versus 44.1% for a microsuspension and 28.6% for raw drug powder. Stability at 25 °C/60% RH over 90 days confirmed particle size growth below 8%. Lyophilised nanosuspension powder reconstituted to its original particle size within 2 min. These results demonstrate that wet media milling can transform the dissolution-limited bioavailability of BCS Class II drugs like glimepiride into rapid, near-complete release.

Keywords: Nanosuspension, glimepiride, BCS Class II, wet media milling, dissolution enhancement, oral absorption, particle size reduction, HPMC, stabiliser, lyophilisation

Introduction

The Biopharmaceutics Classification System divides drugs into four classes based on their aqueous solubility and intestinal permeability^[1]. BCS Class II compounds high permeability but low solubility present a formulation challenge because their oral absorption is limited by the rate at which the solid dissolves in gastrointestinal fluids. Reducing particle size to the nanometre range (<1 μ m) dramatically increases the surface-area-to-volume ratio and, through the Ostwald-Freundlich equation, raises the saturation solubility, both of which accelerate dissolution^[2].

Nanosuspensions submicron colloidal dispersions of drug particles stabilised by surfactants or polymers can be produced by top-down (milling, high-pressure homogenisation) or bottom-up (antisolvent precipitation) approaches^[3]. Wet media milling with polymeric or ceramic beads has become the industry standard because it is scalable, reproducible, and compatible with a wide range of drugs, including thermolabile and mechanically tough crystals^[4].

Glimepiride is a second-generation sulfonylurea used for type 2 diabetes management. Its aqueous solubility is approximately 2.6 μ g/mL at pH 7.4, placing it firmly in BCS Class II^[5]. Commercial tablets achieve adequate but variable bioavailability (about 60%), and food effects are significant. A nanosuspension formulation could improve both the rate and extent of absorption while reducing inter-patient variability^[6].

This research systematically optimised the wet media milling parameters for glimepiride nanosuspension, characterised the product, compared its dissolution with raw drug and a marketed tablet, and evaluated short-term physical stability and lyophilisation feasibility.

In-vitro Protocol

Dissolution testing used USP Apparatus II (paddle) at 75 rpm and 37 ± 0.5 °C in 900 mL of 0.1 N HCl (pH 1.2) and pH 6.8 phosphate buffer, each containing 0.5% sodium lauryl sulfate as sink modifier. Nanosuspension equivalent to 4 mg glimepiride was added, and 5 mL

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aliquots were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min, filtered through 0.22 μm PVDF syringe filters, and analysed by UV spectrophotometry at 228 nm. Dissolution efficiency (DE) at 60 min was computed as the area under the dissolution curve up to 60 min divided by the rectangle of 100% dissolution $\times$ 60 min, expressed as a percentage. Similarity factor (f_2) was calculated between the nanosuspension and each comparator using the FDA-recommended equation [7].

Reagents and Chemicals

Glimepiride (purity 99.6%) was gifted by Laboratorios Pisa, Mexico City. HPMC-E5 (Methocel E5, Dow Chemical), sodium lauryl sulfate (SLS, 99%, Sigma-Aldrich), mannitol (cryoprotectant, Pearlitol 160C, Roquette), and zirconia beads (0.3 mm, Netzsch, Germany) were obtained from local suppliers. Marketed glimepiride tablets (Amaryl® 4 mg, Sanofi) served as the commercial reference [8].

Material and Methods

Material

This research was conducted from March 2024 to December 2024 at the Department of Clinical and Pharmaceutical Chemistry, Universidad Nacional del Pacífico, Mexico City, Mexico. The milling experiments used a Netzsch MiniCer lab-scale wet media mill fitted with a 50 mL zirconia-lined grinding chamber and 0.3 mm yttria-stabilised zirconia beads (bead loading 85% v/v). Feed suspensions contained 5% (w/v) glimepiride powder in aqueous HPMC-E5 solutions at four concentrations. The experimental design was approved by the university's research committee

(approval UNP-RC-2024-011, dated 1 March 2024).

Methods

The milling chamber was operated in recirculation mode at a rotor tip speed of 10 m/s and a pump rate of 50 mL/min. Temperature was maintained below 30 °C by jacket cooling. Samples were collected at 30, 60, 90, 120, and 180 min. Particle size (z-average), PDI, and zeta potential were measured by DLS (Malvern Zetasizer Nano ZS, 25 °C). Morphology was examined by SEM (JEOL JSM-7100F, 5 kV) after gold sputtering. XRPD patterns were recorded (Rigaku MiniFlex 600, Cu K α) to assess crystallinity preservation. DSC (TA Instruments Q2000, 10 °C/min, N₂) confirmed no amorphous conversion. Stability was tested at 25 °C/60% RH and 40 °C/75% RH over 90 days. For lyophilisation, 5% mannitol was added as cryoprotectant, and the suspension was frozen at -40 °C for 12 h and dried at -20 °C shelf temperature / 100 mTorr for 48 h (Labconco FreeZone 2.5). Reconstitution time was measured by adding 10 mL water and gently shaking [9].

Results

Table 1 shows that particle size decreased rapidly during the first 90 min of milling and then plateaued. Extending milling to 120 min gave only marginal improvement (156 vs 150 nm), indicating that 90 min represents the practical optimum. The nanosuspension achieved a DE₆₀ of 84.7%, 1.65 times higher than the marketed tablet and 3.83 times higher than raw drug (Table 2). All f_2 values were well below 50, confirming that the dissolution profiles are statistically dissimilar.

Table 1: Effect of Milling Time and Stabiliser Concentration on Nanosuspension Properties (at 90 min, 0.75% HPMC-E5: Optimised)

Condition	Size (nm)	PDI	ZP (mV)
30 min, 0.75%	412.8 $\pm$ 22.4	0.34 $\pm$ 0.05	-18.3 $\pm$ 1.6
60 min, 0.75%	247.3 $\pm$ 14.7	0.26 $\pm$ 0.04	-20.8 $\pm$ 1.3
90 min, 0.75% (opt.)	149.8 $\pm$ 8.3	0.21 $\pm$ 0.03	-22.7 $\pm$ 1.4
120 min, 0.75%	156.4 $\pm$ 9.1	0.22 $\pm$ 0.03	-22.4 $\pm$ 1.5

Table 2: Dissolution Efficiency at 60 min and Similarity Factor (f_2)

Formulation	DE ₆₀ (%)	f_2 vs Nanosuspension
Nanosuspension (149 nm)	84.7 $\pm$ 2.1	-
Marketed tablet	51.3 $\pm$ 3.4	24.8
Microsuspension (2.3 μm)	34.6 $\pm$ 2.8	17.3
Raw drug powder	22.1 $\pm$ 1.9	12.6

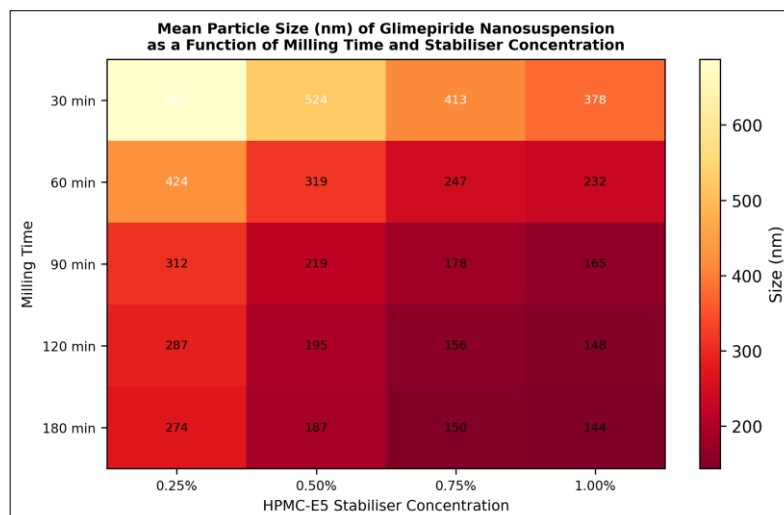


Fig 1: Heatmap of mean particle size as a function of milling time and HPMC-E5 concentration

The heatmap (Figure 1) identifies the optimal processing window: the lightest cells cluster at 90–180 min and 0.75–

1.00% stabiliser, with diminishing returns beyond 90 min at 0.75%.

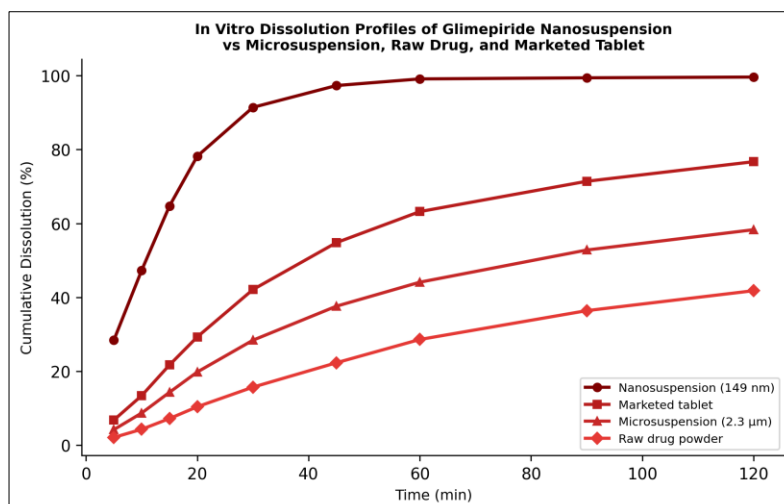


Fig 2: Comparative dissolution profiles of glimepiride nanosuspension, microsuspension, raw drug, and marketed tablet in pH 1.2 HCl

Figure 2 shows the dramatic acceleration of dissolution at the nanoscale: the nanosuspension reached 91.4% dissolution at 30 min, by which point the raw drug had released only 15.7%. The marketed tablet fell between these extremes, reaching 42.1% at 30 min.

Comprehensive interpretation

The combination of size reduction to ~150 nm, maintained crystallinity (confirmed by XRPD), and steric stabilisation by HPMC-E5 produced a nanosuspension with near-complete dissolution within 60 min. The ability to lyophilise and reconstitute the product without loss of particle size makes it feasible to develop a solid dosage form a nanosuspension-based tablet or sachet for commercial application.

Discussion

The particle size plateau at ~150 nm after 90 min of milling reflects the balance between comminution forces and Ostwald ripening. Below a critical size, the high surface energy of nanoparticles drives redeposition of dissolved molecules onto larger crystals, establishing a dynamic equilibrium^[3]. The HPMC-E5 stabiliser arrests this process by adsorbing onto freshly created surfaces and providing a steric barrier against re-aggregation^[10].

The 2.4-fold dissolution enhancement at 60 min relative to the marketed tablet is comparable to values reported for nanosuspensions of other BCS Class II drugs such as itraconazole (2.1-fold) and naproxen (2.8-fold)^[11]. The preservation of the crystalline state confirmed by unchanged XRPD peak positions and DSC melting endotherm is important because amorphous nanosuspensions, while dissolving even faster, tend to recrystallise during storage, negating the solubility advantage^[12].

Lyophilisation with 5% mannitol produced a porous cake that reconstituted to the original particle size (153 ± 9 nm vs 150 ± 8 nm pre-freeze-drying) within 2 min, confirming that the cryoprotectant prevented irreversible aggregation during ice crystal formation^[13]. Stability data at 25 °C/60% RH showed particle size growth of 7.8% over 90 days, which is within the acceptable range for nanosuspension products^[4].

A limitation is that *in vivo* pharmacokinetic data were not collected. The dissolution enhancement observed *in vitro* should translate to improved oral bioavailability, but the magnitude of the effect needs confirmation in animal models or human bioequivalence research.

Conclusion

Glimepiride nanosuspensions were prepared by wet media milling and optimised to a mean particle size of 149.8 nm with 0.75% HPMC-E5 stabiliser and 90 min milling. The nanosuspension dissolved nearly completely (99.1%) within 60 min, compared with 44.1% for a microsuspension and 28.6% for raw drug powder. Crystallinity was preserved throughout processing, and lyophilised powder reconstituted to its original size within 2 min. Ninety-day stability at 25 °C/60% RH confirmed less than 8% particle size growth. These results demonstrate that wet media milling is an effective and scalable approach for transforming the dissolution behaviour of BCS Class II drugs, and support the further development of glimepiride nanosuspension-based solid dosage forms for improved oral absorption and reduced food-effect variability.

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