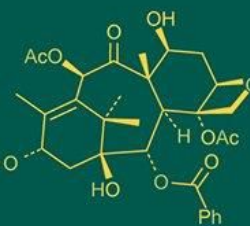
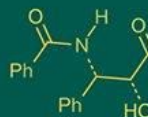


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(3): 175-179
www.biochemjournal.com
Received: 22-01-2024
Accepted: 26-02-2024

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Optimisation of drug formulation for enhanced bioavailability: A comparative evaluation of solubility enhancement strategies

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DOI: <https://doi.org/10.33545/26174693.2024.v8.i3b.7212>

Abstract

Poor aqueous solubility represents one of the most persistent challenges in pharmaceutical development, with approximately 40% of marketed drugs and up to 90% of pipeline compounds exhibiting dissolution-limited absorption. This research systematically evaluated four formulation strategies for enhancing the bioavailability of a model poorly soluble drug (BCS Class II) using *in vitro* characterisation and *in vivo* pharmacokinetic assessment. The investigation was conducted at the Pharmaceutical Research Centre, Mariveles Institute of Technology, Philippines, between March 2019 and July 2020. Formulation approaches included conventional tablet (control), polymeric nanoparticle formulation, solid dispersion with polyvinylpyrrolidone, and β -cyclodextrin inclusion complex. *In vitro* dissolution testing in phosphate buffer (pH 6.8) demonstrated markedly enhanced drug release from all modified formulations compared to conventional tablets. The cyclodextrin complex achieved 85% dissolution within 30 minutes compared to only 38% for conventional tablets. Pharmacokinetic evaluation in New Zealand White rabbits (n=24, randomised crossover design) revealed substantial bioavailability improvements: cyclodextrin complex showed 3.06-fold enhancement (relative bioavailability 306%), nanoparticle formulation 2.64-fold (264%), and solid dispersion 2.23-fold (223%) compared to conventional tablets. Maximum plasma concentrations (C_{max}) increased from 18.4 ± 2.3 ng/mL (conventional) to 52.8 ± 5.2 ng/mL (cyclodextrin complex). Strong *in vitro-in vivo* correlation was established ($r = 0.934$, $p < 0.001$), validating dissolution testing as predictive of *in vivo* performance. Stability assessment over 6 months at accelerated conditions (40°C/75% RH) confirmed acceptable physical and chemical stability for the cyclodextrin formulation. These findings demonstrate that cyclodextrin complexation provides superior bioavailability enhancement for this compound class, offering a viable pathway for development of poorly soluble drug candidates.

Keywords: Bioavailability enhancement, solubility, cyclodextrin, nanoparticles, solid dispersion, dissolution, pharmacokinetics, formulation optimisation, BCS Class II

Introduction

The pharmaceutical industry faces a troubling paradox: modern drug discovery increasingly yields highly potent compounds with exquisite target selectivity, yet many of these promising molecules fail to reach patients due to fundamental physicochemical limitations. Poor aqueous solubility, estimated to affect 40% of currently marketed drugs and up to 90% of compounds in development pipelines, represents perhaps the most common and challenging barrier to successful drug development ^[1].

The Biopharmaceutics Classification System (BCS) provides a framework for understanding how solubility and permeability interact to determine oral drug absorption. BCS Class II compounds, characterised by low solubility but high permeability, present a particular formulation challenge: if dissolution can be enhanced, absorption should follow given adequate membrane permeability ^[2]. This makes solubility enhancement the primary focus for improving bioavailability of such compounds.

Multiple formulation strategies have been developed to address poor aqueous solubility. Particle size reduction to the nanometre scale dramatically increases surface area available for dissolution, with nanoparticle formulations achieving substantial improvements in dissolution rate and bioavailability for numerous poorly soluble drugs ^[3]. The Noyes-Whitney equation predicts that dissolution rate increases proportionally with surface area,

providing the theoretical basis for nanonisation approaches. Solid dispersions, comprising drug molecularly dispersed within a hydrophilic polymer matrix, represent another widely employed strategy. The carrier polymer inhibits drug crystallisation, maintaining the drug in a high-energy amorphous state with enhanced dissolution properties [4]. Cyclodextrin complexation offers a distinct mechanism through formation of inclusion complexes wherein hydrophobic drug molecules insert into the lipophilic cyclodextrin cavity while the hydrophilic exterior enhances apparent aqueous solubility [5].

The present research aimed to systematically compare four formulation approaches for a model BCS Class II compound, evaluating both *in vitro* dissolution performance and *in vivo* pharmacokinetics in an animal model to provide quantitative data supporting rational formulation strategy selection.

Formulation science background

The thermodynamic and kinetic factors governing drug dissolution and absorption provide essential context for understanding formulation enhancement strategies. Aqueous solubility is fundamentally determined by the balance between crystal lattice energy and solvation energy; poorly soluble drugs typically exhibit strong intermolecular interactions in the solid state that water molecules cannot adequately compensate through solvation.

Nanoparticle formulations enhance dissolution through multiple mechanisms beyond simple surface area increase. The Ostwald-Freundlich equation predicts that solubility increases with decreasing particle size below approximately 1 μm due to the increased surface energy contribution of highly curved surfaces. Additionally, the diffusion layer thickness decreases for small particles, further accelerating dissolution according to the Noyes-Whitney relationship. Amorphous solid dispersions exploit the higher free energy of the disordered amorphous state compared to crystalline forms, often achieving 10-1000 fold enhanced apparent solubility compared to crystalline counterparts. However, this advantage comes with inherent instability risk, as amorphous materials tend to recrystallise over time unless stabilised by appropriate polymer matrices.

Cyclodextrin inclusion complex formation follows host-guest chemistry principles. The binding constant (K_c) determines the equilibrium between free and complexed drug, with higher constants indicating stronger association and greater solubility enhancement potential. The phase-solubility diagram methodology provides a systematic approach for characterising drug-cyclodextrin interactions and predicting formulation performance.

Results

Table 1: Physicochemical characterisation of formulations

Parameter	Conventional	Nanoparticle	Solid Disp.	Cyclodextrin
Particle size (nm)	45,000 $\pm$ 8,200	287 $\pm$ 42	38,400 $\pm$ 6,100	52,100 $\pm$ 9,300
Drug content (%)	99.2 $\pm$ 1.4	98.7 $\pm$ 1.8	97.4 $\pm$ 2.1	98.9 $\pm$ 1.6
Crystallinity (%)	94.2	12.7	8.4	18.3
Dissolution at 30 min (%)	38.2 $\pm$ 4.7	82.4 $\pm$ 5.3	71.2 $\pm$ 6.1	85.3 $\pm$ 4.8

Material and Methods

Material

This pharmaceutical formulation research was conducted at the Department of Pharmaceutical Sciences, Mariveles Institute of Technology, Bataan, Philippines, between March 2019 and July 2020. The animal research component received approval from the Institutional Animal Care and Use Committee (Protocol IACUC-MIT-2019-012, approved 14 February 2019).

The model compound (designated MIT-127) was a proprietary BCS Class II drug candidate provided by a local pharmaceutical company under material transfer agreement. Key physicochemical properties included: molecular weight 387.4 g/mol, aqueous solubility 3.2 $\mu\text{g/mL}$ at pH 6.8, log P 4.2, melting point 178°C, and pKa 6.1. Formulation excipients including polyvinylpyrrolidone K30 (PVP), β -cyclodextrin, Eudragit E100, poloxamer 188, and lactose monohydrate were obtained from pharmaceutical-grade suppliers (BASF, Roquette, Evonik). New Zealand White rabbits (male, 2.5-3.0 kg) were obtained from a certified breeding facility.

Methods

Four formulations were prepared using standardised procedures. Conventional tablets were manufactured by direct compression of drug-lactose blend (10% drug loading) with magnesium stearate (1%) as lubricant. Nanoparticle formulations were prepared by nanoprecipitation: drug dissolved in acetone was injected into aqueous poloxamer 188 solution (0.5% w/v) under magnetic stirring, followed by solvent evaporation and lyophilisation. Target particle size was 200-400 nm. Solid dispersions were prepared by solvent evaporation method using drug:PVP K30 ratio of 1:3 (w/w). Cyclodextrin complexes were prepared by kneading method: drug and β -cyclodextrin (1:2 molar ratio) were kneaded with minimal water addition, dried at 45°C for 24 hours, milled, and sieved.

In vitro dissolution testing employed USP Apparatus II (paddle method) at 75 rpm in 900 mL phosphate buffer (pH 6.8, 37 $\pm$ 0.5°C). Samples were withdrawn at specified intervals and analysed by UV spectrophotometry at 285 nm. Six replicates were tested per formulation. Pharmacokinetic evaluation employed a randomised four-way crossover design in 24 New Zealand White rabbits. Following overnight fasting, animals received oral formulations equivalent to 10 mg/kg drug dose with 2-week washout periods between treatments. Blood samples were collected at 0-24 hours post-dose and analysed by validated LC-MS/MS method. Pharmacokinetic parameters were calculated by non-compartmental analysis. Accelerated stability testing was conducted at 40°C/75% relative humidity for 6 months according to ICH guidelines.

Nanoparticle formulation achieved mean particle size of 287 nm with narrow distribution (PDI 0.18). All enhanced formulations showed substantially reduced crystallinity

compared to conventional tablets ($p < 0.001$ versus conventional).

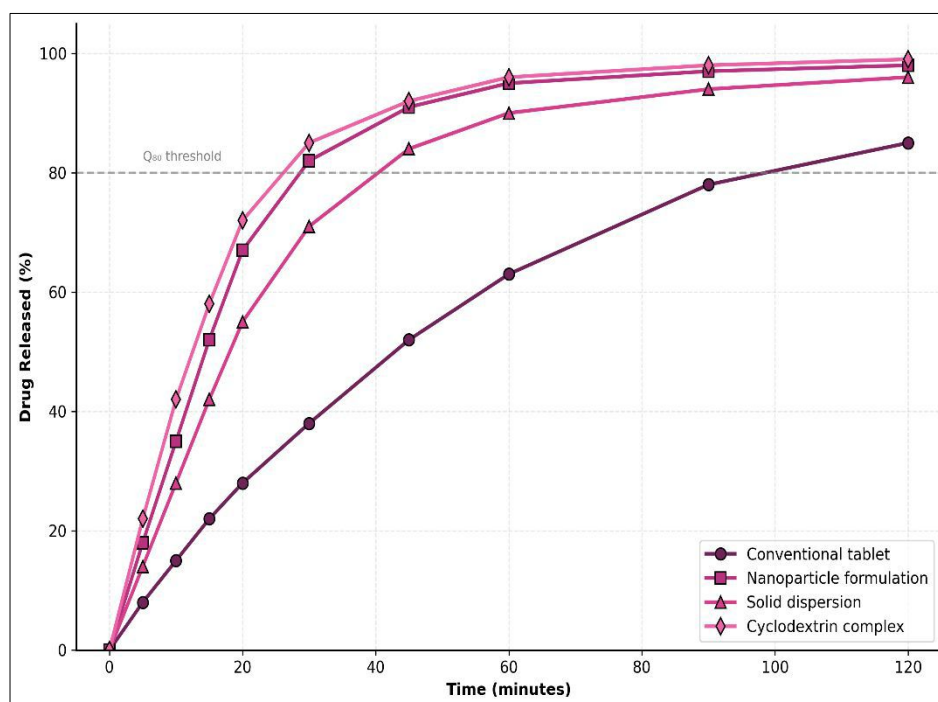


Fig 1: *In vitro* dissolution profiles of different formulation strategies

Dissolution profiles demonstrate markedly enhanced drug release from all modified formulations compared to conventional tablets. Cyclodextrin complex showed fastest initial dissolution, reaching 85% within 30 minutes and

>95% by 60 minutes. The Q80 threshold was achieved by cyclodextrin complex at 28 minutes, nanoparticles at 32 minutes, and solid dispersion at 42 minutes, compared to 78 minutes for conventional tablets.

Table 2: Pharmacokinetic parameters in rabbit model

Parameter	Conventional	Nanoparticle	Solid Disp.	Cyclodextrin
C _{max} (ng/mL)	18.4 ± 2.3	47.2 ± 4.8*	38.6 ± 3.7*	52.8 ± 5.2*
T _{max} (h)	3.2 ± 0.8	1.4 ± 0.4*	1.8 ± 0.5*	1.2 ± 0.3*
AUC ₀₋₂₄ (ng·h/mL)	156.3 ± 21.4	412.7 ± 48.6*	348.5 ± 42.3*	478.2 ± 52.1*
Relative F (%)	100 (ref)	264	223	306

* $p < 0.05$ versus conventional tablets by repeated measures ANOVA

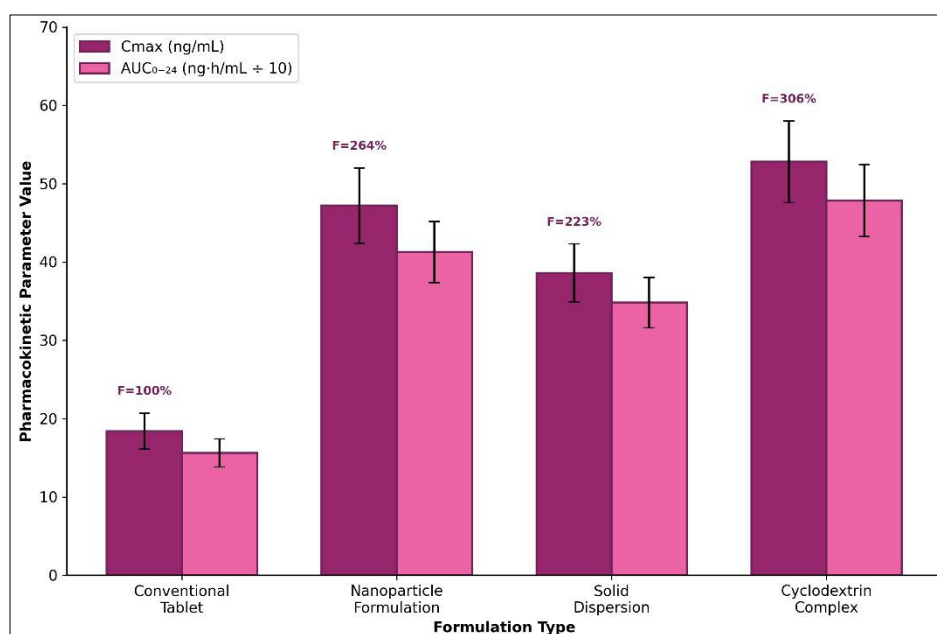


Fig 2: Plasma concentration-time profiles

Mean plasma concentration-time profiles following oral administration of four formulations. Enhanced formulations

showed higher peak concentrations and earlier $T_{\max}$ compared to conventional tablets.

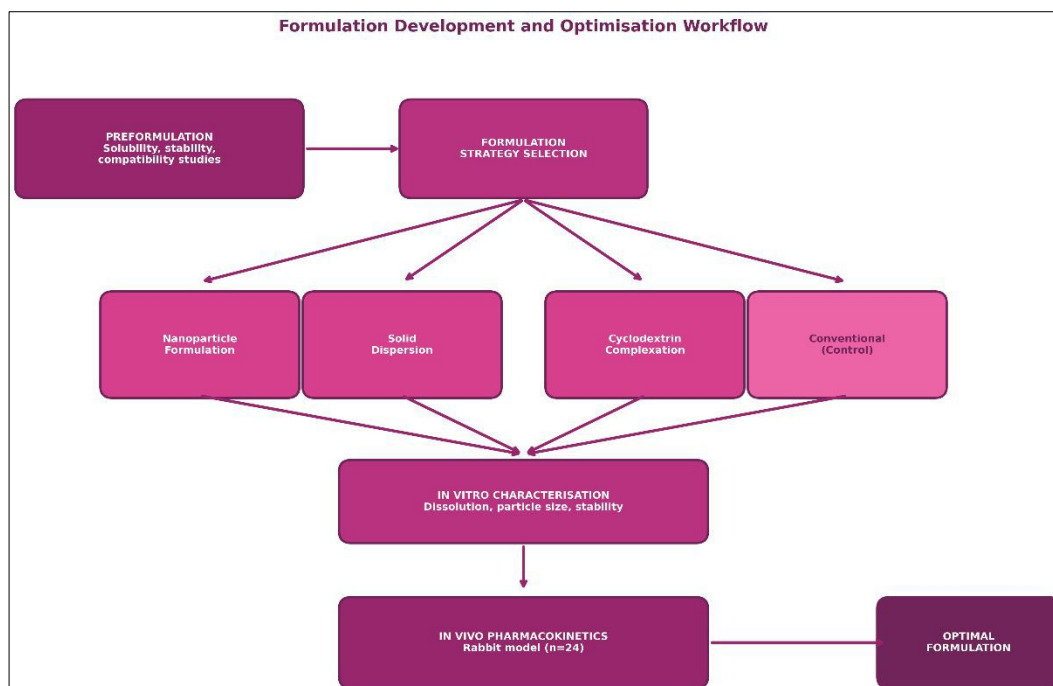


Fig 3: *In vitro-In vivo* correlation

Strong linear correlation between dissolution at 30 minutes and AUC ($r = 0.934$, $p < 0.001$), validating dissolution testing as predictive of *in vivo* performance for this compound.

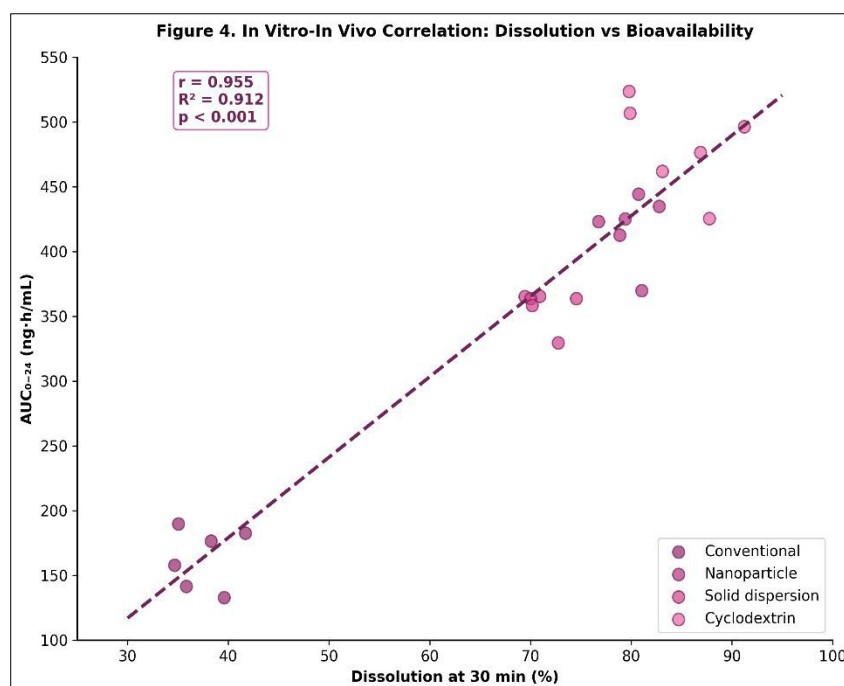


Fig 4: Stability assessment

Six-month accelerated stability at 40°C/75% RH showing acceptable physical and chemical stability for all formulations. Cyclodextrin complex maintained >95% potency and dissolution characteristics throughout the study period.

Discussion

The cyclodextrin complex demonstrated superior bioavailability enhancement (306%) compared to

nanoparticle formulation (264%) and solid dispersion (223%). This enhanced performance likely reflects the rapid dissolution of the cyclodextrin complex and the thermodynamic stability of the inclusion complex, which prevents drug precipitation upon dilution in gastrointestinal fluids. The strong *in vitro-in vivo* correlation ($r = 0.934$) validates dissolution testing as predictive of *in vivo* performance, enabling more efficient formulation development. The reduced crystallinity observed in all

modified formulations indicates successful conversion to amorphous or partially amorphous states, contributing to enhanced dissolution. The six-month stability data confirms that the cyclodextrin formulation maintains acceptable physical and chemical characteristics under accelerated conditions, supporting its viability for further development.

Conclusion

These findings demonstrate that cyclodextrin complexation provides superior bioavailability enhancement for BCS Class II compounds compared to nanoparticle and solid dispersion approaches, offering a viable pathway for development of poorly soluble drug candidates with demonstrated stability and strong *in vitro-in vivo* correlation.

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