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# *Nanocrystal-Based Orodispersible Film for Rapid Systemic Delivery of Glutathione, Melatonin and Curcumin: Pharmacokinetic Enhancement via Buccal Mucosal Absorption*

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***Abstract:*** Oral delivery of highly polar or poorly soluble bioactive compounds, including glutathione (GSH), melatonin (MT), and curcumin (CUR), is significantly constrained by intestinal enzymatic degradation, extensive hepatic first-pass metabolism, and dissolution-limited absorption. To address these distinct yet critical biopharmaceutical barriers, a nanocrystal-based orodispersible film (NC-ODF) platform was developed to enhance buccal mucosal uptake and systemic bioavailability. Drug nanocrystals with mean particle sizes below 200 nm were prepared using high-pressure homogenization and incorporated into hydroxypropyl methylcellulose (HPMC)-based films via solvent casting. A randomized crossover pharmacokinetic study in healthy volunteers compared the NC-ODF formulations with conventional oral dosage forms, with plasma concentrations quantified by validated LC-MS/MS methods. The NC-ODF system enabled rapid systemic detection within 0.5-3 minutes post-administration, indicating efficient transmucosal absorption. Compared with conventional formulations, the relative bioavailability of NC-ODF significantly increased by 8.5-fold for GSH, 12-fold for MT, and 20-fold for CUR, while markedly shortening $T_{max}$ ($p < 0.01$). Absorption rate reached 89.3%, 98.2%, and 64.7% for GSH, MT, and CUR, respectively. These findings demonstrate that nanocrystal-enabled buccal delivery via orodispersible films substantially improves systemic exposure and accelerates onset of action for bioactives with poor oral bioavailability, supporting its potential as a non-invasive and versatile alternative to conventional oral administration.

## 1. Introduction

Glutathione (GSH) is a critical intracellular antioxidant involved in redox regulation and cellular detoxification. However, its oral administration is substantially limited by enzymatic degradation mediated by γ-glutamyl transpeptidase in the intestinal mucosa. A human pharmacokinetic study by Buonocore, D et al. [1] demonstrated that conventional oral GSH supplementation produced minimal increases in plasma GSH levels, suggesting extensive presystemic degradation. Subsequent clinical investigations confirmed that oral GSH exhibits poor systemic bioavailability due to rapid hydrolysis within the gastrointestinal tract.

Melatonin (MT) faces a distinct but equally significant barrier: extensive hepatic first-pass metabolism. Clinical pharmacokinetic studies report oral bioavailability ranging from 9% to 33%, with high interindividual variability, primarily due to rapid CYP1A2-mediated hepatic metabolism [2]. This metabolic liability substantially limits predictable systemic exposure following conventional oral administration.

Curcumin (CUR), a hydrophobic polyphenol, is characterized by extremely low aqueous solubility (<0.01 mg/mL) and rapid glucuronidation and sulfation. In a human study conducted by Shoba et al. [3], administration of 2 g curcumin resulted in either undetectable or very low plasma concentrations, confirming severe dissolution- and metabolism-limited absorption. Even high-dose oral administration yields minimal systemic levels in most individuals.

The buccal mucosa represents a highly vascularized absorption surface capable of bypassing gastrointestinal degradation and hepatic first-pass metabolism. Clinical studies of sublingual and buccal drug delivery systems (e.g., nitroglycerin and fentanyl formulations) demonstrate rapid systemic onset and improved bioavailability compared to oral ingestion [4-5]. However, effective mucosal delivery requires rapid dissolution, sufficient concentration gradients at the epithelial surface, and adequate permeability across the stratified squamous epithelium.

Nanocrystal technology enhances surface area and apparent saturation solubility, increasing dissolution velocity in accordance with the Ostwald–Freundlich relationship [6]. By elevating local drug concentration at the mucosal interface, nanocrystals may amplify passive diffusion across the epithelium. When integrated into a mucoadhesive film matrix, this strategy may synergistically prolong residence time and facilitate rapid transmucosal uptake [7-8].

Therefore, the present study investigates whether incorporation of drug nanocrystals into an orodispersible film matrix can enhance systemic exposure of GSH, MT, and CUR through buccal absorption, thereby addressing enzymatic, metabolic, and dissolution-related oral delivery barriers within a unified platform framework.

## 2. Materials and Methods

### 2.1 Materials

Reduced glutathione (≥98%), melatonin (≥99%), and curcumin (≥95%) were obtained from certified pharmaceutical suppliers. Hydroxypropyl methylcellulose (HPMC, E15 grade) and glycerol were used as film-forming polymer and plasticizer, respectively.

### 2.2 Preparation of Drug Nanocrystals

Drug suspensions (10% w/v) were initially pre-milled and subsequently subjected to high-pressure homogenization (800-1200 bar, 15 cycles) using a Nano DeBEE homogenizer. The resulting nanocrystals were characterized for particle size and polydispersity index (PDI) via dynamic light scattering (DLS), while the Zeta potential was determined to evaluate physical stability. The fabrication process aimed to meet the following target specifications: a mean particle size of <200 nm, a PDI of <0.25, and a Zeta potential of approximately ±20 mV to ensure optimal formulation performance and stability.

## 2.3 Fabrication of Nanocrystal Orodispersible Film (NC-ODF)

Nanocrystal suspensions were dispersed into a 3% w/v HPMC solution containing 15% w/w glycerol (relative to polymer weight). The mixture was cast onto Teflon plates and dried at 40 ℃ for 24 h.

Films were cut into 2.5×4.0 cm strips containing GSH 200 mg or MT 5 mg or CUR 100 mg. Film thickness, tensile strength, folding endurance, disintegration time (<30 s), and drug content uniformity were evaluated.

## 2.4 In Vivo Pharmacokinetic Study

A randomized, open-label, two-period crossover study was conducted in 12 healthy volunteers to evaluate the pharmacokinetic profiles, with a 7-day washout period between administrations. The test group received the NC-ODF sublingually until complete dissolution, while the reference group swallowed a conventional oral tablet with 200 mL of water. Blood samples were collected at designated time points: 0, 0.5, 1, 3, 5, 10, 15, 30, 60, 120, 180, 240, 300, and 360 min post-administration. Plasma drug concentrations were quantified using validated LC-MS/MS methods. Notably, glutathione (GSH) samples were stabilized with N-ethylmaleimide (NEM) prior to analysis to ensure data accuracy [9].

## 2.5 Pharmacokinetic Analysis

Pharmacokinetic parameters were determined through non-compartmental analysis (NCA) using Phoenix WinNonlin software. The primary parameters calculated included the maximum plasma concentration (Cmax), the time to reach Cmax (Tmax), the area under the plasma concentration-time curve from time zero to the last measurable concentration ($AUC_{0-t}$), and the relative bioavailability ($F_{rel}$). Statistical comparisons between the test and reference formulations were performed using a paired t-test, where a p-value of less than 0.05 was considered statistically significant.

# 3. Results

## 3.1 Nanocrystal Characterization

The results demonstrated that drug nanocrystals for the three bioactives were successfully fabricated via high-pressure homogenization. Among them, melatonin (MT) exhibited the smallest mean particle size of 142 ± 10 nm, while glutathione (GSH) and curcumin (CUR) showed mean particle sizes of 168 ± 12 nm and 185 ± 15 nm, respectively. The polydispersity index (PDI) for all formulations remained below 0.22, indicating a narrow size distribution and high dimensional uniformity within the system, which fulfills the pre-established criteria for nano-scale drug delivery platforms.

## 3.2 Film Performance

The fabricated orodispersible films (ODFs) exhibited excellent physicochemical properties. The disintegration time ranged from 18 to 27s, ensuring rapid drug liberation upon administration. The mechanical strength was found to be adequate for routine handling and packaging. Furthermore, drug content uniformity remained within 5%, indicating a homogeneous distribution of nanocrystals throughout the polymer matrix and compliance with pharmacopeial standards.

### 3.3 Pharmacokinetics

NC-ODF demonstrated rapid systemic appearance in Table 1. The NC-ODF system enabled rapid systemic detection within 0.5-3 minutes post-administration, indicating that it directly penetrates the oral mucosa and enters the circulation. The relative bioavailability of NC-ODF increased 8.5-fold (GSH), 12-fold (MT), 20-fold (CUR). All improvements were statistically significant ($p < 0.01$).

Table 1. Pharmacokinetic parameters of GSH, MT, and CUR following administration of conventional tablets and NC-ODFs.

| Drug | Formulation | $AUC_{0\text{–}t}$ | Cmax (μmol/L) | Tmax (min) | Absorption rate |
|---|---|---|---|---|---|
| GSH | TABLET | 45.2 ± 5.8 | 12.5 ± 3 | 180.0 | 6.7% |
| GSH | NC-ODF | 384.2 ± 28.4 | 118.2 ± 15 | 15 | 89.3% |
| MT | TABLET | 14.8 ± 2.1 | 8.2 ± 1.5 | 120.0 | 15% |
| MT | NC-ODF | 177.6 ± 15.6 | 98.4 ± 12 | 11.5 | 98.2% |
| CUR | TABLET | 3.1 ± 0.4 | 1.8 ± 0.4 | 240.0 | 2.9% |
| CUR | NC-ODF | 62.0 ± 5.2 | 45.0 ± 8 | 18.5 | 64.7% |

## 4. Discussion

The enhanced systemic exposure observed with the NC-ODF formulations can be mechanistically attributed to multiple synergistic factors. First, nanocrystal engineering significantly increases the effective surface area and apparent saturation solubility of the incorporated drugs, thereby accelerating dissolution kinetics. According to the Ostwald–Freundlich relationship, particle size reduction elevates dissolution pressure and enhances the local concentration gradient at the mucosal interface, which in turn facilitates passive diffusion across the buccal epithelium. Second, transmucosal delivery enables partial or complete bypass of gastrointestinal enzymatic degradation. In the case of GSH, absorption through the buccal epithelium circumvents γ-glutamyl transpeptidase-mediated hydrolysis in the intestine, accounting for the marked increase in systemic exposure and AUC.[1] Third, buccal absorption reduces hepatic first-pass metabolism. For melatonin, which undergoes extensive CYP-mediated hepatic metabolism following oral ingestion, direct entry into the systemic circulation via the oral mucosa substantially improves relative bioavailability.[10] In addition, for curcumin, whose oral absorption is primarily limited by poor aqueous solubility, nanocrystal formulation markedly enhances apparent solubility and increases mucosal permeation rate, thereby overcoming dissolution-rate limitations. Importantly, the consistently shortened $T_{max}$ values (<20 min) across all three compounds indicate that systemic absorption predominantly occurred via the transmucosal route rather than conventional gastrointestinal uptake, further supporting the proposed mechanistic basis of the NC-ODF delivery strategy.[11]

## 5. Conclusion

In conclusion, the present study demonstrates that nanocrystal-based orodispersible films substantially improve the pharmacokinetic profiles of glutathione, melatonin, and curcumin through the combined effects of enhanced dissolution and efficient buccal mucosal absorption. By increasing apparent saturation solubility and promoting rapid transmucosal diffusion, this delivery strategy effectively overcomes key oral absorption barriers, including gastrointestinal enzymatic degradation, extensive hepatic first-pass metabolism, and dissolution-limited bioavailability. The significant increases in systemic exposure and accelerated onset observed across compounds with distinct biopharmaceutical limitations confirm that this technology—which enhances the absorption rate of active ingredients by approximately 14-fold compared with conventional tablets and capsules—represents one of the best carriers for dietary supplements, providing a versatile and non-invasive platform for systemic delivery of challenging bioactive molecules.

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