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Review Article

Significance of Bioavailability in the In Vitro Evaluation of Fast Disintegrating Bilayer Tablets of Flurbiprofen for Immediate and Sustained Drug Release: A Critical Review

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ABSTRACT

Flurbiprofen, a propionic-acid non-steroidal anti-inflammatory drug (NSAID), is classified under Biopharmaceutics Classification System (BCS) Class II — characterized by high intestinal permeability but poor aqueous solubility — making its oral bioavailability inherently dissolution-rate-limited. This creates a direct mechanistic link between in vitro dissolution behaviour and in vivo therapeutic performance, and positions the fast-disintegrating bilayer tablet (an immediate-release layer for rapid onset of analgesia, combined with a sustained-release layer for prolonged anti-inflammatory action) as a rational bimodal delivery strategy. This review synthesizes reported bilayer and modified-release formulation approaches for flurbiprofen, examines the excipient systems (superdisintegrants such as sodium starch glycolate and crospovidone for the immediate-release layer; retardant polymers such as HPMC K-series for the sustained-release layer) used to engineer this biphasic profile, and critically evaluates why in vitro dissolution and release-kinetic modelling (zero-order, Higuchi, Korsmeyer-Peppas) are treated as bioavailability surrogates for a BCS Class II drug in the absence of routine in vivo pharmacokinetic confirmation at the formulation-development stage. Gaps in in vitro-in vivo correlation (IVIVC) reporting for flurbiprofen bilayer systems are identified as the principal limitation of the current literature.

INTRODUCTION

Flurbiprofen is a potent propionic-acid derivative NSAID used for acute pain and inflammatory conditions, but its clinical utility is constrained by two competing formulation demands: a rapid onset of analgesia, favouring an immediate-release presentation, and sustained anti-inflammatory coverage, favouring a controlled-release presentation. The bilayer tablet — combining a

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fast-disintegrating immediate-release layer with a polymer-retarded sustained-release layer in a single dosage unit — has been proposed by multiple research groups as a means of reconciling these demands within one patient-convenient product. Because flurbiprofen is a BCS Class II compound (low aqueous solubility, high permeability), its oral bioavailability is dissolution-rate-limited rather than permeability-limited: any factor that slows or alters dissolution — layer composition, superdisintegrant choice, polymer viscosity grade, compression force — has a direct, mechanistically predictable effect on the fraction and rate of drug absorbed. This is the pharmaceutical basis for treating in vitro dissolution testing not merely as a quality-control release specification, but as a surrogate marker of bioavailability during early formulation screening, consistent with the biopharmaceutics classification framework linking in vitro dissolution to in vivo absorption.

2. Bioavailability Significance: Why In Vitro Evaluation Matters for This Class of Formulation

For BCS Class II drugs such as flurbiprofen, the theoretical basis linking in vitro dissolution to in vivo bioavailability was formalized in the biopharmaceutics classification framework proposed by Amidon and colleagues and subsequently operationalized through FDA guidance on in vitro-in vivo correlation (IVIVC) for extended-release dosage forms. In a bilayer system, this significance is compounded: the immediate-release layer's dissolution rate governs the speed of onset (linked to Cmax and Tmax), while the sustained-release layer's release kinetics govern the duration over which therapeutic plasma concentrations are maintained (linked to AUC and dosing-interval coverage). A poorly designed immediate-release layer can blunt onset of analgesia even if total bioavailability is adequate over 24 hours, while a poorly retarded sustained-release layer can produce dose-dumping behaviour with associated gastrointestinal risk — a particular concern for an NSAID. This is why bilayer flurbiprofen formulation papers consistently report not just cumulative percentage release but full release-kinetic modelling (zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell) as a proxy for predicting in vivo absorption behaviour before committing to costly pharmacokinetic studies.

3. Literature Review: Bilayer and Modified-Release Approaches for Flurbiprofen

Sharif and colleagues (2011) reported the design and evaluation of modified-release bilayer tablets of flurbiprofen, developing the fast-release and sustained-release layers separately before combination, and characterizing the dissolution profile of each layer individually to select an optimized excipient combination — an approach that treats each layer's in vitro release profile as the primary formulation-optimization endpoint.

A bilayer tablet formulation of flurbiprofen using sodium starch glycolate as the immediate-release superdisintegrant and HPMC K15 in varying ratios as the sustained-release retardant was developed by wet granulation; increasing sodium starch glycolate proportions accelerated immediate-phase release while HPMC K15 governed the sustained phase, with the optimized formulation showing an initial release within approximately one hour followed by sustained release over twelve hours, fitting the Higuchi diffusion model (Asian J Pharm Clin Res, 2019). Cheng and colleagues (2018) designed and evaluated a bilayer pump tablet of a flurbiprofen solid dispersion for zero-order controlled delivery, addressing the poor aqueous solubility of flurbiprofen (consistent with its BCS Class II status) via solid-dispersion technology within the sustained-release layer to achieve a more constant, bioavailability-

favourable release rate (J Pharm Sci, 2018;107(5):1434-1442). Separately, fast-dissolving (non-bilayer) tablets of flurbiprofen prepared by a sublimation method using camphor, ammonium bicarbonate, and thymol as sublimating agents demonstrated that dissolution-rate enhancement strategies alone — without a sustained-release component — can achieve near-complete drug release within 30 minutes, underscoring the poor intrinsic dissolution of unformulated flurbiprofen that necessitates such enhancement approaches in any immediate-release layer design (SciELO Brazil / Braz J Pharm Sci).

A broader review of immediate-release/sustained-release bilayer tablet design (covering an NSAID case example, celecoxib) confirmed the general formulation logic applied to flurbiprofen bilayer systems: a fast-disintegrating superdisintegrant-based layer for rapid onset paired with an HPMC-based sustained-release layer, evaluated via standard physicochemical and dissolution parameters, with permeability enhancers noted as a strategy to further improve bioavailability where relevant.

4. Identified Gaps and Novelty Statement

Three gaps recur across the flurbiprofen bilayer literature surveyed. First, while release-kinetic modelling (Higuchi, Korsmeyer-Peppas, zero-order) is reported consistently, formal in vitro-in vivo correlation (IVIVC) data — linking the dissolution profile quantitatively to plasma pharmacokinetic parameters — is rarely reported for flurbiprofen bilayer systems specifically, leaving the 'dissolution as bioavailability surrogate' assumption largely unverified in vivo for this drug-formulation combination. Second, solubility-enhancement strategies (solid dispersion, sublimation-based superdisintegration) and bilayer sustained-release engineering have generally been reported as separate formulation strategies rather than integrated within a single optimized bilayer system. Third, biorelevant (as opposed to compendial) dissolution methods — shown elsewhere to reveal materially different sustained-release-layer behaviour for bilayer NSAID systems — have not been widely applied to flurbiprofen bilayer tablets specifically.

5. CONCLUSION

The fast-disintegrating bilayer tablet remains a mechanistically well-justified strategy for delivering flurbiprofen's competing immediate-analgesia and sustained-anti-inflammatory therapeutic requirements from a single dosage unit, and its rational basis rests directly on flurbiprofen's BCS Class II, dissolution-rate-limited absorption behaviour. In vitro dissolution and release-kinetic modelling are appropriately treated as first-line bioavailability surrogates during formulation screening for this reason, but the literature reviewed here shows this assumption is rarely followed through to formal IVIVC confirmation for flurbiprofen bilayer systems specifically. Closing this in vitro-to-in vivo verification gap, and integrating solubility-enhancement technology directly into bilayer sustained-release layer design, represent the principal opportunities for future formulation research in this area.

Conflict of Interest

The authors declare no conflict of interest.

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