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AMORPHOUS SOLID DISPERSIONS: POLYMER SELECTION AND PHYSICAL STABILITY CONSIDERATIONS

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Abstract

Amorphous solid dispersions (ASDs) remain one of the most widely used routes to improve the oral exposure of poorly soluble drugs, yet their commercial success depends on choosing the right polymer and keeping the amorphous state intact through shelf life. This narrative review draws on published reviews and experimental papers to describe how polymers are selected, how drug-polymer miscibility and specific interactions influence stability, and how moisture, temperature and manufacturing route modify risk. It also considers the dissolution and precipitation behaviour that decides in vivo benefit, and the analytical tools used to follow phase change. No new data are reported. Predictive tools remain imperfect, and long-term stability is still established largely by empirical studies.

1. INTRODUCTION

A large share of compounds emerging from modern discovery programmes dissolve poorly in water. Analyses of medicinal chemistry practice described this drift towards higher molecular weight and lipophilicity nearly two decades ago, and the pattern has not reversed [1]. Under the biopharmaceutics classification system, such molecules fall into class II or IV, where dissolution rather than permeability limits absorption [2]. Reducing particle size, forming salts or using lipid vehicles will help some candidates, but a good many remain stubbornly under-exposed. Formulators therefore keep returning to a strategy that

sacrifices the crystal lattice itself. If the drug is held in a disordered state, the energy needed to break the lattice is already paid and the apparent solubility rises [3, 4].

The idea is old. Sekiguchi and Obi proposed in 1961 that a poorly soluble drug could be dispersed in a water-soluble carrier as a eutectic mixture to speed absorption [5]. Early products relied on low-melting, water-soluble carriers such as polyethylene glycol and tended to recrystallise on storage, a problem that Serajuddin traced through the 1980s and 1990s before newer polymer carriers rescued the approach [6]. Mechanistic accounts of release from dispersions in water-soluble polymers have helped the field move decisively towards amorphous drug molecularly dispersed in a glassy polymer [7]. Dedicated textbooks now treat the subject as a discipline in its own right [8], and several marketed products rely on it [8, 9].

Two questions dominate practical development. The first is which polymer, and at what drug loading, will hold the drug in a single amorphous phase long enough to support a commercial shelf life. The second is whether that same polymer will release the drug in a form that can be absorbed, instead of letting it crash out as crystals or colloidal droplets in the gut [10, 11]. The answers are linked but not identical, and a polymer that excels at one task can be mediocre at the other. This review follows the logic a development team would use, starting with the thermodynamic and kinetic basis of stability, then polymer properties, then manufacturing, performance and characterisation.

The review is a narrative synthesis of published literature, including pharmaceutical science reviews, mechanistic studies on model compounds such as indomethacin, felodipine and celecoxib, and manufacturing papers on spray drying and hot-melt extrusion. It reports no new experimental data. Where numerical statements are made they are restricted to well-established concepts rather than to the outcome of any single study. A synthesis of reported findings across polymers is given in table 1, and the distribution of those entries by theme is shown in fig. 1. The aim is practical, namely to help formulators frame the early decisions on polymer class, drug loading and storage conditions with the evidence in view [12, 13].

Table 1: Representative published findings on polymer selection and stability of amorphous solid dispersions

Polymer or system	Reported finding	Ref.
PVP with indomethacin infrared study	Hydrogen bonding between drug and polymer suppressed crystallisation in the amorphous dispersion	[14]
PVP with celecoxib	Stability followed the strength of the drug-polymer interaction	[15]
Several polymers with felodipine	Polymer type changed crystallisation tendency; stronger interactions inhibited it more	[16]
Flory-Huggins analysis melting point depression	Drug-polymer solubility can be estimated, giving a guide to safe drug loading	[17, 18]
Gordon-Taylor equation	Departures from predicted Tg indicate non-ideal mixing or phase separation	[15, 19]
PVP dispersions under humidity	Absorbed water induced amorphous phase separation before crystals appeared	[20, 21]
Pharmaceutical glasses	Molecular mobility persists below Tg and governs crystallisation time scales	[22, 23]
HPMCAS spray-dried dispersions	Stabilised the solid and maintained supersaturation after dissolution	[24, 25]
Dissolution of ASDs loading effects	Release pathway changed with drug loading; high loading limited release	[10, 26]
Phase separation in solution	Drug-rich droplets formed in supersaturated solutions before crystallisation	[27]
Spray drying and extrusion	Both routes gave stable products if composition was miscible and moisture controlled	[28, 29]

2. THERMODYNAMICS AND KINETICS OF THE AMORPHOUS STATE

An amorphous solid is a kinetically trapped, higher-energy state. Reviews of amorphous pharmaceutical solids set out its characteristic

features: no long-range order, a glass transition, greater molecular mobility, and higher enthalpy, entropy and free energy than the crystal [3]. The solubility advantage follows directly from that excess free energy. Hancock and Parks estimated that the advantage could, in principle, be of the order of tens to thousands of times, though they cautioned that the practical benefit is usually much smaller because the amorphous form converts to a less soluble phase during dissolution [4]. Pudipeddi and Serajuddin made a related point for polymorphs, where solubility ratios between forms are usually modest [30]. The amorphous form is the extreme case of the same principle.

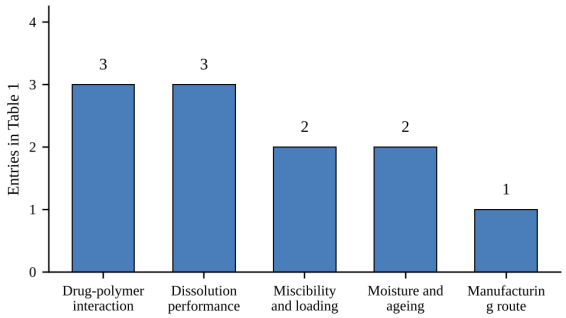


Fig. 1: Number of entries in table 1 by principal theme

Thermodynamics tells whether a system will eventually crystallise, but kinetics decides whether it does so within the product lifetime. Molecular mobility is the central quantity. Shamblin and colleagues measured relaxation times in pharmaceutical glasses and showed that mobility does not vanish at the glass transition temperature (Tg), it merely slows [23]. Kawakami and Pikal later examined how calorimetric measurements of structural relaxation can be used to estimate it, and warned about the assumptions hidden in each method [31]. Bhugra and Pikal brought these threads together, arguing that crystallisation from the amorphous state depends jointly on thermodynamic driving force, molecular mobility and the intrinsic ability of the molecule to nucleate [22].

A practical rule of thumb says that storage at least 50 °C below Tg offers a reasonable margin for stability, although the figure is a convention and not a law. Several authors have shown that crystallisation can occur well below Tg in systems where local mobility, often called beta relaxation, remains active [22, 23]. For polymer dispersions the Tg of the mixture is often estimated by the Gordon-Taylor equation or the related Couchman-Karasz treatment, which treats the blend as an ideal mixture of two components [19]. Departures from the predicted line signal non-ideal mixing, either through specific interactions that raise Tg or through phase separation that produces two glass transitions [15, 17].

Crystallisation tendency also varies enormously between molecules. Baird and colleagues classified a large group of organic compounds according to how easily they crystallised from an undercooled melt, creating three groups that range from compounds that crystallise on cooling to those that stay amorphous indefinitely [32]. This classification has since been used as an early triage tool, because a class III compound can often be stabilised by a modest amount of polymer whereas a class I compound may be difficult to stabilise at any useful drug loading. Molecular flexibility, hydrogen bonding capacity and molecular weight all feature in the explanation, but no single descriptor reliably predicts the outcome [32, 33].

Water complicates all of this. Because most pharmaceutical polymers are hygroscopic, absorbed moisture acts as a plasticiser, lowering Tg and raising mobility. Rumondor and colleagues followed phase behaviour of povidone-containing dispersions at different relative humidities and found that moisture can induce amorphous phase separation well before crystallisation becomes detectable [20]. Purohit and Taylor later showed by kinetic studies that the rate of phase separation on exposure to water depends on composition, and that such separation can precede crystal growth [21]. The practical implication is straightforward: humidity control during storage and packaging is part of the stabilisation strategy, not an afterthought [20, 21].

The formation of crystal nuclei in a dispersion is not a single event but a competition between several processes. Nucleation requires a cluster of drug molecules to reach a critical size, and the polymer hinders this by diluting the drug, by raising viscosity and by

binding to drug surfaces. Growth, on the other hand, needs molecules to diffuse to an existing crystal face and to orient correctly. The two stages respond differently to polymer: Konno and Taylor, for example, observed that some polymers were better at inhibiting growth than nucleation [16]. Appreciating the distinction helps to interpret stability results, since a sample that shows no crystals after months may simply be one in which nuclei exist but growth is too slow to detect [16, 22].

Surface effects deserve a short mention. Crystallisation in amorphous powders often starts at the surface, where mobility is higher and where contact with moisture occurs first. Reports on drug-rich domains at particle surfaces suggest that the average composition of a dispersion may not describe the region that matters most. For this reason, bulk techniques alone may miss the earliest signs of failure, and some groups complement them with surface-sensitive methods or with microscopy of stored samples [20, 33]. Whether such surface events are representative of the whole batch is rarely examined, and the question is often left open in published stability reports.

3. POLYMER SELECTION AND DRUG-POLYMER INTERACTIONS

Polymer choice begins with a small set of familiar candidates: povidone (PVP), copovidone (PVP-VA), hydroxypropyl methylcellulose (HPMC), its acetate succinate derivative (HPMCAS), and various methacrylate copolymers. Each combines a glass transition high enough to restrict mobility with functional groups able to interact with drug molecules. Reviews of polymeric dispersions emphasise that no polymer works universally, and that the best choice emerges from matching polymer chemistry to the drug's lipophilicity, hydrogen bonding groups and ionisation behaviour [9, 34]. Practical screening typically starts with solvent casting or film evaporation, which uses little drug and allows dozens of drug-polymer pairs to be compared in a short time.

Specific interactions are the most reliable stabilising force. Taylor and Zografi used infrared spectroscopy to show hydrogen bonding between indomethacin and PVP, and demonstrated that the interaction suppressed crystallisation in the dispersion [14]. Gupta and colleagues reached a similar conclusion for celecoxib and PVP, with the stability of the system following the strength of the interaction [15]. Konno and Taylor compared several polymers with felodipine and found that polymer type affected crystallisation tendency differently, with the more strongly interacting polymers giving the better inhibition [16]. These studies are small in scope, yet the same message recurs: a drug-polymer hydrogen bond or ionic pairing lowers mobility and raises the barrier to nucleation [12, 16].

Miscibility and solubility of the drug in the polymer set the upper limit on safe drug loading. The Flory-Huggins model can be used to estimate an interaction parameter from the melting point depression of the crystalline drug, and from it the equilibrium solubility in the polymer and a drug-polymer phase diagram [17]. Qian and colleagues discussed the practical meaning of such calculations, noting that a drug loaded above its equilibrium solubility is supersaturated in the polymer and therefore only kinetically stable [18]. Many commercial dispersions are in fact kinetically stabilised, so the estimated solubility is best read as a guide to risk rather than a pass-fail threshold, particularly at the elevated temperatures used in accelerated studies [17, 18].

Cellulosic polymers bring a different set of benefits. HPMCAS in particular has been developed as a spray-dried dispersion polymer with amphiphilic character, a relatively high Tg and pH-dependent ionisation. Friesen and colleagues reviewed its use and described how it can stabilise the amorphous drug in the solid state while also maintaining supersaturation after dissolution [24]. Curatolo and colleagues made a similar case, arguing that HPMCAS inhibits crystal growth from supersaturated solutions in gastrointestinal media [25]. Grades differ in acetyl and succinoyl content, which alters pH threshold for dissolution and the polymer's affinity for lipophilic drugs, so grade selection becomes a second optimisation step

within the polymer class [24, 25].

The trade-offs can be summarised in terms of hygroscopicity, solubilising capacity and processability. PVP-type polymers interact strongly with many drugs but take up considerable water, whereas HPMCAS takes up less and remains glassy longer at high humidity [20, 24]. Methacrylate copolymers can be melt-extruded at moderate temperatures and offer pH-triggered release, which is useful for enteric targeting [35]. Several syntheses of marketed products show that the polymer class is frequently dictated by the manufacturing route as much as by performance [8, 9]. Table 1 collects representative findings from the literature on these points, with the group tag indicating the principal theme of each entry.

Ionisable polymers add another dimension. An acidic polymer such as HPMCAS can form ionic or hydrogen bonds with basic drugs, and the strength of that interaction varies with microenvironmental pH. Where drug and polymer carry opposite charges, salt-like pairing may stabilise the amorphous state to a degree that neutral polymers cannot match, though too strong an interaction can slow release. Friesen and colleagues noted the value of matching the polymer's dissolution pH to the site of absorption, so that the polymer and drug are released together and do not separate in the stomach [24]. The principle is easy to state and harder to apply when the drug's own solubility is steeply pH dependent [9, 25].

4. MANUFACTURING ROUTES AND THEIR INFLUENCE ON STABILITY

Two industrial processes dominate: spray drying and hot-melt extrusion. Spray drying dissolves drug and polymer in a volatile solvent, atomises the solution and removes the solvent rapidly, which freezes the components in a mixed state. Davis and Walker reviewed recent strategies for improving bioavailability by spray drying and highlighted the importance of solvent choice, feed concentration and drying kinetics [28]. A common finding is that very rapid drying favours a homogeneous glass, but residual solvent can act as a plasticiser and cause trouble later, so secondary drying is nearly always required [24, 28]. The technique suits thermolabile compounds and poorly meltable polymers, which is why it is so widely used for cellulosic systems.

Hot-melt extrusion avoids organic solvents by mixing drug and polymer at elevated temperature under shear. Early pharmaceutical studies moved extrusion from plastics processing into drug products, and later reviews covered critical process parameters and scale-up [29, 35]. The process is continuous, scalable and attractive on environmental grounds. Its limitation is thermal: the drug and polymer must withstand the processing temperature, which is sometimes above the drug's melting point, and the drug may degrade. Plasticisers can lower the required temperature but also depress the final Tg, so a balance has to be found between processability and storage stability [19, 29].

The two routes can produce dispersions of the same nominal composition with different physical properties. Spray-dried particles are small, porous and of low density, whereas extrudates are dense and need milling. Differences in specific surface area, residual solvent, thermal history and degree of mixing can all affect both stability and dissolution. Comparative work on model compounds generally shows that each route can give a stable product, provided that the composition lies within the miscible region and that moisture is controlled [28, 29]. Process choice is therefore usually driven by drug properties such as melting point, thermal stability and solubility in organic solvents rather than by an inherent superiority of one technique [13, 36].

Scale-up introduces its own risks. Laboratory spray dryers operate at throughputs that differ by orders of magnitude from commercial units, and droplet drying conditions are not easily transferable. Similarly, the residence time and shear profile of a small twin-screw extruder do not match those of a production machine. Reviews of insoluble drug delivery strategies point out that many failures at scale are traced to inadequate understanding of process parameters, with unexpected crystallinity or poor content uniformity as the usual symptoms [8, 36]. Quality-by-design

approaches, in which critical process parameters are linked to measured product attributes, are the accepted response, although they require substantial early investment in characterisation [36].

Downstream processing also matters. A dispersion must be milled, blended, compressed or filled, and each step can introduce mechanical stress, local heating and exposure to humidity. Compaction can induce crystallisation in some amorphous systems, and the choice of tablet excipients may change moisture partitioning within the dosage form. Stability data on the isolated dispersion powder are therefore not a substitute for data on the final packaged product, a point that reviews of formulation design for poorly soluble drugs make repeatedly [8, 37]. Final-blend and tablet stability studies are consequently run in the intended primary pack, not in open dishes.

5. DISSOLUTION, SUPERSATURATION AND PRECIPITATION

A stable solid is only half the story. The purpose of an ASD is to deliver a supersaturated solution, and the polymer controls how long that state survives. Brouwers and colleagues defined supersaturating drug delivery systems and discussed the role of precipitation inhibitors, noting that the extent and duration of supersaturation, not just its peak, determine absorption [11]. Newman and colleagues reviewed performance assessment of ASDs and urged that dissolution tests be designed to reveal both release rate and the fate of the supersaturated solution [26]. Compendial tests that use sink conditions can overestimate performance, because they never allow the precipitation that would occur in vivo [11, 26].

Alonzo and colleagues studied dissolution of dispersions in detail and showed that the process can follow different pathways depending on drug loading [10]. At low loading, release is often controlled by the polymer dissolving and carrying drug with it. At high loading, drug-rich phases may form at the interface and release becomes limited by the drug itself. This distinction explains why increasing loading does not produce a proportional increase in dissolved drug, and why the highest loading that is physically stable is not always the best one biopharmaceutically [10, 26]. The concept of a loading limit for dissolution, separate from the stability limit, has become a standard point in formulation discussions [10].

Liquid-liquid phase separation is a further complication. When a highly supersaturated solution of a lipophilic drug is generated, the drug may separate into drug-rich colloidal droplets before crystallising. Ilevbare and Taylor described this behaviour for a range of poorly soluble compounds and discussed its implications for solubility-enhancing formulations [27]. The droplets are not necessarily harmful, since they can act as a reservoir that replenishes dissolved drug as absorption proceeds, but they may also coalesce and crystallise. Polymers influence these events by adsorbing to interfaces, increasing viscosity and, in some cases, interacting with the drug in solution, which is the same property that stabilises the solid [25, 27].

The link between in vitro supersaturation and in vivo exposure is encouraging but incomplete. Reviews of supersaturating systems describe animal and human studies in which dispersions with longer-lasting supersaturation produced higher exposure than those with rapid precipitation [11, 38]. Equally, there are examples where the in vitro ranking did not predict the outcome, largely because intestinal fluid components, bile salts and absorption rate all interact with the system. A review of formulation strategies for poorly soluble compounds, from early development to proof of concept, recommended matching the formulation approach to the dominant barrier for each compound, and treated ASDs as one option among several [37].

Choice of dissolution medium deserves care. Simple buffers may suit quality control, but biorelevant media containing bile salts and phospholipids often alter the extent and duration of supersaturation, sometimes dramatically. Alonzo and colleagues and Newman and colleagues both argued for non-sink or transfer-type experiments, in which the dispersion is first exposed to an

acidic stage and then moved to an intestinal medium, as these better reflect the real sequence of events [10, 26]. Such tests are still more laborious than a paddle apparatus run, and their predictive power has been tested for only a modest number of compounds, which limits how firmly the rankings they give can be interpreted [11, 38].

6. CHARACTERISATION AND STABILITY ASSESSMENT

Powder X-ray diffraction remains the first-line test for crystallinity, but its sensitivity is limited. A low level of crystalline drug, often a few per cent, can be missed, especially in a polymer matrix with a broad halo. Differential scanning calorimetry adds information on Tg, melting and recrystallisation events, and modulated methods help to separate overlapping signals [8, 31]. Because a single Tg is taken as evidence of miscibility, detection of two Tg values or a broadened transition is a warning of phase separation [17, 21]. Neither technique, however, shows how the drug and polymer are arranged at the nanometre scale, which is where early instability begins.

Spectroscopic methods fill part of that gap. Infrared and Raman spectroscopy reveal hydrogen bonding and, with mapping, show the spatial distribution of components. Solid-state nuclear magnetic resonance can probe domain sizes through relaxation measurements, and it is often regarded as the most informative way of detecting nanoscale heterogeneity [9, 14]. Thermogravimetric and dynamic vapour sorption measurements quantify water uptake and show how sorption relates to the humidity at which a given dispersion starts to plasticise [20]. Together these methods allow a development team to define a humidity limit for storage and to design suitable packaging with desiccant, rather than relying only on long-term real-time data.

Accelerated stability testing for ASDs needs care. The accelerated conditions of 40 °C and 75% relative humidity can place a dispersion above its Tg, so the observed failure may not represent what happens at 25 °C [19]. Practitioners therefore combine formal studies with supporting experiments at several temperatures and humidities, and use the results to build a model of crystallisation kinetics that can be extrapolated to labelled storage [22, 23]. Zografi and Newman argued that the relationship between structure, mobility and stability should be understood well enough to interpret such extrapolations, but they also made clear that they remain approximate [33]. Real-time data are still needed to confirm the prediction [39].

Prediction tools are increasingly used in early screening. Solubility parameters, Flory-Huggins theory and molecular dynamics simulation can rank candidate polymers before any material is made [17, 18]. Machine learning methods trained on published stability data have appeared in recent years, though their reliability beyond the chemical space of the training set has not been firmly established. The sensible position is that computational screening narrows the field and saves material, while experimental confirmation remains mandatory. Case histories such as the late appearance of a less soluble crystal form of ritonavir, which forced a reformulation, are a reminder of how costly an unexpected solid-state change can be [40].

Quality control of the finished product adds a further layer. Methods that are suitable for development, such as solid-state NMR, are rarely suitable for routine release, so simpler surrogate tests must be validated against them. Typical release specifications for ASD products combine dissolution, water content and an X-ray or thermal test for crystallinity, with the limit set from the development batches and the stability data [8, 39]. Specifications that are too tight reject acceptable material, while loose ones risk missing early crystallisation. Some sponsors add a periodic confirmatory test by a more sensitive method on retained stability samples, which is a reasonable compromise between cost and assurance.

7. LIMITATIONS AND FUTURE DIRECTIONS

The literature on ASDs is large but uneven. Most mechanistic work uses a small group of model compounds, notably indomethacin, felodipine, itraconazole and celecoxib, and the results may not transfer to drugs with

different structures [16, 32]. Many studies also use thin films or small laboratory batches, which dry and age differently from commercial powders. Reports of negative or ambiguous outcomes are scarcer than those of successful stabilisation, so the published record probably overstates the proportion of drug-polymer pairs that work [13, 34]. These biases should be kept in mind when using any published table, including table 1, as the basis for a formulation decision.

Several gaps are widely acknowledged. First, there is no validated method to predict long-term physical stability from short experiments with the confidence needed for regulatory use. Second, the relationship between supersaturation in vitro and exposure in vivo is still examined mainly case by case [11, 26]. Third, the role of polymer degradation, residual monomers and peroxides on chemical stability of the drug is less well documented than the physical aspects, even though oxidative degradation can occur in povidone-containing systems [8, 24]. Finally, the field would benefit from open, standardised datasets that include failures, which would allow machine learning tools to be trained and validated honestly [18, 32].

Emerging directions include ternary dispersions with a surfactant or second polymer, amorphous salts and co-amorphous systems with small-molecule co-formers, and continuous manufacturing platforms that combine extrusion or spray drying with downstream tableting. Each promises either higher drug loading or better control of the process, and each introduces new interactions that need study [13, 29, 36]. Whether any of them will displace the established polymer dispersions is unclear. For now, the best evidence supports a disciplined approach: characterise the molecule, screen polymers by interaction and miscibility, test under realistic humidity, and judge performance by the behaviour of the dissolved drug as well as the solid [9, 22, 26].

8. CONCLUSION

Amorphous solid dispersions work when three conditions are met together: the drug is held in a single phase at a loading the polymer can accommodate, the glass is protected from moisture and heat through its shelf life, and the polymer then lets the drug dissolve into a supersaturated solution that persists long enough to be absorbed. The published evidence shows that specific drug-polymer interactions and low molecular mobility are the strongest stabilisers, that water is the commonest saboteur, and that the manufacturing route matters mainly through its effect on mixing and residual solvent [14, 15, 20, 28]. Polymer choice is thus a matter of fit, not of ranking.

Current prediction tools help to narrow the options but cannot yet replace long-term data, and much of the literature rests on a small set of model compounds [16, 17, 18, 32]. Practical guidance from the evidence is simple enough: screen polymers for interaction and miscibility, set loading below the estimated solubility where possible, test under realistic humidity and judge performance by the dissolved drug as well as the solid state [9, 26, 39]. Better shared datasets, including failures, and clearer links between in vitro supersaturation and exposure in people would do most to strengthen future work [11, 38].

9. ABBREVIATIONS

ASD-Amorphous solid dispersion, BCS-Biopharmaceutics classification system, DSC-Differential scanning calorimetry, HPMC-Hydroxypropyl methylcellulose, HPMCAS-Hydroxypropyl methylcellulose acetate succinate, ICH-International Council for Harmonisation, NMR-Nuclear magnetic resonance, PVP-Povidone (polyvinylpyrrolidone), PVP-VA-Copovidone (vinylpyrrolidone-vinyl acetate copolymer), Tg-Glass transition temperature

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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