A Review of the New Insulin Oral Drug Delivery System

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Abstract

Chronic hyperglycaemia brought on by either inadequate insulin synthesis or a compromised cellular response to insulin is a hallmark of diabetes mellitus, a metabolic disease. Pancreatic β-cells produce the hydrophilic hormone insulin, which controls the entry of glucose into tissues. About 589 million individuals worldwide (~11.1% of people aged 20–79) had diabetes in 2024; by 2050, that number is expected to rise to 853 million (13.0%). The disease is linked to 3.4 million deaths and healthcare expenses that exceed $1 trillion USD. Traditional insulin therapy relies on subcutaneous injection, which poses challenges such as poor compliance, infection risk, and a short duration of action. Multiple gastrointestinal (GI) barriers, including acidic pH, enzymatic breakdown by pepsin, trypsin, chymotrypsin, and brush-border peptidases, mucus binding, and epithelium impermeability, make oral insulin delivery extremely undesirable. Improved bioavailability (<1%) necessitates creative delivery methods. These nano-based carriers have demonstrated encouraging preclinical results, including lipid nanoparticles (solid lipid nanoparticles [SLNs], nanostructured lipid carriers [NLCs], liposomes, niosomes, and nanoemulsions), polymeric nanoparticles (PLGA, PLA, chitosan derivatives), metal-organic frameworks (MOFs), and inorganic nanoparticles (e.g., mesoporous silica). Strategies involve enzyme shielding, pH-responsive coatings, mucus penetration, epithelial permeation, and targeted delivery. While these systems improve stability, uptake, and pharmacodynamics, safety concerns remain, including nanoparticle toxicity, immunogenicity, biodistribution, and manufacturing scalability. Regulatory guidance from FDA underscores thorough characterization and preclinical evaluation. This review collates recent advancements in oral insulin delivery approaches using nanoscale technologies and identifies key challenges for clinical translation.

1. Introduction

A person with the condition diabetes mellitus (pronounced /or often just called diabetes) has a high blood sugar (glucose) level because their body either does not create enough insulin or their cells do not react appropriately to the insulin that is produced. The pancreas produces the hormone insulin, this permits glucose to be absorbed by bodily cells and transformed into energy. When glucose is not absorbed by the body's cells, it builds up in the blood (hyperglycemia), which can result in a number of possible health issues [1].

Diabetes comes in a variety of forms, the most prevalent being: Type 1 diabetes: Previously referred to as juvenile diabetes or insulin-dependent diabetes, type 1 diabetes, is far less frequent than Type 2. Type 1 diabetes affects 5–10% of diabetics, according to CDC estimates. Individuals who have a close relative with Type 1 diabetes are more vulnerable. The pancreas either produces very little or no insulin in people with Type 1 diabetes, which is insufficient to let blood sugar reach your cells and be used as fuel. Blood sugar levels are excessively elevated as a result.

Type 2 diabetes: Type 2 diabetes affects around 90–95% of the 34 million Americans who have the disease. The body still has trouble transferring sugar into cells in Type 2 diabetes, just like in Type 1 diabetes, but this isn't because the pancreas isn't making insulin anymore. Although the pancreas still produces insulin, cells are not receptive to it and are unable to utilise it as intended. Individuals who are overweight, have a sedentary lifestyle, are over 45, have a family history of Type 2, or have smoked in the past are at a higher risk of acquiring Type 2 diabetes [2].

Even crazier horrors can be found beyond these. Pregnancy joy is unexpectedly invaded by gestational diabetes, which disappears after delivery but leaves an irreversible taint. Unbeknownst to the body, latent autoimmune diabetes secretly destroys beta cells [3]. Type 3c diabetes is a confusing misnomer that refers to a variety of poorly known causes of elevated blood sugar [4]. At every stage, diabetes manifests in unsettling ways that are harder to understand and manage than the last. Diabetes continues to be a relentless monster that steals both life and freedom, even as its disguised threats continue to baffle and confound. The secret to any defence against this evil illness is to comprehend its complicated face.

The global burden of diabetes has reached unprecedented levels and continues to grow. According to the International Diabetes Federation, approximately 589 million adults (20–79 years) — about 11.1% of that age group — were living with diabetes in 2024, with projections

rising to 853 million (13.0%) by 2050 [5,6]. Over 800 million adults are afflicted, and almost 60% of those over 30 are still untreated; A significant percentage of low- and middle-income countries (LMICs) are impacted.The prevalence has more than doubled from about 7% in 1990 to about 14% in 2022 [7, 8]. These figures were informed by the 2021 Global Burden of Disease Study, which estimated 529 million cases in 2021, a global prevalence of 6.1%, and forecasted 1.31 billion cases by 2050 [9]. Diabetes was associated with approximately 3.4 million deaths in 2024, and global diabetes-related health expenditures totaled an estimated US $1.015 trillion [5,8], up from USD $966 billion in 2021 and projected to exceed USD $1.05 trillion by 2045 [6]. Major complications include increased morbidity, mortality, and disability-adjusted life-years (DALYs), particularly in regions with limited access to diagnosis and care [9].

Insulin is a 5800 Da protein hormone made up of two chains, α and β, connected by two disulphide linkages [10]. Insulin's hydrophilic qualities are indicated by its log p value of -1.6, which places it in the Class III category of the Biopharmaceutics Classification System [11]. Currently, subcutaneous injection is used in clinical settings to deliver insulin. However, in addition to disadvantages including limited patient compliance due to injection pain and the potential for injection site infections, the rapid clearance of insulin administered subcutaneously has a short-term therapeutic impact [12,13].

Oral, superficial, inhalational, ocular, and vaginal routes are among the many noninvasive insulin administration techniques that have been extensively researched [14–16]. Among these approaches, injection remains the most widely used medication delivery route due to its ease of use [17]. Orally administered insulin has been suggested to stimulate endogenous insulin secretion, resulting in a lower risk of hypoglycemia compared to subcutaneous injection. Its potential to preserve and maintain beta-cell function has also been reported. However, oral insulin must overcome the harsh gastrointestinal (GI) environment for absorption. The barriers of mucus and epithelial cells in the GI tract result in its limited bioavailability. Therefore, despite the extensive development of various oral delivery systems over a century since the discovery of insulin, oral insulin has not been available in clinical practice [18].

It was also investigated if altering the structure of insulin may increase its permeability across the intestinal wall by converting it into enteric-coated carriers or other novel forms, or it could provide resistance to breakdown by GI acids and enzymes [19]. A unique blend of mucoadhesive polymers was used to create mucoadhesive intestinal patches, which adhered firmly to the intestinal mucosa and enhanced intestinal permeability. They were then covered

with a waterproof coating. The patches also produced site-specific distribution to the gut and inhibited enzymatic breakdown. Intestinal iontophoresis was utilised to help insulin get through the gut and increase the patches' effectiveness [20].

2. Obstacles to insulin uptake orally

Insulin has a number of oral absorption challenges in the GIT, mostly enzymatic, physical, and chemical. Oral drugs go via the gastrointestinal tract, adhere to the mucous layer, cross the intestinal epithelium, and enter the bloodstream [21,22]. Table 1 provides a summary of the physiological obstacles to oral insulin administration and the strategies to get beyond them.

Physiological	**Constitutional Obstacles**	**Mechanisms**	**References**
Breakdown of digestive enzymes	Chymotrypsin, carboxypeptidase, elastase, trypsin, and pepsin	employing a gastro-resistant architecture, having a hydrophobic effect, and shielding effect	23-25
Acidification of the stomach	pH 1–2 gastric acid	pH responsiveness and an acid-resistant polymer coating	21,26-28
Storage by the barriers of the mucus layer	Electrolytes, glycoproteins, lipids, proteins, and water	The charge-reversing and mucus-inert electroneutral interface	22,29
stomach epithelial cell layer contraction	tight junction, lysosome breakdown, apical endocytosis, and basolateral flow	Permeation improvement and increased active transportation level	30,31

3. Need of Novel Drug Delivery System [32]

Both biological and physical mechanisms can serve as the foundation for drug delivery methods. Osmosis, diffusion, erosion, dissolution, and electron transport are all used in physical processes, often known as controlled drug delivery systems. Monoclonal antibodies (immunoglobulin), genetic vector systems, polymer-drug adducts, and liposomes are all employed in biologic procedures. The site of interest can be reached by the drug-loaded system through the aptitude known as targeting. Two primary mechanisms for achieving this contact and the desired drug release sites can be distinguished: (i) passive targeting and (ii) active targeting. Drug delivery systems can optimize the duration of action, reduce the need for frequent dosages, control the site of release, and maintain consistent levels of drugs for patients.

There are advantage of novel drug delivery system

1. Provides defence against deterioration, both chemical and physical.
2. Offers continuous supply.
3. Enhances the dispersion of tissue macrophages.
4. improves stability;
5. boosts pharmacological effectiveness; and
6. guards against harm.
7. Makes it easier to digest.

4. Oral Drug Delivery Systems

The encapsulation of insulin in specific carriers can offer a consider able improvement in oral bioavailability. These methods are intended to increase intestinal permeability and shield insulin from enzymatic and acidic breakdown. At the moment, the preferred oral administration method is nanocarriers.Drugs can be encapsulated within the carrier matrix or core, forming particles with sizes below 1000 nm [33]. Nanocarriers or nanoparticles (NPs) are recognized for their high permeability due to their small particle size [34]. This has made them promising candidates for insulin delivery. Nanoscale formulations are classified as lipid NPs, polymeric NPs, or inorganic NPs based on the carrier material. Solid lipid nanoparticles (SLNs), liposomes, nanoemulsions, polymeric nanoparticles (NPs), polymeric micelles, and mesoporous silica nanoparticles (MSNs) are among the widely utilised drug delivery systems.

In preclinical research, all of these have demonstrated promising outcomes for insulin delivery orally.

4.1 Nanoparticles made of lipids

Lipid-based NPs are nanoscale solid particles, vesicles, or emulsions composed of lipids [35]. Due to the high lipid content of cell mem branes, lipid NPs are considered advantageous for cellular uptake [36] However, their lipophilicity poses a challenge to the encapsulation of hydrophilic proteins such as insulin [37]. Lipid NPs come in two main varieties: SLNs and nanostructured lipid carriers (NLCs) [38, 39]. NLCs are composed of both liquid and solid lipids, while SLNs are usually composed of solid lipids and surfactants [40]. The presence of surfactants allows insulin to be retained in the aqueous phase of NPs. SLN and NLC formulations deliver insulin in solid forms, therefore offering improved stability in the GI tract compared to liposomes, niosomes, and nanoemulsions. However, the solid nature may limit their uptake by intestinal epithelial cells [41]. An SLN formulation for oral insulin achieved a relatively low bioavailability of about 5% in rats [42].

Liposomes

Insulin can be encased in the hydrophilic core of liposomes, which are lipid bilayer-based spherical vesicles. Nonetheless, liposomes are thought to be unstable in the gastrointestinal tract [43]. Bile salts have been loaded into the lipid bilayer in an effort to increase the stability of liposome formulations [44]. Zhang et al. introduced biotin (vitamin B7) onto the surface of liposomes to mimic vitamin absorption in the small intestine. It increased the bioavailability of oral insulin to 8.32% [45]. This significant enhancement in bioavailability can be attributed to the biotin modification, as the unmodified liposome only exhibited a bioavailability of 3.30%.

Niosomes

Nonionic surfactants and cholesterol combine to form vesicles known as niosomes [46]. Drug delivery systems frequently use nonionic surfactants due to their purportedly lower toxicity and affordability [47].They also serve as potent P-glycoprotein efflux inhibitors, thereby enhancing drug absorption [48]. An oral insulin for mulation has been developed with trimethyl chitosan (TMC)-coated niosomes, employing Span 60 as the surfactant. This formulation achieved a high encapsulation efficiency (EE) of 80%, improved stability under simulated gastric conditions, and enhanced intestinal permeability [49].

Nanoemulsions

The components of oil, water, and surfactants combine to generate clear or translucent liquid formulations known as nanoemulsions [50]. For insulin delivery, water-in-oil (w/o) nanoemulsions can trap insulin in the aqueous core [51]. The bioavailability of oral insulin w/o nanoemulsions has been reported to be almost ten times that of free insulin solution [52].

Self-emulsifying systems drug delivery

Oil, surfactants, and cosurfactants combine to generate self-emulsifying system for drug delivery [53]. When introduced to an aqueous phase, they can create emulsions of oil in water. Due to the hydrophilic nature of insulin, it is challenging to dissolve it in the oily core. Therefore, strategies have been developed to increase its lipophilicity. One approach is to form hydrophobic ion pairs (HIPs), in which insulin forms electrostatic interactions with counterions cotaining a hydrophobic portion, resulting in lipophilic complexes [54]. Insulin-guanidine was selected by Claus et al. to form HIPs because of its two additional cations compared to insulin. The Self-emulsifying systems drug delivery produced typically range in size from 200 to 350 nm, with an absolute bioavailability (relative to intravenous injection) of 0.55% in healthy rats [55].

4.2. Polymeric based nanoparticles

Insulin is loaded onto carrier materials to create oral insulin delivery nanosystems. To preserve medication stability and enhance bioavailability, the ideal materials should be pH responsive, bioadhesive, biocompatible, biodegradable, modifiable, and simple to process. Oral delivery nanosystems have frequently been constructed using a range of polymers. Depending on the source, they can be categorised as either natural or synthetic polymers. Common natural polymer carrier materials include amino acids, chitosan, sodium alginate, hyaluronic acid, starch, and bile acid [56,57]. Artificial polymers include polycaprolactone (PCL), polylactic acid (PLA), and poly (lactic-co-glycolic acid) (PLGA).

Polylactic Acid (PLA)

The primary raw material used to make PLA, a type of polyester that is biodegradable, biocompatible, and bioadhesive, is lactide. A lot of medicinal formulations have made use of PLA. Aggregates of PLA-b-Pluronic-b-PLA (PLA-F127-PLA) were created in order to be utilised as oral insulin nanocarriers [58]. For 18.5 hours, the nanoparticle formulation kept the diabetic rats' blood sugar levels low. The charge-negative hydroxyl and carboxyl groups of

PLA had an adverse effect on the nanoparticles' ability to travel, increasing their adhesion to the intestinal wall and prolonging their residence time [59]. After four hours of oral administration, the amphiphilic polylactic acid insulin nanoparticles were able to reduce blood glucose by 40% in comparison to traditional PLA nanoparticles. This implied that after gastrointestinal absorption, changing the carrier materials can enhance drug absorption [60].

Poly (lactic-co-glycolic acid) (PLGA)

Lactide acid and glycolide are two examples of the random polymerisation of two monomers to create PLGA, a biodegradable functional polymeric molecule. PLGA has been used in oral administration systems for macromolecular drugs because of its superior film-forming qualities, nontoxicity, and biocompatibility [61]. Because PLGA degrades more quickly than PLA, it is a better material to use when building oral insulin delivery devices. Due to PLGA's limited water solubility, using the reverse micellar–solvent evaporation method, insulin–phosphatidylcholine complexes were created. To improve permeability and encapsulation, the insulin complexes were loaded onto PLGA nanoparticles using a modified composite emulsion–solvent evaporation technique. First, a combination of insulin and sodium deoxycholate was made utilising the hydrophobic ion-pairing technique. The emulsion–solvent diffusion approach was then used to encapsulate this complex into PLGA nanoparticles, successfully increasing the encapsulation rate to 93.6% and lowering the diabetic rats' blood glucose level to 43% of its starting level.[62]. Spray freeze-drying was used to create polymeric lipid hybrid nanoparticles with a hydrophilic PEG shell, an amphiphilic phosphatidylcholine interlayer, and a hydrophobic PLGA core. Following that, they were put inside stiff gelatin capsules that were covered in hydroxypropylmethylcellulose phthalate (HPMCP-55). Good cellular internalisation and drug encapsulation integrity were demonstrated by the formulation, it could maintain the drug's encapsulation integrity for up to three months [63]. Negatively charged PLGA nanoparticles have a limited ability to pass through the mucous membrane. The penetration rate can be further increased by altering the surface of PLGA with functional molecules or positively charged chemicals [64,65].

A Look at Chitosan and Its Byproduct

N-acetylglucosamine and deacetylated glucosamine combine to form chitosan, a naturally occurring polymeric polysaccharide. Biocompatibility, biodegradability, adhesion, and permeability are among its favourable biological characteristics [66–69]. To improve gastrointestinal tract adherence, the positive charge of chitosan forms hydrogen bonds and

electrostatic interactions with the silicate group in mucin [63]. Tight junction protein-4 (Claudin-4) is an essential protein that maintains cell polarity and tight junction barrier function. Chitosan redirects Claudin-4 from the cell membrane to the cytoplasm. Lysosomes then break down Claudin-4, weakening cell-to-cell tight junctions and immediately increasing paracellular permeability. On the other hand, chitosan is insoluble in alkaline and neutral environments. Its absorption and utilisation are also limited because it is challenging to protonate in the intestine to exercise its cationic characteristics. To increase the aqueous solubility, adhesion, and permeability of nanoparticles at neutral and alkaline pH conditions, chitosan-derived compounds were added, including quaternized chitosan, trimethyl chitosan (TMC), ethyl chitosan, carboxymethyl chitosan (DMEC), carboxymethyl chitosan (CMCS), acrylate-chitosan, and mercapto chitosan. In a broad range of pH and concentration, they are more soluble in water than chitosan, and this does not alter their cationic characteristics.

TMC is more likely to be aminated in neutral and alkaline environments to enhance its water solubility in alkaline conditions and dramatically increase the permeability of insulin. At a pH level comparable to that of the jejunum, TMC is favourable for the absorption of hydrophilic substances because the protons of its main amines are substituted with methyl groups, which prevents TMC from forming hydrogen bonds with the hydroxyl groups. The intrinsic positively charged properties and strong adhesiveness of chitosan and its derivatives make them ideal materials for oral insulin delivery nanosystems. Chitosan's gastrointestinal tract toxicity is a barrier to its use as an insulin carrier. The paracellular route allows dangerous chemicals to readily enter the bloodstream whereas chitosan relaxes tight junctions [70,71].

Metal Organic Frameworks (MOFs)

Metal organic frameworks (MOFs), also known as porous coordination polymers, are dimensional ordered porous materials composed of inorganic clusters joined by organic ligands. They are frequently utilised in drug administration because of their stable porosity, regular three-dimensional structure, and the ability to intentionally modify their chemical and structural properties. Iron-based MOFs were created by Zhou et al. that could physically adsorb insulin. The insulin-loaded MOFs could be coated with poly (ethylene glycol-b-lactide), an amphiphilic polymer, to maintain their stability in the acidic environment of gastric juice [72]. Additionally, this MOF's structure remained stable in acidic environments, limiting the release of the insulin in gastric juice; in contrast, in PBS, the structure of this MOF might break down, allowing the loaded insulin to be released. Nevertheless, the rate at which these drug delivery

elements were released was excessively rapid. Under physiological conditions, almost 80% of insulin was released after 40 minutes, which could result in adverse effects including hypoglycemia. Currently, the delayed release of medications needs to be optimised and controlled. Furthermore, the metabolism mechanism and degradation profile are still unclear, which could potentially harm human health. Therefore, more study is needed on MOF materials for oral insulin administration [66].

Additional Resources

Insulin oral delivery nanosystems also make extensive use of a wide range of other materials, including inorganic nanoparticles and natural polysaccharides. The purpose of anionic surface silica nanoparticles was to enhance the gastrointestinal tract's absorption of insulin. The negative electrical characteristics of the nanoparticle surface may cause the nanoparticles to relax the tight junctions among small intestinal epithelial cells by binding integrins and activating myosin light chain kinase (MLCK). This would improve intestinal permeability and the ability of small intestinal epithelial cells to absorb the nanoparticles. This action is very biocompatible, reversible, and won't cause intestinal tissue inflammation or necrosis [73]. Substances made of ions with a melting point lower than 100 °C are known as ionic liquids. They are liquid at or near room temperature and are used extensively in a variety of industries, including medicine. Banerjee et al. developed a highly successful oral insulin formulation using choline and geranylate (CAGE) ionic liquids, which significantly reduced blood glucose to 45% of its initial level. Strong biocompatibility and storage durability for at least four months in a refrigerator were two of the formulation's exceptional pharmacokinetic and pharmacodynamic results [74]. Insulin is frequently administered orally using natural polysaccharides such sodium alginate and starch [66,75,76].

4.3. Inorganic nanoparticles

Drug delivery platforms known as inorganic nanocarriers are made of elements like gold and silica that serve as their structural foundation. Over recent years, these inorganic substrates have gained substantial traction in pharmaceutical research owing to their exceptional drug-loading capabilities [77]. Mesoporous Silica nanoparticle [MSNs] has become one of the most popular inorganic drug delivery systems. MSNs modified with PEG have been reported to improve the stability of insulin in the GI environment [78]. However, concerns have been raised about the hepatotoxi city, renal toxicity, and neurotoxicity of inorganic nanocarriers [79]. This highlights the need for careful assessment of their long-term. Another inorganic nano scale

formulation is known as quantum dots (QDs), which are nanocrystals [80]. QDs based on silver sulfide (Ag2S) were used to deliver metformin. The resulting accumulation in the liver and improved metformin bioavailability indicates their potential for insulin delivery [81].

5. Safety Factors

To guarantee patient safety, the safety issues surrounding nanomedicine, such as possible toxicity, immunogenicity, and long-term impacts on physiological systems, still need to be properly addressed [82]. Nanoparticles (NPs) have the ability to interact with biological molecules and cellular structures, potentially leading to toxicity, due to their small size and huge surface area. Furthermore, some nanomaterials have the potential to trigger an immunological reaction, leading to immunogenicity problems that could jeopardise the effectiveness of treatment. The long-term effects on physiological systems remain a worry because little is known about the biodistribution and storage of NPs in organs over time [83]. In an attempt to allay these worries, the FDA has issued recommendations to promote the safe development of clinically relevant products based on nanotechnology [84].

6. Future Directions

Future developments in the field of precision insulin administration using nanomedicine have the potential to be revolutionary in order to overcome present constraints and improve therapeutic results. Due to problems like poor intestinal epithelial absorption and gastrointestinal tract enzymatic degradation, which make it challenging to attain sufficient oral bioavailability, the potential of oral insulin formulations as a non-invasive alternative to injections is limited. Another major issue that could jeopardise the therapeutic benefits of nanoparticles utilised in insulin delivery systems is their immunogenicity. Nanoparticles' performance and safety are impacted by variations in their dimensions, form, and surface properties, which makes it challenging to scale up production and ensure uniformity in their synthesis. Nanoparticles' performance and safety are impacted by variations in their dimensions, form, and surface properties, which makes it challenging to scale up production and ensure uniformity in their synthesis. Researchers are investigating remedies like surface alterations to lessen immunogenicity, protective coatings or modifications to prevent insulin from degrading, and sophisticated manufacturing processes to guarantee consistent nanoparticle output.

7.Conclusion

The need to address the drawbacks of injectable insulin, such as pharmacokinetic inefficiencies, patient pain, and noncompliance, is driving the hunt for noninvasive oral insulin delivery. Lipids, polymers, and inorganic frameworks are examples of nano-based oral delivery methods that provide multipurpose solutions. These approaches improve pharmacokinetic profiles and glycaemic control in preclinical models by encapsulating insulin in protective matrices, using coatings that are resistant to enzymes, focussing on mucus penetration, and promoting epithelial uptake (via the use of ligands or permeability enhancers). Notably, polymeric nanoparticles produced extended hypoglycemic effects in diabetic rats that lasted up to 18.5 hours, while liposomes modified with biotin attained oral bioavailability of approximately 8%. However, preclinical achievements highlight how important it is to overcome translational barriers prior to clinical adoption. The most important of these is safety: products containing nanoparticles may cause immunogenic reactions, toxicity specific to a particular organ, or unpredictable biodistribution. Large-scale manufacturing consistency is still an issue; differences in particle size, surface chemistry, and release behaviour can jeopardise both regulatory compliance and efficacy. Future research must concentrate on improving biocompatibility by using non-toxic, biodegradable materials and surface changes that reduce immunological activation while adjusting release kinetics for physiological absorption of insulin. Standardisation is necessary for scalable production techniques like self-assembly or repeatable spray-drying. The incorporation of in vitro–in vivo correlation (IVIVC) models helps direct dosage and formulation improvement. Nanomedicine-assisted oral insulin delivery has revolutionary potential for diabetes treatment, offering enhanced adherence, physiological insulin profiles, and beta-cell preservation. However, pharmacokinetics, immunology, material science, and scalable engineering must all come together for translation to be successful. Coordinated interdisciplinary research and thorough regulatory review are necessary to achieve this intersection. If these issues are resolved, oral insulin has the potential to completely transform the management of diabetes by providing a safe, effective substitute for injections.

8. References

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