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Review Article

MUCOADHESIVE DRUG DELIVERY SYSTEM: FORMULATION AND EVALUATION MODELS

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ABSTRACT

Mucoadhesion, the phenomenon wherein materials, adhere for prolonged durations through interfacial forces, presents a compelling approach to address the challenges of traditional drug delivery systems, such as first-pass metabolism and the localized delivery of biomolecules, including proteins, peptides, and oligonucleotides. Mucoadhesion has significant potential for the delivery of many substances through multiple routes of administration, including ophthalmic, nasal, vaginal, and buccal. Moreover, mucoadhesion facilitates sustained local or systemic medication efficacy. This review study aims to examine the possible applications of mucoadhesion, the mechanisms of mucoadhesion, and various recent advances in formulation-based approaches for mucoadhesive drug delivery. Furthermore, focusing on the new models for *in vitro, in vivo*, and *ex vivo* studies for mucoadhesive drug delivery systems. The development of more effective and patient-friendly drug delivery methods that address issues with first-pass metabolism and low drug solubility is made possible by these findings.

Keywords: Mucoadhesive drug delivery, Polymers, Animal models, Bioadhesive, Film.

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INTRODUCTION

The mucoadhesive drug delivery system is designed to adhere to mucosal surfaces in the body, such as the gastrointestinal tract (GIT), nasal cavity, oral cavity, and vaginal cavity. It increases the retention time of the drug at the absorption site, which in turn improves the therapeutic performance of the drug with prolonged and controlled release of drug [1]. This is a novel approach for the dosage forms to increase the bioavailability of poorly soluble drugs and to avoid GIT degradation and first-pass metabolism of some drugs. It enhances the bioavailability of the drug and hence reduces drug dose. The oral route is accepted majorly both patients and manufacturers due to good general acceptance and easy accessibility. Drugs are absorbed directly through the mucosal lining, bypassing the digestive system and liver. This results in an increase in the number of drugs reaching systemic circulation [2]. In general, because of their molecule instability and poor permeability to the mucosal membrane, it is very difficult to deliver biologics such as peptides, proteins, or other nucleic acids. The physicochemical properties of mucus. Further, the moisture content and the hydration of polymers are crucial for interaction with mucus [3].

Biopolymers are particularly interesting considering their biocompatibility, biodegradability, and formulation variability. Advanced biopolymer study, formulation process improvement, and targeted drug release profile creation are some of the recent developments in this area of research. By improving medication efficacy, enhancing patient compliance, and offering a more patient-friendly approach to medications, these developments have the potential to completely alter drug delivery [4]. Over the past 20 years, polymer mucoadhesive oral administration has gained prominence due to its specific physicochemical properties. It is considered as the most reliable oral mucoadhesive administration strategies [5,6].

Better medication release techniques using transmucosal and transdermal routes would be extremely important since through these routes, the pain factor linked to parenteral drug delivery methods can be completely removed [7,8].

The study bridges the gap by systematically analyzing the mechanisms and theories of mucoadhesion, recent formulation-based advances, various formulation approaches, and *in vitro*, *ex vivo*, and *in vivo* evaluation models. This review provides a novel perspective on optimizing mucoadhesive drug delivery systems for enhanced therapeutic efficacy and patient compliance [9,10].

MUCOADHESION MECHANISM

Certain macromolecules' method of adherence to a mucous tissue surface is still poorly understood. For the mucoadhesive to promote the dispersion of its chains within the mucus, it must spread over the substrate to create tight contact and increase surface contact. There are repulsion and attraction forces at work, and the attraction forces need to be stronger for a mucoadhesive to work [11,12]. The two stages of the mucoadhesion process are commonly referred to as the contact stage and the consolidation stage. The first step is defined by the mucoadhesive contact with the mucus membrane, which causes the formulation to expand and swell and begins to make deep contact with the mucus layer forming a close relationship with the mucous membrane [13]. In a few cases, the delivery mechanism is mechanically affixed over the membrane, as in the case of ocular or vaginal formulations. In other situations – like the nasal route – the aerodynamics of the organ to which the system is delivered encourage the deposition. As the particle gets closer to the mucosal surface, it will encounter both attractive (van der Waals forces and electrostatic attraction) and repulsive (osmotic pressure, electrostatic repulsion, etc.) forces. The particle must thus get beyond this repellent barrier. In the second stage of consolidation, the presence of moisture activates the mucoadhesive components. The mucoadhesive molecules can separate and bind together via weak hydrogen and van der Waals bonds when the solution is plasticized by moisture [14]. In essence, the consolidation stage is explained by two theories: The dehydration

Table 1: Different theories of mucoadhesion with their applications and limitations

Type of theory	Principle	Applications	Limitation	References
Electronic theory	Electrostatic attraction between the polymer and the mucosal surface leads to electrical double-layer formation at the interface	• Modeling interactions • Understanding bonding mechanisms • Predicting adhesive properties • Predicting drug release	• Neglect of structural and rheological properties • Insufficient experimental evidence • Complexity of biological environments	[15]
Wetting theory	Mucoadhesive polymer to wet the mucus surface. Contact angle between the polymer and the mucosal surface, better wetting, and stronger adhesion at low angle	• Surface energy Matching • Measurement of contact angle • To optimize formulation viscosity • Increasing residence time • Improving patient comfort	• Neglect of molecular interactions • Static Assumptions • Inadequate for long-term adhesion • Contact angle limitations	[16]
Adsorption theory	Bond formation such as, hydrogen bonds, Van der Waals forces, and hydrophobic interactions	• Strong adhesion • Polymer design • Controlled release • Surface binding interaction	• Influence of environmental factors • Limited scope of interactions • Short-term adhesion focus	[17]
Diffusion theory	Interpenetration and netting of polymer chains with the glycoprotein chains in the mucus	• Enhanced contact • Increased absorption • Controlling release of drug • Understanding movement of drug	• Assumes constant conditions like pH and temperature, which isn't realistic • Does not address continuous turnover and renewal of mucus	[18]
Fracture theory	Focuses on the mechanical strength and resistance of the adhesive joint	• Mechanical stability • Durability • Bond strength • Biocompatible	• Difficult to measure the properties of thin, soft films and mucosal tissues accurately • Limited in predicting how polymers change physically, such as swelling	[19]
Mechanical theory	Entanglement and mechanical interlocking of polymer rough surfaces and mucus	• Surface contact • Adhesive strength • Drug release • Optimizing viscosity and elasticity	• Assumes uniform material properties • Limited in predicting effects of natural bodily movements	[19]

hypothesis and the diffusion theory. Diffusion theory states that both the mucoadhesive molecules and the mucus glycoproteins interact with one another through secondary bond formation and chain penetration [13]. Features of the mucoadhesive device that favor chemical and mechanical interactions allow this to occur.

THEORIES OF MUCOADHESION

The theory of mucoadhesion encircle the various mechanism and interactions that are responsible for the adhesion of materials to mucosal surfaces. The basic theories that explain mucoadhesion have been demonstrated in Table 1.

FACTORS AFFECTING MUCOADHESION

Polymer-based factors

The polymer-based factors include molecular weight, flexibility, hydrogen bonding capacity, cross-linking capacity, charge, polymer concentration, and swelling. Molecular weight: Low molecular weight polymers favor the interpenetration of molecules, whereas entanglement is preferred at higher molecular weights [20]. Mucoadhesive polymers are being used more often to change the way formulation dosage forms are released, as well as for buccal and gastro-retentive drug delivery systems.

Environmental and physiological factors

Environmental factors generally include factors like pH, temperature, moistening, and presence of enzymes, and physiological factors like diseased state, mucosal pH, saliva, and other body fluids. For mucoadhesive drug delivery systems to function properly, physiological and environmental factors are both important as given in Table 2. To create formulations that work well and endure the dynamic conditions of the mucosal habitats in the body, a full understanding of these aspects is necessary.

FORMULATION BASED ADVANCES IN MUCOADHESION SYSTEM

Advances in mucosal drug delivery strategies have significantly improved the effectiveness and patient compliance of treatments. These strategies enhance the bioavailability, enable targeted drug delivery, and also provide prolonged drug release. Such strategies include nanoparticle-based systems, mucoadhesive systems, films and patches, hydrogels, liposomes and niosomes, mucoadhesive microspheres, and mucus-penetrating particles. Nowadays, combining vesicular drug delivery systems with mucoadhesive drug delivery systems is a novel concept. These developments have the potential to completely transform drug delivery by boosting medication effectiveness, enhancing patient adherence, and offering a more patient-friendly method of pharmacological therapy [4]. The use of carrier technology for medicine delivery offers an intriguing and clever strategy. This combination utilizes the advantages of vesicular drug delivery systems like liposomes, niosomes, micospheres, etc., with the adhesive properties of mucoadhesive systems which are highly useful for drug encapsulation, prolonging drug release at the site of action (Table 3). Represents the different formulation strategies using natural and synthetic polymers.

MUCOADHESIVE FILM

Several drugs can be administered directly to specific mucosal membranes using flexible bio-adhesive films [18]. The most recent invention, mucoadhesive films, are favored over tablets due to their flexibility, improved absorption, affordability, and patient compliance. When applied to the tongue or oral cavity, films' water-dissolving polymer enables the dosage form to rapidly hydrate, attach, and dissolve, resulting in systemic drug distribution. As an example, white striations, papules, or plaque with or without erythema and ulceration are symptoms of oral lichen planus, a chronic autoimmune mucocutaneous inflammatory disease that

Table 2: Various factors affecting mucoadhesion

	Factors	Desired properties	Limitations	References
Polymer-based factors	Molecular weight	a) Interpenetration for polymers increases with lower molecular weight, b) Entanglement is necessary for higher molecular weight Range lies between (2,00,000–7,000,000)	Reduce adhesion effectiveness, higher molecular weight can hinder tissue penetration and often have low solubility in biological fluids.	[7,21]
	Flexibility	High flexibility of polymer increases the diffusion of drug into mucous membrane	May exhibit low mechanical strength and can lead to rapid drug release	[22]
	Hydrogen bonding	Good hydrogen bonding is necessary for mucoadhesion	Low hydrogen bond leads to less durable adhesion, especially in GIT	[23]
	Cross linking capacity	a) Optimal strength and durability b) Balanced flexibility c) Controlled drug release d) Appropriate swelling e) solubility and hydration	Increase in cross-linking capacity results in insufficient swelling of polymer	[10]
	Charge	Optimal charge density is crucial. Compared to anionic polymers, nonionic polymers exhibit a lower degree of adhesion	High charge of polymer can result in aggregation or repulsion, whereas too low can lead to weak adhesion	[20]
	Polymer concentration	Polymer concentrations may range from 0.1% up to around 10% or higher	Low concentration- unstable interaction between polymer and mucin High concentration- increases strength of mucoadhesive bonds	[19,24]
	Swelling	a) Helps in enhancing contact area b) Improves residence time c) Enhances adhesive strengthmaintains stability.	Overhydration can result in poor adhesion, complicates the sustained or controlled release of drug	[17]
Environmental factor	pH	a) Oral mucosa: ranges approximately from 6.5 to 7.5 b) GIT: pH 1.5 to 3.5 c) Vaginal mucosa: 3.5–4.5 d) Nasal mucosa: 5.5–6.5 Ocular mucosa: 7.0–7.4	Local irritation, which provoke immune responses, and reduced effectiveness, can cause adverse effects	[4,7]
	Diseased state	a) Enhanced adhesion strength. b) Selective adhesion. c) Ability to penetrate mucus layer. Compatibility with other therapies	Decreased mucoadhesive strength of mucoadhesive dosage form and impaired barrier function	[7]
	Moistening	Facilitates polymer chain mobility in order to allow suitable diffusion of mucoadhesive polymer in the mucin layer	Biocompatibility concerns, adhering to mucosa can get weakened by excessive moisture or dryness.	[4,7]

affects the mucosal lining of the oral cavity [25]. In such case, we can use mucoadhesive films for delivering the drug directly into the mucosal lining of the mouth [26]. Following are some examples of mucoadhesive films which have been used for several diseases or target sites.

MUCOADHESIVE PATCHES

Mucoadhesive patches are an innovative drug delivery system designed to adhere to mucosal surfaces, which allows the controlled and sustained release of drugs. In order to improve their effectiveness and adhesion qualities, they have been investigated for the treatment of numerous illnesses using a variety of polymers. For the controlled and extended administration of topical corticosteroids, mucoadhesive polymer patches have been studied as an effective alternative. This strategy aims to improve the biopharmaceutical qualities, including lowering systemic toxicity and raising local bioavailability [27]. The buccal route is highly suitable for both systemic and local drug delivery due to its rich blood supply and relatively permeable tissue. Mucoadhesive buccal patches have been developed for various drugs which help in prolonged residence time and improved patient compliance. Various natural and synthetic polymers are used as they offer good film-forming properties and can be combined with other polymers to modulate drug release profiles [28].

MUCOADHESIVE GELS

Gel-based formulations present potent characteristics as buccal systems since they have great physicochemical properties and providing localized and sustained drug delivery [29]. Research utilized sodium carboxymethylcellulose (CMC) as a mucoadhesive polymer to create a mucoadhesive budesonide solution. In order to treat pediatric eosinophilic esophagitis, this formulation successfully improved medication retention at the target site. The choice of polymer plays a major role in the formulation of mucoadhesive gels, as it influences the gel's adhesion strength, drug release profile, and biocompatibility. Commonly used polymers include Sodium CMC, Pluronic F127, etc. Thermoresponsive polymers are also used which are sensitive to temperature and can they can reversibly form a gel

when the temperature rises and typically have a lower critical solution temperature [30].

IN SITU GELS

The *in situ* gel formulation has been used for both systemic and local effects. This kind of formulation is initially in the form of a solution, but after being delivered, it gels. For effective drug delivery systems, we can use this technique [31]. *In situ* gels have been investigated as a potential therapy for periodontitis. These systems' sol-gel transition properties react to physiological cues, allowing for both controlled and sustained release [32]. Poloxamers are known for their thermo-responsive behavior in forming gels at body temperature and are widely used for this formulation [33]. Also, carbopol is widely used and exhibits pH-sensitive gelation properties [34]. Coupling with mucoadhesive polymers is greatly desired for the development of such systems in order to extend the time spent at the site of action or absorption [35].

MODEL APPROACH FOR MUCOADHESIVE DRUG DELIVERY SYSTEMS

The distinctive characteristic of the mucus barrier is that it provides a problem when developing model systems to study drug or drug carrier transporters. The mucus layer's spatial layout and function inside the body are specifically influenced by its anatomical location. Mucus and lipid layers line the stomach's epithelium, protecting enzymes and gastric acid. Inhaled particles are eliminated via the respiratory system by the periciliary, mucus, and surfactant layers. Microbe and sperm motility are controlled within the intestinal and vaginal tracts, respectively, by an adhering and a loosely adherent mucus layer. Source-specific differences in mucus thickness, mucin type, and glycosylation also have a direct impact on the diffusion of medications and particles. The reported values of mucus thickness in the human small and large intestine range from 10 to 750 μm, while in rats, it is between 100 and 800 μm. The effects of medications and other stimuli on mucus secretion can also be investigated using cell culture models, and several mucus stains can be used for this purpose [47-49].

Table 3: Various formulation approaches for mucoadhesive drug delivery system

Formulations		Polymer used	Targeting site	Key findings	References
Films	Enalapril maleate film	Hydroxypropyl methylcellulose, Sodium carboxymethylcellulose, hydroxyethyl cellulose, poly vinylpyrrolidone K-90	Buccal mucosa	The formulation having 2% w/v SCMC and 2% w/v HEC exhibited optimal mucoadhesion, swelling index and residence time	[36]
	Estradiol film	Polyvinyl alcohol, polyvinylpyrrolidone, Hydroxypropyl methylcellulose	Buccal mucosa	Co solvency method exhibit better mucoadhesive properties, the nano emulsion films exhibited faster drug release (80% in 6 min) and higher drug permeation	[37]
Patches	Losartan potassium patch	HPMC (K4M and K100M), polyvinyl pyrrolidone-K30	Buccal mucosa	The patches showed suitable mucoadhesion, controlled drug release, and ideal swelling behavior	[38]
	Methotrexate patches	HPMC, hydroxyethyl cellulose, PVA, polyethylene glycol and chitosan	Oral mucosa	*In vitro* studies on HSC-3 cells showed enhanced cytotoxicity, apoptosis, and reactive oxygen species levels	[39]
	Methotrexate bilayer patch	Sodium alginate, sodium carboxy methylcellulose, polyvinylpyrrolidone and carbopol 934, Ethyl cellulose	Buccal mucosa	Showed good mucoadhesive strength, optimal swelling index, and sustained release pattern. Zero-order kinetics, indicating effective, controlled drug delivery for localized treatment	[40]
Gels	Silymarin gel	Carbopol 934, methyl paraben, propyl paraben, propylene glycol and triethanolamine	Oral mucosa	Gel improved mucoadhesive properties, drug delivery and bioavailability to the oral mucosa	[41]
	Clotrimazole gel	Xanthan gum, tragacanth, Propylene glycol, myrj52	Vaginal mucosa	Showed controlled release, high mucoadhesion (77.71 dyne cm^{-1}), and excellent drug content (94.47%)	[42]
	Natamycin gel	Carbopol 940, Hydroxypropyl methylcellulose	Ocular surface	NAT-SLNs showed high encapsulation efficiency of 99.167% and strong mucoadhesion and efficient activity against effective against *Candida* keratitis	[43]
In-situ gels	Tenofovir Disoproxil Fumarate *in situ* gel	Poloxamer 407, Carbopol 934	Vaginal mucosa	Exhibited good mucoadhesion, i.e., 0.324±0.036N, and was proven nonirritating to vaginal tissue in the HET-CAM test	[44]
	Rizatriptan *in situ* gel	Carbopol 934, HPMC K4M	Nasal mucosa	The statistical analysis result showed a strong correlation between viscosity (R^2=0.97758) and mucoadhesive strength (R^2=0.948931). Intra-nasal administration of RZT resulted in higher Cmax (340.27 ng) and AUC compared to the oral route	[45]
	Dolutegravir loaded nanoparticles *in situ* gel	HPMC, Poloxamer 407	Nasal mucosa	In vivo pharmacokinetic results revealed markedly higher ($p<0.0001$) Cmax (2fold) and AUC_{0-t} (3-fold) values in the targeted brain tissue as compared to IV route.	[46]

RESPIRATORY TRACT *IN VITRO* CELL CULTURE MODELS

Drug and particle diffusion has been studied using a range of transformed, cancerous, and primary bronchial epithelial cells [50]. Table 4 describes the different types of cells for *in-vitro* evaluation of mucoadhesive drug delivery systems. There are two types of cells that are found in the bronchial epithelial cells which means they might be cancerous cells and they can be normal epithelial cells.

INTESTINAL TRACT *IN VITRO* CELL CULTURE MODELS

Monolayers of enterocyte-like cells can be produced using the Caco-2 cell line, which was created from human colorectal adenocarcinoma. These cells are commonly used to study intestinal drug absorption.

MULTI-ORGAN MODELS

Recent developments in microfluidic platforms make it possible to examine how many tissues, especially mucosal tissues, interact with one another. For example, one on-chip organ model created liver and airway modules using primary human hepatocytes and bronchial epithelial cells. After being cultivated for 14 days at the air-liquid interface, the bronchial epithelial cells exhibited mucus secretion and barrier function similar to that of the *in vivo* airway epithelium [49]. Another system used intestine and human liver modules to study the relationship between the gut and liver. Endotoxemia was simulated by introducing lipopolysaccharide to the circulating medium. Non-linear cytokine responses were shown by this. Furthermore, kidney, skin, liver, and intestinal modules were merged on a distinct platform. The intestinal module, known as EpiIntestinal™ (MatTek Corporation), demonstrated notable absorption of glucose. Drug diffusion across mucous and epithelial barriers is studied using these organ-on-chip platforms, taking note of the effects of organ cross-talk [48].

TISSUE AND ANIMAL MODELS TO INVESTIGATE MUCOSAL DRUG DELIVERY

The role of mucus in drug delivery can be greatly enhanced by using purified mucin, *in vitro* cell cultures, and native collected mucus;

Table 4: Different types of cells for *in-vitro* evaluation of mucoadhesive drug delivery systems

Cell lines	Characteristics	Culture condition	Drug permeability and diffusion study	References
16HBE14o-cells Immobilized with SV40 large T-antigen	• Differentiated epithelial morphology • Functional tight junctions • Do not secrete mucins	• Both with and without liquid in the uppermost chamber • Liquid required for zonula-occludens-1 expression	• Correlated with lipophilicity • Inversely related to molecular weight for hydrophilic drugs • Correlated with primary rabbit tracheal cells and rat lung absorption	[48,49]
Calu-3 Cells	• Mixture of ciliated and secretory cells • Secrete mucin	• Immersed in liquid or at an air-liquid temperature interface • Submerged: shorter, thicker cilia ALI: TEER >300 Ohms*cm^2 for drug transport studies	• Correlated with lipophilicity • Inversely related to molecular weight for hydrophilic drugs • Correlated with primary rabbit tracheal cells and rat lung absorption	[36,48]
Primary airway epithelial cells	• Heterogeneous population • Includes ciliated, secretory, and basal cells • Secrete tissue-specific mucins	Culture on Trans well®- • Formed cilia and released mucous following 6 weeks at ALI. • MPT used for particle diffusion analysis in mucus • More storage space and flexible moduli with higher mucus solid weight percentage	• Dependency on partition coefficient • Higher PAPP values for lipophilic compared to hydrophilic compounds	[47,48]
Normal human bronchial epithelial cells	• Cultured at ALI for 6 days • Expressed MUC5AC mRNA and protein	NA	• Dependency on partition coefficient • Higher PAPP values for lipophilic compared to hydrophilic compounds	[48]
Caco-2 cell line	• Produces membrane-bound mucins (MUC1) • Does not produce secreted mucins (MUC2, MUC5AC	• Mucus-containing cultures can be compared with cultures lack of cells producing mucus • Drugs that induce mucus secretion enable comparison of the effects of various mucus concentrations • From cultures that produce mucus, the mucus layer can be eliminated chemically • To a culture without mucus-producing cells, pure mucin can be added	• Mucus thickness in Caco-2/HT29-MTX planted at a 3:1 ratio was about 4 μm. • The produced mucus in these *in vitro* cell cultures is significantly thinner than the mucus layers on animal and human colonic explants	[36,51]
Primary epithelial cells	• Produce mucin proteins, the main components of mucus • Mucins hydrate upon release, forming a gel-like protective layer.	• Primary monolayers have not been thoroughly studied in terms of differentiation state or their effect on drug or particle diffusion due to the small number of studies conducted on them too far.	• Thickness of mucus in ileal and rectal monolayers was roughly 26 and 36 μm. This has more thickness than mucus. • Cell lines (less than 10 μm) yet thinner than *in vivo* mucus layers (between 200 and 700 μm).	[36]

however, *ex vivo* and *in vivo* studies of the mucus layer on actual tissue better capture the composition, thickness, architecture, and dynamic nature of the native mucosal environment, but purified mucin, *in vitro* cell cultures, and native collected mucus can all significantly improve the role of mucus in drug delivery. The respiratory tract (e.g., by inhalation or intranasal/intratracheal administration), vaginal tract (e.g., by intravaginal administration), or GIT (e.g., by oral administration, gastric gavage, injection into ileal loops, or intestinal perfusion) can all receive drugs and drug delivery systems before *ex vivo* or *in vivo* analysis. Research can be conducted both *in vivo* and *ex vivo* on tissue from different anatomical sites to examine site-specific drug diffusion and penetration through mucus and underlying epithelium. However, both *in vivo* and *ex vivo* research is limited by tissue availability, and animal-to-animal variability may arise [47].

CONCLUSION

Mucoadhesive drug delivery systems hold promise for enhancing the effectiveness of medications, particularly when those medications need to target specific body parts like the lining of the mouth, nose, or stomach. By using specific polymers that adhere to the body's wet surfaces, these systems assist the medicine to remain in place longer and improve absorption. We can better understand how these systems function and what influences their propensity to stick by considering several hypotheses, such as how molecules spread and interact. The type of material, the acidity (pH), and the surrounding environment all affect how effectively they adhere. New methods for developing these systems have produced a variety of forms, such as films, gels, and patches, which improve therapeutic efficacy and patient convenience. Scientists can now more accurately forecast how these devices will function in the real world because to advancements in testing techniques. Researchers are creating even better materials and designs as the area expands to increase the effectiveness and adaptability of these systems. Mucoadhesive drug delivery is expected to become a crucial medical tool in the future, enhancing medication efficacy and patient outcomes.

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