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Multiparticulate Drug Delivery Platforms for Anti-Inflammatory Therapeutics: Harnessing Lipid Nanoformulations and Protective Coatings to Mitigate Gastrointestinal Burden

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Abstract

Chronic inflammatory musculoskeletal diseases are a large and increasing global burden and pharmacological treatment is largely based on anti-inflammatory drugs, many of which have a basic gastrointestinal side effect that limits their long-term use. Non-selective NSAIDs cause injury to gastrointestinal mucosa by suppressing prostaglandins, uncoupling mitochondria and oxidative phosphorylation, disrupting tight junctions and causing direct injury to the epithelial surface by topically administered acid drugs, and anthraquinone derivatives (such as diacerein) cause dose-dependent diarrhea that may be related to reduced absorption in the upper gastrointestinal tract and hydrolysis of unabsorbed drug in the colon to glucuronolactone, a laxative metabolite. The current review focuses on the scientific rationale, principles of formulation, and translation evidence for an integrated oral delivery platform based on lipid-based nanoformulations (classified by the Lipid Formulation Classification System) and multiparticulate pellet architectures and enteric polymer protection. Lipid nanocarriers, solidification strategies (mesoporous carriers, extrusion spheronization), their mechanisms to enhance drug solubilization, to promote lymphatic transport, and to reduce free mucosal drug exposure are critically evaluated. The science of enteric coating polymers, plasticizer-lipid incompatibilities and sub-coating requirements are discussed in relation to the physicochemical stability data. Preclinical pharmacokinetic data shows that there are meaningful improvements in bioavailability with a corresponding decrease in gastrointestinal adverse events. Challenges in formulation and development, lack of validated in vitro-in vivo correlation models and regulatory gaps are highlighted as key translational hurdles, and future trends include microbiota-responsive coatings and co-loaded multiunit systems, 3D printing, and formulation design using machine learning.

Keywords: bioavailability enhancement, enteric coating, gastrointestinal toxicity, lipid-based drug delivery systems, multiparticulate drug delivery, self-nanoemulsifying drug delivery systems

1. Introduction

Chronic inflammatory musculoskeletal diseases are one of the largest and fastest growing sources of global disability. The Global Burden of Disease Study shows that the number of years lived with disability due to osteoarthritis has risen by 114.5% since 1990. Estimates for the number of people with RA, an autoimmune inflammatory polyarthritis that differs in etiology but is similar in functional burden, were 17.6 million in 2020 and had risen by 14.1% over the previous 30 years [1]. As both age and obesity continue to increase in the population, both disease burdens are expected to grow through 2050. Non-steroidal anti-inflammatory drugs (NSAIDs) and related analgesics for suppression of inflammation and pain are among the most extensively prescribed classes of pharmaceuticals in the world, and their gastrointestinal (GI) toxicity profile poses a

significant challenge for chronic use in the management of these conditions [2]. The seemingly paradoxical nature of anti-inflammatory pharmacotherapy for long-term MSDs is well recognised: the most commonly used medications to treat long-term MSDs are a primary risk factor for clinically important upper gastrointestinal damage [3]. Endoscopic surveys have regularly reported mucosal erosions, ulceration and subepithelial haemorrhage in up to 70% of long term NSAID use, which very few people (less than 10%) report as dyspeptic symptoms. Peptic ulcers have been found in 15–40% of people taking NSAIDs and major complications such as bleeding and perforation are about five times more common in NSAID users than in nonusers [4]. However, the GI burden of these agents is not entirely pharmacodynamic the gastric insult caused by the low pH of lipophilic drug molecules at the gastric epithelial surface is a formulation-dependent effect, and it can be effectively mitigated by the appropriate formulation design [5].

There are two converging pharmaceutical strategies that provide a scientifically coherent way forward. Lipid based nanoformulations such as self-nanoemulsifying drug delivery systems (SNEDDS), solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are developed to overcome the solubility and bioavailability issues that are faced by many anti-inflammatory drugs of BCS class II and IV (in which poor aqueous solubility, rather than permeability, is the rate limiting step for absorption) [6]. These systems take advantage of the pathways of lipid digestion in the intestine and/or lymphatic transport to increase the absorption of the drug, while decreasing the concentration of the free, undissolved form of the drug at the gastric mucosa [7]. Multiparticulate dosage platforms such as pellets, granules, mini-tablets, provide distribution of drug release over a large mucosal surface area, lower concentration of the drug at any given location in the stomach and pass through the stomach with predictable gastric emptying rates irrespective of the food consumed [8]. Combined, that is, if the lipid-loaded pellets are additionally coated with enteric polymers, the resulting dosage form solves the problem of GI safety from three perspectives: at a nanoscale level by solubilizing the lipid, at a microscale level by controlling the dose release and at a macroscale level by ensuring pH-triggered gastric bypass [9]. This review aims to discuss the scientific foundation, working mechanisms, preclinical and clinical data and translation issues of this combined platform for anti-inflammatory drug delivery. The discussion moves from the molecular mechanisms that cause GI injury and the classification and mechanistic features of the lipid nanoformulations, to the design and solidification of the pellet based architectures, the polymer science of enteric protection and the regulatory considerations and future directions that will determine the success of this convergent platform in the clinic.

2. Gastrointestinal Toxicity of Anti-Inflammatory Drugs: Pathophysiology and the Therapeutic Dilemma

The molecular structure of these conventional NSAIDs is both lipid soluble and a weak acid with pKa values usually between 3 and 5 and is responsible for both anti-inflammatory activity and their ability to damage gastrointestinal mucosa via both COX-dependent and COX-independent mechanisms. The more well known is the COX-dependent pathway, where COX-1, which is constitutively expressed in the gastric epithelium, is responsible for the synthesis of prostaglandins E2 and I2, which maintain mucosal blood flow, stimulate mucus and bicarbonate secretion and maintain epithelial proliferation [10]. Non-selective NSAIDs inhibit the action of COX-1, which decreases the production of these cytoprotective prostaglandins leaving the mucosa exposed to the injury effects of acid and pepsin. Experimental studies in rats have shown that subulcerogenic doses of selective COX-1 inhibitors reduces mucosal prostaglandin E2 levels, stimulate gastric motility and increase mucosal permeability, and that the ulcerogenic phenotype requires concomitant COX-2 inhibition to produce macroscopic ulcers, indicating that prostaglandins derived from COX-2 were able to partially compensate for COX-1 inhibition under physiological stress [11]. The COX-independent mechanism is mechanistically different and formulation relevant and is mainly located in the small intestine. By virtue of their acidic physicochemical structure, conventional NSAIDs bind directly to the mitochondrial membrane phospholipids and uncouple the process of oxidative phosphorylation and dissipate the inner mitochondrial transmembrane

potential in the intestinal enterocytes. This uncoupling results in loss of intracellular ATP, release of calcium from the mitochondrial matrix, production of reactive oxygen species such as superoxide anion and hydrogen peroxide, and finally, loss of integrity of tight junction proteins that regulate epithelial permeability [12]. The pattern of small intestinal erosions and ulcerations that video capsule endoscopy studies have consistently shown in chronic NSAID users is explained by the three-step hypothesis of NSAID enteropathy: mitochondrial uncoupling, tight junction disruption, and exposure of the permeable mucosa to luminal aggressors, such as bile acids, proteolytic enzymes, and commensal bacteria. Importantly, this small intestinal injury is not pH-dependent and does not prevent by co-administration of proton pump inhibitors, making it mechanistically different from the gastric injury component [13].

The ion-trapping phenomenon gives another level of topical injury. In the acidic stomach the molecules of acidic NSAIDs are unionized and pass easily across the apical membrane of gastric epithelial cells into the neutral intracellular space, where they are ionized and concentrated, resulting in a greater concentration of drug in the cell than would be predicted by plasma concentrations [14]. How much of this topical injury would occur is directly related to the molecular pKa and lipophilicity of the NSAID so formulation interventions that can ensure drug delivery in a dissolved, lipid associated form, that would not require direct contact with the mucosa as the free acid, have a true pharmacological basis for reducing mucosal damage beyond the simple gastric transit bypass [15]. Diacerein, which is a BCS Class II anthraquinone derivative with an aqueous solubility of ~7-10 µg/mL and a log P of ~2.4, has a different mechanism of GI injury. Diacerein does not inhibit prostaglandin synthesis and thus does not cause COX-mediated mucosal damage, unlike NSAIDs. It is known to cause some adverse effects in the gastrointestinal tract, mostly due to the fact that it is incompletely absorbed in the upper gastrointestinal tract where it is hydrolysed in the colon by acid- and base-catalysis to anthraquinone metabolites, notably Rhein, which has a laxative effect. In clinical trials, 37-42% of diacerein-treated patients developed diarrhoea; for this reason, in 2014 the Pharmacovigilance and Risk Assessment Committee of the European Medicines Agency (EMA) recommended restrictions of the use of diacerein; this recommendation includes that patients should be advised that they may experience diarrhoea while taking diacerein, and the elderly (over 65 years of age) should not be treated with diacerein because they are more likely to have problems with diarrhoea [16]. The mechanistic connection between poor bioavailability and GI toxicity is straightforward any formulation strategy that increases absorption in the upper GI tract decreases the amount available for colonic hydrolysis and provides a better therapeutic outcome with less dose-related anthraquinone laxative burden. This association puts advanced solubilization by using lipid-based nanoformulation ahead not as an afterthought, but as a safety requirement and is summarized across drug classes in Table 1 [17].

Table 1: Gastrointestinal Adverse Event Profiles of Representative Anti-Inflammatory Drug Classes: Mechanistic Basis, Incidence Data, and Formulation-Level Mitigation Approaches [18,19]**.**

Drug Class	Representative Agents	Primary GI Injury Mechanism	Reported GI Adverse Event Incidence	Formulation-Level Mitigation Strategy
Non-selective NSAIDs	Ibuprofen, naproxen, indomethacin, diclofenac	COX-1 inhibition → prostaglandin depletion; mitochondrial uncoupling → tight junction disruption; ion	Peptic ulcer prevalence: 15–40% in endoscopic surveys; GI bleeding/perforation risk 2–6-fold above nonusers; GI symptoms in ~33% during 3-month therapy	Enteric coating; lipid-based systems to eliminate free acid mucosal contact; multiparticulate distribution to reduce local mucosal concentration

		trapping in gastric epithelium		
Selective COX-2 inhibitors	Celecoxib, etoricoxib	Selective COX-2 inhibition; no mitochondrial uncoupling; lower topical injury potential	Upper GI complication relative risk 1.9 (vs. nonusers); lower incidence than non-selective NSAIDs but not eliminated	Standard oral dosage forms generally tolerated; enteric formulations occasionally employed in high-risk patients
Anthraquinone derivatives	Diacerein	No COX inhibition; incomplete absorption → colonic hydrolysis to rhein → laxative effect; hepatic adverse events (idiosyncratic)	Diarrhea in 37–42% of clinical trial patients; EMA restriction implemented 2014; hepatic enzyme elevation reported as uncommon	Lipid nanoformulation to maximize upper GI absorption; enteric-coated multiparticulate to delay release to intestinal pH; dose reduction through enhanced solubilization
Conventional DMARDs	Methotrexate, sulfasalazine	Mucosal folate depletion (methotrexate); sulfapyridine-mediated colonic mucosal injury (sulfasalazine)	Nausea and GI intolerance in 10–30% of methotrexate users; GI events contribute to approximately 40% of sulfasalazine discontinuations	Enteric-coated sulfasalazine tablets (established); folate supplementation for methotrexate; modified-release formulations under investigation
Biologic DMARDs (TNF-α inhibitors)	Infliximab, etanercept	Predominantly parenteral; oral GI toxicity limited; reactivation of GI infections reported	GI infections and opportunistic colitis reported; low direct mucosal toxicity	Not primarily a formulation challenge; systemic infection risk management

3. Lipid-Based Nanoformulations: Mechanistic Rationale, Classification, and Relevance to Anti-Inflammatory Drug Delivery

Lipid-based drug delivery systems take advantage of the natural physiological processes of fat digestion in the intestine to transport poorly water-soluble drugs from dosage form into systemic circulation, without first having to be dissolved in the aqueous luminal bulk fluid. The main mechanism is the ability to keep the drug in the dissolved state in a lipid vehicle that is lipolysed in the intestine, by the bile salts and pancreatic lipases, into monoglycerides and free fatty acids that mix spontaneously into the mixed micellar structure. These vehicles are able to keep the drug in molecular solution at concentrations well above the aqueous solubility, and provide the drug to the enterocyte brush border in a molecularly dissolved state instead of in a particulate form that would be dissolution rate limited [20]. The accepted classification of these systems is the Pouton's Lipid Formulation Classification System (LFCS) that was first proposed in 2000, and in 2006, a fourth formulation type was added. Type I formulations are simple oil solutions which need to be dispersed in the gut and are appropriate for highly lipophilic drugs which are soluble in oil, but don't include a surfactant [21].

Type II formulations are made by mixing oils with water-insoluble surfactants (HLB < 12) which self-emulsify with low agitation to create coarse dispersions (droplet diameter > 250nm). The third type of formulations (Type III) includes SEDDS, SMEDDS and SNEDDS, in which the spontaneous emulsification occurs at the time of aqueous dilution and that are characterized by the presence of water soluble surfactants (HLB>12) and cosolvents with a content of 40-80% (Type IIIA) and <20% (Type IIIB), respectively [22]. Type IV systems do not contain oil and rely solely on the use of surfactants and cosolvents, which results in fast drug release with a downside of limited solubilization capability. Of these, SNEDDS, which have droplet size of < 100 nm after spontaneous emulsification, are the most successful types of lipid formulation for drugs with intermediate lipophilicity, with literature indicating optimal performance for drugs showing log P in the range of 2–4 [23].

Self-nanoemulsifying systems (SNES) are preconcentrates of the essential components of an oil-in-water nanoemulsion, which are isotropic and spontaneously form the nanoemulsion upon addition to gastrointestinal fluids, with only the mechanical energy of gut motility. The emulsification creates a great expansion of the interface surface area for drug partitioning and absorption, while the nanosized droplets are small enough to be internalized by the enterocytes through endocytic routes [24]. Apart from the solubilization benefit, SNEDDS formulation using some of the surfactants or cosolvents such as poloxamers, polyoxyethylene sorbitan esters, and cremophor EL have been shown to have an additional bioavailability benefit by inhibiting the P-glycoprotein efflux-pumps located at the apical membrane of the enterocyte. Since early 1990s, solid lipid nanoparticles (SLNs) have been introduced as the first generation of lipid nanoparticles, which are solid lipid matrix consisting of highly purified triglycerides, complex glyceride mixtures or waxes, stabilized by surfactant which usually ranges from 0.5 to 5% w/v and particle size ranges from 40 to 1000nm [25]. Although SLNs offer advantages of drug protection and controlled drug release due to the highly ordered crystalline lattice, they have the drawback that the highly ordered lattice may lead to expulsion of drug during storage due to polymorphic transition of the lipid matrix which also reduces the accommodation space in the lattice. Developed at the end of the 1990s, nanostructured lipid carriers (NLCs) represent another type of second-generation lipid nanoparticles, which overcomes this limitation by mixing solid and liquid lipids, leading to the formation of nanostructured lipid carriers with more defects and higher drug loading capacity, to minimize the crystallization-induced drug expulsion and to create a more controllable drug release profile than SLNs [26].

SLNs and NLCs enable the oral absorption in several complementary pathways. The lipid nanparticles are transcellularly and paracellularly taken up after oral administration and also by M-cells of Peyer's patches that transport them to the mesenteric lymphatics [27]. The thoracic lymph duct system transports to the systemic circulation at the junction between the jugular and left subclavian vein and thus avoids first-pass hepatic metabolism, especially of importance for drugs with high extraction ratios. Some drugs were formulated as SLN suspensions and studies with chylomicron flow-blocking agents have indicated that the lymphatic uptake may account for about 30% of the drug's oral bioavailability [28]. NLCs also allow for chylomicron formation by triggering the enterocyte's endogenous lipid packaging machinery, which allows the drug to associate with the nascent chylomicrons and to be transported to the lymph. The significance of these mechanisms in the delivery of anti-inflammatory drugs is straightforward. Diacerein, with an aqueous solubility of ~7–10 µg/mL, is exactly the type of molecule for which the lipid nanoformulations were developed, that is, a molecule whose aqueous solubility is limited by dissolution rate, moderately lipophilic and requires prior solubilization for meaningful mucosal movement. Celecoxib, indomethacin and aceclofenac have the same BCS Class II profile and have been formulated as lipid nanocarriers with proven bioavailability enhancements in vivo [29].

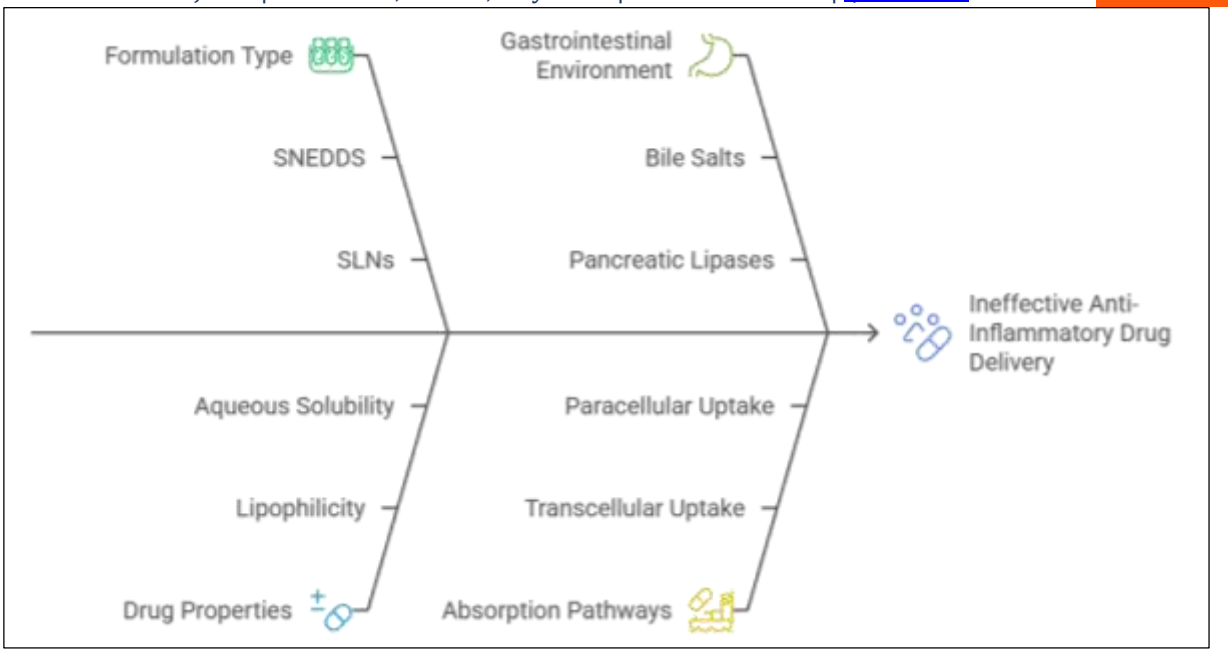

Figure 1: Enhancing Anti-Inflammatory Drug Delivery with Lipid Nanoformulations

4. Multiparticulate Drug Delivery Systems: Architectural Principles and Superiority Over Monolithic Dosage Forms

One of the major differences between multiparticulate dosage forms (pellets, granules, mini-tablets, microspheres) and monolithic tablet and capsule forms is this fundamental architectural principle: the dose is spread over hundreds or thousands of individual small parts, each of which is a small, individual drug reservoir with a unique release profile. This dose-spreading effect is responsible for the pharmacokinetic and safety benefits which make multiparticulate systems attractive for drugs with an established history of GI irritation. If a monolithic tablet does not empty quickly from the stomach or its enteric coating is disrupted too early, the whole dose is delivered in one place and a high local concentration of the drug is present that can cause localized damage to the mucosa [30]. For multiparticulate systems, failure of a coating on an individual unit only takes a small fraction of the drug dose and spreading the drug release over the surface of the GI mucosa helps to prevent concentration of the drug at one point that could cause irritation. Gastric emptying behaviour of pellets is a different mechanism as compared to monolithic tablets. Particles smaller than about 2 mm are transported through the pylorus by the interdigestive migrating motor complex and are not strongly dependent upon the contractile patterns induced by a meal that control the emptying of larger single units. This pharmacokinetic decoupling from fed/fasted state leads to more predictable gastric emptying, less intra- and inter-subject variability and more consistent intestinal drug absorption. The smaller size of enteric-coated pellets also results in faster gastric transit than enteric-coated tablets, which decreases the likelihood of premature release in the acidic gastric compartment, which is important for drugs that must not be exposed to the gastric environment (for drug stability or mucosal safety reasons) [31].

The extrusion-spheronization is the most widely used and largest scale method of preparing the pellets for pharmaceutical formulations, and the typical size is 0.5 - 1.5 mm; however, formulation-specific designs may vary. Sphericity is a very important quality attribute of coating efficiency because highly spherical pellets have a uniform and calculable surface area, allowing for precisely and repeatably coating the surface area of the pellets, batch to batch. The porosity of the pellet matrix (which in turn depends on the content of microcrystalline cellulose and the parameters of the spheronisation process) affects the density of the pellets, which in turn affects the sedimentation behaviour in the stomach and the speed with which they pass through the pylorus [32]. The size distribution is also desirable for multiparticulates to be enteric coated, since a variation in the diameter of the pellets will result in a variation in the coating weight per surface area. The development of multiparticulate systems is based on the design logic of IPDAS (Intestinal Protective Drug

Absorption System) technology, which was developed specifically for GI-irritant drugs, and consists of compressed pellets, which rapidly disintegrate in the gastrointestinal tract and spread drug-containing particles throughout the stomach and intestine. The multiparticulate pellet architecture has been shown to be compatible with enteric protection and commercial scalability across marketed MUPS products in other therapeutic classes such as Nexium (esomeprazole), Prevacid SoluTab (lansoprazole) and Antra MUPS (omeprazole), giving the platform translational credibility for anti-inflammatory applications [33].

Multiparticulate systems can also be administered with functional coatings designed to release the drug at the appropriate pH to ensure that the drug is absorbed in the upper small intestine where the absorptive capacity and mucosal tolerance is greater than in the stomach and the drug is not irritant or poorly soluble. The advantage of this architecture is multiplied in the case of lipid-loaded pellets: the multiparticulate format serves as the physical bed on which the lipid nanoformulation is solidified, and the enteric coating over the pellets gives the outermost pH-sensitive protective layer. The outcome is a dosage form where the nanoscale solubilization, microscale dose distribution, and macroscale pH protection work in concert; that is, a three-in-one dosage system, which cannot be achieved by any single-unit formulation [34].

5. Solidification of Lipid Nanoformulations into Multiparticulate Pellet Platforms

The critical technical point of this platform is maintaining SNEDDS or lipid nanoformulation self-emulsification properties from the thermodynamically optimized liquid formulation to the solid multiparticulate dosage form. The liquid nature of SNEDDS offers the benefit of excellent drug solubilisation and fast nanoemulsion formation, but it may also lead to phase separation, oxidative degradation of oils, chemical incompatibility of drug and surfactant during extended storage and most importantly inability to apply a working enteric coating to a liquid fill. Solidification can overcome these restrictions, but each technique has unique compromises in terms of drug loading, physical stability of the pellet, pellet shape, and reconstitution fidelity that must be assessed for the requirements of a given therapeutic [35]. The simplest solidification method is physical adsorption of the liquid SNEDDS to a porous solid carrier to give a free-flowing powder that can be used directly in capsules or further processed by extrusion-spheronization [36]. Mesoporous magnesium aluminometasilicate, commonly sold as Neusilin US2, with its extremely high surface area of ~300 m^2/g, high pore volume of 1.82 ± 0.55cm3/g, and high oil adsorbing capacity of 2.7-3.4mL/g, along with acceptable compressibility for tableting downstream, became the reference carrier for the purpose. In comparison studies, the US2 grade (particle size ~100 µm) shows higher efficiency in oil adsorption than the colloidal silicon dioxide [37]. Comparative studies with SNEDDS powders based on colloidal silicon dioxide reveal that colloidal silicon dioxide-based powders invariably exhibit poorer flowability and agglomeration tendency in the powder bed. The results of direct comparison showed that mesoporous silica grade MS (XDP 3150) could solidify the one unit dose of liquid SNEDDS with a dosage of 300 mg, while the colloidal silicon dioxide and magnesium stearate needed 410 mg and 1600 mg respectively, implying the superior adsorption efficiency of mesoporous inorganic carriers [38].

The lipid loaded pellets are most often obtained by the extrusion-spheronization route, in which Neusilin or mesoporous silica is combined with microcrystalline cellulose (MCC). MCC is still the proven spheronization aid, because of its rheological properties in the wet state, i.e. its ability to bind up water and to disperse it uniformly throughout the wet mass, thereby providing the cohesion to the wet mass for the purpose of extrusion without clogging, and the plasticity for the purpose of spheronizing into smooth dense spheres. But MCC is not unlimited: drug molecules can be directly adsorbed on the fibers of MCC, thereby reducing the amount of drug available for dissolution; pellets made with MCC alone can exhibit long and sometimes incomplete dissolution profiles for poorly soluble drugs. The successful approach for lipid-loaded pellets is to combine Neusilin and MCC both using the adsorptive properties of Neusilin and the spheronisation properties of MCC. When ibuprofen loaded SEDDS were impregnated onto the Neusilin US2/MCC pellet cores by the fluid bed

coater, the level of lipids loaded onto the Neusilin containing pellets was found to be 8-14 times higher than the MCC alone pellets, which indicated the importance of the mesoporous component to have a sufficient level of lipids loading [39].

Alternatively, the fluid bed coating route for solidification may be considered, by which the liquid SNEDDS is sprayed directly onto the pellet cores, either inert ones or drug-loaded, in a fluidized bed processor to produce multiparticulate structures with the SNEDDS as a defined surface layer. This architecture has been shown to significantly decrease drug degradation during storage compared with a single-layer drug-SNEDDS design, in which the drug is in direct contact with the SNEDDS layer, and can be applied to multi-layer SNEDDS pellets (ML-SNEP) design. The multi-layer SNEDDS pellets were found to be stable for a 6 month period, and after this established stability period, the drug integrity of the multi-layer SNEDDS was found to be within ICH acceptance criteria, but the single-layer systems were found to be undergoing continuous degradation following acid-base catalysis at the drug-lipid excipient interface. A third solidification pathway that has manufacturing scale advantages is hot melt extrusion (HME) [40]. Polymers such as Soluplus and Kollidon VA-64 was demonstrated to bind up to 50% w/w of liquid SEDDS and to form amorphous extrudates that in water at 37°C self-emulsify into droplets in the range of 50–300 nm. Continuous manufacturing without use of solvents is one of the advantages of HME, but the thermal stability of the drug and the SNEDDS excipients at the high temperatures used for the extrusion process (110-160°C) should be established before this route is considered. Spray congealing and spray drying are additional possibilities, the former being important if the lipid components are solid at room temperature and can be atomized in the molten form. The major criterion for carrier selection is the reconstitution fidelity which is the ability of the solidified system to reform the nanoemulsion with droplet characteristics similar to the original liquid SNEDDS when it gets in contact with the aqueous media. The post reconstitution droplet size distribution, zeta potential and drug level in the droplet fraction of nanoemulsion should be compared to the liquid reference formulation [41].

Table 2: Solidification Excipients and Techniques Used in SNEDDS/SEDDS-Based Multiparticulate Systems: Comparative Properties, Drug Loading Capacity, and Reconstitution Performance [42,43]**.**

Carrier Excipient / Technique	Type	Surface Area / Key Property	Drug Loading or L-SNEDDS:Carrier Ratio	Reconstitution Droplet Size	Key Limitation	Published Drug Example
Neusilin US2 (mesoporous Mg aluminometasilicate)	Inorganic mesoporous adsorbent	~300 m^2/g; pore vol. 1.82 cm^3/g; oil adsorption 2.7–3.4 mL/g	Optimal 1:1.5 to 1:2	Excellent; nanoemulsion re-formed rapidly	Moderate drug loading for high-dose drugs	Morin hydrate, valsartan, rhubarb anthraquinone
Mesoporous silica MS (XDP 3150) (Syloid variant)	Inorganic mesoporous adsorbent	High surface area; best adsorption efficiency	300 mg carrier per unit dose	Good; sub-100 nm droplets achievable	Limited pH range stability	DHA-loaded SNEDDS
Colloidal silicon dioxide (Aerosil 200)	Amorphous fumed silica	200 m^2/g; hydrophilic surface	410 mg carrier per unit dose	Acceptable but slower reconstitution	Poor flowability; agglomeration in powder bed	Various SNEDDS models

MCC + Neusilin blend (extrusion-spheronization pellets)	Composite pellet matrix	MCC provides spheronization; Neusilin provides adsorption	SEDDS loading 8–14× higher than MCC alone	Maintained after fluid bed SEDDS impregnation	MCC alone insufficient for adequate SEDDS loading	Ibuprofen
Soluplus / Kollidon VA-64 (hot melt extrusion)	Amphiphilic polymer matrix	HME binding capacity up to 50% w/w SEDDS	Up to 50% drug-loaded extrudate	50–300 nm droplets at 37°C	Thermal stability of drug required at 110–160°C	Carvedilol
Fluid bed spray coating onto inert cores (multi-layer design)	Layered pellet architecture	SNEDDS as defined surface layer; drug layer separated by sub-coat	Layer-by-layer; drug loading controlled by spray deposition	Re-emulsification fidelity confirmed after 6 months	More complex manufacturing; sub-coat weight addition	Cinnarizine (ML-SNEP)

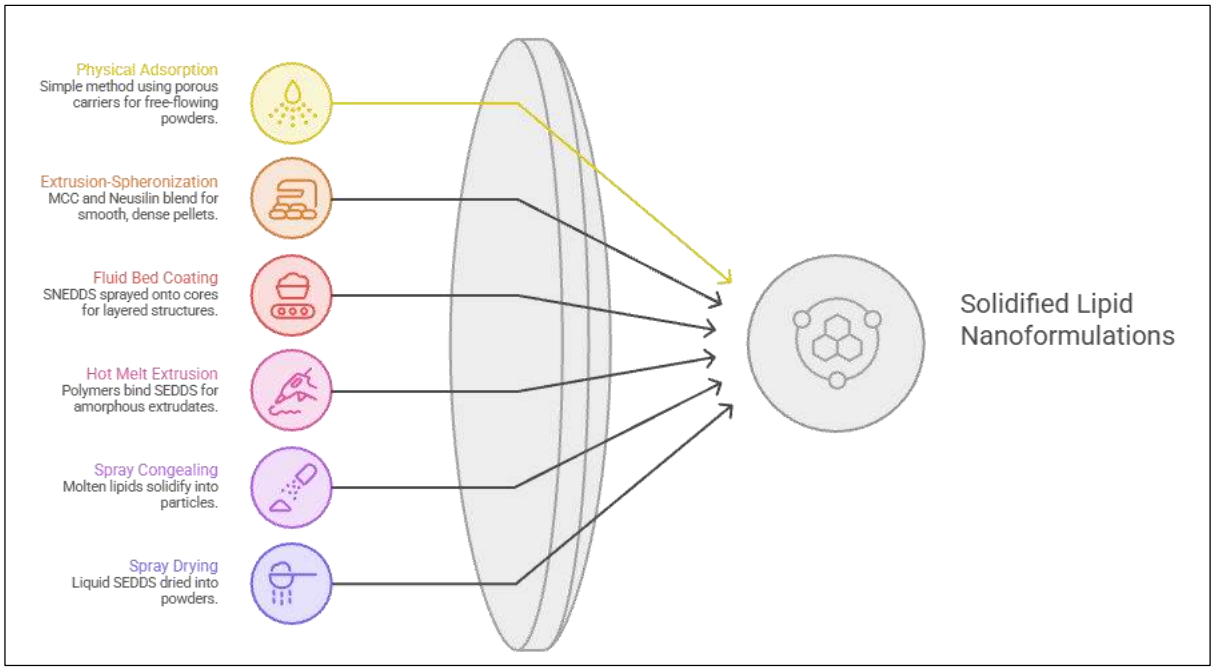

Figure: Pathways to Solidify Nanoformulations

6. Enteric Coating of Lipid-Loaded Pellets: Polymer Science, Functional Design, and GI Protection

Interestingly, the use of an enteric coating on a lipid-filled pellet is also a more challenging process from a mechanistic perspective, as the chemically and mechanically different substrate of lipid excipients forming the core of the SNEDDS or Nanocarrier interacts chemically and mechanistically with enteric polymers and their plasticizers in ways that are not present in simple drug-cellulose matrices. Enteric polymers are the pH sensitive polyanions containing carboxylic or phthalyl functional groups which will remain unionized and water-insoluble at low pH (gastric environment) and get unionized and water soluble at higher pH (proximal small intestine) than the specific pH of the polymer. This pH stimulated solubility switch translates to the very phenomenon of gastric drug release bypass that the platform offers in terms of GI safety. The Eudragit family of methacrylic acid based polymers covers the broadest spectrum of pH levels available from any of the

commercially available enteric polymers. Dispersed in water, Eudragit L30 D-55 is a 1:1 molar ratio of methacrylic acid and ethyl acrylate, which starts to dissolve at pH 5.5 and is by far the most widely used grade for small intestinal targeting; rapid early release is desirable. Eudragit L100 and Eudragit S100 dissolve at pH 6.0 and pH 7.0, respectively, with the latter being useful for lower small intestinal or colonic targeting. The different grades of HPMCAS (LF, MF, and HF) are soluble at pH 5.5, 6.0, and 6.5, respectively, and provide graded upper intestinal release profiles and improved aqueous dispersion film forming properties than HPMCP. Cellulose acetate phthalate (CAP) is soluble at about pH 6.0, but has been found to be somewhat less stable under accelerated stress conditions where the phthalate ester groups have been cleaved after a relatively long storage period, which limits its use to products for which a longer shelf-life is desired [44].

Polymer-lipid incompatibility is the unique technical challenge for enteric coating lipid loaded pellet cores. In solid-state NMR experiments, the Eudragit L30 D-55 coated SEPs, where the pellet core contained Neusilin US2-adsorbed SEDDS comprising propylene glycol (as co-solvent) were analyzed and it was found that regardless of the amount of TEC the standard plasticizer for Eudragit L aqueous dispersions was subject to a phase transition from solid to liquid state in interaction with propylene glycol contained in the underlying SEDDS. This TEC liquefaction caused degradation of the mechanical integrity of the enteric film, leading to premature drug release in acid and other gastrointestinal fluid conditions, and the loss of gastro-resistance during the proposed shelf life. Small lipophilic molecules in the SEDDS formulation were also observed to have a plasticizing effect in a supplementary manner, which is due to the partitioning of these molecules into the polymer bulk during storage. These results provide evidence that this polymer-lipid interaction is not a process-related fault but a characteristic of this type of formulation and thus should be considered for excipient selection. The main engineering solution is to use sub-coating strategies. A hydrophobic barrier sub-coat (practically an ethylcellulose aqueous dispersion like Surelease) is applied between the lipid core and the enteric topcoat thus physically separating the SNEDDS excipients from the enteric polymer and plasticizer. The sub-coat also has a second purpose: it is to prevent migration of the water soluble drug molecules from the pellet core to the aqueous enteric coating dispersion during the coating process, thereby circumventing the problem of the formation of drug-polymer complexes at the coating interface. A HPMC E5 seal coat, preceding the enteric coat, has been reported to fulfil this function in the conventional enteric-coated pellet formulation of NSAID class drugs. Blend coating systems are an alternative to pure polymer films. In addition, it has been found that Eudragit L/HPMCAS blend dispersions have improved coating processability when compared to pure HPMCAS dispersions, which is due to the higher zeta potential of the Eudragit L dispersion (approx. 55 mV) compared to HPMCAS (approx. 10 mV), which results in better colloidal stability of the mixed dispersion and reduces spray nozzle blockages. Pellets coated with Eudragit L/HPMCAS blends have been shown to exhibit greater drug stability following accelerated storage conditions and to provide higher AUC values in beagle dog bioavailability assessment studies than pellets coated with either polymer alone, indicating that a blend approach may benefit both the processing and biopharmaceutical aspects of the enteric multiparticulate design [45].

7. Preclinical and Clinical Evidence: Bioavailability Enhancement and Gastrointestinal Safety Outcomes

The existing preclinical published data on lipid-based nanoformulations of anti-inflammatory drugs cover a broad spectrum of drug classes and carrier types: even though no one study has investigated all three tiers of the platform outlined in this review lipid nanocarrier, solidification on pellets, and enteric coating the published literature contains converging pharmacokinetic and safety data for each tier that substantiate the integrated design. The most pharmacokinetically interesting in vivo data of diacerein are derived from solid lipid nanoparticle studies in rats. The diacerein SLNs prepared by high shear homogenization and ultrasonication using stearic acid, Pluronic F68 and soy lecithin as stabilizers showed up to 88.1% entrapment efficiency and prolonged drug release up to 12 hours in phosphate buffer (pH 5.8). An in vivo rat pharmacokinetic study showed the area under the plasma concentration-time curve (AUC) was increased from 26.68 ± 1.63 to 71.25

± 1.25 hr·µg/mL, representing about 2.7-fold improvement in bioavailability of the drug compared to the unformulated drug. Importantly, the diarrheal side effect of diacerein was shown to be decreased by as much as 37% in the SLN-treated group compared to plain drug suspension, thus giving a quantitative proof of the mechanistic relationship between increased upper GI absorption, decreased colonic rhein formation, and reduced laxative toxicity. This is the most direct published evidence that the formulation-level solubilization of diacerein does not only result in pharmacokinetic gain, but in a measurable decrease in the drug's major GI adverse event. In a follow-up study, it was found that surface functionalization of lipid nanocarriers with chondroitin sulfate to direct anti-inflammatory drug accumulation to the joint reduces systemic GI burden by a factor of 2.8-fold; the drug concentration in the target site for chondroitin sulfate-surface modified diacerein SLNs was 7.8 ± 1.23 µg/mL, compared to 2.9 ± 0.45 µg/mL for the unmodified drug dispersion [46].

In case of celecoxib, SLN formulation with glyceryl monostearate showed relative oral bioavailability of 2.5 fold higher for drug solubilised in lipid matrix as compared to celecoxib reference formulation and statistically significant difference in pharmacokinetic parameters. The in vitro release data of these SLN were best fit with the Weibull model and the data correlated with observed in vivo bioavailability differences, indicating that these SLN systems may be potentially predictable IVIVC for lipid loaded anti-inflammatory formulations with a drug which is fully solubilized in the lipid matrix and not suspended [47]. Among all the NSAID, the lipid SNEDDS and nanoemulsion systems consistently show dissolution improvement in the biorelevant media and pharmacokinetic improvement in animal studies. In the dissolution testing, Ibuprofen SNEDDS containing lemon essential oil, Cremophor RH40 and Transcutol HP demonstrated significantly greater release of the drug than did the ibuprofen suspension, which was consistent with the anticipated increase in drug solubilization in the lumen. In the case of aceclofenac, enteric-coated multiarticulate pellet systems prepared by extrusion-spheronization showed less than 5% drug release in 0.1N HCl within a 2 hour gastric residence period followed by rapid and extensive drug release in 1 hour at pH 6.8, which is ideal for avoiding gastric mucosal exposure while providing rapid and complete drug delivery in the intestine. Preclinical models of the GI safety evidence are not organized systematically like the pharmacokinetic evidence but support the mechanistic premise of the platform [48]. The 37% reduction in the incidence of diarrhoea in rats treated with diacerein SLN is directly related to the increase in drug absorption in the upper GI tract and thus the decrease in the drug delivery to the colon. It is important to note that topical acid injury mechanism is entirely removed from the stomach compartment with NSAID class drugs because of the enteric multiarticulate architecture of the drug that protects it from dissolution in the stomach. Histopathological endpoints for comparison of NSAID-induced mucosal damage have been performed in rats treated with conventional tablets vs enteric-coated pellet formulations, showing significantly lower erosion scores and neutrophil infiltration in the latter, where the concentrated drug exposure has been removed from the gastric epithelium. The lack of finished phase III clinical trial data for enteric-coated lipid-loaded pellets of anti-inflammatory drugs is due to the developmental stage of the platform, and most evidence is at a formulation proof-of-concept stage at this point. The FDA approval of celecoxib oral SMEDDS solution for the treatment of acute migraine is the most advanced clinical translation of the self-emulsifying technology for anti-inflammatory drug delivery, and shows that an SEDDS class formulation can provide the desired clinical benefit of a favorable pharmacokinetic profile and GI tolerability in humans that is predicted in the preclinical models [49].

8. Formulation Challenges, Regulatory Considerations, and Industrial Scale-Up

The formulation hurdles associated with enteric-coated lipid multiparticulate systems are compounded by the complexity of the formulation development process at each level and become more complicated as each tier of the platform is added. The thermodynamic instability that is responsible for this high efficacy in the GI absorption is also responsible for the tendency of liquid SNEDDS to precipitate drugs upon dilution with aqueous media, that is, when the lipid vehicle is diluted in the intestinal lumen, drug, which is previously solubilized at a concentration higher than its aqueous solubility, will phase separate out [50]. To manage supersaturation and to prevent precipitation, crystallization inhibitors like hydroxypropyl methylcellulose or

polyvinylpyrrolidone need to be added to the composition, increasing the complexity, and have to be characterized separately for solid-state interactions with the carrier excipient. The same phenomenon is clinically relevant, but analytically challenging: Preclinical IVIVC studies showed that cinnarizine and halofantrine SNEDDS formulations which were prone to rapid drug precipitation during in vitro lipolysis showed similar in vivo bioavailability to formulations with no sign of precipitation, as the precipitate was in the amorphous form, with a high rate of redissolution. This equivalence can make in vitro lipolysis as a predictive IVIVC tool difficult to use for lipid-based formulations; and the lack of in vitro models that are validated and accepted by everyone is one of the most critical gaps in the regulatory science of this platform [51].

The regulations for multiparticulate systems based on solid SNEDDS are under-defined. There is no FDA or EMA product-class-specific guidance for solid self-emulsifying multiparticulates, and these are evaluated within the current frameworks for complex oral modified-release dosage-forms. To demonstrate in vitro–in vivo correlation within a biopharmaceutics framework acceptable to regulatory authorities, validated biorelevant dissolution media and digestion models are needed, which are capable of simulating fasted and fed intestinal environment with appropriate amounts of bile salts and lipases, and which is not available in all laboratories and no standardized protocols exist. Although ICH Q8, Q9, and Q10 guidelines for Quality by Design, risk assessment, and pharmaceutical quality systems offer a general guide on how to approach systematic formulation development, the adoption of these guidelines to lipid multiparticulates needs a certain level of interpretive expertise that is not yet written in regulatory guidance documents [52]. To date, the most practically limiting challenge of the fluidized bed processor is the ability to reproduce the sphericity of the pellets, the uniformity of the coating and performance of SNEDDS reconstitution at manufacturing scale. In the fluid bed operation, coating weight gain uniformity is closely related to the inlet air temperature to the fluid bed, the rate of spray, and the product bed temperature, and slight variations in the process parameters can result in coating thickness variation, which can lead to failure of the acid resistance requirements or to premature release in the intestine. The performance of SNEDDS reconstitution post solidification in terms of droplet size and content of drug in the nanoemulsion fraction is also batch to batch variable due to the moisture content of the pellet matrix during accelerated storage. Process analytical technology (PAT) tools, such as near-infrared spectroscopy to monitor the increase in coating weight gain and dynamic light scattering to monitor reconstitution performance in real time, are being actively developed for these applications, but have not yet been used as a primary control strategy in regulatory submissions. The qualification of the novel mesoporous silicate excipients will introduce another regulatory aspect as Neusilin US2 is GRAS qualified from Fuji Chemical Industries but the direct contact of drug to lipid and use in a multi-unit solid dosage form is a new application, which could lead to extra biocompatibility and/or extractable/leachable evaluations under the ICH M7 and Q3D guideline frameworks, especially when the drug is an anti-inflammatory, and the total drug exposure over the lifetime of the product is high [53].

9. Future Perspectives

Several trends are converging to define the development of enteric-coated lipid-loaded multiparticulate systems for anti-inflammatory drug delivery and will overcome the shortcomings of pH-triggered release alone. A polymer dissolution pH threshold assumes that the luminal pH in the intestines is constant between patients and between different diseases, which is not true in inflammatory bowel diseases, where the pH of the colon is measurably lower than in healthy individuals and varies significantly between patients. To develop a platform for colonic targeting of anti-inflammatory drugs for the treatment of localized inflammatory bowel disease, the next generation of enteric polymers used for this platform will have polysaccharide coatings that are selectively degraded by the enzymes of bacteria present in the colon but not by enzymes located in the upper gut, and these coatings will be independent of the pH of the lumen [54]. Dual-stimuli systems, based on an outer pH-responsive coating and an inner microbiota-responsive coating, are already being developed and

offer a redundancy approach to drug delivery in the colon even in the presence of disease-driven changes in either stimulatory mechanism. In a natural progression of the platform, the therapeutic potential includes co-loaded multiunit architectures where two therapeutics an anti-inflammatory and a mucoprotective compound – are delivered simultaneously from the same capsule using two different populations of pellets with different release profiles. Systemic bioavailability and local mucosal safety are both addressed within a single dosage form: co-encapsulating a COX-inhibiting NSAID with a prostaglandin analog or co-delivering diacerein with a colonic mucus-stimulating agent in separate layers of a pellet formulation. The separation of incompatible therapeutic functions in space within a single multiparticulate capsule is architecturally simple to implement and provides a clear route to translation to a product not possible with tablet co-formulation [55].

The 3-D printing technology, in particular fused deposition modeling using drug loaded filaments followed by enteric topcoat application, is allowing the production of dosage form geometries (fractal toroids, hollow cylinders, and lattice scaffolds) that are only possible with 3-D printing that give surface area controlled drug release profiles not attainable with conventional extrusion-spheronization. The printability of the pellet geometry, rather than drug content, allows for patient-specific dose adjustment, a paradigm well suited to personalized medicine, especially in the treatment of chronic anti-inflammatory conditions in elderly patients, where dose flexibility, without the need for reformulation, is a great clinical benefit. Machine learning models constructed from published SNEDDS composition databases are showing to predict the ratio of oils to surfactant to co-solvent which can result in a target droplet size and drug loading, thus decreasing the number of experimental iterations needed for excipient screening at the formulation discovery stage [56]. These AI-supported tools have the potential to accelerate the development path for new lipid-based anti-inflammatory drugs from bench to IND when combined with physiologically based pharmacokinetic modeling. An additional application for AI is in enteric polymer selection where the compatibility of a specific SNEDDS excipient matrix with the candidate coating polymers can be predicted from their physico-chemical descriptors in a systematic manner, thus reducing the current empirical process of trial and error for sub-coat and topcoat polymer selection within the development of a lipid multiparticulate. In the more distant future, the potential for combining this delivery platform with new and developing biologics and disease-modifying anti-inflammatory drugs is exciting. The lipid multiparticulate framework represents a convenient formulation strategy for small-molecule inhibitors and soluble selective cytokine modulators without altering the structure of the lead compound, which are entering the development pipeline. The precedent set by marketed MUPS products in other therapeutic classes, ranging from proton pump inhibitors to cardiovascular agents, is that multiparticulate enteric pellet systems are commercially viable and have been embraced clinically, thus easing the burden of technology implementation for anti-inflammatory application, which has been comparatively under-served by this dosage form category [57].

Conclusion

These data reviewed here show that gastrointestinal burden of chronic anti-inflammatory pharmacotherapy is not inherent to drug pharmacology but formulation-dependent and suggests a formulation-level solution. A three-tiered delivery system is accomplished by combining the science of lipid nanoformulation with the science of multiparticulate pellets and the science of enteric polymer protection; at the nanoscale, the free undissolved acid species that cause topical mucosal injury and colonic metabolite accumulation are eliminated, at the microscale, the dose is distributed across hundreds of independent pellets to prevent localized mucosal drug concentrations that drive erosive damage, and at the macroscale, the enteric polymer protection removes the gastric compartment from the drug's exposure altogether. The key to pharmacotechnical insight given by this platform is that these three mechanisms work synergistically, and that no one-unit dosage form can duplicate the effect of these three mechanisms. The most direct quantitative evidence for diacerein SLNs comes from preclinical pharmacokinetic data where 2.7-fold improvement in bioavailability and 37% reduction in the incidence of diarrheal incidences is observed, thus confirming that absorption enhancement and safety enhancement are not just parallel phenomena, but are causally related through the same mechanistic

pathway. The field now needs most of all the science that will make bench performance into regulatory acceptability, rather than additional proof of concept. The three most significant areas where the science has not yet caught up to what the clinic needs are: validated biorelevant in vitro lipolysis models that can provide a good in vitro-in vivo correlation for multi-component solid SNEDDS systems; regulatory guidance for enteric-coated lipid multiparticulate dosage forms; and comprehensive process analytical technology frameworks for monitoring reconstitution fidelity and coating uniformity at the manufacturing scale. For the next generation of formulation scientists, translating enteric-coated lipid multiparticulates for anti-inflammatory drugs is no longer a dream, but a tangible development objective, whose success will hinge on both precision and ambition in the field.

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