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Drygels – A promising porous solid state carriers as a Novel Pharmaceutical Dosage Form

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Abstract

Traditional gel-based dosage forms, such as hydrogels and organogels, have been utilized extensively in topical and semi-solid pharmaceutical formulations. Nevertheless, constraints include inadequate compatibility with hydrophobic active pharmaceutical ingredients (APIs), vulnerability to microbial contamination, restricted shelf life, and insufficient mechanical stability have prompted the advancement of alternate delivery strategies. Drygels, which include aerogels, xerogels, and cryogels, represent a promising category of porous solid-state carriers derived from gel precursors via controlled drying or freeze-processing methods.These characteristics facilitate the effective loading of hydrophobic pharmaceuticals in an amorphous form, markedly enhancing water solubility and oral bioavailability. Prominent production techniques encompass supercritical CO_2 drying, freeze-drying, and ambient-pressure evaporative drying, each yielding unique structural attributes. Drygels exhibit extensive applicability in oral, transdermal, pulmonary, nasal, and implantable drug delivery systems, as well as biosensing. Drygels constitute a revolutionary platform in pharmaceutical formulation, providing improved performance and versatility. This review rigorously analyzes their composition, manufacturing techniques, gelation mechanisms and stability properties.

Keywords: Drygels, Aerogels, Organogels, Xerogels, Cryogels, Controlled drug release , Supercritical CO2 drying.

1. Introduction

The global pharmaceutical formulation landscape has predominantly featured various dosage forms, as well as semi-solid systems like gels, creams, and ointments. Among semisolid dosage forms Gels hold a significant role among semi-solid formulations due to their simplicity of application, patient adherence, and adaptability in integrating various active pharmaceutical ingredients (APIs) [1].

Hydrogels and organogels, despite their clinical utility, face inherent formulation barriers. The hydrophilic networks of hydrogels are poorly suited to the nearly 40% of marketed small-molecule drugs that fall under BCS Classes II or IV [2]. This resulting in limited drug loading, premature release, uneven dispersion, and microbial stability concerns in water-rich matrices. Organogels address the lipophilicity gap but introduce their own liabilities, including oxidative degradation, an undesirable oily skin feel, regulatory scrutiny over non-biocompatible excipients, and poor thermal stability[3].

These combined limitations have driven interest toward drygels, a solid-state class comprising aerogels, xerogels, and cryogels formed by removing the liquid phase from gel precursors through distinct physicochemical processes. The resulting structures retain or enhance mechanical integrity while acquiring a highly porous, three-dimensional architecture[4], [5]. Importantly, it is not merely shorthand for a dried gel; the transformation confers distinct physicochemical properties, including nanoporosity, ultra-high surface area, low bulk density, and tunable surface chemistry, that set drygels apart from their parent materials[6].

The purpose of this review is to provide a cohesive pharmacological framework for the ever-changing scientific knowledge of drygels. Using process-structure-property relationships as a lens, it analyzes preparation methodologies, classifies drygels in comparison to conventional gels and jellies, discusses the diversity of their composition and the functionality of excipients, explains the mechanisms of gelification and structural formation, and evaluates their applications across various drug delivery paradigms.

2. History and characteristics of dry gels

A drygel can be defined as a porous three-dimensional solid or quasi-solid network material obtained from a gel precursor through the controlled elimination of the liquid phase, maintaining the integrity of the three-dimensional polymeric or inorganic network architecture with minimal structural collapse[7]. The distinguishing characteristics of drygels, in contrast to mere dried powders or amorphous glassy matrices, encompass the preservation of an interconnected porous microarchitecture, a significant ratio of internal surface area to bulk volume, and physicochemical properties largely dictated by the characteristics of the initial gel and the drying method utilized [8].

Aerogels have been used in pharmaceutical research for some time now. In the early 2000s, Smirnova et al., showed that silica aerogels, which have a mesoporous structure, could significantly increase the dissolution rates of medications that were not very water-soluble when adsorbed onto them [9]. Research on organic cryogels, oral, transdermal, pulmonary, nasal, and implantable drug delivery systems, as well as polysaccharide-based bio-aerogels, has grown at an exponential rate in the last several decades [10], [11]. Using supercritical CO_2 drying to characterize aerogel-drug interactions and set production parameters has been incredibly impactful [12], [13].

Drygels are often categorized according to the method used to remove the liquid phase. This is the most important variable since it determines the mechanical characteristics, surface area, density, and distribution of pore sizes in the final product [14].

- Aerogels
- Xerogels
- cryogels

Aerogels: Aerogels are synthesized using supercritical fluid drying (SFD), predominantly utilizing supercritical CO_2 (sc-CO_2), which eliminates the liquid phase without subjecting the material to surface tension forces at liquid–vapor interfaces. [15].

Xerogels: Xerogels are produced by standard ambient-pressure drying of a gel, generally via evaporation at room or slightly increased temperatures. [16], [17].

Cryogels: Cryogels are produced by initiating the crosslinking or gelation of a polymer solution at sub-zero temperatures, typically between −10°C and −30°C. [18], [19]

A subsequent subclassification based on material composition differentiates inorganic drygels , organic biopolymer-based drygels ,synthetic polymer drygels and hybrid organic–inorganic composite systems [20].

3. Comparision of conventional gels and dry gels

Traditionally, hydrogels and jellies have been used in pharmaceutical applications, but their high free-water content often exceeding 90% by mass makes them prone to hydrolytic drug instability, microbial growth, and limited shelf life [21], [22]. In contrast, drygels are increasingly favored today: removal of the liquid phase yields non-aqueous, dimensionally stable solids with high internal surface area that can adsorb drugs directly into their pore network, offering superior stability and formulation flexibility. Table 1 presents a systematic comparative analysis.

Table 1: Comparative Overview of Gels, Jellies, and Drygels

Parameter	Gels	Jellies	Drygels
Physical State	Semi-solid (liquid-like with elastic behaviour)	Semi-solid, firm, transparent	Solid, dry, porous structure
Water Content	70–99% (hydrogels)	65–90%	<5% (essentially anhydrous)
Drug Compatibility	Primarily hydrophilic drugs; poor for BCS II/IV	Mainly hydrophilic; some amphiphilic drugs	Both hydrophilic and hydrophobic (BCS II/IV) drugs
Porosity	Low (essentially non-porous)	Very low	Very high: 80–99% (aerogels); 40–80% (xerogels/cryogels)
Specific Surface Area	<10 m^2/g	<5 m^2/g	200–1000 m^2/g (aerogels); 50–500 m^2/g (xerogels)
Density	~1.0 g/cm^3 (aqueous gels)	~1.0–1.2 g/cm^3	0.005–0.50 g/cm^3
Microbial Stability	Poor; requires preservatives	Poor; often contains preservatives	Excellent; essentially anhydrous environment
Drug Release Profile	Diffusion-controlled; often rapid	Diffusion/erosion controlled	Sustained/controlled; modifiable by pore architecture
Shelf Life	Limited (3–24 months typical)	Limited (12–24 months)	Extended (>2 years possible for aerogels)
Routes of Administration	Topical, transdermal, oral, rectal	Topical, urological, mucosal	Oral, transdermal, pulmonary, nasal, implantable
Preparation Complexity	Moderate	Moderate	High (specialised drying required)
Scale-Up Potential	Good	Good	Developing (sc-CO_2 increasingly feasible at scale)

4. Excipient used in dry gel

The excipient used in dry gels are as follows

- Polymer marix
- Cross liking agent
- Active pharmaceutical ingredients

4.1 Polymer matrix

The physicochemical characteristics of a drygel are mostly dictated by the composition of the polymer or inorganic matrix forming its three-dimensional structure. This matrix functions as the structural framework, the drug-adsorption substrate, and the principal factor influencing drug release kinetics[23].

4.2 Crosslinking Agents

The three-dimensional structure of a drygel is preserved by crosslinks in the polymer network, which can be either covalent or physical [24], [25].

4.3 Active Pharmaceutical Ingredients and Loading Strategies

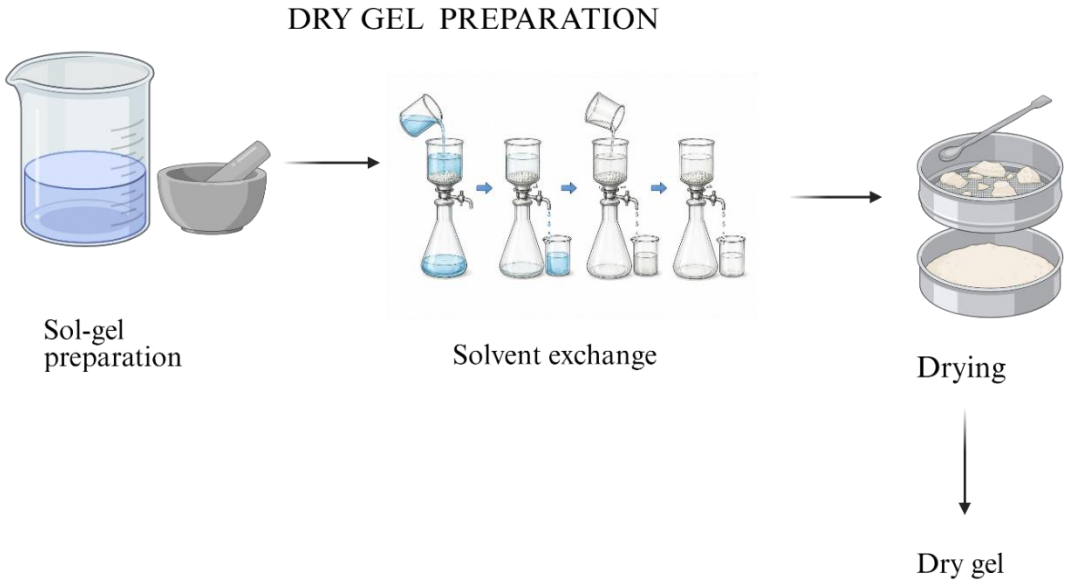
The drug-loading capacity and release profile of a drygel are highly dependent on the physicochemical characteristics of the active pharmaceutical ingredient, especially its molecular size, polarity, and solid-state behavior. Drygels are particularly advantageous for poorly water-soluble pharmaceuticals (BCS Class II/IV), as they can be adsorbed onto the interior surface area of mesopores in an amorphous state, circumventing the dissolving rate-limiting step that restricts the bioavailability of crystalline medications[26].

5. Fabrication method of dry gels

The fabrication of drygels consistently adheres to a three-stage process [27] and it is shown in figure 1.

- Sol gel preparation
- Solvent exchange
- Drying

Figure 1: Fabrication of dry gel



5.1 Sol gel formulation methods

- Inorganic Systems
- Biopolymer Gel Preparation

5.1.1 Inorganic Systems

The sol-gel procedure serves as the fundamental synthesis method for silica-based xerogels and aerogels. A silica precursor, usually TMOS (tetramethoxysilane), undergoes acid- or base-catalyzed hydrolysis in an aqueous-alcoholic environment, producing silanol groups (Si–OH). The silanol groups undergo polycondensation, resulting in the formation of Si–O–Si siloxane linkages that gradually establish the three-dimensional silica network . The resultant silica gel - a translucent, physically robust hydrogel undergoes aging (often 24–72 hours at 40–60°C) to enhance the network via ongoing condensation prior to drying. The ultimate pore size, surface area, and mechanical characteristics of the dried silica matrix are significantly influenced by the precursor molar ratio, catalyst concentration, water-to-precursor ratio (R value), aging circumstances, and the employed drying method[28].

5.1.2 Biopolymer Gel Preparation

In polysaccharide-based drygels, gelation occurs via ionic, thermal, or chemical processes. Alginate gels are typically produced via external ionic gelation, where an alginate solution is extruded through a nozzle, either conventional or coaxial for core-shell configurations, into a $CaCl_2$ bath, resulting in the immediate formation of spherical or capsular gel beads upon contact. Pectin gels develop under acidic circumstances or in the presence of calcium ions. Cellulose necessitates dissolution in specialized solvents (NaOH/urea at low temperatures, or ionic liquids like [BMIM]Cl) before coagulation in water. Chitosan generates gels at high concentrations when the pH is adjusted above its pKa (about 6.2). To prepare cryogel, the polymer solution is either cast or injected into a mold and then subjected to controlled freezing at sub-zero temperatures; the crosslinking reaction predominantly occurs in the non-frozen liquid microphase (NFLMP) surrounding the developing ice crystals [29].

5.2 Solvent Exchange method

The gel network must be treated with a CO_2-miscible organic solvent, such as ethanol, acetone, or isopropanol, before supercritical drying can be performed. This is done in a stepwise gradient exchange process to prevent osmotic shock and the subsequent collapse of the pores . Aerogel structural integrity is directly related to this successive exchange — for instance, 25%, 50%, 75%, 90%, and ultimately 100% ethanol. At the end of the supercritical drying process, the residual solvent content must be brought down to the limits specified by the ICH Q3C guidelines for pharmaceutical applications [30].

5.3 Drying Methods

Methods used for drying are as follows

- Supercritical CO_2 Drying
- Freeze-Drying (Lyophilisation)
- Ambient-Pressure Drying (APD)

5.3.1 Supercritical CO_2 Drying (SFD): A supercritical drying autoclave is then used to deposit the gel, which now contains organic solvent. The circumstances are brought up to a level where the CO_2 critical point (Tc = 31.1°C, Pc = 73.8 bar) is exceeded by pumping in CO_2. There is no capillary force acting on the pore walls due to the displacement and venting of solvent under supercritical circumstances since there is no clear liquid-vapor interface. Aerogels with surface areas ranging from 300 to 1000 m^2/g and porosities close to 95 to 99% are the end product. The nanopore architecture is totally retained. Additional benefits of SFD in pharmaceutical manufacture include the ability to protect API integrity in an oxidation-free environment, simultaneously extract residual solvents, and scale up the process in a way that complies with GMP standards [31].

5.3.2 Freeze-Drying (Lyophilisation): The aqueous gels are usually frozen at temperatures ranging from -40 to -80°C, and then the ice is evaporated through reduced pressure sublimation, which is known as primary drying. Then, the bound water is desorption, which is known as secondary drying. The macroporous architectures of the cryogels and aerogel-like xerogels that are produced by freeze-drying mirror those of the ice crystal templates. Importantly, the size of the ice crystals and, by extension, the distribution of pore diameters, are modulated by the freezing rate and temperature [32]. Pores are smaller and more uniform when frozen quickly (by quench-freezing in liquid nitrogen), whereas anisotropic, large-pore structures are produced by slow directional freezing. Because of its well-established GMP compliance, scalability, and API compatibility, freeze-drying finds extensive use in pharmaceutical manufacturing.

5.3.3 Ambient-Pressure Drying (APD): The most basic drying method is permitting the gel to evaporate its solvent at normal temperature or slightly increased temperatures under atmospheric pressure. Although industrially simple and economical, APD consistently results in significant pore network collapse due to capillary forces at the retreating solvent–vapor boundary, producing dense xerogels. Modifying the gel pore walls with hydrophobic chemicals (e.g., trimethylsilylation) before ambient pressure drying (APD) might alleviate collapse by decreasing surface energy and capillary pressure, facilitating the creation of 'spring-back' aerogel-like xerogels by APD [33].

6. Drygels drug release mechanism

There are three types of gelling mechanism includes:

- Gelation in Biopolymer Systems
- Cryogelation Mechanism
- Gel-sol condensation

6.1 Gelation in Biopolymer Systems

The gelation mechanism is the process via which a polymer solution converts from a viscous sol to an elastic, three-dimensional gel network is the fundamental event that occurs prior to drygel formation. [34]. Alginate gels through calcium coordination with guluronate (G-blocks) on adjacent chains, forming 'egg-box' junction zones. Progressive G-block binding raises viscosity until an elastic network forms, governed

by alginate concentration, M/G ratio, calcium concentration, and temperature [35]. In contrast, κ-carrageenan and gelatin gel via a coil-to-helix shift upon cooling [36].

6.2 Cryogelation Mechanism

Cryogelation involves crosslinking within the non-frozen liquid microphase (NFLMP) at sub-zero temperatures. Growing ice crystals concentrate polymer and crosslinker in the residual liquid, accelerating chemical or physical crosslinking. Subsequent freeze-drying sublimates the ice, leaving interconnected macropores mirroring the original crystal geometry giving cryogels their signature supermacroporous structure (10–200 µm) without any sacrificial template.[37].

6.3 Gel sol condensation

The wet-to-dry gel transformation involves structural reorganization dictated by the drying mechanism. Supercritical drying eliminates the liquid–vapor interface, avoiding the capillary stress ($\sigma = 2\gamma\cos\theta/r$) that otherwise collapses pore walls, so the network retains its native structure as an aerogel with nanoscale pores (2–50 nm) and open, interconnected porosity. Freeze-drying instead generates macropores (0.1–200 µm) reflecting ice crystal size, while ambient-pressure drying exposes the network to full capillary stress, causing a 10–100-fold reduction in pore volume and surface area in xerogels [38].

7. Drygels - Pharmaceutical Applications

Drygels have wide application in pharmaceutical healthcare like oral ,transdermal, pulmonary, Nasal, implants ,wound healings and it was shown in figure 2

7.1 Oral Drug Delivery of drygels

Drygels improve oral bioavailability primarily by converting crystalline drugs into an amorphous state within nanoscale mesopores, eliminating the lattice energy barrier that limits dissolution [39]. Nano-confinement below the critical nucleus radius further blocks recrystallization, stabilizing the amorphous form without heavy polymer loading [40]. Foundational research by Smirnova and associates revealed that supercritical impregnation of ibuprofen, miconazole, dithranol, and flurbiprofen into silica aerogels far exceeded the dissolution rates of crystalline drug or physical mixtures [41]. Dry gels in oral delivery system shows various advances in controlled ,sustained ,colonic and targeted systems. The ability of drygels to regulate medication release over prolonged durations, ranging from hours to weeks has been thoroughly established. [42] [43]. This compositional method for bimodal or pH-triggered release constitutes a persuasive technique that traditional gel dosage forms cannot emulate. The gastrointestinal tract serves as a compelling target for localized therapeutic delivery, especially to the colon for addressing inflammatory bowel disease, colorectal cancer, and colonic infections. Eudragit S100-coated starch aerogels were shown to endure stomach and small intestine pH environments while releasing the medicine selectively upon contact with colonic bacterial enzymes.[12].

The incorporation of stimuli-responsive elements into drygel networks has facilitated tailored medication delivery. pH-sensitive cryogels containing carboxylated monomers (e.g., methacrylic acid, carboxymethyl cellulose) exhibit preferential swelling in alkaline conditions, facilitating pH-triggered drug release aimed at intestinal regions or tumor microenvironments with inherently lower pH levels [44]. Cryogels

synthesized under mild sub-zero conditions, devoid of organic solvents or elevated temperatures, are exceptionally conducive to protein encapsulation. Santos et al. shown that trypsin inhibitor may be effectively encapsulated in silica xerogels using sol-gel processing at mild pH levels, maintaining enzymatic activity after encapsulation [45].

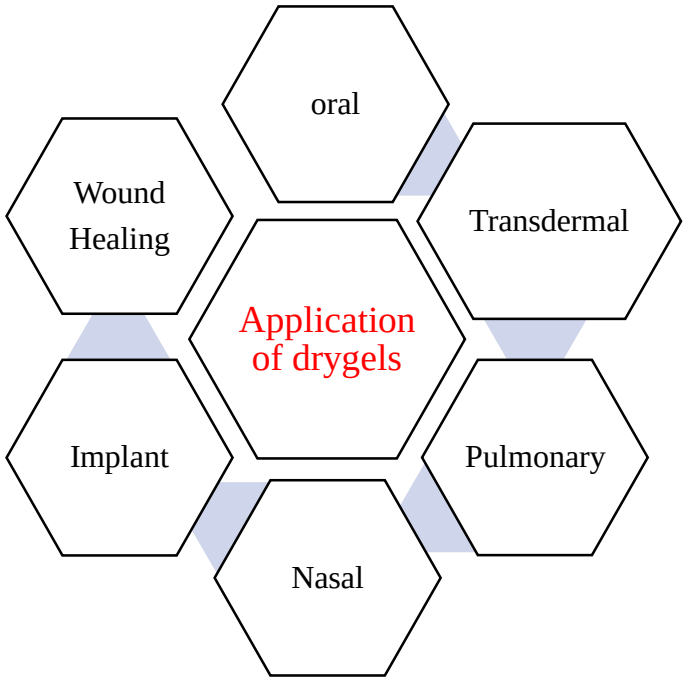
7.2 Transdermal and Topical Drug Delivery

Drygels, especially aerogels quickly absorb transepidermal water and skin surface lipids when applied to skin surfaces, creating a localized hydrogel-like environment that modifies the concentration gradient causing medication penetration. [46].

7.3 Pulmonary Drug Delivery

Aerogels are ideal for pulmonary delivery by dry powder inhalers (DPIs) due to their extremely low density and high porosity, which directly translate into aerodynamic characteristics. Aerogel particles that are designed to have mass median aerodynamic diameters (MMAD) within the therapeutic respirable range of 1-5 µm, which is achieved by controlling the particle size and true particle density appropriately, outperform traditional excipient-dense carrier blends in terms of both deep lung penetration and dispersion from DPI devices [47].

Figure 2: Applications Overview of Drygels in Pharmaceutical Science



7.4 Nasal Drug Delivery

Nasal medication delivery has several appealing properties, such as a quick onset, the ability to bypass the liver's first-pass metabolism, and the ability to reach the central nervous system through the olfactory pathway [48].

7.5 Implantable and Parenteral Drug Delivery

Silica xerogels were initially used in the pharmaceutical industry as implantable matrices for controlled drug release over an extended period of time that might be biodegradable [49].

7.6 Wound Healing property

Drygels, specifically aerogel beads and cryogel sheets exhibit a distinctive amalgamation of substantial exudate absorption capacity, antimicrobial drug loading potential, haemostatic properties, and biodegradability, rendering them exceptionally effective as wound dressings [50].

8. Stability of drygels

The evaluation of stability is a crucial regulatory and scientific necessity for any new pharmaceutical dosage form, and drygels exhibit a different and somewhat unusual stability profile in comparison to traditional gels or solid dosage forms [51].

8.1 Physical Stability: Amorphous Drug Recrystallisation

The thermodynamic instability of the amorphous drug form, encapsulated within drygel pores to improve dissolution, constitutes the primary worry about physical stability. Ibuprofen and naproxen encapsulated in mesoporous silica beneath their monolayer loading capacity (MLC) maintained physical stability for 18 months under ambient conditions. In contrast, drug loaded above MLC occupying areas beyond the stabilizing surface monolayer and pore confinement recrystallized under dry storage conditions and consistently recrystallized under humid storage (40°C/75% RH), irrespective of loading level [52].

8.2 Structural Stability of the Pore Network

The porous structure of drygels, especially aerogels, is prone to partial collapse when subjected to extended high humidity, due to capillary condensation of water vapor in mesopores and the resulting destabilizing capillary tensions. This behavior is particularly evident in hydrophilic silica aerogels and carbohydrate-based aerogels, where many surface hydroxyl groups facilitate water adsorption [53].

8.3 Chemical Stability of drygels

The anhydrous conditions of drygels significantly mitigate hydrolytic degradation; however, the chemical stability of the incorporated active pharmaceutical ingredient (API) must still be assessed concerning thermal degradation, oxidation, especially pertinent for lipid-based aerogels or APIs with oxidation-sensitive functional groups and possible interactions between the API and the matrix surface. Drug-matrix interactions, although frequently advantageous for enhancing dissolution, may occasionally induce chemical reactivity via catalytic surface groups or modified solid-state reactivity in the amorphous state [54].

9. Recent Advances and Future Perspectives

Recent advances in drygel pharmaceutical research have been accelerated in formulation development with the application of artificial intelligence (AI) and machine learning (ML). The optimization of core-shell alginate-konjac glucomannan aerogel beads for controlled drug delivery using a neural network-assisted design approach. This method predicted the best formulation parameters with much less experimental effort than traditional Design of Experiments methods [55]. New drygel system formulation

development timeframes could be slashed in half with the use of AI and high-throughput characterization platforms. Personalized drygel dosage forms with exact geometric control, programmable drug release patterns, and patient-specific dose calibration can now be manufactured using additive manufacturing, specifically extrusion-based 3D printing of gel precursors [56] followed by cryodrying [57]. Hybrid drygel systems, which integrate the best structural features of different materials, are becoming more popular in the scientific community [58]. It has wide market potential in future for various pharmaceutical manufacturers.

10. Keytakeaways

Drygels, such as aerogels, xerogels, and cryogels, constitute a sophisticated category of pharmacological carriers that address numerous constraints of traditional gel systems. Their extensive surface area, adjustable porosity, low density, and capacity to maintain poorly water-soluble medicines in an amorphous form facilitate improved drug solubility, bioavailability, and stability. They provide benefits including extended shelf life, enhanced microbiological stability, and adaptability across various drug administration methods. Despite the hurdles associated with large-scale manufacture, regulatory uniformity, and long-term stability, advancements in materials science, continuous manufacturing, and customized medicine are anticipated to expedite their clinical translation. Thus, drygels exhibit considerable potential as advanced pharmaceutical drug delivery systems in the management of various diseases.

11. Conflict of Interest

The authors declare that there is no conflict of interest associated with this review.

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