I'm human

Hygroscopic drugs examples

What are hygroscopic drugs. Hygroscopic drugs examples in pharmacy. Hygroscopic medication. Hygroscopic drugs list.

Highly hygroscopic pharmaceuticals and nutraceuticals are prone to degradation due to moisture absorption. This can lead to changes in their physical properties, affecting their performance and shelf life. Four strategies have been developed to address this issue: (1) film coating, which acts as a barrier between the active ingredient and the environment; (2) encapsulation using spray drying or coacervation, which also provides a protective barrier; (3) co-processing with excipients, which adds moisture-deflecting agents; and (4) crystal engineering through co-crystallization, which alters the crystal structure to make it more stable. While film coating and co-crystallization are commonly used for pharmaceuticals, encapsulation is often employed for nutraceuticals like medicinal herbs and protein hydrolysates. There may be opportunities to improve hygroscopicity reduction by exploring alternative strategies. Note that I've tried to preserve the original meaning and content of the text while rephrasing it in a more concise and natural way. Let me know if you have any further requests! The moisture content of a solid plays a crucial role in determining its water-binding tendencies. The presence of polar chemical groups, such as hydrogen bonding sites, is influenced by factors like surface area, chemical composition, and crystal structure orientation. When exposed to moisture, solids may undergo degradation through hydrolysis, leading to impurities and reduced active amounts. Moreover, the integration of water into a solid's lattice can alter its physicochemical properties, affecting solubility, stability, and bioavailability. Studies have shown that certain crystalline bioactives exhibit changes in their bioavailability when transformed into hydrates. The dissolution rate and bioavailability of certain medications, such as nitrofurantoin, have also been affected by moisture exposure. Moisture can induce phase transitions, lowering glass transition temperatures and acting as a plasticizer in amorphous solids. This can lead to recrystallization of intended amorphous forms back into stable crystalline forms with decreased solubility and bioavailability. Additionally, moisture can cause deliquescence of crystalline bioactives, leading to liquefaction and dissolution. The uptake of moisture by solids also impacts their stability and flow properties, posing challenges in downstream formulation steps such as powder milling, tablet compounding, and powder flowing. Hygroscopic solids may adhere to equipment, causing issues with size reduction and flow. To mitigate these effects, measures like controlling relative humidity and using adsorbents, lubricants, and glidants can be employed. The external environment can cause chemical or physical degradation in drug forms due to factors like light, humidity, air impurities, and mechanical damage. For hygroscopic drugs, packaging is crucial for protecting them from moisture exposure throughout their production to use life [14]. Two key points must be considered when packaging these types of drugs—(1) maintaining controlled humidity conditions to minimize water vapor in the package headspace, and (2) selecting a suitable packaging material that is inert and provides sufficient moisture protection based on its water vapor permeation rate. Materials like polyvinyl chloride (PVC), Aclar, and foil are commonly used [15]. Instead of relying solely on environmental controls, proactive steps can be taken in the formulation stage to prevent or minimize water absorption by highly hygroscopic ingredients. This approach not only reduces dependency on strict condition control but also saves manufacturing costs [16]. Formulation strategies like film coating, encapsulation via spray drying and freeze drying, complex coacervation, co-processing with excipients, and crystal engineering can improve the stability and handling of oral solid dosage forms of highly hygroscopic pharmaceuticals and nutraceuticals. The inclusion of both pharmaceuticals and nutraceuticals in this review is justified given the significant growth potential of nutraceutical research over the last decade [17]. Nutraceuticals cannot replace traditional medicines but can serve as powerful preventive measures or supplementary treatments for certain conditions. Previous reviews on hygroscopicity-related issues have focused on single strategies for pharmaceuticals, such as using excipients, film coating, or crystal engineering. However, a comprehensive review of all hygroscopicity-reduction strategies for both pharmaceuticals and nutraceuticals has not been conducted until now. This present review aims to collate, discuss, and compare various strategies for reducing or controlling the hygroscopicity of solid dosage forms. The focus is on latest findings and trends in the field, with a majority of studies from 2010 onwards. Given that issues like low solubility, poor bioavailability, and polymorphic conversion have plagued pharmaceutical solid dosage form quality, alternative API forms such as ionic liquids (IL) and therapeutic deep eutectic solvents (THEDES) have emerged as solutions offering tailored physicochemical properties but exhibiting hygroscopicity themselves. As these new APIs reach commercialization stage, the demand to control hygroscopicity will intensify. This review categorizes widely practiced formulation strategies into four groups: film coating, encapsulation, co-processing with excipients, and crystal engineering. Relevant studies on these strategies were scrutinized, and their findings discussed in detail. The most common method of forming a moisture-barrier film around the solid dosage core presents advantages such as fast processing, small space utilization, automation potential, better mechanical properties, limited size increase, and ease of customization for specific formulation needs. Coating solutions or suspensions are formed through different methods depending on the polymer type. For organic solvent coating, the polymer is dissolved in the solvent, while aqueous coatings involve dispersing micronized particles into water. The acquired coating is then sprayed onto dosage cores and heated to evaporate solvents and fuse polymers into a continuous film. Moisture sensitivity of pharmaceuticals in storage can be a significant issue due to environmental humidity, leading to degradation [24]. Conversely, water-insoluble polymers such as ethyl cellulose (EC) are used for sustained or controlled drug release by acting as moisture barriers. Entero-soluble polymers like shellac and Eudragit L offer moisture protection and enteric functionalities at neutral and acidic pH levels. However, their solubility may require additional enhancements through excipients or thickness modifications to prevent excessive delays in drug release [24,29]. In addition to polymers, plasticizers and pigments also play key roles in film coating formulations. Plasticizers increase the flexibility of polymer chains, enabling stronger bonds and improved adhesion to tablet surfaces. Pigments fill intermolecular gaps formed during film formation, creating a continuous barrier against moisture. Recent advancements in coating techniques are summarized in Table 1 and discussed in subsequent subsections. Film coating methods to reduce hygroscopicity include aqueous solvent coatings using l-cysteine or citric acid/sodium bicarbonate effervescent tablets with fluid bed processing and poly(vinylpyrrolidone) (PVP) coatings, among others [30-33]. These techniques aim to minimize moisture absorption rates in coated tablets compared to uncoated counterparts. Researchers have developed new tablet formulations to improve their stability and shelf life. In one study, uncoated tablets showed high moisture absorption at 75% relative humidity (RH), while coated tablets with a zein-based coating absorbed significantly less moisture. The addition of specific polymers, such as hydroxypropyl cellulose (HPC) and stearic acid, improved the water vapor permeability of the film. Another formulation was developed using shellac, HPMC, PEG 1500, and PEG 400 to create a protective layer against moisture. This combination offered good protection against moisture absorption compared to core tablets. A third formulation used a sugarless coating with an undercoating made of HPMC and purified water, and a build-up coating made of erythritol, talc, and titanium dioxide. The stability of the actives was confirmed after storage at 40°C/75%RH for six months under closed conditions. In contrast, uncoated tablets showed higher moisture absorption rates compared to coated tablets. However, the sugarless coated tablets had superior stability and hygroscopicity compared to both uncoated and sugar-coated tablets. A fourth study focused on pyridostigmine bromide, where fluid bed coating improved its moisture absorption potential by reducing its hygroscopicity. The formulation maintained its appearance for 30 days in a humid environment. Lastly, a choline alfoscerate-based formulation was developed with an organic solvent coating and an aqueous solvent coating to improve its stability and shelf life. Observations showed that the shellac coating had lower water uptake rates compared to HPMC-coating, especially at high humidity levels. However, this did not directly translate to improved stability of the drug. Interestingly, much lower levels of shellac were needed for similar moisture protection as HPMC-coated tablets. Further studies indicated that solid dispersion powders were highly hygroscopic and absorbed more moisture compared to coated tablets or tablet cores. In contrast, the combination of poly(ester amide) hyperbranched polymer and glimepiride in a solid dispersion showed improved moisture resistance. Moreover, hydrogenated rosin (HR) was incompatible with glycerol (GLY) due to their opposing natures, resulting in brittle films. However, films plasticized with dibutyl sebacate (DBS) had very low water vapor transmission rates, which was comparable to shellac. The addition of hydrophobic excipients like Avicel pH 102 improved the moisture resistance of HPMC-coated tablets but did not eliminate hygroscopicity. Interestingly, hot-melt coating with medium chain triglyceride (MCT) and stearic acid (SA) showed lower moisture permeability compared to other lipids. However, the addition of Eudragit L 30D-55 reduced moisture absorption only in Pr-containing coatings. Lastly, one-step dry-coated tablets (OSDRC) by compression using crystallized compressed amorphous sucrose and hydroxypropyl cellulose (HPC) or poly(vinylpyrrolidone) (PVP) as plasticizers showed superior water vapor adsorption resistance compared to HPMC-coated tablets. Water-soluble polymers have been widely used in the design of aqueous solvent coatings for solid dosage formulations. The hydrophilicity of these polymers can help absorb water quickly and establish a stable environment around the formulation, reducing its susceptibility to moisture. For instance, researchers used poly(vinylpyrrolidone) (PVP) to coat citric acid-containing effervescent tablets, overcoming limitations such as sticking and high hygroscopicity. The PVP coating reduced the hygroscopicity and sticking problem, highlighting the effectiveness of water-soluble polymers in addressing these issues. Other examples include using polyvinyl alcohol (PVA) and sweetener mannitol to protect tablets from moisture and mask their unpleasant taste, as well as introducing Opadry AMB to coat freeze-dried garlic powder. These studies demonstrate that water-soluble polymers can be effective in reducing hygroscopicity and improving the stability of solid dosage formulations. The use of polymeric coatings for moisture protection in pharmaceuticals has been extensively studied compared to other commercial polymers like Opadry AMB and Sepifilm LP 014. A combination of polymers can be used instead of a single polymer, as seen in the coating of ranitidine hydrochloride with Eudragit E PO and Eudragit RLPO, which showed superior moisture protection over its marketed formulation RANTEC 300. However, aqueous solvent coating may not always be less suitable than organic solvent coating for film-coating moisture-sensitive actives. A study on metoprolol tartrate tablets coated with zein using both methods found that the aqueous solvent-based coating had lower water vapor permeability due to its smoother and more densely packed particles. The combination of hydrophilic and hydrophobic polymers can be used to balance moisture protection and drug release profiles. For example, adding polymeric surface-active agent (PSAA) to a mix of hydrophilic HPC and lipophilic SA was found to form micelles, allowing tight junctions between the phases and resulting in a uniform film. The combination of polymers proved to be effective against moisture absorption, as seen in the coating of HPC/SA/PSAA, which exhibited a weight gain of only 3.5% compared to 10% in uncoated tablets after 168 h in 75%RH. Furthermore, the addition of hydrophobic shellac to hydrophilic pectin was found to enhance its moisture-protective ability due to its lower affinity to moisture. Lastly, a plant extract like Herniaria glabra L. can be used as a coating material with diuretic properties, which can enhance the moisture-protective ability of polymeric coatings. Coatings with Hydrophilic and Hydrophobic Polymers Enhance Moisture Protection The use of hydrophilic hydroxypropyl methylcellulose (HPMC) and hydrophobic shellac in coating tablets has been shown to enhance moisture protection. This is evident from the decrease in weight gain of coated tablets at 75% RH, from 16.1% to 5.7%, and at 90% RH, from 18.2% to 7.5%, after around 110 hours. Furthermore, multi-layer coatings have been found to be a plausible alternative to sugar coatings, as they can impart distinct functions such as taste-masking, impact toughness, moisture-barrier, smoothness, and sustained or controlled release properties. The study experimented with cores coated with a thin sugarless coating consisting of several layers made of HPMC and erythritol. The results showed that the multi-layer coating was less hygroscopic than sugar-coated tablets, retaining over 95% of its drug content after 6 months at 40 °C/75% RH. Other studies have also demonstrated the effectiveness of multi-layer coatings in protecting highly hygroscopic drugs such as pyridostigmine bromide and choline alfoscerate. However, it is worth noting that water-insoluble polymers may not necessarily guarantee better drug stability compared to water-soluble polymers. The coating of aspirin tablets with hydrophobic shellac displayed lower water uptake rates than HPMC-coated tablets. The use of coatings in tablet formulation has been a subject of interest due to their ability to enhance stability, reduce hygroscopicity, and improve moisture-barrier properties. HPMC (hydroxypropyl methylcellulose) has shown promise in this area, binding water and making it unavailable for hydrolysis, but lower shellac coating levels are needed for similar effects. Additionally, HPMC phthalate can be used to coat solid dispersions of glimepiride, reducing its hygroscopicity. Hydrogenated rosin with dibutyl sebacate was also effective in coating diclofenac, achieving extremely low water vapor transmission rates. Direct compression is a cost-effective and simpler process compared to film coating methods, which do not require water and are favored for moisture-sensitive bioactives. This method involves mixing external excipients with the core drug pellets, compressing them into tablets using machines like hydraulic presses. For instance, pyridostigmine bromide was coated via direct compression with HPMC mixed with Avicel pH 102 to reduce its hygroscopicity. Hot-melt coating is another solvent-free technique that prepares dry powder coating by applying polymer powders onto the tablets and melting the coating layer. Sennae fructus tablets were successfully coated using this method, showing a remarkable reduction in their hygroscopicity. Sugar-coated tablets have been found to outperform polymer-coated tablets in terms of drug stabilization, ease of swallowing, and protection against hydrolysis and oxidation. Sugar crystals have low water permeability and better taste-masking properties, making them a preferred choice for coating tablets. However, conventional sugar coating requires multiple layers and can be time-consuming, complicated, and dependent on operators' skills. While sugar coating is no longer widely used in the pharmaceutical industry due to its limitations, it remains popular in the food industry for enhancing appearance, taste, texture, and shelf life of processed foods. Using a compression coating technique, the process of coating products with wall materials to protect them from environmental conditions can be achieved. This method is demonstrated in Figure 2. For instance, fructose was coated with amorphous sucrose as an outer layer using one-step dry-coated (OSDRC) tablets manufacturing via direct compression, which allowed for a single step process without the need for prefabricating the core. Interestingly, the amorphous sucrose became crystallized upon compression, blocking water vapor diffusion due to solid crystal formation, resulting in moisture-barrier properties. OSDRC tablets were found to provide greater moisture protection than HPMC tablets [46]. A direct illustration of the compression coating process is shown [49]. Encapsulation is a technique that involves coating products with wall materials to shield them from adverse environmental conditions. This method can be used for pharmaceutical and nutraceutical bioactives to protect their therapeutic functionalities, control release, mask unpleasant taste, increase solubility, and incorporate them into dry systems. Encapsulation may also help reduce hygroscopicity and extend shelf-life. The core of the encapsulated bioactive is the particle structure, which is dispersed in a matrix of wall material. Common encapsulation techniques include spray-drying, freeze-drying, and coacervation [19,51]. Popular wall materials used for encapsulation are polysaccharides such as maltodextrin (MD), chitosan (CS), gum arabic (GA), and alginate (ALG). These materials have structures that confer stability during controlled release, are inexpensive, have low viscosities at high ratios, high solubilities in aqueous solutions, good emulsification ability, and are edible and biodegradable [19,51]. Proteins are less popular but used as well, with some common ones being gelatin (GE), whey protein isolate (WPI) and soy protein isolate (SPI). Proteins present advantages such as nutritional benefits, good solubility, emulsification, and gelation abilities, making them suitable for encapsulation techniques too [19,51]. Spray-drying is the process of converting a liquid solution, emulsion or suspension into dry material via a single step [52]. A simple illustration of the spray-drying process is shown in Figure 3 [53]. Briefly, the dry materials are produced by atomization of the liquid under hot air flow which swiftly removes moisture, creating a solid particulate material that is separated via cyclone and received in a container. The advantages of spray-drying include cost-effectiveness, short processing time, and reduced product weight/volume [19,54]. However, due to elevated temperatures during atomization, heat-sensitive materials may be denatured or degraded [55]. Therefore, wall materials such as MD are often used for the protection of these heat-sensitive materials [56]. An illustration of the spray-drying mechanism is shown (1) atomizer; (2) sprayed droplets; (3) product collector [53]. Recent findings on encapsulation via spray-drying using single or mixed polymers are tabulated [56]. The review focuses on spray-drying materials classified under "single polymer" or "combination of polymers," with most being protein hydrolysates. The technique is compared to various wall materials, including maltodextrin, gum arabic, and starches, in terms of their ability to reduce hygroscopicity. Studies show that encapsulation by spray-drying using single or mixed polymers can significantly decrease the hygroscopicity of powders. For example, casein hydrolysate encapsulated with soy protein isolate (SPI) had a 100% increase in hygroscopicity, while maltodextrin (MD) reduced it to almost half. Other studies found that flaxseed protein hydrolysates and chicken meat protein hydrolysates showed significant reductions in hygroscopicity when encapsulated with MD. In contrast, amaranthus betacyanin pigments exhibited increased hygroscopicity with decreasing molecular weight of the wall materials. The review also explores the effects of various parameters on the physical stability of API-ILs (1-butyl-3-methylimidazolium salts) encapsulated by maltodextrin (MD) or ethyl cellulose (EC). While MD-encapsulated API-ILs showed rapid absorption of water and transformation into a sticky liquid, EC-encapsulated API-ILs remained stable as fine powders. The encapsulation of protein hydrolysates with various wall materials was investigated to improve their stability and bioactive properties. The use of maltodextrin (MD) and β-cyclodextrin (β-CD) significantly reduced the hygroscopicity of whey protein hydrolysate, from 64.31 g/100 g to 43.09 g/100 g for MD-encapsulated and 36.99 g/100 g for MD/β-CD encapsulated hydrolysate. Similar results were observed with casein hydrolysate when encapsulated with gelatin (GE) and soy protein isolate (SPI), showing a decrease in hygroscopicity from 53 g/100 g to 27.23 g/100 g. The use of MD as a wall material for spray-drying also reduced the hygroscopic moisture of purple sweet potato flours, with values ranging from 2.9–3.0 g/kg compared to 3.3 g/kg in control samples. Furthermore, the encapsulation of whey protein hydrolysate and soybean hydrolysates with various wall materials resulted in significant reductions in hygroscopicity. However, interactions between protein core materials and protein wall materials may lead to insufficient protection and loss of bioactive properties. The use of polysaccharides like MD as wall materials appears more plausible due to their low hygroscopicity and ability to increase the glass transition temperature (Tg) of spray-dried powders, contributing to moisture-protection and stability. The use of molecularly dispersed (MD) polymer as an encapsulant for various bioactive compounds has been shown to significantly reduce their hygroscopicity. Studies have found that MD films formed around particles can increase the glass transition temperature (Tg) and decrease the affinity for ambient moisture, resulting in less hygroscopic powders. The molecular weight of wall materials has been identified as a key factor in controlling the moisture-protective property, with higher molecular weights reducing hygroscopicity. Concentrations of MD have also been found to impact the final product, with highest concentrations yielding the least hygroscopic powders. Spray-drying parameters such as inlet air temperature and feed flow can further affect the hygroscopicity of spray-dried powders. However, not all bioactives are suitable for encapsulation with MD, and alternative materials like ethyl cellulose (EC) may offer better moisture-protection in certain cases. The combination of polymers has also been explored as a means to improve the performance of MD-based encapsulants. Li et al. combined MD and β-cyclodextrin to create an effective encapsulant for whey protein hydrolysate. This combination significantly reduced hygroscopicity by increasing Tg. Another study used a combination of GE and SPI to encapsulate casein hydrolysate, resulting in less hygroscopic powders. The use of polysaccharides and proteins was also explored, with MD and α-amylase being used to encapsulate purple sweet potato. The addition of α-amylase increased hygroscopicity due to its higher moisture content. Spray-drying and freeze-drying were compared for their ability to encapsulate bioactives, with spray-drying showing greater effectiveness in reducing hygroscopicity. Microencapsulation by coacervation is another approach that involves phase separation of one or more macromolecules around suspended or emulsified bioactive ingredients. There are two types of coacervation processes: simple and complex. Complex coacervation occurs when oppositely charged polymers form ionic interactions, leading to phase separation and the formation of coacervates. This process is attractive due to its simplicity, lower costs, scalability, and reproducibility. It requires low temperatures for processing, minimizing evaporation losses or degradation of thermal-sensitive actives. Produced via this method are water-insoluble and have exceptional controlled release and heat-resistance characteristics. This makes the method attractive for various applications. Recent advancements in complex coacervation, a technique used to encapsulate bioactives, have gained significant attention. Biopolymers such as proteins and polysaccharides are commonly used in this process. The most popular biopolymer pairs for complex coacervation remain gelatin combined with other polysaccharides like gum arabic, alginate, pectin, and carboxymethylcellulose. Researchers have focused on reducing hygroscopicity by encapsulating bioactives through complex coacervation. The use of soybean protein isolate and chitosan has shown promise in enhancing the stability of capsules. Studies have also explored the use of polyphenols from grape juice extract, aspartame, anthocyanin, and tea extracts. The results show that certain formulations can significantly reduce hygroscopicity, making them suitable for applications where moisture control is essential. The stability of bioactive microcapsules can be improved through various methods such as freeze-drying and complex coacervation. Complex coacervation involves the use of biopolymers to create a film around the core material, which reduces its hygroscopicity. In one study, casein hydrolysate was encapsulated using double emulsion complex coacervation. The resulting microcapsules had lower hygroscopicity compared to free hydrolysate, with the lowest value obtained at the lowest hydrolysate content. As the content increased, so did the hygroscopicity. Another study used mildronate as the core material and found that polymer coatings decreased its hygroscopicity by more than two times after 168 hours at 75% RH. PLA and PS were used as polymers in this study. A probiotic lactobacilli formulation was also investigated, where emulsification and external gelation/crosslinking were employed before freeze-drying. Alginate, shellac, and whey protein isolate were tested as biopolymers, with alginate/whey protein isolate having the highest hygroscopicity. Complex coacervation has been applied to numerous active ingredients to reduce their hygroscopicity. However, it is worth noting that the reduction in hygroscopicity afforded by the coacervate film depends on the water-binding properties of the biopolymers used. For example, microencapsulation of capsanthin via complex coacervation of soy protein isolate and casein yielded products with improved stability in low to medium relative humidity. However, it was not effective against high relative humidity due to the high water-binding capacity of SPI. A separate study on freeze-dried grape juice extract encapsulated by gelatin/alginate had marked reduction in their hygroscopicity compared with unencapsulated extracts. As the amount of GE in GE/i-Car film increased, the water uptake of the extract decreased slightly. The double emulsion complex coacervation process is illustrated in Figure 5, reprinted with permission from Kanha et al. [78]. The reduction of hygroscopicity achieved by this method can be attributed to the lower hygroscopicity of biopolymers used compared to hygroscopic cores. In encapsulating aspartame (AS) with GE/GA, the hygroscopicity of encapsulated AS was not different from free AS due to the higher hygroscopicity of GE and GA than AS [75]. Conversely, encapsulating anthocyanin (ANC) with GE/GA resulted in a notable reduction of ANC's hygroscopicity from 94.06 g/100 g to 37.05-49.05 g/100 g due to the lower hygroscopicity of GE and GA compared to ANC [76,77]. Therefore, biopolymers used for encapsulating hygroscopic cores should be less hygroscopic than the cores for hygroscopicity reduction to be possible. Apart from the hygroscopicity of biopolymers, the drying step after coacervation also affects the hygroscopicity of products. ANC encapsulated by GE/GA and CS/CMC showed similar extents in their reductions in hygroscopicity. However, spray-dried extracts were found to have much lower hygroscopicities than freeze-dried extracts due to more driving force and surface area for moisture evaporation in spray drying. Moreover, freeze-dried samples possess highly porous surfaces, increasing their susceptibility to water absorption [78]. The encapsulation of protein hydrolysate core materials with protein wall materials may result in weakened protection due to interactions between the core and the wall materials. The hygroscopicity of casein hydrolysate with soy protein isolate (SPI)/pectin was significantly reduced. However, as the amount of content increased, hygroscopicity increased due to more hydrophobic interactions between the core and SPI, causing SPI's hydrophobic groups to turn towards the core, decreasing surface hydrophobicity [72]. Therefore, it may be more efficient to utilize other polysaccharides as wall materials for encapsulating protein cores. Apart from that, hygroscopic mildronate, a cardioprotective drug, was encapsulated by poly(lactic acid) (PLA) and polystyrene (PS), and had its hygroscopicity significantly reduced in the long run by more than two times, from 66.28% to 26.18% in PLA to 22.04% in PS after 168 h in 75%RH [79]. Gelation is a form of simple coacervation as it requires a single polymer and crosslinker to enable coacervation with itself. Although less popular than complex coacervation, a simple coacervation method such as gelation can still be effective to encapsulate hygroscopic bioactives. For instance, different combinations of biopolymers ALG, shellac (LAC) and WPI were used for the encapsulation of probiotic lactobacilli, where crosslinking between ALG or LAC with calcium ions is the main coacervation mechanism for the formation of films around cell microcapsules. Films with incorporated LAC demonstrated more obvious reductions in hygroscopicity due to its hydrophobicity and good moisture-protective properties [80]. Excipients play a crucial role in preparing and enhancing the therapeutic properties of pharmaceuticals. These additives should be inert and not alter the stability or phase changes of the active ingredients during manufacturing and storage [81]. Excipients can improve the hygroscopicity and stability of solid dosage forms by interacting with ambient moisture. They are incorporated into formulations through various techniques, including wet granulation, dissolution, physical mixing, followed by freeze drying, oven drying, fluid bed drying, or ambient drying [81]. Recent findings on formulation with excipients are summarized in Table 4. For instance, co-processing with amorphous excipients can impede hydrate formation of the drug at high water content [82]. In contrast, partially amorphous excipients may hinder hydrate formation at low water contents, while crystalline excipients are unable to control hydrate formation [82]. Other examples include the use of mortar silicon dioxide (SiO_2) in dissolution and freeze drying, which resulted in a water sorption rate of less than 20% from 30% RH to 70% RH, indicating non-hygroscopic nature of the powder [83]. Similarly, physical mixtures of cladophora cellulose, microcrystalline cellulose (MCC-SLM), and agglomerated micronized cellulose (AMC) showed varying degradation rates, with lowest crystallinity cellulose (LCC) exhibiting highest stability [84]. In another study, high crystallinity cellulose (HCC), MCC, and LCC were used in physical mixtures, showing that drug degradation increased with high amounts of HCC and MCC, while decreasing with higher amount of LCC despite its higher moisture content [85]. Traditional Chinese Medicines (TCM) powder was successfully formulated using wet granulation and oven drying techniques, incorporating porous calcium silicate (Florite RE, FLR), which allowed for slow transfer of water to the hygroscopic material during granule formation [86]. Lastly, dissolution and freeze drying techniques were used to formulate limaprost with dextran40, dextrin, and pullulan, resulting in stabilization of the drug even at extremely high water content (>10%) [87]. Similarly, herbs such as radix ophiopogonis and rhizomapolygonati were formulated using physical mixing and oven drying techniques, incorporating dextrans T10, T40, and T70 to depress moisture sorption [87]. The addition of dextrans increased the glass transition temperature (Tg) of extracts at various relative humidities (RH), resulting in reduced tackiness and improved water absorption properties. This modification led to the transformation of the extract's class III hygroscopicity to class II, making it slightly less prone to absorbing moisture. Combining corn starch with microcrystalline cellulose enhanced the powder's ability to handle humidity, shifting its classification from moderately to slightly hygroscopic. Furthermore, this formulation helped prevent deliquescence in the extract. The degradation rate of aspirin in formulations with excipients of varying crystallinity was investigated. It was observed that the lowest degradation rate occurred when using low-crystallinity cellulose (LCC), which had a higher moisture content. This is likely due to LCC's ability to bind more water molecules, limiting their interaction with hygroscopic bioactives. Similar findings were reported in another study, where the use of lower crystalline cellulose reduced the hygroscopicity of aspirin formulations. Additionally, research suggested that water is more tightly bonded to LCC than higher crystalline celluloses, reducing the likelihood of hydrolytic drug degradation. Hydrophilic excipients can also contribute to stability by absorbing and binding significant amounts of water, restricting its interaction with hygroscopic bioactives. For instance, porous excipients like calcium silicate were used in traditional Chinese medicine formulations to enhance granule formation despite high extract hygroscopicity. While hydrophilic polymers can absorb moisture, they do not necessarily increase hygroscopicity or destabilize bioactives. A study on limaprost formulation with dextran 40, dextrin, and pullulan demonstrated stable products even with high water content. The ratio of excipients used significantly impacts product hygroscopicity, as increased ratios can limit more water from interacting with bioactives. This was observed in formulations using dextran, where higher masses resulted in decreased hygroscopicity due to increased water-binding sites and dilution effects. The formulation of physalis peruviana fruit extract and other traditional medicines has shown a similar trend of reducing hygroscopicity by using non-hygroscopic excipients. Bernal et al. (2016) found that adding large proportions of corn starch and microcrystalline cellulose to the extract changed its properties, making it less hygroscopic. Maltodextrin (MD), a high molecular weighted polymer, has been shown to raise glass transition temperatures, contributing to moisture protection and stability. Studies have also explored the use of dextrans as excipients to reduce hygroscopicity. The addition of high molecular weighed dextrans helped to increase the extracts' Tg, counteracting the plasticizing effects of moisture and reducing their hygroscopicity and tackiness. However, most studies focused on using hydrophilic or water-binding excipients. Recent research has also highlighted the potential of non-hygroscopic excipients, such as tricalcium phosphate, to reduce hygroscopicity due to their water-repellent properties. For example, the formulation of betahistine dihydrochloride with Quick Tab exhibited a lack of moisture uptake and improved stability. Furthermore, research has shown that β-cyclodextrins (β-CD) can be used to prevent rapid deliquescence and improve stability of hygroscopic bioactives by forming inclusion complexes. This provides an interesting doorway to discover more inclusion-complex-forming excipients. Crystal engineering, which involves altering the crystal packing arrangements of solids to boost physical stability, has also been explored as a potential strategy for improving the properties of bioactives. Most active ingredients can't form stable salts or hydrates due to the instability of water and solvents, which are prone to being lost over time. However, they can create stable cocrystals with the right co-formers. Cocrystals have become a popular way to improve physicochemical properties without altering therapeutic functions by modifying crystal structures. These multicomponent systems consist of active ingredients and co-formers in a stoichiometric ratio bonded via non-ionic interactions like hydrogen bonds in a crystal lattice. Recent studies on cocrystal formation, including those related to hygroscopicity control, have been summarized, with reviews suggesting that aqueous solubility of the co-former is crucial for stability enhancements and efficient crystal packing may also be important factors. Research has shown that the exposure of hydrophilic functional groups due to surface anisotropy or crystal defect sites generated during processing can lead to hydrate formation. Several cocrystals were tested for their hygroscopicity (ability to absorb moisture from the air). The results showed that some cocrystals formed hydrates when exposed to high humidity, while others did not. For example, BCl-GLA and BCI-SUA did not form hydrates, but ISO (isosorbide) and its derivatives did. ISO deliquesced at 95% relative humidity (RH), whereas ISO-HCT, ISO-35DHBA, and ISO-GAA remained solid. PMTCl-GAA cocrystals were found to be more hygroscopically stable than PMTCl alone. MET (metformin) and its derivatives had higher hygroscopicity than EP-MET and EP-MET monohydrate. VAL (sodium valproate) absorbed a significant amount of water, whereas TMA-VAL was much less hygroscopic. Amorphous VEM (vemurafenib) absorbed some water at 95% RH, while cocrystals with D-CSA, L-CSA, and DL-CSA absorbed even less. BCl (berberine chloride) rapidly absorbed water to form dihydrate at low RH, but was more stable up to 70% RH. BCl-CA exhibited lower hygroscopicity than BCl alone. LVFX (levofloxacin) formed a hydrate at low RH, while LVFX-AMAP did not. In general, the cocrystals that formed hydrates at high RH tended to have higher hygroscopicity than those that did not. However, some cocrystals like TMA-VAL and BCl-CA were found to be more stable and less hygroscopic than their individual components. The formation of cocrystals between LA-D-T and LA-3-N at low water content was confirmed through visual observation, with no changes observed in the cocrystalline state even at high relative humidity (96%). The reduction in hygroscopicity is attributed to the formation of hydrogen bonds between the cocrystal compounds, reducing the availability of hydrogen-bonding sites for interactions with water. Additionally, crystal packing arrangements can also contribute to reduced hygroscopicity by packing bioactives away from exposure to ambient moisture. Cocrystals can be prepared through various solution-based and solid-based techniques, including solvent evaporation, antisolvent method, cooling crystallization, reaction co-crystallization, slurry conversion, neat grinding, liquid-assisted grinding, and melting crystallization. Solvent evaporation is the most widely used method, involving the dissolution of cocrystal components in a suitable solvent at stoichiometric ratio followed by evaporation. The formation of cocrystals has been shown to reduce moisture absorption, as seen in the case of phloroglucinol-progesterone cocrystals, which transformed into a non-hygroscopic compound. Similarly, Berberine chloride (BCl) cocrystals with aliphatic dicarboxylic acid co-formers exhibited negligible moisture adsorption. The behavior of co-crystallization has also been demonstrated in studies on isosorbide-piperazine and palmatine chloride-gallic acid cocrystals, which showed higher critical relative humidity and reduced deliquescence. Furthermore, the co-crystallization of metformin (MET) and epalrestat (EP) resulted in marked reduction in hygroscopicity, with EP anions acting as a physical barrier to environmental moisture. Water molecules are less likely to interact with EP-MET due to its lower number of hydrogen bonding sites compared to METCl and MET. Liquid-assisted grinding can produce cocrystals that reduce moisture sorption, as seen in the case of berberine chloride (BCl) formed with L-Lactic acid or citric acid (CA). These cocrystals exhibited improved physical stability by reducing hygroscopicity. The stabilization of BCl was attributed to a dense hydrogen bonding network between Cl^- anions and carboxylic groups, making it more difficult for water molecules to bind. Studies have also shown that cocrystals of sodium valproate with carbamazepine or tromethamine reduced water absorption at high humidity over a week. Additionally, cocrystals of vemurafenib (VEM) with camphorsulfonic acids improved its hygroscopicity by occupying available hydrophilic binding sites on VEM. Neat grinding methods have also been used to produce non-hygroscopic cocrystals, such as that of levofloxacin (LVFX) with metacetamol (AMAP). Melt crystallization has also been employed to produce stable cocrystals, including those formed with L-lactic acid and co-formers D-tryptophan or 3-nitrobenzamide. The review highlights the use of similar strategies to reduce hygroscopicity in pharmaceuticals and nutraceuticals, such as film coating using water-soluble and/or water-insoluble polymers to form moisture-barrier films surrounding API or nutraceutical particles. The use of non-solvent coating methods like aqueous solvent coating and dry powder coating should replace organic solvent coating due to environmental and safety concerns. Despite their advantages, such as shorter processing times and lower energy usage, these methods are not widely used. Encapsulation techniques like spray-drying or coacervation have emerged as viable alternatives for controlling hygroscopicity. However, more research is needed on polymers with low hygroscopicity and high molecular weight to expand the list of suitable materials for spray-drying. Parameters that allow higher moisture content in final products may yield less hygroscopic powders, but this is not universally applicable. While freeze-drying can be effective for certain active ingredients, its limitations, such as heat sensitivity, must be considered. Spray-drying encapsulation shows promise in controlling hygroscopicity, especially for nutraceuticals, and should be explored further for pharmaceutical applications. Some bioactive cores, like hydrolysates and pigments, may exhibit high hygroscopicity due to their inherent properties or interactions with wall materials. Alternative coacervation methods involving biopolymers with high hydrophobicity or lower hygroscopicity could improve encapsulation efficiency. For protein cores, polysaccharide walls may be a more suitable choice than protein walls to prevent moisture obstruction. Besides coating and encapsulation, co-processing with excipients offers another strategy for controlling hygroscopicity, albeit with different mechanisms of action. The control of hygroscopicity in pharmaceutical and nutraceutical solid dosage formulations is crucial to maintain the stability and bioavailability of active pharmaceutical ingredients (APIs). Four strategies have been employed to reduce hygroscopicity: using water-binding excipients, high Tg excipients, non-hygroscopic excipients, and inclusion-complex-forming excipients. While limited research exists on non-hygroscopic and inclusion-complex-forming excipients, crystal engineering through cocrystallization has emerged as a popular method for reducing hygroscopicity by modifying the physical stability of APIs. However, co-crystallization remains an empirical process, particularly in selecting optimal co-formers, making it technically more challenging than other strategies. In the future, combining multiple strategies could lead to improved control over hygroscopicity and enhanced stability of APIs. For instance, processing a hygroscopic bioactive core with a moisture-repellent excipient followed by film coating may yield a superior formulation compared to single-strategy approaches. Despite the significance of high hygroscopicity in pharmaceutical/nutraceutical solid dosage formulations, research efforts on this topic remain lagged behind other important formulation issues. The study on hygroscopicity in pharmaceutical materials is a crucial aspect of research, as it can affect the stability and efficacy of drugs. The authors declare no conflict of interest and acknowledge the funding from Singapore's Ministry of Education for L.H.N.'s postgraduate scholarship. The text references various studies, including those by Newman et al., Rajabi-Siahboomi et al., Thakur et al., Helmenstine, Edgar and Swan, Khankaria and Grant, Poole et al., Gouda et al., Ebian et al., Otsuka et al., Cheow et al. Controlling humidity is essential in the pharmaceutical industry to ensure the quality and efficacy of medicinal products. Research has shown that moisture can cause degradation of pharmaceutical ingredients, leading to reduced stability and potency (Emery et al., 2009). To overcome this challenge, various methods have been developed, including the use of hygroscopicity-controlling materials and techniques for determining and mitigating the effects of humidity on pharmaceutical ingredients (Arigo et al., 2019; Roy et al., 2018). The selection of suitable packaging materials is also crucial in controlling humidity. Waterman and MacDonald (2010) recommend using packages with moisture-resistant coatings to protect solid oral drug products from moisture. Additionally, the use of electrostatic powder coating has been explored as a method for pharmaceuticals (Yang et al., 2017). Encapsulation of bioactive peptides can also help improve stability and bioactivity (Aguilar-Toala et al., 2022). Other research focuses on the development of innovative packaging materials, such as enteric coatings to improve drug bioavailability (Maderuelo et al., 2019) and complex coacervation for microencapsulation (Timilsena et al., 2019). Crystal engineering techniques have also been explored to enhance solubility and bioavailability of poorly soluble drugs (Varshosaz et al., 2018). Overall, controlling humidity in the pharmaceutical industry requires a comprehensive understanding of the principles of hygroscopy, packaging selection, and innovative technologies for improving stability and bioavailability. References: Arigo A., Jawahar N., Nikhitha K., Jubie S. (2019). Effect of Hygroscopicity on pharmaceutical ingredients, methods to determine and overcome: An Overview. J. Pharm. Sci. Res., 11(6), 6-10. Aguilar-Toala J.E., Quintanar-Guerrero D., Liceaga A.M., Zambrano-Zaragoza M.L. (2022). Encapsulation of bioactive peptides: A strategy to improve the stability, protect the nutraceutical bioactivity and support their food applications. RSC Adv., 12(44), 6449-6458. Emery E., Oliver J., Pugsley T., Sharma J., Zhou J. (2009). Flowability of moist pharmaceutical powders. Powder Technol., 189, 409–415. 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Research on deep eutectic solvents, ionic liquids, and film coatings has made significant progress in recent years. These substances have been explored as tools to tailor active pharmaceutical ingredients, enhance moisture protection, and improve the stability of hygroscopic drugs. Deep eutectic solvents have been shown to exhibit unique properties that make them useful for various applications, including pharmaceuticals. Recent advances in their fabrication approaches have expanded their potential uses. Ionic liquids have also been investigated as a means to tailor active pharmaceutical ingredients. They have been found to enhance the stability and bioavailability of certain drugs. Film coatings, particularly those designed to mask taste and protect against moisture, have been extensively studied. Researchers have developed various formulations that improve the sticking properties, hygroscopicity, and compactibility of effervescent systems. The importance of understanding the glassy-to-rubbery state transitions in moisture-protective polymer coatings has also been emphasized. This knowledge is crucial for developing effective film coatings that can protect sensitive drugs from moisture. Furthermore, research on aqueous coating dispersions, pseudolatex, and hybrid solid dispersion films has shown promising results. These formulations have been used to improve the formulation of sustained-release tablets containing hygroscopic drugs. Overall, these studies highlight the potential of various substances and formulations in enhancing the stability and bioavailability of pharmaceuticals. Research has been conducted on various aspects of tablet formulation, including improvement and investigation of dissolution properties in vitro and in vivo (45-44). Studies have also focused on bioequivalence comparisons between different dosage forms, such as tablets and soft gelatin capsules (40). The use of shellac in pharmaceutical applications has been explored for its moisture-protective and taste-masking properties (41). Additionally, research has been done on the preparation and characterization of tablet formulations based on solid dispersion of certain medications, such as glimepiride and poly(ester amide) hyperbranched polymer (42). The film-forming property of hydrogenated rosin has also been evaluated (43), as well as the formulation design of sustained-release tablets for highly hygroscopic model drugs like pyridostigmine bromide (44). Other studies have investigated the combination of hot-melt subcoating and enteric coating for moisture protection of hygroscopic Sennae fructus tablets (45). A novel sugar coating method has been evaluated for its moisture-protective properties (46), as well as a composite film made from shellac and plasticizer that enhances moisture protective properties and stability of pectin (47). Other research has focused on the use of aqueous film coating in pharmaceutical applications (48) and the development of tablet-in-tablet techniques (49). Finally, there have been studies on the global food sugar coating market, which is expected to witness steady expansion growth (50), as well as the encapsulation of dairy protein hydrolysates using various methods (51). Given article text here: Spray drying is a widely used technique for preserving lactic acid starter cultures, which has been reviewed in this study. The application of spray drying for the preservation of lactic acid starter cultures has been discussed, highlighting its advantages and limitations. Additionally, various studies have explored the use of spray drying for encapsulating food flavours and oils, as well as bioactive peptides and protein hydrolysates. The production and properties of casein hydrolysate microencapsulated by spray drying with soybean protein isolate have also been studied. Furthermore, the influence of spray drying encapsulation on the retention of antioxidant properties and microstructure of flaxseed protein hydrolysates has been investigated.

The effect of carrier agents on the physicochemical properties of a spray dried chicken meat protein hydrolysate has also been examined. Moreover, studies have explored the production and properties of spray-dried amaranthus betacyanin pigments and the spray-drying of cactus pear juice. Additionally, the influence of process conditions on the physicochemical properties of acçai powder produced by spray drying has been studied. The provided list contains 76 research articles related to spray drying, a process used to dry and preserve food products, pharmaceuticals, and other materials. The studies explored various aspects of spray drying, including its effects on the taste, stability, and functionality of different compounds. Some studies focused on optimizing the conditions for spray drying of specific powders, such as jujube (Zizyphus jujuba miller) and whey protein hydrolysate, to improve their properties. Others investigated the use of spray drying to reduce the bitterness taste in casein hydrolysate and other compounds. Another group of studies explored the effects of spray drying on the immunomodulatory activity and hygroscopicity of whey protein concentrate-derived hydrolysates. Some researchers also investigated the impact of alpha-amylase and maltodextrin on the physicochemical, functional, and antioxidant capacity of purple sweet potato flour. Additionally, some studies examined the use of spray drying as a method for encapsulating compounds, such as anthocyanins in black raspberry extract, and developing self-assembled gelatin-iota-carrageenan structures for intestinal-targeted release applications. The research articles also highlighted the importance of microencapsulation techniques, such as complex coacervation, to protect and prolong the activity of various compounds. Overall, the studies demonstrate the versatility and potential of spray drying in food science, pharmaceuticals, and related fields. **Microencapsulation and Encapsulation Techniques** Several studies have explored the use of microencapsulation techniques to protect sensitive compounds, such as anthocyanins, probiotics, and pharmaceuticals, from degradation or loss of potency. * Researchers used gelatin and gum Arabic to encapsulate black raspberry anthocyanins through complex coacervation (Shaddel et al., 2018). * Another study demonstrated the use of spray and freeze-drying techniques for producing microcapsules containing anthocyanin-rich compounds (Kanha et al., 2021). * A separate investigation showed that mildronate, a pharmaceutical compound, can be microencapsulated in biodegradable and non-biodegradable polymers (Loca et al., 2014). **Probiotic Encapsulation** The encapsulation of probiotics has also been explored to improve their stability and controlled release. * Researchers used shellac as a moisture barrier for encapsulating probiotic lactobacilli, allowing for controlled release (Huang et al., 2021). **Dry Powder Inhaler Formulations** Studies have investigated the use of microencapsulation techniques for producing dry powder inhaler formulations. * A study demonstrated the formulation of lipid-polymer hybrid nanoparticles using electrostatically-driven nanoparticle assembly onto microscale carrier particles (Yang et al., 2012). **Solid-State Phase Transformation and Excipient Selection** Researchers have explored how excipients can affect solid-state phase transformation in formulations during wet granulation. * A study found that excipient selection can significantly impact the stability of solid dosage forms (Airaksinen et al., 2004). * Another investigation demonstrated that silicon dioxide can improve the hygroscopicity and bioavailability of red ginseng extract (Jin et al., 2021). **Moisture-Induced Degradation** Studies have investigated how moisture can affect the stability of pharmaceutical compounds, such as acetylsalicylic acid. * Researchers found that the structure of cellulose powder can influence moisture-induced degradation of acetylsalicylic acid (Mihranyan et al., 2006). * A separate investigation demonstrated that water-cellulose binding energy can impact the stability of pharmaceutical compounds (Heidarian et al., 2006). **Granulation Techniques** Studies have explored how granulation techniques, such as agitation granulation, can affect the stability of hygroscopic drugs. * Researchers found that the agitation granulation method can improve the stability of granules containing a high content of a very hygroscopic drug (Hirai et al., 2006). **Stabilization Mechanisms** Researchers have investigated how to stabilize pharmaceutical compounds in solid dosage forms. * A study demonstrated that limaprost, a pharmaceutical compound, can be stabilized through solid-state phase transformation (Moribe et al., 2007). * Another investigation showed that dextrans can provide anti-hygroscopic effects for herbal formulations (Tong et al., 2008). Dry powder formulation from fruits of Physalis peruviana L. standardized extract with hypoglycemic activity was studied. Powder technology and cocrystallization strategies were employed to improve physicochemical properties. A new method for producing date powder granules was developed, featuring physicochemical characteristics of powder. Co-processed QuickTab™ was used to formulate tablets of hygroscopic drug betahistine dihydrochloride. Inclusion complexes of betahistine with β-cyclodextrin were characterized and evaluated for anti-humidity properties. Pharmaceutical cocrystals were reviewed, including preparations, physicochemical properties, and applications. Drug-drug cocrystals were found to provide significant improvements in drug properties, including treatment with progesterone. A novel salt-coccrystal of berberine hydrochloride with aliphatic dicarboxylic acids was developed, featuring odd-even alternation in physicochemical properties. Reduced deliquescency of isosorbide by cocrystallization and mechanisms for hygroscopicity were studied. A pharmaceutical salt cocrystal of palmatine chloride-gallic acid with neutral molecule was formulated to improve hygroscopic stability of palmatine chloride. Novel drug-drug multicomponent crystals of epalrestat-metformin were developed, featuring improved solubility and photostability of epalrestat and reduced hygroscopicity of metformin. Crystal engineering of valproic acid and carbamazepine was employed to improve hygroscopicity and dissolution profile. The cocrystallization strategy was used to simultaneously improve the physicochemical and pharmacokinetic properties of vemurafenib. Pharmaceutical studies have explored the properties of berberine hydrochloride cocrystals with lactic acid and citric acid, showcasing improved solid-state characteristics. Research on pyridostigmine bromide (PB) has led to the development of sustained-release pellets through extrusion-spheronization and fluid-bed methods. These pellets demonstrated optimal release rates, moisture absorption, and bioavailability in both in vitro and in vivo studies, outperforming commercial immediate-release tablets. The findings highlight the potential for formulation design to enhance pharmaceutical properties and achieve desired therapeutic effects.