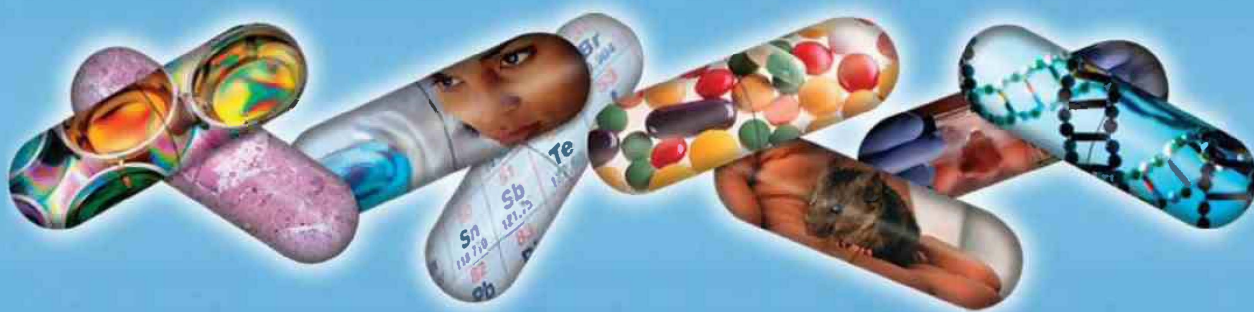


VOLUME 1

Encyclopedia of PHARMACEUTICAL TECHNOLOGY

Third Edition



edited by
James Swarbrick

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Adsorption at Solid Surfaces: Pharmaceutical Applications

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INTRODUCTION

Adsorption at solid surfaces is involved in nearly every aspect of pharmaceutical development, from formulation design, process development, and manufacturing to storage of finished dosage forms. Achieving content uniformity, especially for low-dose drugs, exhibits a challenge faced in the manufacturing of solid dosage formulations. One of the solutions is by adsorbing small drug particles onto the surface of large excipients. The adsorption of binder solution onto solid surfaces is the basis for granulation, which can improve excipient properties such as flowability, compactibility, and bulk density. In compaction, moisture adsorption generally facilitates particle deformation and increases the area of contact between particles during compression. However, when compressible and non-compressible excipients are mixed together, the adsorption of non-compressible excipients onto the surface of compressible excipients will reduce mixed powder compressibility. During storage, water molecules adsorbed on solid surface have significant impacts on pharmaceutical development such as compaction and tensile strength of tablets. Therefore hygroscopicity needs to be taken into consideration for selecting excipients in formulation design.

Solid dispersion is frequently used to improve the dissolution rate of poorly water-soluble compounds. By adsorbing drug molecules onto the surface of adsorbents with large surface areas, the total surface area of the drug is increased, and the drug may even be transformed from crystalline form to amorphous form. By adsorbing a surfactant onto the crystal surface of poorly water-soluble drugs, dissolution rate can also be enhanced, even though the mechanism is yet not fully understood. In many approaches used to increase dissolution rate, because drugs exist in higher-energy state than their crystal state, dissolved or amorphous drugs can be crystallized and may cause a decrease in dissolution rate. To maintain a high dissolution rate, polymers have been widely used to inhibit crystallization by adsorbing onto crystal surfaces.

Besides process development and dissolution rate enhancement, the phenomenon of adsorption at solid surfaces is also useful in many other aspects of pharmaceuticals. By adsorbing moisture onto its large surface area, colloidal silica has been frequently used as a

desiccant for stabilizing moisture-sensitive drugs such as aspirin. Some special formulation designs, such as dry powder inhalation (DPI) and sublingual nitroglycerin tablets, have been designed based on the adsorption of drugs onto a carrier surface. Additionally, the adsorption of liquid and gas on solid surfaces is utilized to measure the surface area of solid materials.

OVERVIEW

The basic approach regarding how adsorption at solid surfaces affects different aspects of pharmaceutical development, especially for solid dosage forms, is briefly reviewed. The three broad fields addressed are: general pharmaceutical processing, dissolution rate enhancement for poorly water-soluble compounds, and some other applications using adsorption at solid surfaces. Case studies are introduced to aid in understanding the applications and/or principles involved.

Adsorption could generally be classified as physical adsorption and chemical adsorption.^[1] Forces involved in adsorption include van der Waals force, hydrogen bonding or electrostatic force in physical adsorption, and covalent chemical bonds in chemical adsorption. Adsorption could occur between solid and solid, solid and liquid, or solid and gas. In pharmaceutical development, these adsorptions could take place during different processing stages, and affect the properties of the final products. There are cons and pros of these adsorptions, which will be discussed in this article.

ADSORPTION IN GENERAL PHARMACEUTICAL PROCESSING

Because of the interactions existing between different materials as well as between like materials, the performance of excipients in a formulation could be different from the performance of the excipients themselves. The most frequently used procedures in pharmaceutical processing for solid dosage formulations are mixing, granulation, and compaction, as well as storage of finished dosage forms. The effects of adsorption on these procedures have been studied, observed, and utilized widely in the pharmaceutical industry.

Adsorption in Mixing

Adsorption of drugs onto the solid surfaces of excipients plays an important role in the preparation of pharmaceutical mixtures and can affect many aspects of the final formulations, especially the content uniformity of low-dose drugs. During mixing, there are many factors that can affect the content uniformity of mixtures, and adsorption generally plays a role when the average particle size is $\leq 400\text{ }\mu\text{m}$.^[2] In drug manufacturing, it is a challenge to achieve content uniformity when mixing a small amount of one material with a much larger amount of another material. To achieve content uniformity for potent drugs in solid dosage forms, it is beneficial to produce mixes with good homogeneity if drugs can be dispersed very finely.^[3] If there are no interactions between mixed particles, ordered mixing and random mixing should achieve the same results. However, due to interactions between particles, such as aggregation between small particles and adsorption of small particles onto large carrier particles, ordered mixing and random mixing may have significantly different outcomes.^[4]

Adsorbing drugs onto carrier particles (Fig. 1) by ordered mixing can be very beneficial in several ways,^[5] such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage. For excipient particles, larger size and better flowability are beneficial for achieving content uniformity.^[3] Those excipients that can adsorb drugs more strongly exhibit a faster disintegration of agglomerates, and achieve higher homogeneity in both random and ordered mixing. Tablets of 120 mg containing 0.1 mg of digitoxin have been manufactured with very good content uniformity by adsorbing small particles onto

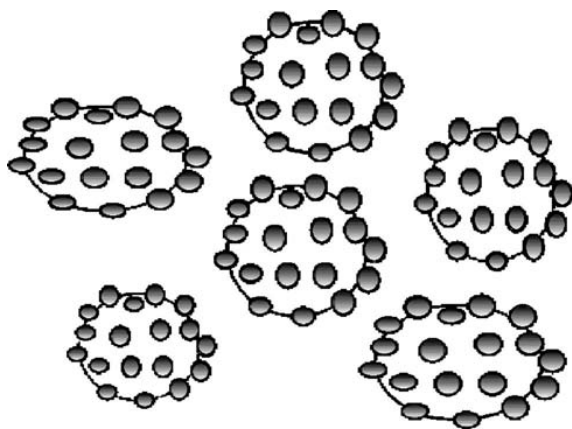


Fig. 1 Adsorption of small particles onto the surfaces of larger carrier particles.

larger carrier particles in ordered mixing.^[4] In the design, digitoxin, dissolved in a mixture of methylene chloride and methanol, is first deposited onto milled critical micellar concentration (CMC). After mixing, the solvent is removed, and this dry blend is mixed with crystalline lactose. Other excipients are added later without affecting the content uniformity.

The most important factors in the adsorption process are moisture content and particle size distribution.^[6-8] Moisture content and the state of adsorbed water affect the adsorption of fine antibiotic powders onto the surface of sorbitol by plasticizing sorbitol, forming an adherent monolayer that affects the capillary forces and hydrogen bonding interactions between sorbitol and the drugs, as well as masking the interparticle forces. It was observed that high moisture content has caused higher adsorption onto sorbitol for those fine antibiotic powders with low interfacial energy, internal location of adsorbed water, and the ability to form hydrogen bonding with sorbitol. When stored under high humidity, moisture adsorbed onto the surfaces of drugs and carriers could form a liquid bridge whose capillary interaction may significantly increase adhesion in the mixture.

However, high moisture does not always increase the adsorption of drugs onto the solid surface of excipients.^[6] For example, as to antibiotics with high interfacial energy and external location of adsorbed water, low moisture content is beneficial for achieving higher adsorption onto sorbitol.^[6] Overall, the mechanism by which moisture content affects the adsorption of drugs onto the solid surfaces of other excipients is very complex and can be affected by many factors.

Other factors such as the surface structure of particles, reduction of interparticle distance (e.g., by means of intensive mixing processes), as well as particle size also affect surface adsorption.^[4] It was observed that irregular particles of sorbitol with a structured surface could adsorb more vitamins than regular particles.^[4] By adjusting the ratio of three vitamins in the starting mixture, the proportions of vitamins B1, B2, and B6 in the adsorbed state can be changed. Because of the high fraction of vitamins not adsorbed onto sorbitol surface, the ordered mixing was arranged, at first, by mixing each vitamin with sorbitol separately, then by combining the individual mixtures to make the final mixture.

Milling can affect the adsorption of actives on the carrier surface by altering the surface properties of excipients.^[9] It was noticed that milled actives frequently failed blend uniformity criteria, but unmilled active batches consistently met the blend uniformity criteria. By adding lubricant magnesium stearate, the blending content uniformity of the milled batches can be significantly improved. A small amount of amorphous materials could affect the blending characteristics of a direct compression formulation.^[9]

Overall, factors that might affect the adsorption of actives on the carrier surface include surface properties, moisture content, the type and particle size/shape of carriers and actives, as well as the mixing ratio of actives and carriers. Pharmaceutical processes (i.e., milling and granulation) could affect the adsorption process by altering carrier and active properties (i.e., surface properties, size, and shape), hence the characteristics of blending and the quality of the final dosage form.

Adsorption in Granulation

In solid dosage forms, granulation is frequently used to improve excipient properties such as flowability, compactibility, bulk density, granule strength, dissolution rates, and so on.^[10–14] The granulation process generally includes binder atomization, fluidization, adsorbing and spreading on powder surfaces, particle agglomeration, and so on. In addition, binder adsorbed onto the particle surface can also provide solid bridges between particles. Of course, due to the complexity of the granulation process, many factors can affect the process and the final properties of the granules. However, the adsorption of the binder solution on solid surfaces, especially at the point of contact between particles or granules, is the key to the granulation process.

The adsorption process can be affected by the surface tension and the viscosity of a binder, and more energy may be consumed during granulation. As shown in Fig. 2, the surface tension and the viscosity of a binder play important roles in granulation because these properties influence the liquid bridges between the particles, as well as the distribution of the binder

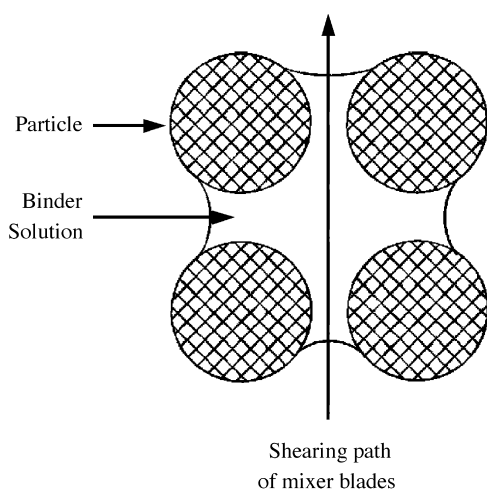


Fig. 2 Shearing path of mixer blades through wet mass at capillary state. (From Ref.^[10]. © John Wiley and Sons, Inc.)

during the wet massing stage.^[10–12] For similar polymer binders, even at an equivalent viscosity, different molecular weights can affect binder surface tension and thus influence the granulation process and related granule properties. It is worthwhile to note that source and batch variation of both drugs and excipients can have profound effects on the final product performance.

A suitable amount of binder adsorbed onto the granular surface at the points of contact, as well as their physical properties such as viscosity and flowability, are very important for granule growth.^[13,14] Four mechanisms of granule growth are shown in Fig. 3, and the mechanism that plays the main role is determined by the degree of binder dispersion in the powder.^[13,14] Many factors, such as binder atomization, addition rate, state of fluidization, and shear forces in the mixer, can affect the degree of binder dispersion. In the “nucleation” mechanism, particles stick together with the help of the liquid binder adsorbed on the powder surface; in the “coalescence” mechanism, through deformation and bonding, two large agglomerates combine to form one granule with the help of a surface-adsorbed binder; and in the “layering” mechanism, fine particles stick to either a large granule or a binder droplet. In a mixer, shear forces will cause particles to collide and bond together if some binder is present at the point of contact, as shown in Fig. 4.

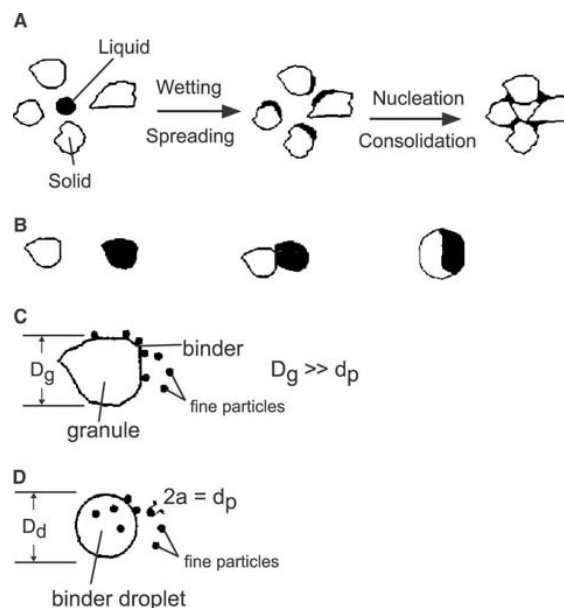


Fig. 3 Granule growth mechanisms: (A) agglomerate formation by nucleation of particles; (B) agglomerate growth by coalescence; (C) layering of a binder-coated granule; and (D) layering of a partially filled binder droplet. (From Ref.^[13]. © John Wiley and Sons, Inc.)

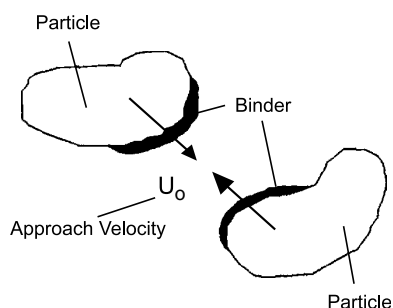


Fig. 4 Coalescence of two binder-covered particles. (From Ref.^[13]. © John Wiley and Sons, Inc.)

Of course, two colliding particles may not always bond together, but may rebound and fail to achieve granule growth. Once granules have been formed and reach a certain size, they have to survive the shear forces in the mixer, which are determined by the relationship between shear forces of the outer shearing mass and the inner strength of the granules.

Besides the traditional wet granulation, surface adsorbents, especially porous materials, are very helpful for maintaining liquid in a granulation. For example, calcium silicate, a fine porous powder, has been successfully used to adsorb an oily medicine, tocopheryl nicotinate.^[15] Due to the high capillarity of the pores inside calcium silicate, the adsorbent has an excellent liquid-holding ability. In the formulation preparation, after drug dissolved in ethanol was adsorbed on calcium silicate, hydroxypropylcellulose (HPC) was added to the mixture and granulated to improve flowability.

Adsorption in Compaction

In the manufacturing of tablets, compaction is a very important step, and many factors are involved in affecting the properties of excipients and final products, such as surface structure and wettability of excipients.^[16] For formulations, the larger is the surface area of compressible excipients, the greater is the compressibility.^[17–19]

When compressible and non-compressible excipients are mixed together, the adsorption of the non-compressible excipients onto the surface of the compressible excipients will reduce mixed powder compressibility. Lerk et al.^[18] and te Wierik et al.^[19] studied a new generation of starch products, which have a high surface area as excipients in pharmaceutical tablets, and confirmed that there is a positive relationship between the specific surface area and the binding capacity (i.e., compactibility). The surface area that takes part in the interparticle attraction is small, and only a minor fraction of the

geometrical surface area may be available for tablet bonding.^[20] The addition of some materials, such as binder and lubricant, may decrease particle fragmentation during compression and affect the “true” bonding surface area. In tablet manufacturing, lubricants such as magnesium stearate act by adsorbing onto the surface of granules and forming a film, thus decreasing the crushing force and ejection force during compression.^[21] It was noticed that the distribution of adsorbed magnesium stearate was non-uniform on the surface of excipients, and much more lubricant existed on edges and defective parts of the sodium chloride crystals in their study, thus increasing the effective area for compaction.

Besides the surface area of the excipients, moisture adsorbed to the excipients is one important factor in compaction. Nyqvist^[22] reported that by affecting the surface structure of excipients, a small amount of water in furosemide could significantly affect the compaction properties of the direct compressible formulation. When water content was increased from 0.06% to 0.24%, the elastic recovery was increased and network was decreased at compaction. Besides, by adjusting the water content of furosemide, it was possible to avoid tablet capping as well. Because adsorption of water in furosemide did not change the internal structure of the crystals, water may be adsorbed onto the crystal surface with weak forces detectable with thermal analysis. The area of contact formed between particles was increased during compression due to the particle deformation facilitated by the higher moisture content. Two types of interparticulate bonds, adsorption bonds and diffusional bonds, have been involved in the increased bond strength between particles. It has been observed that increased moisture content in amorphous lactose particles could increase tablet tensile strength and reduce tablet porosity by direct compression.^[23] Overall, moisture content can influence bonding forces by affecting both the contact area between particles and the relative fractions of adsorption and diffusion bonds in the tablet.

Adsorption in Storage

The physical and chemical stabilities of finished dosage forms stored at high humidity have always been concerns in the pharmaceutical industry and have been extensively studied. The adsorption of water molecules onto the solid surface can affect tablet strength. For tablets stored under humid conditions, the tensile strength of tablets increases initially when relative humidity (RH) increases; however, as RH further increases, the tensile strength of tablets starts to decrease.^[8,24–31] During storage, the sublimation of drugs such as bromhexine HCl (BHCl) can be prevented by

selecting suitable excipients based on their surface adsorption capacity.^[32,33]

Hygroscopicity of excipients

Based on hygroscopicity (i.e., the tendency of materials to absorb water under different conditions of humidity), solids have been classified into four categories, as follows:^[34]

1. Non-hygroscopic: No increase in water content at RH below 90%.
2. Slightly hygroscopic: No moisture increases at RH below 80% with less than 40% moisture increase at RH above 80% after 1 week.
3. Moderately hygroscopic: Less than 5% water content increase at RH below 60%, with less than 50% water content increase at RH above 80% after 1 week.
4. Very hygroscopic: Substantial water content increases at RH as low as 40–50%.

Different drugs and excipients have different hygroscopic properties, and the amount of moisture absorbed by drugs and excipients can affect not only their own properties but also the properties of the finished dosage forms, such as flowability, compression properties, and hardness of granules and tablets. The hygroscopicity of different excipients has been studied,^[34,35] and research on moisture adsorption may provide useful information in selecting excipients such as disintegrants, binders, and fillers in formulation design, as well as in choosing suitable manufacturing and storage conditions.

Effects of moisture on tablet strength

Increasing RH during storage will increase tensile strength and decrease the surface area of tablets initially.^[29,30] Water can adsorb onto solid surfaces at three locations: monolayer-adsorbed moisture, normally condensed moisture, and adsorbed moisture, as shown in Fig. 5.^[24] Adsorbed water molecules affect tablet tensile strength by influencing interparticle separation and interparticle forces, especially van der Waals interactions, as well as the ratio of the binding to diffusion forces for water molecules on the solid surface. The initially adsorbed water molecules on the solid surface may form a monomolecular layer, increase the van der Waals interactions between particles, smooth out surface microirregularities, and reduce interparticle separation, thus increasing tensile strength.^[25] As more water molecules adsorb onto the particle surface, they are subjected to both surface binding and diffusion forces, and the diffusion forces induce water to

Adsorption at Solid Surfaces: Pharmaceutical Applications

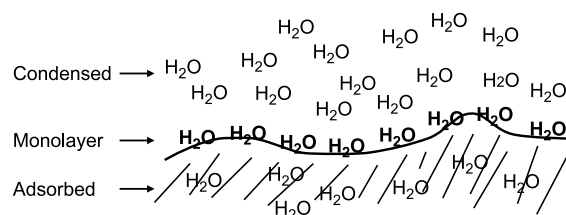


Fig. 5 Three locations of adsorbed water molecules in solid materials: monolayer adsorbed moisture, condensed moisture, and moisture adsorbed inside solid.

penetrate into the particles.^[26] The penetrated water may soften the particle surface, increase contact area between particles under high pressure due to plastic deformation, and form more solid bonds.^[27] All those effects may explain the observed initial increase in tensile strength when RH increases.

However, as RH further increases, tablet strength decreases for most tested tablets, and it was suggested that condensed water on the solid surface at high RH weakens intermolecular attraction forces between particles in the tablets and the further softened particles and solid bonds cause the tensile strength to decrease.^[24] In addition, at high RH, water may form multilayers on the solid surface, which can act as a lubricant and reduce the frictional forces between particles, thus decreasing tensile strength as well.^[28] Ultimately, the effects of adsorbed moisture on particle surfaces are very complex, affected by many factors, especially the properties of the tablet excipients.

Preventing drug sublimation during storage

During storage, BHCl can sublime away from solid dosage formulations and reduce the dosage potency.^[32,33] It was observed that BHCl prefers to adsorb to the surface of magnesium aluminum silicate (MAS) rather than to the package material polyethylene film. The adsorption to MAS was accelerated at high temperature and reduced pressure, and the BHCl adsorbed onto the surface of MAS was amorphous rather than crystalline. BHCl could also adsorb onto many other solid excipients, such as kaolin, Avicel PH101, and Avicel PH102, and many factors affect the adsorption. When pH increased, adsorption by microcrystalline cellulose (MCC) increased moderately. As particle size increased, adsorption decreased. Within the range of 20–46°C, temperature did not affect the adsorption of BHCl on MCC. Thermodynamic analysis showed that both entropy and enthalpy changes favored the adsorption on MCC. Overall, selecting suitable excipients to keep BHCl from sublimating during storage proved a very useful application of adsorption at solid surfaces.

EFFECTS OF ADSORPTION ON DISSOLUTION

Solid Dispersion

Solid dispersions are frequently used to improve the bioavailability of poorly soluble compounds for enhancing the dissolution profiles of these compounds.^[36,38–43] Boraie, El-Fattah, and Hassan^[40] have successfully used the approach of adsorbing poorly water-soluble compounds onto the surface of adsorbents to improve dissolution rate. The main idea is to increase the surface area of the compound in contact with the dissolution medium, thus increasing dissolution rate. Aerosil, MCC, montmorillonite, and modified starch were tested as adsorbents. An obvious improvement of dissolution rate is observed—100% of the drug was released from tablets containing 50% Avicel, whereas only 32% was released from pure drug tablets. The weak physical bonding between the drug and the adsorbent was proposed to explain the rapid release of the drug from the adsorbent surface.

Due to their large surface area for adsorption, porous materials are useful excipients for solid dispersions. For example, 2-naphthoic acid (2-NPA) solid dispersion with porous crystalline cellulose (PCC) has been successfully prepared by heat treatment of 2-NPA and PCC mixture.^[44] PCC is derived from MCC, but with a larger surface area. Different from 2-NPA mixed with PCC, 2-NPA mixed with MCC still maintained a crystalline form under the same mixing and heating conditions. Various experimental data such as X-ray powder diffraction, Fourier transform infrared (FT-IR) spectroscopy, and solid-state fluorescence measurements suggest that 2-NPA is adsorbed onto the surface of PCC and becomes molecularly dispersed into the system.

Using a combination of solid dispersion and surface adsorption, the dissolution of a poorly water-soluble drug, BAY 12-9566, has been enhanced significantly.^[36] Gelucire 50/13 was used as the solid dispersion carrier, and the melt of the drug and Gelucire 50/13 was adsorbed onto the surface of Neusilin US2 (magnesium aluminosilicate), the surface adsorbent (Fig. 6), using hot

melt granulation. The dissolution of BAY 12-9566 increased as Gelucire 50/13 and Neusilin US2 loading increased, but decreased as drug loading increased. The solid dispersion granules were successfully compressed into tablets. Different from the usually observed decrease in dissolution on storage at 40°C/75% RH, the dissolution rate increased at 2 and 4 weeks.

The transformation of drugs in solid dispersion from amorphous form to crystalline form is one critical obstacle to making solid dispersion a practical approach in pharmaceutical industry. Utilization of surface adsorbents can be used as one approach to solve the problem. Gupta et al.^[38] used seven different poorly water-soluble compounds and observed that the dissolution rates for some compounds in solid dispersions increased when stored at 40°C/75% RH. In their study, crystalline drugs were prepared as ternary solid dispersion granules using hot melt granulation, two solid dispersion carriers, poly(ethylene glycol) (PEG) 8000 and Gelucire 50/13, as well as Neusilin US2 as surface adsorbent.

Drug adsorption onto Neusilin US2 through hydrogen bonding interactions (Fig. 7) was proposed to explain the drug transformation from crystalline form to amorphous form, and to cause the increase in drug dissolution during storage. However, during storage especially under high humidity, crystallization will decrease the dissolution rate of drugs. Whether or not a drug is highly soluble in the dispersion carrier is a very important factor in determining which of the two competing mechanisms, tendency to crystallize or to stay in amorphous state, plays the dominant role in solid dispersions during storage.^[38] When a drug is highly soluble (>10% wt/wt) in the dispersion carrier, the molecularly dispersed drug can diffuse significantly onto the surface of Neusilin and form more hydrogen bonds with Neusilin in the formulations. For a drug with low solubility in the dispersion carrier, the drug in a molecularly dispersed state cannot readily diffuse onto the surface of Neusilin and form more hydrogen bonds with the adsorbent. For drugs with low solubility, even though they may have formed hydrogen bonds with Neusilin and will not revert to

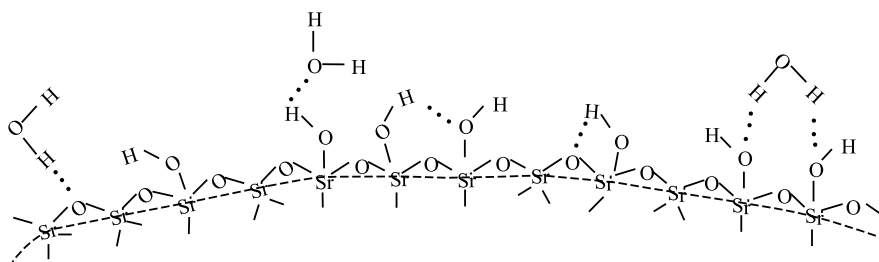


Fig. 6 Some possible hydrogen bonding arrangements on the surfaces of silica gel particles. (From Ref.^[37].)

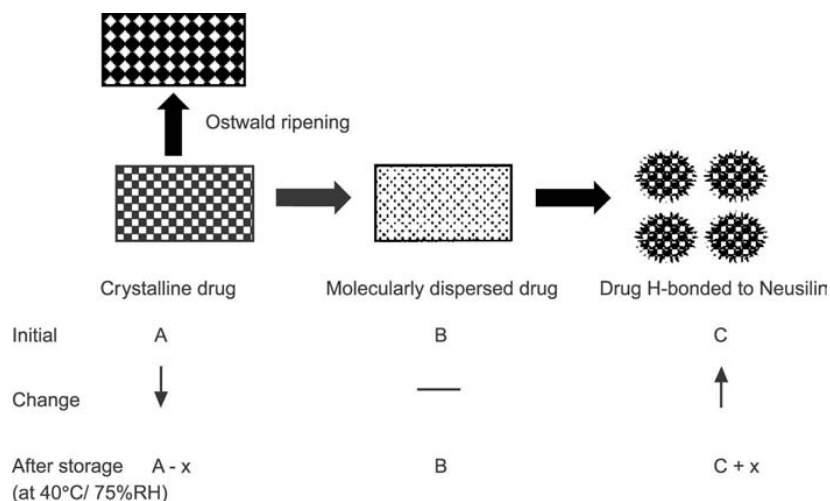


Fig. 7 Proposed mechanism for further increase in dissolution after storage. (From Ref.^[38]. © Kluwer, Inc.)

the crystalline state, crystallization will become the dominant mechanism and cause the dissolution rate to decrease during storage.

As to the mechanism of drug adsorption onto the surface of adsorbents, besides hydrogen bonding interactions, Pignatello, Ferro, and Puglisi^[45] noticed that there exist electrostatic interactions between ammonium groups in a polymer backbone and the carboxyl group in selected drugs. The polymers examined were Eudragit S100 (RS) and RL100 (RL), and the drugs were three non-steroidal anti-inflammatory drugs: diflunisal (DIF), flurbiprofen (FLU), and piroxicam (PIR). In the presence of Tris-HCl buffer (pH 7.4), due to the competition between the chloride ions and drug anions for the polymer-binding sites, drug adsorption on polymer particles was reduced. Overall, these interactions are stronger for drugs with a carboxylic moiety and lower pK_a values, and the interactions can be utilized to design a suitable drug release profile from a solid dispersion.

Effects of Surfactant on Dissolution

It has been observed that by adsorbing surfactants onto the crystal surfaces of poorly water-soluble drugs, dissolution rate can be enhanced. Chen et al.^[46] showed that the dissolution rate of CI-1041, a poorly water-soluble compound, in 0.1 N HCl may be affected by the surfactant Tween 80. The effects of surfactant are complicated, and many factors are involved. Above the CMC of Tween 80, the adsorption of the surfactant onto the crystal surface may inhibit crystal nucleation on the surface, and causes the dissolution rate to increase. By adsorbing a very small amount of poloxamer onto the hydrophobic drug particle surface,

the dissolution profile can be significantly improved compared with untreated drugs.^[47,48]

Utilizing the adsorption of surfactants at solid surfaces, the release profile of a drug can be controlled.^[49] For example, the release profile of oxprenolol can be controlled by adsorbing different amounts of the wetting agent sodium laurylsulphate (SLS) onto microporous polypropylene powder. In the process, matrix tablets containing oxprenolol HCl, polypropylene powder, and other excipients were made first, then were dry-coated with a drug-polymer mixture by a single compression. The coat contained polypropylene powder pretreated with a suitable amount of SLS and a small amount of oxprenolol HCl. With the adsorbed SLS, both wetting problems of hydrophobic polypropylene powder and food effects on release profile were successfully solved.

The reason why the adsorption of some polymers onto a drug particle surface can improve the dissolution rate, but some cannot, is not fully understood. Some surfactant molecules may adsorb onto solid surfaces by utilizing the strong hydrophobic interactions between hydrophobic moieties of drugs and surfactants and orient the polar headgroups to the aqueous phase, thus increasing the overall wettability of the drug surface. Some polymers may specifically interact with drug molecules at the drug crystal surface, and either increase or decrease the dissolution rate of drugs.^[50] Acetaminophen has been dissolved in aqueous solutions of different polymers. Fig. 8 shows that surface etching patterns have been altered in the presence of polymers. In the absence of polymers, on the (010) face, the etching patterns follow the a -axis and c -axis exactly. However, polymers such as polyvinylalcohol (PVA), PEG, and polyvinylpyrrolidone (PVP) can adsorb onto crystal surface, and alter the etching patterns of acetaminophen on the (010) face, thus affecting dissolution rate.

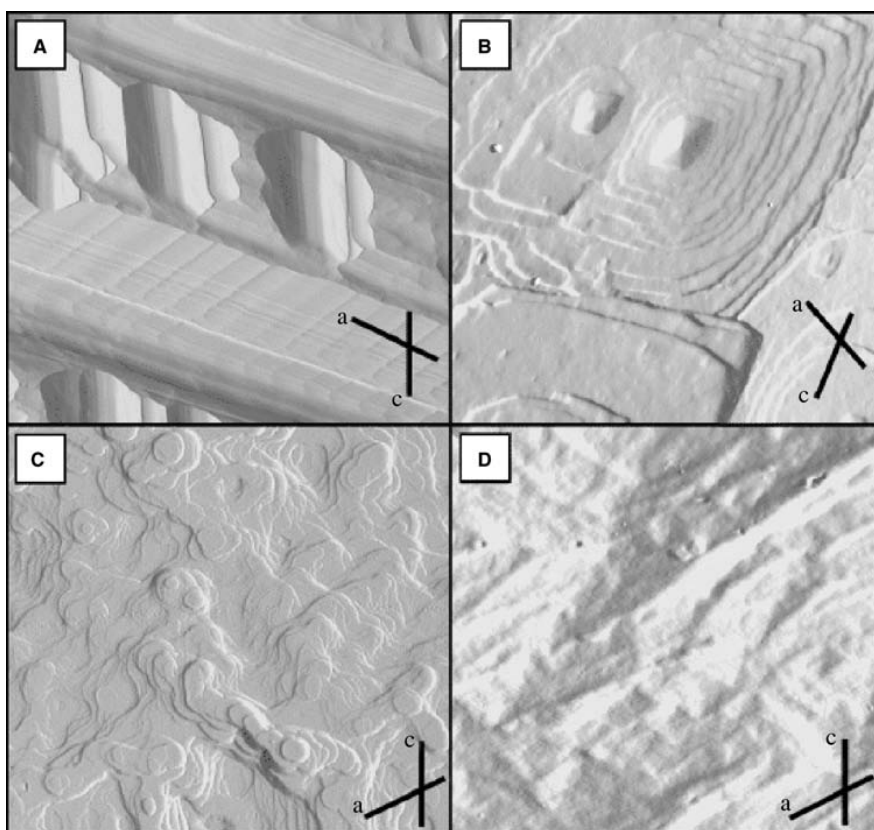


Fig. 8 Atomic force microscopy (AFM) images of the acetaminophen (010) face etched by (A) water; (B) 25 mg/mL PVA (15K); (C) 12.5 mg/mL PEG (1000); and (D) 1 mg/mL PVP (K30). The *a* and *c* axis were marked on corresponding images. (From Ref.^[50].)

Crystallization Inhibition

In the formulation designs used to improve dissolution rate, drugs adsorbed onto the surface of adsorbents exist completely or partially in the amorphous state. The drug in solution becomes supersaturated relative to the solubility of the crystalline drug. Because the free energy of both amorphous drug and supersaturated drug in solution is higher than the free energy of the crystalline drug, crystallization may occur for both amorphous drugs and supersaturated drugs in solution.^[51]

Polymers that can interact with drug molecules especially adsorbed onto crystal surfaces have been widely used to inhibit drug crystallization to maintain supersaturated states for drug delivery systems.^[52–55] Raghavan et al.^[52,53] observed that methylcellulose (MC) and HPMC could significantly inhibit the crystallization of supersaturated hydrocortisone acetate (HA). The mechanism of nucleation retardation was believed to be due to the hydrogen bonding interactions between HA and the polymers. As to the

inhibition of crystal growth and crystal morphology change by polymers, it is believed to be due to the hydrodynamic boundary layer surrounding the crystal, and the adsorption of polymer molecules onto the crystal surface. Hasegawa et al.^[54] found that carboxymethylcellulose (CMEC) could inhibit the crystallization of drugs from supersaturated solutions. The inhibitory effect of CMEC might be due to the adsorption of CMEC at the solid–water interface in which a hydrophobic drug crystal surface is formed, and hinders the deposition of drug molecules on the crystal surface. There were significant differences for the dissolution profiles of nifedipine, spironolactone, and griseofulvin solid dispersions in the presence or absence of CMEC in the dissolution medium. Because CMEC is an anionic polymer whose hydrophobicity increases with decreasing pH, the inhibitory effect of CMEC on crystallization increases as pH decreases. The observation of the pH effect also supports the hypothesis that CMEC inhibits drug crystallization by adsorbing onto the hydrophobic surface of poorly water-soluble drugs.

Due to the difference of the polymer adsorption onto different faces of different crystal forms, polymer adsorption onto the crystal face has played an important role in crystal polymorphic transformation.^[56–58] Garti and Zour^[56] have studied the effects of surfactants on the polymorphic transformation of glutamic acid. Glutamic acid has two crystal forms, α and β , with the β -form being more stable than the α -form. Those surfactants that preferentially adsorb onto the surface of the α -growing crystals retard the transformation of the α -form to the β -form. A Langmuir analysis indicates that the kinetic coefficient of crystal polymorphic transformation is related to the volume of the surfactant adsorbed at the crystal surface.

Trace amounts of impurity that adsorbed onto the surface of a growing crystal can cause a marked difference in dissolution rate. Grant, Chow, and Chan^[59] reported that in the presence of even trace amounts of *n*-alkanoic acid, the adipic acid crystal grown from an aqueous solution will have changes in crystal energy and dissolution rate. It was suggested that additive *n*-alkanoic acid could adsorb onto the surfaces of growing crystals even when incorporated into adipic acid crystals. The additive-induced difference in intrinsic dissolution rate (IDR) cannot be ignored.

OTHER APPLICATIONS USING ADSORPTION AT SOLID SURFACES

Desiccant for Stabilizing Moisture-Sensitive Drug

Colloidal silica has been successfully used by Gore and Banker^[60] to improve the chemical stability of aspirin, whose hydrolytic tendency is well-known. Colloidal silicas have a large surface area and a highly polar silanol surface, which imparts a high moisture adsorption capacity. Water adsorbs onto the surface of colloidal silicas by forming hydrogen bonds with silanol. Colloidal silicas are commonly used as desiccants in the pharmaceutical industry, especially for hygroscopic or hydrolyzable drugs. Even though the desiccant effect of colloidal silica is not the only factor that helps to stabilize aspirin in the studied formulation, its strong moisture adsorption capacity has played a very important role.

Dry Powder Inhalation

The surface adsorption approach has been used to make a DPI device.^[61] First, a fatty acid or fatty alcohol derivative or a poloxamer is dissolved or dispersed in a solvent in which drugs and carriers are insoluble. The preferred solvent is *n*-hexane or

cyclohexane. Second, the fatty acid solution or suspension is adsorbed onto the surface of soluble micronized drugs and/or acceptable carriers such as lactose monohydrate, anhydrous glucose, polylactides, or PVA. The surface modification of drugs via adsorption has several advantages in making DPI formulations, such as the reduction of electrostatic charge during processing and handling, reduction of adhesion on contact surfaces, improvement of powder flowability in pneumatic transport, and improvement of drug content uniformity. This approach has made the scaling up of DPI formulations easier, and has significantly improved the inhalation properties of powders.

Sublingual Nitroglycerin Tablets

Waalder et al.^[62] have successfully applied the adsorption approach to make sublingual nitroglycerin tablets by direct compression with better content uniformity, lower weight variation, and much higher stability than tablets made from a molding approach. In the molding approach, nitroglycerin will migrate to the surface of a tablet during the drying process. During manufacturing as well as storage, there may be potency loss due to the volatility of nitroglycerin. Tablets can also be made by wet granulation, where drying may also induce unblending. In the direct compression approach, nitroglycerin dissolved in alcohol was first added to MCC, and triturated slowly for about 5 min to assure content uniformity. The powder is left at room temperature for 12 hr with occasional stirring. Then alcohol is evaporated and nitroglycerin becomes adsorbed onto MCC. Afterward, MCC/nitroglycerin is mixed with other excipients to achieve suitable properties for the finished tablets, including solubility and disintegration rate.

Surface Area Measurement

Besides liquid adsorption on solid surfaces, gas adsorption on solid surfaces is also very useful in measuring surface area in the pharmaceutical industry.^[63–69] Based on the Brunauer–Emmet–Teller (BET) equation, Vertommen, Rombaut, and Kinget^[63] used krypton adsorption to measure the specific surface area of pellets made from wet granulation, extrusion, and spheronization. Westermarck et al.^[64] noticed that nitrogen adsorption was more sensitive to changes in the surface area of mannitol tablets caused by compression. In measuring pore size, nitrogen adsorption can measure smaller pores (diameter range 3–200 nm) than high-pressure mercury porosimetry, with a range of 7 nm–14 μ m. It is the large number of small pores with diameters <200 nm that contribute to the

increased compactibility of granules and, ultimately, greater tablet strength.

The surface morphology of five commonly used excipients has been studied using both particle size distribution and nitrogen adsorption methods.^[70] The five tableting excipients were unmilled dicalcium phosphate dihydrate (Di-Tab), MCC (Avicel PH102), corn starch, croscarmellose sodium (Ac-di-sol), and sodium starch glycolate (Primojel). A surface irregularity index (SII) was established to indicate surface roughness due to porosity, and its value was consistent with the direct microscopic observation of a powder sample. The nitrogen adsorption-desorption isotherms showed certain hystereses, especially for Avicel PH102, Di-Tab, and Ac-di-sol, and the remaining nitrogen adsorbed on the surface during desorption process was believed to be due to pores on the powder surface.

CONCLUSIONS

Adsorption at solid surfaces has been addressed in relation to many aspects of pharmaceutical development. Besides process development and dissolution rate enhancement, the phenomenon of adsorption at solid surfaces is also useful in many other aspects of the pharmaceutical industry, such as making special formulations such as DPI, surface area measurement, and so on. In pharmaceutical processing, adsorbing drugs onto the solid surface of other excipients can help to achieve content uniformity, especially for low-dose drugs, during the mixing process. The adsorption of binder solution onto solid surfaces is important in granulation for improving excipient flowability, compactibility, and so on. The adsorption of moisture onto excipients not only facilitates compression, but also affects both the physical and chemical properties of finished solid dosage forms during storage. Desiccants can help to control environmental humidity by adsorbing moisture via their large hydrophilic surface and to stabilize moisture-sensitive drugs.

Adsorption at solid surfaces has also been applied in different approaches to improve the dissolution rate of poorly soluble compounds. In solid dispersions, by adsorbing drug molecules onto the surface of adsorbents with a large surface area, the dissolution rate can be significantly increased due to the increase in surface area and/or the decreased crystallinity of drugs. Adsorbing surfactant onto solid surfaces of poorly soluble drugs can enhance the dissolution rate by mechanisms that are not fully understood. The adsorbed surfactant may affect dissolution rate through mechanisms such as improving the wettability of drug surfaces, having specific interactions with drug molecules on the crystal surface, or increasing equilibrium drug solubility in aqueous solution.

By adsorbing onto crystal surfaces, polymers have been widely used to inhibit the crystallization of dissolved drugs or unstable amorphous drugs during dissolution, to maintain good dissolution rate during dissolution, and to improve the bioavailability of poorly soluble compounds. Exactly how polymers adsorb onto, and interact with, solid surfaces and why some polymers are more effective as crystallization inhibitors than others are topics of ongoing investigation.

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