Contact Angle Measurements and Applications in Pharmaceuticals and Foods: A Critical Review

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Abstract: Contact angle (CA) analysis is a noninvasive and rapid method to determine the wettability of various materials including biomaterials. Contact angle measurements and interpretations have been performed since the beginning of the 19th century. This review provides an overview of contact angle analysis and measurements performed on surfaces of pharmaceuticals and foods in relation to other analytical approaches. The contact angle method represents an analytical approach widely applied in order to determine the surface free energy of complex materials in these fields. Our review is focused on contact angle analysis and surface free energy characterization of pharmaceutical powders, injectable drugs, and foods. Correlations between chemistry, rheology and surface properties of these materials were considered in order to demonstrate the importance of the integrated analytical approach (IAA) for a complete characterization of these kinds of materials and the critical issues encountered in CA measurements. This review is organized in two parts: the first one is an overview of the history of research in CA method since its beginning, and the second one is focused on an overview of particular applications of CA method in pharmaceuticals and foods. In this work, it is shown that the topic of the surface properties of materials in the new "*pharma-food*" field is currently a very important area of research for the interpretation of the phenomena and the control of the quality and processing of these materials.

Keywords: Contact angle, skin hydration, pharmaceutics, foods, cosmetics, surface free energy

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1 Introduction

The contact angle measurements have been carried out since the 19th century during which for the first time the contact angle (CA; deg) was described as the result of the contact between a solid (s) and a liquid (l). The curvature of l depends on the equilibrium of three interfacial tensions (ST) at liquid- vapor ($\gamma_{l/v}$), solid-liquid ($\gamma_{s/l}$), and solid-vapor ($\gamma_{s/v}$) interfaces [1]. These first studies provided the basis for the concept of wettability of materials which is measurable through the determination of the CA at the interface between s and l and which depends on the balance between the gravity force and the cohesion force within the liquid depending on its chemical composition and the force of adhesion at the interface between the two materials [2]. During this period the first technique for measuring the surface pressure by surface tension (ST; mN/m) measurement was developed [3], opening new perspectives in the interpretation of the CA formation. All the studies performed in these years were developed from the investigations of the capillary phenomenon in which the measurement of the height reached by the liquid that rises in a capillary represented the main method for testing the theories of capillary action [4]. In the 19th century, important studies using the thermodynamic approach for the explanation of CA were also performed [5] and the influence of vapour (v) on the work of adhesion (W_A; mJ/m^2) was studied [6], opening a new aspect of CA investigations. Successively, in the first part of the 20th century the attention of researchers was focused on the observation of the behaviour of drops deposited on a substrate with the aim to characterize the orientation of the molecules present in the surface of liquids taking in account the total energy, the chemical composition and its influence on the ST [7]. These investigations helped to demonstrate the correlation between CA and polarity of solid surfaces [8] and underlined the importance of flat surfaces in the determination of CA at s/l interface in relation to the liquid drop size [9]. Other studies demonstrated the influence of the roughness on the CA analysis also [10] (Figure 1).

The upper left-hand sketch of Figure 1 presents a plan view of the solid surface and the line M-N represents a segment of the periphery of the wetted area advancing from left to right. The studies on the capillary flow in a bundle of parallel cylindrical tubes previously conducted in the 19th century were extended to the imbibition phenomenon of a liquid drop into porous materials [11]. Successively, it was possible to develop a method for determining CA on a finely divided substrate [12]. All these new researches performed during the first years of the 20th century on different kinds of solid surfaces opened the application of the CA method in different research fields for ST and surface free energy (SFE; mJ/m^2) characterization of liquids and solid materials. Other studies started to take into account the surface area occupied by a drop of liquid onto a solid in relation to the measured CA, the volume of the drop, the density of the liquid and its ST [13]. At the beginning of 1940s, the need for determining the film pressure of a liquid for the determination of the pressure at the interface between a solid and aqueous solutions of organic

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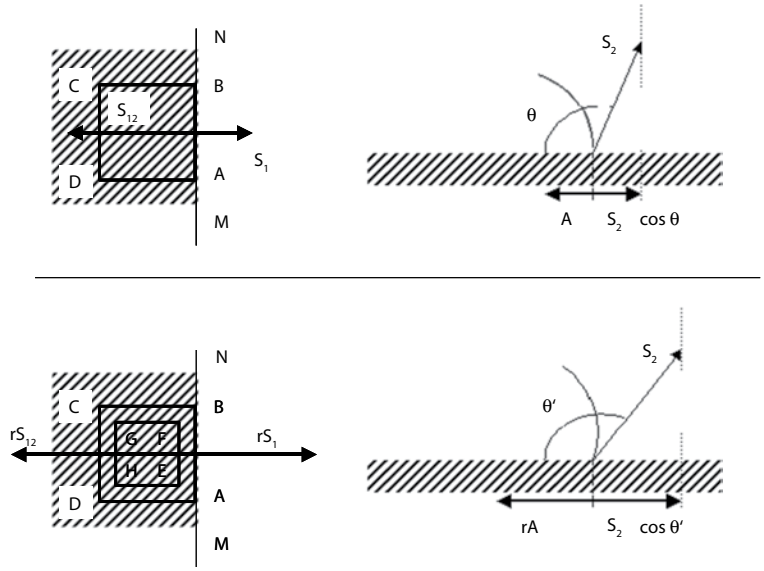

Figure 1 Vector relations of surface forces:; (above) smooth solid surface, (below) rough solid surface where S_1 and S_2 are force vectors acting on a unit length of the periphery, A-B is unit length of the periphery, A is the adhesion tension, S_2 is the surface tension of the liquid, r is the roughness factor, EFGH is the area on which the specific interfacial energy is concentrated. rA is the product measured by the term $S_2 \cos \theta$ calculated for real solids, and θ the contact angle (Adapted from [10]).

substances led to the development of a new apparatus for CA measurements using a tilting plate coupled with a Wilhelmy type film balance [14].

In the 1940s the attention was focused on the surfaces of solids and the first studies were performed by Washburn [11] and Bartell and Whitney [12] in order to confirm the suitability of the CA method for the determination of micropore-size distribution in porous solids. The micropore-size distribution can be obtained by calculating the pressure required to force a liquid into a pore depending on the radius of the pore, the ST of the liquid and the CA (deg) measured at the interface [15]. The studies performed on porous solids were accompanied in the same period by the works of Cassie and Cassie-Baxter [16] whose equation was used to describe the phenomenon of superhydrophobicity shown by natural and artificial surfaces characterized by extremely high (> 150°) CA at the interface with water [17].This approach opened up the investigation on low surface energy substrates [16]. The Cassie-Baxter approach was based on the concept of advancing (θ_a) and receding (θ_r) CA measurements. This approach focuses on the interfacial force between a drop and an inclined substrate. The difference between θ_a and θ_r is called Contact Angle Hysteresis (CAH) and it influences the determination of the surface tension (ST) of a liquid [18, 19]. In order to determine in an easy way

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the CA of a liquid on a solid surface, in the 1940s a novel goniometer was built and from which the concept was developed for the modern tensiometers [20]. Due to the employment of the new goniometer and on the basis of previous studies, new concepts of CA (θ) were studied in which it was demonstrated that its value was linked directly with the interfacial tensions at solid-liquid ($\gamma_{s/l}$),solid-vapour ($\gamma_{s/v}$) and liquid-vapour ($\gamma_{l/v}$) interfaces [21]. In Figure 2 is reported an example of CA measured at the interface between a heated solid surface and a drop of liquid.

In the 1950s the attention of many researchers was focused on investigation of the wettability property of solids with low SFE e.g., for fluorinated compounds [22]. In Figure 3 is reported the cosine of CA for n-alkanes on surfaces composed of -CF_3, -CF_2H, -CF_2- and -CH_3 groups in correlation with ST (dynes/cm) by a linear equation.

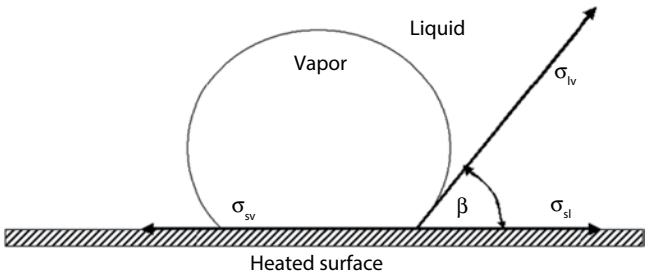

Figure 2 Scheme of a drop of liquid on a heated solid surface where β is CA, σ_{lv} is interfacial tension at liquid-vapour interface, σ_{sv} is interfacial tension at solid-vapour interface, and σ_{sl} is the interfacial tension at solid-liquid interface (Adapted from [21]).

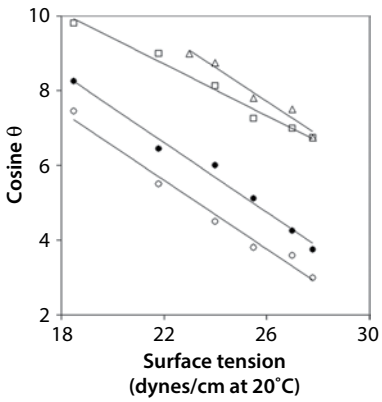

Figure 3 Linear correlations between CA (deg) and ST (dynes/cm) of n-alkanes on low energy surfaces of -CF_3 (O), -CF_2H (•), -CF_2 (□) and -CH_3 (Δ) groups, (Adapted from [22]).

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These works compared the wettability of fluorinated compounds (CF_2H and CF_3 groups) after reactions with esters, amines, alcohols, organic acids and other polar components such as glycerol based on the previous studies performed by Fox and Zisman which demonstrated that the wettability of low energy solids depends on the atomic composition of their surfaces [23–25]. All these studies demonstrated that in the case of solid surfaces with low SFE, the CA variations and the ST of a large variety of liquids are linked and the wetting of the substrate depends on the kind of surface. New thermodynamic approaches at solid-liquid-vapour (s/l/v) systems by using the techniques of Gibbs gave the possibility to derive the Young's equation for a sessile drop on a solid in which adsorption and gravity were also considered [26]. This approach demonstrated for the first time that Young's equation was valid in all situations studied. From these observations in the early 1960s a relation between the critical ST of spreading for low energy solid surfaces and the constitution of their surfaces was found, formulating for the first time the constitutive law of wettability [27] (Figure 4).

Zisman studies on low SFE solids performed in the 1950s and 1960s proved to be fundamental for the successive developments of mathematical models for the evaluation of the interfacial tension (IF; mN/m) between liquids having different ST values [28].

In light of these considerations, an equation relating the free energies of cohesion of separate phases to the free energy of adhesion, and the ST to the IF was developed using CA as the main parameter [29]. In the same period, the CAH, previously studied by Cassie&Baxter [16] and McDougall and Ockrent [18], was described using a digital model able to determine θ_a and θ_r on ideal heterogeneous surfaces. By this digital model it was possible to define the CAH as a balance between the vibrational energy of the drop and the heights of energy barriers

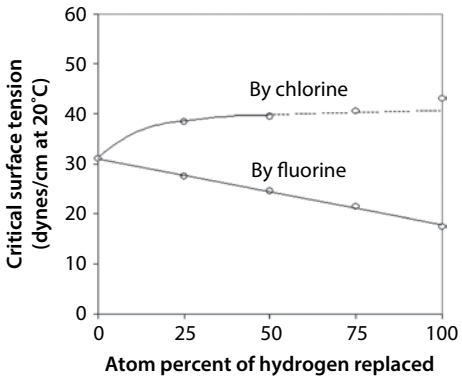

Figure 4 Effect of progressive halogen substitution on the critical surface tension of polyethylene-type surfaces (Adapted from [27]).

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between different metastable states [30]. In the 1960s, new investigations on the interfacial force (IF) between a solid and a liquid by the CA method opened a new frontier of science evoking new fields of applications [30]. In this context, further new studies were conducted for the evaluation of liquid flow in a dynamic wetting situation [31] demonstrating its influence on the phenomena that occur at l/s interface and opening new perspectives in the analysis of the drop motion time by the CA method (Figures 5, 6).

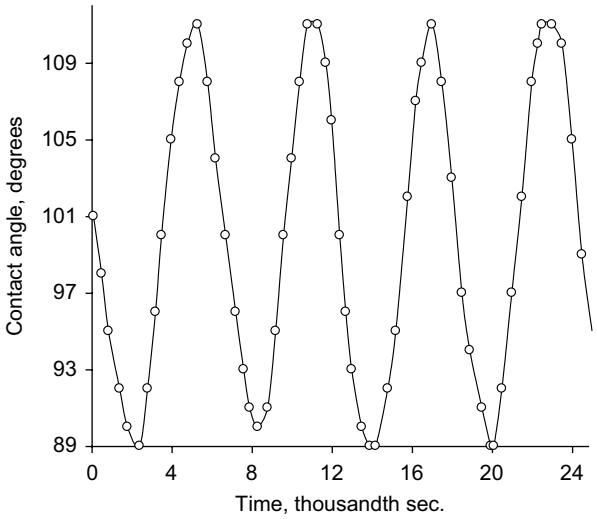

Figure 5 Experimental characteristic of drop oscillation relative to time (Adapted from [32]).

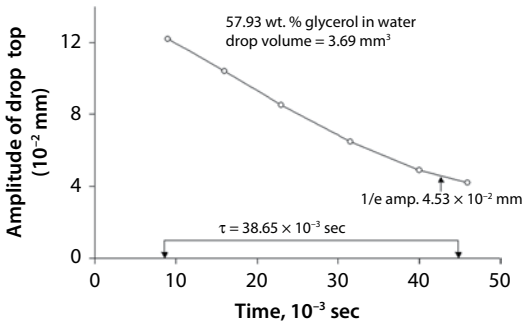

Figure 6 Correlation between the decrease of the amplitude of drop top (mm) and time (sec) where τ represents the experimental decay time, 1/e is the decrease value of the amplitude of drop's top motion (AMP.) from the original value where e is the base of the natural logarithms (Adapted from [32]).

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The increased need for CA research in a number of scientific fields led to an improvement in instruments for CA measurements with the objective to enhance the performance of the goniometer apparatus by modifying the instrument developed by Zisman in the 1940s (goniometer) and Hayman in the 1950s and the tangentometer scheme is reported by Fenrick [33] while a modification of the Langmuir & Shaeffer apparatus was performed with an increase in the simplicity of manual operation, ruggedness, high precision and, consequently, the accuracy of the drop profile method [34]. All the researches performed by the CA method in more than a century and reported above led to the development of mathematical conversion models capable to determine in a precise and accurate way the surface free energy (SFE; mJ/m^2) and dispersion (DC; mJ/m^2) and polar components (PC; mJ/m^2) of liquids and solids of different nature in the 1970s, 1980s and 1990s. The aim of this review is to present a condensed overview of the recent progresses and perspectives of the CA method for the characterization of systems in "*pharma-food*" field with the main focus on some recent methods applied to some particular situations in which the tensiometric technique has been used for the characterization of the wettability.

1.1 Prospects

Various theoretical approaches have been developed for the determination of the ST of liquids and SFE of solids by the CA method in the fields of food and pharmaceutics. On the basis of the fact that the SFE of a solid dictates its surface properties and interfacial phenomena such as adsorption, wetting or adhesion with liquid phases, the knowledge of ST and SFE is of great interest in many fields which consider the interfacial phenomena useful for numerous industrial applications. For example, in the cases of packaging, food science, biomedical applications and pharmaceutical products, cleaning processes, adhesive technology, painting, coating and many other applications in many fields in relation to wettability of their systems, the CA analysis can be applied widely [35]. The CA method has been known since the 19th century, during which the theoretical basis of CA phenomena and surface free energy of materials was developed; actually the measurements and interpretations of CAs are still debated in the scientific literature because of the need to better understand the fundamental mechanisms at s/l interface. The novel applications of the CA method in different research fields linked to the human health within the Integrated Analytical Approach (IAA) can give more information about the links between the structure and surface of the systems investigated. In particular, the ST and SFE characterization in the field of food science is deeply investigated, especially for packaging and coating applications and suggests different strategies in order to improve the processing and quality of these materials [35]. These experimental results demonstrated that the wettability is one of the fundamental parameters in food emulsions and cosmetics industries as the water-oil (W/O) emulsions and oil-water (O/W) emulsions are stabilized by fine solid

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particles and the stability of these formulations depends directly on the particle wettability. In the pharmaceutical industry the wettability of powders is important for the production of formulations and the manufacturing and optimization of the production process of drugs [36]. We focus on some recent studies on particular and innovative aspects and applications of CA approach in the study of pharmaceutics and foods of actual industrial and commercial interest within the novel "*pharma-food*" field. In this context in the last years the *pharma-food* concept has had impact on pharmacological and food research because several food components are employed as medicines and pro-drugs [37]. Visioli [37] recently reported that in the context of "*pharma-food*" there are areas in which the difference between food and pharma is not well-defined because nutrition could involve bioactive compounds (drugs), fibers, plant molecules and other substances (nutrients). The chronic diseases can be treated by controlling the macro- and micronutrients in pharmacological doses (supplements, nutraceuticals, functional foods). Visioli highlighted that the traditional pharmacotherapy is often accompanied by supplementary treatments with nutrition-derived remedies to decrease the doses of medicines and reduce their side effects [37]. In the context of *pharma-food*, the CA approach for a non-invasive investigation of different pharmaceutical forms can be useful for the determination of the quality and processing in food systems also and can be considered as a common analytical approach capable to link these two fields.

2 Contact Angle Measurements in Pharmaceutical Field

2.1 Pharmaceutical Powders

Generally, the CA analysis of pharmaceutical products has considered mainly the powder form in which the wettability of small particles influences their ability to float on a liquid. One of the most common methods for the CA determination of particles is the h-epsilon (h-ε) method [38] which involves e.g. the measurement of the maximum height of a droplet containing solid particles (Figure 7).

In general the data obtained from the h-epsilon method are independent of the size of the particles and the porosity of the material, making this method applicable for investigation of any powder system. The most important result obtained from the application of the h-epsilon method is that hydrophobic powder materials are characterized by large particle size [39]. According to Lerk *et al*. [39], the CA method was found to be suitable for investigations on hydrophobic powders also and the wettability becomes an important parameter for a non-invasive characterization of many kinds of pharmaceutical powders together with the calculation of their dispersion (DC: mJ/m^2) and polar (PC: mJ/m^2) components. In this context, Marston *et al*. investigated the dynamics of the drop impact onto powder surfaces, opening the possibility to study the temporal evolution of the spreading

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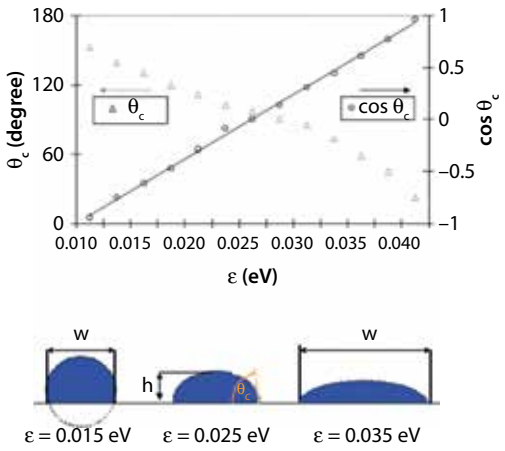

Figure 7 CA measurements method for molten Ag droplets on graphene where θ_c can be determined from height (h), ε is the energy supplied (eV) and w changes clearly with ε between 0.01 eV and 0.04 eV (Adapted from [38]).

phase, drop deformation and the resulting crater morphology [40]. For water drop impacting on dry and partially saturated powders, a low impact speed 0.15 m/s and a high impact speed (2.2 m/s) were investigated. In particular, when a drop wets a pharmaceutical powder bed, the corresponding times available for the penetration should be considered as a function of moisture content as demonstrated by the analysis of apparent contact diameter with time as a function of the speed of drainage (u_i). After the impact of the liquid drop on the powder, the imbibition is characterized by two limited cases: the constant drawing area (CDA) (Equation 1) and decreasing drawing area (DDA) (Equation 2) both depending on CA measurements.

$$t_{CDA} = 1.35 \frac{V_0^{2/3}}{\varepsilon^2 R_{pore}} \frac{\mu}{\sigma \cos \theta_p} \tag{1}$$

$$t_{DDA} = 9 t_{CDA} \tag{2}$$

where V_o is the drop volume, μ is the liquid dynamic viscosity, ε the porosity of powder bed, σ is the ST of the liquid drop and θ_p is the apparent CA. The time of penetration depends on the size of the pore (R_{pore}) of the powder bed (Equation 3).

$$R_{pore} = 2\varepsilon / ((1\text{-}\varepsilon) S0 \rho_s \tag{3}$$

where ε is the porosity of the bed, S0 is the particle specific surface area and ρ_s is the packing density of the pores. Marston *et al*. [40] showed that in the case of

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pharmaceutical powders, the CA values can be determined by the capillary rise method using a force tensiometer and Equation (4).

$$m^2 = c\frac{\rho^2\sigma\cos\theta_p}{\mu}t \tag{4}$$

where m is the mass of liquid in the capillary at time t, ρ is the density of the liquid that rises and c is a constant depending on the material used. As reported by Marston *et al*. [40], many experimental and application studies have been performed in order to investigate the impact of a water drop on pre-wetted moisturized pharmaceutical powders demonstrating that the moisture content has only a little influence on CA measurements and drop spreading appears similar for different moisture contents. However, the maximum drop spread and subsequent drainage into the powder are significantly influenced by the liquid and the impact speed. Marston *et al*. [40] showed that in the case of a low impact speed, the imbibition moment during the initial spreading phase is small. In the case of a dry powder, after the impact on the surface the drop can drain at both low and high impact speeds. The high impact speed can cause the formation of granules, while for wet powders with various moisture contents the drop drainage into the powder occurs without the formation of granules and splashing in pre-wetted powders. As evidenced previously, the spreading time is a strong function of the moisture content of the powder bed and the drop impact speed determines the maximum spread diameter from impact to complete drainage, and the penetration time in the case of a pre-wetted powder is shorter than for dry powders whose saturation influences the speed of penetration. The analyses of these parameters are very important for the study of the granulation process of pharmaceutical powders for which the effective pore radius, pore size, CA and permeability represent fundamental parameters. Anyway, considering the dynamics of the penetration process of a liquid into a powder bed, Han *et al*. proposed the droplet penetration method (DPM) as a new tool capable of characterizing the wettability of pharmaceutical powders [41]. The DPM considers that the capillary pressure inside the porous powder is the only dominant driving force for the imbibition of drops, and the contact area between the penetrating drop and the powder bed is constant. The DPM was developed on the basis of the penetration process observed after the deposition of droplets of two different liquids on a slightly compressed powder bed and recording their penetration [41]. Han *et al*. demonstrated that DPM can evaluate in a new way the influence of the particle size distribution on the wetting behavior of pharmaceutical powders [41]. Han *et al*. considered, as an example, the lactose monohydrate excipient powder with particles in 38–45, 45–53, 53–63, 63–75, 75–90, 90–106 size ranges (μm), and anhydrous caffeine as active pharmaceutical ingredient (API). The test liquid used was deionized water. In this case, DPM demonstrated that the lactose powder with particle size smaller than 75 μm has approximately the same CA and a significant decrease occurs when its particles are larger

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than 75 μm [41]. In the case of caffeine powder Han *et al*. found that larger particles resulted in smaller CA values. In light of these experimental evidences, the DPM represents a useful tool for controlling the granulation process of pharmaceutical powders [41]. However, Marston *et al.* [40] demonstrated that a force tensiometer was efficient for CA measurements on powders, and the wettability of dispersed materials of pharmaceutical powders could be determined through the capillary penetration method using the traditional Washburn apparatus (Figure 8) [42].

Teipel and Mikonsaari [42] reported that the Washburn equation combines the Hagen-Poiseuille Equation (5) with the equation developed for the evaluation of the capillary pressure of liquids or Laplace equation (Equation 6) to obtain an expression that describes the liquid through a cylindrical capillary (Equation 7).

$$\frac{dV}{dt} = \frac{\pi \Delta p r^2}{8\eta h} \tag{5}$$

$$\Delta p = 2\gamma_{lv} \cos\Theta \frac{1}{r} \tag{6}$$

$$h^2 = \frac{tr\gamma_{lv} \cos\Theta}{2\eta} \tag{7}$$

where h is the length wetted by the liquid with volume dV in time t, the term Δp represents the Laplace pressure, r is the capillary radius, η represents the viscosity of the liquid, t is the flow time of the liquid, γ_{lv} is the ST of the liquid and Θ is the advancing CA. The Washburn equation is a common method to analyze the increase in mass measured as a function of time. Teipel and Mikonsaari [42]

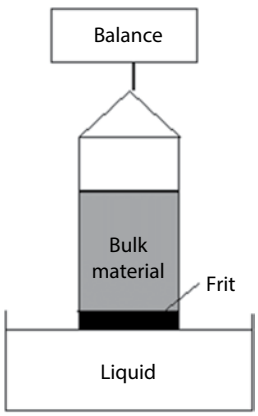

Figure 8 Apparatus for the Washburn method (Adapted from [42]).

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reported that in the Washburn method the pharmaceutical powder is placed in a closed tube with a frit at the bottom end. The liquid rises through the glass frit into the powder and the increase in weight with time is measured with a balance. Teipel and Mikonsaari showed that the application of the Washburn equation allows to characterize the wetting behavior of powders, and in particular the critical SFE of pharmaceutical powders such as amylobartbitone, acetaminophen and adipic acid could be correlated with other methods such as sedimentation. The capillary rise method is comparable to the sessile drop measurements performed on pharmaceutical powders previously compacted or on large single crystals and the agreement between these two methods for the analysis of pharmaceutical powders led to the estimation of the value of SFE of solid (γ_s) using an equation of state. As reported by Teipel and Mikonsaari, and more recently Thakker *et al*. developed a modified Washburn apparatus for the measurement of powder wettability (Figure 9) [43].

As reported by Thakker *et al*. [43], the traditional Washburn apparatus was coupled to a high resolution electromagnetic microbalance system which can give a resolution R of 1 mg (equation 8) depending on the resistivity of the metal wire (ρ), the length of the wire (l) and the change in the area of the wire (A) which influences the resistance and, consequently, a voltage signal proportionally to the force is produced.

$$R = \frac{\rho l}{A} \tag{8}$$

The CA measurements obtained with this novel Washburn apparatus are precise and accurate and demonstrate that the changes in the powder wettability

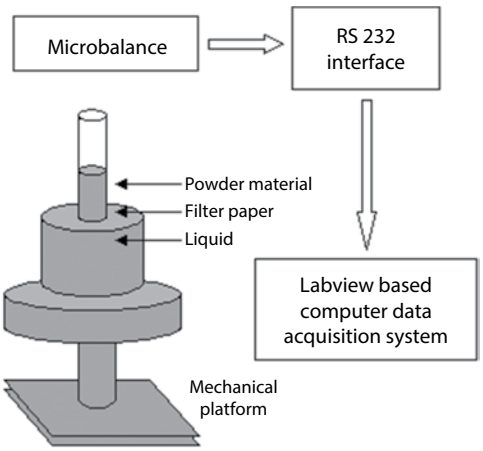

Figure 9 Modified Washburn apparatus (Adapted from [43]).

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are in accord with the hydrophilic and hydrophobic nature of the materials used [43, 44] (Table 1).

The results obtained by Thakker *et al.* [43] are in accord with those obtained with a standard instrument. As an example, the new instrument can be used to evaluate the uncoated or nano-coated powders and treated polytetrafluoroethylene (PTFE) powders. The PTFE increases the water sorption of the powder providing a wide range of applications in food and pharmaceuticals (Figure 10).

Table 1 Wettability results of uncoated and nano-coated starch [43].

Powder sample	Test liquid	Time (s)	Mass^2 (g^2)	Material constant C × 10^{-15}	Contact angle θ (deg)
Starch uncoated	Water	3	0.34	7.97	80.3
0.5% R972 coated (hydrophobic)	Water	3	0.29	11.0	83.7
1.0% R972 coated (hydrophobic)	Water	3	0.13	12.80	87.1
1.0% 200P coated (hydrophilic)	Water	20	4.04	13.5	78.8
1.5% 200P coated (hydrophilic)	Water	20	5.11	15.1	77.8
2.0% 200P coated (hydrophilic)	Water	20	6.82	15.9	74.5

R972: Aerosil nano-silica (hydrophobic) coating.
200P: Aerosil nano-silica (hydrophilic) coating,

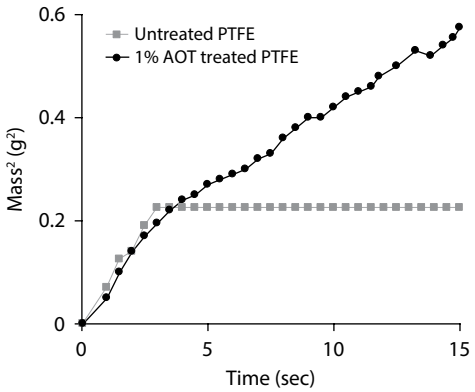

Figure 10 Mass versus time graphs of untreated and 1% AOT treated PTFE in water (Adapted from [43]).

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The analysis of wettability of powders is of fundamental importance for the control of the granulation process of pharmaceutical powders and also the sample preparation method has a strong influence on the results after the process of penetration of the liquid into the powder [42]. The first step in the granulation process involves wetting and nucleation phases and is crucial for the preparation of the final pharmaceutical form. In the case of non-wettable powders, the lifetime of the drop on the surface increases significantly enabling the use of hydrophobic powders for the production of granules. The analysis of hydrophobic and hydrophilic pharmaceutical powders performed by the CA method led to the calculation of their γ_s^d (dispersion component) and the selection of an appropriate solvent for the granulation process during which the liquid is added to the powder with the aim to form granules and product tablets [40]. In the case of the pre-wetted powders, the moisture content is generally not considered as a control parameter and the penetration time is commonly longer than that for a dry powder. This is because during the granulation process the moisture changes systematically and the drop impacts dry, partially wet and saturated powder. In this context, Zhang *et al*. [45] demonstrated that the prediction of the performance of granulating solvent is based on the solvent–drug spreading coefficient which is linked to the density, porosity and friability of the granules obtained. Ahfat *et al*. [46] were the first to demonstrate that the dispersion component determined from the mathematical conversion of CA (deg) to surface free energy SFE (mJ/m^2) was consistent with that determined by traditional analytical approach such as inverse gas chromatography (IGC); however, the correlation between CA and IGC techniques showed that the CA approach was difficult to apply to hydrophilic pharmaceutical powders due to the penetration of the drop in the core of the pharmaceutical form [46] (Tables 2 and 3). The retention time, i.e., the time taken by the probe to elute from the column, was used to calculate the dispersion component and polar acid/base parameters (K_A and K_D) of the powders using a series of thermodynamic equations. The W_A can be obtained from the free energy of adsorption (Equation 9).

$$\Delta G^{\circ}_{ads} = N * a * W_A \tag{9}$$

Table 2 The dispersion components and acid / base parameters of powders determined by IGC with the standard deviations shown in parentheses [46].

Sample	γ^d_s (mJ m^2)	K_A (10^{-2})	K_D (10^{-2})	K_D/K_A
Zamifenacin	46.8 (0.8)	0.3 (0.1)	27.3 (1.4)	94.3
Spray dried lactose	41.4 (0.7)	4.8 (0.2)	24.9 (0.6)	5.2
Anhydrous lactose	41.3 (1.3)	4.3 (0.6)	28.8 (11.6)	6.7
Starch	39.8 (0.7)	5.1 (0.2)	7.7 (0.3)	1.5
Lactose monohydrate	39.3 (1.1)	1.9 (0.1)	39.8 (2.5)	20.5

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Table 3 Surface free energy components of the test powders using the contact angle data for the three polar liquids (mJ/m^2) [47].

	γ^{TOT}_s	γ^{LW}_s	γ^{AB}_s	γ^{+}_S	γ^{-}_S
Theophylline	44.5	43.8	0.7	0.0	6.7
Caffeine	47.9	44.5	3.4	0.5	5.9

γ^{TOT}_s = total surface energy of the solid, γ^{LW}_s = Lifshitz-van der Waals contribution, γ^{AB}_s = acid-base contribution, γ^{+}_S = electron-acceptor acid-base contribution, γ^{-}_S = electron-donor acid-base contribution

where W_A is the work of adhesion, N is the Avogadro number, and a is the surface area of the liquid probe molecule. The W_A can be expressed as the geometric mean of the dispersion components of the solid (γ^d_s) and liquid (γ^d_l) (Equation 10).

$$W_A = 2 * (\gamma^d_s * \gamma^d_l)^{1/2} \tag{10}$$

By combining equations (9) and (10) it is possible to correlate surface free energies with IGC data (Equation 11).

$$\mathrm{RT ln} V_N = 2N (\gamma^d_s)^{1/2} * a * (\gamma^d_l)^{1/2} + C \tag{11}$$

where V_N is the net retention volume, $a*(\gamma^d_l)$ is the product of the surface area and dispersion component of an apolar liquid such as alkane, (γ^d_s) is the dispersion component of the unknown solid and C is a constant which takes into account the weight, surface area and vapour pressure of the probe in the gaseous state. The γ^d_s of the solid can be obtained from the slope of the line (Figure 11).

The comparison of the values of dispersion component of the surface free energy of powders obtained by IGC and dynamic angle tester (DAT) showed that both techniques ranked the powders in the same order. In Table 2 are reported the acid and base parameters determined from the slope and intercept of the line.

As an example, the CA/IGC combined approach was applied to study the wetting behaviour of caffeine and theophylline powders using the infinite dilution IGC [47]. According to Dove *et al*. [47], the pharmaceutical powders were adhered to a glass slide (glass slide method) and analyzed in tablet form using a classic Wilhelmy plate wetting method by which it is possible to determine the CA on a tablet surface (Equation 12).

$$\cos\theta = mg/p\gamma_{LV} \tag{12}$$

where θ is the contact angle on the powder, m is the mass (mg), g the acceleration of gravity, p the perimeter of the compact solid and γ_{LV} is the surface tension of the liquid (mN/m). Using the CA data it is possible to obtain the surface free energy components of powders such as theophylline and caffeine by using the models such as the van Oss, Chaudhury and Good [48] (Table 3).

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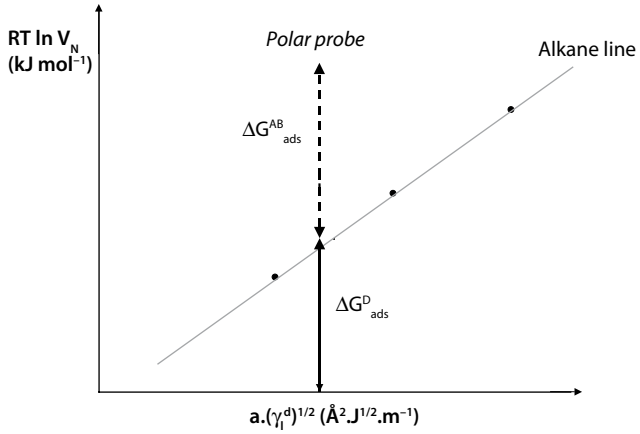

Figure 11 The free energy of adsorption of a polar probe in relation to the alkane line (Adapted from [46]).

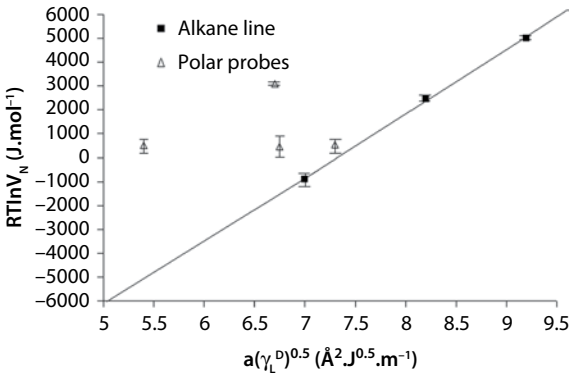

Figure 12 Passage of gaseous polar probes through a theophylline powder column at 35 °C where on the x axis is reported the dispersion contribution to the surface tension of the liquid (γ^D_L) and the molecular area of adsorbed molecule (a) (Adapted from [47]).

According to Ahfat *et al*. [46], plotting a graph of RT In V_N against a∗ $(\gamma^d_l)^{1/2}$ it is possible to determine the DC of the powders $(\gamma^d_s)^{1/2}$ from the gradient of the straight line (Figure 12).

On the other hand, to determine the polar character of the powders, a selection of polar probes with known acid-base characteristics is needed. Plotting RT In V_N with ΔH^d_{vap} (dispersion component of the heat of vaporization of the probe) it is possible to determinate the free energy of adsorption (ΔG_{a-sp}) (Figure 13).

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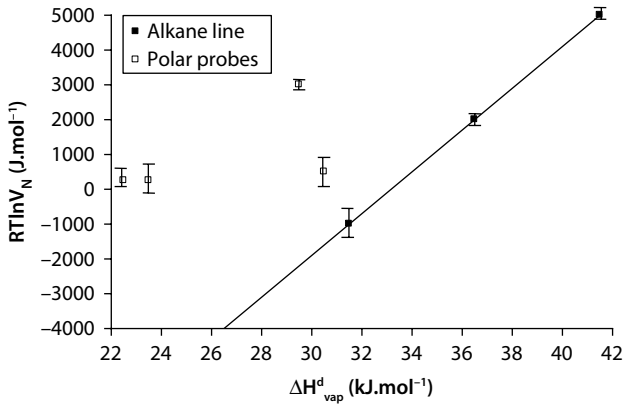

Figure 13 Passage of gaseous polar probes through a theophylline powder column at 35 °C where ΔH^d_{vap} reported on the x axis is the dispersion component of the heat of vaporization of the probe (Adapted from [47]).

As reported in Figure 13, the distance separating each polar probe from the point on the apolar straight line vertically below corresponds to the specific ΔG_{a-sp}. The ΔG_{a-sp} can be used to calculate the acid/base parameters of the powders (K_A, K_D). Dove *et al.* [47] showed that the critical issue in the analysis of a powder tablet by the Wilhelmy plate method is that the data obtained are inconsistent with very high values of γ_s because the complexity due to topography and porosity of the powder plate. In general, the application of the Wilhelmy plate method is suitable for γ_s values of about 44.5 and 47.9 mJ/m^2 as shown in the case of theophylline and caffeine surfaces (Table 3). Another issue that can affect the values of CA in the Wilhelmy plate method is the possibility that data can partially reflect the CA of the underlying adhesive used to fix the powder on the support. For these reasons, the γ_s values obtained by IGC cannot be correlated with those from CA measurements. This situation demonstrated that the Wilhelmy plate method is not suitable for the analysis of the wettability of most of the pharmaceutical powders. The wettability of pharmaceutical powders is a fundamental parameter for the preparation of dispersed systems. The analysis of the wettability of pharmaceutical powders leads to the determination of the quantitative relationships between wettability and chemical structure parameters of pharmaceutical powders. However, still potential problems with interpretation of capillary wetting data for swellable solids using combined capillary wetting and IGC approaches (CA/IGC) persist. These two methods are suitable for the analysis of SFE of a wide range of industrial microcrystalline cellulose powders commonly used in the pharmaceutical sector, such as morphine sulfate powder, the wettability of which can be determined by the capillary rise approach. However, the wetting rate data

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are reproducible for the liquids, and the sessile drop CA method on pharmaceutical compacted powder is not possible because the wetting tension data depend on its different crystal faces. As reported by Williams [49] in his recent review, this particular issue can be solved only if CAs are measured onto crystal faces with sufficiently large surfaces and data are correlated with other analytical techniques such as AFM and ToF-SIMS analytical techniques that provide information on the composition of the crystal facets of pharmaceutical compounds [49]. In Figures 14a and 14b are reported the surface free energy distributions as a function of size fraction, the lines show the surface free energies for specific facets of d-mannitol determined by contact angles on large d-mannitol crystals [49]. The work confirmed that the surface free energy distribution is sensitive to the shape and thus to the population of crystal facets found in a crystalline powder system [49].

Table 4 shows the surface free energy of untreated and silanised d-mannitol as determined with the Owens-Wendt [50] approach [49].

Using this combined approach, the CA method can effectively discriminate between different crystal facets in terms of their specific surface chemistries. As

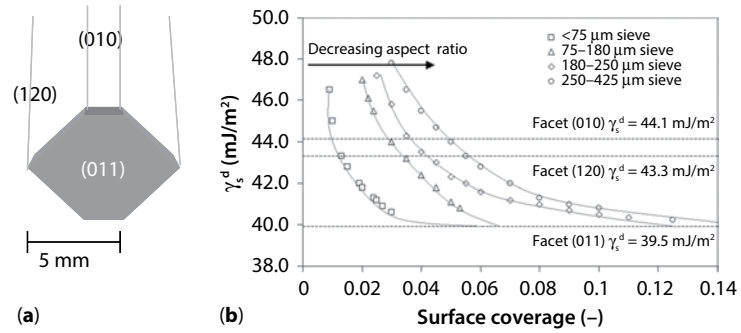

Figure 14 (**a**) Scheme of a macroscopic crystal of d-mannitol grown from aqueous solution (Adapted from [49]). (**b**) γ^d_s distribution of d-mannitol obtained with different sieve sizes where γ^d_s reported on the y axis is the dispersion component (Adapted from [49]).

Table 4 Surface free energy of d-mannitol crystal facets (010, 011 and 120) [49].

Facet	Untreated			Silanised	
	γ^d_{sv}	γ^p_{sv}	γ_{sv}	$\gamma^p_{sv}/\gamma_{sv}$	γ^d_{sv}
(010)	44.1 ± 0.6	12.8 ± 0.3	56.9 ± 0.9	0.23	34.9
(120)	43.3 ± 0.7	18.6 ± 0.4	61.9 ± 1.1	0.30	34.5
(011)	39.5 ± 0.4	35.4 ± 0.7	75.9 ± 1.0	0.47	34.9

γ^d_{SV} = dispersion component, γ^p_{SV} = polar component, γ_{SV} = surface free energy.

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reported by Williams [49], the CA/AFM/ToF-SIMS is a multidisciplinary combined approach that can be successfully used for the surface properties characterization of acicular crystal (CEL-A) and plate-shaped crystal (CEL-P) habits in the Celecoxib pharmaceutical powder. These data confirm the differences in the wettability and surface free energy (SFE) of the two habits and demonstrate that the dissolution of Celecoxib, and in particular the pharmaceutical performance of CEL-P, is due to the presence of higher hydrophilic surfaces in this habit with respect to CEL-A. Williams highlighted also that the CA determinations on large macroscopic crystals are widely used for aspirin, racemic Ibuprofen, S-(+)-Ibuprofen and Paracetamol forms (I and II) also. The Paracetamol powder tablets are one of the most sold drugs. The anisotropic surface energetics and wettability of the macroscopic crystals (I form) of Paracetamol powder tablets are largely studied in detail together with the XPS surface chemical composition analysis of its crystal facets. These investigations demonstrated that the relative surface polarity of the facets is in agreement with the fraction of polar hydroxyl groups as determined by XPS (Table 5).

The CA/IGC/XPS combined approach demonstrated that the surface of the crystals of Paracetamol (I form) is apolar and shows strong hydrophobic characteristics due to its high dispersion component (γ^d_S = 45 mJ/m^2). The CA/IGC/XPS combined approach can evaluate the differences between forms I and II in relation to the variations of their wetting behaviour (CA). Following the same approach, it was demonstrated that the surface energetics of aspirin powder was anisotropic and facet-dependent and linked to the presence of surface carboxylic groups. As regards the excipients, the studies of d-mannitol, a typical and largely used excipient for many pharmaceutical powder forms, and methyl silanised d-mannitol, as its hydrophobic model, can be performed on their large single crystals by the CA/IGC/XPS combined approach. Williams [49] reported that the IGC data for hydrophilic and hydrophobic d-mannitol are consistent with the CA values obtained from the analysis of wettability of the single crystal facets. The surface free energy

Table 5 Paracetamol form I crystals---surface free energy, unit cell characteristics and OH group density [49].

Facet	Unit cell length (Å)	Unit cell depth (Å)	Unit cell angle (°)	Unit cell area (Å^2)	No. of free OH groups	OH group density (Å^{-2})
(201)	14.44	9.4	90	135.7	2	0.0147
(001)	12.93	9.4	90	121.5	2	0.0165
(011)	11.78	12.93	74.74	146.9	2	0.0136
(110)	15.99	7.1	69.31	106.0	1	0.0094
(010)	12.93	7.1	64.1	82.59	0	0.0000

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value corresponds to the results obtained from the CA measurements (34.5 to 35.0 mJ/m^2) and varies between the different facets (39 to 44 mJ/m^2) with a maximum at about 47 mJ/m^2. The γ_S of different size fractions of d-mannitol having different aspect ratios and large surface confirmed that the distribution of γ_S was sensitive to the shape of the crystal facet normally found in a general crystalline pharmaceutical powder system. Ahfat *et al*. [46] and Dove *et al*. [47] demonstrated that the triboelectric charging of a powder should be taken into account because it reflects the ability of a pharmaceutical powder to accept or donate electrons at the interface with another surface with which it is in dynamic contact. The triboelectric charging was considered only recently because of the phenomenon occurring on the surfaces of equipment or containers used to store or dispense the pharmaceutical powders. Many powder processes are influenced by these charging effects which will represent an important parameter in the near future. In this context, the surface free energies γ_S of pharmaceutical powders can be determined using the IGC/CA approach on the powder deposited on a glass slide. The powder tribocharging data can be obtained using the Faraday technique. The charges per gram and unit area of the powder on contact with stainless steel are reported in Table 6 [46].

In this way it is possible to determine the influence of charging effect on the wettability of a pharmaceutical powder and its effects on its adhesion to stainless steel surfaces of equipments normally employed in the production of pharmaceutical powders and granulation processes. Ghafourian and Khan [51]demonstrated that to correlate the CA data to chemical structure parameters of powder samples it is necessary to use a specific software developed for theoretical chemistry and statistical analysis. This software shows that the chemical parameters of powders such as atomic charge, nucleophilic superdelocalizability index, energy of vaporization, number of oxygen or nitrogen atoms, accessible surface area, negative atomic charge on heteroatoms, number of hydrogens, and solubility influence and control the CA of different kinds of pharmaceutical powders. Barbiturates and sulfonamides are typical pharmaceutical powders commonly analyzed using this combined approach [51].

Table 6 Charges per gram and per unit area (nCg^{-1} m^{-2}) of the powders, with the standard deviations in parentheses, on contact with stainless steel under the stated conditions of temperature and relative humidity [46].

Sample	**(nCg^{-1} m^{-2})**	**%RH**	**Temperature (°C)**
Zamifenacin	2.2 (0.4)	34.1 (0.3)	20.0 (0.2)
Lactose monohydrate	–8.9 (0.8)	34.0 (0.8)	20.6 (0.1)
Anhydrous lactose	–9.0 (0.8)	44.7 (4.2)	20.4 (0.3)
Spray dried lactose	–10.6 (0.7)	36.1 (0.8)	20.5 (0.2)
Starch	–13.4 (0.7)	34.2 (0.7)	20.0 (0.1)

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2.2 Solvents for Pharmaceutical Use

The various solvents used in the field of pharmaceuticals are commonly tested for their surface tension (ST) and also for CA. Many pharmaceutical dosage forms use different solvents for their production and related processes. Of great importance in the pharmaceutical sector is the characterization of the typical solvents by static CA and the evaluation of the behaviour of the CA with time and the interfacial tension (IFT; mN/m) by the drop shape analysis. These studies demonstrated that IFT and viscosity of solvents affect the CA measured by the sessile drop technique on test solids such as glass and poly(dimethylsiloxane) (PDMS) which belongs to a group of polymeric organosilicon compounds commonly referred to as silicones. As reported by Phaechamud and Savedkairop [52], the characterization of the hydrophilic nature of these solvents by CA variation with time on glass and PDMS and their IFT were demonstrated to be useful for selecting the suitable solvents for pharmaceutical applications [52]. For example, the increase in the amount of amphiphilic poly(maleic anhydride-*alt*-octadecene) polymer (PAM-18K) (Sigma-Aldrich, St. Louis, MO, USA) in the ampicillin trihydrate tablets causes an increase in the hardness and disintegration time of the resulting tablets. In the case of tablets with PAM-18K polymer at 10% and 20%, Phaechamud and Savedkairop demonstrated that the disintegration times were lower than when the polymer was 30% to 40%. This situation was confirmed by the thermal analysis that evidenced a strong interaction between the polymeric materials and the ampicillin drug. The interaction between them increases with increasing polymer in the mixture. From the surface thermodynamic viewpoint, the increase of the PAM-18K polymer in tablets leads to an increased CA and a decrease in the SFE showing that the surface of tablet becomes more hydrophobic. However, it is necessary to investigate in detail the correlation between the parameters associated with CA and the surface roughness because the issues caused by the porosity in the solid can influence the liquid absorption influencing the CA measurements. On the other hand, the degree of hydrophobicity of the surface of the tablet influences the release mechanism of drug from the tablet during the dissolution process. In general, Phaechamud and Savedkairop [52] demonstrated that if the PAM-18K is used in low concentration, the drug release is controlled by the Fickian diffusion process, while when the percentage of this polymer is higher, the release mechanism becomes a controlled release process driven by swelling and erosion of the tablet. Yarce *et al.* [53] confirmed the findings of Phaechamud and Savedkairop showing that the amount of PAM-18K polymer in the tablet can modulate the release of a very soluble drug in aqueous media by variation of the release mechanism from immediate release to an extended release [53]. In Figure 15 is reported the variation of CA measured on a tablet surface with the concentration of PAM-18K (Sigma-Aldrich, St. Louis, MO, USA).

Figure 16 shows the absorption profiles of ultra-pure water for tablets of ampicillin trihydrate and PAM-18K containing different percentages of

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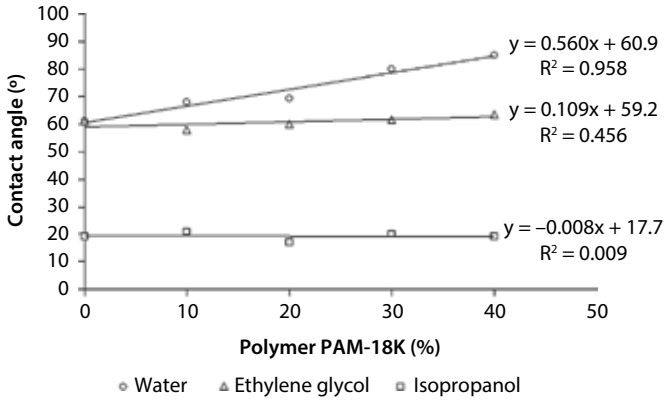

Figure 15 Variation of contact angle (θ) for ampicillin trihydrate-PAM-18K tablets for three test liquids (Adapted from [53]).

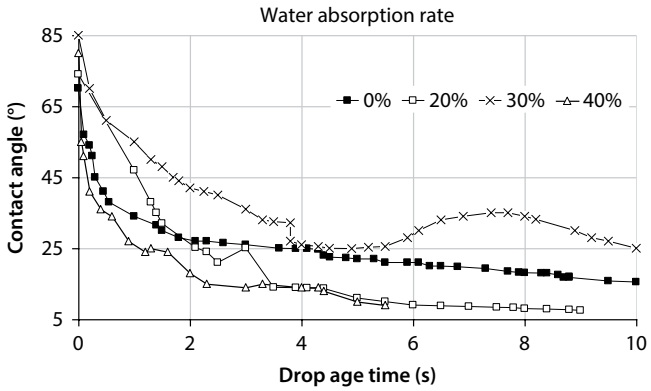

Figure 16 CA measurements with time of drops containing different concentrations of polymer (Adapted from [53]).

polymer. The variations of CA were investigated as a function of the time (drop age). (Figure 16).

The increase of CAs with the percentage of PAM-18K present in the tablet is linked to the water absorption with time The dissolution profiles of ampicillin trihydrate tablets at pH 1.2 and containing different amounts of PAM-18K are reported in Figure 17. The same experiments were performed at pH 7.4.

The increase in the percentage of polymer in the tablet leads to a change in the in vitro dissolution profile of the model drug in the dissolution media. These results

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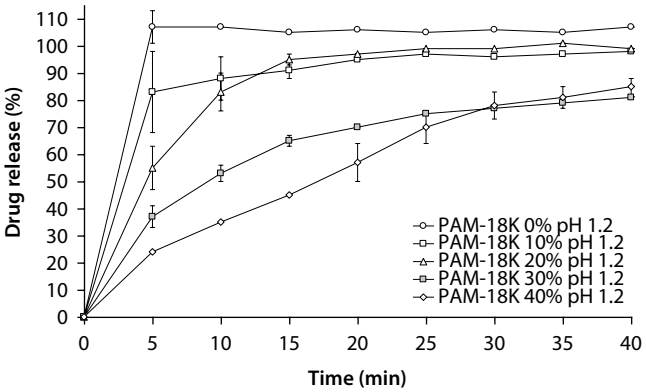

Figure 17 Dissolution profiles of ampicillin trihydrate from compressed tablets containing different proportions of PAM-18K polymer in dissolution media with ionic strength of 0.15 M at pH 1.2 (Adapted from [53]).

are in accord with those observed in surface property studies of the tablets where increasing the PAM-18K polymer levels modify their properties [53]. In recent years, the solubility of poorly soluble drugs has assumed strategic importance for their development in the pharmaceutical industry. For this reason, many methods such as that proposed by Chokshi *et al*. [54], have been developed to improve the bioavailability of solid dispersions and solid solutions, where solid dispersions contain a generic drug (Hoffmann-La Roche, Nutley, NJ, USA) in a microcrystalline form constituting a two-phase system with polymers, such as Poloxamer 188 (P188) and polyvinylpyrrolidone K30 (PVPK30) hydrophilic carriers (BASF Corporation, Mount Olive, NJ, USA). and solid solution contains the drug in amorphous form constituting a monophase system with polymers [54]. The solubility of the drug increased with an increase in polymer concentration (Figure 18) and it can be supported from the wetting effect of the polymer (Figure 19).

Today there are new methods for improving the bioavailability of formulations constituted by solid dispersions and solid solutions that have attracted an enormous attention. On the basis of these considerations with respect to the dissolution process, now it is possible to assess the process of wetting and wetting kinetics by a novel and alternative approach capable of describing the enhanced dissolution rate of a solid dispersion constituted by a poorly water-soluble drug. As an example, Verma and Rudraraju [55] reported the use of Cilostazol (CIL) as a drug model and polyvinylpyrrolidone (PVP) (Plasdone K-29/32), copovidone (CPVP) (Plasdone S-630), and hypromellose (HPMC) (MethoCel E5) as polymers evaluated on the basis of their capability to generate and maintain a supersaturated drug solution. Verma and Rudraraju [55] demonstrated that in this case the wetting kinetics can be evaluated by the CA method in order to correlate the enhanced

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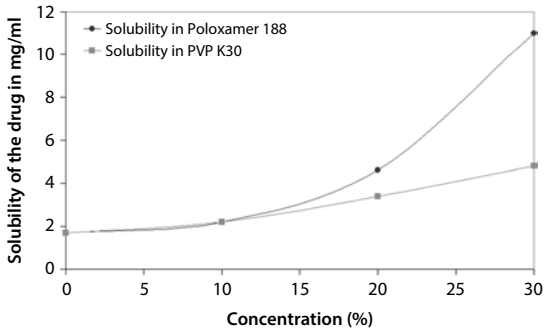

Figure 18 Solubility of the drug as a function of P188 and PVP K30 concentrations (Adapted from [54]).

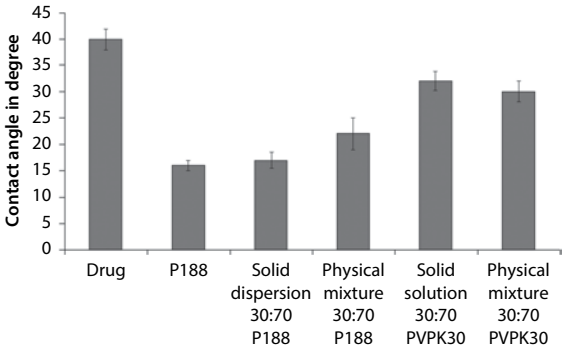

Figure 19 Contact angle studies comparing drug, physical mixtures (P188 and PVP K30), solid dispersion and solid solution (Adapted from [54]).

dissolution rate to the processes of adhesion and spreading [55] in which the variation of contact angle of CIL with water, related to the polymer amount (%) in solid dispersion (drug and polymer), was investigated [55]. This study demonstrated that the variations in CA were insignificant when the polymer content increased from 65% to 80% and the decrease in contact angle of CIL was due principally to the presence of PVP. Thanks to this recently developed method, it was possible to demonstrate that both the type and concentration of the polymer affected the supersaturation of a poorly water-soluble drug. This result was obtained from the comparison between the dissolution processes of an amorphous solid dispersion prepared with supersaturated PVP and the same solid dispersion prepared with CPVP and HPMC. Verma and Rudraraju [55] demonstrated the fundamental role of the polymer and its concentration in a solid dispersion in the stabilization

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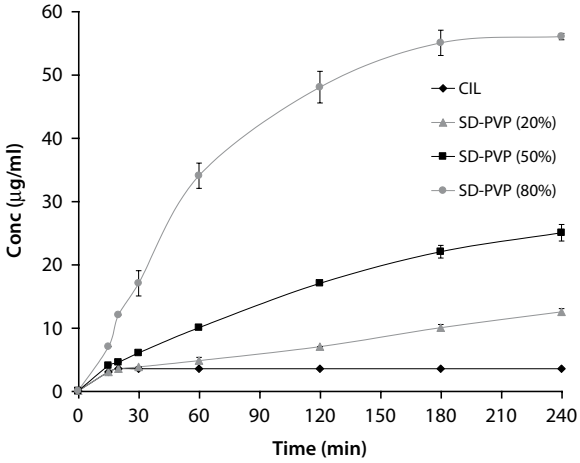

Figure 20 Dissolution curves of Cilostazol (CIL), along with solid dispersions (SD) containing PVP (Adapted from [55]).

of a supersaturated solution as a function of the dissolution of the amorphous solid (Figure 20).

Considering the initial contact angle measured after 0.2 s between CIL and the investigated polymer, CIL (crystalline), PVP, CPVP, and HPMC demonstrated initial contact angles of 68±0.6°, 27±0.5°, 33±0.7°, and 52±0.9°, respectively. Considering that HPMC is also water soluble as well as PVP and CPVP, the contact angle of 52° means a mixture of hydrophilic and hydrophobic characteristics but struggled to dissolve in water because the rate of dissolution in water was very slow. As regards the solid dispersion of CIL, using these polymers at different contents (20%, 50%, 65%, or 80%), the contact angle is inversely proportional to the increase in polymer content. The reduction in contact angle of CIL was most favored by PVP followed by CPVP while the contribution from HMPC was insignificant. These studies demonstrated also that the analyses of CA and the study of wetting kinetics showed that the surface free energy of a solid dispersion is inversely proportional to W_A. In Figure 21 is reported the behaviour of W_A with the concentration of polymer.

The solid dispersions of CIL with PVP and CPVP showed a spontaneous improvement of W_A over the pure CIL, indicating that the introduction of the specific polymer in the solid dispersion had improved the work of adhesion (more negative) while it was not significantly improved with HPMC. As a consequence, the interaction between the liquid and solid surface in a solid dispersion appears higher than for pure drug. This fact is underlined by the good correlation existing between the enhanced dissolution rate, depending on the kind and concentration of the polymer in the solid dispersion, and the CA data and the wetting kinetics

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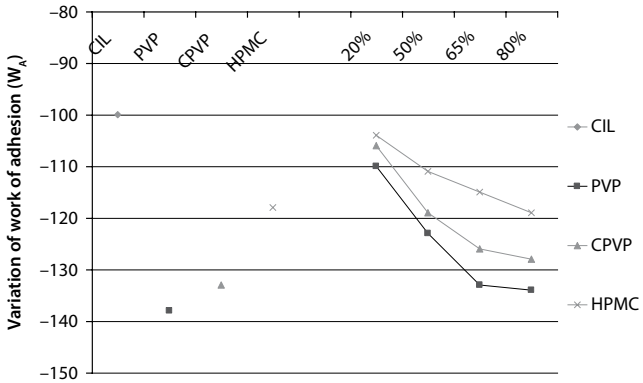

Figure 21 Variation of the work of adhesion (W_A) (y axis) with water with polymer amount (%) in the solid dispersion (Adapted from [55]).

Table 7 Particle Size, Specific Surface Area and Contact Angle of Raw Material and SAS Processed Particles with or without Additives where a) is Mean±S.D. (n = 3), b) is Mean±S.D.(n = 6), c) is the raw material whose diameter value is $(d_{90} - d_{10})/d_{50}$ where d_{10}, d_{90} and d_{50} are the diameters of particles associated with the percentage of particles smaller than the value of the diameter of raw material [56].

Samples	Mean particle size[a] (μm)	Specific surface area[a] (m^2/g)	Contact angle [b] (°)	
			10s	180s
Raw material	47.95 ± 5.58 (3.15)[c]	0.49 ± 0.02	65.5 ± 2.9	60.7 ± 2.7
No additive	3.12 ± 0.10 (1.79)	4.09 ± 0.06	62.1 ± 2.3	57.8 ± 2.4
Poloxamer 188	2.17 ± 0.28 (1.75)	4.30 ± 0.08	56.1 ± 3.8	47.9 ± 3.6
Poloxamer 407	3.03 ± 0.27 (1.94)	4.11 ± 0.09	54.5 ± 3.6	49.5 ± 3.3
TPGS 1000	4.76 ± 0.19 (2.14)	3.27 ± 0.03	54.9 ± 4.6	46.5 ± 3.5
Gelucire 44/14	5.77 ± 0.07 (2.30)	2.32 ± 0.04	57.1 ± 1.9	51.8 ± 3.3
Gelucire 50/13	6.41 ± 0.07 (2.38)	2.10 ± 0.02	58.3 ± 2.2	52.5 ± 2.6

studies. Verma and Rudraraju [55] confirmed that the tensiometric approach was capable of demonstrating that a solid dispersion with faster dissolution rate shows fast wetting kinetics and vice versa. On the other hand, Min-Soo *et al.* [56] demonstrated that the wettability of CIL could be improved using supercritical antisolvent (SAS) micronization process in order to increase the dissolution rate of this poorly water-soluble drug. The decrease of the particle size led to an enhancement in the wettability of the drug using hydrophilic additives (Poloxamer® 188 and 407) and can be determined by the CA method (Table 7). The analysis of wettability gives dissolution profiles of unprocessed CIL, CIL processed with supercritical antisolvent (SAS), CIL processed with SAS and with Poloxamer 188,

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Poloxamer 407, D-*α*-tocopheryl polyethylene glycol 1000 succinate (TPGS 1000), Gelucire 44/14 and Gelucire 50/13 [56].

In this context, Khan *et al*. [57] recently developed a particular technique called Liquisolid (LS) capable of improving the dissolution and bioavailability of this class of drugs such as Cilostazole the solubility of which presents a great problem for development of most kinds of pharmaceutical dosage forms [57] (Figure 22).

The efficacy of the LS technique is based on the employment of microcrystalline cellulose, silica, sodium starch glycolate and magnesium stearate as carrier and coating materials. The wettability of the compact tablet can be determined by the CA method and this explains the increase in the dissolution rate from the LS system [57]. The presence of a non-volatile solvent helps wetting of drug particles by decreasing the interfacial tension between the liquid medium used for the dissolution and the tablet surface. Khan *et al*. [57] demonstrated that the increase in the wettability of the particles in an LS system was due to the low ST. In this case, the test liquid employed for the CA measurements was composed of a saturated solution (ss) of the drug in a simulated gastric or intestinal fluid medium. As a result, the CA measured on an LS tablet is less than the traditional one and is influenced

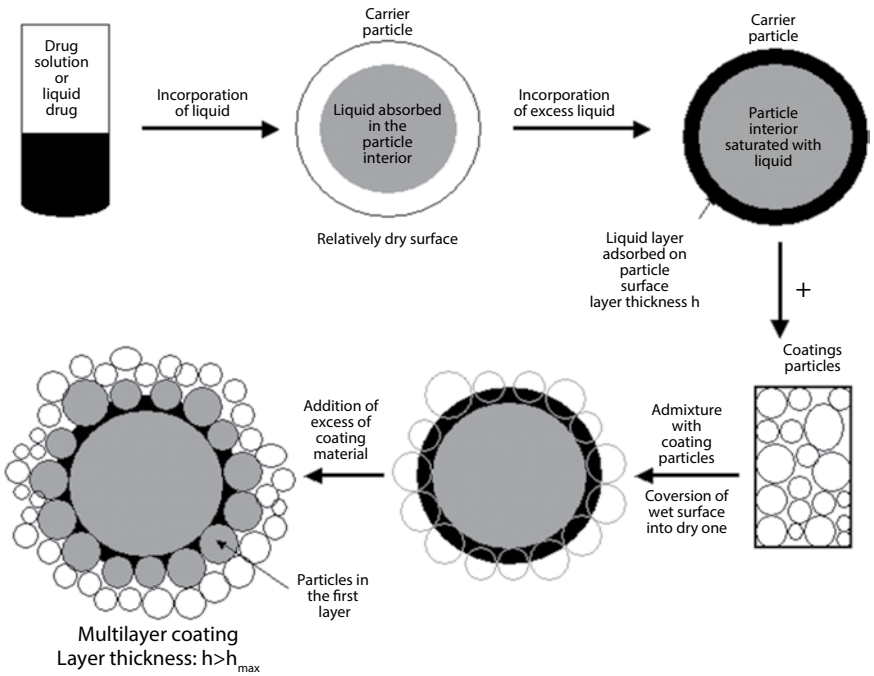

Figure 22 Mechanism representing formulation of Liquisolid system (LS) (Adapted from [57]).

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by the presence of Polysorbate 80. Thanks to the CA approach performed in the study of Khan *et al*. [57] it was demonstrated that the LS compact technique could be effectively used to prepare rapid release tablets of water insoluble drugs with acceptable flowability, hardness, and friability. The quality of the product was demonstrated by the analysis of the weight variation and through the disintegration test whose results were within acceptable limit. The high dissolution rate demonstrated by LS compacts indicated an improvement in oral bioavailability due to the increased wetting property and surface of the drug available for dissolution that led to an increase in the absorption in the gastrointestinal tract of poorly water soluble drugs in general.

2.3 Injectable Solutions for Parenteral Use

The injectable suspensions contain hydrophilic powders generally suspended in aqueous systems. In this context, Patel demonstrated in his overview that the wettability of the ingredients assumes a crucial importance [58]. In this case, Patel considered nonionic surfactants and non-aqueous solvents such as glycerol and propylene glycol as wetting agents commonly used in the preparation of injectable suspensions [58]. This is because glycerol and propylene glycol reduce the CA at the interface between the particles and the liquid, increasing the wetting efficiency and stability of the final product. Patel highlighted that the surfactants with hydrophilic/lipophilic balance (HLB) values in the range of 7 to 9 are considered suitable for the preparation of this kind of drugs [58]. Proper concentrations of the surfactants (range 0.05%-0.5%) were found to be important because foaming or caking processes gave undesiderable issues in the case of their excessive concentration. Patel [58] indicated that the most common wetting agents used for the preparation of non-aqueous suspensions of drugs such as Cefazolin sodium in peanut oil are lecithin, Polysorbate 20, Polysorbate 80, Pluronic F68 and Sorbitan trioleate (Span 85). As reported by Patel, the solvent systems normally used in parenteral suspensions can be aqueous or non-aqueous and their choice is made on the basis of their solubility, stability and desired release characteristics of the final product. Non-aqueous solvents include both water miscible and water immiscible vehicles and the agents used as cosolvent with water lead to the formation of soluble and stable parenteral preparations (ethanol, glycerin, propylene glycol, n–lactamide). As reported by Patel, the most common undesiderable effects of injectable drugs are myotoxicity and hemolysis (propylene glycol). These negative effects depend mainly on modifications of factors such as dielectric constant, pH, viscosity, and surface tension (ST). In this context, Patel provided evidence that these issues occur when the cosolvent is present in inadequate concentration which causes interactions with tissues such as skeletal muscle fibers and red blood cells. For these reasons, the CA approach assumes an important role in the evaluation of the quality of the injectable drugs. On the basis of these, Trivino and Chauhan [59] demonstrated in their review that the CA approach showed its

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usefulness in the characterization of solid lipid nanoparticles (SLNPs) carrier systems (50–1000 nanometers) that also use solid lipids as a matrix for drug delivery [59]. The lipids with a high CA may affect the stability and production of nanoparticles and the lipid chain length influences drug supersaturation levels and precipitation inhibition in self-emulsifying drug delivery systems. Thus, the appropriate selection of lipids for the preparation of Solid Lipid Nanoparticles (SLNPs) is important for a successful formulation (Figure 23).

Considering that in the case of SLNPs the drugs are dispersed in the lipid matrix and are stabilized with an emulsifier, Trivino and Chauhan demonstrated that the fine size of SLNPs leads to a real drug release system because of the high surface area with the advantage to reduce the potential issues that can affect the final formulation. As reported by Trivino and Chauhan, the SLNPs can be considered very important for the pharmaceutical industry due to their capability to incorporate both lipophilic (poorly water soluble drugs) and hydrophilic drugs (highly water soluble drugs). The SLNPs have great advantages because these are constituted by biocompatible lipids that substitute the organic solvents traditionally

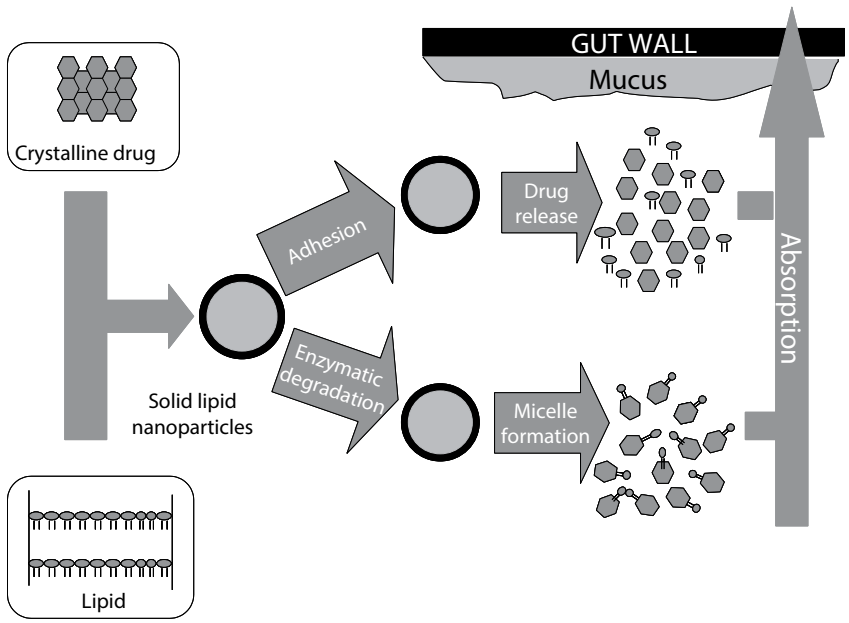

Figure 23 The effects of lipids in prepared SLNPs on drug absorption. An immobilized crystalline drug is molecularly dispersed in the crystalline solid lipids forming the SLNPs whose stability depends on the bulk properties and the length of the lipids influencing the release and the absorption of the drug due to the adhesion and enzymatic degradation of SLNPs (Adapted from [59]).

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used. The enzymatic degradation of lipids results in the formation of micelles that improves the solubility of the drug, increasing its release. Trivino and Chauhan showed that the CA analysis is an important tool for selecting the different lipids excluding those that show high CA. This is important because lipids with high values of CA influence negatively the stability and production of nanoparticles. An appropriate selection of lipids for the preparation of SLNPs on the basis of their wettability is important for a successful formulation. In the field of nanotechnology, more recently De Solorzano *et al*. [60] reported that the poly(D,L lactic-co-glycolic acid) (PLGA) is particularly important as a biodegradable polymer widely used in drug delivery field in many areas such as vaccines, cancer treatment and inflammatory diseases [60]. De Solorzano *et al*. highlighted that the wide use of PLGA is due to its biodegradability and biocompatibility, usability in parenteral administration, capability to encapsulate hydrophilic/hydrophobic active pharmaceutical ingredients (APIs), and capability to protect the pharmaceutical form from biochemical degradation. Other characteristics of PLGA are capability to carry the nanoparticles (NPs) to specific tissues or cells, capability to sustain the release process over time, and possibility to easily modify its surface properties. In this context, in 2017 Nakashima *et al*. [61] developed a particularly highly dispersible PLGA in an aqueous fluid to solubilize a model drug. Aripiprazole (model drug) was dissolved in an aqueous fluid (containing PLGA) and successively spray-dried to produce microparticles (MRPs) and further co-processed with water-soluble additives (ADDs) and surfactants (S) to improve their dispersion behavior [61]. The preparation of MRPs and granulated microparticles (G-MRPs) is performed by a Spray Drying Process step (step 1) and a Drop Freeze-Drying Process second phase (step 2) [61]. The physicochemical properties of the complex system constituted by MRPs and MRPs with ADDs(G-MRPs) were evaluated by X-ray powder diffraction (XRPD)/DSC/CA combined approach taking into account the possibility to consider them as injectable pharmaceutical forms having long-acting release properties. In this case, Nakashima *et al*. [61] showed that the CA measurement of water gave important information about the wettability of the materials investigated and measurements were performed onto the surfaces of compressed G-MRPs considering the height of the drop (H) and the diametrical length of the water lens formed on the surface of the tablet (L) as the main parameters. The height (H) and diametrical length (L) of the water lens were measured immediately after formation of the droplet. The CA (θ) was calculated by equation 13:

$$\theta = 2\tan^{-1}(2H/L) \tag{13}$$

The crystalline state of the G-MPRs was evaluated by XRPD. The XRPD analysis was performed on intact Aripripazole (ARP) crystals, and various G-MRPs such as MRP, G-MRP 20%HPC, G-MRP 20%PVA (poly (vinyl alcohol)), G-MRP50%MNT (granulated microparticles with 50%D-Mannitol) in relation to bulk mannitol (δ-form) and bulk mannitol (β-form) [61]. As reported by Nakashima *et al*. [61], the

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CA values of the MRPs and G-MRPs underlined that G-MRPs are more wettable than the association between drug and MRP only and, consequently, are characterized by an excellent dispersibility in the aqueous phase (Figure 24).

However, in the studies of Nakashima *et al*. [61] the CA method was applied as an analytical support for traditional analytical techniques such as X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) that characterized the above-mentioned crystals and particles as ARP and its mixture, MRP, G-MRP, and G-MRP 50%MNT [61]. Asiri *et al*. [62] recently applied SEM/AFM/CA combined approach in which CA measurement was performed for the evaluation of the wettability of complex systems constituted by carbon nanofibers (CNFs) embedded in PLGA [62]. The main objective of Asiri *et al*. [62] was the demonstration that the cardiomyocyte functions increase with CNFs aligned in PLGA. The CNFs aligned in PLGA (poly(lactic-co-glycolic acid) showed greater cardiomyocyte density than both CNFs randomly oriented in PLGA and pure PLGA (CNFs in the PLGA matrix at 50:50 wt%). The alignment mimics the natural anisotropy of the cardiac tissue. The AFM (atomic force microscopy) analysis of the 50:50 CNF:PLGA aligned composite demonstrated an alignment of the CNFs on the PLGA surface [62]. This increase is because CNFs are characterized by high hydrophobicity and thus enhance the adsorption of key proteins such as fibronectin, laminin, and vironectin that are considered promoters of the cardiomyocyte adhesion. The increase of the cardiomyocyte adhesion is considered an expression of the cardiomyocyte functions. Asiri *et al*. [62] demonstrated that the CA method could help to improve the design of CNF/PLGA composites for numerous cardiovascular applications, opening new perspectives in the application of the CA method in the field of medicine also (Table 8).

The cardiomyocyte cultured in vitro in the designed CNFs/PLGA by the CA method represented a greater expression of important cardiomyocyte biomarkers (cTNT, Cx43, α-SCA) [62].

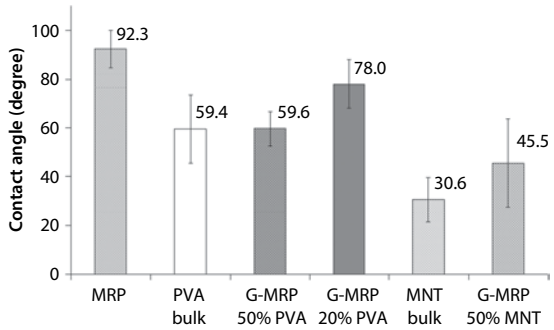

Figure 24 CA of Purified Water Droplets on Compacts Prepared by Compressing Various Formulations of Granulated Microparticles (G-MRPs) and D-mannitol (MNT) (Adapted from [61]).

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Table 8 Comparison between the wettability of carbon nanofibers (CNFs) and poly(D,L lactic-co-glycolic acid (PLGA) [62].

Sample	Contact angle (degrees)
Pure PLGA	82 ± 3
50:50 wt% randomly oriented CNFs in PLGA	135 ± 2
50:50 wt% aligned CNFs in PLGA	145 ± 3

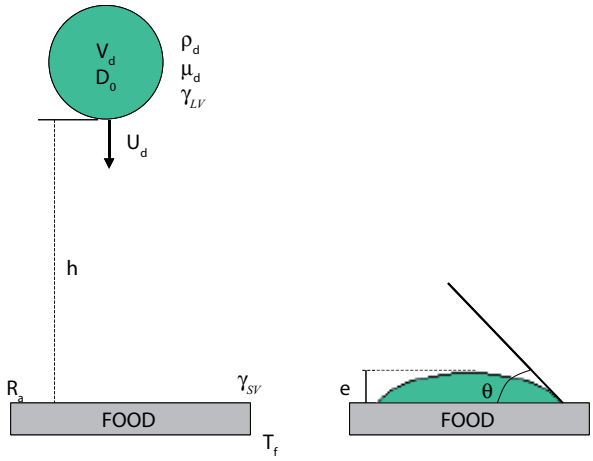

Figure 25 Drop impact on a food surface where V_d is drop volume, μ_d is drop viscosity, ρ_d is drop density, D_0 is drop diameter, U_d is drop velocity, γ_{LV} is drop surface tension, T_f is temperature, h is food surface distance from drop, R_a is food surface roughness, γ_{SV} is surface free energy and θ is the CA at s/l interface (Adapted from [63]).

3 Contact Angle Measurements in Foods

3.1 Solid Foods

As in the case of pharmaceutical powders, the tensiometric parameters SFE, DC and PC of solid foods need investigations on the impact of a drop of liquid on their surfaces as reported in the studies of Andrade *et al*. [63] (Figure 25).

The main parameters involved in the dynamics of drop impact at controlled temperature and pressure are drop volume (V_d), drop viscosity (μ_d), drop density (ρ_d), drop diameter (D_0), drop velocity (U_d), drop surface tension γ_{LV} and temperature (T_f), food surface distance from drop (h), food surface roughness (R_a), food surface free energy (γ_{SV}) and CA(θ) for food surfaces [63]. Wetting behavior of impinging drops such as deposition, splash and rebound was investigated, respectively,

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onto banana, eggplant, and purple cabbage surfaces. The drop deposited into a thin disk (banana); disintegrated into secondary droplets, splashed (eggplant); or rebounded (cabbage) demonstrating that splashing was due to high drop kinetic energy whereas rebound was the result of low food surface energy [63]. Andrade *et al*. [63] report that the Reynolds-Re (14), Weber-We (15) and Ohnesorge-Oh (16) numbers describe the behaviour of the impact of a drop on the surface of a solid food.

$$\mathrm{Re} = \frac{\rho D_0 U_0}{\mu} \tag{14}$$

$$We = \frac{\rho D_0 U_0^2}{\gamma_{LV}} \tag{15}$$

$$Oh = \frac{\sqrt{We}}{\mathrm{Re}} \tag{16}$$

where U_0 is the impact velocity of the drop on the surface.

An optimized edible coating for food is defined as a uniform coating with a constant thickness of controlled microstructure [63]. For a good coating for the food, the drop impact behavior must be controlled, without splash, without rebound and with a controlled thickness. For a single drop impact, the thickness e is a function of the drop volume V and the maximum spreading diameter $D_{\max}$. Equation (17) shows that at constant drop volume the $D_{\max}$ must be large to obtain a small thickness e.

$$V_d = \frac{\pi}{6} D_0^3 = \frac{\pi D_{\max}^2}{4} e \tag{17}$$

Andrade *et al*. [63] also highlighted that the effect of surface temperature on drop impact length behavior depends on the surface free energy. In the case of high surface free energy (hydrophilic substrate), the effect of substrate temperature appears to be more pronounced than for hydrophobic substrate. Another parameter that controls the wettability characteristics of the surface (hydrophobic or hydrophilic) of foods is the surface free energy [63]. Also in the case of foodstuffs, the value of the equilibrium CA depends on the anisotropy of the surface. The surface roughness is another important physical property of solid foods that influences the visual, sensorial attributes and their behavior during processing and storage. In particular, in the coating process, the surface roughness has a great effect on the adhesion between the coating solution and the food surface [63]. An increase in the roughness of the surface leads to prompt splashing. Andrade *et al*. [63] reported also that the ST plays a vital role in the splashing and rebounding rates. For example, in the case of cabbage, the rebounding phenomenon is weaker

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when ST of the liquid decreases [63]. The drop viscosity is also an important parameter affecting the impact process during which in the first stage of spreading the inertial force of impact is much larger than the viscous force [63]. Andrade *et al*. [63] highlighted that all the parameters that influence the drop impact behaviour can be stored in a database. In this way, from the physical properties of the coating solution, it is possible to find the optimal drop impact conditions to obtain the desired deposition on a food surface [63] (Figure 26).

As in many other fields, the main issues with the tensiometric analysis of solid foods are represented by the roughness and the irregularity of their surfaces which influence the CA measurements [64]. To address this issue, Parreidt *et al*. [64] applied a new CA measurement method for food materials and irregular surfaces in general. The new CA method called "DropSnake" and performed using ImageJ software was able to characterize foods such as strawberries (SFE; 21.26 mJ/m^2, DC: 19.96 mJ/m^2, PC: 0.99 mJ/m^2) and endive salad (DC: 19.72 mJ/m^2; PC: 23.39 mJ/m^2) that are characterized by rough and irregular surfaces. For these kinds of surfaces the "DropSnake" approach was demonstrated to be a useful tool for CA measurements on irregular and rough solid food surfaces in general (Figure 27).

The "DropSnake" plug-in reported by Parreidt *et al.* [64] and Kurkuri *et al.* [65] is ideal for the analysis of asymmetric drops because no shape assumptions are used. As reported by Reinke *et al*. [66] also, the CA approach performed with

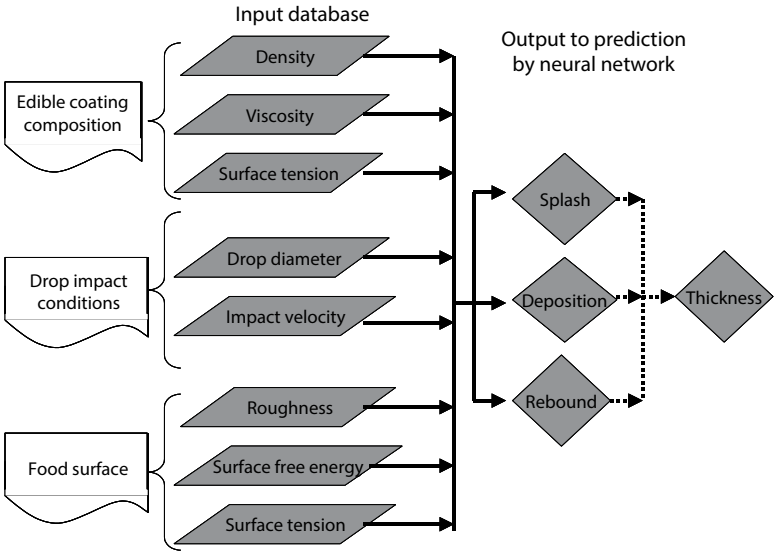

Figure 26 Influential parameters (input) for predicting the drop impact behavior (output) (Adapted from [63]).

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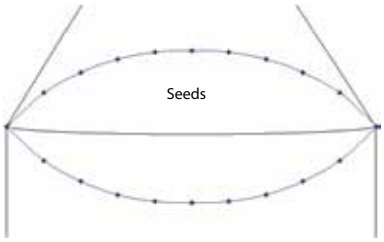

Figure 27 The "DropSnake" optical method to measure CA on a stacked grain (Adapted from [64]).

ImageJ demonstrated the possibility to evaluate the alteration of some kinds of food surfaces such as chocolate blooming. These alterations are represented by the formation of white spots on the surface of chocolate products due to the presence of sugar or fat crystals on the surface. These white spots cause issues such as aesthetic changes and deterioration of the taste that are often associated with polymorphic changes of the crystal structure on the surface [66]. The analysis of the CA variation with time on the cocoa butter surface was investigated by the sessile drop directly after droplet deposition at 0s (92 deg), 5s (68 deg), 10s (64 deg) and 30s (61 deg). The variation of CAs of water was studied on untempered cocoa butter stored for 1 week at 20 °C at 0s (95 deg), 5s (94 deg), 10s (94 deg) and 30s (91 deg). The CAs of ethylene glycol were measured on tempered cocoa butter at 0s (91 deg), 5s (87 deg), 10s (86 deg) and 30s (83 deg), and on the same kind of cocoa butter the CAs of diiodomethane were measured at 0s (59 deg), 5s (45 deg), 10s (43 deg) and 30s (40 deg) [66]. Reinke *et al*. [66] demonstrated that the CA measured by imageJ on inclined surfaces can distinguish tempered and untempered foods such as chocolate and cocoa butter in accord with SEM results (Figure 28).

Microscopic investigations using SEM were also performed on cocoa butter, dark chocolate,milk chocolate, freshly untempered cocoa butter and dark chocolate and milk chocolate [66]. Reinke *et al*. [66] demonstrated that the influence of the roughness of the surface on CA measurements depends mainly on the wetting ability of the liquid (Figure 29) [66].

Contact angles of water, ethylene glycol and diiodomethane on tempered cocoa butter (CB) and directly after production and after storage at 30 °C for 1 week [66] were also investigated. A particular field in the food industry is the sector of the dairy powders frequently used for their convenience in transportation, handling, processing, and for product formulations. As reported by Sharma *et al*. [67] in their review, the powdered foods in the nutrition field have particular physical and functional properties that control their structure, particle size distribution, powder density, bulk density, particle density, wettability, sinkability, dispersibility, solubility, hygroscopicity, heat stability, emulsifying properties, glass transition temperature, water activity, stickiness, and caking [67]. In particular, the wettability of

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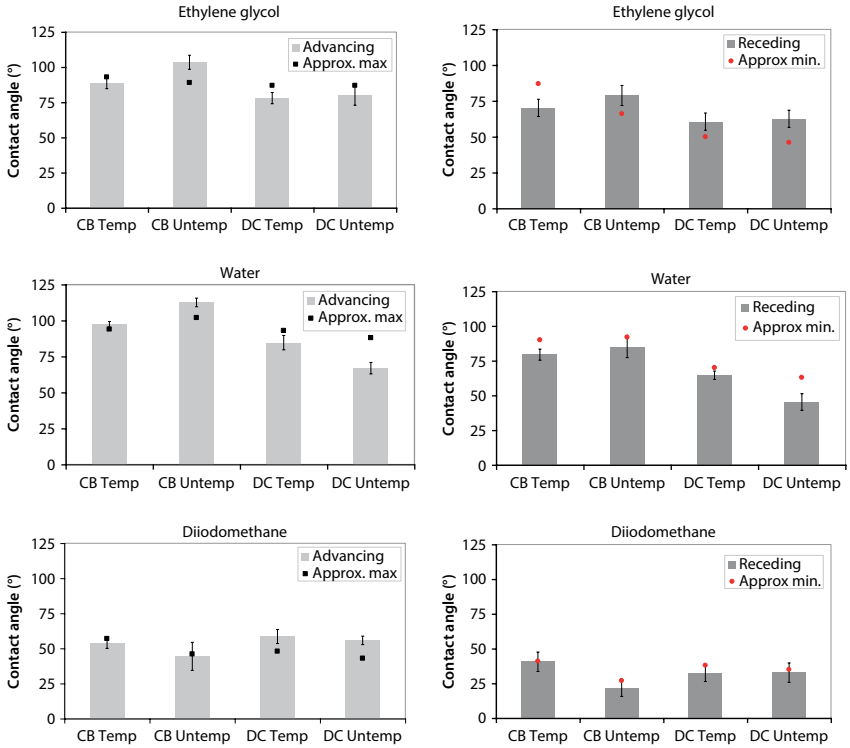

Figure 28 Advancing and receding contact angles of ethylene glycol, water and diiodomethane measured on inclined tempered and untempered cocoa butter (CB), and tempered and untempered dark chocolate (DC). Approximated maximum and minimum contact angles are from approximated experimental data (Adapted from [66]).

a food powder depends on particle size, density, porosity, surface charge, surface area, the presence of amphipathic substances, and the surface activity of the particles. Surface coverage with hygroscopic components such as lactose yields good wetting properties because of the small CA. The wettability of food powder such as milk depends also on temperature. In particular, when milk powder is instantly prepared its wettability and CA values change rapidly over 15s. A rapid wetting of milk powder is also favored by large particles of high porosity, and natural surfactants such as soy lecithin are commonly used to increse the wettability of the powder [68]. The characterization of food powders is similar to that of pharmaceutical powders and Górnicki *et al.* [68] have emphasized that in the nutritional field the rehydration process of dried fruits has a particular importance and is based on the capillary movement of water in the powder samples as shown for pharmaceuticals [66]. The flux of water through a dried material follows the capillary motion as

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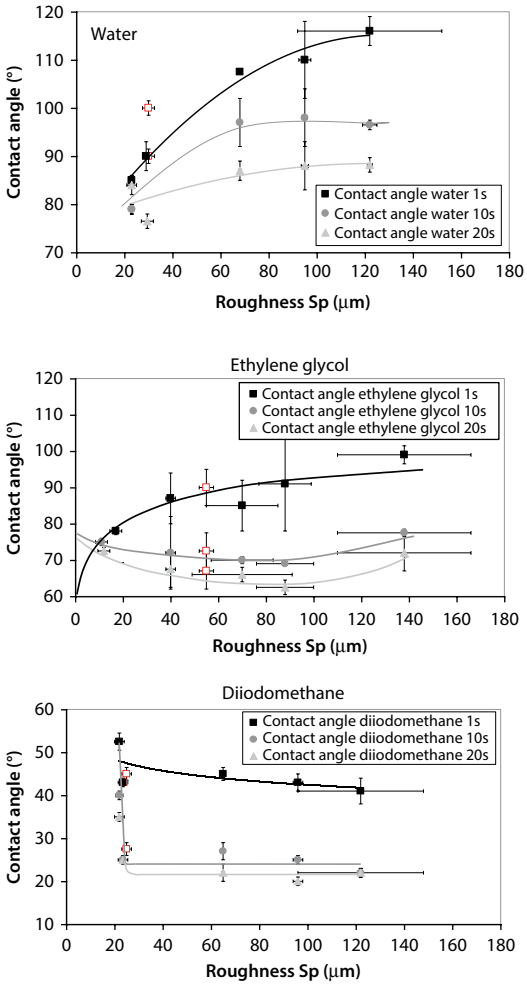

Figure 29 Contact angles of water, ethylene glycol and diiodomethane on dark chocolate with variation in roughness where Sp values are the maximum peak heights for roughness determination at different times (Adapted from [66]).

described by the Washburn equation. In the case of foods, the Washburn equation can also be applied. As reported by Górnicki *et al*. [68], the milk powder is one of the most consumed dried foods and its wettability can be evaluated easily and quickly by CA measurements using the Washburn equation and apparatus. The application of the Washburn equation is possible because of the ability of milk powder to adsorb water on the surface. Górnicki *et al*. [68] highlighted that the wettability of dry milk is linked to its solubility and depends on the particle

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size, density, porosity, surface charge, surface area, presence of amphipathic substances, and surface activity of the particles. Consequently, dried milk with fast wetting property is characterized by large particles which represents an essential condition for their solubilization in water. The control of the insolubility index (II) of dry milk after the addition of surfactants such as soy lecithin is a method commonly used to enhance and control the wettability of the food powder in relation to the sediment formed as II is considered a typical correlation parameter to CA measurements. In particular, the movement of water through the dried powder material follows the capillary motion as described by the Lucas-Washburn equation, assuming that the food structure consists of multi-individual pores; the flow is one dimensional, steady state and fully developed; and the liquid is Newtonian with negligible inertia effect. On these bases, equation 18 was obtained [68].

$$\frac{dh(t)}{dt} = \frac{k_1}{h(t)} - k_2 \tag{18}$$

where k_1 and k_2 are parameters linked to the wettability of powder and are expressed in terms of CA (equations 19 and 20) [68].

$$k_1 = \frac{r\gamma\cos\Theta}{4\eta} \tag{19}$$

$$k_2 = \frac{r^2 g\rho}{8\eta} \tag{20}$$

where ρ is liquid density (kg m^{-3}), η the liquid viscosity (Pa.s), γ the surface tension (N m^{-1}), r the the mean pore radius, θ the advancing liquid contact angle (rad), and g gravitational constant (m s^{-2}).

In light of these considerations, recently Banach [69] in his PhD thesis showed that the proteins pattern represents one of the more important ingredients of milk and in the food industry the dry milk is one of the main sources of milk protein concentrate (MPC) from which it is possible to obtain high-protein nutrition (HPN) food forms [69]. It is well known that MPCs produce HPN bars commonly commercialized, however one of the main issues is represented by the changes in their texture that could occur during their storage [69]. Banach [69] recorded also confocal micrographs of high-protein nutrition (HPN) bars formulated with unmodified spray dried milk protein concentrate with 80% protein (MPC80), 4h toasted MPC80 at 75 °C and 110 °C, and extruded MPC80 at die temperature of 65 °C and 120 °C. Confocal micrographs showed that changes in MPC80 occurred during the storage [69]. The changes in HPN bars are also visible in the images of the model high-protein nutrition (HPN) bars after storage for 6 and 29 weeks (Week 0 represents t_0) at 22 °C or 32 °C. MPC80 represents spray dried milk protein concentrate with 80% protein, while E105 and E116 are two extrudates of HPN formulated with unmodified spray dried milk protein concentrate with 80%

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protein (MPC80) with die-end melt temperatures of 105 and 116°C respectively [67]. The protein ingredient, storage temperature, and storage time all had significant effects ($P < 0.05$) on maximum force, shear force, adhesiveness, cohesiveness, and crumbliness. In particular, adhesiveness, cohesiveness and crumbliness of HPN bars were evaluated with time after storing at 22°C and 32°C and comparing them with the two extrudates [69]. Banach demonstrated that the quality and the functionality of MPC ingredient could affect the performance of the derived HPN bars. The functionality of MPCs can be evaluated by apparent dynamic CA (ADCA) measurements of a drop that can be used to compare the surface hydrophobicity and the wettability of the protein powders that could change in presence of pressed protein onto the surface of extruded MPC (Figure 30).

Banach [69] reported that the hydrophobicity of modified protein powders can also be measured by CA, demonstrating that the physically modified MPC85 powder maintained greater hydrophobicity than the control (Figure 31) [69]. In this case Banach [69] considered the unmodified spray dried MPC85; JM-Fine, finely jet-milled MPC85; JM-Coarse, coarsely jet-milled MPC85; and FD (freeze-dried) MPC85.

Banach [69] demonstrated that the water droplet CA on the control sample decreased rapidly within 1s, but after its stabilization, it decreased at a rate similar to the jet-milled and freeze-dried MPC85. The average slope for CA change with time was apparently greater for JM-fine and the control, but no significant difference was observed between the protein powders ($P > 0.05$). However, some observations show that MPCs are wettable, but it appears that these high-protein powders are not wettable. On the basis of these experiments, Banach [69] demonstrated that by ADCA method it is possible to evaluate the water absorption speed of the extruded MPC and its modifications in the 0–60s range and the instant at which the

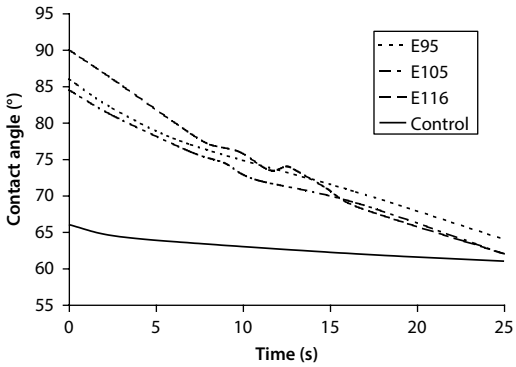

Figure 30 Apparent contact angle of a water droplet on each protein pressed powder where MPC80 is the control spray dried milk protein concentrate with 80% protein, while E95, E105, and E116 represent the MPC80 extruded at die-end melt temperatures of 95 °C, 105 °C, and 116°C, respectively (Adapted from [69]).

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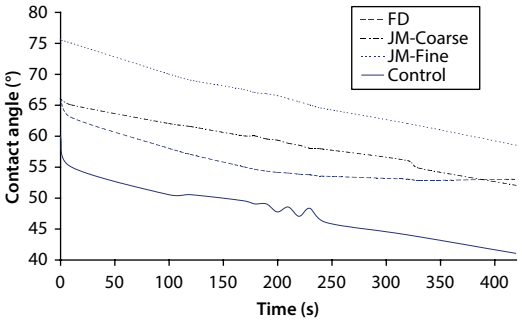

Figure 31 Apparent contact angle of a water droplet on a pressed surface made from control, jet-milled (JM-Fine and JM-Coarse), and freeze-dried milk protein concentrate with 85% protein (MPC85) where Control is the unmodified spray dried MPC85, JM-Fine is the finely jet-milled MPC85, JM-Coarse is the coarsely jet-milled MPC85, and FD is the freeze-dried MPC85 (Adapted from [69]).

volume of water droplet changes. This demonstrated that the ST decreases when the protein is dissolved in the water droplet. For this reason, the CA method can be considered as an important tool for the control of MPC quality. MPC with high protein content (hydrophobic) is less wettable with respect to the same containing high concentration of lactose (hydrophilic). This explains why the extruded MPC powder particles easily hydrate during the process of manufacture of HPN bars. Consequently, a fast decrease of CA occurred. In this context, Banach [69] demonstrated that the CA approach for the study of MPCs is particularly important because it is able to evaluate the integrity of the structure of HPN bars which could be modified when water molecules separate from the protein during storage. By CA analysis it is possible to show also that the extrusion process of MPCs causes a decrease in protein solubility and surface hydrophobicity, improving the ability to interact with water and, consequently, a rapid powder hydration occurs during the production of HPN bars. This allows a good and constant hydration of the protein during storage. More recently Nushtaeva focused on the role of the emulsifiers in medicine and gastronomy fields [70]. It is well known that some natural insoluble powders, such as mustard and ground cinnamon, can be used as solid emulsifiers for O/W emulsions that are formed by aqueous dispersions of food powders and olive oil. In the work of Nushtaeva [70] the mustard and cinnamon powders demonstrated their emulsifying property, and in particular the ground cinnamon ensures high stability of food emulsions in general with antioxidant and antimicrobial properties also. As reported by Nushtaeva, the evaluation of these properties can be performed by investigating the hydrophile/lipophile ratio (HLR) of the powders. Nushtaeva demonstrated that HLR can be expressed by using the CA values (CA/HLR combined approach). The hydrophile-lipophile ratio for solid particles is the analog of hydrophilicity/hydrophobicity coefficient

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β and the hydrophile-lipophile ratio (HLR) can be expressed via the heats of wetting (Equations 21 and 22).

$$HLR_{wt} = \frac{\Delta H_w}{\Delta H_o} \tag{21}$$

$$HLR_{\theta} = \left(\frac{1+ \cos \theta_{ow}}{1-\cos \theta_{ow}} \right)^2 \tag{22}$$

where ΔH is the heat of wetting of 1g of solid phase, ΔH_w is the heat of water wetting of the powder, ΔH_o is the heat of oil wetting, θ_{ow} is the contact angle measured on the surface of O/W emulsions stabilized by powder particles such as natural milk powder, ground ginger, mustard powder, ground cinnamon, potato starch and ground nutmeg. The HLR of a powder is strongly linked to the hydrophilicity/hydrophobicity coefficient (β) that is based on the heat of wetting of solid phase and characterizes both water and oil wetted powders. By employing CA measurements for HLR determination, Nushtaeva demonstrated that mustard and cinnamon powders have a high capacity to protect the O/W food emulsions from coalescence and sedimentation. Another interest in the food industry is the quality of the reconstitution process of a beverage from a dehydrated powder. As reported by Dupas *et al*. [71], in this process many physical mechanisms occur which make it very difficult to produce a homogeneous drink even under the best conditions. In this case the particle size distribution and the role of CA measurements for the prediction of the wettability behaviour of food powders assume great importance. Considering CA and porosity as the main parameters for the evaluation of the particle size distribution of a dehydrated powder, it is possible to calculate the fraction of particles that float to improve the wettability of the powder. The CA measurements can be done at the interface between water and tablets obtained from high compaction of powders of milk, cocoa, chocolate and coffee for beverages production. Following this method, the wettability of the food powders for beverages can be determined by measuring the percentage of the powder that remains at l/v interface after 45s.

3.2 Liquid Foods and Beverages

Liquid foods are represented generally as food suspensions containing lipid coated particles. In this case Wang *et al*. [72] demonstrated that the CA measurements can evaluate the wettability of lipid surfaces as well as the influence of pH, salt concentration, protein concentration, surfactant type and concentration [72] (Figure 32a–32d). The glass slides were immersed in surfactant solutions for 16 h and the measurement were made after 15min [72].

Generally, the increase in the concentration of the emulsifier causes a decrease in CA measured for a drop of water on lipid surface, while low values of pH are linked to high values of CA and vice versa. Wang *et al*. [72] showed that the very

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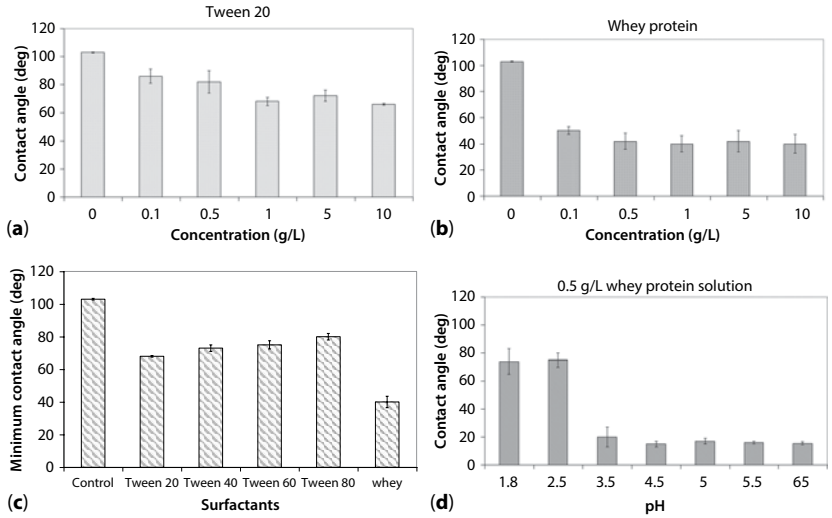

Figure 32 (**a**) Contact angle (degrees) of water on lipid coated glass slides treated with different concentrations of Tween 20 solutions (Adapted from [72]). (**b**) Contact angles (degrees) of water on lipid coated glass slides treated with whey protein (Adapted from [72]). (**c**) Minimum contact angles (degrees) of water on lipid coated glass slides treated with different surfactant solutions (Adapted from [72]). (**d**) Contact angles (degrees) of water on lipid coated slides treated with 0.5g/L whey protein solution (50g/L citrate buffer) (Adapted from [72]).

low CA obtained in the presence of high concentration of emulsifier with high pH is due to the effect of the ionic strength (e.g., high concentration of Na citrate) independent of the concentration of protein. As a consequence, high concentration of protein and high ionic strength increase the wettability of hydrophobic surfaces (e.g., for protein 5 g/L and NaCl 0.5mol/L) with CA about 10.7 ± 2.7. The best emulsifiers present in nature are the proteins of whey that have shown to be very efficient at low concentration in water (0.5g/L). In the study of food suspensions, the CA value evaluates the surface pressure (SP) $\prod_c$ at the air–water interface also by the Langmuir equation for planar surfaces obtained by using the tensiometer (goniometer) (equation 23) [70].

$$\Pi_c = \frac{\pi\gamma_{LA}(1\pm\cos\theta)^2}{2\sqrt{3}} \tag{23}$$

where Π_c is the critical SP, γ_{LA} is the ST of liquid (water), and θ is the CA. These studies of Wang *et al*. [72] on food suspensions were of fundamental importance because many micronutrients are added to liquid foods including beverages and the role of the liquid foods as suspensions, makes the intake of micronutrients fundamental for

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the iron fortification in food suspensions depending on its encapsulation. Wang *et al*. [72] demonstrated that the adjustment of parameters such as pH, ionic strength and emulsifier concentration based on the CA method leads to obtain more stable and also with good flavor food suspensions with micronutrients. In the field of foods, the tensiometric characterization of liquid foods can be used for the determination of the quality of food oils also. One of the most interesting results obtained from CA analysis of food oils was the characterization of their polar component [73]. As reported by Michalski *et al*. [73], the food oils tested and the CA values converted into SFE by the Owens-Wendt model showed some degree of PC; however, in general it is considered negligible because it is only 5% of the dispersion component. The measurement of the interfacial tension between apolar and polar liquids was performed by the DuNoüy ring method. The γ^{d}_{L} component of polar liquids was calculated using Equation (24):

$$\gamma_L^d = \frac{(\gamma_a + \gamma_L + \gamma_{aL})}{4\gamma_a} \tag{24}$$

where γ_a is the the surface tension of apolar liquid (*a*) and γ_L is the surface tension polar liquid (L). The device for CA measurements used by Michalski *et al*. [73] is shown in Figure 33.

The measurements of CAs were useful for the determination of DC (γ^{d}_{oil}) and PC (γ^{p}_{oil}) of food oils (Equations 25 and 26). The dispersion component of oils was determined from the measurements of CAs on the surface of Parafilm®. The polar component was obtained from the total surface free energy.

$$\gamma_{oil}^d = \frac{\left[\gamma_{oil}(\cos\theta_{oil,Parafilm} + 1)\right]^2}{4\gamma_{Parafilm}} \tag{25}$$

$$\gamma_{oil}^p = \gamma_{oil} - \gamma_{oil}^d \tag{26}$$

This residual PC (γ^{p}_{oil}) is due mainly to the presence of fatty acids that are commonly present in similar concentrations in food oils from olive, sunflower, and soybean. The effect of surface polarity, calculated by polar, acid-base, or hydrogen bonding ST components, on oil experimental adhesion was determined through van Oss, Chaudhury and Good; and Owens and Wendt equations that were also used to investigate the adhesion of inks to polymer surfaces (Equation 27) [73].

$$W_A = 2\sqrt{\gamma_L^d \gamma_S^d} + 2\sqrt{\gamma_L^p \gamma_S^p} + 2\sqrt{\gamma_L^h \gamma_S^h} \tag{27}$$

where γ^{h} is the surface free energy component due to hydrogen bonding.

These studies led to the evaluation of the effects of surface hydrophilicity on oil experimental adhesion [73].

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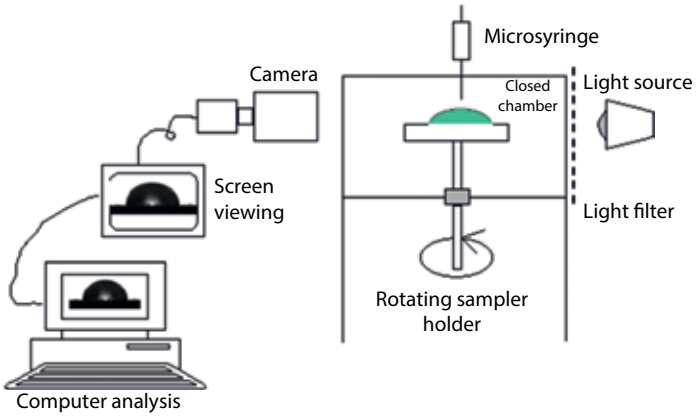

Figure 33 Device for contact angle measurement by image analysis (Adapted from [73]).

There are small differences between the surface tensions of the different oils, and the differences between them can be evaluated by considering parameters such as viscosity, nature of the components, and physico-chemical properties of the test solids used for CA measurements. On the other hand, the studies of the sensorial perception of liquid foods in relation to the oral perception due to the mouth friction have recently found a great interest in the food industry. For this reason, some studies were recently performed on the adhesion and spreading of food emulsion droplets on solid surfaces in relation to their capability to decrease the friction on the oral surface [74]. The main interactions occurring between the droplets and solid surfaces are electrostatic, steric and hydrophobic because they determine the adhesion and spreading of the food emulsion droplets. In particular, the hydrophobic interactions are crucial for developing stable emulsions capable of spreading on oral surfaces due to a low friction phenomenon at the interface. As reported by Dresselhuis [74], in the case of lipids, the increase in drop spreading is related to an increase in the perception of fats at tongue level. Generally, the increase in adhesion is due to the presence of protein-poor emulsion droplets that adhere better to hydrophobic surfaces than protein-rich droplets. Dresselhuis [74] demonstrated that it was due to the presence of various colloidal forces causing a decrease in electrostatic and steric repulsions. In particular, the distinction between adhesion and spreading of emulsion droplets is commonly used for investigations on the correlation between the degree of aggregation and the droplet size. Normally, the CA analysis applied in this kind of studies is performed with light microscopy (LM) and flow cell (FC) analysis by LM/FC/CA combined approach [74]. In this case, the CA method analyzes the spreading of emulsion droplets and the change in their diameter with time. The LM/FC/CA combined approach can distinguish between non-adhered, adhered and spread emulsion droplets. Dresselhuis [74]

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first considered the pig tongue as an ideal tissue for the investigation of fat perception. The CAs were measured on slightly moist pig tongue surface with water droplet after 2 sec, after 5 sec, dry tongue surface, dry tongue after 1.5 min and dry tongue after 3 min [74]. Dresselhuis [74] explained that the tongue can be considered as a surface in need of lubrication and requires protection against external agents, e.g., acids. A hydrophobic surface in combination with coverage by mucins makes possible the lubrification and protection function [74]. Dresselhuis [74] demonstrated the friction forces between the tongue and glass with the emulsion acting as a lubricant. This can be measured in a reproducible manner despite the biological material originating from different pigs tongues (measurement performed 5 times with different pieces of tongue) [74]. The friction force (N) was investigated on an emulsion such as 1 wt% of Whey Protein Isolate (WPI) and 40 wt% of sunflower oil sheared between tongue and glass [74]. Dresselhuis [74] measured also the friction force (N) when shearing the same kind of emulsion between glass and poly(dimethylsiloxane) (PDMS) rubber [74]. On the basis of these observations, Dresselhuis [74] demonstrated that a knowledge of the characteristics of pig's tongue enables modification of PDMS surfaces in order to make them more closely mimic a tongue surface. PDMS is an ideal surface for this since it is easily moulded in various shapes, allowing control of the surface roughness. The decrease in CA means an increase in spreading of protein-poor emulsion droplet which is very efficient as a lubricant [74]. As a consequence of these properties, the protein-poor emulsions show high sensorial potential in fats perception [74].

3.3 Food Packaging

The increase in environmental, economic and safety concerns caused by the traditional food packaging materials has prompted in recent years to partially substitute the petrochemical-based polymers such as polystyrene with biodegradable ones [75]. An example of a biodegradable thermoplastic polymer for food packaging is the poly(lactic acid) (PLA) that can be obtained from renewable sources. The properties of PLA and their possible modifications by using various modifiers for blending, copolymerizing are fundamental for the production of PLA films, wrappings, laminates and containers such as bottles and cups. As reported by Jamshidian *et al.* [75], the PLA possesses antimicrobial and antioxidant characteristics that are fundamental requisites for the conservation of foods. The nanotechnology has helped the development of new PLA nanocomposites combined with nanomaterials which has improved the quality and functions of PLA, thus decreasing concentrations and prices. Jamshidian *et al*. [75] demonstrated that the PLA with added antioxidants can be evaluated by XPS/AFM/RAMAN/FTIR/TEM combined approach in order to verify the influence of antioxidants on the surface of PLA [75]. In particular Jamshidian *et al.* [75] recorded also FTIR spectra of PLA films, PLA-antioxidant films and pure PLA. TEM analyses were performed on PLA films containing antioxidants. The surface energy of

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a polymer influences its adhesion property [76] and it is important for processes such as printing and heat sealing in the packaging field. PLA is biocompatible and is widely used in the medical field. Due to its low wettability and low surface energy, PLA influences the proliferation of cells. Considering that the SFE of a polymer is an important factor that can influence its adhesion property, the CA measurements and the determination of SFE, DC, and PC of PLA films with and without antioxidants becomes a useful tool for the characterization of biodegradable packaging materials [75]. Synthetic phenolic antioxidants (SPAs) including butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), and tert-butylhydroquinone (TBHQ) were added (1%, w/w) to a poly (lactic acid) (PLA) film [75]. The contact angle of the PLA film with 1% SPA decreases from approximately 75.3° to the lowest value 44.5° for PLA-AP (recto), 69.4° for PLA-AP (verso), 70.5° for TBHQ (recto) where *recto* is the surface in contact with air, and *verso* is the surface in contact with Teflon. As regards other antioxidants, the modification is negligible. In the case of PLA, the CA level increases after the addition of antioxidants because of their hydrophobic nature and the variation depends on the concentration of antioxidant in the PLA film, and its distribution on the surface and throughout the polymer network. Jamshidian *et al*. [75] found a slight increase in CA values measured on PLA surface with added antioxidants. Jamshidian *et al.* [75] also showed that the increase in the number of hydrophobic groups present on the PLA surface improves the printing processes. One of the first parameters that characterizes the quality of foods and the packaging materials is the absence of various microbial classes (*Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Enterococcus faecalis*) which improves the efficiency with respect to the conservation of these materials. The novel Non-Thermal Plasma (NTP) technology has shown high potential for decontamination in the food industry and it can be used for the surface treatment of raw products, dry food powders such as dried milk, herbs, spices and packaging materials for the dry disinfection of food surfaces such as meat, poultry, fish, fresh vegetables and sprouted seeds [77]. The NTP technology involves an intense bombardment of micro-organisms with radicals causing deep biological surface lesions. As reported by Tiwari [77] the damage to the surfaces of microorganisms is due to the action of the electrostatic forces occurring from the accumulation of charges on the surfaces of cell membranes. In this context, the CA measurements on food surfaces is a useful tool for the evaluation of NTP performance [77]. As an example, the surface of lettuce shows an increase in its wettability after plasma treatment and the decontamination can be confirmed by FTIR and SEM investigations [77].

4 Summary

This review has focused on the applications of CA in the study of pharmaceuticals and foods. In this context, we evidence new perspectives in the applications of the CA method in the novel "*pharma-food*" combined field. In our opinion, the

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application of the tensiometric technique in this novel field is in its beginning stage because the tensiometric investigations actually are performed separately in pharmaceutical and foods fields. Actually, the CA investigations are still sparse and do not take into account yet the concept of an Integrated Analytical Approach (IAA) by which it is possible to obtain a broad view of a material. The IAA approach can give more information about the *elements-strucrure-surface* correlations that govern all natural and artificial materials. The studies reported here demonstrated that the CA method is still considered as an analytical support in the pharmaceutical and food sectors in which other traditional techniques are more widely used. The other critical point is that the development of new tensiometric methods based on mathematical models such as Owens, Wendt, Rabel&Kaelble; Wu; van Oss, Chaudhury and Good; etc. for the characterization of surface free energy (SFE; mJ/m^2) and surface tension (ST; mN/m) of pharmaceutical and food products is quite absent. This could be caused by the fact that although there are several methods for determination of surface free energy of a liquid (surface tension of liquid), the experimental determination of surface free energy of a solid is still not a fully solved problem [78–79]. In particular, Della Volpe and Siboni [80] have focused on many misleading concepts presented in the scientific literature such as confusion between sliding angle and contact angle hysteresis, inaccurate definition of superhydrophobicity, uncriticized occurrence of meaningless negative contact angles, the so-called "petal effect," or the lotus leaf described as a chemically hydrophilic surface with a superhydrophobic behaviour attributable to only its geometrical structure. On the basis of the results of this first review on recent *pharma-food* sector, we can conclude that the CA method can be a non-invasive analytical approach capable to lead the investigations towards the correlation between the pharmaceuticals and foods. This could help in developing an IAA based common investigation protocol for the non-invasive determination of the surface free energy and surface tension of products. The same concept can be extended to a non-invasive and rapid evaluation of the quality of the industrial processes in order to improve these, with the aim to increase the quality of the final product. For these reasons, we think that we are at the beginning for the application of IAA approach in *pharma-food sector* in which the tensiometric approach could play a crucial role for solving the several issues in pharmaceutical and food sectors.

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References

1. T. Young, An essay on the cohesion of fluids. *Phil. Trans. R. Soc. Lond.* **95**, 65–87 (1805)
2. T. Tate, On the magnitude of a drop of liquid formed under different circumstances. *Phil. Mag.* **27**, 176–180 (1864).

DOI: 10.7569/RAA.2018.097308

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3. L.A. Wilhelmy, Ueber die abhängigkeit der capillaritäts-constanten des alkohols von substanz und gestalt des benetzten fasten körpers. *Annals Phys. Chem.* **119**, 177–217 (1863).
4. F. Bashforth and J. C. Adams, *An Attempt to Test the Theories of Capillary Action by Comparing the Theoretical and Measured Forms of Drops of Fluid*, *Cambridge University Press*, Cambridge, UK, 1883, With an Explanation of the Method of Integration Employed in Constructing the Tables which Give the Theoretical Form of Such Drops, by J. C. Adams.
5. A. Dupre, *Theorie Mechanique de la Chaleur*. Gauthier-Villars, Paris, p 369 (1869).
6. D. Berthelot, Sur le mélange des gaz. *Comptes Rendus Hebdomadaires Séances Académie Sciences*. **126**, 1803–1855 (1898).
7. I. Langmuir, The constitution and fundamental properties of solids and liquids. II. Liquids. *J. Am. Chem. Soc.* 39, 1848–1906 (1917).
8. N. K. Adam and G. Jessop, Contact angles and polarity of solid surfaces *J. Chem. Soc. Trans*. **127**, 1863–1868 (1925).
9. L. Mack, The determination of contact angles from measurements of dimensions of small bubbles and drops I: The spheroidal segment method for acute angles and II: The sessile drop method for obtuse angles. *J. Phys. Chem*. **40**, 159–167 (1936).
10. R.N. Wenzel, Resistance of solid surfaces to wetting by water. *Ind. Eng. Chem.* **28**,988–994 (1936).
11. E. W. Washburn. The dynamics of capillary flow. *Phys. Rev.* **18**, 273–283 (1921).
12. F. E. Bartell and C.E. Whitney, Adhesion tension III. *J. Phys. Chem.* **36**, 3115–3126 (1932).
13. J.J. Bikermann, A method of measuring contact angles. *Ind. Eng. Chem. Anal. Ed.* **13**, 443–444 (1941).
14. F. M. Fowkes and W. D. Harkins, The state of monolayers adsorbed at the interface solid—aqueous solution. *J. Am. Chem. Soc.* **62**, 3377–3386 (1940).
15. H.L. Ritter and L.C. Drake. Pore size distribution in porous materials. *Ind. Eng. Chem. Anal. Ed.* **17**, 782–786 (1945).
16. S. Baxter and A.B.D. Cassie, The water repellency of fabrics and a new water repellency test. *J. Textile Inst.* **36**, 67–90 (1945).
17. A. Carré and K.L. Mittal (Eds.), *Superhydrophobic Surfaces*, CRC Press, Boca Raton, FL (2009).
18. G. McDougall and C. Ockrent, Surface energy relations in liquid/solid systems I. The adhesion of liquids to solids and a new method of determining the surface tension of liquids. *Proc. Royal Soc. A.* **180**, 151–173 (1942).
19. V.R. Gray, Surface aspects of wetting and adhesion. *Chem. Ind*. **23**, 969–977 (1965).
20. W.C. Bigelow, D.L. Pickett, and W.A. Zisman, Oleophobic monolayers: I. Films adsorbed from solution in non-polar liquids. *J. Colloid Sci*. **1**, 513–538 (1946).
21. W.M. Rohsenow, A method of correlating heat transfer data for surface boiling of liquids. *Trans. ASME*. **74**, 969–975 (1952).
22. A. H. Ellison, H. W. Fox, and W. A. Zisman, Wetting of fluorinated solids by hydrogen bonding liquids. *J. Phys. Chem.* **57,** 622–627 (1953).
23. H. W. Fox and W. A. Zisman, The spreading of liquids on low energy surfaces. I. Polytetrafluoroethylene. *J. Colloid Sci.* **5**, 514–531 (1950).
24. H. W. Fox and W. A. Zisman, The spreading of liquids on low-energy surfaces. II. Modified tetrafluoroethylene polymers. *J. Colloid Sci*. **7**, 109–121 (1952).
25. H. W. Fox and W. A. Zisman, The spreading of liquids on low-energy surfaces. III. Hydrocarbon surfaces. *J. Colloid Sci.* **7**, 428–442 (1952).

DOI: 10.7569/RAA.2018.097308

 © 2018 Scrivener Publishing LLC

26. R. E. Johnson Jr., Conflicts between Gibbsian thermodynamics and recent treatments of interfacial energies in solid-liquid-vapor systems. *J. Phys. Chem*. **63**, 1655–1658 (1959).
27. E. G. Shafrin and W. A. Zisman, Constitutive relations in the wetting of low energy surfaces and the theory of the retraction method of preparing monolayers. *J. Phys. Chem.* **64**, 519–524 (1960).
28. F. M Fowkes, Determination of interfacial tensions, contact angles, and dispersion forces in surfaces by assuming additivity of intermolecular interactions in surfaces. *J. Phys. Chem*. **66**, 382–390 (1962).
29. L. A. Girifalco and R. J. Good, A theory for the estimation of surface and interfacial energies. I. Derivation and application to interfacial tension, *J. Phys. Chem.* 61, 904–909 (1957).
30. R. E. Johnson Jr and R. H. Dettre, Contact angle hysteresis. III. Study of an idealized heterogeneous surface. *J. Phys. Chem.* 68, 1744–1750 (1964).
31. W. A. Zisman, The solid/liquid interface—An essential and active frontier of science, *Adv. Chem. Sci.* **87**, 1–9 (1968).
32. D. E. McIntyre, A study of dynamic wettability on a hydrophobic surface. Doctor Dissertation, The Institute of Paper Chemistry, Appleton, Wisconsin, USA (1969).
33. W. J. Fenrick, Simple tangentometer. *Rev. Sci. Instrum*. **35**, 1616–1617 (1964).
34. T. Fort Jr and H.T. Patterson, A simple method for measuring solid-liquid contact angles. *J. Colloid Sci*. **18**, 217–222 (1963).
35. T. Karbowiak, F. Debeaufort, and A. Voilley, Importance of surface tension characterization for food, pharmaceutical and packaging products: A review. *Critical Rev. Food Sci. Nutrition*. **46**, 391–407 (2006).
36. E. Nowak, G. Combes, E. H. Stitt, A. and A. W. Pacek, A comparison of contact angle measurement techniques applied to highly porous catalyst supports. *Powder Technol.* **233**, 52–64 (2013).
37. F. Visioli, Pharma and nutrition: Crossing the Rubicon. *Pharma Nutrition* **1**, 9 (2013).
38. D. Schebarchov and S. C. Hendy, Uptake and withdrawal of droplets from carbon nanotubes. *Nanoscale* **3**, 134–141 (2011).
39. C. F. Lerk, A.J. Schoonen, and T. Fell, Contact angles and wetting of pharmaceutical powders. *J. Pharm. Sci*. **65**, 843-847 (1976).
40. J. O. Marston, J. E. Sprittles, Y. Zhu, E. Q. Li, I. U. Vakarelski, and S.T. Thoroddsen, Drop spreading and penetration into pre-wetted powders. *Powder Technol*. **239**, 128–136 (2013).
41. Y. Han, G. Drazer, G. Callegari, and Z. S. Shojaei, Droplet penetration method as a wettability test for pharmaceutical powders. Ph.D. dissertation, Rutgers University, New Brunswick, New Jersey, USA (2017).
42. U. Teipel and I. Mikonsaari, Determining contact angles of powders by liquid penetration. *Particle Particle Syst. Charact*. **21**, 255–260 (2004).
43. M. Thakker, V. Karde, D. O Shah, P. Shukla, and C. Ghoroi, Wettability measurement apparatus for porous material using the modified Washburn method. *Measurement. Sci. Technol*. **24**, 1–8 (2013).
44. E. Chibowski, L. Holysz and A. Szczes, Wettability of powders, in: *Adhesion in Pharmaceutical, Biomedical, and Dental Fields*, K.L. Mittal and F.M. Etzler (Eds.) pp. 23–49, Wiley-Scrivener, Beverly, MA (2017).
45. D. Zhang, J. H. Flory, S. Panmai, U.Batra, and J. Kaufman, Wettability of pharmaceutical solids: Its measurement and influence on wet granulation. *Colloids Surfaces A*. 206, 547–554 (2002).

DOI: 10.7569/RAA.2018.097308

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46. N. M. Ahfat, G. Buckton, R. Burrows, and M. D. Ticehurst, An exploration of interrelationships between contact angle, inverse phase gas chromatography and triboelectric charging data. *Eur. J. Pharm. Sci.* **9**, 271–276 (2000).
47. J. W. Dove, G. Buckton, and C. Doherty, A comparison of two contact angle measurement methods and inverse gas chromatography to assess the surface energies of theophylline and caffeine. *Int. J. Pharm.* **138**, 199–206 (1996).
48. C. J. van Oss, M.K. Chaudhury, and R.J. Good, Interfacial Lifshitz-van der Waals and polar interactions in macroscopic systems. *Chem. Rev.* **88**, 927–941 (1988).
49. D. R. Williams, Particle engineering in pharmaceutical solids processing: Surface energy considerations. *Current Pharmaceutical Design* **21**, 2677–2694 (2015).
50. D. K. Owens, and R. C., Wendt, Estimation of the surface energy of polymers. *J. Appl. Polym. Sci.* **13**, 1741–1747 (1969).
51. T. Ghafourian and P. A. Khan, Quantitative relationships between contact angles of pharmaceutical powders and computable molecular descriptors. *Pharm. Sci.* **3**, 69–77 (2000).
52. T. Phaechamud and C. Savedkairop, Contact angle and surface tension of some solvents used in pharmaceuticals. *Res. J. Pharm. Biol. Chem. Sci.* 3, 513–529 (2012).
53. C. J. Yarce, D. Pineda, C. E. Correa and C. H. Salamanca, Relationship between surface properties and in vitro drug release from a compressed matrix containing an amphiphilic polymer material. *Pharmaceuticals* **9**, 34–54 (2016).
54. J.R. Chokshi, Z. Hossein, K. S. Harpreet, H. S. Navnit, and A. M. Waseem, Improving the dissolution rate of poorly water soluble drug by solid dispersion and solid solution—pros and cons. *Drug Delivery* **14**, 33–45 (2007).
55. S. Verma, and S. V. Rudraraju, Wetting kinetics: An alternative approach towards understanding the enhanced dissolution rate for amorphous solid dispersion of a poorly soluble drug. *AAPS Pharm. Sci. Technol*.**16**, 1079–1090 (2015).
56. K. Min-Soo, K. Jeong-Soo, and H. Sung-Joo, Enhancement of wettability and dissolution properties of Cilostazol using the supercritical antisolvent process: Effect of various additives. *Chem. Pharm. Bull*. **58** 230—233 (2010).
57. I. Khan, M.I. Khan and U. Khan; Liquisolid technology: An emerging and advanced technique for enhancing solubilization. *PharmaTutor* **2**, 31–41 (2014).
58. R. M. Patel, Parental suspension : An overview. *Int. J. Current Pharm*. Res. **2**, 5–13 (2010).
59. A. Trivino and H. Chauhan, Drug-excipient compatibility for the formulation development of solid lipid nanoparticles. *Amer. Pharmaceutical Review* **18**, 2–6 (2015).
60. I. O. De Solorzano, L. Uson, A. Larrea, M. Miana, V. Sebastian and M. Arruebo, Continuous synthesis of drug-loaded nanoparticles using microchannel emulsification and numerical modeling: Effect of passive mixing. *Int. J. Nanomedicine* **11**, 3397–3416 (2016).
61. A. Nakashima, T. Izumi, K. Ohya, K. Kondo and T. Niwa, Design of highly dispersible PLGA microparticles in aqueous fluid for the development of long-acting release injectables *Chem. Pharm. Bull*. **65**, 157–165 (2017).
62. A. M. Asiri, H. M. Marwani, S. B. Khan, and T. J. Webster, Understanding greater cardiomyocyte functions on aligned compared to random carbon nanofbers in PLGA. *Int. J. Nanomedicine* **10**, 89–96 (2015).
63. R. Andrade, O. Skurtys, and F. Osorio, Drop impact behavior on food using spray coating: Fundamentals and application. *Food Res. Int*. **54**, 397–405 (2013).

DOI: 10.7569/RAA.2018.097308

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64. T. S. Parreidt, M. Schmid and C. Hauser, Validation of a novel technique and evaluation of the surface free energy of food. *Foods* **6,** 1–14 (2017).
65. M. D. Kurkuri, C. Randall, and D. Losic, New method of measuring the angle of repose of hard wheat grain. *Intl. Proc. Chemeca,* Wellington, New Zealand (2012).
66. S. K. Reinke, K. Hauf, J. Vieira, and S. Palzer, Changes in contact angle providing evidence for surface alteration in multi-component solid foods. *J. Phys. D: Appl. Phys.* **48**, 1–15 (2015)
67. A. Sharma, A. H. Jana, and R. S. Chavan, Functionality of milk powders and milk-based powders for end use applications—A review. *Comprehensive Rev. Food Sci. Food Safety*. **11**, 518–529 (2012).
68. K. Górnicki, A. Kaleta, R. Winiczenko, A. Chojnacka and M. Janaszek, Some remarks on modelling of mass transfer kinetics during rehydration of dried fruits and vegetables, *Mass Transfer*. **16**, 431–457 (2013).
69. J. C. Banach, Modifed milk protein concentrates in high-protein nutrition bars. PhD Dissertation, Iowa State University, Ames, Iowa, USA (2016).
70. A.V. Nushtaeva, Natural food-grade solid particles for emulsion stabilization. *Colloids Surfaces A* **504**, 449–457 (2016).
71. J. Dupas, L. Forny, and M. Ramaioli, Powder wettability at a static air–water interface. *J. Colloid Interface Sci.* **448**, 51–56 (2015).
72. Z. Wang, G. Narsimhan, and D. Kim, Characterization of the effect of food emulsifier on contact angle and dispersibility of lipid coated neutrally buoyant particles. *Lebensmittel-Wissenschaft Technologie,* **41**, 1232–1238 (2008).
73. M. C. Michalski, S. Desobry, M. N. Pons and J. Hardy, Adhesion of edible oils to food contact surfaces. *J. Amer. Oil Chem. Soc* **75**, 447–454 (1998).
74. D. M. Dresselhuis, The fate of fat: Tribology, adhesion and fat perception of food emulsions. Wageningen Universiteit, Nederland (2008).
75. M. Jamshidian, E. A. Tehrany, M. Imran, M. Jacquot and S. Desobry, Poly-Lactic Acid: Production, applications, nanocomposites, and release studies. *Comprehensive Rev. Food Sci. Food Safety* **9**, 552–571 (2010).
76. K.L. Mittal, The role of the interface in adhesion phenomena. *Polym. Eng. Sci*. **17**, 467–473 (1977).
77. B. K. Tiwari, Nonthermal plasma inactivation of food-borne pathogens. *Food Eng. Rev.* **3**, 159–170 (2011).
78. F. M. Etzler, Characterization of surface free energies and surface chemistry of solids, in: *Contact Angle, Wettability and Adhesion, Volume 3*, K.L. Mittal (Ed.) pp. 219–264, CRC Press, Boca Raton, FL (2003)
79. F.M. Etzler, Determination of the surface free energy of solids: A critical review. *Rev. Adhesion Adhesives* **1**, 3–45 (2013).
80. C. Della Volpe and S. Siboni, Use, abuse, misuse and proper use of contact angles: A critical review. *Rev. Adhesion Adhesives* **3**, 365–385 (2015).

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