Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 353 (2008) 176–186
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Development of a rapidly dispersing tablet of a poorly wettable compound—formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib

Xiaorong He [a,*], Michael R. Barone [b], Patrick J. Marsac [b], David C. Sperry [a,1]

[a] *Pfizer Inc., Kalamazoo, MI, USA*
[b] *Michigan State University, East Lansing, MI, USA*

Received 10 July 2007; received in revised form 16 November 2007; accepted 19 November 2007
Available online 22 January 2008

Abstract

Celecoxib has extremely poor aqueous wettability and dispersibility. A dispersibility method was developed to study the effects of formulation excipients and processing methods on wetting of celecoxib. In this method, a tablet or powder was placed in water and the turbidity of the resulting "dynamic" suspension was measured. Higher turbidity values reflect better dispersibility. Results show that wet granulation facilitates better drug dispersion than does dry granulation or direct compression. Results from a screening formulation statistical design of experiments (DOE) show that sodium lauryl sulfate (SLS), an anionic surfactant, gives higher celecoxib dispersibility than polysorbate 80, a neutral surfactant. Polyplasdone XL as a disintegrant results in better celecoxib dispersibility than sodium starch glycolate. The binder Kollidon 30 leads to better dispersibility, but slower disintegration than Kollidon 12. Jet-milling celecoxib with excipients not only improves dispersibility of the drug but also the ease of material handling. The method of microcrystalline cellulose addition does not significantly impact tablet properties. The effect of critical formulation variables on the wettability of celecoxib was further examined in prototype formulations. It is found that ionic surfactant resulted in better dispersibility than a neutral surfactant, probably due to charge dispersion. Kollidon 30 gives better drug dispersion than hydroxypropylmethyl cellulose and hydroxypropyl cellulose. This may be explained through a surface energy calculation, where the spreading coefficients between Kollidon 30 and celecoxib indicate formation of open porous granules in which pores can facilitate water uptake. The mode of disintegrant addition also impacts dispersibility of the drug. Dense granules were formed when the disintegrant, Polyplasdone, was added intra-granularly. As the extra-granular portion of the disintegrant increases, the dispersibility of the drug increases as well. The drug initial dispersibility (turbidity at 5 min during the dispersibility test) increases as the tablet porosity increases. A 3-factor face-centered experimental design was conducted to optimize the levels of surfactant (SLS), binder (Kollidon 30) and disintegrant (Polyplasdone). Within the range that was studied, the dispersibility of micronized drug increases as the amount of SLS and Kollidon 30 increases. The level of Polyplasdone has no significant impact on the dispersibility of micronized drug; however, higher levels of Polyplasdone lead to significantly harder tablets.

Keywords: Wetting; Celecoxib; Dispersion; Disintegration; Surface energy; Porosity; Poorly soluble; Agglomeration

1. Introduction

According to the biopharmaceutical classification system (BCS), celecoxib is a BCS class II compound (Amidon et al., 1995) with an aqueous solubility of less than 5 μg/ml, and it is non-ionizable over the physiologic pH range. Earlier human pharmacokinetic studies suggested that dissolution of celecoxib is the rate-limiting step for its absorption (unpublished data). It is desirable to enhance the dissolution rate of the drug to increase its rate of absorption. According to the Noyes–Whitney equation

* Corresponding author at: GlaxoSmithKline Corp., Five Moore Drive, Mail Stop Number Building 2.3055, Research Triangle Park, NC 27709, USA. Tel.: +1 919 483 6965.
E-mail addresses: xiaorong.x.he@gsk.com, he_xiaorong@yahoo.com (X. He).
[1] Present address: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA.

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.11.045

(Noyes and Whitney, 1897), the rate at which a solid dissolves is directly proportional to the surface area of drug exposed to the dissolution medium. One common method of enhancing the dissolution rate, especially for poorly soluble compounds, is to increase the surface area of a drug through particle size reduction (Amidon et al., 2003). In this paper, we describe how fluid-bed jet milling can be used to reduce the drug particle size from a D50 of 7 μm to a D50 of 2 μm (50% of the mass of the particles in a sample are less than the diameter defined by D50). An early pharmacokinetic study in dogs showed that the bioavailability of a suspension containing jet-milled celecoxib is significantly enhanced (unpublished data). However, initial attempts to formulate jet-milled celecoxib into a tablet failed to match the *in vivo* performance of the suspension formulation. This is believed to be due to the fact that celecoxib is poorly wettable and tends to aggregate upon contact with water. The aggregation reduces the effective surface area of the drug, thereby diminishing or negating the benefit of particle size reduction. This is a common problem associated with formulating small particles of poorly wettable materials. Very often, a surfactant is added to a formulation to aid in wetting the drug (Buckton, 1995a). However, addition of a surfactant is not sufficient to solve the wetting problem of celecoxib. Despite the general importance of wetting on bioavailability of the poorly wettable compounds, methods to overcome the wetting problem by formulation manipulation are not well understood. The objectives of this study are three-fold. The first goal is to identify critical processing and formulation variables that influence the wetting properties of celecoxib. The second goal is to obtain a mechanistic understanding as to why certain excipients improve the dispersibility/wetting of celecoxib. The third goal is to optimize the excipient levels through statistical design of experiments (DOE) to maximize the dispersion of celecoxib.

2. Material and methods

2.1. Materials

Celecoxib, supplied by Pfizer, Inc. as is, has a particle size with a D50 of 7 μm and D90 of 16.7 μm. The drug was milled, either with or without excipients, using a fluid-bed jet mill (Alpine AFG-100, Hosakawa Micron, Summit, NJ) to achieve a particle size distribution with a D50 of 2 μm and a D90 of less than 4 μm. The following excipients are present in at least one of the formulations used in this study: spray dried lactose monohydrate (Foremost Farms USA, Baraboo, WI), sodium lauryl sulfate (SLS) (Stepan, Northfield, IL), polysorbate 80 (Uniquema, Newcastle, DE), cetrimide (Aldrich, Milwaukee, WI), sodium bicarbonate (SB) (Mallinkcrodt Baker Inc., Paris, KT), sodium starch glycolate (SSG) (Penwest Pharmaceuticals, Cedar Rapids, IA), microcrystalline cellulose (MCC), Avicel PH 101 (FMC, Philadelphia, PA), a variety of grades of povidone, including Kollidon 12, and Kollidon 30 (BASF Inc., Ludwigshafen, Germany), hydroxypropyl cellulose EXF NF (HPC) (Hercules Aqualon, Wilmington, DE), hydroxypropylmethyl cellulose (HPMC) 2910 3 cps (Biddle Sawyer, New York, NY), crosslinked povidone or Polyplasdone XL (ISP Inc., Wayne, NJ) and magnesium stearate (Mallinkrodt Inc., St. Louis, Missouri).

2.2. Manufacturing procedure

2.2.1. Effect of processing methods on celecoxib dispersibility

Three different processing methods were used to prepare a single tablet formulation, containing jet-milled celecoxib, lactose, SLS, povidone, MCC and Polyplasdone. These methods are: direct compression (DC), dry granulation (DG) and wet granulation (WG).

In the direct compression process, formulation components were mixed well in a bag prior to compression. In the dry granulation process, intra-granular components were mixed well in a plastic bag, then processed on a roller compactor (Model TF Mini, Freund Industrial Corp., Tokyo, Japan) at a screw feed rate of 52 rpm, roller speed of 8 rpm and a roller pressure of 65 kg/cm^2 (equivalent to 65 bar) to form ribbons. The ribbons were hand-screened through a 20-mesh screen and mixed with extra-granular excipients. In the wet granulation process, intra-granular excipients were mixed well in a bag, and placed into a mortar. A surfactant was dissolved in water (0.042 g surfactant per g of water) and sprayed onto the powder bed. An appropriate amount of solution was sprayed so that the sprayed surfactant is about 0.4% (w/w) of the final formulation. The resulting wet granules were hand-screened through a 20-mesh screen then dried in a vacuum oven (Model 5851, Napco Scientific Corp., Tualatin, Oregon) at room temperature for 2 h. The moisture level in the granules was tested with a Computrac Moisture Analyzer (Model MA-5A, Compu-Trac Inc., Tempe, AZ). The final moisture level ranged from 0.9% to 1.9% by weight. After drying, the granules were mixed with an appropriate amount of extra-granular excipients.

Prior to compression, upper and lower punches along with the die were lubricated with magnesium stearate to prevent sticking. Formulated powder was compressed into two sets of tablets with 14/32 in. round tooling with a standard concave punch using a Carver Press (Carver Inc., Wabash, Indiana). In one set, compression force was adjusted to achieve a target tablet hardness of 70.1 N; in the other set, tablets were manufactured to have the same porosity ($\sim 0.175 \pm 0.003$), defined as follows:

$$\text{porosity} = 1 - \frac{W}{V \times \rho} \quad (1)$$

where W is the tablet weight, V the tablet volume, ρ is the true density, which was measured by helium pyconometry (AccuPyc 1330, Micromeritics Inc., Norcross, GA). The tablet volume was determined from the physical dimensions of the tablet. Compression pressure was varied to create desired tablet thickness, while the tablet porosity remained the same for each lot. Tablets with the same porosity were analyzed by hardness and turbidity tests, while tablets with the same hardness were subject to a disintegration test.

Table 1
Prototype formula used in the screening formulation design of experiments

Material	Tablet (mg)	Percentage of the tablet (%, w/w)	Batch size (g)
Intra-granular			
Co-mill or blend[a]	392.90	78.9	20.0
Binder: Kollidon 12 or Kollidon 30	20.80	4.2	1.06
Surfactant: SLS or polysorbate 80[b]	2.00	0.4	0.10
Microcrystalline cellulose (MCC)	0 or 20.60	0 or 4.1	0 or 1.05
Extra-granular			
MCC	41.20 or 20.60	8.2 or 4.1	2.10 or 1.05
Polyplasdone XL	41.30	8.3	2.10
Total	498.20	100.0	25.36

[a] "Co-mill" refers to the mixture of celecoxib and excipients jet-milled together. "Blend" refers to the mixture where the jet-milled celecoxib alone, was blended with the same excipients present in the "co-mill" mixture. Both the "co-mill" and "blend" had the same overall formulation composition, which contained 50.9% celecoxib, 45.7% lactose, 2.9% SB and 0.5% SLS.
[b] Both SLS and polysorbate 80 were first dissolved in water (0.042 g of polysorbate 80 or SLS/g of water) and sprayed onto the powder bed.

2.2.2. Screening formulation statistical design of experiments (DOE)

A 5-factor 1/2 fraction factorial statistical design was used to study the effect of formulation components on dispersion of the jet-milled drug. The factors include:

(1) Type of surfactant: SLS (−) vs. polysorbate 80 (+).
(2) Type of binder: Kollidon 12 (−) vs. Kollidon 30 (+).
(3) Type of disintegrant: Polyplasdone XL (−) vs. SSG (+).
(4) The drug-processing method: co-mill (−) vs. blend (+), where "co-mill" refers to a process by which the mixture of drug and excipients were milled together, and "blend" refers to the process where excipients were blended with the milled drug.
(5) Method of MCC addition: EXT (−) vs. INT + EXT (+), where EXT means that MCC was only present in the extra-granular portion, and INT + EXT means that MCC was present both intra-granularly and extra-granularly.

The statistical design is comprised of 19 experiments, three of which are triplicate runs. Table 1 summarizes the prototype formula used in the DOE studies. The formulations were manufactured by a wet granulation process, following the procedure described in the Section 2.2.1.

2.2.3. Mechanistic studies

Following the screening formulation DOE, more prototype formulations were made to study the effect of surfactants and binders on the wettability of celecoxib using the wet granulation procedure described in Section 2.2.1. In the surfactant study, three formulations were made containing SLS, polysorbate 80 or cetrimide (Table 2). In the binder study, three formulations were made containing Kollidon 30, HPMC or HPC (Table 3). In the disintegration study, four formulations were prepared where the ratio of intra- to extra-granular proportions of Polyplasdone was varied (Table 4). These were 100% intra-granular; 50% intra-granular and 50% extra-granular, 20% intra-granular and 80% extra-granular, or 100% extra-granular. The combined level of intra- and extra-granular Polyplasdone was always equal to 8.3% of the formulation.

Table 2
Prototype formulations containing different types of surfactants

Materials	Amount per tablet (mg)	Percentage of the tablet (%, w/w)
Intra-granular		
Jet-milled celecoxib[a]	200.00	55.6
Lactose	79.00	21.9
Surfactant[b]	3.00	0.8
Kollidon 30	18.00	5.0
Extra-granular		
MCC	30.00	8.3
Polyplasdone XL	30.00	8.3
Total tablet weight (mg)	360.00	100.0

[a] Celecoxib jet-milled without excipients present.
[b] Surfactant could be SLS, polysorbate 80 or cetrimide.

The effect of tablet porosity on the drug dispersion was also studied. The formula is shown in Table 3, where Kollidon 30 was used as a binder. Tablets were made under appropriate compression force to achieve a target porosity, ranging from 0.340 (most porous) to 0.115 (least porous) (Table 5).

Table 3
Prototype formulations containing different types of binders

Materials	Amount per tablet (mg)	Percentage of tablet (%, w/w)
Intra-granular		
Co-milled celecoxib[a]	392.90	78.8
SLS	1.95	0.4
Binder[b]	20.83	4.2
Extra-granular		
MCC	41.57	8.3
Polyplasdone XL	41.57	8.3
Total tablet weight (mg)	498.82	100.0

[a] Co-milled celecoxib is a mixture of celecoxib and excipients jet-milled together. It was composed of 50.9% celecoxib, 45.7% lactose, 2.9% SB and 0.5% SLS.
[b] Binder could be Kollidon 30, HPMC or HPC.

Table 4
Prototype formulations containing different ratios of intra- to extra-granular disintegrants

Materials	Amount per tablet (mg)	Percentage of tablet (%, w/w)
Intra-granular		
Jet-milled celecoxib[a]	200.00	55.6
Lactose	79.00	21.9
SLS	3.00	0.8
Kollidon 30	18.00	5.0
Polyplasdone XL[b]	Varied	Varied
Extra-granular		
MCC	30.00	8.3
Polyplasdone XL[b]	Varied	Varied
Total tablet weight (mg)	360.00	100.0

[a] Celecoxib jet-milled by itself.
[b] The intra- to extra-granular portions of Polyplasdone in the prototype formulation could be 100% intra-granular; 50% intra-/50% extra-; 20% intra-/80% extra-; 100% extra-granular. The combined level of intra- and extra-granular Polyplasdone was equal to 8.3% of the formulation.

Table 5
Tablet porosity and tablet hardness in the porosity study

Tablet porosity[a]	Tablet hardness[b] (N)
0.115	210.2
0.175	140.1
0.259	70.1
0.340	35.0

[a] The standard deviation for tablet porosity ($n = 3$) is typically less than 0.003.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

2.2.4. Optimization design of experiments (DOE)

Using the appropriate excipients identified in the studies described above, a 3-factor face-centered design was utilized to optimize the level of these excipients in tablets containing jet-milled drug. The design is outlined in Table 6. Prototype formulations used in the DOE are shown in Table 7. The analytical measurements representing response factors in the study were turbidity, granule moisture level and tablet hardness. Design Expert (Stat-Ease, Inc., Minneapolis, MN) was used to analyze the results.

Table 7
Prototype formulations of micronized celecoxib tablets

Material	Amount per tablet (mg)
Intra-granular portion	
Jet-milled celecoxib	200.00
Spray dried lactose	80.00
SLS (surfactant)	Varied from 3.60 to 25.20 mg
Kollidon 30 (binder)	Varied from 3.60 to 32.40 mg
Extra-granular portion	
MCC	30.00
Polyplasdone XL (disintegrant)	Varied from 7.20 to 36.00 mg
Total tablet weight	

2.3. Analytical methods

2.3.1. Turbidity test

A turbidity method was developed to quantitatively assess how well the jet-milled celecoxib dispersed into finely divided particles upon tablet disintegration in water. If a formulation disperses into small particles, the resulting 'dynamic' suspension will be more turbid than that resulting from a formulation that disperses into larger particles. Higher turbidity reflects better dispersion. The method was developed as a substitute for dissolution testing. Efforts to develop a discriminating dissolution test were not successful because the necessary addition of surfactant to the media to provide sink conditions suppresses the discriminatory ability of the method. The dispersion characteristics of

Table 6
Design of experiments—optimization studies (3-factor face-centered design)

Run	A: Polyplasdone XL (mg)	B: SLS (mg)	C: Kollidon 30 (mg)	Fixed excipients[a] (mg)	Total tablet weight (mg)
1	36.00	25.20	32.40	310.00	403.60
2	7.20	3.60	32.40	310.00	353.20
3	36.00	25.20	3.60	310.00	374.80
4	21.60	14.40	18.00	310.00	364.00
5	36.00	3.60	3.60	310.00	353.20
6	7.20	14.40	18.00	310.00	349.60
7	21.60	14.40	18.00	310.00	364.00
8	21.60	25.20	18.00	310.00	374.80
9	21.60	14.40	3.60	310.00	349.60
10	21.60	14.40	18.00	310.00	364.00
11	21.60	14.40	32.40	310.00	378.40
12	36.00	3.60	32.40	310.00	382.00
13	21.60	14.40	18.00	310.00	364.00
14	36.00	14.40	18.00	310.00	378.40
15	21.60	3.60	18.00	310.00	353.20
16	21.60	14.40	18.00	310.00	364.00
17	7.20	25.20	3.60	310.00	346.00
18	7.20	3.60	3.60	310.00	324.40
19	7.20	25.20	32.40	310.00	374.80

[a] Every tablet contained 200.00 mg jet-milled drug, 80.00 mg spray dried lactose in the intra-granular portion and 30.00 mg of MCC in the extra-granular portion.

the formulations were tested in a USP II dissolution apparatus (SR8 Plus, Hanson Research Corporation, Chatsworth, CA, USA or Dissolution System 2100, Distek, North Brunswick, NJ, USA) containing 500 ml of de-ionized water at 37 °C and 50 rpm paddle speed. The tablet or powder sample was placed into the dissolution flask at the start of the test. At selected time points (typically 5, 20 and 35 min), 8 ml samples were manually withdrawn 0.75 in. from the water/air interface with a 10 ml syringe fitted with a stainless steal cannula. The first 4 ml of the sample was filtered through an acrylic copolymer membrane filter, collected in a vial, representing the "filtered" sample. The membrane pore size was selected such that what passed through the filter membrane were mostly primary particles. For the jet-milled drug (D50: 2 μm, D90: 4 μm), a filter membrane with 5 μm pore size was chosen (Acrodisc 25 mm Syringe Filter, Part no. 4489T, Gelman Sciences, Ann Arbor, MI, USA). The remaining 4 ml of sample was retained in a vial as "unfiltered" sample. The turbidity (a unitless quantity) of both filtered and unfiltered samples was measured using a spectrophotometer (Cinitra 40, GBC Scientific Equipment, Dandenong, Victoria, Australia) at 650 nm using a 1 cm quartz cuvette and reported as the log of the ratio of the incident and transmitted light intensity. The placebo ingredients in the formulation had negligible contribution to the turbidity measurement (turbidity < 0.0001) because the excipients were either water-soluble or swelled quickly and sank to the bottom of the vessel. Therefore, the turbidity results accurately reflected how well the drug was dispersed. Note that because of the low solubility, very little (<0.5% of the total dose) of the drug being tested dissolved in the media.

2.3.2. Contact angle analysis

To measure the contact angle, microscope slides were sprayed with a thin coating of adhesive. A solid (in powder form) of unknown surface energy was sprinkled onto the slide to create a uniform layer of coverage. Excess powder was removed by tapping the slide. Equilibrium contact angle between the test liquid and the solid was used for surface energy calculations. The contact angle was measured using the Dynamic Contact Angle Instrument (Model No. FTÅ 200, First Ten Ångstrom Inc., Portsmouth, VA) which was equipped with a high speed camera.

2.3.3. Microscopy test

Either a tablet or test powder was placed in a beaker containing 50 ml of water. If the sample was a tablet, it was allowed to fully disintegrate. The sample was then shaken for a minute prior to withdrawing an aliquot to observe under the microscope (Axioplan2, Carl Zeiss Inc., Thornwood, NY), equipped with a MC100 Spot Camera (Carl Zeiss Inc., Thornwood, NY). Photos were taken at 100× and 400× magnifications.

3. Results and discussions

3.1. Contact angle analysis

The contact angle between water and the drug is 127°, indicating that the drug has very poor wettability in water. The drug powder tends to form agglomerates in water and the agglomerates cannot be re-dispersed into small particles even with manual shaking.

3.2. Effect of the processing method on celecoxib dispersibility

The choice of processing method has a significant effect on drug dispersion in an aqueous environment. During disintegration testing (USP <701>, with disks, using water as medium), tablets made by dry granulation and direct compression disintegrated into large aggregates that quickly sank to the bottom of the flask, yielding a clear disintegration medium. However, tablets made by the wet granulation process produced a fine turbid dispersion in the disintegration test. This agrees well with the turbidity results (Table 8), where wet-granulated tablets have much higher turbidity in both filtered and unfiltered samples than those made from dry granulation and direct compression. Microscopy observations of samples from the disintegration medium indicate that the particle size of samples from the wet granulation process is much smaller than that of the dry granulation and direct compression processes. It is hypothesized that wet granulation facilitates an intimate contact between the poorly wettable drug and wetting agents such as surfactant and binder, thereby enhancing the wettability of the drug. Based on these results, the wet granulation processes was chosen to further study the effect of excipients on the dispersibility of celecoxib.

3.3. Screening formulation DOE

The statistically significant factors (with a p-value < 0.05) are summarized in Table 9.

3.3.1. Surfactant

Both "co-mill" and "blend" celecoxib formulations contained 0.4% anionic surfactant-SLS. To investigate the effect of surfactant type on drug dispersion, an additional 0.4% SLS or

Table 8
Effect of processing methods on celecoxib dispersion[a]

	Wet granulation	Dry granulation	Direct compression
Turbidity of filtered sample	0.291 (0.004)	0.097 (0.018)	0.048 (0.002)
Turbidity of unfiltered sample	1.950 (0.031)	0.540 (0.027)	0.365 (0.030)

[a] Tablets with the same porosity were used in these experiments. Values in parentheses are standard deviation.

Table 9
Summary of significant effects of screening formulation design of experiments[a]

Factors	Surfactant	Binder	Disintegrant	Method of MCC addition	Drug process
Tablets with the same porosity					
Turbidity of filtered sample	−	+	−		
Turbidity of unfiltered sample	−		−		−
Tablet hardness	−		−		−
Tablets with the same hardness					
Disintegration time		+	+		−

[a] Factors with p-value less than 0.05 are considered statistically significant. "−" means the low level variable results in a statistically significant higher value in the corresponding response. For example, SLS (−) results in a higher turbidity than polysorbate 80 (+); similarly, "+" means a high level variable results in a significant higher value in the corresponding factor. The key for "−" or "+" is described in Section 2.2.2.

polysorbate 80 was added to the formulation. Tablets containing 0.8% SLS (total) produced significantly higher turbidity values than those containing 50/50 mixture of SLS and polysorbate 80 (Table 9). In addition, tablets containing 0.8% SLS were also significantly harder than those containing polysorbate 80–SLS combination. Neutral surfactants such as polysorbate 80 are not expected to interact with ionic surfactants to adversely affect dispersion (Buckton, 1995). Thus, SLS appears to be a better surfactant than polysorbate 80 in terms of improving dispersibility of celecoxib. The effect of anionic, cationic and neutral surfactants on celecoxib dispersion is compared in a later study described in Section 3.4.1.

3.3.2. Binder

For tablets made at the same porosity, tablets containing Kollidon 30 as a binder produce significantly higher turbidity in filtered samples than those containing Kollidon 12, indicating that the formulation containing Kollidon 30 disperses celecoxib more readily into primary particles. For tablets made at the same hardness, tablets containing Kollidon 30 disintegrate significantly slower than those containing Kollidon 12. This is probably due to the higher molecular weight and solution viscosity of Kollidon 30.

3.3.3. Disintegrant

Tablets containing Polyplasdone XL as a disintegrant give significantly higher turbidity in both filtered and unfiltered samples than those containing SSG, indicating that Polyplasdone XL promoted better celecoxib dispersion. The poor dispersibility of tablets containing SSG may be due to the fact that SSG tends to form a gel at high concentrations. The gel formation can trap the celecoxib particles and slow drug release into the test medium. This hypothesis is consistent with visual observation that tablets containing SSG seem to "flake off" and released more coarse particles than those containing Polyplasdone XL. In addition to improving the overall dispersibility of celecoxib, tablets containing Polyplasdone XL are harder than those containing SSG, when the tablet porosity is controlled, or have a shorter disintegration time, when the tablets hardness is controlled. These data suggest that Polyplasdone XL should be selected as the tablet disintegrant.

3.3.4. Drug processing

Two drug-processing methods are examined. In one scenario, celecoxib and excipients were mixed and then jet-milled together; this is referred to as the "co-milled" process. In the other scenario, celecoxib was first jet-milled by itself and then the milled celecoxib was blended with un-milled excipients; this is referred to as the "blended" process. Tablets containing co-milled celecoxib disperse significantly better than those containing blended celecoxib, although both formulations have comparable turbidity for filtered samples. Since the excipient particle size in the co-milled celecoxib formulations is much smaller than that in the blended celecoxib formulations, the co-milled celecoxib formulations require a higher compaction pressure to achieve the same porosity as those containing blended celecoxib, and as a result, produced much harder tablets. In addition to giving better dispersion, co-milling celecoxib also enhances the ease of handling during the milling process. It was observed that the feed material has much less sticking and enhanced flowability when the excipients were milled together with celecoxib.

3.3.5. Microcrystalline cellulose formulation variables

Microcrystalline cellulose, added to the formulation either as a 100% extra-granular excipient or a 50% intra-granular/50% extra-granular, has no significant effect on dispersion, disintegration or hardness.

3.4. Mechanistic understanding on effect of excipients on wetting of celecoxib

3.4.1. Surfactant study

Surfactant is a very important pharmaceutical excipient that aids in wetting/dispersion of poorly wettable drugs. Surfactant may promote wetting by adsorbing onto the surface of a hydrophobic particle and reducing the interfacial tension between hydrophilic and hydrophobic phases. Results from the screening formulation DOE indicate that SLS may be a better surfactant than polysorbate 80. However, the results are not entirely clear since the formulations which were used for comparison all contained a different level of SLS.

To further study the effect of types of surfactants on wetting of celecoxib, prototype formulations (shown in Table 2) containing anionic surfactant (SLS), cationic surfactant (cetrimide) or neutral surfactant (polysorbate 80) were prepared.

Table 10
The effect of types of surfactants on dispersion of drug in water[a]

Formulation/types of surfactant	Compaction pressure (MPa)	Tablet hardness (N)[b]	Turbidity in water
SLS	10.0	64.4	1.620 ± 0.011
Cetrimide	10.0	86.9	1.037 ± 0.044
Polysorbate 80	6.89	21.0	0.200 ± 0.046

[a] Dispersion at tablet porosity = 0.175 ± 0.003.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

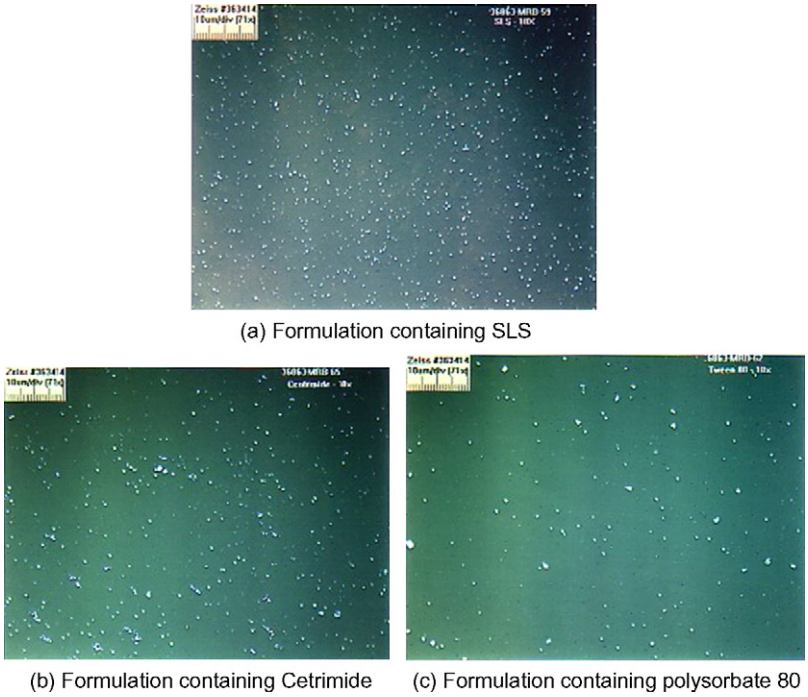


Fig. 1. Photomicrographs of dispersion medium of granules containing different types of surfactants.

As shown in Table 10, turbidity follows the rank order of SLS > cetrimide ≫ polysorbate 80, indicating that ionic surfactants disperse celecoxib more efficiently than neutral surfactants. Visual observations agree well with the turbidity data. The SLS formulation has the largest numbers of primary particles per sample. The cetrimide formulation has a medium number of primary particles, and polysorbate 80 formulation has the least primary particles per sample (Fig. 1). Furthermore, wettability of both the SLS and the cetrimide formulation using contact angle analysis is found to be similar (Fig. 2). It is hypothesized that celecoxib particles covered with negatively charged SLS or positively charged cetrimide were less likely to form agglomerates as compared to particles without any surface charge due to charge repulsion. However, this conclusion would not necessarily hold for an ionizable compound, due to the potential ionic interaction with the surfactant.

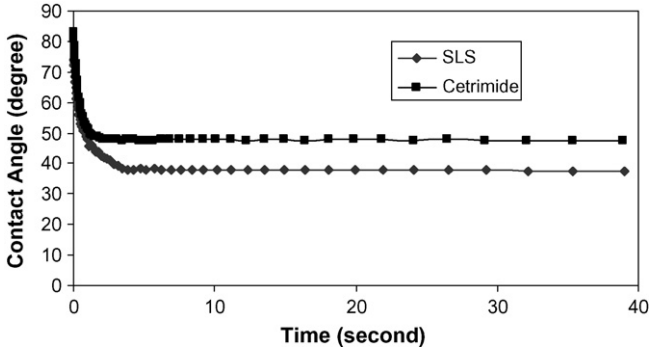


Fig. 2. Contact angles of water on formulations containing SLS or cetrimide.

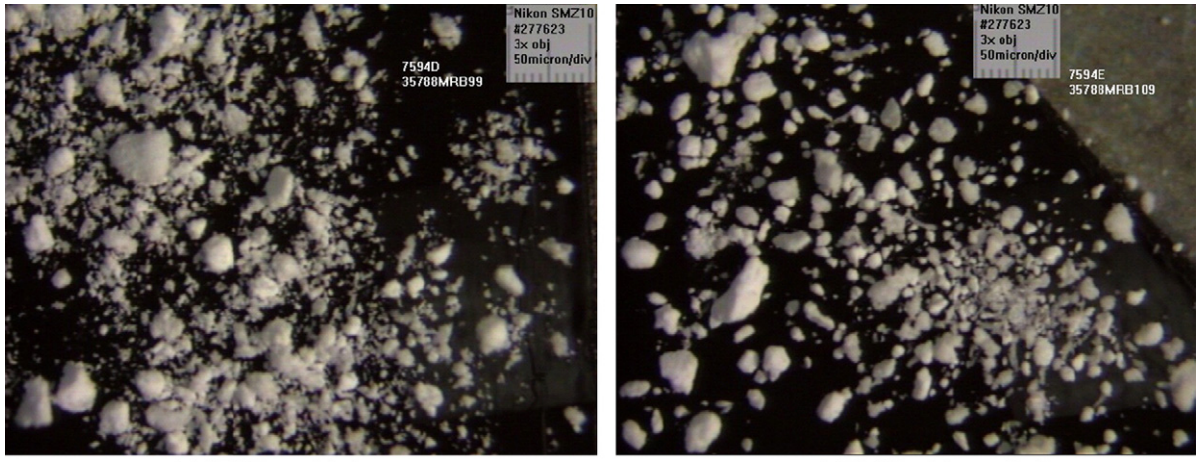
3.4.2. Binder study

As shown in Table 11, turbidity results suggest that the dispersibility of celecoxib follows the rank order of Kollidon 30 > HPC > HPMC. Scanning electron microscopy of formulated powders containing Kollidon 30 and HPMC show that

Table 11
The effect of types of binders on the dispersion of drug in water[a]

Types of binders	Tablet hardness (N) [b]	Turbidity
Kollidon 30	141.5	2.003 ± 0.026
HPMC	105.8	1.260 ± 0.066
HPC	98.1	1.320 ± 0.067

[a] Dispersion in water at tablet porosity = 0.175.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.



(a) HPMC as a binder (b) Kollidon 30 as a binder

Fig. 3. Microscopic view of granules containing Kollidon 30 or HPMC.

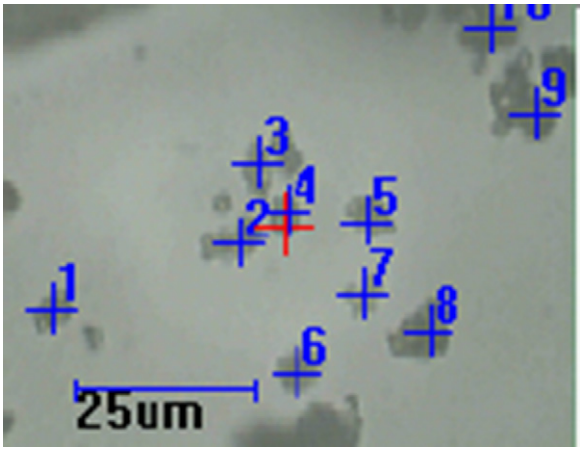


Fig. 4. Photomicrographs view with point map definition superimposed.

the HPMC formulation has a higher percentage of fine particles than the Kollidon 30 formulation (Fig. 3). The fine particles were characterized by the Almega® Raman microscope with point map capability (Fig. 4). Most of the particles analyzed are drug particles (<10 μm in size).

To gain an in-depth understanding on why the Kollidon formulation gives higher drug dispersion than the HPMC formulation, the spreading coefficient of the drug over Kollidon or HPMC is calculated to study the interactions between the drug and the binder.

The interfacial forces between any two phases are given by Young's equation (Young, 1855):

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos\theta \tag{2}$$

where γ_{SV}, γ_{SL} and γ_{LV} are the surface tensions of the solid–vapor, solid–liquid and liquid–vapor interfaces, respectively, and θ is the contact angle between the liquid and the solid.

Wu (Wu, 1971) derived a relationship that allows the calculation of the dispersion and polar components of the surface energy of a solid from two liquids with known dispersion and polar surface energy,

$$\gamma_{LS} = \gamma_{LV} + \gamma_{SV} - 4\left[\frac{\gamma_L^d \gamma_S^d}{\gamma_L^d + \gamma_S^d} + \frac{\gamma_L^p \gamma_S^p}{\gamma_L^p + \gamma_S^p}\right] \tag{3}$$

where γ_L^d and γ_L^p are the dispersion and polar components of the liquid surface tension, respectively, γ_S^d and γ_S^p are the dispersion and polar components of the solid surface, respectively.

Combining Wu's equation with Young's to get Eq. (4)

$$\gamma_{LV}(1 + \cos\theta) = 4\left[\frac{\gamma_L^d \gamma_S^d}{\gamma_L^d + \gamma_S^d} + \frac{\gamma_L^p \gamma_S^p}{\gamma_L^p + \gamma_S^p}\right] \tag{4}$$

where γ_{LV} is the surface tension of the liquid. An Excel program (Microsoft Excel® 2000, Microsoft Corp. Redmond, WA) was written to solve Eq. (4) iteratively.

Table 12
Surface energy of drug and several solvents

	θ (°)	γ_S (mN/m)[c]	γ_S^d (mN/m)	γ_S^p (mN/m)
Formamide[a]	–	58.30	32.30	26.00
Ethylene glycol[a]	–	48.90	33.40	15.50
Drug[b]	44.84° (formamide), 26.83° (ethylene glycol)	43.84	31.45	12.39

[a] Data was obtained from reference (Zografi and Tam, 1976).
[b] Surface energy of Drug was calculated using Eq. (4) (Young, 1855; Wu, 1971).
[c] γ_S is defined as the surface tension of the test substance.

Table 13
Surface energy and spreading coefficients of drug and binders

	γ_S (mN/m)[c]	γ_S^d (mN/m)	γ_S^p (mN/m)	S_{21} (binder over drug)[d]	S_{12} (drug over binder)[d]
HPMC[a]	48.40	18.40	30.00	−15.29	−6.71
Kollidon 30[b]	53.60	28.40	25.20	−14.28	5.24
Celecoxib	43.84	31.45	12.39		

[a] Data was obtained from reference (Rowe, 1989).
[b] Data was obtained from references (Krycer et al., 1983a,b).
[c] γ_S is defined as the surface tension of the test substance.
[d] Spreading coefficients of binder over drug (S_{12}) and drug over binder (S_{21}) were calculated using Eq. (5).

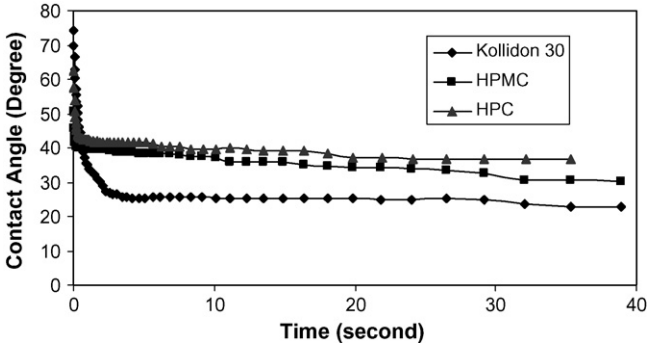


Fig. 5. Contact angle comparisons of formulations containing different binders.

The spreading tendencies between solids can then be predicted by Eq. (5) (Buckton, 1995b).

$$S_{12} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}\right] - 2\gamma_1 \quad (5)$$

where S_{12} is the spreading coefficient of solid 1 onto solid 2, γ_1 is the surface energy of solid 1, γ_1^d and γ_1^p are the dispersive and polar components, respectively, of solid 1, and γ_2^d and γ_2^p are the dispersive and polar components, respectively, of solid 2. A positive value of the spreading coefficient indicates that spreading is energetically favored while a negative value indicates that spreading is not favored. The more positive the number the more the spreading is favored.

The contact angles of two test liquids, formamide and ethylene glycol, on the drug powder were measured. These, combined with the polar and dispersive surface energies of the test liquids, which are known from the literature (Zografi and Tam, 1976), allow one to calculate the polar and dispersive surface energies of the drug using Eq. (4) (Table 12). The polar and dispersive surface energies of the drug, combined with those of HPMC and Kollidon 30, which are also known from the literature (Rowe, 1989; Krycer et al., 1983a,b), allow one to calculate the spreading coefficients of celecoxib over binder and binder over celecoxib using Eq. (5) (Table 13). According to Rowe's work (Rowe, 1989), the spreading coefficient can be used to predict the type of granules formed. Positive spreading coefficient of substrate over binder (S_{12}) indicates that the substrate tends to spread over the binder to form an open porous granule. A negative S_{12} combined with positive S_{21} (binder over substrate) indicates a tendency to form strong granules with the binder film covering the substrate. The spreading coefficients of celecoxib over HPMC (S_{12}) and HPMC over celecoxib (S_{21}) are both negative, indicating that there is not a favorable interaction between celecoxib and HPMC (Table 13). This may explain why the granules containing HPMC as a binder have a high percentage of fine granules (Fig. 3), where the fine particles are characterized to be primarily celecoxib particles (Fig. 4). The positive S_{12} of celecoxib over Kollidon 30 and negative S_{21} of Kollidon 30 over celecoxib indicates that celecoxib has a tendency to spread over Kollidon, creating open porous granules in which pores may facilitate water uptake. This finding may explain why the formulation containing Kollidon 30 results in the highest celecoxib dispersion.

The aqueous wettability of formulated powders containing different binders are also compared using dynamic contact angle measurement (Fig. 5). The formulation containing Kollidon 30 as a binder has the best wettability because the contact angle in water is the lowest among the three formulations. In addition, the contact angle of the Kollidon 30 formulation reaches

Table 14
The effect of disintegrant location on the dispersion of celecoxib in water[a]

Formulation/disintegrant location	Tablet hardness (N)[b]	Turbidity
100% intra	–	–
50%:50% intra:extra	59.5	0.690 ± 0.008
20%:80% intra:extra	62.3	1.395 ± 0.055
100% extra	64.4	1.620 ± 0.011

[a] Dispersion in water at tablet porosity = 0.175; all formulations contain 8.33% disintegrant.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

Table 15
Hardness and porosity of a tablet when all of the disintegrant is added intra-granularly

Tablet weight (mg)	Compation pressure (MPa)	Thickness (mm)	Porosity	Hardness (N)[a]
360.4	10.00	3.56	0.097	26.6
360.1	6.89	3.65	0.126	21.7
359.9	4.14	3.72	0.148	10.5

[a] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

Table 16
Summary of significant effects (p-value < 0.05)[a]

Response	Disintegrant level	Surfactant level	Surfactant^2 level[b]	Binder level	Binder^2 level[c]	Disintegrant*binder[d]
Turbidity		+ <0.0001	− 0.0026	+ 0.0010		
Moisture				+ (<0.0001)		
Hardness	+ (0.0121)	− (<0.0001)		+ (<0.0001)	− (0.0006)	+ (0.0269)

[a] Factors with p-value less than 0.05 are considered statistically significant.
[b] Surfactant^2: quadratic term for surfactant binder.
[c] Binder^2: quadratic term for binder.
[d] Disintegrant*binder: the interaction term between extra-granular disintegrant.

equilibrium more quickly than those of the HPMC and HPC formulations, indicating a quick and uniform wetting of the Kollidon 30 formulation. These data suggest one could use contact angle analysis as a quick way to screen formulations for which wetting is a concern.

3.4.3. Disintegrant study

The mode of disintegrant addition has long been a topic of interest in solid formulation development. It is often thought that adding disintegrants intra-granularly helps break the granules apart, thereby leading to a faster drug release. However, the turbidity results indicate that as more Polyplasdone is added intra-granularly, celecoxib dispersibility decreases (Table 14). This is probably because intra-granular Polyplasdone can adsorb a large amount of water during the wet granulation process, which leads to the formation of dense granules. Such is the case when all of the Polyplasdone is added intra-granularly, the granules are so dense that it is difficult to achieve the target tablet porosity of 0.175 even with minimum compression force (Table 15). Since porous granules are likely to give higher drug dispersibility, fluid-bed granulation may be a good granulation method because it is known to produce fluffy and porous granules.

3.4.4. Porosity study

The tablet porosity significantly impacts the initial wetting and dispersion of celecoxib (Fig. 6) at $t = 5$ min, but not at later times ($t = 20$ and 35 min). The higher the tablet porosity, the higher the initial dispersibility of the drug. Therefore, one should make tablets as porous as possible to achieve

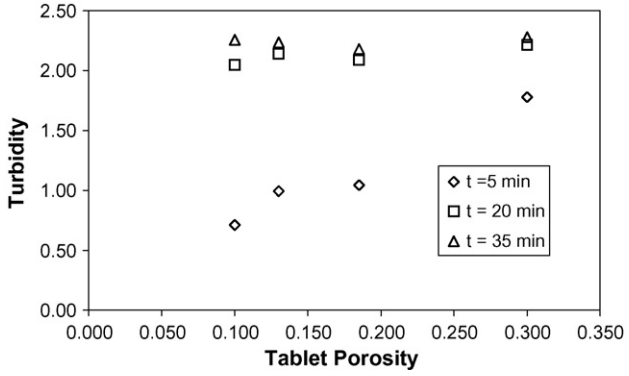


Fig. 6. Effect of tablet porosity on turbidity of celecoxib.

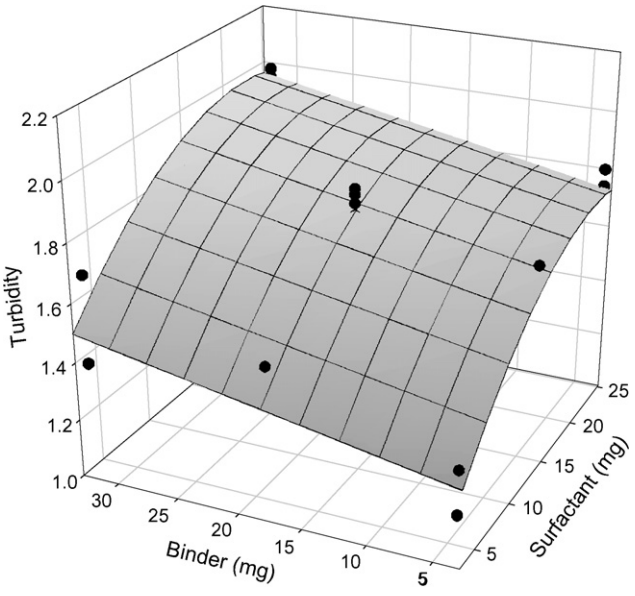


Fig. 7. Surface response plots of turbidity as a function of surfactant and binder levels.

rapid dispersion, as long as the tablet hardness criteria are met.

3.5. DOE optimization study

Statistical analysis shows that the dispersibility of drug increases as the amount of SLS and Kollidon 30 increases (Table 16). No optimum is found within the range that was studied (Fig. 7). Formulations with a higher binder level lead to granules with higher moisture level, and harder tablets (Table 16). Higher disintegrant levels result in harder tablets, while having little impact on dispersibility of the drug.

4. Conclusions

In order to formulate a poorly wettable compound such as celecoxib (the contact angle with water is 127°) into a rapidly dispersible formulation, one has to use optimum excipients to facilitate wetting and dispersion of the drug. It is found that ionic surfactants such as sodium lauryl sulfate can facilitate dispersion/wetting of celecoxib through the charge dispersion

effect. Granule and tablet porosity play an important role in celecoxib dispersion. In general, higher porosity leads to more water uptake and better wetting/dispersibility of the drug. Therefore, fluid-bed granulation may be a desirable way to produce porous granules. Using Kollidon 30 as a binder facilitates dispersion of celecoxib as compared to HPMC and HPC. This may be due to the fact that the surface interaction between celecoxib and Kollidon 30 favors the formation of an open porous granule. Addition of Polyplasdone intra-granularly results in the formation of dense granules that lead to poor dispersibility. Therefore, Polyplasdone should be added in the extra-granular portion of the formulation.

Acknowledgements

We appreciate Martha J. Witt's support on statistical design and analysis, and Mark A. Smith's support on scanning electron microscopy and Raman microscopy analysis.

References

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vivo drug product dissolution and in vivo bioavailablity. Pharm. Res. 12, 413–420.

Amidon, G.E., He, X., Hageman, M.J., 2003. Physicochemical Characterization and Principles of Oral Solid Dosage Form Selection. In Burger's Medicinal Chemistry and Drug Discovery, sixth ed. John Willey & Sons.

Buckton, G., 1995. In: Florence, A.T., Gregoriadis, G. (Eds.), Interfacial Phenomena in Drug Delivery and Targeting. Harwood Academic Publishers, pp. 32, 171, 172.

Krycer, I., Pope, D.G., Hersey, J.A., 1983a. An evaluation of tablet binding agents. Part I, solution binders. Powder Technol. 34, 39–51.

Krycer, I., Pope, D.G., Hersey, J.A., 1983b. An evaluation of tablet binding agents. Part II, pressure binders. Powder Technol. 34, 53–56.

Noyes, A., Whitney, W., 1897. The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc. 19, 930–934.

Rowe, R.C., 1989. Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. Int. J. Pharm. 52, 149–154.

Wu, S., 1971. Calculation of interfacial tension in polymer systems. J. Polym. Sci., Part C 34, 19–30.

Young, T., 1855. In: Peacock, G. (Ed.), Miscenllaneous Works, vol. 1. Murray, London, p. p. 418.

Zografi, G., Tam, S.S., 1976. Wettability of pharmaceutical solids: estimates of solid surface polarity. J. Pharm. Sci. 65, 1145–1149.