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THE ESTIMATION AND APPLICATION OF SURFACE ENERGY DATA FOR POWDERED SYSTEMS.

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ABSTRACT

Estimates of surface energies of powders can be obtained by use of contact angle data, or by use of thermodynamic parameters (e.g. calorimetric determinations). In this review, the applications of surface energy data are considered in both a pragmatic manner, which could be applied directly to the formulation and production environment, and also in a manner that could aid fundamental research into both the understanding of mechanisms by which wetting is achieved and the ways in which wetting contributes to processes such as dissolution. The approaches, which are introduced and considered, centre around spreading coefficients and compensation analysis.

INTRODUCTION

Knowledge of the wettability of a powder, which is usually assessed by contact angle measurements, has always been regarded as a valuable piece of

information. Typical examples of the pharmaceutical applications of wetting can be obtained from any standard pharmaceutical text e.g. Fell [1], and are quoted as:- the wetting of powders by binders during wet granulation, the spreading of film coating polymers over tablets, the dispersion of solids to form suspensions and the dissolution of solid oral dosage forms. The use of contact angle measurements in the study of these areas has justifiably received considerable attention in the literature (for examples the reader is directed to the following texts: wet granulation[2], film coating[3], and suspension formulation[4]). Other general texts[5] also consider the role of wetting in further aspects of drug delivery (e.g. the wetting of human skin by topical preparations) and allude to the confusion that is a central part of the literature:- "Wetting clearly plays a role in the dissolution of tablets although, as yet, that role has not been clearly defined"[5]. The complex relationship between wettability, solubility and dissolution has formed the subject of previous publications (for example[6,7,8,9]), and will be alluded to in this work.

Despite a general acceptance of its inherent value, the practical application of contact angle data has been limited, often only providing crude correlations between a perceived cause and an observed effect. An example of this is the work of Wells and Walker [10] where an assessment of wettability of a powder by a granulating fluid was linked to granule properties; a demonstration of the obvious fact that wetting plays a role, but providing little extra information. A more satisfactory situation would be to use wettability data in such a way that it would lead to accurate predictions of the properties and behaviour of pharmaceutical products. The purpose of this work is to describe two approaches by which the role of wettability may be characterised (spreading coefficients and compensation analysis), to demonstrate their applicability and to extrapolate their potential usefulness.

ASSESSING WETTABILITY

Estimating Surface Energies by Use of Contact Angles

The preferred measure of the wettability of a powder is its surface energy (the analogous term to the surface tension of a liquid) as this is a parameter which describes the property of the solid surface, rather than a contact angle which describes the interaction between a solid surface and a particular probe liquid. However, as a solid surface energy cannot be measured directly it must be estimated from other measurements, such as contact angles and surface tensions. A contact angle (Θ) describes an equilibrium of the interfacial free energies (γ) between the solid (S), liquid (L) and vapour (V) phases, as expressed by Young's equation [11]:-

$$\gamma_{LV} \text{Cos } \Theta = \gamma_{SV} - \gamma_{SL} \qquad (1)$$

For a smooth flat surface (e.g. a polymer film) it is comparatively easy to measure a contact angle for any liquid, but for powders, which do not present a smooth surface and which have many surface heterogeneities, there are significant problems. It is not unreasonable to state that there is no ideal method of measuring a contact angle of a liquid on a powder, and that the use of the different (flawed) techniques may be partially responsible for the state of confusion that exists in various aspects of the literature. If any meaningful predictions are to be made on the basis of contact angle data, then the method must be selected, and the experiments performed, with care. The problems and advantages of different approaches to measurement of contact angles for powdered systems forms too large a subject to be considered here, for information on the subject of powder contact angle measurement the reader is directed to a recent review [12].

As reported above, contact angle data can be used to estimate values for the surface energies of powders. One approach to this calculation is based upon the work of Fowkes [13] who pioneered the process of splitting surface energies into polar and dispersion components, his geometric mean theory was later adapted by Wu [14] who demonstrated the advantage of the reciprocal mean approach. If Wu's equation [14] is combined with equation (1):-

$$\gamma_2(1+\cos\Theta) = 4\left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \qquad (2)$$

(where the subscripts refer to phases 1 and 2, and the superscripts to the polar and dispersion components) then it is possible to calculate the polar and dispersion components of the surface energy of a powder, providing that contact angles are obtained for two liquids of known surface energy and polarity (where polarity is defined as the polar component of the surface energy term divided by the surface energy). An iterative computer program maybe used to solve the two simultaneous versions of equation 2, as described previously [15]. The surface energies of liquids can either be calculated by a similar method[15] or obtained from the literature.

The Use of Thermodynamics

An alternative to using contact angle data to estimate surface energies is to assess powder / liquid or powder / vapour interactions in terms of thermodynamic functions of immersion or adsorption (respectively). Modern calorimeters allow such interactions to be monitored with accuracy[16,12,17], and in many cases offer some advantages over the methods of obtaining a contact

angle for powders. The disadvantages being that the equipment is more costly and the experiments are much more time consuming.

THE APPLICATION OF SURFACE ENERGY DATA

As outlined above, it is possible to obtain an indication of powder surface energies by use of contact angle data (albeit with the reservations about contact angle methodology for powdered systems) and / or by describing thermodynamic functions (including a free energy term). The contact angle data can be used to provide a crude indication of interaction between the powder and other phases by the calculation of spreading coefficients. Thermodynamic functions offer the hope of more exacting fundamental studies, one use of such data being to investigate relationships between different systems by use of compensation analysis.

SPREADING COEFFICIENTS

The spreading coefficient (λ) of any one phase over another is the difference between the work of adhesion between the two phases (W_a) and the work of cohesion (W_c) of the phase that is to spread, thus:

$$\lambda_{12} = W_{a12} - W_{c1} \quad (3)$$

$$\lambda_{21} = W_{a21} - W_{c2} \quad (4)$$

and it follows that:-

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

$$\lambda_{21} = 4\left[\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_2}{2}\right] \quad (6)$$

The spreading coefficient allows a quantitative assessment of the interaction between the two phases, and can be used to compare any two phases for which the surface energy and polarity have been estimated (i.e. solving Equation 2 following the measurement of contact angles formed on a solid by any two liquids of known surface tension and polarity).

Applications of Spreading Coefficients

Wet Granulation

As was mentioned in the introduction, it has always been recognised that wetting plays an important role in the interaction between the binder fluid and the powder, however, quantification of this process in such a way as to allow prediction has only occurred since spreading coefficients have been used to model the system [18,19,20,21].

In, what is believed to be, the first study on the use of spreading coefficients to predict binder / powder interactions during granulation[18], literature values for contact angles and surface energies were used to calculate the spreading coefficients for five binders (hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), polyvinyl pyrrolidine (PVP), acacia and starch) over ten drug powders (and vice versa). The drugs had a range of surface free energies from 30 to 70 mN/m (griseofulvin and ethinamate respectively) and polarities from 0.06 to 0.42 (griseofulvin and aspirin respectively). The calculated spreading coefficients revealed that for the drugs with the highest surface free energies and polarities (i.e. aspirin, hydrocortisone and ethinamate), positive

values were obtained for the spreading coefficients of all the binders over the powders, thus all the binders will produce good granules with strong adhesion between the binder and the powder. For powders of low polarity (e.g. griseofulvin, beta-sitosterol and phenacetin), the spreading coefficient for the binder over the powder was negative for each of the five binders. The spreading coefficient for the powder over the binder was, however, positive for PVP and starch, but negative for HPMC, MC and acacia. This leads to two conclusions, firstly, there are two types of granules that can be formed, one where the binder spreads over the powder (e.g. HPMC over polar materials) and one where the binder will not spread, but the powder will adhere to the binder at contact points (e.g. PVP and griseofulvin). Secondly, for low polarity substrates it would be advisable to use PVP or starch as a binder, but for high polarity substrates acacia or HPMC may be appropriate. It was reported[18] that current formulations, which were assembled by experience and / or trial and error, support this prediction in that all griseofulvin formulations in Dictionnaire Vidal[22] are granulated with either PVP and / or starch, while acacia is the binder of choice for theophylline formulations.

The theoretical predictions outlined above were tested in practice[19,20]. Rowe[19], discussed the work of Cutt et al[23], who had studied the granulation of untreated and surface coated glass beads with different polymeric binders, in terms of spreading coefficients. The untreated glass beads all gave positive spreading coefficients for the spreading of the binders over the solid, this correlated well with the assessment of granule properties reported by Cutt et al[23]. The spreading coefficients for the binders over the silanised glass were, however, all negative, but positive values were obtained for the spreading coefficient of the glass over the polymer. Therefore, the silanised beads would granulate successfully, but as the binder would not spread the granules would probably formed by the beads adhering to a centralised region of binder, thus producing

granules of a more open porous structures (than would be formed in the cases where binder spreads evenly over a number of beads i.e. the untreated glass will form dense granules as the binder will spread over the surface). Scanning electron micrographs[23], support the theory of two different granule structures[19].

The granulation of microcrystalline cellulose (Avicel PH-101) by PVP and HPMC was investigated by Zajic and Buckton[20], in an attempt to correlate the values of spreading coefficients with the properties of real granules. A number of variables were investigated, including the particle size of the powder, the quantity of powder granulated, and the volume and strength of the binder solutions. The granules were tested for bulk density, tapped bulk density, angle of repose, density and friability. The spreading coefficients predicted that HPMC would spread over the Avicel to a greater extent than PVP. On the basis of the work of Rowe[18,19], the favourable spreading of the binder should produce a dense granule. Although the true densities did not change significantly for the different binders, the bulk densities were higher for the HPMC granulation. The HPMC granules were also of a larger size and were much less friable than those produced by PVP. The spreading coefficient was, therefore, a successful predictor of granule properties.

Rowe[21], has suggested a parabolic relationship between (a function of) the binder / drug spreading coefficient and the fractional polarity of the solid. This has allowed the construction of "master curves", from which it is possible to predict the correct choice of binder directly from a knowledge of the polarity of the drug. Such an approach makes the formulation of products by computer (expert systems) a realistic option.

Having demonstrated that spreading coefficients can be used to predict the performance of granules, the next step was to investigate the effect that this had on the properties of the final tablet. Paracetamol was granulated with four different binders (ranked from best to worst in terms of spreading coefficient, these were :- HPMC, acacia, PVP and starch)[24]. Only starch had a negative spreading coefficient for the binder over the powder (and a positive spreading for the powder over the binder). The products were tested for granule friability, tablet strength at highest lower punch work, and tablet capping index; in each case a clear correlation existed with the spreading coefficient, and in one instance (granule friability) this was linear. The deviations from linearity were explained on the basis of binder cohesion[24].

Suspension Properties

There are many factors that will influence the properties of pharmaceutical suspensions. One aspect is the interfacial energy between the continuous and disperse phases. In a recent publication[25], the spreading coefficient of the continuous phase over the disperse phase has been related to the increase in particle size (aggregation rather than growth) for the suspensions of four powders. The continuous phase was water and the powders were amylobarbitone, phenobarbitone, barbitone and butobarbitone. Of these powders only amylobarbitone does not spontaneously immerse in water, but phenobarbitone is at the limit of wettability (i.e. wets only if work is applied to the system in the form of agitation). In all cases the spreading coefficient for water over the powder was negative, indicating a disfavoured interaction. A linear relationship existed between the actual increase in particle size of the three immersible powders and spreading coefficient. Perhaps more interestingly, a parabolic relationship existed between the limiting particle size

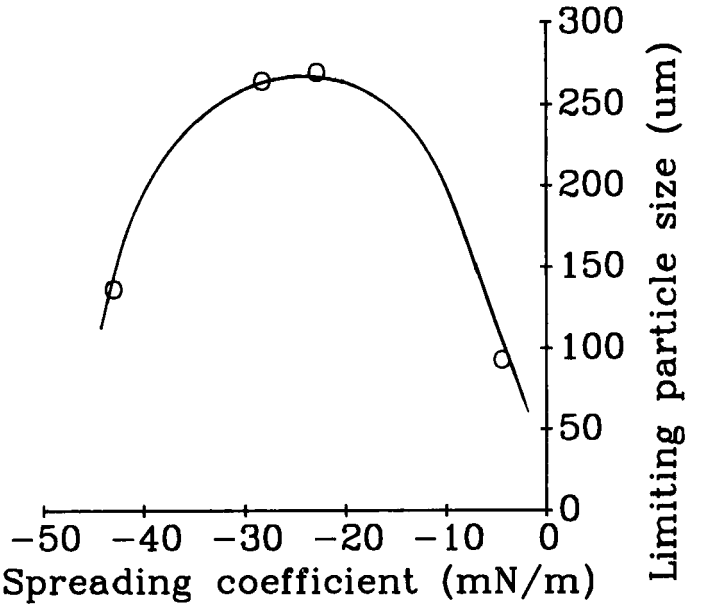

FIGURE 1. Limiting particle size of suspensions of barbiturates in water, as a function of spreading coefficient, showing a miximum value corresponding to a spreading coefficient equal to the dispersion component of the surface energy of water. Reproduced from Young and Buckton[25]

(the extrapolation of the size / log time plot to infinite time) and the spreading coefficient (Figure 1), with the maximum coinciding with a spreading coefficient equal to the dispersion component of the surface energy of water (23.2 mN/m). Thus, for powders with a spreading coefficient greater than -23.2 mN/m it is possible to obtain immersion, but if the spreading coefficient is more negative than the dispersion component of water, then there is not enough energy in the system to allow immersion. This finding is interesting because the contact angle data does not allow an easy prediction of wetting; for example, the contact angles for water on the barbiturates were[25]:- amylobarbitone 66.1, phenobarbitone 52.6, barbitone 47.2 and butobarbitone 41.6, these data do not obviously reflect the fact that amylobarbitone will not

immerse in water and that phenobarbitone is at the very limit of that which will immerse (these facts become clear by empirical practical observation). If, however, the water / powder spreading coefficients are considered :- amylobarbitone -43.0, phenobarbitone -28.3, barbitone -22.9 and butobarbitone -4.5; then using the dispersion value for the surface energy of water as being 23.2 mN/m[15] it can be seen that butobarbitone will be easily dispersed, barbitone and phenobarbitone will be harder to immerse without some external work, and amylobarbitone will be almost impossible to wet as such a large difference exists between the driving force (23.2 mN/m) and the force needed for spreading (43.0 mN/m).

Recently[26], spreading coefficients, polarities and works of adhesion have been used to aid the prediction of the physical properties of non-polar non-aqueous suspensions (i.e. suspension metered dose inhaler systems), in terms of the ease of drug dispersion, the tendency to aggregate, and the probability of drug adhering to the container wall.

Other applications

In the introduction it was reported that wetting plays a vital role in the adhesion of film coating materials to tablets. In a manor directly analogous to the work on the use of spreading coefficients to predict the optimum binder for tablets, it should be possible to predict the success of a film coating process based upon adhesive and cohesive interactions. Solubility parameters, which consider adhesion and cohesion in a bulk (rather than surface) context, have been used successfully to make predictions in this area[27], thus it would be expected that spreading coefficients would be of value in such studies.

The interaction between lubricants and powders has also been considered in terms of solubility parameters[28]. It is obviously important for lubricants to be well distributed over the surface of the powder which is to be compressed. The success of predictions based upon solubility parameters would suggest that predictions based upon surface energies would also be valuable.

It must be stressed at this point that wettability is not only affected by changes in the molecule, but also by physical treatment (crystallisation method, milling techniques used etc.[29]), so the process may on occasions be complicated further. The fact that wettability and surface energy are affected by processing history is probably instrumental in the variability of many pharmaceutical production processes (e.g. batch to batch variation), and the possibility exists that assessment of changes in wettability (either by surface energy specification, as described above in relation to spreading coefficients, or by thermodynamic parameters) may allow problems to be predicted and sorted out at a much earlier stage.

COMPENSATION ANALYSIS

The concept of linear free energy relationships (LFER) (and quantitative structure activity relationships (QSAR)), such as that of Hammett[30] is well established, particular in the field of drug design, however, the use of such approaches to investigate the influence of structure on physical aspects of drug properties has been curiously limited. The concept of any LFER (and QSAR) is that for any compounds which follow a common mechanism of action there will be a linear relationship between the free energy change for the process, and the response. For example, partition coefficient (which is an equilibrium constant (K), and which is related to free energy, as $\Delta G = -RT \ln K$; where

R is the gas constant and T is the absolute temperature) is often linearly related to biological response for similar compounds.

Thus, by definition, for any LFER a linear relationship exists between ΔG and the property under study, and as

$$\Delta G = \Delta H - T\Delta S \quad (7)$$

(where ΔH and ΔS are the changes in enthalpy and entropy respectively), then either ΔH must remain constant and ΔS varies in a linear manor with ΔG, or ΔS must remain constant and ΔH varies in a linear manor with ΔG, or (and most likely) ΔH varies in a linear manor with ΔS i.e. a LFER exists because changes in ΔH are compensated for by changes in ΔS. Thus compensation analysis is simply the investigation of common mechanisms by looking for linear relationships between thermodynamic parameters, the existence of which demonstrates a LFER.

Calculation of Thermodynamic Parameters

Thermodynamic parameters can be calculated for many physical processes in pharmaceutics, either by calorimetric methods or by use of van't Hoff (for equilibrium processes) or Arrhenius (for rate processes) relationships. However, Krug et al[31,32] have demonstrated that it is necessary to use a modification of these standard approaches to avoid statistical artifacts which lead to a possibility of false correlations between the derived thermodynamic parameters. Thus, all compensation analysis should be plots of enthalpy as a function of free energy, and the values should be calculated at the harmonic mean experimental temperature in the manner described by Krug et al [31,32].

Application of compensation analysis

A few publications have dealt with the application of compensation analysis to problems of pharmaceutical interest, other than biological response; these include those of Tomlinson[33], Vachon and Grant[34] and Buckton[7].

Wetting and Solubility

As was noted above, both wettability and solubility affect processes such as dissolution. It is often assumed that water soluble drugs are well wetted, and that water insoluble drugs are poorly wetted; this is not true. Microcrystalline cellulose is a good example of a solid which is not soluble in water, but which is readily wetted. The interest in being able to ascertain the role played by both wettability and solubility in controlling dissolution, and indeed being able to modify these processes, has been the aim of many studies. In this section the possibility of utilising compensation analysis to this end is described, using barbiturate powders as a model drug series (as considerable data is available for these compounds).

The thermodynamic functions for adsorption of water vapour onto different barbiturate powders have been determined using gravimetric and calorimetric adsorption data[17] and these have been shown to fit to a linear compensation plot[6] i.e. a linear relationship existed between the thermodynamic parameters for adsorption for each of the powders. The ranking of the four powders was in the order butobarbitone, phenobarbitone, pentobarbitone and amylobarbitone (ranging from most hydrophilic to most hydrophobic respectively). This linear relationship is indicative of a common mechanism for wetting i.e. a demonstration that there is chemical causality for the changes in wetting. A

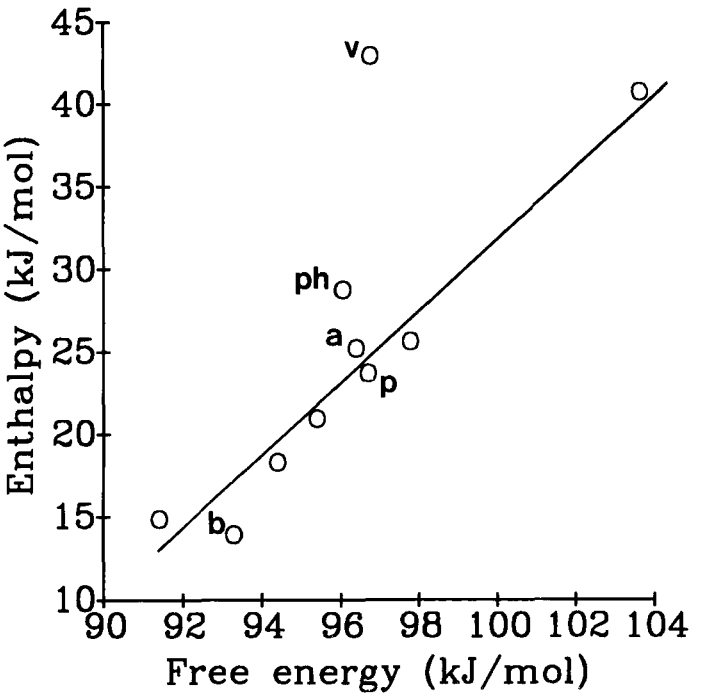

FIGURE 2. A Free energy - enthalpy compensation plot for the solution thermodynamics of substituted barbituric acids. ph - phenobarbitone; v - vinbarbitone; a - amylobarbitone; b - butobarbitone; p - pentobarbitone. Reproduced from Buckton[7].

calculation of the thermodynamic parameters of solution for a series of barbiturates, using published data on the equilibrium solubility of these compounds at different temperatures in a van't Hoff relationship (modified in the manner described by Krug et al[31,32]), has demonstrated that many of the compounds fit a linear compensation relationship[7] (Figure 2), however, those compounds which do not have saturated structures (i.e. vinbarbitone and phenobarbitone) deviate from this linear trend. It would appear, therefore, that changes in the substitution of the barbiturate ring structure do have an effect on solubility, which follows a common mechanism only for the saturated

compounds, but that changes in the substitution of the barbitone ring all seem to affect wetting by the same mechanism irrespective of saturation. Thus, the structure of the molecules are linked to both wettability and solubility, but the mechanism by which structure affects wettability and solubility are different. This presumably relates to the fact that wetting is a reflection of the functional groups that are present at the surface of the solid, but solubility is inevitably related to the structure of the entire molecule (which must be both detached from the solid and incorporated in a suitable cavity in the solvent). It follows that it should be possible to alter the structure of a molecule to independently vary, and hence optimise, wettability and solubility.

Other Aspects Relating to Dissolution

Although the thermodynamic parameters relating to dissolution are not directly related to surface energy data, and thus not directly applicable to this review, it should be noted that by considering the temperature dependence of dissolution release rate constants, it is possible to calculate thermodynamic parameters, and then to compare release mechanisms from different dosage forms (or the same dosage form under different conditions)[35,36]. For example it is possible to investigate the effect of adding different excipients, and also to consider the effect of different methods of production (e.g. direct compression or wet granulation) on drug release mechanism from products[36]. It has been noted that if the aim of the study is to investigate drug release mechanism(s), then the use of compensation analysis offers advantages of currently favoured methods of dissolution data analysis[37]. The extension of the work would be to utilise compensation analysis to investigate the mechanisms of all relevant parts in the drug absorption process (these may be wetting, solubility, disintegration of the product, dissolution, partition etc.), and from

the understanding of the factors which do and / or do not yield common mechanisms, to be able to modify drug delivery in a logical and controlled manner.

CONCLUSION

It has been demonstrated that complex processes, such as granulation, and the behaviour of products, e.g. tablets and suspensions, can be modelled by spreading coefficients. It can, not unreasonably, be speculated that many other systems can be modelled in a similar manor.

When it is accepted that every process which we, as pharmaceutical scientists, study is (either in total or in part) an interfacial phenomena, and that the behaviour of the interface between any two phases (even solid / solid) can be modelled (albeit crudely) by simple measurements, then it becomes clear that a considerable amount of activity that is currently undertaken by a best guess approach could be given a more firm scientific basis.

Compensation analysis is a method by which free energy changes can be compared for different systems to investigate the presence or absence of common mechanisms. In this review, the subject of wettability has been considered (in particular its relationship to solubility, and dissolution), but clearly the potential for application of compensation analysis is far wider than this.

The use of surface energy data in terms of spreading coefficients, and compensation analysis are potentially valuable tools for both fundamental research workers and for immediate practical application to product

development. Setting a specification for surface energies would seem to be valuable to prevent production difficulties arising from changes in powder source or processing.

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