Powdered Solution Technology: Principles and Mechanism

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The concept of powdered solutions can be used to formulate liquid medications in dry, nonadherent, free-flowing, and readily compressible powders. The technique is based on simple admixture of drug solution or liquid drug with selected carrier and coating materials. Improved drug release profiles are exhibited by such delivery systems even for poorly water-soluble drugs. Previous work using this method has rendered its industrial application impractical because of the unsatisfactory flow properties of the powder admixtures. This article presents a theoretical model based on the principles and mechanism of powdered solutions and introduces a new physical property of powders termed the flowable liquid-retention potential (Φ value). Mathematical expressions are derived that can be used to calculate the optimum amount of excipients required to yield powder admixtures with acceptable flowability. The validity and applicability of these expressions have been verified experimentally using clofibrate and prednisolone as test materials. The proposed model is shown to be superior to previously reported studies in optimizing the amount of excipients needed to prepare powdered solutions with acceptable flow properties.

KEY WORDS: powdered solution technology; powdered solutions of drugs; flowable liquid-retention potential (Φ value); carrier material; coating material; excipient ratio (*R*); liquid layer; mono- and multilayer coating.

INTRODUCTION

The concept of powdered solutions can be used to formulate drug solutions or liquid drugs in powders. A liquid drug or a poorly water-soluble solid drug dissolved in a suitable nonvolatile solvent may be converted into a dry, nonadherent, free-flowing, and readily compressible powder by its simple admixture with selected carrier and coating materials. This method does not involve drying or evaporation.

It is well established that better bioavailability of a relatively water-insoluble drug is achieved when the drug is in solution form (1). That is why soft gelatin capsules of such drugs demonstrate higher bioavailability compared to the conventional oral solid dosage forms (2). The same principle governs powdered solutions and is solely responsible for their improved dissolution profiles. In this instance, even though the drug is in a tableted or encapsulated dosage form, it is held in solution thus enhancing its release (3).

Several investigators have utilized the concept of powdered solutions to improve the dissolution profile of poorly water-soluble drugs (3–6). Lipophilic liquid drugs (e.g., chlorpheniramine and clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, polythiazide, and spironolactone) dissolved in nonvolatile, high-boiling point solvent systems (e.g., polyethylene and propylene glycols, glycerin, *N,N*-dimethylacetamide, and various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., celluloses) and coating materials (e.g., silicas). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products.

Liao (4) proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. In this study, microcrystalline cellulose and silica were used as the carrier and coating material, respectively. The major drawback of this approach was that the final product exhibited poor and erratic flowability due to the inadequacy of the proposed model to calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties.

The purpose of the present article is to propose a theoretical model for the formulation of powdered solutions. Mathematical expressions based on powder properties and the fundamental principles and mechanism of powdered solutions are derived. A new physical property of powders, termed the flowable liquid-retention potential (Φ value), is introduced. It is shown that these mathematical expressions can be used to calculate the optimum amount of excipients required to yield free-flowing powdered solution formulations. The validity and applicability of the proposed relationships have been verified experimentally using clofibrate and prednisolone as test materials.

THEORETICAL CONSIDERATIONS IN POWDERED SOLUTION FORMULATIONS

Flowable Liquid-Retention Potential (Φ Value) of a Powder

Absorption of a liquid by a powder material occurs when the absorbate molecules diffuse inside the absorbent and are eventually captured and held by the powder particles within their bulk. In some cases, the liquid is not truly absorbed, and instead of being dispersed throughout the interior of the solid, the liquid molecules only cling to its available surface, i.e., internal and external. This process is known as adsorption (7). Sometimes, however, depending on the sorbent properties, both of these processes may occur simultaneously. The combined process is termed sorption. For instance, if a liquid is incorporated into a material which has a porous surface and closely matted fibers in its interior, e.g., cellulose, both absorption and adsorption take place. The liquid is initially absorbed in the interior of the particles captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. One can generalize this liquid retention capacity of the powder material by referring to it as the total liquid-retention potential or "holding capacity" of the sorbent.

The flowable liquid-retention potential (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ value is defined as the maximum weight of liquid,

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W_{liquid}, that can be retained per unit weight of the sorbent, W_{solid}, yielding a mixture with acceptable flowability; thus

$$\Phi = \frac{W_{liquid}}{W_{solid}} \quad (1)$$

As the flowable liquid-retention potential of the carrier material is approached, the liquid is held entirely in the interior of the particles maintaining their surfaces relatively drier, thus yielding powders with acceptable flow properties. When the Φ value is exceeded, the interior of the particles becomes saturated, resulting in the formation of a liquid layer on the carrier particles' available surface (Fig. 1).

For the clarity of theories proposed in this article, the following terms must be well distinguished. The term "interior of the particles" implies the solid bulk of the powder particles, which is assumed to be a homogeneous mass of closely packed material, excluding pores, that constitutes the solid intrastructure of each particle. The term "internal surface of the particles" implies surfaces created throughout the interior of the particles by the scattered penetrating pore network. Internal surface is a direct indication of the porosity of the material. The term "external surface of the particles" implies their outer surface, with which particles come in contact with each other. Therefore, the sum of internal and external surfaces is termed the total surface of the particle; and the total surface area per unit weight of the material represents its specific surface. Since internal and external surfaces of the particle are physically interconnected, the thickness of the liquid layer formed around them is assumed to be uniform.

Principal Hypothesis for the Mechanism of Powdered Solutions

Suppose that a liquid drug or a drug solution having a total volume V is incorporated into a carrier powder material. Depending on the holding capacity of the material, a part of the liquid, say, V_{Φ}, is absorbed and retained in the interior of the carrier particles. This volume is dependent on the flowable liquid-retention potential (Φ) of the carrier material. The remaining liquid, V_L, is uniformly distributed and adsorbed onto the internal and external surfaces of the particles, forming a layer of certain thickness, h (Fig. 1). Thus, mathematically, the volume distribution can be expressed as

$$V = V_{\Phi} + v_L \quad (2)$$

When a coating material, having a very small particle size, large specific surface, and high flowable liquid-retention potential, e.g., silica, is added to such a mixture,

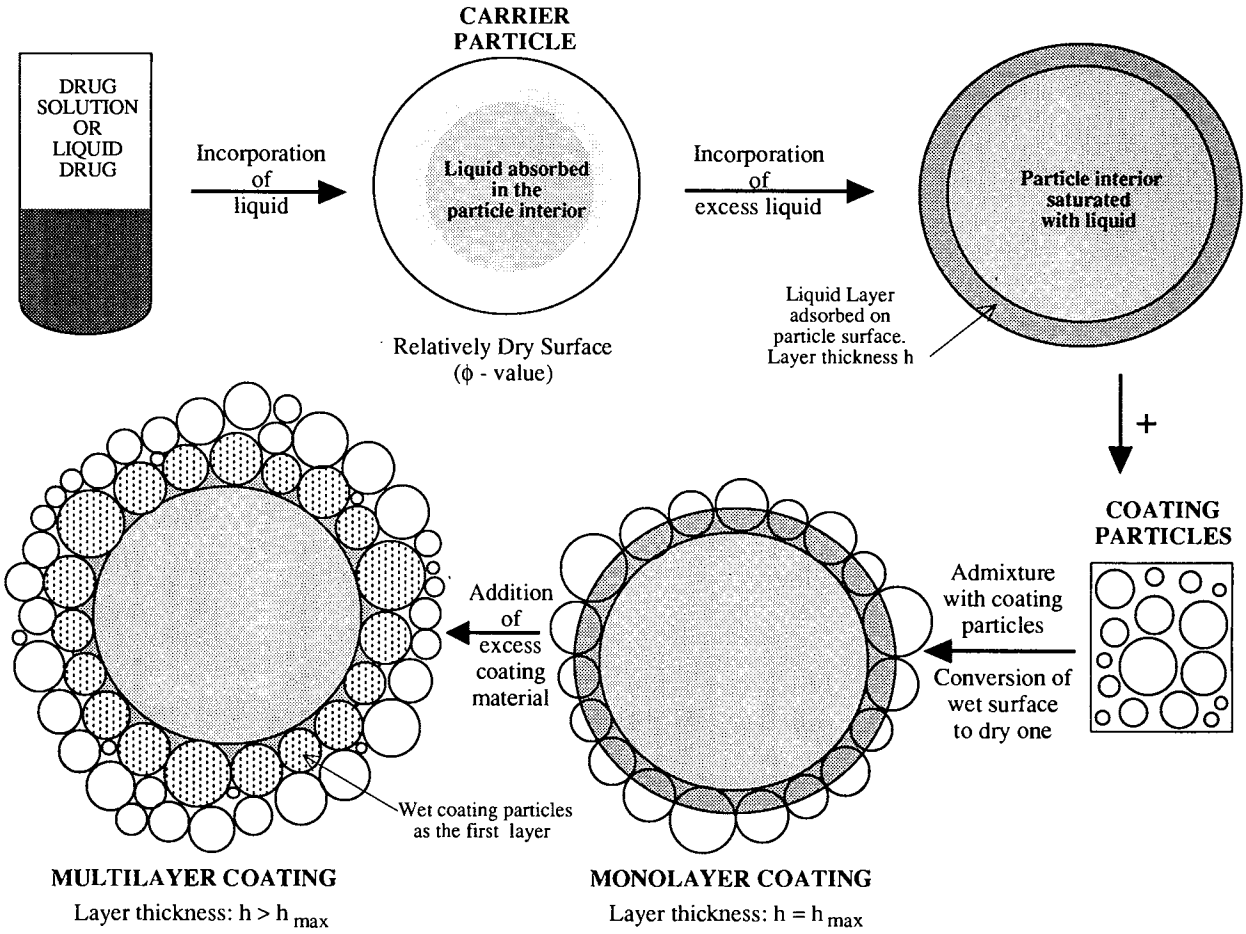

Fig. 1. Theoretical model of powdered solutions. When the weight of incorporated liquid per unit weight of carrier material exceeds the Φ value of the carrier material, a liquid layer is formed around the carrier particle which must be effectively covered by coating particles. Depending on the amount of coating material, the coating may be monolayered or multilayered.

its fine particles will cover the wet carrier material retaining the excess liquid, thereby maintaining acceptable flow properties. Eventually, a dry, nonadherent, and free-flowing powder mixture will be produced. Depending on the amount of coating material required to yield such powdered solutions, the type of coating may be monolayer or multilayer (Fig. 1).

If only a specific volume (e.g., V_Φ) of liquid is incorporated into the carrier material, the liquid would be absorbed in the interior of the particles without significantly wetting their surface, and consequently, the powder would be dry and free-flowing. This portion of the liquid is represented by V_Φ, since it depends on the flowable liquid-retention potential, Φ, and the quantity, Q, of the carrier material used. Since $W_{solid} = Q$ and $W_{liquid} = V_\Phi\rho$, where ρ is the density of the liquid incorporated into the carrier material, Eq. (1) can be expressed as

$$\Phi = \frac{V_\Phi \rho}{Q} \tag{3}$$

which can be rearranged to give

$$V_\Phi = \frac{Q\Phi}{\rho} \tag{4}$$

Principle of Sufficient Coating

In order for the coating to be sufficient to convert the wet surface of the carrier particles to dry surface, the volume V_L of the adsorbed liquid must be retained by the coating particles while maintaining their free-flowing texture (Fig. 1). In other words, the volume V_L must be equal to a volume, v_ϕ, of the liquid which a quantity, q, of the coating particles can retain and yet maintain acceptable flowability. Therefore, Eq. (2) can be rewritten as

$$V = V_\Phi + v_\varphi \tag{5}$$

By definition, v_ϕ represents the same characteristics of the coating material as represented by V_Φ for the carrier material in Eq. (4). Using the same line of reasoning as was used in deriving Eq. (3), it can be concluded that

$$V_\varphi = \frac{q\varphi}{\rho} \tag{6}$$

where φ is the flowable liquid-retention potential of the coating material. Thus, v_φ is dependent on the flowable liquid-retention potential, φ, and quantity, q, of the coating material.[3]

Substituting the values of V_Φ [Eq. (4)] and v_φ [Eq. (6)] in Eq. (5), we obtain

$$V = \frac{(Q\Phi) + (q\varphi)}{\rho} \tag{7}$$

[3] In the theoretical analysis of this report, capital letters, i.e., Q, V_Φ, Φ, and A, represent the quantity, volume of liquid retained, flowable liquid-retention potential, and specific surface, respectively, of the carrier material, whereas lowercase letters, i.e., q, v_φ, φ, and a, refer to the same values of the coating material.

Equation (7) can be rearranged in terms of Q, the quantity of the carrier material required to retain a specific volume V of the liquid, as

$$Q = \frac{(V\rho) - (q\varphi)}{\Phi} \tag{8}$$

Similarly, Eq. (7) can be rearranged in terms of q, the quantity of coating material needed to cover the wet carrier particles effectively, as

$$q = \frac{(V\rho) - (Q\Phi)}{\varphi} \tag{9}$$

Excipient Ratio (R)

In some cases, however, the dosage formulation may require a specific ratio of carrier/coating material in the final powder admixture. This ratio may be termed the excipient ratio, R, and written as

$$R = \frac{\text{amount of carrier material}}{\text{amount of coating material}} = \frac{Q}{q} \tag{10}$$

For such cases, Eqs. (7), (8), and (9) can be modified to include the excipient ratio, R.

Combining Eqs. (7) and (10), and considering a predetermined quantity, Q, of the carrier material, we obtain

$$V = \frac{Q[(R\Phi) + \varphi]}{R\rho} \tag{11}$$

Furthermore, solving for Q and considering a predetermined volume V of liquid, Eq. (11) will become

$$Q = \frac{V\rho R}{(R\Phi) + \varphi} \tag{12}$$

Accordingly, combining Eqs. (7) and (10), and considering a predetermined quantity, q, of the coating material, one obtains

$$V = \frac{q[(R\Phi) + \varphi]}{\rho} \tag{13}$$

For a predetermined volume V of drug solution, Eq. (13) can be solved for q to give

$$q = \frac{V\rho}{(R\Phi) + \varphi} \tag{14}$$

Principle of Monolayer Coating

Conversion of the wet surface of each carrier particle into a dry one by application of a single layer of coating particles implies that a specific amount, q_M (subscript M stands for monolayer), of the coating material is needed to coat adequately a certain quantity, Q_M, of the carrier material wetted by a maximum volume, V_{max}, of the liquid. It must be emphasized that monolayer coating represents a boundary case, since for a given amount, Q_M, of carrier particles, there is always the same, geometrically specified quantity, q_M, of coating particles that will produce a single coating layer. Consequently, the amount of coating material

required depends on the total surface area of the carrier powder material, i.e., its quantity, Q_M, and specific surface, A. In fact, for given carrier and coating materials, the monolayer excipient ratio, R_M (i.e., Q_M/q_M), is always a characteristic constant.

Therefore, for monolayer coating, there is always a maximum volume, V_{max}, of liquid that can be incorporated into a specific quantity of carrier material to form a layer of thickness, h_{max}, and total volume, V_{Lmax}, onto the external and internal surfaces of the carrier particles which can be effectively covered by a single layer of coating particles (Fig. 1). Thus, the volume distribution equation [Eq. (2)] can be rewritten as

$$V_{max} = V_\Phi + V_{Lmax} \quad (15)$$

where, as in Eq. (2), V_Φ depends on the Φ value and quantity of carrier material, whereas V_{Lmax}, in this case, is equal to V_L.

In general, the relationship of V_L to V_{Lmax} is an indication of the extent of coating needed. If varying volumes, V, of a liquid are to be incorporated into a specific amount, Q_M, of the carrier material, V_Φ being constant by definition, the following conclusions may be drawn from Eqs. (2) and (15) to determine the type of coating required.

a. If $V < V_{max}$, then $V_L < V_{Lmax}$ and $h < h_{max}$: less than monolayer coating.
b. If $V = V_{max}$, then $V_L = V_{Lmax}$ and $h = h_{max}$: monolayer coating.
c. If $V > V_{max}$, then $V_L > V_{Lmax}$ and $h > h_{max}$: multilayer coating.

Before deriving the mathematical model for monolayer coating mode, the following assumptions are made.

- All carrier and coating particles are assumed to be monodispersed, smooth spheres having a total surface area equal to the sum of their internal and external surfaces.
- Accordingly, the volume-surface mean diameter is used as a quantitative means of particle size description (7).
- If D and d are the volume-surface mean diameters of the carrier and coating particles, respectively, then D is assumed to be much greater than d ($D \gg d$), and therefore, the curvature of the hypothetically smooth and spherical carrier particle is much wider than that of the coating particle.
- Consequently, the contact area between a carrier and a coating particle may be assumed or approximated as being a flat square to d^2.
- Finally, the liquid layer adsorbed on each carrier particle's surface, i.e., internal and external surfaces, is assumed to be of uniform thickness equal to h_{max}.

Schematic representation of the monolayer coating mode is given in Fig. 2.

In order for a single layer of coating particles to convert the carrier particle's wet surface to a dry one, the volume of liquid contained in a parallelepiped (rectangular box) of area d^2 and height equal to the thickness, h_{max}, of the surrounding liquid layer should be efficiently retained by a single spherical coating particle without significant loss of its nonadherent and free-flowing texture (Fig. 2). In other words, the weight of liquid, W_{liq}, contained in this volume, V_{box}, must be equal to the weight, W_{par}, of the liquid that a single coating particle can absorb without compromising its flowability. However, by definition, W_{par} equals φ_{par}, the flowable liquid-retention potential of a single coating particle; therefore,

$$W_{liq} = \varphi_{par} \quad (16)$$

Furthermore, since $W_{liq} = V_{box}\rho$, and $V_{box} = h_{max}\, d^2$, Eq. (16) can be modified as

$$\varphi_{par} = h_{max} d^2 \rho \quad (17)$$

However, φ_{par} is the ratio of the φ value of the coating material to the number of its particles, N_{par}, contained per unit weight. Therefore,

$$\varphi_{par} = \varphi / N_{par} \quad (18)$$

Moreover, $N_{par} = a/a_{par}$, where a is the specific surface of the coating material and a_{par} is the total surface area, i.e., sum of external and internal surface area, of a single spherical coating particle. Thus, Eq. (18) becomes

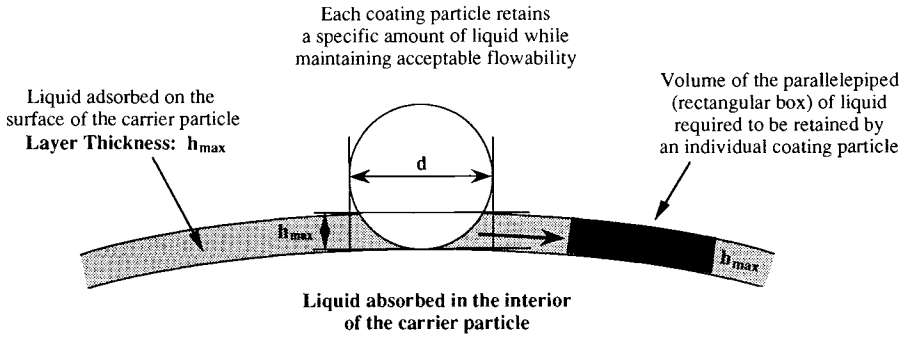

Fig. 2. Diagrammatic representation of monolayer coating. The shaded box represents the portion of liquid that must be efficiently retained by a single coating particle. Due to the extreme difference in curvature, the contact area between a carrier and a coating particle is approximated as being a flat square equal to d^2, where d is the volume-surface mean diameter of the coating particle.

Table I. Physical Properties of Formulation Excipients

Physical property	MCC-1 (Avicel PH 101)	MCC-2 (Avicel PH 102)	EGC (granular amorphous cellulose)	Silica (Syloid 244 FP)
Mean particle size (μm)	50	90	138	3
Specific surface (M^2/g)	1.07 ± 0.005	1.095 ± 0.003	24.22 ± 0.27	363.4 ± 1.06
Φ value (w/w)	0.05	0.15	0.3	1.6

$$\varphi_{par} = \frac{\varphi}{a/a_{par}} \tag{19}$$

Taking into consideration that a_{par} represents the area of a sphere, Eq. (19) can be modified as

$$\varphi_{par} = \frac{\varphi\pi d^2}{a} \tag{20}$$

where d is the volume-surface mean diameter of the coating material.

Substituting the value of φ_{par} [Eq. (17)] in Eq. (20) and solving for h_{max}, one obtains

$$h_{max} = \frac{\varphi\pi}{a\rho} \tag{21}$$

The total volume of the liquid layers, V_{Lmax}, equals the product of liquid layer thickness, h_{max}, and total surface area of all carrier particles. Since the total surface area of the wet carrier material is, by definition, equal to the product of its weight, Q_M, and its specific surface, A, we have

$$V_{Lmax} = h_{max}Q_MA \tag{22}$$

Substituting the value of h_{max} [Eq. (21)] in Eq. (22), we obtain

$$V_{Lmax} = \frac{\varphi\pi Q_MA}{a\rho} \tag{23}$$

Substituting the values of V_Φ [Eq. (4)][4] and V_{Lmax} [Eq. (23)] in Eq. (15), the maximum volume of the liquid, V_{max}, that can be retained by the coating particles in monolayer coating conditions can be calculated as follows:

$$V_{max} = \frac{Q_M[(\Phi a) + (\varphi\pi A)]}{a\rho} \tag{24}$$

Solving for Q_M, Eq. (24) becomes

$$Q_M = \frac{V\rho a}{(\Phi a) + (\varphi\pi A)} \tag{25}$$

As stated earlier, in the case of monolayer coating, $V = V_{max}$ and $V_L = V_{Lmax}$. Therefore, combining Eqs. (5) and (15), it can be concluded that

$$v_\varphi = V_{Lmax} \tag{26}$$

[4] In the case of monolayer coating, Eqs. (4) and (6) can be rewritten as $V_\Phi = Q_M\Phi/\rho$ and $v_\varphi = q_M\varphi/\rho$.

Substituting the values of v_φ [Eq. (6)][4] and V_{Lmax} [Eq. (23)] in Eq. (26) and solving for q_M, one obtains

$$q_M = \frac{Q_M\pi A}{a} \tag{27}$$

In the above derivations, both carrier and coating particles are treated as monodispersed particles possessing a smooth, spherical surface, and with their total surface area being the sum of the external and internal surface areas. Therefore, in monolayer coating, since the liquid layer is assumed to be uniformly distributed over the external as well as the internal surface of the carrier particle, both of these surfaces are to be covered by the coating material. Hence, although theoretically monolayer coating represents a single layer of coating particles onto the external and internal surfaces of the carrier particles, in practice a multilayer of coating particles might form around the carrier particle.

MATERIALS AND METHODS

The validity and applicability of the derived mathematical relationships to calculate the optimum excipient quantities required to yield powdered solutions with acceptable flow properties were tested. In addition, the flowable liquid-retention potential (Φ value) of the formulation excipients was experimentally determined.

Materials

The following materials were used as received: anhydrous micronized prednisolone (Upjohn Co., Kalamazoo, MI), clofibrate (Ayerst Laboratories, Inc., New York), *N,N*-dimethylacetamide (Sigma Chemical Co., St. Louis, MO), polyethylene glycol 400 and white light mineral oil (Ruger Chemical Co., Inc., Irvington, NJ), microcrystalline celluloses, i.e., MCC-1 (Avicel PH 101) and MCC-2 (Avicel PH 102) (FMC Corp., Princeton, NJ), experimental grade of granular amorphous cellulose (EGC) (Edward Mendell Co., Inc., Carmel, NY), and amorphous silicon dioxide (Syloid 244 FP) (Davison Chemical Division, Baltimore, MD).

Relevant physical properties of the excipients are summarized in Table I.

Methods

Flowability Testing

Since all powder materials used in this study were less than 150 μm in size (Table I), the flow property of the powder excipients and powdered solution formulations was determined by angle of slide measurement. This test procedure

has been preferred over other methods of determinations (e.g., angle of repose) for powders with a particle size less than 150 μm (8,9). The angle of slide is defined as that angle to which a polished metal plate must be tilted in order for 10 g of powder to start sliding down the plate. All measurements were carried out in triplicate.

Determination of Φ Values

In order to determine the flowable liquid-retention potential (Φ value) of the formulation excipients, several mixtures of each powder excipient with varying light mineral oil (LMO) contents were prepared, and their angle of slide was determined. An angle of 33° was considered as the limit of acceptable flowability (10). Hence, the LMO content (w/w) in the mixture which exhibited an angle of slide of 33° was taken as the Φ value of the excipient. Results of these determinations are presented in Fig. 3.

Determination of Specific Surface

The specific surface of the powder excipients was determined by the one-point BET method using Quantasorb Sorption System (Quantachrome Corp., Syosset, NY). This method can determine the total surface area of a powder material by assessing its external as well as internal surface area. A mixture of nitrogen and helium (3:7) was employed for these determinations. All determinations were carried out in triplicate. Mean specific surfaces of powder excipients are given in Table I.

Preparation of Powdered Solutions

Powdered solutions of prednisolone, a poorly water-soluble drug, and clofibrate, a lipophilic liquid, were prepared using the derived mathematical relationships. A 10% (w/v) solution of prednisolone was prepared in a *N,N*-dimethylacetamide and polyethylene glycol 400 (7:3, v/v) solvent system. The prednisolone solution and clofibrate were separately incorporated into each of the three cellulosic carriers, i.e., powder and granular microcrystalline celluloses (MCC-1 and MCC-2) and amorphous granular cellulose (EGC). The wet mixtures were then converted into dry powders by incorporating calculated quantities of coating material, i.e., silica (Syloid 244 FP).

Tablet formulations of each drug were made with a fixed drug content per tablet, i.e., 10 mg of prednisolone or 250 mg of clofibrate (Table II). Excipient quantities required for these formulations were determined using derived mathematical relationships. Formulations 1–3 were prepared according to the excipient ratio equations [Eqs. (12) and (14); $R = 5$], whereas formulations 4–6 were prepared by the monolayer coating mode [Eqs. (25) and (27)]. The tablet formulations, angle of slide of the final powder admixtures, and tablet sizes are given in Table II.

For present studies, although the solvent system used for the formulations consisted of *N,N*-dimethylacetamide and PEG 400 (7:3), the Φ values used to calculate the appropriate quantities of excipients required for the formulations were determined using light mineral oil as the model liquid (Fig. 3). This was done because it was determined in our studies that the physicochemical properties (e.g., polarity,

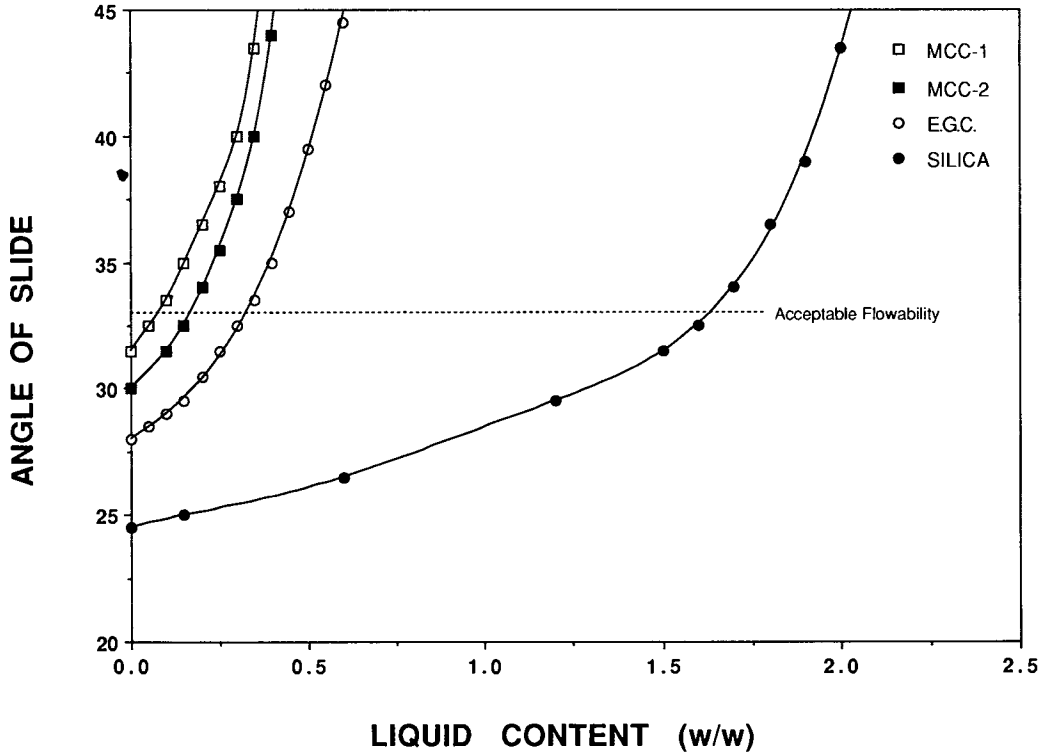

Fig. 3. Determination of the Φ value of powder excipients. The angle of slide of various mixtures of powder excipients with light mineral oil as a function of their oil content. The intersection of each curve with the horizontal dashed line represents the Φ value of the respective powder excipient.

Table II. Powdered Solution Formulations and Their Flowability Determination

Formulation excipient	Weight of excipient per tablet (g) for powdered solution formulation no.[a]											
	1P[b]	1C[b]	2P	2C	3P	3C	4P	4C	5P	5C	6P	6C
Prednisolone solution (10%, w/v)	0.101	—	0.101	—	0.101	—	0.101	—	0.101	—	0.101	—
Clofibrate	—	0.250	—	0.250	—	0.250	—	0.250	—	0.250	—	0.250
MCC-1 (Avicel PH 101)	0.273	0.675	—	—	—	—	1.559	3.858	—	—	—	—
MCC-2 (Avicel PH 102)	—	—	0.214	0.532	—	—	—	—	0.612	1.514	—	—
EGC (granular amorphous cellulose)	—	—	—	—	0.163	0.403	—	—	—	—	0.159	0.394
Silica (Syloid 244 FP)	0.054	0.135	0.043	0.106	0.032	0.080	0.015	0.036	0.006	0.015	0.034	0.083
Tablet weight (g)	0.428	1.060	0.357	0.888	0.296	0.733	1.675	4.144	0.719	1.779	0.294	0.727
Angle of slide (deg)[c]	32.7	32.6	32.4	32.3	32.7	32.4	31.8	31.9	32.4	32.0	32.7	32.1

[a] Formulations 1–3 were made using excipient ratio equations ($R = 5$), and formulations 4–6 according to the monolayer coating mode.
[b] P, Prednisolone; C, Clofibrate.
[c] Mean of three determinations; in all cases the standard deviation was less than 0.5°.

viscosity, and powder wettability) of liquid did not significantly affect the magnitude of Φ value when lab-scale methods, such as mortar and pestle, were employed for mixing.

RESULTS AND DISCUSSION

The concept of flowable liquid-retention potential is depicted in Fig. 3. The Φ value of the powder excipients was determined by plotting the angle of slide as a function of the mineral oil content of the mixtures. The dashed horizontal line represents the limit (33°) for acceptable flowability; the intersection of each curve with the horizontal line represents the Φ value of the respective excipient. Among the three celluloses used, amorphous granular grade (EGC) exhibited the highest Φ value (0.3, w/w), followed by granular microcrystalline cellulose (MCC-2; 0.15 w/w) and powder microcrystalline cellulose (MCC-1; 0.05, w/w). Silica (Syloid 244 FP), which has the largest surface area among all the excipients tested, exhibited the highest φ value (1.6, w/w).

As shown in Table I, the Φ value of a powder material is a function of its specific surface. Moreover, by comparing the mean particle size of each of the celluloses with its specific surface, a general idea about the porosity of the material can be obtained. It seems that the Φ value is also a function

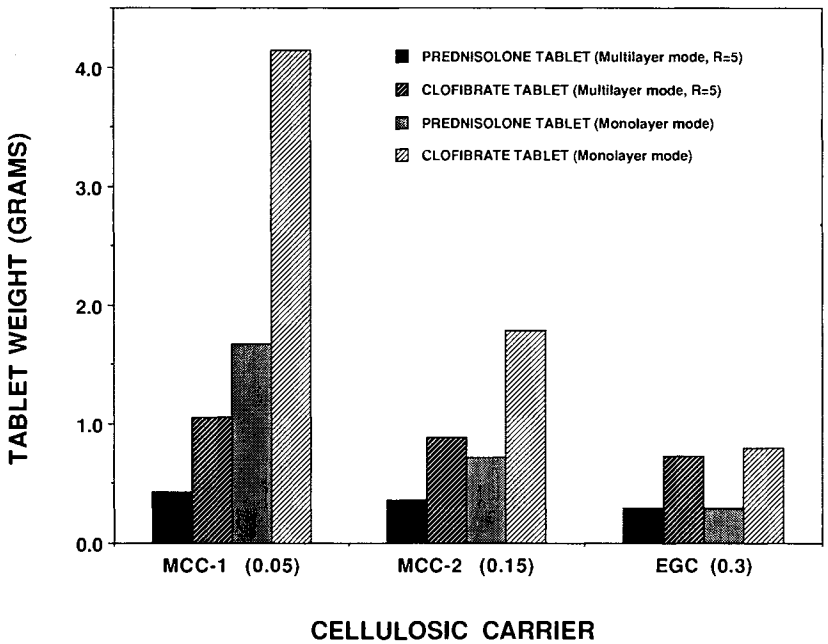

Fig. 4. Tablet weight of powdered solution formulations plotted as the inverse of the Φ value of their cellulosic carrier. The number in parentheses represents the Φ value of the carrier cellulose. In the cases of MCC-1 and MCC-2, the monolayer coating yielded very large tablet sizes due to their relatively smaller specific surface.

of the porosity of the material. However, further studies will be required before a relationship between the Φ value of a powder material and its specific surface and porosity can be established.

The flow property data of various powdered solution formulations are given in Table II. It can be seen that all formulations exhibited acceptable flowability by not exceeding the predetermined limit of angle of slide (33°). These data support the validity of the proposed mathematical model.

From the plot of experimental Φ value against tablet size produced by various celluloses (Fig. 4), it can be observed that the higher the Φ value of cellulose, the smaller is the size of the formulated tablet. Therefore, in powdered solution formulations, selection of powder excipients with a higher Φ value is a definite requirement for the production of tablets with a realistic size and desired drug content.

Furthermore, for the monolayer coating conditions, another physical property that significantly affects the tablet size of powdered solutions is the specific surface of the excipients. As shown in Fig. 4, the monolayer coating mode produced tablets of extremely large sizes for formulations with microcrystalline celluloses (MCC-1 and MCC-2), whereas amorphous granular cellulose (EGC) formulations rendered relatively smaller tablets.

Since EGC possesses a much larger specific surface than MCC-1 and MCC-2 (Table I), according to Eq. (27), EGC formulations will require a higher silica content. This will result in lower quantities of total solids in the formulation since silica has the highest φ value among all the excipients used (Table I). On the other hand, the much smaller specific surface of MCC-1 and MCC-2 will result in formulations with a low silica content; hence higher levels of these celluloses will be required to participate in the final products in order for the same amount of liquid to be absorbed. In other words, in this case, the value of monolayer excipient ratio (R_M) will be very high since larger quantities of low-Φ value carriers are mixed with a smaller quantity of high-φ value coating material. Therefore, in the case of carrier materials with a relatively low specific surface, the monolayer coating mode can be applied when the tablet size is not due to become extremely large, i.e., when small liquid volumes per tablet are required.

CONCLUSIONS

A theoretical model is proposed for the formulation of powdered solutions. Mathematical relationships based on powder properties have been derived which can be used to calculate the optimum excipient quantities needed to prepare free-flowing powdered solution formulations. This approach overcomes the problem of poor flowability, which has rendered powdered solutions as an industrially impractical method. The validity and applicability of the derived mathematical expressions have been verified experimentally by formulating prednisolone and clofibrate powdered solutions with satisfactory flow properties. However, during the formulation of such drug delivery systems, special consideration must be given to the selection of the type of coating mode and the carrier and coating materials. Excipients possessing a high flowable liquid-retention potential and specific surface are most desirable.

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