ISSN : 0974-7419 Volume 10 Issue 9

Trade Science Inc.

Analytical CHEMISTRY

An Indian Journal

Review

ACAIJ, 10(9) 2011 [581-589]

Tablet assessments tests in pharmaceutical industry

A.R.Chandrasekaran

Faculty of Pharmacy, AIMST University, Kedah- 08100, (MALAYSIA)

Received: 24th February, 2011 ; Accepted: 6th March, 2011

INTRODUCTION

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interactions between tablet components may alter the physical tablet properties, and greatly affect the bioavailability of the tablet system. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameters and shape depends on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets[1].

GENERAL APPEARANCE

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet-to-tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odour, taste, surface textures, physical flaws and consistency[2].

Size and shape

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process. At a constant compressive load, tablets thickness varies with changes in die fill, particle size distribution and packing of the powder mix being compressed and with tablet weight, while with a constant die fill, thickness varies with variation in compressive load. Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working condition.

The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within a +_5% variation of a standard value. Any variation in thickness within a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye for consumer acceptance of the product. In addition, thickness must be controlled to facilitate packaging.

The physical dimensions of the tablet along with the density of the material in the tablet formulation and their proportions, determine the weight of the tablet. The size and shape of the tablet can also influence the choice of tablet machine to use, the best particle size for granulation, production lot size that can be made, the best type of tableting processing that can be used, packaging operations, and the cost of production.

The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable

when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form. Twenty tablets are weighed individually and the average weight is calculated. The individual tablet weights are then compared to the average weight. Not more than two of the tablets must differ from the average weight by not more than the percentages stated in TABLE 1. No tablet must differ by more than double the relevant percentage. Tablets that are coated are exempted from these requirements but must conform to the test for content uniformity if applicable.

TABLE 1 : Weight variation requirements

Average weight	Percent difference
130mg or less	10
More than 130mg through 324mg	7.5
More than 324mg	5

Organoleptic properties

Color is a vital means of identification for many pharmaceutical tablets and is also usually important for consumer acceptance. The color of the product must be uniform within a single tablet, from tablet to tablet and from lot to lot. Non uniformity of coloring not only lack esthetic appeal but could be associated by the consumer with non uniformity of content and general poor product quality. Non uniformity of coloring is usually referred to as mottling. The eye cannot differentiate small differences in color nor can it precisely define color and efforts have been made to quantitate color evaluations. Reflectance spectrophotometry, tristimulus colorimetric measurements and micro reflectance photometer have been used to measure color uniformity and gloss on a tablet surface.

Odor may also be important for consumer acceptance of tablets and can provide an indication of the quality of tablets as the presence of an odor in a batch of tablets could indicate a stability problem, such as the characteristic odor of acetic acid in degrading aspirin tablets. However, the presence of an odor may be characteristic of the drug (e.g. vitamins), added ingredients (e.g. flavoring agent) or the dosage form (e.g. film-coated tablets).

Taste is also important for consumer acceptance of certain tablets (e.g. chewable tablets) and many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product. Taste preference is however subjective and the control of taste in the production of chewable tablets is usually based on the presence or absence of a specified taste.

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes. Tablet monographs with a content uniformity requirement do not have weight variation requirements[4]. For content uniformity test, representative samples of 30tablets are selected and 10 are assayed individually. At least 9 must assay within ±15% of the declared potency and none may exceed ± 25%

MECHANICAL STRENGTH OF TABLETS

The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information is useful in the selection of excipients. An excessively strong bond may prevent rapid disintegration and subsequent dissolution of a drug. Weak bonding characteristics may limit the selection and/or proportion of excipients, such as lubricants, that would be added to the formulation.

The mechanical properties of pharmaceutical tablets are quantifiable by the friability[5], hardness or crushing strength[6-8], crushing strength-friability values[7-8], tensile strength[9-11].

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets

are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up[3]. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress[2].

Hardness or crushing strength

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet.

Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets[2]. Oral tablets normally have a hardness of 4 to 10kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10-20 kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increase with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression[7,8].

Another measure of the mechanical strength of pharmaceutical tablets that have been used is the crushing strength-friability ratio (CSFR)[7,8]. The CS provides a measure of tablet strength while F is a measure of tablet weakness. Studies have shown that the higher the CSFR values, the stronger the tablet[7,8].

Tensile strength

A non-compendial method of measuring the mechanical strength of tablets that is now widely used is the tensile strength. This is the force required to break a tablet in a diametral compression test. The radial tensile strength, T, of the tablets can be calculated from the equation:

$$T = 2F / \pi d H \quad (1)$$

where F is the load needed to break the tablet, and d and H are the diameter and thickness respectively. Several precautions must be taken when using the equation. Various factors e.g. test conditions, deformation properties of the material, adhesion conditions between compact and its support and tablet shape may influence the measurements of the tensile strength[6].

Some authors have suggested the determination of axial tensile strength because of the sensitivity of the radial tensile strength measurements to crack propagation variations[13,14]. The axial tensile strength (Tx) can be calculated from the following relationship:

$$Tx = 4F / \pi d2 \quad (2)$$

Tensile strength has been used in combination with indentation hardness to evaluate tabletting performance of materials[12]. The indentation hardness is a time-dependent property used to measure the plastic yield of a material. It can be determined by either static methods (e.g. the Brinell, Vickers and Rockwell hardness tests) or the dynamic methods[15]. The static indentation methods involve the formation of a permanent indentation on the surface of the material tested and the hardness is determined by means of the load applied and the size of the indentation formed[16]. In the dynamic indentation tests, either a pendulum is allowed to strike from a known distance or an indenter is allowed to fall under gravity unto the surface of the test material. The hardness is then determined from the rebound height of the pendulum or the volume of the resulting indentation. Using an apparatus consisting of a steel sphere pendulum acting as an indenter, Hiestand et al.[12] estimated

the hardness (i. e. the mean deformation pressure) of compacted materials by dividing the energy consumed during the impact by the volume of indentation.

Brittle fracture index (BFI)

Hiestand et al.[17,18] have studied the effects of decompression on the tabletting performance of pharmaceutical materials and stated that whether or not fracture occurs during the shear deformation which accompanies decompression depends on the ability of the materials to relieve stresses by plastic deformation without undergoing brittle fracture and this ability is a time-dependent phenomenon. Those materials that relieve stress rapidly are less likely to cap or laminate. The brittleness test is based on the Griffith fracture theory which teaches that, for crack growth to occur, the energy stored at the tip of a crack must just exceed the energy required to form two new surfaces resulting from the propagation of the crack. Also, the amount of energy stored at the tip of a crack is a function of the dimensions of the crack.

In the light of this theory, Hiestand et al.[17] showed that when compacts are made with a small axially-oriented round hole at their centre, the compact is nearly always weakened. Under the conditions of the tensile strength test, elasticity theory predicts that the stress concentration factor for the hole should be about 3.0. Hiestand[18] showed that for isotropic materials, the ratio of compressive stress at the centre of a compact to the tensile stress, which causes fracture, has a value of 3.7. However, recent studies have shown that for a ratio of hole diameter to disc of about 0.1, the stress concentration factor, i.e. the ratio between tensile stress at the inner boundary of the hole and the tensile stress of a tablet having no hole, should be around 10[19,20]. Thus, the BFI is obtained by comparing the tensile strength of tablets with a hole at their centre, which acts as a built-in stress concentration defect, with the tensile strength of tablets without a hole, both at the same relative density[18,21]. The brittle fracture index (BFI) of the tablets was calculated using the following equation

$$BFI = [(T / To) - 1 \quad (3)$$

Where T is the tensile strength of the tablet without a hole and To, to the tensile strength of a tablet with a hole. The theoretical value of BFI range is 0 - 1 when the stress concentration factor is 3. Since the BFI is an inverse measure of localized stress relief, it should indicate the tendency of a tablet to laminate or cap. In principle, BFI values in excess of unity may occur. In practice, however, one probably cannot make an intact tablet of a material with a BFI of 1. Therefore, the observed range of values may not exceed the 0 - 1 range. Where by the closer the value of BFI to 0, the less stress relief takes place. A high value of BFI is an indication of the tendency of the tablet to laminate during the compaction process. A low BFI value is desirable for minimal lamination and capping during production[9,21].

Robert and Rowe[22] extended the determination of the BFI to compact of 'tablet-sized' dimensions. This allows the BFI to be measured at strain rates and conditions approaching those normally used in tabletting. They found the BFI values for microcrystalline cellulose, tablettose and heavy magnesium carbonate to be in good agreement with the results of previous workers[12,17]. Itiola & Pilpel[21] using both granular and powdered metronidazole formulations studied the mechanical properties of the tablets and differentiated between the bond strength of the tablets as measured by their tensile strength and the tendency of the tablets to laminate or cap as measured by the brittle fracture index values. They found that tablets made from granules had lower tensile strength than those made from powders but were also less brittle.

The BFI have also been used to characterize the mechanical properties of pharmaceutical formulations and some local starches, namely cassava, potato and yam starches[23,24]. Tablets of these starches were shown to possess low tensile strength values, but also had low BFI values. Studies have also shown that the BFI is affected by the nature and concentration of binding agent, compression pressure and compression speed. Generally, the higher the BFI values, the more friable a tablet is likely to be.

Tablet evaluation tests/disintegration

Tablet evaluation tests

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration[26]. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which

will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37°C, preferably in a 1L beaker. For compressed uncoated tablets, the testing fluid is usually water at 37°C but some monographs direct that simulated gastric fluid be used. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets. For most uncoated tablets, the BP requires that the tablets disintegrate in 15minutes (although it varies for some uncoated tablets) while for coated tablets, up to 2hours may be required[3]. The individual drug monographs specify the time disintegration must occur to meet the Pharmacopoeial standards.

In the past, the only release index required for a tablet was its disintegration time which does not necessarily measure the physiological availability of the drug in a patient. Studies have shown that the agitation of the gastric contents during normal contractions is quite mild in contrast to the turbulent agitation produced in the disintegration test apparaus. The low order magnitude of agitation in the stomach produces substantially higher disintegration in vivo than those obtained using the USP apparatus. Furthermore, the particles of the disintegrated tablets are not dispersed throughout the stomach but remains as an aggregate. Thus, the tablet disintegration test is limited to manufacturing control of lot-to-lot variations in individual products and is not a measure of bioavailability. Nevertheless, it is used to provide a simple and useful means for monitoring and controlling the quality of tablets.

THEORIES OF DISINTEGRATION

Several mechanisms of tablet disintegration have been proposed. Some of these are given below. Even though these concepts are listed separately, inter-relationships probably occur in almost all tablet formulations.

Evolution of gas

If a gas is evolved by a chemical reaction when the tablet comes into contact with water, then the tablet will disintegrate. This is the basis for the manufacture of effervescent tablets. An example of such a reaction is of sodium bicarbonate with citric and tartaric acids, which yields carbon dioxide. Peroxides incorporated in certain formulations decompose in the presence of oxygen and this also causes disintegration.

Heat of wetting

The heat produced when a tablet is immersed in water causes the entrapped air in the tablet to expand and exert sufficient pressure to disintegrate the tablet.

Effect of water absorption

The water absorbed by the tablet initiate disintegration, but this depends on the solubility of the drug and other ingredients present.

Swelling

The grains of the disintegrant, particularly of starches, swell in the presence of water and exert pressure on the granules to force them apart[30,31]. Shangraw et al[32] reported that tablets of water insoluble drugs disintegrated faster with starches than those of water soluble drugs due to the diminished water absorption capacity of the starches in the latter case.

Porosity of tablets

It has been shown that penetration of water into a tablet is proportional to its mean pore diameter or porosity[33,34]. The porosity and permeability of tablets decrease as the tabletting pressure is increased[35], and as the porosity decreases, the disintegration time increases[31,32]. Though no quantitative relationships have been reported between disintegration and penetration times, generally short disintegration times are associated with rapid fluid penetration[36,37].

IN-VIVO TEST, DISSOLUTION TESTS

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Dissolution is considered one of the most important quality control tests performed on pharmaceutical

Review

dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behaviour of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation, IVIVC[38].

Solid dosage forms may or may not disintegrate when they interact with gastrointestinal fluid following oral administration depending on their design (Figure 1).

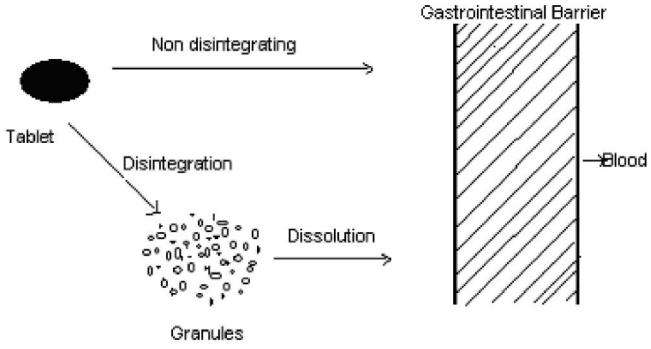

Figure 1 : Schematic diagram of the dissolution process

Dissolution kinetics is important in determining the bioavailability of a drug[39]. Levy[45] and some other workers[46] reported that the dissolution rate controls the rate of build up of certain drugs in the blood stream. It was thus recognised that in-vitro dissolution kinetics provides useful information on the availability of drugs and their subsequent therapeutic effects in-vivo[45]. This led to the inclusion of dissolution tests in the United States NF XIII (1970) and USP XVIII (1970) monographs for one capsule and twelve tablet preparations. In 1975, dissolution tests were included in the British Pharmacopoeia (amendment to BP 1973) for digoxin tablets. The various pharmacopoeias contain specifications on the dissolution requirements of various drugs. A variety of designs of apparatus for dissolution testing have been proposed and tested, varying from simple beaker with stirrer to complex systems with lipid phases and lipid barrier where an attempt is made to mimic the biological milieu. The choice of the apparatus to be used depends largely on the physicochemical properties of the dosage form[47].

THEORIES OF DISSOLUTION

Some workers[48,49] have reviewed the factors which can affect the dissolution of tablets and these include the stirring speed, temperature, viscosity, pH, composition of the dissolution medium and the presence or absence of wetting agents.

Physical models have been set up to account for the observed dissolution of tablets. According to Higuchi[50], there are three models which either alone or in combination, can be used to describe the dissolution mechanisms. These are:

The diffusion layer model

This model (Figure 2) assumes that a layer of liquid, H cm thick, adjacent to the solid surface remains stagnant as the bulk liquid passes over the surface with a certain velocity. The reaction at the solid/liquid interface is assumed to be instantaneous forming a saturated solution, Cs, of the solid in the static liquid film. The rate of dissolution is governed entirely by the diffusion of the solid molecules from the static liquid film to the bulk liquid according to Fick's first law:

$$J = - Df \, dc / dx \qquad (4)$$

where J is the amount of substance passing perpendicularly through a unit surface area per time, Df, is the diffusion coefficient and dc / dx, is the concentration gradient. After a time t, the concentration between the limit of the static liquid layer and the bulk liquid becomes Ct. Once the solid molecules pass into the bulk liquid, it is assumed that there is rapid mixing and the concentration gradient disappears.

The theory predicts that if the concentration gradient is always constant i. e. Cs - Ct is constant because Cs >> Ct ("sink" conditions which usually mean Cs > 10 Ct) then a uniform rate of dissolution is obtained.

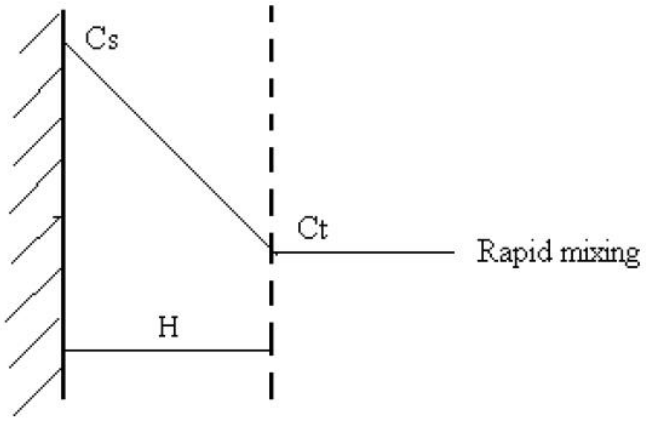

Figure 2 : Diffusion layer model

The interfacial barrier model

In the interfacial barrier model (Figure 3), it is assumed that the reaction at the solid/liquid interface is not instantaneous due to a high activation free energy barrier which has to be surmounted before the solid can dissolve. Thereafter the dissolution mechanism is essentially the same as in (i) above, with the concentration at the limit of the static layer of liquid becoming Ct after time t.

The rate of diffusion in the static layer is relatively fast in comparison with the surmounting of the energy barrier, which therefore becomes rate limiting in the dissolution process.

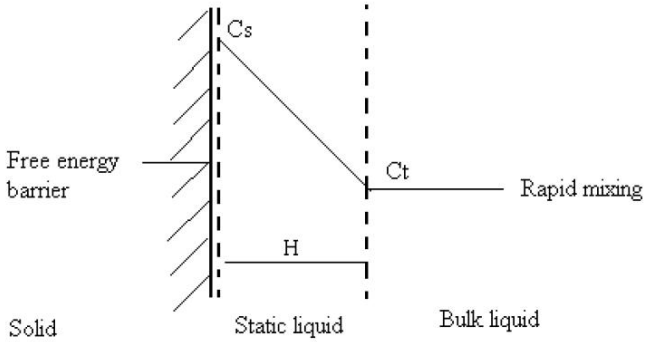

Figure 3 : Diagrammatic representation of the free energy barrier to dissolution

The Danckwert's model

The Danckwert's model (Figure 4) assumes that macroscopic packets of solvent reach the solid/liquid interface by eddy diffusion in some random fashion.

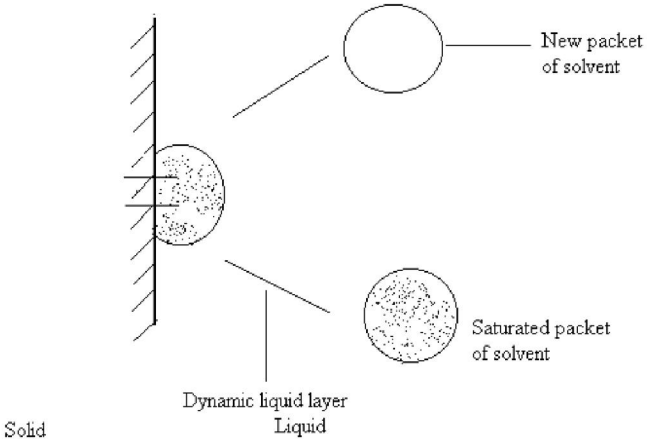

Figure 4 : The Danckwert's model.

At the interface, the packet is able to absorb solute according to the laws of diffusion and is then replaced by a new packet of solvent. This surface renewal process is related to the solute transport rate and hence to the dissolution rate.

The rate laws predicted by the different mechanisms both alone and in combination, have been discussed by Higuchi. However, the earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney as:-

$$dc / dt = k (Cs - Ct) \quad (5)$$

where dc / dt is the rate of change in concentration with respect to time, and k is the rate constant. The integrated form of the equation is:

$$In [Cs / (Cs - Ct)] = kt \quad (6)$$

The equation in resemblance to the other rate law equations, predicts a first order dependence on the concentration gradient (i.e. Cs - Ct) between the static liquid layer next to the solid surface and the bulk liquid. Noyes and Whitney explained their dissolution data using a concept similar to that used for the diffusion model. This considerations relate to conditions in which there is no change in the shape of the solid during the dissolution process (i. e. the surface area remains constant). However, for pharmaceutical tablets, disintegration occurs during the dissolution process and the surface area generated therefore varies with time.

Aguiar et al[52] proposed a scheme which holds that dissolution occurs only when the drug is in small particles. Wagner[53] modified this idea and showed that dissolution occurs from both the intact tablet and the aggregates and/or granules produced after disintegration by using a plot of the percentage of drug dissolved versus time on logarithmic - probability graph papers.

A modification of this approach was proposed by Kitazawa et al[54,55]. Employing the integrated form of Noyes and Whitney equation (equation 6), they determined the dissolution rate constant of uncoated caffeine tablets. The Kitazawa equations have been used to determine the dissolution rates of some pharmaceutical tablet formulations

ACKNOWLEDGEMENT

My sincere thanks to Prof. Dr. Dhanaraj SA, Dean, Faculty of Pharmacy, AIMST University, Kedah-08100, Malaysia, for instigation of this article.

Review

REFERENCES

[1] E.Rippie; Compression of Solids and Compressed Dosage Forms. In: 'Encyclopedia of Pharmaceutical Technology'. J.Swarbrick, (Ed); Marcel Dekker Inc., NY, **3**, 149-166 **(1990)**.

[2] E.Rudnic, J.B.Schwartz; Oral Solid Dosage Forms. In: 'Remington's Pharmaceutical Sciences'. 18th Edition, A.R.Gennaro, (Ed); Mack Publishing Company, Easton, Pennsylvania, USA, 1633-1665 **(1990)**.

[3] British Pharmacopoeia; HMSO, London, **(1998)**.

[4] J.A.Seitz, G.M.Flessland; J.Pharm.Sci., **54**, 1353-1357 **(1965)**.

[5] S.M.Upadrashta, P.R.Katikaneni, N.O.Nuessla; Drug Dev.Ind.Pharm., **18**, 1701-1708 **(1992)**.

[6] J.T.Fell, J.M.Newton; J.Pharm.Sci., **59**, 688-691 **(1970)**.

[7] O.A.Odeku, O.A.Itiola; Drug Dev.Ind.Pharm., **29**, 311-320 **(2003)**.

[8] O.A.Odeku; Acta Pharm., **55**, 263-276 **(2005)**.

[9] O.A.Odeku, O.A.Itiola; Pharm.Pharmacol. Commun., **4**, 183-188 **(1998)**.

[10] J.M.Newton, G.Rowley, J.T.Fell, D.G.Peacock, K.Ridgway; J.Pharm.Pharmacol., **23**, 195S-201S **(1971)**.

[11] G.R.B.Down, J.M.McMullen; Powder Technol., **42**, 169-174 **(1985)**.

[12] E.N.Hiestand, D.P.Smith; Powder Technol., **38**, 145-159 **(1984)**.

[13] S.T.David, L.L.Augsburger; J.Pharm.Sci., **66**, 155-159 **(1977)**.

[14] P.J.Jarosz, E.L.Parrott; J.Pharm.Sci., **71**, 607-401 **(1982)**.

[15] H.Leuenberger, B.D.Rohera; Pharm.Res., **3**, 12-22 **(1986)**.

[16] M.Celik; Drug Dev.Ind.Pharm., **18**, 767-810 **(1992)**.

[17] E.N.Hiestand, J.E.Wells, C.B.Poet, J.F.Ochs; J.Pharm.Sci., **66**, 510-519 **(1977)**.

[18] E.N.Hiestand; Rationale for and the Measurements of Tableting Indices. In: 'Pharmaceutical Powder Compaction Technology', G.Alderborn, C.Nystrom, (Eds); Marcel Dekker, New York, 219-244 **(1996)**.

[19] A.J.Durelli, Y.H.Lin; J.Appl.Mech., **53**, 213-219 **(1986)**.

[20] F.Podzeck, J.M.Newton; Powder Technol., **132**, 10-15 **(2003)**.

[21] O.A.Itiola, N.Pilpel; Int.J.Pharm., **31**, 99-105 **(1986a)**.

[22] R.J.Roberts, R.C.Rowe; J.Pharm.Pharmacol., **38**, 566-571 **(1986)**.

[23] O.A.Itiola; Pharm.World J., **8(3)**, 91-94 **(1991)**.

[24] O.A.Odeku, O.O.Awe, B.Popoola, M.A.Odeniyi, O.A.Itiola; Pharm.Tech., **29(4)**, 82-90 **(2005)**.

[25] O.A.Odeku, B.O.Patani; Pharm.Dev.Tech., **10**, 439-446 **(2005)**.

[26] G.S.Banker, N.R.Anderson; Tablets. In: 'The Theory and Practice of Industrial Pharmacy'. L.Lachman, H.A.Lieberman, J.L.Kanig, (Eds); 3rd Edition, Lea & Febiger, Philadelphia, 301-303 **(1986)**.

[27] Guyot-Hermann; S.T.P.Pharmaceutical Science, **2(6)**, 445-462 **(1992)**.

[28] H.Matsumaru; Yakugaku Zasshi, **79**, 63-64 **(1959)**.

[29] W.Lowenthal; Pharm.Acta Helv., **48**, 589-609 **(1973)**.

[30] J.Ringard, A.M.Guyot-Hermann; Drug Dev.Ind. Pharm., **7**, 155-177 **(1981)**.

[31] J.L.Kanig, C.Rudnic; Pharm.Technol., **8**, 50-62 **(1984)**.

[32] R.Shangraw, A.Mitrevej, M.Shah; Powder Technol., **4**, 49-57 **(1980)**.

[33] P.Singh, S.J.Desai, A.P.Simonelli, W.I.Higuchi; J.Pharm.Sci., **57**, 217-226 **(1968)**.

[34] D.Ganderton; J.Pharm.Pharmacol., **21(suppl.)**, 9S-18S **(1969)**.

[35] T.R.R.Kurup, N.Pilpel; Powder Technol., **16**, 843-847 **(1977)**.

[36] D.Ganderton, E.Shotton; J.Pharm.Pharmacol., **12**, 144T-152T **(1961)**.

[37] H.Nogami, T.Hagai, E.Fukuola, T.Sonobe; Chem. Pharm.Bull., **17(7)**, 1450-1455 **(1969)**.

[38] G.L.Amidon, H.Lennernas, V.P.Shah, J.R.Crison; Pharm.Res., **12**, 413-420 **(1995)**.

[39] G.Levy; J.Pharm.Sci., **50**, 388-392 **(1961)**.

[40] O.A.Itiola, N.Pilpel; J.Pharm.Pharmacol., **38**, 81-86 **(1986)**.

[41] O.A.Itiola, N.Pilpel; Pharmazie, **51**, 997-998 **(1996)**.

[42] O.A.Odeku, O.A.Itiola; Trop.J.Pharm.Res., **2(1)**, 147-153 **(2003)**.

[43] A.T.Florence, G.W.Halbert; Formulation. In: 'Comparative Medicinal Chemistry: The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compound'. C.Hansch, P.G.Sammes, J.B.Taylor, (Eds); 1st Edition, Pergamon Press Plc. Oxford, UK, **6**, 567-592 **(1990)**.

[44] M.Siewert, J.Dressman, C.K.Brown, V.P.Shah; AAPS PharmSciTech., Article 7, http://www.pharmscitech.org, **4(1)**, **(2003)**.

[45] G.Levy, J.R.Leonards, J.A.Procknel; J.Pharm.Sci., **54**, 1719-1722 **(1965)**.
[46] G.Levy, K.E.Miller; J.Pharm.Sci., **53**, 1301-1305 **(1964)**.
[47] O.A.Odeku, O.A.Itiola; 'Advances in Dissolution Test in Pharmaceutical Analysis', **(2005)**.
[48] D.E.Wurster, P.W.Taylor; J.Pharm.Sci., **54**, 169-175 **(1965)**.
[49] J.Swabrick, D.Ma; J.Pharm.Pharmacol., **31**, 787-789 **(1981)**.
[50] W.I.Higuchi; J.Pharm.Sci., **56**, 315-324 **(1967)**.
[51] A.A.Noyes, W.R.Whitney; J.Am.Chem.Soc., **19**, 930-934 **(1897)**.
[52] A.J.Aguiar, J.Krc, A.W.Kinkel, J.C.Samyn; J.Pharm.Sci., **56**, 847-853 **(1967)**.
[53] J.G.Wagner; J.Pharm.Sci., **58**, 1253-1257 **(1969)**.
[54] S.Kitazawa, I.Johno, Y.Ito, S.Teramura, J.Okada; J.Pharm.Pharmacol., **27**, 765-770 **(1975)**.
[55] S.Kitazawa, I.Johno, T.Minouchi, J.Okada; J.Pharm. Pharmacol., **29**, 453-459 **(1977)**.