of the protein. Without treatment, mice died from leukaemia within 15 days, while all treated animals remained healthy. BMS-354825 also slowed the proliferation of cultured bone marrow cells isolated from patients with leukaemia.

Shah says that it is too early to predict whether resistance will occur with the new drug over time but, as it probably has fewer binding requirements than Gleevec, it might be less susceptible to resistance, he says.

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Private prescription:

A thought-provoking tonic on the lighter side

Column by **Raymond C. Rowe**, AstraZeneca, UK

Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

Hard to swallow!

On 3 August 1962, Malcolm Muggeridge (1903–1990), the British author and journalist, wrote in *The New Statesman* [1]:

'I will lift mine eyes unto the pills. Almost everyone takes them, from the humble aspirin to the multi-coloured, king-sized three deckers, which put you to sleep, wake you up, stimulate and soothe you all in one. It's an age of pills.'

Of course, Muggeridge was not referring to pills as such because the process used to manufacture them was unable to produce a three-layered formulation. Indeed, he was writing about the compressed tablet, a product that has, over the past 50 years, consistently 'topped the polls' in its popularity as a drug delivery system. Indeed, recent surveys [2,3] have shown that tablets account for over 30% of the dosage forms used for new medical entities in the USA and over 40% of formulations manufactured in the UK. However, both pills and tablets have a common feature in that they must be swallowed by the patient before the drug that they contain can exert its pharmacological effect. Nothing unusual about that, you might think, but the pattern of pill or tablet taking can, and does, vary from patient to patient. The diversity observed in the idiosyncrasies of patients when taking their tablets prompted a nurse, Cindy LaRue, to publish her findings [4].

Swallowing tablets

In her article, LaRue identifies several broad patient categories depending on their 'pill-taking patterns'. Using LaRue's definitions, plus a couple or so of my own, the characteristics of the different pill-taking patterns are described below.

Shot-glass downers

LaRue defines this technique as simply 'down the hatch'. The patient takes the receptacle of tablets and, irrespective of the quantity, throws the head back and empties the contents into the mouth in one quick motion. A mouthful of water quickly follows and everything is swallowed in one gulp.

Dry swallowers

As the name suggests, these patients simply swallow their tablets without any liquid. As an aside, LaRue describes these patients as unassuming and usually over 40 years of age. LaRue writes that initially she was confident that they were not swallowing their medication but storing it in their cheeks before spitting it out after she had left.

Tongue flippers

LaRue describes this intricate procedure in detail as follows:

'The pill [tablet] is placed on the roof of the mouth behind the front teeth. The water is then taken into the mouth, with the tongue remaining in position and put at the back of the throat ready to swallow. The pill [tablet] is then catapulted into the water with the

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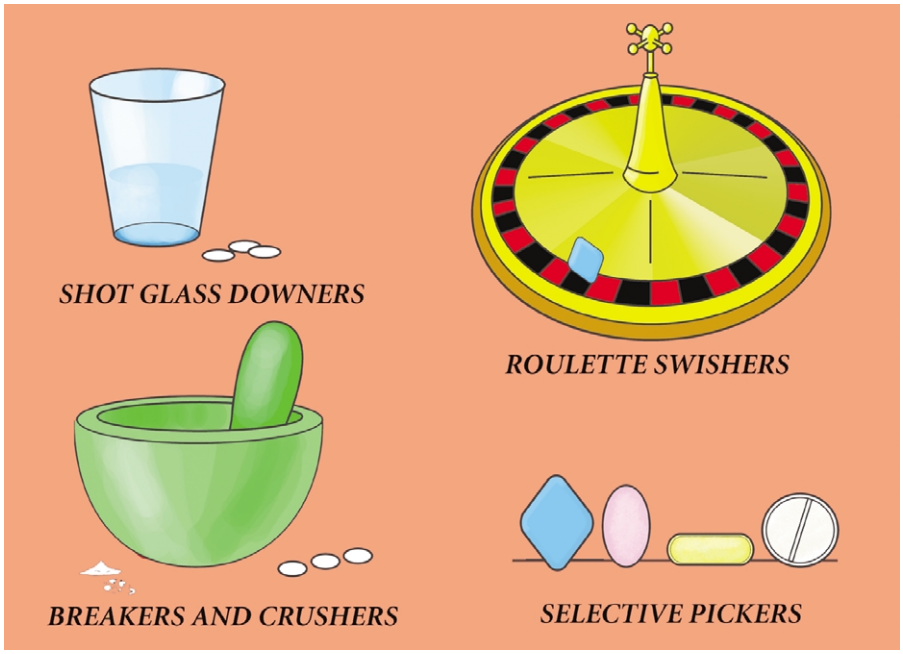

tongue, and all is swallowed in one tremendous gulp.'

Of course, this has to be done with each tablet in turn. There is no way that this technique could be used with multiple tablets.

Roulette swishers

The patient puts both the tablets and water in the mouth at the same time and then swills the contents around and around. At some appropriate time, the patient gives a backward jerk of the head and tablets and liquid are swallowed together.

Gaggers

This group of patients have a natural tendency to cough and choke when taking tablets. Often, the gagging is self-induced by the patient placing the tablet on the back of the tongue using the thumb and index finger. Furthermore, more than one glass of liquid is frequently required to swallow the tablet.

Chewers

This group of patients chew their tablets thoroughly before swallowing, often with a glass of water and they do not appear to worry about the taste of the drug and excipients.

Breakers and crushers

LaRue included these patients with the chewers, but I prefer to separate them. These patients either break their tablets up into small pieces or crush them using the back of a spoon. They often disperse the small pieces or powder in a carrier (jam or milk) before swallowing. Of course, when a tablet has been specifically formulated to provide a controlled release profile for a particular drug, chewers, breakers and crushers need to be educated that their technique is inappropriate because it could cause dose dumping and loss of efficacy.

Preparing medication

In addition to categorising patients depending on their swallowing technique, LaRue also differentiates patients depending on how they prepare their medication before taking it.

Selective pickers

These are patients who must select the sequence in which they take their medication because, invariably, they are prescribed multiple products. Of course, there are an infinite number of sub-groupings depending on the decision process. Some start with the largest tablet, others with the smallest. Some start with coated tablets, others leave these to the end. Often, the idea is to take the more difficult to swallow large uncoated tablets first, but patients are individuals and some prefer the reverse sequence. Occasionally, colour also plays a part – LaRue reports that patients prefer yellow tablets. Some patients alter their selection criteria by the day or week, others without any rhyme or reason.

Droppers

Patients in this group often drop their tablets or spill their drink and frequently the tablet is lost and a new dose has to be administered.

Commentators

When presented with their medication, patients in this group immediately count them and pass comment on their size and colour before launching into a diatribe as to their use and side effects. After this considerable commentary, they swallow the tablets without any difficulty. However, LaRue notes that patients in this group should not be taken lightly because they often recognize when something is wrong with the number or colour of their tablets, thus preventing errors in the dispensing of medications.

Normals

According to LaRue, this group accounts for the vast majority of patients who aid the nurse and facilitate the smooth running of the ward by being by their beds, pouring their own drink and saying 'thank you' when receiving their medication. LaRue remarks that the sickest patients often fall into this category.

Implications

By this time, many of you will have guessed that LaRue's paper is a serio-comic jibe at this area of nursing. However, it does have implications in the way that oral dosage medications, such as tablets, are formulated and presented. Many patients do have problems with swallowing tablets whole, and hence size and shape are important. These are also important considerations for patients who might lack the coordination to pick up small tablets. In recent times, fast dissolving or chewable formulations have been introduced to aid patients with swallowing difficulties.

'Where there's a pill, there's always a way'

A more intractable problem is the dose of the drug because, if this is large, as in the case of some antibiotics, the formulator is on the horns of a dilemma – providing one large dose will necessitate a large tablet but dividing the dose will result in an increased number of tablets, albeit smaller in size. Both options are associated with potential problems. However, formulators will invariably provide the answer – where there's a pill there's always a way!

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Sonophoresis: a 50-year journey

In 1954, Fellinger and Schmid [1] reported the successful treatment of digital polyarthritis using hydrocortisone in combination with ultrasound. Fifty years later, this technique, which is named sonophoresis or phonophoresis, has emerged as a powerful method for the facilitation of transdermal drug delivery. In a recent issue of *Drug Discovery Today*, Lavon and Kost [2] present an excellent review of the current status of sonophoresis.

Following the first report by Fellinger and Schmid, a number of studies were reported on the sonophoretic delivery of small molecules through the skin [3]. These studies were typically performed using ultrasound with frequencies in the range 1–3 MHz. Enhancements in the levels of drugs transported through the skin were only observed for particular drugs. For example, improvements in the transport of hydrocortisone and indomethacin were observed but not in the transport of lidocaine and salicylate [4]. This variation between drugs raised controversy about the use of sonophoresis for drug delivery. An explanation for the variation was recently offered based on the differences in physiochemical properties of drugs, for example, lipophilicity and molecular weight [4]. Specifically, small lipophilic drugs, which rapidly diffuse through the skin under passive conditions, do not show enhanced transport after application of ultrasound.

Several research groups from diverse disciplines, including engineering, pharmacy, physics and medicine, have worked collectively over the past five decades, and particularly over the past ten years, to gain a mechanistic understanding of sonophoresis and to improve the delivery efficiency of this methodology. In the 1990s, sonophoresis received a major boost from the identification of low-frequency conditions (20 kHz < frequency <100 kHz) [5,6] that enabled the application of sonophoresis to the delivery of macromolecules through the skin. To date, *in vitro* and *in vivo* experimental data exist for the sonophoretic transdermal delivery of insulin, heparin and the tetanus toxoid vaccine. The challenge now lies in converting these exciting laboratory investigations into useful products.

The mechanism of sonophoresis has been the focus of considerable attention;