IN VITRO/IN VIVO CORRELATIONS OF THE BIOPHARMACEUTIC PERFORMANCE OF SUSTAINED RELEASE PRODUCTS OF QUINIDINE.

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ABSTRACT

The absorption characteristics of four commercially available quinidine tablet preparations were studied in eight Beagle dogs. Three of the quinidine tablets were sustained release formulations, and the fourth a conventional release formulation. Quinidine concentrations were measured spectrophotofluorometrically in the serum of the dogs after receiving a single dose of each of the four products. Absorption profiles of the three sustained release products were compared with that of the conventional release product, and possible correlations of the *in vivo* results with available *in vitro* dissolution data for the same products were examined. Only two of the three sustained release products exhibited *in vitro* and *in vivo* characteristics of a sustained release formulation.

In spite of certain physiological limitations, the Beagle dog is a useful animal model for the pre-clinical assessment of the *in vivo* performance of sustained release quinidine products.

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CHAPTER I INTRODUCTION

I - A Quinidine

1. Chemistry

Quinidine, a cinchona alkaloid, is the dextrorotatory stereoisomer of quinine with the chemical structure (1) as shown in Figure 1. It is a basic compound forming monobasic and dibasic salts with both inorganic and organic acids. The respective pKa's have been stated as 5.4 and 10.0 (2).

The current method of making quinidine is *via* a base catalysed epimerization reaction of quinine. Quinine from natural sources also contains dihydroquinine. Thus, available quinidine contains a complex mixture of epimers and their corresponding dihydro analogs. A significant amount of hydroquinidine has been detected both in commercial bulk quinidine sulfate and quinidine sulfate tablets (3,4).

2. Pharmacology

Quinidine has played an important role in the prophylaxis and treatment of cardiac arrhythmias since the 1920's. Before the introduction of direct-current shock, quinidine was used for conversion of atrial fibrillation. Today it is much more important as a prophylactic agent against the recurrance of fibrillation after successful conversion (5). It is a myocardial depressant drug having the actions of decreasing excitability, conduction

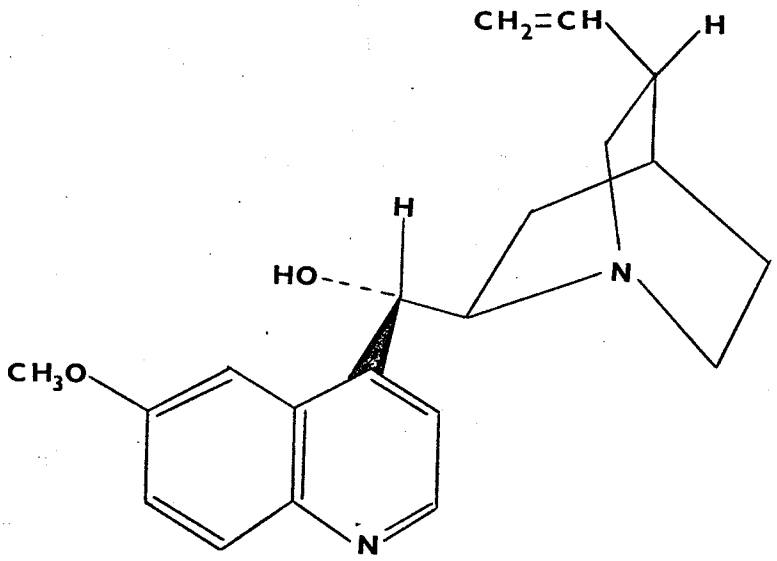

Figure 1. Quinidine (1).

velocity and contractibility of the myocardium. Thus it causes an increase in threshold, effective refractory period and conduction interval. It also increases the duration of the action potential in the cells of the sino-atrial node and decreases the slope of depolarization. This causes a decrease in spontaneous frequency, thus inhibiting ectopic foci (6).

The side effects of quinidine are important. Attacks of syncope related to quinidine treatment are not unusual. Gastrointestinal symptoms, e.g. nausea, vomiting and diarrhoea are common and are probably due to local irritation of the intestinal tract. Neurological effects occur sometimes, e.g. vomiting, blurred vision, headache and vertigo. In rare cases allergic reactions such as urticaria, fever, thrombocytopenia and itching have been described (5,6).

In man the auricular anti-fibrillation action of hydroquinidine is found to be somewhat more powerful than that of quinidine (7). In animals, the intensity of their pharmacological actions is found to be different and the toxicity of hydroquinidine is higher (8).

Work by Huynh-Ngoc and Sirois (4) on the apparent benzene-aqueous buffer partition co-efficient as a function of pH showed the chemical species of quinidine to be more lipophilic than the one of hydroquinidine. This indicates that these alkaloids might each have a different behaviour in biologic systems. It has been

proposed that the presence of hydroquinidine may modify the absorption/excretion rates and pharmacological action of quinidine, and may influence the dissolution rate of some quinidine formulations (9). A study by Goldberg and Chakrabarti (10) showed that single and maintenance doses of quinidine gluconate gave higher blood levels than hydroquinidine gluconate.

3. Absorption Rate and Elimination

Quinidine appears to be absorbed almost completely from the gastrointestinal tract, the main site of absorption being the small intestine (6). It is rapidly bound by plasma albumin. This occurs to the extent of approximately 60% when the total plasma quinidine concentration is in the range of 3-6 mcg/ml (11). Once quinidine is in the biophase, receptor binding and debinding is instantaneous. The rate determining step to decline in response is removal of drug from the biophase which is kinetically indistinguishable from plasma (12).

In contrast to quinine, quinidine is found to be only partially metabolized. Reports on the proportion of an administered dose excreted unchanged in the urine vary. Goodman and Gilman (6) state a range of 10 to 50% but Lyon and Degraff (13) narrow this range to between 20 and 30%.

The amount of quinidine excreted in urine is decreased with increasing urine pH (14). The decreased

excretion leads to an increase in serum concentration. Thus urine pH becomes an important variable to consider particularly during high dose therapy. If the urine becomes alkaline during disease or during alkalizing therapy, quinidine toxicity could develop (14).

Two major biotransformation products are formed when quinidine is given orally to humans. These have been identified by mass-spectroscopy and have the structures shown in Figure 2. Metabolite I results from the oxidative modification of the quinoline ring of quinidine, and the second metabolite II results from the hydroxylation of the quinuclidine ring.

A study by Kessler et al.(15) found that quinidine elimination appeared to be normal in patients both with either poor renal function or congestive heart failure.

4. Therapeutic/Toxic Levels

Despite the occurrence of considerable variation in the therapeutic blood levels of quinidine, it has been generally accepted that the therapeutic response can rarely be expected below 3 mcg/ml of plasma. Potentially toxic levels are reached above 5 mcg/ml and toxic reactions are almost certain to occur at levels above 10 mcg/ml. Thus it is desirable to maintain plasma levels within the relatively narrow range of 3-5 mcg/ml (5,6). Consequently a proper dosage form is necessary in order to ensure obtaining a therapeutic level while avoiding toxic

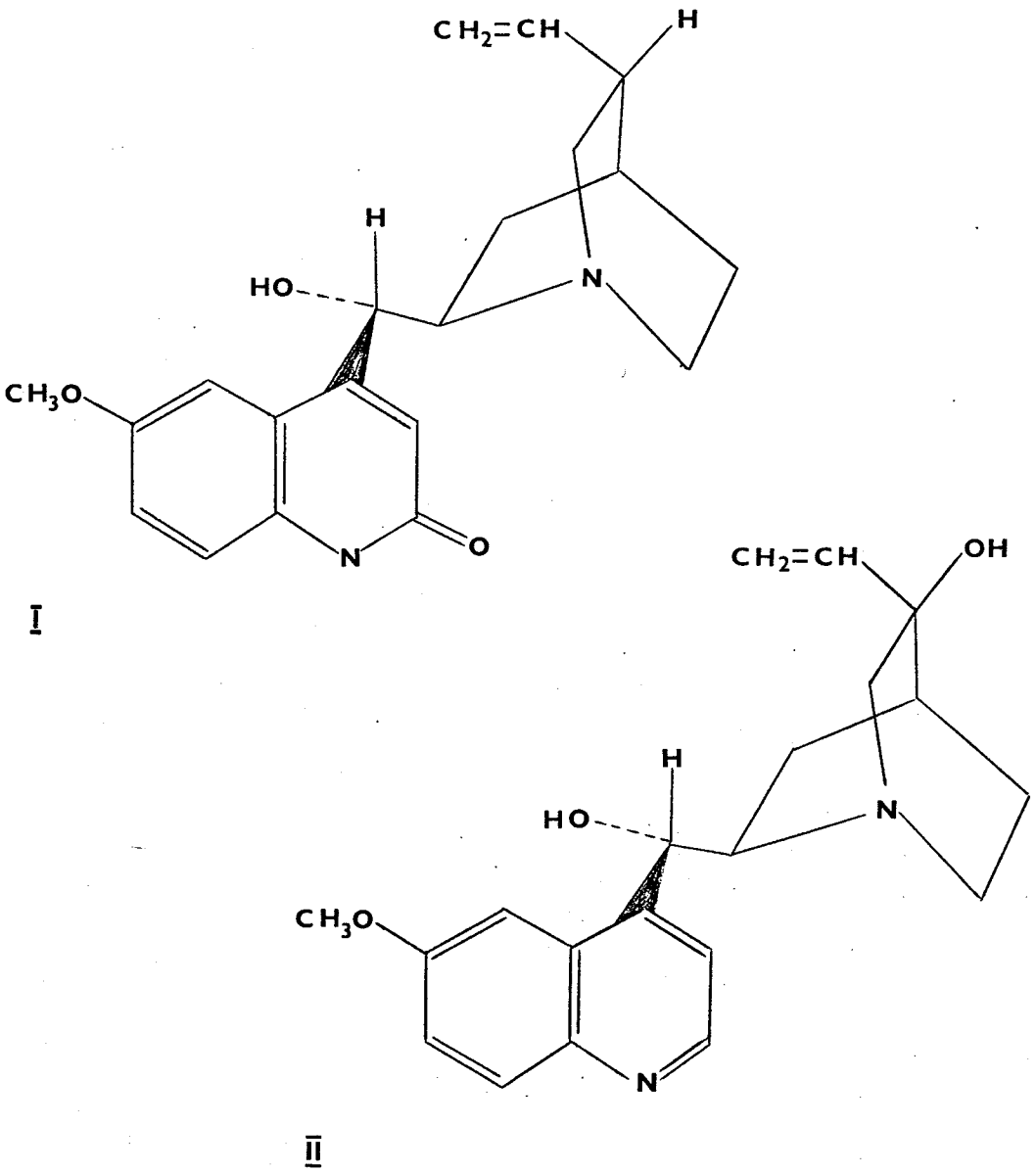

Figure 2. Major metabolites of quinidine in humans after oral administration (1).

effects.

5. Problems with Quinidine Sulfate

Quinidine monsulfate $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ hereafter referred to as quinidine sulfate, was the first salt of quinidine to be employed for oral administration. It is rapidly absorbed in the alkaline milieu of the proximal jejunum and can often be detected in the plasma within 15 minutes after an oral dose. A high initial plasma level is produced which decreases rapidly so that only about 15% of the maximum remains after 24 hours. It is therefore necessary to give quinidine sulfate several times a day (13).

The insoluble free base may precipitate on the surface of the salt crystals when they pass down into the alkaline intestinal regions, or the salt crystals may react with the bile salt or fatty acid to form extremely insoluble reaction products on their surfaces. Along with the many variable factors involved in tablet manufacturing, it is therefore not surprising that the drug is incompletely and irregularly absorbed (16).

In general therapeutic blood levels are achieved by a dose of from 200 to 400 mg of quinidine sulfate given orally 3 to 5 times a day for 1 to 3 days. Maintenance dose thereafter is from 300 to 600 mg daily (17).

At the time of arrhythmia patient motivation is high during periods of acute awareness or discomfort and there-

fore as many as 10 doses a day (2 tablets of standard 200 mg 5 times a day) will be accepted and the proper regimen followed. Following successful conversion however, this frequency of dosage is difficult to maintain. Patients tend to skip doses during periods in which the arrhythmia is diminished or absent, leading to rapid fall off of clinically effective blood levels. These patients are often found to revert to arrhythmia with all the consequences thereof.

Rapid absorption of quinidine sulfate has also resulted in numerous cases of drug toxicity (18,19). In an attempt to overcome this problem of rapid absorption various methods have been employed to slow down the absorption and maintain a steady level of drug in the blood for a longer period of time. One method depends on altering the type of acid salt having different solubility and dissociation constants. Bisulfate, gluconate, polygalacturonate and arabogalactone sulfate salts have been made for oral use. Although chemically equivalent to quinidine sulfate, variations in absorption profile show them to be not therapeutically equivalent (5,16).

Alternatively, or in conjunction with a change of salt, the types of pharmaceutical preparations of quinidine have been altered in an attempt to delay the absorption by physical means in the hope of achieving a sustained response. Thus quinidine is available in various salt forms compressed into tablets of differing degrees of hard-

ness and dissolution characteristics and/or with various coatings supposedly to minimize the nauseating characteristics of the drug as well as to provide a sustained release action.

I - B Sustained Release Dosage Forms

1. Rationale

The primary reason for wanting to increase the duration of action of a drug is to prolong its therapeutic effect, particularly where continuous action at an adequate level is essential for mitigation of the symptoms of the disease process itself. Drugs which are incorporated into long acting dosage forms are generally those whose chemistry, pharmacological properties and therapeutic indications and hazards have been well evaluated. The dosage form does not change the intrinsic effect of the drug, but it is specifically intended to alter the release of the drug to the fluids of the gastrointestinal tract (20).

Before designing a sustained release or prolonged action formulation of a drug, one should know the average half-life of elimination and its variation in a representative panel of human subjects. For drugs with a half life of elimination equal to or less than about 8 hours it is reasonable to attempt to prepare this type of specialized dosage form (21). Quinidine, a drug with an average half-life of about 7.2 hours in humans (22) falls into this

category.

The idealized sustained release product (Figure 3) releases an initial amount of drug sufficient to rapidly achieve a therapeutic level, and this is followed by an additional amount slowly released over time to produce a sustained, essentially unchanging plasma level of drug. The mechanism for attaining this condition is assumed to be the development of a steady-state, in which the amount of drug absorbed is equal to the amount of drug eliminated in the same period of time. The condition might also be described as zero-order absorption and equivalent pseudo-zero-order elimination, where the product of the clearance rate for plasma and the steady-state plasma concentration are represented by a zero-order rate constant (23).

The relationship between the first-order rate constant for plasma loss and clearance rate is:

$$\text{clearance rate} = k_e V_d \qquad \text{(Eq. 1)}$$

where k_e is the first-order rate constant for plasma loss (elimination) and V_d is the apparent volume of distribution of the drug.

For the case of a steady-state plasma or body level, the model that applies may be represented by:

$$A \xrightarrow{k_o} B \xrightarrow{k_e} C \qquad \text{(Eq. 2)}$$

where A = amount of drug in the intestine

B = amount of drug in the plasma or body compartments

C = amount of drug eliminated

k_o = zero-order rate constant for absorption

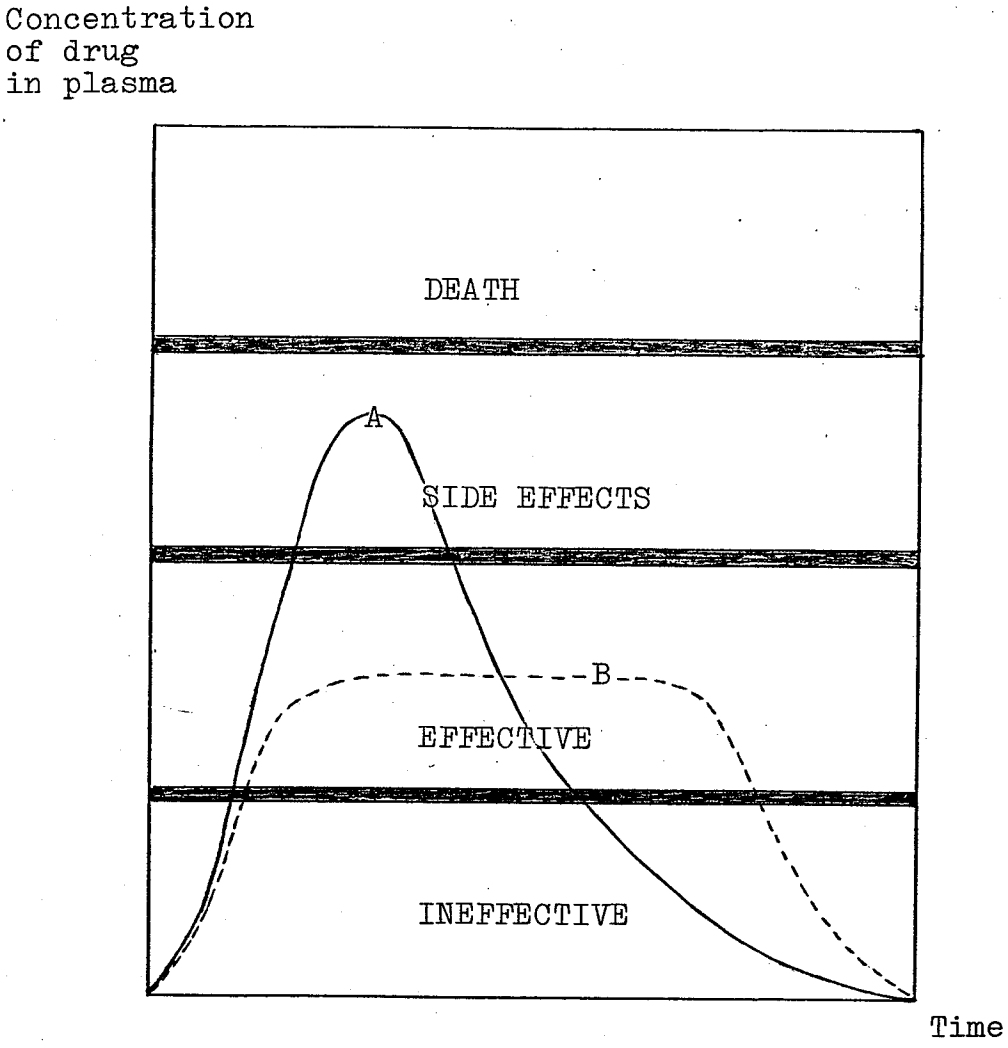

Figure 3. Hypothetical comparison of plasma concentration of drug versus time for equal doses of a quick release (A) and idealized sustained release preparation (B).

k_e = first-order rate constant for plasma loss

The rate of change in the B compartment is given by the equation:

$$\frac{dB}{dt} = k_o - k_eB \qquad \text{(Eq. 3)}$$

in which dB/dt at steady-state is equal to zero. Thus

$$\frac{dB}{dt} = 0 = k_o - k_eB \qquad \text{(Eq. 4)}$$

or

$$k_o = k_eB \qquad \text{(Eq. 5)}$$

Expressing B in concentration/volume terms, equation 5 becomes:

$$k_o = k_eC_bV_d \qquad \text{(Eq. 6)}$$

where C_b is the plasma concentration of the drug and V_d is its apparent volume of distribution. The development of equations 5 and 6 shows that absorption under these conditions must equal the product of the elimination rate constant k_e and the amount of drug in the plasma compartment B, or the product of the clearance rate k_eV_d and the concentration of drug in the plasma, C_b (23).

Turning to the actual situation in practice, experience suggests that the majority of sustained release formulation techniques produce formulations that release drug at roughly a first-order rather than a zero-order rate. Also in striving to obtain idealized results as shown with curve B in Figure 3, one must design the dosage form on the basis of an average half-life of elimination. However, the half-life of elimination varies from subject to

subject and patient to patient. Hence a product designed for the "average" will obviously give different plasma concentration-time curves from patient to patient. Similarly the apparent volume of distribution of a drug varies from patient to patient. Hence this will change the height of the curves when plasma concentration rather than the amount of drug in the body is plotted versus time (21).

2. Advantages

If a sustained release product acts as in the idealized example shown in Figure 3, many advantages become apparent:

1) Convenience
   a) Elimination of the necessity for taking drugs several times a day
   b) Prevention of missed doses due to a patients forgetfullness
   c) Economic advantage because nursing time for drug distribution and administration is kept to a minimum.
2) Maintenance of effective levels during sleep without needing to disturb the patient.
3) Improved control of drug levels by reduction of the variation in drug concentration in the blood and tissues commonly associated with the periodic administration of many drugs. This results in:
   a) a more uniform response

b) reduction of gastrointestinal irritation

c) reduction of systemic toxic effects.

4) If drug absorption is an active saturatable process the low concentrations of drug maintained at the absorption site by the sustained release product may lead to overall increased absorption.

3. Disadvantages

Even if a sustained release product is acting in the idealized fashion, there are some disadvantages:

1) The maintenance dose is generally based on an average elimination rate. Hence, if an individual has either a high or low rate of elimination because of differences in either metabolism or excretion, it may result in under medication or drug accumulation, respectively.

2) Accurate adjustment of dosage is generally not possible since sustained release dosage forms should not be broken in half or ground up. Increase in dosage is limited to the unit dose available or multiples thereof.

3) Many drugs are efficiently absorbed only in the upper part of the small intestine. Hence, component parts of a slow release dosage form may get past the absorbing area before full release of drug occurs.

4) If a drug is metabolised in crossing the gastro-

intestinal barrier during absorption, a fast release form of dosage may saturate the metabolic pathway allowing free drug transfer across the barrier. It is feasible that a greater percentage of an equivalent dose of active drug in a slow release form could be metabolised and thus fail to reach the circulation.

4. Basic Principles in the Design of a Sustained Release Drug Preparation

The pharmaceutical methods employed are based on protecting the drug by some release-delaying method or compound. One of the first patents taken out describing the construction of an oral sustained release preparation was by Lipowski in 1938 (24). The dosage form consisted of a number of small beads containing the dose of drug with several thicknesses of coating utilised to give a slow and constant release of drug on ingestion. The first practical oral sustained action dosage form, designed along Lipowski's principle was not marketed until 1952 (25). Since then many new and varied methods have been developed. The main principles used in manufacturing sustained release products today are set out below and some examples given:

1) Slowly disintegrating substances of a fat or wax nature or cellulose acetate phthalate is coated over the active substance. The material slowly

dissolves or disperses leaving the active substance free for absorption.

a) A part of the drug in a tablet is enclosed in a coat of the above mentioned materials. The most commonly used is an enteric coated tablet with a readily soluble layer containing a certain amount of drug to furnish quickly the initial dose. The inner core protected by the enteric coating contains the maintenance dose which is released over a period of some hours. By using several layers of the active drug each separated by a slowly dissolving coat, several maintenance doses can be gradually released leading to a more even effect.

b) The dose of active drug is divided among granules with coats of different thickness, so that one fraction of granules will disintegrate at once, another in 2-3 hours, a third in 6 hours after administration and so on. The coated granules can be dispensed in capsules or compressed into tablets together with a suitable carrier substance.

c) The active drug is incorporated homogeneously in granules of carrier substances which disintegrate at different rates.

d) The active drug is incorporated in a slowly dissolving tablet made of fat and wax substances mixed with vegetable fibres which swell when exposed to moisture, so that the tablet is gradually softened from the outside and the drug is released continuously by an erosion process.

Halley (26) obtained a patent in 1962 for an uncoated, non-enteric multicoloured tablet prepared from granules having different disintegration times. At least one of the groups of granules was uncoated and free from disintegration-retardent additives.

In the same year Christenson and Dale (27) were issued a patent for a compressed tablet containing a medicinal agent and a hydrophilic gum which rapidly hydrates and swells in aqueous fluids at body temperature to provide a mucilaginous-gel barrier on the surface of the tablet. This barrier provides a constant rate of release of the medicament from the tablet.

2) Non-digestible substances which enclose the active substance so that its free surface is greatly reduced and it can only diffuse very slowly.

a) The active soluble substance is evenly distributed in a tablet of an insoluble sub-

stance; the soluble substance slowly leaches out through the insoluble tablet cage into the gastrointestinal tract.

b) A granule preparation is made in which the drug is fused or embedded in a plastic material through which the drug is able to diffuse out slowly.

One early patent providing for leaching of a drug from a tablet medication was granted to Consolazio (28) in 1949. His patent was obtained for granules surrounded with a water insoluble, non-toxic, permeable membranous film. Leaching occurs when fluid dialyzes into the cellular compartments and the enclosed medication dialyzes out into the surrounding fluid. Also, when the cells become engorged with fluid, the sacs burst to liberate the medicament. When the tablet is completely leached of its active ingredient, the cellular stroma of the impregnating film remains and is eliminated by the system.

A patent issued to Levesque (29) in 1961 describes a composition consisting of a drug dispersed in a non-toxic plastic inert to gastrointestinal fluids. The plastic body may be referred to as an orally-ingestible plastic carrier taking the form of a foraminous body with drug contained in the pockets. This drug is accessible to liquids and may be removed by leaching without affecting the plastic carrier. Being a physical process the release of drug should be independent of the digestive process.

Polymers which can be used are polyethylene, polyethylmethyl acrylate, copolymers of methyl methacrylate, and the like.

3) The active substance is chemically bound to or absorbed by some physiologically inactive substance forming a non-absorbable compound, which slowly releases drug once exposed to the chemical milieu of the gastrointestinal fluids.

a) A complex of drug with ion-exchange resins. After being taken, the drug is exchanged for the ions of the digestive juices and thus becomes free for absorption. This should lead to an even liberation of drug as it is gradually eluted from the drug-resin combination on passage through the gastrointestinal tract.

b) The drug is incorporated in a macromolecular combination, e.g. polyvinylacetate, or in a colloid complex.

5. Bioavailability

It has been stated in the literature that "a preparation which actually succeeds in delaying the disintegration of the administered form, and thereby the absorption of the active ingredient to any dependable degree, inevitably does so at the expense of some loss in precision of dosage" (30). This necessarily introduces the concept of bioavailability which for an orally administered drug can be described as the rate and the extent to which the drug reaches the systemic circulation in an active form.