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SUPERINTENDENCIA DE INDUSTRIA Y COMERC

E. S.

Referencia: Expediente No. 12.152.138
Solicitud de Patente de Invención titulada: "Formulaciones de Apixaban"

Solicitante: Bristol-Myers Squibb Company y Pfizer, Inc.

MEMORIAL DE ALCANCE

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad Bristol-Myers Squibb Company y Pfizer, Inc, me permito dar alcance a mi memorial de Recurso de Reposición en contra de la Resolución 61405, presentado el 4 de diciembre de 2014.

1. Con el fin de brindar mayor sustento a la novedad y al nivel inventivo de la solicitud en estudio, objetado por su Despacho en la Resolución 61405, me permito profundizar en los argumentos presentados en el Recurso de Reposición presentado el 4 de diciembre de 2014:

1.1 **Novedad**

Con relación a la novedad de la presente solicitud de patente el solicitante ratifica que la presente solicitud es novedosa con relación a los documentos citados como arte previo por su Despacho WO2008031782 (D1), WO2010003811 (D2), WO2009135947 (D3), WO2006108643 (D4), US2006160841 (D5) y US2006069258 (D6).

Composición farmacéutica:

Es importante hacer notar que la presente composición es una composición farmacéutica. Una composición farmacéutica difiere de una composición ordinaria, por ejemplo suspensión, solución acuosa, mezcla en que la composición farmacéutica requiere (i) alto

grado de pureza y (ii) agentes e ingredientes a estar presentes en cantidades bien definidas. Ninguna de las citadas referencias D1-D6, revela una composición farmacéutica que incluya una cantidad efectiva terapéuticamente de apixaban en forma cristalina y particulada y un diluyente o portador aceptable farmacéuticamente, donde las partículas de apixaban en la composición farmacéutica tienen un D90 igual a o menor que 89 µm.

1.2 Nivel inventivo

La expectativa de la persona medianamente experta en la técnica a la fecha de presentación de la prioridad de la presente solicitud:

La solicitud expone el problema técnico a resolver el proporcionar formulaciones de apixaban cristalina que logran exposición consistente y la inhibición constante del factor Xa que conduce a la consistencia en el efecto terapéutico, lo que significa que la exposición in vivo de la composición farmacéutica es similar a aquella de la solución de apixaban y no se afecta por las diferencias en las velocidades de disolución (por favor ver párrafos [0005] y [0006].

Con el fin de predecir si la absorción será o no limitada por la velocidad de disolución de apixaban, la persona medianamente experta en la materia habría utilizado el BCS (el sistema de clasificación biofarmaceutica).

El BCS comenzó a ser un punto de referencia en la evaluación de la correlación de la disolución del fármaco in vitro y de la biodisponibilidad in vivo de fármacos dados oralmente tanto en Estados Unidos de América como en otros países (ver página 68, columna derecha del artículo Dressman, et al., Tecnología Farmacéutica, 68-76 (2001). La persona medianamente experta es por lo tanto familiar con esto y depende de este sistema de clasificación.

El BCS clasifica los fármacos en cuatro clases de acuerdo a sus propiedades de solubilidad y permeabilidad:

- En la clase I de acuerdo al BCS, los fármacos tienen una permeabilidad alta y una solubilidad alta.

- En la clase II de acuerdo al BCS, los fármacos tienen una alta permeabilidad y baja solubilidad. Su biodisponibilidad esta limitada por su velocidad de disolución.
- En la clase III de acuerdo al BCS los fármacos muestran permeabilidad baja y solubilidad alta. Su absorción está limitada por su velocidad de permeación pero no por la velocidad de disolución.
- En la clase IV de acuerdo al BCS los fármacos tienen una permeabilidad baja y una solubilidad baja. Estos fármacos tienen una biodisponibilidad pobre.

Dependiendo de la clasificación, la absorción del fármaco podría esperarse que varíe de depender fuertemente de la formulación y del método de fabricación (por ejemplo fármacos clase II) a depender casi de las propiedades de permeabilidad del fármaco (por ejemplo fármacos clase III).

Un fármaco será considerado un fármaco que tiene una solubilidad BCS alta si la dosis /proporción de solubilidad es 250 ml o menos y por lo tanto la solicitud menciona apixaban un fármaco de solubilidad alta como es definido por la BCS (por favor ver párrafos [0005] y [0011] de la solicitud). Un fármaco será considerado que tiene una permeabilidad alta BCS si más del 90% de la dosis administrada oralmente se absorbe en el intestino delgado.

Por lo tanto, el apixaban es un fármaco clase III de acuerdo a BCS. Ver por ejemplo, la última sección en la página 28 de la publicación del FDA's CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS sobre apixaban, que se encuentra en: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000ClinPharmR.pd.

Debido a que el apixaban cristalino es un fármaco clase III de acuerdo a BCS , la absorción del fármaco oral se espera que no sea limitado por la velocidad de disolución del fármaco. Esto está en línea con la solicitud al explicar que "limitaciones de la velocidad de disolución son solamente esperadas cuando la proporción de la solubilidad/dosis es mayor que 250 ml" y "uno esperaría que la proporción de la disolución para un fármaco que tiene solubilidad alta (como se definió por el sistema de clasificación biofarmacéutico) no sea limitado por el tamaño de partícula". Por lo tanto, la persona medianamente versada en la material no esperaría exposición ser dependiente de la velocidad de disolución de apixaban. La persona medianamente experta en la materia esperaría de esta forma que los factores que pueden

influenciar la velocidad de disolución, tal como el tamaño de partícula, no sean críticos para lograr una exposición constante..

Evaluación del nivel inventivo

Habiendo dejado claro los antecedentes científicos que forman la expectativa de la persona medianamente experta en la materia, se afirma que la persona medianamente experta hubiera esperado que la absorción del fármaco sea independiente de la velocidad de la disolución del apixaban y que la exposición no depende del tamaño de partícula del apixaban. Ante esta situación debe evaluarse el nivel inventivo.

La presente invención no es obvia a partir de los documentos del arte previo D1 a D6.

Los documentos D1 a D6 no sugieren la presente invención. Por ejemplo, los documentos D2 y D5 enseñan la biodisponibilidad de fármacos pobremente solubles pueden generalmente ser mejorados mediante el control y la reducción del tamaño de partícula (D2: página 1, párrafo segundo; D5; párrafo 3), pero esta enseñanza obviamente no aplica al apixaban porque el apixaban es un fármaco altamente soluble según la clase III del BCS. Los documentos D2 y D5 por consiguiente no se preocupan con el mejoramiento de la biodisponibilidad del apixaban, mucho menos con alcanzar una exposición constante. Lo mismo se sostiene como cierto para el documento D6, el cual no se preocupa con el mejoramiento de la biodisponibilidad del apixaban ni tampoco con lograr una exposición constante.

Como se mencionó previamente, los documentos D1, D3 y D4 no se preocupan con lograr una exposición in vivo consistente de una composición farmacéutica que comprende apixaban.

Resumen del nivel inventivo

La persona medianamente experta en la material era consiente de que el apixaban es un fármaco de clasificación de clase III según BCS. La persona medianamente experta no esperaría que la absorción del apixaban estuviera limitada por la velocidad de disolución. Esta expectativa no fue lograda por ninguna enseñanza del arte previo. La persona

medianamente experta no tenia por lo tanto ninguna razón en pensar acerca de intentar incrementar la velocidad de disolución del apixaban; y aún asumiendo que la persona medianamente experta lo hubiera hecho, esta persona no habría esperado que utilizar el apixaban cristalino con el tamaño de partícula citado hubiera conducido a una exposición constante. Por lo tanto, la presente invención involucra altura inventiva.

De conformidad con la anterior explicación complementaria, la presente invención no se deriva de manera obvia de los documentos D1 a D6 considerados solos o combinados.

Respetuosamente solicito que los anteriores argumentos adicionales sean tenidos en cuenta por su Despacho como parte de mi Recurso de Reposición presentado el 4 de Diciembre de 2014.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos: - Copia del artículo Dressman, et al., Pharmaceutical Technology.

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The BCS: Where Do We Go from Here?

Jennifer Dressman,* James Butler, John Hempenstall, and Christos Reppas

The Biopharmaceutical Classification System (BCS) has proven to be a valuable tool for the regulation of changes in oral drug products during scale-up and after product approval. This article reviews the criteria for classifying drugs according to the BCS and discusses further potential applications of the BCS, including the development of new drugs, the approval of generics, and the regulation of controlled-release products.

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Since the Biopharmaceutics Classification System (BCS) was introduced several years ago, it has become a benchmark in the regulation of bioequivalence of oral drug products both in the United States and abroad (1). The concept behind the BCS is that if two drug products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration. This concept can be summarized by the following equation

$$J = P_w C_w$$

in which J is the flux across the gut wall, P_w is the permeability of the gut wall to the drug, and C_w is the concentration profile at the gut wall. In terms of bioequivalence, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate bioequivalence of two drug products. The BCS thus enables manufacturers to reduce the costs of approving scale-up and post-approval changes (SUPAC) to certain oral drug products (rapidly dissolving products of Class I drugs; see Table I) without compromising public safety interests.

After several years of experience with the BCS, several issues have arisen: First, is the BCS fail safe? Second, should biowaivers be limited to Class I drugs, or could we extend them to other classes? Third, what about controlled-release dosage forms? Fourth, how early in the development process can we apply the BCS principles, and should the same cutoff values be applied to developing both new drug products and SUPAC applications? Although these issues already have been addressed to some extent in the literature, we must continue to gather data and experience in order to resolve them. In this article we have tried to summarize current thinking and to make some suggestions about where we should head with the BCS in the coming years.

Is the BCS fail safe?

FDA has set quite restrictive limitations on which drugs and drug products would be candidates for biowaivers under the BCS. The permeability requirement states that

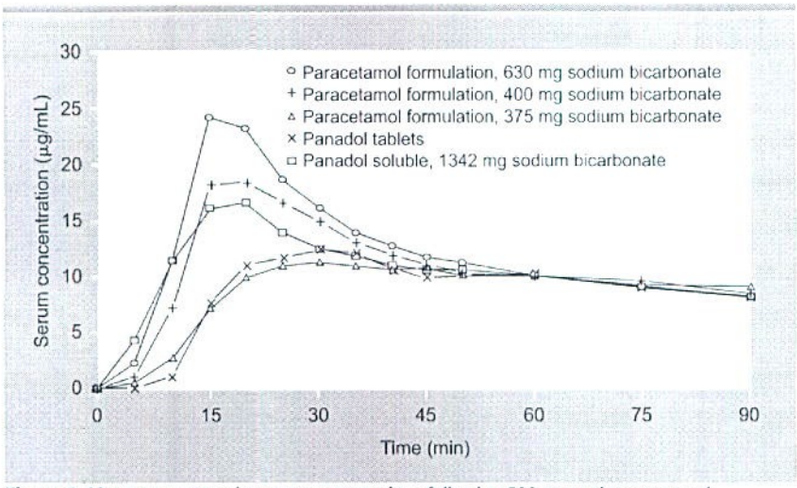

Figure 1: Mean paracetamol serum concentrations following 500 mg oral paracetamol.

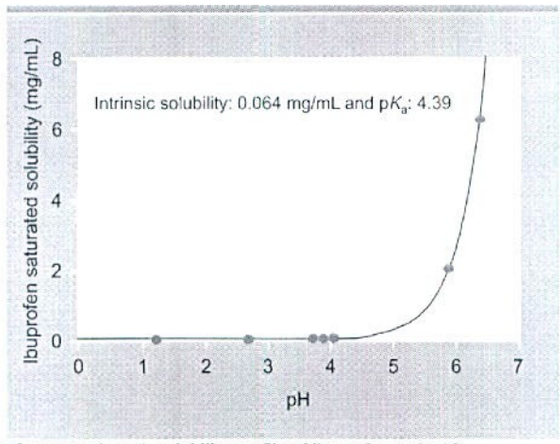

Figure 2: The pH–solubility profile of ibuprofen at 37 °C.

the permeability of the drug is commensurate with ≥90% absorption from a solution. The solubility requirement is that the dose-to-solubility ratio (D:S) of the drug must be ≤250 mL over a pH range of 1 to 7.5, and the dissolution requirement for the drug product is that dissolution must be >85% complete within 30 min (3). For products meeting these criteria, gastric emptying, rather than the release performance of the drug product, will be the key factor in determining the plasma profile; therefore, variability in the plasma profile will be under physiological control and not dictated by the dosage form.

Even for rapidly dissolving products of Class I drugs, however, it is possible to manufacture bioinequivalent products if excipients that modify gastric emptying are added. For example, Grattan et al. showed that the addition of sodium bicarbonate to the paracetamol (acetaminophen) formulation produced a faster and higher peak concentration of paracetamol in plasma (see Figure 1) even though the dissolution of the products in vitro was similar (4). This example shows that even though an excipient change may seem completely innocuous, if the new excipient alters the GI physiology, then it may very well alter the plasma profile also. Regulatory authorities must be very careful about defining what constitutes a "major change" to the formulation to address the potential physiological issues.

Are the BCS criteria too restrictive?

On the other hand, some drugs that are currently classified as Class II are consistently and completely absorbed after oral administration. These are typically poorly soluble weak acids with pK_a values of ≤4.5 and intrinsic solubilities (solubility of the un-ionized form) of ≥0.01 mg/mL. At pH values typical of the fasted state in the jejunum (about pH 6.5), these drugs will have solubilities of ≥1 mg/mL, resulting in fast and reliable dissolution of the drug. Currently, these drugs are classified as Class II drugs because they are poorly soluble at gastric pH, in which pH<< pK_a. Figure 2 shows a typical solubility versus pH profile for ibuprofen (5).

Because the small-intestinal transit time is more reliable, and in the fasted state, longer than the gastric residence time (generally on the order of 3 h), drugs with these physical characteristics will have ample time to be dissolved. As long as these drugs meet the permeability criterion, biowaivers for products that dissolve rapidly at pH values typical of the small intestine could be considered.

Table I: The biopharmaceutics classification system (2).

Class I	Class II
Highly soluble	Poorly soluble
Highly permeable	Highly permeable
Class III	**Class IV**
Highly soluble	Poorly soluble
Poorly permeable	Poorly permeable

Another issue is that the requirement for "not less than 85% dissolution within 30 min" may be too conservative in some dosing circumstances. Although in the fasted state it is quite possible that transit time through the stomach is short (half-emptying times for water as short as 8–10 min have been reported in the literature), if the dosage form is given with a meal, more than likely it will spend at least an hour or two in the stomach. Under these circumstances even slowly dissolving products still may show absorption patterns that are controlled by gastric emptying. A case example is that of certain immediate-release (IR) paracetamol tablets. Galia et al. showed that Panadol tablets release very slowly in simulated fed state conditions (milk) (6). It was subsequently shown by Reppas and Nicolaides that gastric emptying continues to be rate limiting to absorption of paracetamol, even in the fed state (7). These results suggest that in cases in which the drug is routinely administered with meals, it may be possible to relax the criteria for dissolution.

Can the BCS be extended to rapidly dissolving products of Class III substances?

It has been suggested by Blume and Schug that because the absorption of Class III drugs is essentially controlled by the gut wall permeability to the drug and not by the drug's solubility, biowaivers for rapidly dissolving products of Class III drugs also could be justified (8). Although in terms of the BCS theory this concept is clearly valid, some physiological issues would have to be addressed on a case-by-case basis. First, one must establish why the

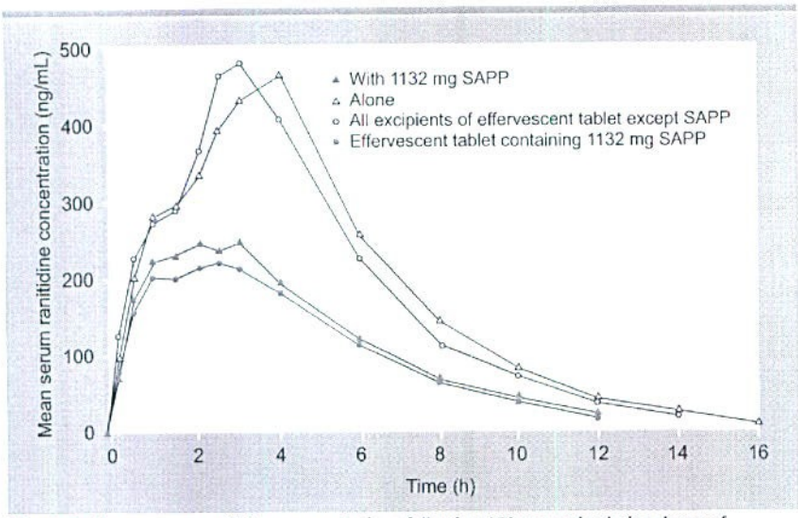

Figure 3: Mean serum ranitidine concentrations following 150 mg oral solution doses of ranitidine.

permeability of the gut wall to the drug is low. If the permeability is low but uniform along the entire GI tract (including the proximal colon), biowaivers might be considered. However, if there is an absorption window or a gradient in the permeability of the gut wall to the drug (with decreasing permeability in distal regions), excipients that accelerate gut motility could significantly reduce the contact time of the drug with the sites at which permeability is favorable and therefore lower the bioavailability of the drug.

Several compounds belonging to the H2 receptor antagonist group are classical examples of Class III drugs. It was shown in the literature some years ago that the shape of the plasma profile of cimetidine is highly dependent upon the gastric pH at the time of administration, with the characteristic double peak eliminated if the drug is given under elevated gastric pH conditions (9). Further, excipients that accelerate transit in the upper GI tract such as sodium acid pyrophosphate (10) and mannitol (11) have been clearly shown to reduce the extent of absorption of ranitidine and cimetidine, respectively. The results from Koch et al. are shown in Figure 3 (10). The 50% reduction in C_{peak} illustrates how important the influence of excipients that can alter the GI motility can be to the absorption of Class III drugs.

Can the BCS be applied to controlled-release drug products?

Under the current definition, the BCS is applicable only to immediate-release dosage forms because only the permeability in the jejunum is considered. To extend the BCS to controlled-release (CR) dosage forms, one must assess the permeability at all points in the GI tract where release of the drug is foreseen (12). As pointed out by Corrigan, it is unlikely that drugs with low permeability in either the ileum or colon will prove to be suitable candidates for CR dosage forms, let alone for biowaivers based on dissolution tests (5). He has proposed a useful subclassification scheme for CR products that is based on the site dependency of both the drug solubility and permeability.

A further consideration is the selection of appropriate dissolution conditions to simulate the release profile of the dosage form as it moves through the GI tract. Conditions for dissolution in the stomach, the small intestine, and the colon differ greatly. Important parameters that vary with location in the GI tract include the volume of fluid available for dissolution, osmolarity of the contents, the hydrodynamic (motility) conditions, and the secretion of various enzymes and other para-GI secretions that could potentially affect the release rate. Similarity of the dissolution profiles under all appropriate GI conditions would have to be shown for the two drug products. Although our understanding of the composition of lumenal contents as they move along the GI tract is far better than it was a decade ago, a more complete characterization is still needed. Still almost totally lacking is an understanding of the relationship between the hydrodynamics in the gut and those in the currently available dissolution testers. This throws a degree of uncertainty into the interpretation of dissolution results in terms of in vivo performance, even when the composition of the lumenal contents can be simulated well in the in vitro tests. Although a problem is posed by the limitation to establishing in vivo–in vitro correlations for IR products, the problem is compounded for CR dosage forms because the hydrodynamics at several sites within the GI tract must then be simulated. As a result, in vitro release profiles of CR dosage forms with different release mechanisms must be interpreted very cautiously.

Application of the BCS to the development of new drug substances

Because the BCS was originally developed as a basis for determining bioequivalence of oral drug products, it assumes that the drug is sufficiently well absorbed to make an oral dosage form feasible. When new drug substances are being developed, however, this assumption is not appropriate, and one must consider other factors than just the solubility and permeability to determine whether an oral dosage form can be successfully developed. An overview of the events in the GI tract following oral drug administration is depicted in Figure 4.

First, it should be remembered that the drug substance does not have to meet the Class I criteria of high permeability and solubility for the drug to be successfully formulated in an oral solid dosage form. Many Class II and Class III drugs are available on the market, and several that meet Class IV criteria are available (see Table II).

One problem with applying the BCS criteria to new drug substances is that, early in preformulation/formulation, the dose is not yet accurately known. So at this point, the D:S can only be expressed as a likely range. A helpful rule of thumb is that compounds with aqueous solubilities >100 µg/mL seldom exhibit dissolution rate–limited absorption. Alternatively, one can estimate the maximum absorbable dose on the basis of the usual volumes of GI fluids available under the anticipated dosing conditions and the solubility of the drug. With regard to the solubility of the drug, it may be useful to consider the

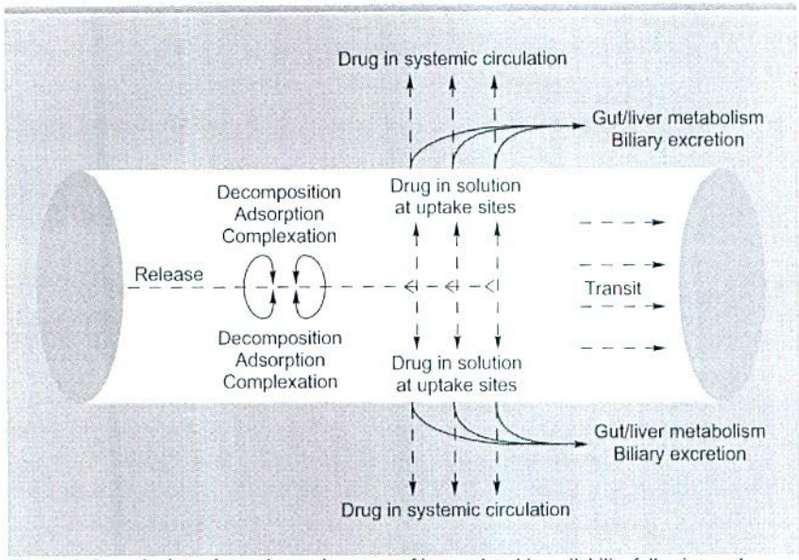

Figure 4: Steps in drug absorption and sources of incomplete bioavailability following oral administration of a solid dosage form.

Table II: Examples of orally administered Class I, II, III, and IV drugs.

Class I	Class II
Paracetamol	Atovaquone
Metoprolol	Carbamazepine
Theophylline	Danazol
	Glibenclamide
	Griseofulvin
	Ketoconazole
	Troglitazone
Class III	**Class IV**
Acyclovir	Chlorothiazide
Atenolol	Furosemide
Cimetidine	Cyclosporin A (?)
Ranitidine	Itraconazole (?)

physicochemical properties of the drug when deciding which media to use for the solubility determinations. For example, measuring solubility at all pH values recommended by the BCS is unnecessary for neutral compounds in early development. Later, when formulations are compared, dissolution data for the drug product over the entire GI pH range will be useful in establishing the robustness of release from the formulation under GI conditions. Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the GI fluids they can often be solubilized by the bile to a significant extent. Increases in solubility of one to two orders of magnitude are possible for compounds with log P values of ≥4. In some cases this would lead to a quite different interpretation of the chances for absorption in vivo. For promising compounds that are both ionizable and lipophilic, extensive solubility experiments in biorelevant media will help characterize the likely solubility behavior in vivo. Several publications address the composition and applications of these media (6,13–16). An alternative approach is to use aspirates from human volunteers, although volumes aspirated typically are small and the choice of experiments and apparatus therefore is limited (17).

Another issue is the use of 250 mL as the volume in which a dose must be dissolved. This amount is a conservative estimate of the volume of fluid available in the gut under fasting-state conditions and is based on the volume usually ingested along with the dosage form in a pharmacokinetic study (the so-called FDA glass of water). The actual volume available is a composite of the ingested fluid and the secretions of the GI tract. Although these amounts tend to be modest in the fasted state, secretions in the fed state contribute substantially to the overall fluid volume, which may be as high as 1.5 L in both the stomach and upper small intestine. Depending on whether drug administration is to be on an empty stomach or with meals, it is reasonable to adjust the volume used to assess the capacity of the GI fluids to dissolve the dose. A useful starting point would be to use a volume of 300 mL for the fasted stomach, 500 mL for the fasting small intestine, and up to 1 L for the postprandial stomach and small intestine.

A further consideration is the choice of model for assessing the permeability. Although perfusions in humans will produce the most reliable results (18) and are clearly the "gold standard," these require too much time and money to make them practicable for screening new drug substances. Many animal- and cell-culture models have been developed, each with its own set of advantages and disadvantages. For example, the *Caco 2* cells can be used with confidence to assess transcellular diffusion and can be standardized to ensure reproducible results, but they tend to underestimate paracellular and active mechanisms, cannot be employed to determine regional permeability within the gut, and tend to overestimate efflux via the P-glycoproteins. In situ perfusions in rats, although they are much better in terms of forecasting active transport and can be used to determine regional permeability, take more time and effort to produce a reliable permeability estimate. In any case, it is a good idea to have more than one permeability screen at the disposal of the laboratory in order to build confidence and robustness into the screening system.

If the drug is poorly soluble but highly permeable, formulation efforts will concentrate on improving the dissolution profile. For example, the combined effects of formulating the drug as amorphous solid dispersion and administering it in the fed state are shown for troglitazone in Figure 5. Combined, these two approaches shift the solubility–dissolution characteristics from those of a very poorly soluble drug (D:S >10,000 mL) to those of a drug product with a D:S within the range of values encountered in the gut after meals.

Figure 6 summarizes some further possibilities for improving the absorption of drugs with less than optimal permeability and solubility characteristics. If permeability rather than solubility is the main problem, formulation approaches are less numerous and less reliable. In extreme cases, it may be appropriate to consider developing another analog with more appropriate biopharmaceutical characteristics.

Even when allowance is made for the differences in solubility and permeability

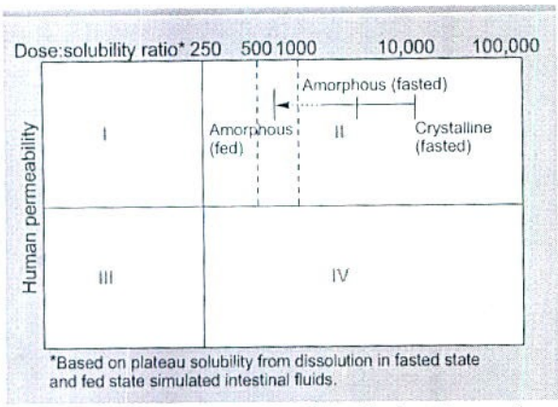

Figure 5: Troglitazone 200 mg: the effect of food and form on the potential for solubility limited bioavailability.

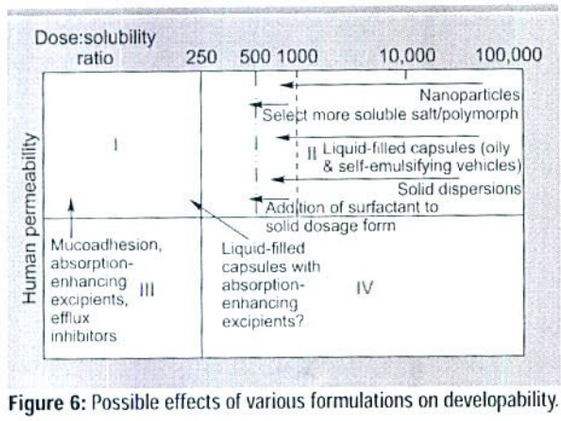

Figure 6: Possible effects of various formulations on developability.

requirements for oral drug product development vis-à-vis biowaiver criteria according to the BCS, further factors still must be considered for new drugs. These include the possibility of decomposition under GI conditions and the assessment of first-pass metabolism both in the gut wall and the liver. Appraising decomposition in the gut is relatively simple using biorelevant media and exposure times based on longest anticipated exposure times. For sensitive compounds, appropriate enzymes (e.g., pepsin and gastric lipases for the stomach, pancreatic enzymes for the jejunum, and bacterial enzymes for the colon) must be added to the medium in relevant concentrations. As far as first-pass metabolism in the gut wall is concerned, it may be possible to screen for metabolites in the permeability model depending on how the model is set up.

Summary

In summary, the BCS has proven to be an extremely useful tool for the regulation of bioequivalence of drug products during scale-up and postapproval. In the future, BCS concepts probably will be used increasingly in the early development of new drugs, including for analog selection as well as for initial formulation approaches. As our knowledge of GI physiology becomes more sophisticated, in vitro dissolution tests will be able to better simulate the conditions in the GI tract. This in turn will lead to more powerful predictions of in vivo performance and ultimately to a significant reduction in the number of animal and human studies required to optimize the formulation. Together with screens for other limitations to oral absorption, the BCS paves the way for (r)evolution in the drug development process.

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