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Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (paracetamol)

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Abstract

Literature data are reviewed on the properties of acetaminophen (paracetamol) related to the biopharmaceutics classification system (BCS). According to the current BCS criteria, acetaminophen is BCS Class III compound. Differences in composition seldom, if ever, have an effect on the extent of absorption. However, some studies show differences in rate of absorption between brands and formulations. In particular, sodium bicarbonate, present in some drug products, was reported to give an increase in the rate of absorption, probably caused by an effect on gastric emptying. In view of Marketing Authorizations (MAs) given in a number of countries to acetaminophen drug products with rapid onset of action, it is concluded that differences in rate of absorption were considered therapeutically not relevant by the Health Authorities. Moreover, in view of its therapeutic use, its wide therapeutic index and its uncomplicated pharmacokinetic properties, in vitro dissolution data collected according to the relevant Guidances can be safely used for declaring bioequivalence (BE) of two acetaminophen formulations. Therefore, accepting a biowaiver for immediate release (IR) acetaminophen solid oral drug products is considered scientifically justified, if the test product contains only those excipients reported in this paper in their usual amounts and the test product is rapidly dissolving, as well as the test product fulfils the criterion of similarity of dissolution profiles to the reference product.

INTRODUCTION

A monograph based on literature data is presented on acetaminophen, also widely known as paracetamol, with respect to its biopharmaceutical properties and the risk of waiving in vivo bioequivalence (BE) testing for the approval of new and/or reformulated immediate release (IR) solid oral dosage forms. The purpose and scope of these monographs has been discussed previously.[1] Briefly, the aim of the present study is to evaluate all pertinent data available from literature sources to assess the appropriateness of such a biowaiver from the biopharmaceutical point of view and also from the perspective of public health. Monographs have been published on atenolol,[1] chloroquine,[2] propranolol,[1] ranitidine,[3] and verapamil.[1]

EXPERIMENTAL

Published information was obtained from PubMed, up to 08/2004 and through the International Pharmaceutical Abstracts. Key words used were: paracetamol, acetaminophen, indication, solubility, polymorphism, partition coefficient, dose, permeability, stereospecificity, absorption, distribution, metabolism, excretion, and dissolution. No other selection criteria were used.

GENERAL CHARACTERISTICS

Acetaminophen has INN name: paracetamol. Its chemical name is N-(4-hydroxyphenyl)acetamide. Its structure is shown in Figure 1.

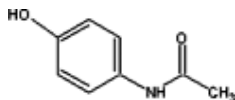


Figure 1. Structure of acetaminophen.

Therapeutic Indication and Therapeutic Index

Acetaminophen has analgesic and antipyretic properties and weak anti-inflammatory activity and is used in the symptomatic management of moderate pain and fever.[4] When taken at recommended doses it has an excellent safety profile, notably lacking the gastrointestinal (GI) side effects of aspirin and ibuprofen.[5]

However, acute overdosage with acetaminophen, whether accidental or deliberate, is relatively common and can be extremely serious. Ingestion of 10-15 g of acetaminophen by adults may cause severe hepatocellular necrosis and doses of 20-25 g are potentially fatal.[4],[6]

CHEMICAL PROPERTIES

Polymorphism

Three metastable forms of acetaminophen are known.[7-12] Orthorhombic acetaminophen is suitable for direct compression tableting and may also be slightly more soluble[13] but has been crystallized only in small quantities and the only commercially available form is monoclinic acetaminophen, the thermodynamically most stable modification.[14]

Solubility

One part of acetaminophen is soluble in 70 parts of water at room temperature[15],[16] and soluble 1 in 20 parts in boiling water.[4],[15] Other sources report an aqueous solubility of 14.7 mg/mL at 20°C,[17] 14.3 mg/mL at 25°C,[18] and 23.7 mg/mL at 37°C.[17]

Partition Coefficient

A logP (n-octanol/water) value of 0.2 has been measured.[19] Calculations using fragmentation methods based on atomic contributions to lipophilicity and by using the ClogP program (version 3.0, Biobyte Corp., Claremont, CA) gave values of 0.31(log P),[20] 0.49(ClogP),[21] and 0.89(log P).[21]

pKa

An acidic pKa of 9.5 at 25°C is reported.[16],[22]

Dose and Dosage Forms Strengths

The WHO recommended dose is 100-500 mg.[23] The optimum single dose for adults is 1 g.[24] Acetaminophen drug products with a marketing authorization (MA) are conventional IR tablets and capsules. However, MAs have been also given to granulates,[4],[25-27] effervescent tablets,[4],[25-27] and syrups.[4],[25-28] Drug products containing acetaminophen in combination with other active pharmaceutical ingredients (APIs) can have a MA.[4],[25-28] However, this monograph pertains to conventional IR solid oral dosage forms

containing acetaminophen as the sole API. Such formulations contain 500 mg per tablet.[25-28]

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

The absolute bioavailability (BA) in the fasted state was reported in the range 62%-89%.[29-32] The incomplete absolute BA is caused by a presystemic clearance of about 20% of an oral dose.[31-34] Peak plasma concentrations are reached within 0.17-1.2 h postdosing.[29],[35-43] The oral absolute BA was reported not to vary with the dose in range between 5 and 20 mg/kg,[31] but other authors reported AUC values and peak plasma concentrations to be dose-dependent at doses between 325 and 2000 mg.[43] Food reduces the absorption of acetaminophen tablets by increasing t_{max} and decreasing C_{max} values.[44],[45] Food effect is primarily due to delays in gastric emptying.[46] Although there are no direct published data on the absolute BA in the fed state, food does not affect the total amount of acetaminophen reaching the blood.[44],[45]

Permeability

Stewart et al.[47] using a single-pass intestinal rat perfusion technique, measured the wall permeability, P_w , for acetaminophen to be $0.86 \pm 0.5 \times 10^{-4}$ cm/s and they estimated the fraction absorbed to be 80%. Using rat perfusions, Lu et al.[48] estimated the dimensionless wall permeability, ρ , of acetaminophen 0.6 ± 0.2 whereas using the chronically isolated rat jejunal loop model they estimated the dimensionless effective wall permeability of 0.9 ± 0.1 . From acetaminophen's diffusivity value (6.86×10^{-4} cm²/min)[47] and assuming 0.2 cm for the radius of rat intestine, the wall permeability and the effective wall permeability in the rat can be calculated for the corresponding dimensionless numbers to be 0.34 and 0.54×10^{-4} cm/s, by using the relationship $P_w = P_w^*(D/R)$ [Note a], where D is the solute aqueous diffusivity and R is the radius of the intestine.[49] Recently, using the Ussing chamber, the permeability of acetaminophen through the rat jejunal wall was measured to be 0.09×10^{-4} cm/s.[50] This value is much lower than the values estimated from intestinal perfusion. However, the Ussing chamber technique leads to P_w values that are often lower than the values estimated from intestinal perfusions.[51]

Distribution

The apparent volume of distribution of acetaminophen is reported to be 0.69-1.36 L/kg.[22],[35],[52-56] Plasma protein binding is 20%-25% at usual therapeutic concentrations.[41],[56],[57] After overdosage, 20%-50% of the drug may be bound to proteins.[58] Binding to red blood cells is reported to be 10%-20%.[56] Acetaminophen crosses the placenta and is present in breast milk[56] with an average milk/plasma concentration ratio of about 1.24.[59] Of the acetaminophen present in breast milk, 85% is bound to milk proteins.[60]

Metabolism and Excretion

Acetaminophen is metabolized by microsomal enzymes in the liver, with 85%-90% of the drug undergoing glucuronidation and sulfation to inactive metabolites that are eliminated in the urine. A smaller amount is conjugated with cysteine and mercapturic acid and only 5% of the drug is eliminated unchanged in the urine.[61] Total urinary recovery of acetaminophen in 24 h is reported to be 71.5%-95%, as free and/or conjugated.[56],[62-64] The clearance ranges between 11.8 and 22.3 L/h[32],[35],[36],[53],[62],[65],[66] and the total plasma clearance of acetaminophen has been reported to show a 12% difference after 20 and 5 mg/kg doses.[31] The elimination half life is reported to be between 1.9 and 4.3 h.[22],[32],[53],[54],[56],[62]

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

The relative BA of acetaminophen from solid dosage forms has been studied frequently. Most studies were carried out in humans, but two animal studies have been also reported. In rabbits, no significant differences in C_{max} and AUC_0 were found between rapidly disintegrating tablets and conventional tablets.[67] In dogs, no significant differences were found between two conventional tablets.[68]

Studies in humans in general show similar results. While most studies report no difference in extent of absorption, differences in rate of absorption between drug products were sometimes found. In one of the earliest relevant studies, Sotiropoulos et al.[69] evaluated three tablets and one liquid acetaminophen product for their comparative BA, reporting a BA relative to the liquid dosage form of 82%, 87%, and 92%, respectively. However, based on urinary excretion data, these differences were not statistically significant and only the amount excreted from 0 to 4 h varied with the formulation. Hekimoglu et al.[70] evaluated the BA of three brands of acetaminophen tablets in comparison to a solution. BAs of the brands relative to the solution were 98%, 95% and 99%, respectively, with differences being not statistically significant. However, the amount excreted during the first hour varied among the formulations. Walter-Sack et al.[71] compared a solid and a liquid oral dosage forms that did not show differences in the AUC_{0-12 h} and in C_{max}. An evaluation of four brands of acetaminophen tablets by Hekimoglu et al.[72] did not display statistically significant differences in BA, but differences in the urinary excretion during the first hours, reflecting differences in rate of absorption, were observed. Retaco et al.[73] studied the BA of two lots of paracetamol tablets and although the total amount excreted in urine was similar between the two formulations, differences were found during the early stages of the absorption process. Dominguez et al.[74] using urinary excretion data, reported nonsignificant differences in the rates and relative BA's ranging from 94% to 131% of three commercial formulations versus the innovator. Bababola et al.[75] reported a study of two commercial brands versus the innovator. While the absorption rate of one brand, as indicated by t_{max}, was significantly shorter than those of the innovator, the extent of absorption, as indicated by AUC, was comparable among the three brands. Sevilla-Tirado et al.[76] compared three tablets, one effervescent tablet, and a powder sachet, and found that the extent of absorption, expressed as AUC₀, did not exhibit differences between formulations. However, for the rate of absorption, expressed as C_{max} and partial AUC values, differences were observed; two tablets had a rate of absorption as fast as the effervescent tablet, but the other tablet, being the innovator, had a somewhat slower absorption rate.[76]

Of special interest are recently introduced acetaminophen products containing large amounts of sodium bicarbonate. Such dosage forms are claimed to have fast drug absorption. Grattan et al.[37] compared the pharmacokinetics of one commercially available acetaminophen tablet and one soluble commercially available acetaminophen tablet with two development tablet formulations, one containing 400 mg sodium bicarbonate and the other containing 630 mg sodium bicarbonate. The results demonstrated that addition of 630 mg sodium bicarbonate increased the rate of absorption of acetaminophen relative to both the conventional tablets and the soluble tablets, as indicated by a shorter t_{max} and higher C_{max}, whereas the addition of 400 mg sodium bicarbonate increased the absorption rate of acetaminophen relative to conventional acetaminophen tablets only. These findings were recently confirmed by Kelly et al.[77] who compared an acetaminophen tablet containing 630 mg sodium bicarbonate with a conventional tablet. The rate of absorption, indicated by t_{50%} and t_{90%}, was about twice as fast compared to the conventional tablets, both in the fasted state and the fed state. It was suggested that a combination of faster disintegration and gastric emptying of the tablets containing sodium bicarbonate is responsible for the faster rate of absorption. The differences in gastric emptying were thought to be more pronounced in the fasted state and the differences in disintegration more pronounced in the fed state.[77] The data of Grattan et al. and Kelly et al. are supported by earlier reports that effervescent tablets show faster absorption characteristics than conventional solid tablets.[76],[78]

The excipients used in IR solid oral dosage forms having a MA in Germany (DE), Finland (FI), Greece (GR), and The Netherlands (NL) are shown in Table 1. In previous monographs, MAs of solid oral dosage forms were taken as indicators that these drug products had successfully passed an in vivo BE test.[1] However, for acetaminophen, this cannot be assumed. The bioavailability committee of the regulatory authorities of DE classified acetaminophen in 1998 as an API for which in vivo BE testing was not required.[79] Also in NL, acetaminophen is on such a list.[80] The DE list was recently withdrawn, but the MA granted under that provision remained in place.[81]

Table 1. Excipients^a Present in Acetaminophen^b IR Solid Oral Drug Products^c with a Marketing Authorization (MA) in Germany (DE), Finland (FI), Greece (GR), and The Netherlands (NL)

Carnauba wax	FI (1), NL (2)
Cellulose	DE (3-13), FI (1, 14-16), GR (17), NL (2, 18-27)
Croscarmellose	NL (21)
Croscarmellose sodium	DE (4, 8, 11), FI (15), GR (28), NL (29-31)
Crospovidone	DE (3, 10, 32), NL (27)
Ethyl parahydroxybenzoate	NL (33)
Gelatin	DE (3, 34), FI (14), NL (29-31)
Glyceryl palmitostearate	NL (24)
Hydroxypropylcellulose	DE (35), GR (36), NL (19, 23, 27)
Hypromellose	FI (1, 37-39), GR (17), NL (2, 21, 40, 41)
Lactose	NL (22)
Macrogol	FI (1), NL (2, 21)
Magnesium stearate	DE (3, 4, 6-8, 10, 11, 13, 42), FI (1, 14-16, 37), GR (17, 43), NL (2, 19, 21-23, 25-27, 29-31, 33)
Maize starch	DE (4, 6-11, 13, 42, 44, 45), FI (1, 15, 38, 39, 46), GR (28, 36, 43), NL (2, 18, 20-22, 27, 29-31, 33, 40, 41, 47-52)
Maize starch, pregelatinised	DE (32), NL (2, 22, 47)
Methyl parahydroxybenzoate	NL (33)
Polydextrose	FI (1), NL (2)
Potassium sorbate	DE (42), FI (1, 38, 39), GR (36, 43), NL (2, 40, 41)
Potato starch	FI (37), NL (24, 33)
Potato starch, modified	NL (23)
Povidone	DE (4-8, 11-13, 21, 32, 44, 53), FI (1, 15, 16, 37-39, 46), GR (28,36), NL (2, 24, 25, 33, 40, 41, 48-52)
Propyl parahydroxybenzoate	NL (33)
Propylene glycol	FI (37)
Silica	DE (3-11, 42, 44, 45), FI (14, 15, 46), GR (43), NL (18-20, 23, 27)
Sodium cyclamate	NL (24)
Sodium hydrogen carbonate	FI (1), NL (2)
Sodium lauryl sulfate	NL (29)
Sodium starch glycolate	DE (5, 9,44, 45, 53), FI (14, 16, 46), GR (17), NL (18-20, 22, 24-26, 48-52)
Sodium stearate	NL (18, 20)
Starch, pregelatinised	FI (1, 16, 38, 39), NL (26, 41)
Starch, soluble	NL (40)
Stearic acid	DE (5-7, 9, 10, 35, 44, 45, 53), FI (16, 38, 39, 46), GR (28, 36), NL (33, 40, 41, 47-52)
Stearic palmitic acid	DE (12, 32)
Talc	DE (3, 4, 8, 11, 34, 44), FI (14, 15, 37-39, 46), GR (17, 36), NL (21, 33, 40, 41)
Triacetin	FI (1, 38, 39), GR (36), NL (2, 40, 41)

1, Panadol Zapp 500 mg tabletti, kalvopäällysteinen; 2, Panadol Zapp, filmomhulde tablett 500 mg; 3, Captin® Tabletten 500 mg; 4, Fensum® 500 Tabletten; 5, Mono Praecimed® Tabletten; 6, Paracetamol 500-1 A Pharma Tabletten; 7, Paracetamol 500 HEXAL® bei Fieber und Schmerzen Tabletten; 8, Paracetamol 500 von ct Tabletten; 9, Paracetamol BC 500 mg Tabletten; 10, Paracetamol beta® 500 Tabletten; 11, Paracetamol-ratiopharm® 500 Tabletten 12, Paracetamol Tabletten Lichtenstein; 13, Sinpro® N Tabletten; 14, Para-Tabs 500 mg tabletti; 15, Paracetamol-ratiopharm 500 mg tabletti; 16, PARAMAX Rap 500 mg tabletti; 17, Apotel Uni-Pharma filmcoated tablets 500 mg; 18, Pijnstillende en koortsverlagende paracetamol-tabletten 500 mg Samenwerkende Apothekers, tabletten; 19, Pijnstillende en koortsverlagende paracetamol tabletten 160 mg/250 mg Samenwerkende Apothekers, tabletten; 20, Paracetamol 500 mg Therapeuticon, tabletten; 21, Democyl 500, omhulde tabletten 500 mg; 22, Paracetamol 500 PCH, tabletten 500 mg (MA number: 50480); 23, Paracetamol 500 PCH, tabletten 500 mg (MA number: 50954); 24, Kinderparacetamol CF 100 mg, tabletten; 25, Paracetamol CF 500 mg, tabletten; 26, Paracetamol, tabletten 500 mg (MA holder: Imgroma); 27, Paracetamol Sandoz 500, tabletten 500 mg; 28, Depon Bristol,

Squibb tab 500 mg; 29, Momentum, capsules 500 mg; 30, Paracetamol 500 mg, tabletten (MA holder: KATWIJK FARMA); 31, Paracetamol 500 mg Katwijk, tabletten; 32, Paracetamol Sandoz® 500 mg Tabletten; 33, Paracetamol 500, tabletten 500 mg (MA holder: H. Ten Herkel); 34, Ben-u-ron® Kapseln; 35, Enelfa® Tabletten; 36, Panadol Sterling tab 500 mg; 37, PAMOL® 500 mg, kalvopäällysteinen tabletti; 38, Panadol 500 mg tabletti, kalvopäällysteinen; 39, Panadol Forte 1g tabletti, kalvopäällysteinen; 40, Panadol Gladde Tablet, tabletten 500 mg; 41, Panadol 1000 mg Artrose, omhulde tabletten; 42, Paracetamol STADA® 500 mg Tabletten; 43, Apotel Uni-Pharma tab 500 mg; 44, Benuron® Tabletten; 45, Paedialgon® Tabletten; 46, Paraceon® 500 mg tabletit; 47, Paracetamol Alpharma 500 mg, tabletten; 48, Paracetamol FLX 500 mg, tabletten; 49, Paracetamol 500 mg, tabletten (MA holder: GENRX); 50, Paracetamol 500 mg, tabletten (MA holder: HEALTHYPHARM); 51, Paracetamol CF 500 mg, tabletten; 52, Paracetamol 500 mg, tabletten (MA holder: Delphi Pharmaceuticals); 53, Paracetamol AL 500 Tabletten.

a Printing ink, colorants and flavors are not included.

b Drug products containing other drug substances than acetaminophen are excluded.

c Excluded are dosage forms that are swallowed by the patient in liquid form: effervescent tablets, orodispersible tablets, dispersible tablets, oral powders and granulates, oral suspension, oral solution, and powders for oral solution. Chewable tablets are also excluded.

The NL list is still valid for national applications.[80] It is also possible that FI and GR have granted MAs without requiring in vivo BE studies. So, these MAs not necessarily indicate that in vivo BE studies among these drug products have been conducted. Differences in rate of absorption between the different acetaminophen drug products are tolerated by regulatory authorities, as can be derived from the MA's granted to acetaminophen syrups and effervescent tablets, showing faster absorption than conventional solid dosage forms.

Dissolution and In Vitro-In Vivo Correlation

The USP 26 specification for acetaminophen tablets is not less than 80% (Q) of the labeled amount dissolved in 30 min in 900 mL pH 5.8 phosphate buffer using the paddle apparatus operated at 50 rpm.[82]

To the best of our knowledge there are only three reports that claim some kind of correlation of in vitro dissolution data with in vivo data. Sotiropoulos et al.[69] found that the rate and amount of acetaminophen excreted may be related to the in vitro dissolution rate in 0.1 N HCL, using the rotating basket apparatus at 85 rpm. The T50% values for in vitro dissolution were 50 min for a generic tablet and 1 min for Tylenol® and Datriil®, respectively, whereas the relative BAs with respect to acetaminophen powder were 82%, 87%, and 92%, for the generic tablet, Tylenol® and Datriil®, respectively, showing that the in vitro dissolution rates needed to be vastly different to predict differences in relative BAs. Dominguez et al.[74] established a weak correlation between mean dissolution time and mean residence time. In vitro dissolution data in Dominguez et al.[74] study were obtained in phosphate buffer pH 5.8 using the rotating paddle apparatus at 50 rpm.

Rostami-Hodjegan et al.[83] using the USP dissolution method with medium pH 5.8, but at a stirring speed of 30 rpm instead of 50 rpm, established a level A correlation between the percentage dissolved in vitro and percentage absorbed in vivo. The authors explained this correlation from the low stirring speed, by which the in vitro dissolution kinetics under that condition was supposed to resemble the population gastric emptying kinetics in vivo.

In contrast, there are many reports showing no correlation between in vitro dissolution and in vivo data. Bababola et al.[75] has suggested that the systemic absorption of acetaminophen might not be dissolution rate limited and hence using in vitro dissolution rate studies alone to establish BE of acetaminophen tablets should be done with caution.[75] This is supported by the study of Retaco et al., in which in vivo BE was observed despite differences in in vitro dissolution, carried out in phosphate buffer pH 5.8 and in HCl 0.1 N in the paddle apparatus operated at 50 rpm.[73] Similar results were observed in the study of Hekimoglu et al., where a comparison of the dissolution data obtained in phosphate buffer pH 5.8, at 50 rpm, using the paddle apparatus, from three brands of acetaminophen tablets, did show differences in in vitro dissolution although their BA's relative to a solution were close to 100% for all brands.

Moreover, a series of studies show that different acetaminophen formulations meeting USP dissolution criteria were all bioequivalent.[37],[44],[72],[83]

In vivo dissolution of IR tablets in media simulating the contents of the GI lumen in the fasting state is usually rapid.[68],[84],[85] The same is true in media simulating the fed state conditions in the small intestine.[68],[84] Although in the fed stomach[77] or under conditions that simulate the fed intragastric conditions[68],[84],[85] dissolution can be significantly retarded, data in humans[77] and in dogs[68] suggest that at least the products that are currently in the European market are unlikely to show dissolution dependent rate in absorption in the fed state because the gastric emptying limits the absorption kinetics.[68],[77]

Although delayed in vivo dissolution has been observed in the fed state[71],[77] and this has been reported to affect blood levels,[71] products that are currently in the European market are unlikely to show dissolution dependent BA.[68],[77]

DISCUSSION

Solubility

Acetaminophen is not substantially ionized at pH less than 9 and, therefore, its solubility does not vary with the pH. For the highest strength, i.e., 500 mg, the dose to solubility ratio is 21 mL, taken the value of 23.7 mg/mL at 37 °C for the solubility. This value is less than 250 mL, the cut-off limit for an API to be highly soluble as defined by the present BCS Guidances.[86],[87]

Permeability

To date, permeability data for acetaminophen have been collected with rat perfusions and/or using the Ussing chamber only. Although internal standards were not used, these data suggest that acetaminophen should be classified as low permeability compound because wall permeability is less than the generally considered borderline value of $2-4 \times 10^{-4}$ cm/s.[88] More important is the fraction dose absorbed in humans, which is the basis of the permeability classification in the present BCS Guidances.[86],[87] The percent of dose absorbed can be estimated by adding the percent biotransformed during first-pass from the liver to the absolute BA. This suggests that the fraction of dose absorbed is higher than 80%. The cut-off limit for an API to be classified as highly permeable by the present BCS Guidances[86],[87] is a fraction of dose absorbed to be higher than 90%.

These data lead to classifying acetaminophen as low permeable, although on the borderline. Classifying acetaminophen as low permeable has also been suggested by others.[21],[89] Intestinal metabolism, i.e., glucuronidation and/or sulfation, after administration, will occur to the test product as much as to the reference product. In in vivo BE studies, the data are always collected on a crossover basis, so, these effects of intestinal metabolism cancel each other out.

Surrogate Techniques for In Vivo Bioequivalence Testing

Only in vitro dissolution has been used as a surrogate technique to detect in vivo bioequivalence up to now. For an API that is on the borderline between BCS Class I and III, in vitro dissolution can be expected to be over-discriminatory, detecting differences in in vitro dissolution between products that are actually in vivo bioequivalent. Also, in vivo-in vitro correlations are not expected. Most experimental results confirm these expectations, although few workers have found limited correlations, as reported above. The important question is whether in vitro dissolution is able to detect bioequivalent products and if so, then by which method. Only one report claimed that the USP test at pH 5.8 was inadequate to detect in vivo bioequivalence.[74] However, in this study bioequivalence was declared on the basis of urinary excretion data, using the wider confidence intervals without showing the power of the statistical analysis.

Risks for Bioequivalence Caused by Excipients and/or Manufacturing Parameters

As discussed above, literature suggests BE of acetaminophen products with respect to extent of absorption. However, absorption rate, differences between brands and test formulations have been observed, as in the case of tablets containing high amounts of sodium

bicarbonate. It was suggested that these differences were caused by differences in disintegration and/or gastric emptying rates. Although data in humans are lacking, data in rabbits suggest that high concentrations of osmotically active excipients such as mannitol may have an impact on the t_{max} of acetaminophen.[67]

Patient's Risks Associated with Bioequivalence

When considering a biowaiver for a drug substance, its therapeutic use and therapeutic index also needs to be taken into account.[86],[87] The therapeutic indications of acetaminophen are not critical and there is a wide difference between the usual therapeutic dose and toxic doses. So it can be assumed that acetaminophen is not a narrow therapeutic index drug.

CONCLUSION

According to the present regulations, acetaminophen is a BCS class III API, although possessing properties borderline to BCS Class I. Other workers also classified acetaminophen as BCS Class III.[89] The classification of Kasim et al.[21] as BCS Class IV is probably due to use of incorrect solubility data.

Both of the current BCS Guidances allow the possibility for a biowaiver exclusively for BCS class I drugs.[86],[87] The permeability of acetaminophen, just below the critical value of 90% absorbed, formally excludes it from the present biowaiver criteria. However, extensions of the present requirements to BCS Class III APIs have received increasing attention.[90-93]

Formulation effects giving rises to differences in the extent of absorption, i.e., to differences between the AUC of the test product and the AUC of the reference product, are not known and can be further minimized if the test product is formulated with excipients used in those drug products already having an MA. Comparative in vitro dissolution testing will provide even greater assurance of BE with respect to at least the extent of absorption.

Absorption rate differences, i.e., differences between the C_{max} of the test product and the C_{max} of the reference product, cannot be ruled out. But there is some evidence that comparative in vitro dissolution testing is capable of detecting such rate differences. And the risk of differences in absorption rates between a test product and the reference product can be further minimized if it is assured that the test product does not contain osmotically active agents in large quantities, and/or agents that can modify gastric emptying rates, i.e., the test product contains only those excipients shown in Table 1, in amounts usually present in IR solid oral dosage forms. An indication of the amounts usually present in dosage forms for drug products with a MA in the USA can be obtained from the FDA Inactive Ingredients Database.[94]

Lastly, even when comparative in vitro dissolution testing was to fail to detect an in vivo difference in rate of absorption, the consequences in terms of public health are not considered serious, as is evident from the MA's of existing drug products that can be supposed to differ in their rates of absorption.

In summary, it is concluded that for IR acetaminophen solid oral dosage forms, containing acetaminophen as sole API, refraining from in vivo BE studies is scientifically justified, provided that: the dosage form is rapidly dissolving under the conditions stated in the Guidances[86],[87] and

the test product contains only those excipients identified in Table 1, in the amounts normally used in IR solid oral dosage forms,[94] and

the test product shows dissolution profile similarity to the reference product under the conditions stated in the Guidances.[86],[87] It may be questioned if comparative dissolution testing in three different pHs as described in the present Guidance's is meaningful as acetaminophen remains unionized in all relevant pHs.[86],[87] However, maybe some excipients might cause of difference in dissolution profiles, making comparative dissolution testing at three different pH values not redundant.

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Endnotes

a In most situations P_{aq}^* (the dimensionless aqueous permeability[49]) is not rate limiting, i.e., the controlling resistance is . Thus, the equation could also be written as $P_{eff} = (D/R)$.

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