Dissolution profile of paracetamol generics

1 – Introduction

The pharmaceutical industry had an estimated turnover of $773 billion in 2008, 1 however not all of this revenue was taken as profit; a significant cost goes into research and industry guideline compliance. With regards to new generic medications, proving bioequivalence is crucial to success, however necessary in vivo testing can be costly. 2 Drugs which meet certain Biopharmaceutics Classification System (BCS) criteria may be exempt from these expensive tests and can be permitted a biowaiver. 3 This allows in vitro dissolution testing in place of in vivo plasma analysis. Paracetamol is one such drug that has qualities which place it at the borderline of biowaiver suitability. 3 It is the world's most commonly used analgesic4 and the question arises as to whether all preparations are as effective as each other? More specifically we ask, is there is any significant difference between the dissolution profile of paracetamol generics? This literature review is in preparation of experimental tests designed to ascertain if there is any difference in dissolution profile of eight bioequivalent preparations listed on the Australian Pharmaceutical Benefits Scheme (PBS), and whether this difference may correlate to a clinical significance in such a common place drug.

2 – Search Strategy

All data was sourced through internet databases, i. e. Medline, Pubmed, and the Cochrane Library. The search engines Google Scholar and UWA library were also utilized. Keywords included. KEY WORDS – Paracetamol, acetaminophen, bioequivalent (therapeutic equivalency), Delayed-action Preparations, Pharmaceutical Preparations, Tablets, Drug Compounding,

Chemistry, Pharmaceutical, Observer Variation, Dissolution, Metabolism, in vitro, in vivo, IVIVC, Drug Content, Bioavailability and Correlation. Boolean searching was utilised to broaden or narrow search results and once appropriate articles were sourced, citing and cited articles were also evaluated.

3 – Paracetamol

3. 1 – History

Paracetamol (acetaminophen) is one of the world's most popular drugs for the treatment of pain and fever. 4 It was first synthesized in 1878 by Morse, and was used clinically for the first time in 1887 by von Merring. 4, 5 Paracetamol fell into obscurity shortly thereafter in favour of other chemically related drugs such as phenacetin. 5 However, phenacetin was later found to be nephrotoxic, and the search for a substitute arose. 5 In 1950, a study from Brodie and Axelrod rediscovered paracetamol's suitable analgesic properties. 4 Although, this drug did not experience widespread acceptance until the 1970's due to unfounded concerns about safety; but from then on, it became the most commonly used medication for pain. 4 In many countries, such as the United Kingdom, paracetamol sales have exceeded those of aspirin since 1980. 4

3. 2 – Physicochemical properties

Paracetamol or N-(4-hydroxyphenyl) acetamide, is a white crystalline powder with a melting point of 168-172'C (Martindale). It is sparingly soluble in water, ie. one part of paracetamol is soluble in 70 parts of water at room temperature. 3 It is also freely soluble in alcohol. (Martindale) Paracetamol

shows maximal UV absorption at a wavelength of 249nm and is reported to have a pKa of 9. 5 at 25’C. 3

3. 3 – Pharmacology & Pharmacokinetics

3. 3. 1 – Pharmacodynamics & Mechanism of Action

The exact mechanism of action of paracetamol has remained largely unknown for some time. 6-9 For years it has been thought to inhibit the enzyme cyclooxygenase (COX) in a similar manner to non-steroidal anti-inflammatory drugs, however definitive proof of analgesia and antipyresis being dependent on COX inhibition is still lacking. 4 Recently, two independent groups have produced experimental data that has demonstrated that analgesia involves the potentiation of the cannabinoid vanilloid tone in the brain and in the dorsal root ganglia. 4 Blockade of cannabinoid (CB1) receptors in rats has eliminated any analgesic properties of paracetamol and suggests that paracetamol is in fact a cannabinomimetic. 4

3. 3. 2 – Pharmacokinetics

3. 3. 2. 1 – Absorption & Bioavailability: Paracetamol has been reported to have a bioavailability of 62%-89% in those of a fasted state, 3, 8 this divergence from absolute bioavailability is attributed to first pass hepatic metabolism. Peak plasma concentrations are reached between 0. 17-2. 0 hours post-dosing. 10 As expected, food has been shown to reduce absorption by increasing tmax and decreasing Cmax values. Food has not been shown to affect the amount of acetaminophen reaching the blood. 3

3. 3. 2. 2 – Distribution: Paracetamol has a reported volume of distribution of 0. 69-1. 36L/Kg. 11 Around 20%-25% of the drug is bound to plasma proteins at therapeutic dosages; however this value has been shown to increase to 20%-50% in over dosage. Paracetamol has also been shown to cross the placenta, and has a 1. 24 milk/plasma ratio in breast milk. 3 Paracetamol is an ADEC category A drug, i. e. it is safe to use in pregnancy, as well as breastfeeding. 9

3. 3. 2. 3 – Metabolism & Excretion: Around 85%-90% of paracetamol is metabolized within the liver via the process of glucuronidation and sulfation. 3 These inactive metabolites are then eliminated by the kidney in the urine. Approximately 5% of paracetamol is passed out unchanged in the urine, the remaining drug is conjugated with cysteine and mercapturic acid. 3, 8 The half-life of paracetamol has been reported as 1. 9 – 4. 3 hours3, 8, 10 but longer in those with renal impairment.

3. 4 – Indication

Paracetamol is indicated in the symptomatic treatment of mild-to-moderate pain as well as fever3, 9 and has also been described to have mild anti-inflammatory properties. 3

3. 5 – Dose & Dosage Forms

For adults, the optimal single dose of paracetamol is 1g, 3, 9 with a maximum dose of 4g daily. 9 Hepatocellular necrosis can occur from doses of 10-15g, and death may result in doses in excess of 20-25g. 3 Paracetamol is available in many dosage forms, as a single active pharmaceutical ingredient (API), or in combination with other analgesics such as codeine (Panadeine), dextropropoxyphene (Di-Gesic), metoclopramide (Metomax), as

well as in combination with decongestants such as pseudoephedrine in cold-and-flu preparations. 9 This drug is available as immediate release (IR) tablets, sustained release (SR) tablets, chewable, elixirs, IV injections and suppositories. 9

4 – Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is a method of grouping active pharmaceutical ingredients (API) based on their solubility and intestinal permeability. 12-16 The system allows for easy identification of those drugs whose in vivo absorption can be easily anticipated based on their in vitro dissolution. 12, 15, 16 This implies that two different products containing the same drug will have the same rate and extent of absorption if, over time, they both have the same concentration profile at the intestinal membrane. 12 Since it is the dissolution profile of a drug which determines its concentration profile in the intestinal lumen, comparability of this parameter in vitro should produce comparable absorption results in vivo. 12 In reality however, only those drugs with high permeability which are formulated into IR preparations can be easily and reliably applied to this logic. 12, 15, 16

4. 1 – BCS Drug Classes

There are four classes within the BCS to which a drug can be assigned (as outlined in figure 1). Class I is comprised of those drugs with high permeability and solubility, these drugs are expected to be well absorbed and, providing dissolution is slower than gastric emptying, show a good correlation between in vitro dissolution rate and the rate and extent of in vivo absorption (IVIVC). 12, 15, 16 Class II drugs also have high permeability

but their solubility is low which ensures in vivo dissolution is the rate limiting step in drug absorption and thus IVIVC is expected. 12 Class III drugs have a low permeability with high solubility, traditionally these drugs were believed to have little or no IVIVC, 12 however recent studies have shown that if a class III drug is very rapidly dissolving then a correlation may exist. 18, 19 Finally Class IV drugs have both low permeability and solubility these drugs are not expected to show any IVIVC. 12

For each of the four BCS classes “ a drug substance is considered highly soluble when the highest [IR] dose strength is soluble in 250mL or less of aqueous media over the pH range of 1-7. 5.” 16 The permeability of a drug is considered high if greater than 90% of a dose is absorbed across the intestinal membrane. 16, 20 Using these definitions, paracetamol is classified as a BCS class III drug but it is also described as borderline class I because it is only just on the cusp of low permeability. 3

4. 2 – Utility of the BCS

The genius of the BCS is that it allows easy identification of drug candidates for which relatively cheap and fast in vitro dissolution testing can replace the more expensive, time consuming and invasive in vivo absorption testing. 2 The system does away with complex bioavailability modeling that must account for fasted and fed states as well as cyclical changes in motility and gastric emptying. 12, 14 The impact of the BCS on the pharmaceutical industry was so great that in 2006, creator Dr. Gordon Amidon was awarded the International Pharmaceutical Federation (FIP) Distinguished Scientist Award. 21

5 – Correlation between in vitro dissolution and bioavailability

Following the introduction of the BCS a great deal of research was conducted exploring the power of IVIVC. It became a main focus not just of the pharmaceutical industry but also of academia and regulatory authorities. 2 IVIVC became popular because it can be used as a substitute for resource intensive bioavailability testing; the concept has essentially improved the speed and cost of drug development as well as quality control in pharmaceutical manufacturing. 2

5. 1 – Bioavailability and Bioequivalence

Bioavailability is an important concept because it determines the efficacy, safety and reproducibility of the therapeutic effect of drugs and the many formulations in which they come. 22 For the purpose of drugs that produce a systemic therapeutic effect, the Australian Therapeutic Goods Administration (TGA)22 defines bioavailability as " the extent and the rate at which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation." Bioavailability is therefore inherently linked to drug absorption and may also be predicted using IVIVC as defined by the BCS.

If two pharmaceutically equivalent (same active ingredient and content in the same formulation) products have the same bioavailability they are considered bioequivalent and will essentially have the same efficacy and safety. Bioequivalence is important because it is the basis for which innovator medicines can be substituted with generics.

5. 2 – Strength of in vitro – in vivo correlations

The BCS is a predictive tool for determining which drugs will have an IVIVC. Table 1 demonstrates that under the BCS only class II along with some class I drugs are expected to have IVIVCs. 12 Research subsequent to Dr. Amidon's first BCS publication has generally upheld his initial findings however exceptions to the rule have been found.

5. 2. 1 – Drugs with IVIVC

The BCS suggests that if the bioavailability of a drug is dissolution rate limited then a good IVIVC should be possible. This notion has been demonstrated for flutamide a very poorly soluble high dose compound which is not expected to have IVIVC but has dissolution rate limited absorption. 23 A paper published by Posti, Katila & Kostiainen23 concluded that there is a strong IVIVC for flutamide and this was identified on four separate occasions where bioavailability was studied. All four studies were of single dose, cross over design and each subsequent study increased the number of subjects tested (study I: n = 6, Study IV: n = 24). The strength of the papers methodology provides good support for its conclusions however this was undermined by a lack of documented statistical analysis.

Much more compelling evidence comes from a study by Sakuma et. al. 24 which was able to show an IVIVC for two BCS class I drugs after they received an enteric coating, thus eliminating the possibility that gastric emptying was the rate limiting step. The results were statistically significant, however the tablets were tested in rat models rather than human subjects and the dissolution test may not have adequately reflected the in vivo environment that enteric coated tablets are subject to. 24 Further studies in

human subjects demonstrating the difference in IVIVC between enteric and non-enteric coated tablets could not be identified in the literature.

There are hundreds of other drugs which have an IVIVC and these are neither limited to BCS class II drugs or drugs with dissolution rate limited absorption. Theophylline is a BCS class IV drug and yet in a complete cross over study of four different theophylline tablets the in vitro dissolution was able to significantly predict several in vivo pharmacokinetic parameters (AUC & Cmax) which dictate bioavailability. 25 The study was small (n = 6) and not all pharmacokinetic parameters could be correlated. Other common drug examples with IVIVC include digoxin, 26 rifampicin, 27 diclofenac28 and lamotrigine29 and these are by no means exhaustive.

5. 2. 2 – Drugs without IVIVC

Not all drugs have an IVIVC and this can also include some BCS class II drugs. A research paper by Frick, Moller & Wirbitzki 199830 demonstrated that the in vitro dissolution of glimepiride (BCS class II) is not comparable to dissolution in vivo. The study employed a single dose cross-over design with 12 subjects, Latin-Square statistical analysis was employed and the results were assumed to be significant however not all the data was accompanied by supporting confidence values. No correlation was possible because the solubility of glimepiride is low and strongly pH dependent. 30

Unlike glimepiride, ciprofloxacin a quinolone antibiotic, is classified as a BCS class III drug and as a consequence would not be predicted to have an IVIVC. Correspondingly, when tested for this possibility none could be found

between dissolution and any of the parameters for bioavailability (Tmax, Cmax, AUC & Ka). 31

5. 2. 3 – Strength of BCS in predicting IVIVC

There is a wide variance between IVIVCs that are anticipated according to the BCS and those that are actually demonstrated after experimental testing. Examples have been provided where both expected and unexpected correlations occur and this suggests that the BCS system while helpful should only be taken as a guide. Laboratory testing is still the only reliable method for determining if a correlation is occurs. Paracetamol is a BCS class III medication and as such is not expected to demonstrate strong IVIVC. Given the fact that paracetamol has a wide therapeutic index and the BCS can only be used as a guide, a safe and useable IVIVC may still exist.

5. 2. 4 – IVIVC of paracetamol

The prodigious use, vast quantities manufactured and the presence of many generic products in the marketplace makes paracetamol a prime candidate for IVIVC testing. In 1996 Retaco et. al. 32 conducted a small crossover study using five subjects to assess whether an IVIVC for paracetamol may exist. The study stated that the absorption data from “ saliva partially correlated with those found in vitro,” 32 this however is not a valid conclusion. One of the subjects studied produced in vivo data that opposed a correlation and this anomaly was further confounded by the fact that statistical analysis was not performed on the IVIVC but rather covered the in vitro and in vivo data separately. This pilot study was later contradicted by Babalola et. al. 33 who found limited IVIVCs and suggested that paracetamol absorption may not be

limited by its dissolution rate. Similarly, a thorough, well designed, complete crossover (4×4) study that balanced for first order residual effects, suggested that it was dangerous to use dissolution as the sole test for paracetamol bioequivalence. 34 Interestingly, all of these studies demonstrated bioequivalence between the various products of paracetamol even if they showed no IVIVC.

6 – Biowaiver for bioequivalence testing

In vivo bioequivalence studies are required to ascertain the potential differences in bioavailability between innovator and generic products which, may lead to therapeutic inequivalence. A biowaiver provides the authority and grounds for fiscally intensive bioequivalence testing to be replaced by more tolerable in vitro testing. For the most part, IVIVC must first be established in order for a drug to be considered for a biowaiver. The BCS has outlined properties of solid preparations which require evaluation in biowaivers, i. e. solubility, permeability, and dissolution rate. 35 In addition to this, the non-critical therapeutic range of a drug should also be considered35 and this is the basis for which paracetamol has gained biowaiver status. 3 It should be noted that products produced by the same manufacturer at the same site are exempt from bioequivalence studies. 36

6. 1 – Paracetamol Biowaiver

Several characteristics must be considered when a drug presents as a candidate for a biowaiver through dissolution testing. Paracetamol is not a classic biowaiver candidate because it is classified as a BCS Class III drug, it does however possess properties borderline to Class I3 and these enable it to fulfill the requirements of a biowaiver.

6. 2 – Biowaiver requirements

6. 2. 1 – Characteristics relevant to the active ingredient

6. 2. 1. 1 – Risk of therapeutic failure or adverse drug reactions– i. e. the need for critical plasma concentrations. When considering a biowaiver for a drug substance, its therapeutic use and therapeutic index also needs to be taken into account. 16 In the case of paracetamol, the therapeutic indications are not critical, and there is a wide difference between the usual therapeutic dose and toxic doses. Given that an optimal therapeutic dose for an adult is 1g, and that hepatocellular necrosis can result from ingestion of 10-15g, it can be assumed that paracetamol is not a narrow therapeutic index drug. 3

6. 2. 1. 2 – Risk of bioinequivalence: Previous evidence of bioavailability problems for an active substance can complicate the justification of in vitro dissolution bioequivalence correlation. 35 For paracetamol, the absolute bioavailability has not been shown to vary between therapeutic dose ranges of 5-20mg/kg. 3 Other studies have also demonstrated that bioequivalence in different IR paracetamol preparations is achievable. 11, 32, 37

6. 2. 1. 3 – Solubility: If a drug is highly water soluble it generally lends to exemption of bioequivalence testing, however polymorphism and particle size are major determinants of dissolution and must be considered. 35 A drug is considered highly soluble if the amount contained in a preparation of maximal strength dissolves in 250mL of three buffered solutions ranging between a pH of 1-8 at 37’C. 35 Paracetamol has a pKa of 9. 5 and is therefore not substantially ionized at a pH less than 9. As a result, it can be said that its solubility does not vary with pH. 3 The highest strength IR

preparation of paracetamol is 500mg. Experimentally, this has been shown to dissolve in 21mL, 3 which is significantly less than the 250mL that is required by the BCS guidance to prove solubility. 16, 35

6. 2. 1. 4 – Pharmacokinetic properties: High permeability which is typically indicated by a linear absorption pattern, reduces the potential influence of an IR preparation on bioavailability. 35 For paracetamol, the permeability is slightly below the cut-off value of 90%, i. e. one study by Stewart et al. 38 found permeability to be 80% once absorbed. This formally excludes paracetamol from being considered for a biowaiver, although extensions to BCS Class III drugs have recently been given more attention. 20, 39

6. 2. 2 – Characteristics relevant to the medicinal product

6. 2. 2. 1 – Rapid dissolution: Dissolution profiles can be regarded as equal when more than 85% of the active ingredient is dissolved within 15 minutes. 35 This comparison must occur between test and reference product in three buffers which with a pH range between 1-8, at 37’C. 35 Paracetamol tablets have been shown to dissolve within 30 minutes, 32 however this rate does not satisfy BCS exemption standards.

6. 2. 2. 2 – Excipients: Those included are to be well established and not in atypically large quantities. Kalantzi et al. 3 details a table of acceptable excipients which can be used within paracetamol IR tablet formulations which are considered for in vitro dissolution biowaiver.

6. 2. 2. 3 – Manufacture: Critical parameters such as particle size and polymorphism should be addressed and documentation should be provided in the dossier that is submitted to TGA. 35 Paracetamol has three metastable

forms, the only commercially available from is the monoclinic acetaminophen as it is the most thermodynamically stable polymorph. 3

From review of the literature, it can be concluded that in vivo bioequivalence testing of solid, oral IR paracetamol dosage forms may not be necessary. This can be justified given that a paracetamol formulation can be shown to: 3

- Rapidly dissolve under USP guidelines
- Contain only the acceptable excipients, in usual quantities
- Demonstrates dissolution profile similar to reference product under conditions stated in USP guidelines

7 – Statement of Purpose

7. 1 – Aim & hypothesis

The purpose of the proposed study is to compare the dissolution profiles of bioequivalent IR paracetamol preparations listed on the PBS. In particular, comparisons between every preparation will be made, rather than a single comparison against a referent. We hypothesize that there will be no significant difference between the dissolution profile of IR paracetamol tablets when dissolved according to USP specifications.

7. 2 – Methodology

We propose to analyse the dissolution profiles of eight PBS listed bioequivalent paracetamol preparations, namely; APO-paracetamol, Chemmart Paracetamol, Dymadon P, Febridol, Panamax, Paracetamol Sandoz, Paralgin, and Terry White Chemist’s Paracetamol. Sixteen tablets of each preparation will be dissolved in compliance with USP dissolution test for tablets and capsules, using apparatus II. As mandated, tablets are to be

dissolved in 900mL phosphate buffer at a pH of 5. 8 with a paddle set to 50rpm. Samples will be taken at intervals of 2, 5, 10, 15, 30, 45, 60 minutes in concordance with practice by Dominguez et al. 34 these aliquots will be examined for paracetamol by UV spectrophotometry at 289nm. These data will be statistically analysed by ANOVA.

7. 3 – Timeline

Date

Tasks to be performed

Work Deadlines

Week 11 (15. 03 – 21. 03)

Create paracetamol standard curves, Test expected dissolution time, Order materials, Source test tablets, Visit school of statistics for advice.

Literature Review Due Monday 15th March 12pm

Week 12 (22. 03 – 28. 03)

Testing of tablets 1 & 2: Dissolution & UV vis

Week 13 (29. 03 – 04. 04)

Testing of tablets 3 & 4: Dissolution & UV vis

Week 14 (05. 04 – 11. 04)

Testing of tablets 5 & 6: Dissolution & UV vis

Week 15 (12. 04 – 18. 04)

Testing of tablets 7 & 8: Dissolution & UV vis

Week 16 (19. 04 – 25. 04)

Week in lieu to finish experiments in case of unforeseen circumstances

Week 17 (26. 04 – 02. 05)

Data collation & statistical analysis

Briefing on the writing of the final report Wed 28. 04 2pm

Week 18 (03. 05 – 09. 05)

Writing draft report

Week 19 (10. 05-16. 05)

Editing final draft report

Week 20 (17. 05 – 23. 05)

Powerpoint presentation format

1st Draft Research Project Due Friday 21st May

Week 21 (24. 05 – 30. 05)

Correcting draft report

Week 22 (31. 05 – 06. 06)

Amending powerpoint presentation

Final report due Mon 31. 05 12pm

Week 23 (07. 06 – 13. 06)

Amending final report

Week 24 (14. 06 – 20. 06)

Presentation rehearsal

Seminars, submission of amended report to pharmacy office