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Application of Surge Dose[®] technology to prednisolone

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1 Executive Summary

Imaginot has evaluated the potential for application of its patented Surge Dose[®] technology to prednisolone, a potent glucocorticosteroid drug used for a wide range of clinical indications. The physicochemical, pharmacokinetic (PK) and pharmacodynamic (PD) properties of this drug have been reviewed to determine if faster dissolution of a solid dosage form is likely to lead to improved therapeutic outcomes.

In general, slow dissolution of solid dosage forms leads to slow gastric emptying of the drug in solution. Low concentrations provide a low driving force across the gastrointestinal wall, leading to slow absorption and lower peak plasma concentrations (C_{max}). Imaginot has demonstrated that slow absorption of paracetamol can lead to a high proportion of low C_{max} values which may be sub-therapeutic. In contrast, fast dissolution of a drug in co-administered water will be emptied more rapidly from the stomach, and the higher concentrations will lead to faster absorption and higher peak plasma concentrations.

Reformulating a drug such as prednisolone that is readily absorbed across the intestinal mucosa to ensure rapid dissolution in vivo is likely to lead to:

- (i) rapid absorption and rapid onset of peak effect
- (ii) a reduction in slow absorption occasions, associated with low, possibly sub-therapeutic plasma concentrations

The solubility of prednisolone relative to typical therapeutic doses means that absorption will be dissolution rate limited particularly when higher doses of the drug are used.

Although the drug is readily absorbed from the gastro-intestinal tract with around 100 % oral bioavailability, there is significant inter-subject variability which in some cases results in sub-therapeutic dosing. The bioavailability is reported to depend on the dissolution rate of tablet formulations particularly when used at high doses.

While there is generally a lag time between the maximum effect and the time to C_{max} (T_{max}) as a result of distribution to the site of action and high levels of protein binding, there is evidence of faster absorption from solutions of prednisolone, which suggests an opportunity to achieve faster and more consistent absorption with a fast dissolving tablet formulation. Pre-dissolved formulations offer faster absorption with T_{max} values around 40 – 55 minutes compared with 1 – 3 hours for conventional tablets. Liquid suspensions and solutions are available to achieve this faster absorption but these are less convenient than swallow tablets and may have associated palatability problems. An orally disintegrating tablet utilising the more soluble sodium phosphate salt of prednisolone, which is designed to dissolve in the mouth before swallowing, has comparable PK to oral solutions.

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Application of Surge Dose[®] technology to prednisolone shows that the rate of in vitro dissolution can be significantly increased compared with commercial tablets using relatively low levels of sodium bicarbonate with an equimolar quantity of an organic acid such as fumaric acid. Unoptimised Surge Dose[®] tablets tested in 900 mL 0.0033 M HCl using USP dissolution apparatus 2 exceeded 70 % dissolution after 180 seconds at 30 rpm, and 60 % at 300 seconds at 0 rpm. It was notable that the two strengths of commercial tablets showed quite different in vitro dissolution profiles consistent with the reported high in vivo variability and solubility limitations at higher doses. The 5 mg commercial tablet achieved 42 % dissolution after 180 seconds at 30 rpm and the 25 mg achieved only 10 %.

The results from Imaginot's proof of concept PK study in 25 fasted subjects showed faster absorption from Surge Dose[®] formulations than conventional slower dissolving tablets, with good in vitro in vivo correlations (IVIVC). Further PK studies in fasted subjects with the two NSAIDs (non steroidal anti-inflammatory drugs) lornoxicam and diclofenac showed that optimized Surge Dose[®] formulations achieved improved PK with faster absorption and higher C_{max} comparable with parenteral administration.

Based on these PK studies, optimized Surge Dose[®] prednisolone tablets are expected to demonstrate faster in vivo absorption and faster onset of action than standard tablets and even dispersible tablets with PK similar to solutions. The formulations described in this report have not been optimized with respect to pH modulating agents (pHMA) and water uptake agents (WUA) but provide a starting point for further development and clinical evaluation. Faster in vivo dissolution, regardless of the gastric acidity, should lead to a consistent and increased rate of absorption with the benefit of faster onset of action and improved therapeutic outcomes for a higher proportion of patients. Biomarkers can be used to measure prednisolone PD which would allow the clinical effects of the drug to be monitored in a PK study in healthy subjects.

Based on available published data, Surge Dose[®] prednisolone tablets would be expected to provide faster absorption than regular tablets with T_{max} values of 1 – 2 hours, to at least match if not better absorption from ODTs with T_{max} values in the region of 1.1 – 1.3 hours, and to approach those values reported for solutions in the range 0.6 – 0.9 hours.

Compared with liquid formulations and ODTs, fast dissolving Surge Dose[®] tablets are convenient to carry and take and eliminate the problems of and palatability. In addition it is possible to use conventional manufacturing methods and the readily available less soluble prednisolone base rather than more soluble salts.

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2 Introduction

2.1 Surge Dose[®] drug delivery technology

The Surge Dose[®] formulation technology for ultra-fast dissolution and fast absorption of oral drugs has been developed by Imaginot Pty Ltd <Imaginot>, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] formulations provide faster and more consistent drug absorption resulting in faster and more reliable onset of action. Surge Dose[®] significantly reduces mean and median times to peak plasma drug concentration (T_{max}) and reduces absorption variability as demonstrated for paracetamol (acetaminophen, APAP) and lornoxicam in PK studies in man. Based on PK-PD modelling, Surge Dose[®] paracetamol is predicted to achieve improved efficacy as the variable absorption of currently marketed tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy in some patients.

Imaginot's Surge Dose[®] technology provides clinical benefits for drugs with:

- a clinical requirement for fast and reproducible onset of action when taken on demand for acute episodic indications
- high passive absorption without significant intestinal metabolism or active efflux
- evidence of variable absorption associated with the gastric emptying cycle and/or *in vivo* dissolution seen when comparing absorption from aqueous drug solutions and solid dosage forms
- a direct temporal relationship between plasma concentrations and PD effects with no significant lag time

Surge Dose[®] maximizes the impact of pH dependent solubility to increase the rate of absorption, but is also effective for drugs where solubility is independent of pH. Surge Dose[®] formulations are designed to achieve ultra-fast activated dissolution even under unfavourable physiological conditions so that consistent absorption and efficacy can still be achieved independent of gastrointestinal (GI) activity and pH. While this is important for drugs taken on demand for acute episodic indications, it is equally important for drugs taken on a regular basis where GI conditions are variable.

2.2 IP status

The Surge Dose[®] technology is covered by three patent families filed in US, Canada, Europe, India, Japan and Australia:

- i. PCT/AU 2006/001798 published as WO/2007/059591 covering acidic and unionized, basic and amphoteric therapeutic agents claiming priority from three

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Australian provisionals, one on acids and unionized drugs filed on 28 Nov 2004, and two others filed on 13 May 2005. Claims have now been limited to cover only acidic and unionized drugs. This patent has been granted in Australia and expedited examination is progressing in the US under the PPH and in Japan.

- ii. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. A clean ISR report was issued in Europe. Patents have been granted in Australia and Canada without limitation and examination is progressing in Europe, India, Japan and the US.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations. This patent has been granted in Australia, Canada and US and assigned to a third party in Australia, Europe, India and Japan.

Patents are based on *in vitro* dissolution and *in vivo* PK results for paracetamol as a model drug and *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs other than those exemplified are covered by the broad claims in these patents.

2.3 Technical strategy

Formulation optimization is aimed at achieving total dissolution of the drug in available liquid in the stomach to provide a high concentration gradient for rapid absorption from the small intestine driving high plasma concentrations. Surge Dose[®] uses optimized levels and ratios of pH modulating agents and water uptake agents for each drug or drug combination to provide an activated dissolution system which will maximize the extent and rate of dissolution as demonstrated by *in vitro* testing.

The reaction between acidic and basic components produces effervescence which disrupts the boundary layers around the dissolving drug particles independent of the gastric pH, whilst controlling the pH to maximize solubility. This provides a higher concentration of drug in solution in the first few minutes after administration with the resultant drug solution draining from the stomach independent of the Migrating Motility Complex (MMC) and driving faster absorption. In contrast, traditional tablet formulations release drug into solution by passive diffusion across stagnant boundary layers around dissolving drug particles which provide a barrier to fast dissolution. Such slow dissolving tablets produce only low concentrations of dissolved drug and rely on MMC gastric emptying for drug absorption.

For ionized drugs, the pH modulating agents are optimized to favour the proportion of drug present in the more readily absorbed unionized form. At its pKa, 50 % of a drug will be present in its unionized form in equilibrium with 50 % in the ionized form. **Basic** drugs are

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present predominantly unionized at pH values above their pKa, whereas **acidic** drugs are present predominantly unionized below their pKa. **Amphoteric** drugs are zwitterions which have a net neutralisation of charge at their isoelectric point.

Surge Dose[®] formulations use approved GRAS excipients and conventional tablet manufacturing equipment prepared by direct compression or wet granulation, and so do not require any major capital outlay or present any regulatory hurdles through the use of unusual or new raw materials. Film coatings can be selected to have minimal impact on dissolution. For maximum stability and an acceptable shelf life of 2 years, low relative humidity (RH) manufacturing facilities around 10 - 20 % RH and unit packing in a suitable moisture-impervious laminate such as used for soluble effervescent tablets will be required. Small scale batches of a wide range of different drugs and a drug combination have been manufactured, and formulations of a basic drug and an acidic drug have been successfully scaled-up for commercial manufacture.

Testing is conducted using a range of highly discriminating *in vitro* dissolution methods as a development rather than a QC tool. These use standard dissolution equipment such as USP dissolution apparatus II with paddles using different media at 37 °C, different volumes and different stirring speeds to simulate *in vivo* conditions:

- 900 mL 0.05 M HCl at 30 rpm is frequently used in pharmacopoeial test methods, where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.2, containing the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, is the dissolution medium used to characterise Surge Dose[®] formulations in the Imaginot patents
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, contains 3 mmoles of acid in a typical physiological volume based on 170 mL co-administered water with around 30 mL acidic gastric contents in the fasted state
- 200 mL 0.0033 M HCl at 30 rpm simulates a typical physiological volume with lower gastric acidity as occurs in many subjects in the general population
- 900 mL 0.0033 M HCl at 0 rpm simulates gut stasis such as occurs in migraine and the fed state where there is little gastric motility

2.4 Commercialization

Imaginot is now seeking partners to commercialize its Surge Dose[®] technology. To date, deals involve a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA), one of India's largest pharmaceutical companies

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(Abbott Healthcare Pvt Ltd). Imaginot has an agreement with Piramal Healthcare Ltd. in India for the contract development and manufacture of Surge Dose[®] formulations. Piramal can undertake formulation optimisation, scale, up, stability studies and Phase I studies comparing a Surge Dose[®] formulation to an existing formulation to demonstrate the improved kinetics, at low cost for companies interested in exploring the use of the Surge Dose[®] technology for their drugs.

A number of Surge Dose[®] formulations have been developed which demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions, with the first Surge Dose[®] product, lornoxicam 4 and 8 mg launched in 2011 and a second product to be launched late 2012. Additional drugs are under development with formulation and process optimization in progress.

3 Clinical premise for Surge Dose[®]

3.1 Factors affecting oral drug absorption

3.1.1 *Gastrointestinal (GI) motility*

The underlying MMC (migrating motor complex) influences gastric emptying, contributing to the inter- and intra-subject variability seen in oral PK studies with solid dosage forms and solutions. MMC effects are significant and can mask differences between formulations and other variables particularly in fasted PK studies.

In the fasted state, subjects will be cycling through the three MMC phases which together generally last from 80 to 150 min. Phase I lasts 20 – 90 min, a quiescent period with little gastric motility; Phase II lasts 10 – 135 min, with intermittent contractions increasing in strength; Phase III (known as the housekeeper wave) is the shortest, most active phase lasting 3 – 25 min, characterised by intense contractions emptying gastric contents into the small intestine.

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half life in the region of 20 min during Phase I, reduced to 12 and 5 min respectively in Phase II and Phase III¹.

When a drug is administered to a fasted subject, they may be in any phase of the MMC. Thus, for the same formulation, a subject in Phase I will absorb the drug slower than if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III.

¹ Oberle RL, Chen T-Z, Lloyd C, Barnett JL, Owyang C, Meyer J, Amidon GL. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroent* (1990) 99:1275-82

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This means that even a slow dissolving product can result in fast absorption occasions as well as slow absorption occasions according to the phase of the MMC. However the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Gastric emptying effects are responsible for the double or multiple absorption peaks often seen during the first two hours in individual subject PK profiles particularly where there is frequent plasma sampling. These are well documented for a variety of different drugs^{2,3,4,5,6,7,8,9,10,11} and differ from later peaks due to entero-hepatic recycling. Multiple peaks are reported for the acidic NSAID diclofenac¹² which has low solubility at under acidic gastric conditions but higher solubility under the alkaline pH of the small intestine.

- ² Mummaneni V, Amidon GL, Dressman JB. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral-administration in dogs Pharm Res (1995) **12**(5):780-786
- ³ Metsugi Y, Miyaji Y, Ogawara K, Higaki K, Kimura T. Appearance of double peaks in plasma concentration-time profile after oral administration depends on gastric emptying profile and weight function. Pharm Res (2008) **25**(4):886-95
- ⁴ Langguth P, Lee KM, Spahn-Langguth H, Amidon GL. Variable gastric emptying and discontinuities in drug absorption profiles: dependence of rates and extent of cimetidine absorption on motility phase and pH. Biopharm Drug Dispos (1994) **15**(9):719-46
- ⁵ Charman WN, Rogge MC, Boddy AW, Barr WH, Berger BM. Absorption of danazol after administration to different sites of the gastrointestinal tract and the relationship to single- and double-peak phenomena in the plasma profiles. J Clin Pharmacol (1993) **33**(12):1207-13
- ⁶ Suttle AB, Pollack GM, Brouwer KL. Use of a pharmacokinetic model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration-time profiles. Pharm Res (1992) **9**(3):350-6
- ⁷ Marathe PH, Sandefer EP, Kollia GE, Greene DS, Barbhaiya RH, Lipper RA, Page RC, Doll WJ, Ryo UY, Digenis GA. In vivo evaluation of the absorption and gastrointestinal transit of avitriptan in fed and fasted subjects using gamma scintigraphy. J Pharmacokinet Biopharm (1998) **26**(1):1-20
- ⁸ Takamatsu N, Welage LS, Hayashi Y, Yamamoto R, Barnett JL, Shah VP, Lesko LJ, Ramachandran C, Amidon GL. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. [erratum appears in Eur J Pharm Biopharm (2002) 54(2):255]. Eur J Pharm Biopharm (2002) **53**(1):37-47
- ⁹ Yin OQ, Tomlinson B, Chow AH, Chow MS. A modified two-portion absorption model to describe double-peak absorption profiles of ranitidine. Clin Pharmacokinet (2003) **42**(2):179-92
- ¹⁰ Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. J Pharmacokinet Biopharm (1987) **15**(5):529-44
- ¹¹ Lunell E, Andersson KE, Borga O, Fagerstrom PO, Johannesson N, Kjellin G, Persson CG, Sjolund K. Absorption of enprofylline from the gastrointestinal tract in healthy subjects. Eur J Clin Pharmacol (1984) **27**(3):329-33
- ¹² Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Szelenyi I, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. Br J Clin Pharmacol (2005) **59**:80-84

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In late Phase II or Phase III, fast absorption will occur as the gastric contents are rapidly emptied into the small intestine resulting in a short T_{max} . However, in Phase I or early Phase II, there will be slower absorption with a longer T_{max} although there will be fast absorption of any dissolved drug that drains passively from the stomach. This is followed by a later absorption phase when remaining gastric contents are emptied by Phase III MMC. Gastric contents include any dissolved drug retained in the mucosal folds of the stomach as well as any tablet fragments and undissolved drug particles. The amount of dissolved drug in the initial absorption phase and the relative sizes of any multiple peaks will depend on drug solubility and the dissolution characteristics of the dosage form.

In addition to the MMC, GI motility can be influenced by other factors, and where slowing occurs, this will have an impact on gastric emptying and subsequent drug absorption. Delayed absorption and reduced variability in fed studies result from interruption of the underlying MMC by food which triggers Phase I MMC¹³. Certain pathological conditions will reduce GI activity such as diabetes mellitus and also migraine where drug efficacy can be delayed by gut stasis. Opiates generally reduce GI activity which will slow absorption and hence slow onset of action.

Surge Dose[®] formulations are designed to achieve ultra-fast activated dissolution of drug in co-administered liquid and stomach contents allowing the resultant solution to drain passively from the stomach independent of MMC activity

3.1.2 Gastric pH

Although gastric contents are acidic in the fasted healthy state, there is significant variability in inter- and intra-subject gastric pH. Gastric pH typically varies between 1 and 7 during the course of the day in the general population depending on age, presence of food, concomitant medication and pathophysiology:

- A significant proportion of the population has low gastric acidity such as those with achlorhydria where gastric pH does not drop below pH 4, and hypochlorhydria which affects up to 50 % of the population increasing with age or pathology such as diabetes mellitus and autoimmune conditions
- Patients taking drugs such as antacids and proton pump inhibitors will experience relatively high gastric pH most of the time

¹³ Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. Gut (1979) 20(Nov):963-970

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- Food increases gastric pH and patients using 'on demand' medication will often be in the post-prandial or partial prandial state where gastric pH will be less acidic

Many drugs exhibit pH dependent solubility and the proportion present as the more readily absorbed unionized species will depend on the pKa of the drug. Higher solubility favours faster dissolution. Acidic drugs with a low pKa are more soluble and will dissolve faster at high pH but the proportion of the readily absorbed unionized species is lower. Basic drugs with a high pKa are more soluble and dissolve faster in acidic conditions but the proportion of readily absorbed unionized species will be lower.

When formulating for fast absorption, both solubility and degree of ionization must be considered. However for drugs with a high permeability coefficient, the effects of increased solubility more than compensate for the ionization effects.

Consequently gastric pH significantly affects the rate of dissolution of an orally administered drug depending on its physicochemical properties. Increased drug solubility is associated with an increased dissolution rate in any co-administered water before it empties from the stomach. Conversely reduced solubility slows the rate of dissolution, with less dissolved drug available for absorption when emptied into the small intestine.

Hence the importance of optimizing drug formulations to ensure adequate solubility and fast dissolution under a wide range of physiological conditions.

Surge Dose[®] formulations are designed to maximize solubility by controlling the pH in the micro-environment of the dissolving drug particles, ensuring fast dissolution into available liquids in the stomach independent of gastric pH

3.2 Clinical rationale

Drug absorption following oral administration is influenced by:

- the rate at which the drug dissolves from the dosage form into available fluids in the stomach including any co-administered liquid,
- the underlying GI motility or phase of the MMC which periodically empties the stomach contents into the small intestine, and
- the rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine which is independent of the MMC.

While dosage forms will not change physiological conditions, strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*. Surge Dose[®] tablets achieve ultra fast activated dissolution under the wide range of conditions occurring in the

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general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

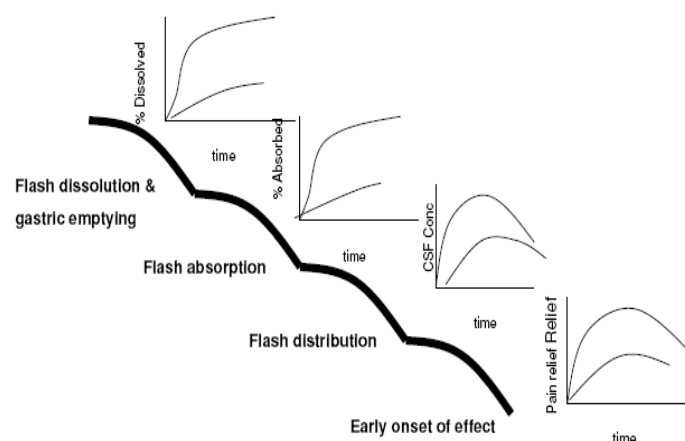
Where speed and consistency of *in vivo* dissolution directly impact the clinical outcome, improvement in the *in vitro* dissolution profiles relative to currently marketed formulations can offer significantly improved patient outcomes and associated compliance.

Dissolved drug will reach the small intestine quickly independent of gastric motility. The higher the drug concentration, the greater will be the driving force across the intestinal mucosa for rapid absorption and high C_{max} . Total dissolution of the drug from a solid dosage form into the co-administered liquid and gastric contents provides the maximum concentration to drive absorption and distribution to effect compartments by passive diffusion resulting in faster onset of action and improved efficacy.

Conversely, slow dissolution generally leads to slow absorption associated with lower and sometimes sub-therapeutic plasma concentrations. Where there is slow drug dissolution, gastric emptying will be the major factor in transferring drug into the small intestine where dissolution and absorption occur. This means that early absorption can occur with slow dissolving formulations on some occasions if Phase III MMC occurs soon after ingestion. There may be some initial dissolution which results in absorption from the resultant solution, but drug concentrations will be low and absorption slow as a result of the low driving force. Such variability is evident in many PK studies reporting individual subject data and may explain the lack of efficacy demonstrated by some patients.

Surge Dose[®] formulations are designed to maximize the rate and extent of drug dissolution *in vivo* leading to improved clinical outcomes. The following Surge Dose[®] cascade is summarized in Figure 1:

Figure 1 Surge Dose[®] cascade resulting in faster onset of action



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- i. Drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents
- ii. Dissolved drug empties rapidly and passively from the stomach in both fed and fasted states independent of the MMC i.e. the drug empties as fast as if it had been taken as a solution
- iii. The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption
- iv. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes achieving earlier therapeutic plasma concentrations with short T_{max} , high C_{max} and reduced intra- and inter-subject variability
- v. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect

3.3 PK proof of concept

Imaginot developed its Surge Dose[®] ultra-rapid activated dissolution formulation technology based on in vitro dissolution testing with a wide range of different drugs, and in vivo evaluation of fast dissolving paracetamol tablets in fasted subjects. Formulations are optimised with respect to levels of pH modulating agents (pHMA) and water uptake agents (WUA) to maximise the rate and extent of in vitro dissolution using highly discriminating in vitro test methods.

Fast in vitro dissolution of paracetamol has been shown to be associated with fast in vivo absorption. Paracetamol is a well recognised marker of gastric emptying and the in vivo results demonstrated the effect of the different phases of gastrointestinal motor activity known as the MMC on the absorption profile. Optimized Surge Dose[®] film coated tablets of two NSAIDs (non steroidal anti-inflammatory drugs) lornoxicam and diclofenac have also demonstrated improved PK in fasted subjects with faster absorption and higher C_{max} comparable with parenteral administration.

3.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects¹⁴ demonstrated significantly faster absorption with two fast dissolving preliminary Surge Dose[®] paracetamol formulations that have subsequently been improved, compared with Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol[®]>:

¹⁴ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

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- Median T_{max} values for the Surge Dose[®] formulations were 17 and 25 min compared with 45 min for Tylenol[®]
- Surge Dose[®] AUC_{0-30} values indicated 3 times as much absorbed in the first 30 min compared with Tylenol[®]
- 64 and 76 % subjects receiving Surge Dose[®] tablets exceeded the reported minimum therapeutic level for paracetamol of 10 µg/mL in the first 15 min compared with only 20 % subjects receiving Tylenol[®]
- 16 % subjects taking Tylenol[®] never reached 10 µg/mL indicating sub-therapeutic dosing compared with only 4 % for Surge Dose[®] formulations

This study showed good *in vitro in vivo* correlations (IVIVC). Although paracetamol absorption was variable from one dose to another reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher C_{max} values. Slow absorption occasions were more frequent with Tylenol[®], and were associated with lower C_{max} values sometimes failing to reach reported minimum therapeutic plasma concentrations.

PK-PD modelling to quantify pain relief following oral administration predicted more rapid onset and greater analgesia with Surge Dose[®] paracetamol than Tylenol[®] tablets¹⁵. Improved clinical efficacy was predicted for Surge Dose[®] formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol[®]. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

As paracetamol is a well-established marker for liquid gastric emptying, similar improved PK would be expected for other drugs where *in vitro* dissolution can be significantly improved with Surge Dose[®] formulations. Increasing the probability of rapid absorption will lead to an increased probability of reaching therapeutic plasma levels quickly, with a faster onset of action. Where sub-therapeutic plasma levels can occur as a result of slow absorption, increasing the rate of absorption can lead to improved clinical efficacy through a higher frequency of doses exceeding minimum therapeutic plasma concentrations.

3.3.2 Lornoxicam

A PK study in 24 fasted subjects with the NSAID lornoxicam has also demonstrated the benefits of Surge Dose[®] to maximise *in vitro* drug dissolution compared with a conventional

¹⁵ Green B, Chandler S, Macdonald G, Elliott G, Roberts MS. Quantifying pain relief following administration of a novel formulation of paracetamol (acetaminophen) J. Clin. Pharmacol. (2010) Online First doi 10.1177/0091270009359181

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commercial tablet¹⁶. Surge Dose[®] tablets significantly reduced T_{max} and resulted in significantly higher C_{max} levels similar to parenteral administration¹⁷. Faster and more consistent absorption has the potential to improve efficacy. Absorption from Surge Dose[®] lornoxicam tablets was twice as fast as from the reference commercial product:

- Mean and median T_{max} values for Surge Dose[®] lornoxicam were comparable at 0.51 and 0.50 h respectively, ranging from 0.3 to 1 h
- Median T_{max} for the reference tablet was 0.83 h ranging from 0.5 to 2.3 h with a longer mean T_{max} of 1.06 h indicating more subjects with slow absorption
- 75 % subjects on Surge Dose[®] lornoxicam achieved T_{max} within the first 0.5 h compared with only 8 % for the reference tablet
- Surge Dose[®] lornoxicam achieved mean C_{max} of 1098 ng/mL (CV 18.71 %), around 40 % higher than the reference tablet with mean C_{max} 788 ng/mL (CV 18.69 %)
- Although $AUC_{0-\infty}$ was the same for both Surge Dose[®] and reference lornoxicam tablets with values around 4,200 ng.h/mL, early exposure AUC values after 10, 20 and 30 min demonstrated significantly faster absorption with Surge Dose[®] lornoxicam, respectively 3.9, 2.8 and 2.2 times higher

3.3.3 Diclofenac

An optimized film coated Surge Dose[®] diclofenac sodium 50 mg tablet was compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration containing 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium. Despite the marketing of the Voveran[®]-D dispersible tablets for fast pain relief, this dispersed product showed slow absorption, low C_{max} and multiple peaks indicating that gastric emptying was absorption rate limiting. Although some dissolved drug emptied into the small intestine and was quickly available for absorption, a significant proportion of each dose was retained in the stomach until emptied during Phase III MMC.

Surge Dose[®] provided 4- 5 times faster absorption of diclofenac than from a dispersible tablet:

¹⁶ Wellquest Clinical Research. Report No CR-BE-267-LORN-2009. An open label, balanced, randomised, two-treatment, two-period, two-sequence, cross-over, single-dose bioequivalence study of Lornoxicam Rapid Release 8 mg tablets comparing with Lornoxicam 8 mg tablets in healthy adult human subjects under fasting conditions. 11 Aug 2010

¹⁷ Radhofer-Welte S, Dittrich P, Simin M, Branebjerg PE. Comparative bioavailability of lornoxicam as single doses of quick release tablet, standard tablet and intramuscular injection – a randomized, open-label, crossover Phase I study in healthy volunteers. Clin Drug Invest. (2008) 28(6): 345-51

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- Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min) indicating fewer slow absorption profiles with a high T_{max} . Voveran[®]-D showed slower and more variable absorption with a median T_{max} of 1.5 h (15 min – 4 h) indicating a tail of slow absorption profiles.
- Surge Dose[®] produced significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. Surge Dose[®] C_{max} values were comparable with those obtained following IV^{18,19} or IM^{20,21} administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets²².
- With Surge Dose[®], 76 % subjects had a T_{max} equal to or less than 20 min and 100 % reached T_{max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{max} equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{max} , with 6 (30 %) waiting at least 2 h.

Based on PK studies to date, PK-PD modelling and in vitro dissolution profiles with many different drugs, Surge Dose[®] formulations are expected to achieve improved therapeutic outcomes with faster onset of action and greater efficacy as a result of more consistent absorption exceeding minimum effective plasma concentrations compared with conventional solid dosage forms. Maximising the amount of drug dissolved in co-administered liquid will provide high concentrations of drug reaching the small intestine independent of gastric motility, to drive rapid absorption of drug across the small intestinal wall. High plasma concentrations in turn drive rapid distribution to the tissues and site action for earlier onset of action.

In contrast, if a drug dissolves slowly or to a limited extent in any co-administered water, slower gastric emptying of the dose will result and the lower drug concentration in solution provides lower driving forces across the gastrointestinal wall. This leads to slow absorption

¹⁸ Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* (2005) 59(1):80-84

¹⁹ Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur J Clin Pharmacol* (1979) 16:405-10

²⁰ Auler JO, Espada EB, Crivelli E, Quintavalle TBG, Kurata A, Stolf NAG, Issy AM, Paschoa OED, Danhof M, Breimer DD, Chamone DAF, Santos SRCJ. Diclofenac plasma protein binding: PK-PD modelling in cardiac patients submitted to cardiopulmonary bypass. *Braz J Med Biol Res* (1997) 30:369-74

²¹ Derendorf H, Mullersman G, Barth J, Gruner A, Mollmann H. Pharmacokinetics of diclofenac sodium after intramuscular administration in combination with triamcinolone acetate. *Eur J Clin Pharmacol* (1986) 31:363-5

²² Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arznein-Forsch/Drug Res* (2001) 51(11): 885 – 890

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and lower C_{max} . Imaginot has demonstrated that slow absorption is associated with low C_{max} which may be sub-therapeutic.

Where the solubility of a drug is pH dependent, its solubility and hence rate of dissolution will depend on the acidity of the gastric contents. Since the acidity of the gastric contents varies, variable drug solubility will lead to variability in dissolution and absorption in some cases. Acidic gastric conditions increase the solubilities of basic and amphoteric drugs which results in enhanced dissolution. However if the gastric contents are less acidic or neutral such as in the fed state and in patients taking antacids or proton pump inhibitors, then the solubility of such drugs will be reduced with associated slower, and possibly limited dissolution. This would result in slower absorption and lower peak plasma concentrations which may be sub-therapeutic.

The opposite effect is seen with acidic drugs where the solubility is low under acidic conditions but increases as the pH rises.

For a drug that is readily absorbed across the intestinal mucosa, reformulation to ensure rapid dissolution in vivo is likely to lead to:

- (iii) rapid absorption and more rapid onset of peak effect
- (iv) a reduction in slow absorption occasions, which lead to low, possibly sub-therapeutic, plasma concentrations

3.4 Intellectual Property

The Surge Dose[®] technology is covered by three patent families filed in US, Canada, Europe, India, Japan and Australia:

- iv. PCT/AU 2006/001798 published as WO/2007/059591 covering acidic and unionized, basic and amphoteric therapeutic agents claiming priority from three Australian provisionals, one on acids and unionized drugs filed on 28 Nov 2004, and two others filed on 13 May 2005. Claims have now been limited to cover only acidic and unionized drugs. This patent has been granted in Australia and expedited examination is progressing in the US under the PPH and in Japan.
- v. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. A clean ISR report was issued in Europe. Patents have been granted in Australia and Canada without limitation and examination is progressing in Europe, India, Japan and the US.
- vi. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations. This patent has been granted in Australia, Canada and US and assigned to a third party in Australia, Europe, India and Japan.

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Patents are based on *in vitro* dissolution and *in vivo* PK results for paracetamol as a model drug and *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs other than those exemplified are covered by the broad claims in these patents.

This report details the features of prednisolone that suggest application of the Surge Dose[®] technology will offer faster *in vivo* dissolution and absorption, with improved and more consistent therapeutic outcomes. It includes the preliminary screening work that has been conducted on prednisolone to demonstrate the significantly improved *in vitro* dissolution that is possible with Surge Dose[®] tablet formulations of this drug.

4 Technical requirements for Surge Dose[®]

Formulation optimization aims to maximize drug dissolution in available liquid in the stomach to provide a high concentration gradient to drive absorption. Optimized levels and ratios of pH modulating agents (pHMA) and water uptake agents (WUA) provide a pH-controlled activated dissolution system to maximize the extent and rate of *in vitro* drug dissolution, exceeding 70 % dissolution in 3 minutes even using *in vitro* methods that simulate adverse *in vivo* conditions.

The reaction between acidic and basic components produces effervescence which disrupts the boundary layers around dissolving drug particles independent of the gastric pH, whilst controlling pH to maximize solubility. This provides a higher concentration of dissolved drug in the first few minutes after administration with the drug solution draining from the stomach independent of the MMC. In contrast, traditional tablets release drug into solution slowly by passive diffusion across stagnant boundary layers around dissolving drug particles which are a barrier to fast dissolution. Such slow dissolving tablets produce low concentrations of dissolved drug so that absorption is more dependent on MMC gastric emptying.

For ionized drugs, pHMA are optimized to favour the proportion of drug in the more readily absorbed unionized form. At its pKa, 50 % of a drug will be present in its unionized form in equilibrium with 50 % in the ionized form. **Basic** drugs are predominantly unionized at pH values above their pKa, whereas **acidic** drugs are predominantly unionized below their pKa. **Amphoteric** drugs are zwitterions with a net neutral charge at their isoelectric point.

Surge Dose[®] formulations use GRAS excipients and traditional manufacturing equipment for direct compression or wet granulation. Low RH manufacturing facilities around 10 - 20 % RH and unit packing in a suitable moisture-impervious laminate such as used for effervescent tablets provide maximum stability and an acceptable shelf life of 2 years. No major capital investment is required and use of conventional ingredients should not present

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any regulatory hurdles. Film coatings can be selected to have minimal impact on dissolution. Small scale Surge Dose[®] batches of several drugs have been manufactured, with successful scale-up to commercial batches undertaken.

A range of highly discriminating *in vitro* dissolution methods is used as a development rather than a QC tool, with standard equipment such as USP dissolution apparatus II with paddles, different media at 37 °C, different volumes and different stirring speeds to simulate *in vivo* conditions:

- 900 mL 0.05 M HCl at 30 rpm where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.3, used to characterise Surge Dose[®] formulations contains the finite amount of acid (3 mmoles) estimated to be present in the fasted state
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, contains 3 mmoles of acid in a typical physiological volume based on co-administered water with 30 mL fasted acidic gastric contents
- 200 mL 0.0033 M HCl at 30 rpm simulates a typical physiological volume with lower gastric acidity as occurs in many subjects in the general population
- 900 mL 0.0033 M HCl at 0 rpm simulates gut stasis such as occurs in migraine and the fed state where there is little gastric motility

5 Prednisolone as a potential Surge Dose[®] candidate

5.1 Clinical use

Glucocorticosteroids are used frequently and intensively for their anti-inflammatory, anti-allergic, anti-rheumatic and immunosuppressive effects in a diversity of different clinical indications. These include bronchial asthma, emphysema, pulmonary fibrosis, allergic skin reactions, blood disorders such as autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura, selected collagen and rheumatoid disorders, connective tissue disorders such as arteritis and systemic lupus erythematosus (SLE), inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, some hepatic disorders such as chronic active hepatitis, nephritic syndrome and other renal disorders, selected inflammatory ocular diseases, acute exacerbations of eczema, exfoliate dermatitis and pemphigus, some neurological disorders such as infantile seizures and sub-acute demyelinating polyneuropathy and organ transplantation.

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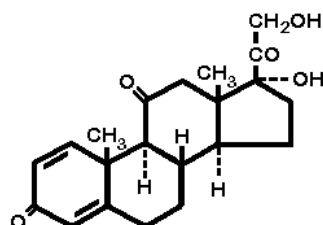
Prednisolone is a potent glucocorticosteroid, metabolically inter-convertible with prednisone. It is administered as prednisolone, or as the prodrug prednisone which is converted to prednisolone in vivo and has a pre-conversion half life of around 60 minutes. Prednisolone is used orally in doses of 5 to 60 mg a day taken in divided doses, as a single dose after breakfast or as a double dose up to 120 mg on alternate days²³. The usual adult prescribing limit is 250 mg daily.

Oral corticosteroids are convenient and safer to administer than high IV doses, and although they take longer to reach therapeutic plasma levels, the difference does not appear to be clinically significant in acute asthma where patients continue to use inhaled corticosteroids and bronchodilators²⁴. Hence an oral solid dosage form that is rapidly and consistently absorbed is desirable.

5.2 Physicochemistry and solubility

Prednisolone has a molecular weight of 360.44 with the molecular formula $C_{21}H_{28}O_5$ and the structural formula shown in Figure 1. It is a large molecule which is unionised over the normal physiological pH range of 1 to 7.5. A BCS Class 1 classification is suggested which would warrant a biowaiver on the grounds that higher exposure to the drug would be unlikely to be associated with any increased risks to the patient²⁵.

Figure 1 Structural formula for prednisolone



It is very slightly soluble in water, with a quoted solubility (S) of 0.243 mg/mL at 25 °C. This means that a dose of 50 mg (D) will dissolve in 206 mL water at 25 °C compared with the critical BCS high solubility limit for D/S of < 250 mL at 37 °C. However a double dose of

²³ Martindale. The complete drug reference. 33rd edition. Editor SC Sweetmwn. Pharmaceutical Press 2002 1078-1079

²⁴ Cunnington D, Smith N, Steed K, Rosengarten P, Kelly AM, Teichtal H. Oral versus intravenous corticosteroids in adults hospitalised with acute asthma. *Pulmon Pharmacol Ther* (2005) **18**:207-12

²⁵ Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. Biowaver monographs for immediate release solid oral dosage forms: prednisolone. *J Pharm Sci* (2007) **96**(1):27-37

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120 mg will require 494 mL for complete dissolution at 25 °C which indicates that some dissolution rate limitation would be expected.

Although the more soluble forms, prednisolone sodium phosphate or prednisolone steaglate, are used in oral syrup formulations, the less soluble base prednisolone is used for oral dosage forms. Attempts have been made to increase the solubility of prednisolone using solid dispersions with agents such as sorbitol, polyvinylpyrrolidone, polyethylene glycol, sorbitol, mannitol and Cremophor, increased the dissolution rate compared with drug alone or physical mixtures of the drug and carrier²⁶. Polyethylene glycol 6000 used as a solubilising agent in immediate release tablets of prednisone, which is converted in the body to prednisolone, resulted in faster in vitro dissolution achieving 80 % dissolution within 30 minutes compared conventional tablets releasing less than 25 % within 30 minutes²⁷.

5.3 PK and PD

The PK and PD of glucocorticosteroids have been extensively reviewed²⁸.

Prednisolone is readily absorbed from the small intestine with an oral bioavailability of 99 ± 8 %, and is readily distributed to all body tissues. Elimination occurs by hepatic metabolism followed by renal excretion of the metabolites. Its biological half life of 2 - 4 hours makes it suitable for alternate day dosing. Prednisolone PK can be described by one and two compartment models.

Its PK are complicated by nonlinear protein binding decreasing from 95 % to 60 - 70%, as the concentration increases from 200 µg/L to 800 µg/L at which level the protein binding reaches a plateau. This is of relevance as only free unbound drug can reach the site of action and interact with receptors.

It is noted that there is significant inter-subject variability in prednisolone absorption and bioavailability depends on the dissolution rate for tablet formulations. Early erratic blood

²⁶ Jachowicz J. dissolution rates of partially water-soluble drugs from solid dispersion systems. I Prednisolone. *Int J Pharmac* (1987) **35**:1-5

²⁷ Leonardi D, Barrera MG, Lamas MC, Salomon CJ. Development of prednisone:polyethylene glycol 6000 fast-release tablets from solid dispersions: solid state characterization, dissolution behavior and formulation parameters. *AAPS PharmSciTech* (2007) **8**(4):Article 108

²⁸ Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* (2005) **44**(1):61-98

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level doses, particularly seen with higher doses, have been attributed to limited solubility of the drug and dissolution rate variability²⁹.

5.4 Formulation effects

Prednisolone is a generic drug which is mostly presented as conventional tablet formulations. Liquid prednisolone formulations which offer faster absorption are becoming available such as TaroPharm's Flo-Pred[®] suspension with the market for oral liquid products estimated at approximately US\$ 55 million in 2007³⁰. However such presentations are not as convenient and portable as solid dosage forms and require formulation to prevent palatability problems.

T_{max} for oral prednisolone is generally achieved 1 - 2 hours after administration of solid dosage forms with some evidence of formulation effects on absorption.

A 1 mg tablet has been reported to achieve a mean T_{max} of 1.3 ± 0.7 hours (0.9 – 1.6) and C_{max} of 18.1 ± 5.5 µg/L (7.6 – 30.7)³¹. A study comparing two formulations with different dissolution rates showed faster absorption from the faster dissolving formulation in fasted healthy volunteers³². In this study, T_{max} values were 39.6 ± 6.4 minutes for the faster dissolving tablet compared with 52.8 ± 9.0 minutes.

Faster absorption has been reported for liquid prednisolone formulations taken with 240 mL co-administered water achieving peak plasma concentrations within 40 – 55 minutes³³ compared with 1 – 3 hours for conventional tablets.

When administered as the prodrug prednisone, prednisolone T_{max} values are longer, around 2 – 3 hours as a result of the in vivo conversion to the active prednisolone³⁴.

²⁹ Fleisher D, Johnson KC, Stewart BH, Amidon GL. Oral absorption of 21-corticosteroid esters: A function of aqueous stability and intestinal enzyme activity and distribution. *J Pharm Sci* (1986) **75**(10):934-9

³⁰ TaroPharma media release 22 Jan 2008. Taro receives FDA approval of New Drug Application (NDA) for Flo-Pred[®] (prednisolone acetate oral suspension)

³¹ Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* (2005) **44**(1):61-98

³² Luippold G, Schneider S, Marto M, Benohr P, Muhlbauer B. Pharmacokinetics of two oral prednisolone tablet formulations in healthy volunteers. *Arzneim – Forsch* (2001) **51**(11):911-5

³³ Ahmed M, Morrel EM, Clemente E. Bioavailability and pharmacokinetics of a new liquid prednisolone formulation in comparison with two commercially available liquid prednisolone products. *Curr Ther Res* (2001) **62**(7):548-56

³⁴ Penzak SR, Formentini E, Alfaro RM, Long M, Natarajan V, Kovacs J. Prednisolone pharmacokinetics in the presence and absence of ritonavir after oral prednisone administration to healthy volunteers. *J Acquir Immune Defic Syndr* (2005) **40**(5):573-80

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The initial absorption of prednisolone, but not its overall bioavailability, is affected by food. In fasted healthy subjects, peak plasma concentrations of $309 \pm \text{SD } 59.0 \text{ ng/mL}$ were achieved in $0.98 \pm \text{SD } 0.34$ hours for immediate release (IR) tablets³⁵. Food was found to interfere more with the absorption of prednisolone from enteric coated tablets than the IR tablets producing higher variability. Based on these findings, it is recommended that enteric coated tablets should not be taken within 2 hours of food, and that IR formulations are preferable for more predictable absorption avoiding the risks of therapeutic failures.

The sodium phosphate salt is used in the orally disintegrating tablets, Orapred[®] ODT, designed for the drug to disperse and dissolve in the mouth before swallowing. The ODTs contain sodium bicarbonate and citric acid which contribute to fast disintegration in the mouth as well as colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, mannitol, methacrylate co-polymer, microcrystalline cellulose, sucrose, sucralose and grape flavour to provide acceptable mouth feel and palatability.

The ODT has been approved as bioequivalent to the solution prednisolone product, Pediapred[®] and the new Orapred[®] solution^{36, 37}. However T_{max} values show marked differences with the ODT showing slower absorption (mean 1.33 ± 0.55 hours) than Orapred[®] solution (mean 0.64 ± 0.19 hours) and Pediapred[®] solution (mean 0.90 ± 0.34 hours).

In a separate study comparing the effect of swallowing the ODT with 240 mL water, similar T_{max} results were obtained, mean 1.15 ± 0.48 hours with water and mean 1.27 ± 0.65 hours without water swallowed only with saliva. The relatively slow absorption of drug from ODTs is seen with other drugs and is consistent with relatively slow dissolution in the saliva and co-administered water or saliva.

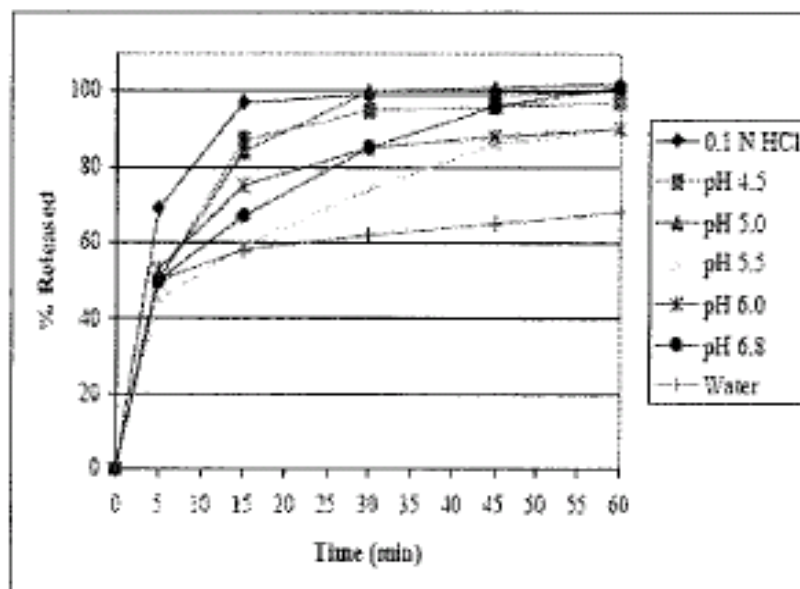
In vitro dissolution data are also provided in support of a proposed specification in 500 mL 22 mM sodium acetate buffer at pH 4.5 with paddles at 50 rpm which has been redacted from the submission. Dissolution profiles for the 30 mg ODT are shown in Figure 2. In 500 mL of buffers and water which volume significantly exceeds in vivo volumes, around 50 % dissolution was achieved in 5 minutes increasing to 58 – 87 % by 15 minutes and 62 – 100 % by 30 minutes. Fastest dissolution is seen in 500 mL 0.1 N HCl which is not representative of in vivo conditions for the administration of these dosage forms.

³⁵ Al-Habet SMH, Rogers HJ. Effect of food on the absorption and pharmacokinetics of prednisolone from enteric-coated tablets. *Eur J Clin Pharmacol* (1989) **37**(4):423-6

³⁶ Cima Labs Inc. Prescribing Information for Orapred[®] ODT, May 2006

³⁷ Orapred[®] ODT Product Approval Package FDA website
http://www.fda.gov/cder/foi/nda/2006/021959s000_ClinPharmR.pdf

Figure 2 *In vitro* dissolution profiles for 30 mg ODTs in various dissolution media (from FDA submission)



Overall based on published information and given solubility considerations and the reported variability in bioavailability depending on the dissolution rate of tablet formulations, prednisolone would appear to be a good candidate for fast dissolution Surge Dose[®] technology to increase the rate of in vivo dissolution and hence the rate of absorption.

5.5 PK-PD relationship

A number of biomarkers have been used to analyse the PD of prednisolone and other glucocorticosteroids, with some well-evaluated surrogate endpoints identified³⁸. These include HbA1c for complications of diabetes mellitus and bone mineral density for the risk of fractures in osteoporosis. At the molecular level, endogenous cortisol is used as a biomarker for HPA suppression, and at the cellular level in vivo, the number of T cells which play a role in the immune response.

The onset of action of prednisolone varies considerably depending on the dose and indication, and the effects last between 18 and 36 hours. A lag time is generally seen between the maximum effect and the time to maximum plasma concentration as a result of distribution to the site of action. For example, maximal lymphocyte suppression occurs 4 – 6 hours after maximum prednisolone concentrations are reached. However in this case, it

³⁸ Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* (2005) **44**(1):61-98

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is important to consider whether the plasma concentrations relate to total or unbound drug since only free unbound drug is active.

6 Surge Dose[®] prednisolone

6.1 Fast dissolving tablet formulations

Work conducted by Imaginot has demonstrated that ultra-rapid in vitro dissolution of prednisolone tablets can be achieved compared with conventional tablets³⁹. Reference tablets were Panafcortelone[®] 5 mg (BN 7201118) and Panafcortelone[®] 25 mg (BN 7201120) manufactured by Aspen Pharmacare Australia Pty Ltd. These were uncoated round tablets with a break-bar. The 5 mg tablet was flat bevelled edge with a diameter of 6.5 mm containing lactose, povidone, maize starch, crospovidone and magnesium stearate. The 25 mg tablet was shallow convex with a diameter of 10 mm containing hypromellose as an additional excipient.

Provisional Surge Dose[®] tablet formulations were prepared using a micronized grade of prednisolone (Crystal Pharma SA, Spain) with sodium bicarbonate, microcrystalline cellulose, crospovidone, fumaric acid and magnesium stearate. Drug was blended with sodium bicarbonate and microcrystalline cellulose and the powder blend passed through a 280 µm screen. This mix was then blended with the crospovidone. The magnesium stearate was passed through a 280 µm screen and incorporated into the powder blend with a short period of mixing. The resultant powder was compressed on a 16 station rotary Cadmach CMD₃ B-16 tablet press using a single set of 8 mm round shallow concave punches to achieve the hardest tablet which achieved a disintegration time of around 60 seconds in 0.0033 M HCl at 37 °C.

Formulations are summarized in Table 1 with the presence of unquantified excipients in the commercial tablets shown as ✓ and excipients classified as WUA designated with an asterix (*).

Table 1 Prednisolone tablet formulations

Formulation/ Ingredient (mg) /Characteristic	0522110	0522120	Panafcorte lone [®] 5	0522130	0522140	Panafcorte lone [®] 25
Prednisolone	5	5	5	25	25	25
Sodium bicarbonate	20	20	0	40	40	0

³⁹ Imaginot Pty Ltd. DR 05-01-01 Development of fast dissolving prednisolone tablets. 12 April 2006

IM 05-01-02

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Fumaric acid	0	14	0	0	28	0
Microcrystalline cellulose*	80	70	0	80	80	0
Crospovidone*	10	10	✓	13	14	✓
Povidone*, Maize starch*, Lactose*			✓			✓
Magnesium stearate	1.2	1.2	✓	1.5	1.6	✓
Total tablet weight	116.2	120.2	141	159.5	188.6	182
Hardness (Kp)	10	8	-	8	10	-
Disintegration time in 0.0033 M HCl (s)	35	57	143	10	49	330

Formulation characteristics of the formulations relative to the levels of pHMA and WUA are summarized in Table 2. These are based on the disclosed formulations assuming 1 % w/w magnesium stearate as a tablet lubricant.

Table 2 Key formulation characteristics for prednisolone tablets

Ingredients	0522110	0522120	Panafcort elone [®] 5	0522130	0522140	Panafcort elone [®] 25
Wt % bicarbonate (SB)	17.2	16.6	0	25.1	21.2	0
Wt % pHMA	17.2	28.3	0	25.1	36.1	0
Wt % WUA	78.5	67.6	~ 94	58.3	50.7	~ 85
Wt ratio pHMA : drug	4 : 1	6.8 : 1	n/a	1.6 : 1	2.7 : 1	n/a
Wt ratio SB : drug	4 : 1	4 : 1	n/a	1.6 : 1	1.6 : 1	n/a
Wt ratio WUA : drug	18 : 1	16 : 1		3.7 : 1	3.8 : 1	~ 17 : 1
Wt ratio WUA : SB	4.5 : 1	4 : 1	n/a	2.3 : 1	2.3 : 1	n/a
Wt ratio WUA : pHMA	4.5 : 1	2.4 : 1	n/a	2.3 : 1	1.4 : 1	n/a

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6.2 In vitro dissolution methods

Dissolution was measured in 900 mL 0.0033 M HCl which contains the same amount of acid as 30 mL residual gastric acid estimated to be present in a fasted subject. When diluted with 170 mL water co-administered with the formulation, the resultant solution contains approximately 3 millimoles HCl in 200 mL, equivalent to 0.015 M HCl. However, when used for dissolution at a volume of 900 mL, there will be significantly more acid than present in vivo, masking any pH shift during dissolution. Therefore for testing in 900 mL, 0.0033 M HCl is used which contains the same absolute amount of acid as 200mL 0.015 M HCl. This will show the effect of any pH changes when formulations containing pH modulating agents are tested which is important when the solubility of the drug is pH dependent. This low concentration also mimics low gastric acid conditions such as in fed subjects or those with low gastric acid secretion.

Dissolution testing was conducted in 900 mL 0.0033 M HCl at 37 °C using USP Apparatus II comprising VanKel VK 7010 Dissolution bath, VanKel VK 750 D Heater/Circulator and a Gilson Minipuls peristaltic pump for automatic continuous sampling using the flow through cell. Paddle stirrers rotated at 30 rpm. Testing was repeated without stirring at 0 rpm. Dissolution media were prepared by diluting 32 % v/v concentrated HCl (AR quality from Rowe Scientific) into purified water from the in-house Millipore Elix[®] water system. The solutions were filtered and degassed before use.

Drug concentrations were measured using a Varian Cary 50 UV-Vis Spectrophotometer set at the optimal wavelength. The % dissolved was calculated based on the maximum reading achieved after high speed stirring. The solution pH was measured at the beginning and end of each run. Results were based on the mean of 2 replicates.

6.3 Dissolution profiles

6.3.1 Acidic dissolution media at 30 rpm

The dissolution profiles for prednisolone tablets at 30 rpm are summarized in Table 2 and Figures 3 and 4 for the 5 mg and 25 mg tablets respectively. Dissolution profiles highlight the need to include an organic acid with a soluble carbonate such as sodium bicarbonate to maximize the in vitro dissolution of prednisolone.

Table 2 Prednisolone dissolution in 900 mL 0.0033 M HCl at 30 rpm

	% drug dissolved in 900 mL 0.0033 M HCl at 30 rpm					
Formulation	0522110	0522120	Panafcort- elone [®] 5	0522130	0522140	Panafcort- elone [®] 25
Dose	5 mg			25 mg		

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120 sec	9	69	34	14	77	5
180 sec	14	78	42	21	82	10
240 sec	19	81	46	24	85	14
300 sec	23	83	50	26	86	20
Final pH	2.3	2.3	2.3	2.3	2.3	2.3

Figure 3 Prednisolone 5 mg dissolution profiles in 900 mL 0.0033 M HCl at 30 rpm for tablets containing 20 mg sodium bicarbonate alone (0522110) and with 14 mg fumaric acid (0522120)

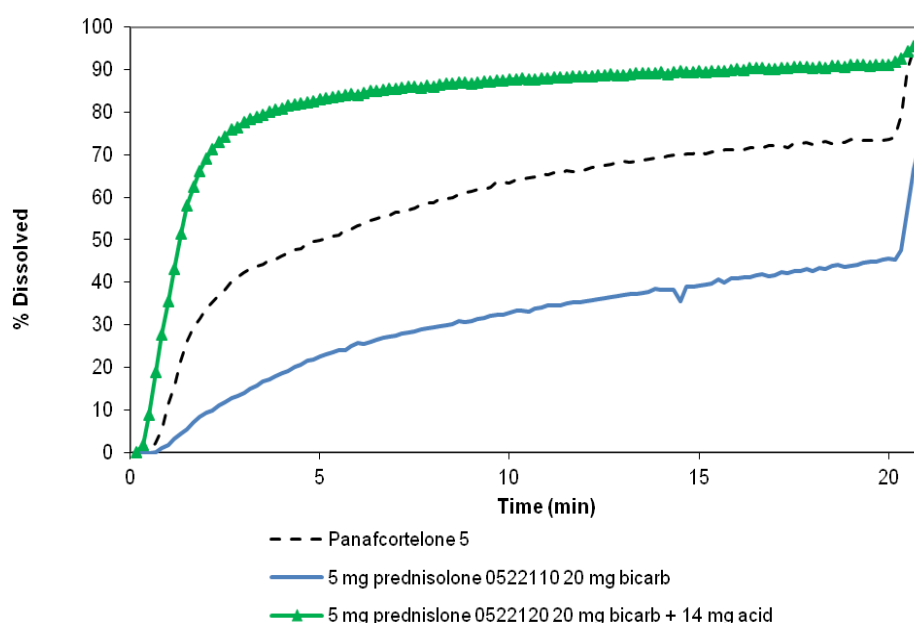
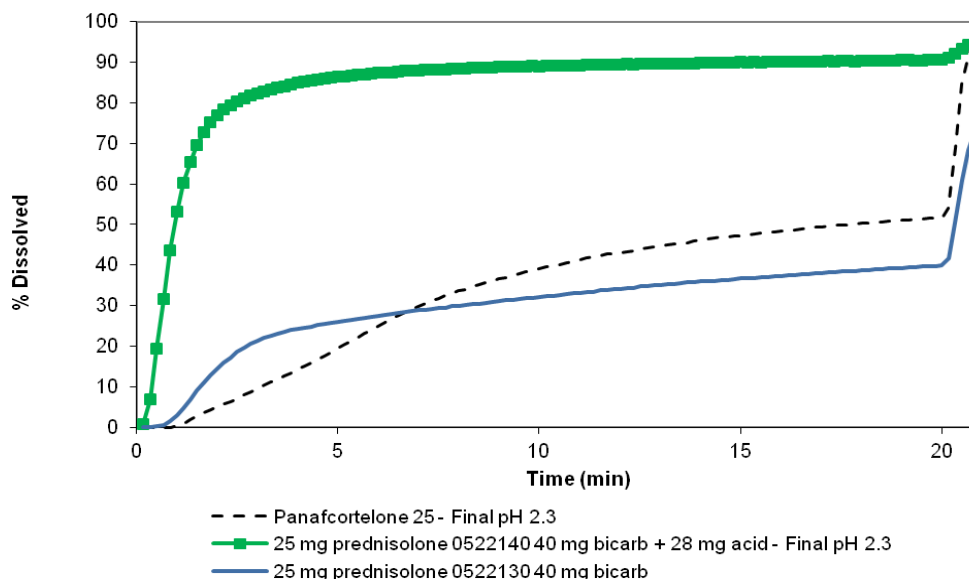


Figure 4 Prednisolone 25 mg dissolution profiles in 900 mL 0.0033 M HCl at 30 rpm for tablets containing 40 mg sodium bicarbonate alone (0522130) and with 28 mg fumaric acid (0522140)

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Prednisolone is a neutral drug and therefore its solubility is independent of pH. The main influence on the dissolution rate of prednisolone is therefore provided by the micro-stirring derived from the effervescent reaction between bicarbonate and acid in the vicinity of the dissolving drug particles. The stirring provided by sodium bicarbonate alone reacting with the external 0.0033 M HCl in the dissolution medium is insufficient to enhance the dissolution of prednisolone. However a combination of sodium bicarbonate and fumaric acid which can react in the immediate vicinity of the dissolving drug particles, provides more effervescence and therefore greater agitation, leading to more rapid dissolution.

It is notable that with the Surge Dose[®] formulations, similar results were achieved for both tablet strengths, 5 mg and 25 mg. However dissolution profiles for the two strengths of commercial tablets were quite different with the 5 mg achieving 42 % after 180 seconds at 30 rpm and the 25 mg achieving only 10 %. These results are consistent with the relatively low solubility of this drug, where dissolution becomes solubility limited as the dose increases. This would impact on in vivo dissolution.

6.3.2 Intrinsic active dissolution at 0 rpm

Testing in unstirred conditions at 0 rpm demonstrates the intrinsic active dissolution of the Surge Dose[®] formulations containing low levels of sodium bicarbonate with an equimolar quantity of fumaric acid as a result of the effervescence in the presence of the dissolving drug particles as the acid-base couple reacts. These conditions also simulate gut stasis and low gastrointestinal activity which occur in many patients who may be taking tablet formulations.

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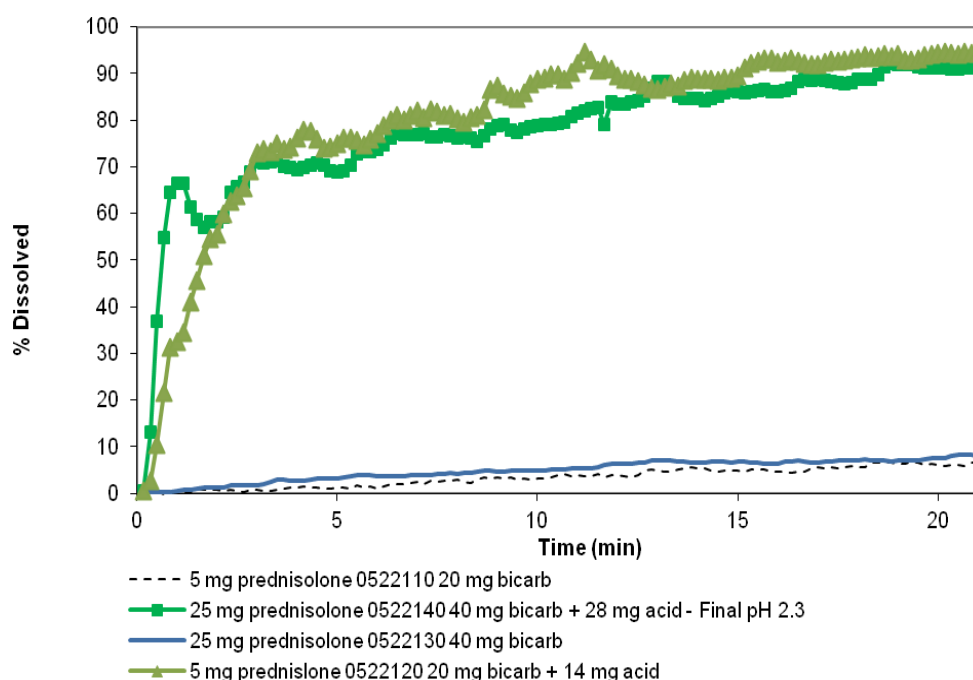
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The dissolution results are summarised in Table 3, and the dissolution profiles for the 5 mg and 25 mg tablets are shown in Figure 5 at 0 rpm.

Table 3 *Prednisolone dissolution in 900 mL 0.0033 M HCl at 0 rpm*

Formulation	% drug dissolved in 900 mL 0.0033 M HCl at 0 rpm					
	0522110	0522120	Panafcort- elone [®] 5	0522130	0522140	Panafcort- elone [®] 25
300 sec	1	75	N/A	3	69	N/A
15 min	5	89	N/A	7	86	N/A
30 min	11	97	N/A	9	95	N/A
Final pH	2.3	2.3	N/A	2.4	2.3	N/A

Figure 5 *Prednisolone 5 mg and 25 mg dissolution profiles in 900 mL 0.0033 M HCl at 0 rpm for tablets containing sodium bicarbonate alone (0522110, 0522130) and with fumaric acid (0522120, 0522140)*



These results show that the intrinsic micro-stirring derived from the pH modulating agents in the tablet is sufficient to dissolve the drug rapidly for both the 5 mg and 25 mg experimental formulations. In contrast, tablets containing sodium bicarbonate alone did not exceed 10% in 30 minutes.

Table 4 summarizes the dissolution of the various prednisolone tablets under stirred and unstirred conditions.

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Table 4 Dissolution profiles for prednisolone tablets at 30 rpm stirring speed and 0 rpm in 900 mL 0.0033 M HCl

30 RPM	120 SEC	180 SEC	240 SEC	300 SEC	15 MIN	30 MIN
COMMERCIAL PRODUCT 5MG	34	42	46	50		
5 MG 0522110	9	14	19	23		
5 MG 0522120 SURGE DOSE	69	78	81	83		
COMMERCIAL PRODUCT 25MG	5	10	14	20		
25 MG 0522130	14	21	24	26		
25 MG 0522140 SURGE DOSE	77	82	85	86		
0 RPM	120 SEC	180 SEC	240 SEC	300 SEC	15 MIN	30 MIN
5 MG 0522110				1	5	11
5 MG 0522120 SURGE DOSE				75	89	97
25 MG 0522130				3	7	9
25 MG 0522140 SURGE DOSE				69	86	95

7 Conclusions

Based on this review and dissolution profiles of experimental Surge Dose[®] and commercial tablets, it appears that prednisolone would be a good candidate for application of Imaginot's Surge Dose[®] technology. In vitro dissolution results indicate that unoptimized Surge Dose[®] formulations using a combination of sodium bicarbonate and a pharmaceutically acceptable organic acid will achieve more than 80 % dissolution in 3 minutes in stirred low acid conditions compared with 30 – 40 % for commercial tablets. In tests simulating adverse physiological conditions under no stir conditions, Surge Dose[®] formulations achieved 50 % dissolution in 5 minutes compared with commercial tablets which achieved no more than 10 % dissolution after 30 minutes.

Although the drug is readily absorbed from the gastro-intestinal tract with around 100 % oral bioavailability, there is significant inter-subject variability which in some cases results in sub-therapeutic dosing. This is partly attributed to slow and variable in vivo dissolution which, based on the drug's solubility relative to typical therapeutic doses means that dissolution rate limitation of absorption is greater with higher doses of the drug.

Surge Dose[®] will reduce or eliminate the absorption variability attributed to slow and variable in vivo dissolution with absorption profiles closer to those of solutions. Based on available published data, Surge Dose[®] prednisolone tablets would be expected to provide faster absorption than regular tablets with T_{max} values of 1 – 3 hours, to at least match if not better absorption from ODTs with T_{max} values in the region of 1.1 – 1.3 hours, and to approach T_{max} values reported for solutions in the range 40 – 55 minutes.

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Where prednisolone is administered as a loading dose to treat acute symptoms, fast and consistent absorption is highly beneficial, and for subsequent doses at steady state, consistent absorption becomes more important. Given the potential problems with long term use of oral steroids, the more consistent absorption has the potential for reduced dosing which offers a significant benefit.

A PK study on prednisolone could be designed to provide PD data by monitoring biological markers in healthy subjects, thus reducing the need for separate PK and PD studies with lower clinical development costs.

Compared with liquids and ODTs, fast dissolving tablets eliminate the problems of convenience and palatability, while being able to use the readily available less soluble prednisolone base rather than more expensive soluble salts and conventional manufacturing methods.