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Application of Surge Dose® ultra-fast dissolution technology to ibuprofen

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Executive Summary

Imaginot Pty Ltd <Imaginot> has a portfolio of patents covering its Surge Dose® technology providing fast dissolution with subsequent fast absorption of drugs from swallow tablets. Surge Dose® formulations achieve ultra-fast activated drug dissolution under a wide range of *in vitro* test conditions reflecting both favourable and unfavourable physiological conditions which exist within the general population. These include gut stasis in migraine and neutral gastric conditions such as in patients with impaired gastric function or those taking proton pump inhibitors or antacids.

Fast dissolving Surge Dose® formulations of lornoxicam, diclofenac and paracetamol demonstrate significantly faster absorption in fasted subjects compared with existing commercial products. Typically Surge Dose® reduces individual times to peak plasma concentrations (T_{max}) eliminating the tail of slow absorption profiles seen with conventional slower absorbing tablets. For example, 76 % of subjects taking a Surge Dose® diclofenac tablet achieved T_{max} in 20 min or less, with mean and median values of 20 min. In contrast, for the dispersible commercial tablet mixed with water before administration, only 24 % subjects had a T_{max} less than 1 hour with a median T_{max} of 1.5 h and values ranging from 15 min to 4 h. Such differences have major implications when considering speed of onset of therapeutic effect.

This faster more consistent absorption seen with Surge Dose® formulations is associated with higher peak plasma concentrations (C_{max}) whilst total exposure ($AUC_{0-\infty}$) remains the same. For lornoxicam, the increase in mean C_{max} was around 40 % compared with a commercial tablet and for diclofenac around 350 % compared with a dispersible tablet taken in water positioned as a fast absorption product. This improved Surge Dose® absorption opens up the potential for reduced dosage of drugs where side effects are related to total exposure without compromising efficacy. Faster absorption and achievement of consistent high C_{max} lead to faster onset of action and potentially improved efficacy. This is supported by an increasing number of clinical studies, consistent with the predicted improved efficacy for Surge Dose® paracetamol based on PK-PD modeling.

The Surge Dose® technology has been exemplified with more than 30 commonly used drugs from a wide range of different chemistries including acidic, basic, amphoteric and unionized molecules demonstrating that significantly faster *in vitro* dissolution can be achieved. As part of its ongoing commercialization activities, Imaginot has now reviewed more than 40 drugs as potential Surge Dose® candidates. Published data can provide evidence to assess if faster dissolution *in vitro* is likely to result in faster absorption *in vivo*

leading to faster onset of action. Faster *in vivo* dissolution, particularly under less favourable conditions, should reduce inter- and intra-patient absorption variability seen with many drugs that can result in some sub-therapeutic C_{max}. Reduced variability can lead to increased efficacy for such drugs.

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) is exemplified in the Imaginot patents and is covered by specific and general claims relating to acidic molecules. It has analgesic, antipyretic and anti-inflammatory properties and is widely used in prescription and OTC products for the treatment of conditions where fast onset of action is desirable. It is increasingly being used in fixed dose combinations with other analgesics such as paracetamol and opiates as well as with proton pump inhibitors to reduce the potential for gastrotoxicity. It is a potent inhibitor of cyclo-oxygenase (COX-1 and COX-2) enzyme systems both peripherally and centrally reducing the production of prostaglandins which are implicated in pain and inflammation. This review considers the *in vivo* implications of the faster *in vitro* dissolution of Surge Dose® formulations of ibuprofen alone and in fixed dose combinations with other drugs, predicting the likely clinical benefits.

Ibuprofen is a weak acid with a pKa of 4.4 classified as a BCS Class II drug based on its high permeability and low solubility. For weak acids such as ibuprofen, solubility increases as the pH rises which favours dissolution. In contrast, acidic conditions, where solubility is lower, favour absorption with a higher proportion of the more readily absorbed ionized species present. Although the higher pH In the alkaline environment of the small intestine favours solubility so that more ibuprofen is in the less permeable ionized form, its high permeability coefficient more than compensates for ionization effects.

By promoting dissolution in the stomach into available gastric contents and co-administered water, Surge Dose® formulations produce a higher level of ionized species which reduces the extent of direct absorption by the gastric mucosa, and also leads to a shorter contact time reducing the potential for local gastric damage as the dissolved drug rapidly drains into the small intestine. This will be beneficial for any NSAID including ibuprofen where gastrotoxicity is of major concern. For acute dosing, direct local effects are minimised, and for chronic dosing, there is the potential to reduce the dose whilst maintaining high therapeutic plasma concentrations but reducing the potential for systemic gastrotoxicity.

There is evidence of variable and dissolution rate limited absorption following oral administration of ibuprofen. Fastest absorption occurs from soluble ibuprofen products where T_{max} is around 15 – 30 minutes compared with 1 - 2 hours for conventional swallow tablets. Similar superior performance is seen with liquid filled soft gelatine capsules where rupture time for the capsules does not appear to significantly slow absorption, and also for tablets of the highly soluble salts such as ibuprofen arginate, lysinate and sodium

dehydrate. Fast absorption is associated with fast onset of action with fast absorbed products achieving meaningful pain relief in 15 – 30 minutes compared with 45 – 60 minutes for conventional tablets.

The EC_{50} for ibuprofen is 23 – 25 µg/mL for analgesia and only 6 µg/mL for antipyresis. Perceptible pain relief is achieved within 10 – 15 minutes for fast absorbed products, despite lag times of 2 – 3 hours between C_{max} in plasma and synovial fluid. A plasma concentration in the range of 11 – 30 µg/mL has been shown to be associated with complete pain relief in 50 % of patients following third molar extraction.

PK studies indicate a wide range of C_{max} values following a 400 mg dose of standard ibuprofen tablets with mean values around 30 – 43 µg/mL and coefficients of variation as high as 26 %. These are reduced by some 30 % after food which corresponds to the method of administration for NSAIDs taken after a meal to minimise gastrotoxicity. This means that there will be many patients who experience lower C_{max} levels that may be sub-therapeutic. This will impact efficacy in two ways through the C_{max} per se and also the T_{max} as delayed absorption will be associated with a poor response at early time points. Higher C_{max} values are achieved with more soluble products such as ibuprofen lysinate where mean C_{max} values reach around 40 µg/mL and ibuprofen arginate with mean C_{max} values around 56 µg/mL following a 400 mg dose of ibuprofen.

Good *in vitro in vivo* correlation (IVIVC) has been established for ibuprofen; faster dissolution is associated with faster absorption and faster onset of action. When the Surge Dose® formulation technology is applied to ibuprofen, ultra-fast activated *in vitro* dissolution is achieved in discriminating test methods simulating adverse *in vivo* conditions, faster than that demonstrated for other fast dissolving products. While testing in USP phosphate buffer at pH 7.2 favours dissolution of all products as a result of the high pH on drug solubility, Surge Dose® formulations show more extensive and faster dissolution even under acidic conditions simulating those first encountered *in vivo* when a tablet is swallowed.

Preliminary Surge Dose® formulations containing 200 mg ibuprofen free acid with 400 mg sodium bicarbonate exceed 80 % dissolution in 5 min in 900 mL 0.0033 M HCl at 30 rpm and 37 °C. This compares with less than 5 % dissolution even after 20 minutes from conventional commercial tablets and liquid filled capsules under the same conditions; Advil® where the drug is completely solubilized, and Nurofen® where the drug is encapsulated as a suspension.

Optimised Surge Dose® ibuprofen 400 mg formulations containing 600 mg sodium bicarbonate with 50 mg of an organic acid exceed 60 % dissolution in 5 min. Such performance is superior to the commercial product containing 200mg ibuprofen as the

highly soluble ibuprofen lysinate salt, and the 200 mg brand leader Brufen® achieving 35 % and 6 % dissolution of the lower dose respectively after 5 min.

The dissolution profiles seen with Surge Dose® ibuprofen tablets highlight the importance of pH in both the microenvironment of the dissolving drug particles and the macroenvironment into which dissolution must occur, as well as the effervescence that occurs between the bicarbonate and acidic components such as the drug, added acid and dissolution medium. The Surge Dose® development process allows the key components, namely pH modulating agents and water uptake agents, to be optimized so that the extent and rate of dissolution of each drug are maximized. When two or more drugs are formulated together, the formulation can be optimized to achieve fast release of all actives.

Based on this review, a Surge Dose® ibuprofen tablet is predicted to provide faster and more consistent *in vivo* dissolution driving faster and more consistent absorption with faster onset of action. Such formulations would be expected to achieve similar mean and median T_{max} values of 15 - 30 min, superior to other fast absorbed products such as liquid filled capsules and the various highly soluble salts, and faster than 1 – 2 h seen with conventional tablets. Faster absorption will be associated with higher C_{max} values such as seen with lornoxicam (+40 %) and diclofenac (+350 %) leading to faster time to meaningful analgesia, predicting 15 - 30 min compared with 45 – 60 min for conventional tablets. Faster onset and improved efficacy provide a real opportunity for reduced dosage without compromising efficacy to reduce the gastrotoxicity of this NSAID.

Use of the Surge Dose® technology can be effectively used to improve the dissolution and hence absorption of fixed dose combinations of ibuprofen with other drugs. None of the existing products demonstrate superior PK or PD performance with clinical responses generally being additive rather than synergistic compared with the monotherapies. There is evidence that the acidic nature of ibuprofen enhances the absorption of basic drugs in combination products. This indicates that an optimized Surge Dose® combination product designed to maximise the dissolution rate of both drugs is likely to provide enhanced fast absorption of both drugs. This increases the probability of improving efficacy capturing any potential synergies through faster and more consistent delivery of both drugs. A Surge Dose® combination product is also more likely to allow reduction of dosage to minimise side effects without compromising efficacy.

In summary, ibuprofen alone or in combinations with other drugs appears to be an ideal candidate for application of the Surge Dose® technology with a high probability of achieving improved clinical outcomes.

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1 Introduction

1.1 Technology overview

The Surge Dose® formulation technology providing ultra-fast activated 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® tablets are designed to provide superior performance even under unfavourable physiological conditions so that fast and consistent absorption and efficacy can be achieved independent of gastrointestinal (GI) activity and pH. Surge Dose® maximizes the impact of pH dependent drug solubility to increase the rate of absorption, and is also effective for drugs where solubility is independent of pH. Although low relative humidity (RH) and unit packaging are required, Surge Dose® tablets use conventional excipients and manufacturing processes.

Surge Dose® tablet formulations provide faster and more consistent drug absorption resulting in faster and more reliable onset of action. This has been demonstrated in human pharmacokinetic (PK) studies on fasted subjects with paracetamol (acetaminophen, APAP), lornoxicam and diclofenac, two acidic NSAIDs (non-steroidal anti-inflammatory drugs). While the total exposure ($AUC_{0-\infty}$) remains the same as comparator products, Surge Dose® significantly reduces mean and median times to peak plasma drug concentration (T_{max}) and can increase peak plasma levels (C_{max}) by up to 350 % as seen with diclofenac where oral Surge Dose® absorption profiles are similar to those seen after parenteral administration.

Based on PK-PD (pharmacodynamic) modelling, Surge Dose® paracetamol is predicted to achieve improved efficacy as variable absorption from conventional tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

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® formulations may also provide a clinical benefit for drugs taken on a regular basis, such as in the treatment of Parkinson's disease and other chronic indications, where GI conditions and resultant absorption can be highly variable.

Surge Dose® tablets provide a more convenient alternative to soluble and liquid products which generally result in faster drug absorption than conventional solid dosage forms. Disadvantages of liquid formulations include stability issues, the need for flavouring for acceptable taste, preservation against microbial spoilage, reduced convenience for the patient unless doses are unit packed, the need for controlled storage and higher manufacturing and packaging costs.

Surge Dose® tablets offer benefits over the new, heavily promoted second generation fast acting formulations such as liquid filled soft capsules and oral disintegrating tablets (ODTs). These do not always deliver the promised rapid onset of action required for drugs taken on demand for indications such as pain, migraine, allergy, nausea and erectile dysfunction. Whilst ODTs offer convenience without the need to take with water, a critical review of published data indicates that they result in slower rather than faster absorption, and there is no evidence of faster onset of action or improved efficacy.

Surge Dose® tablets are designed to be absorbed more like a solution as the drug will rapidly dissolve in the stomach contents after oral administration regardless of gastric pH and motility. This means that dissolved drug rapidly reaches the small intestine and is available for absorption. Conventional formulations are associated with variable lag times resulting from *in vivo* capsule rupture, tablet disintegration, dispersion of capsule contents and drug dissolution which typically result in slower and more variable absorption.

1.2 IP status

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

i. PCT/AU 2006/001798 (WO/2007/059591) covering acidic and unionized, basic and amphoteric actives 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. Subsequently the claims in this patent have been restricted to acidic and unionized drugs. The amended patent has been granted in Australia and expedited examination is underway in the US under the PPH.

ii. PCT/AU 2005/00759 (WO/2005/115345) covering basic and amphoteric actives claiming priority from 28 May 2004. Patents have been granted in Australia and Canada without limitation and examination is progressing in the US, Europe, India and Japan.

iii. PCT/AU 2005/00758 (WO/2005/115344) covering paracetamol and combinations. The patent has been granted in Australia and Canada with US patent examination progressing. It has been 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 with *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs not exemplified are covered by broad platform claims.

1.3 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), India's largest pharmaceutical company (Abbott Healthcare Pvt Ltd) and Piramal Healthcare Ltd, an international drug delivery technology contract development and manufacturing company.

Surge Dose® formulations demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions. The first Surge Dose® product lornoxicam was launched in 2011 and a second Surge Dose® product will be launched in 2012. Other drugs are under development with more PK studies planned to further validate this technology.

1.4 Potential for Surge Dose® ibuprofen

Ibuprofen is a member of the class of NSAIDs used therapeutically as the free acid and as various soluble salts at a dose of 200 – 400 mg. Developed as an antirheumatic drug in the 1960s, it is widely used as a prescription and OTC drug for the relief of pain and inflammation in musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, migraine and surgery.

To improve efficacy particularly in moderate to severe pain and reduce the potential for adverse events, the use of ibuprofen in fixed dose combination products is increasing:

- with proton pump inhibitors to increase gastric pH and reduce gastro-toxicity for long term use, and
- with other classes of analgesics such as opiates and paracetamol to increase the therapeutic spectrum and again reduce the potential gastro-toxicity through use of reduced doses of ibuprofen without compromising efficacy.

Ibuprofen is a potent inhibitor of prostaglandin synthesis and is a non-selective COX (cyclo-oxygenase) 1 and 2 inhibitor. It is a weak acid exemplified in the Imaginot platform patent and covered in the general and specific claims in PCT/AU 2006/001798. As an acid, its solubility will be lower under acidic gastric conditions (low pH) which will slow dissolution. Faster *in vivo* dissolution in the stomach prior to emptying into the small intestine is predicted to result in faster absorption.

This review considers the potential of ibuprofen as a candidate for the Surge Dose® ultra-fast activated dissolution technology to achieve faster *in vivo* dissolution and absorption, with improved and more consistent therapeutic outcomes. The benefits of applying the Surge Dose® technology to fixed dose combinations of ibuprofen with other drugs are also considered.

2 Clinical premise for Surge Dose®

2.1 Physiological variability affecting drug absorption

2.1.1 Gastrointestinal (GI) motility

The underlying MMC (migrating motor complex) influences gastric emptying contributing to the inter- and intra-subject variability seen in PK studies with solid dosage forms and solutions administered orally. 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 with the total cycle time generally being 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 or housekeeper wave, the shortest, most active phase (3 – 25 min) characterised by intense contractions emptying gastric contents into the 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, reducing to 12 and 5 min respectively in Phase II and Phase III[1].

[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**:1275-1282

Delayed absorption and reduced variability seen in fed studies result from interruption of the underlying MMC by food triggering Phase I MMC[2].

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 are in Phase II, with the fastest absorption occurring when the subject is in Phase III. This means that even a slow dissolving product can result in some fast absorption occasions as well as slow absorption occasions. However the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Well documented gastric emptying effects are responsible for the double or multiple absorption peaks often seen in individual subject PK profiles particularly with frequent sampling. Multiple gastric emptying peaks occurring during the first two hours differ from later peaks due to entero-hepatic recycling. They are associated with longer T_{max} values and are reported for many drugs including the NSAID diclofenac[3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13].

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

3 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

4 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

5 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

6 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

7 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

8 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

9 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

10 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

11 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

In late Phase II or Phase III, fast absorption will generally occur as the gastric contents are rapidly emptied into the small intestine resulting in a short T_{max}. In Phase I or early Phase II, there will generally be slower absorption with a longer T_{max}. However when subjects are in Phase I or II, there is 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 these multiple peaks will depend on the drug's 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. 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

2.1.2 Gastric pH

Although gastric contents are acidic in the fasted healthy state, there is wide variability in inter- and intra-subject gastric pH ranging from pH 1 to 7 during the day 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
- 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 have relatively high gastric pH most of the time

[12] 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

[13] 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

- 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 is higher

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.

Hence gastric pH will affect the dissolution rate of an orally administered drug depending on its physicochemical properties. Increased solubility will result in faster dissolution in any co-administered water. Conversely, reduced solubility will slow dissolution, with less drug dissolved and available for absorption when emptied into the small intestine. Higher concentrations of dissolved drug will drive absorption and distribution of the drug.

When optimizing drug formulations to ensure adequate solubility and fast dissolution under a wide range of physiological conditions both solubility and degree of ionization need to be considered. However for drugs with a high permeability coefficient, the effect of increased solubility more than compensates for the ionization effects.

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

2.2 Clinical rationale

Drug absorption following oral administration is influenced by:

i. the rate at which the drug will dissolve from the dosage form into available fluids in the stomach including any co-administered liquid,

ii. the underlying GI motility or phase of the MMC which periodically empties the stomach contents into the small intestine, and

iii. the rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine which is independent of the MMC.

While the physiological conditions of the patient cannot be changed by the dosage form, 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® formulations are designed to achieve ultra fast dissolution under the wide range of favourable and unfavourable conditions that occurs in the 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, faster *in vitro* dissolution profiles relative to currently marketed products 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 peak plasma concentrations (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® is designed to maximize the extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC and is absorbed as summarized in Figure 1:

i. Drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents

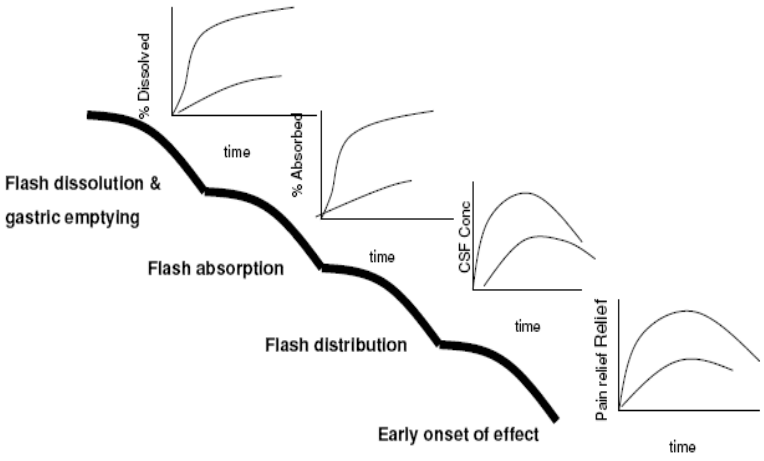
ii. Resultant solution empties rapidly and passively from the stomach in fed and fasted states independent of the MMC i.e. empties as fast as when taken as a solution

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 leading to earlier achievement of therapeutic plasma concentrations with short T_{max} and high C_{max} as well as 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

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



2.3 Proof of concept

2.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects[14] demonstrated significantly faster absorption with two fast dissolving Surge Dose® paracetamol formulations that have subsequently been improved, compared with Tylenol® Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol®>:

- Median T_{max} values for the Surge Dose® formulations were 17 and 25 min compared with 45 min for Tylenol®
- Surge Dose® $AUC_{0\text{-}30}$ values indicated 3 times as much absorbed in the first 30 min compared with Tylenol®

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

- 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 levels.

PK-PD modelling to quantify pain relief following oral administration predicted more rapid onset and greater analgesia with Surge Dose® paracetamol tablets than Tylenol® tablets[15]. Improved clinical efficacy is 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 will lead to increased clinical efficacy through a higher frequency of doses exceeding minimum therapeutic plasma concentrations.

2.3.2 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 commercial tablet[16]. Film coated Surge Dose® tablets produced significantly reduced T_{max} values and

[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

[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

resulted in significantly higher C_{max} levels similar to parenteral administration[17]. 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 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 peak plasma concentrations comparable with parenteral administration, around 40 % higher than the reference tablet with mean C_{max} 1098 ng/mL (CV 18.71 %) compared with 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 than with the reference tablet

2.3.3 Diclofenac

Preliminary results from a PK study in 21 fasted healthy subjects show faster, more consistent absorption of diclofenac with significantly higher C_{max} for a film coated Surge Dose® formulation containing 50 mg diclofenac sodium compared with Voveran®-D (Novartis), a dispersible tablet dissolved in water before administration, containing 46.5 mg diclofenac free acid[18].

Mean and median T_{max} values are similar for Surge Dose® tablets 19.5 min (± 5.0) and 19.5 min (range 5 – 30 min). By comparison the dispersible tablets show much slower more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h).

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[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

[18] Piramal Clinical Research. Report No CR-BE-324-DICL-2011 (draft) An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose comparative pharmacokinetic study of Diclofenac Rapid Release tablets 50 mg sodium diclofenac comparing with Voveran D dispersible tablets 46.5 mg diclofenac free acid in healthy adult human subjects under fasting conditions. March 2012

Although AUC values are similar, the Surge Dose® tablets result in significantly higher C_{max} values as a result of the faster absorption, 3,569 ± 1,515 ng/mL compared with 1,042 ± 518 ng/mL for the dispersible tablets.

Again the absorption profile of Surge Dose diclofenac is more similar to that from parenteral administration than other solid oral dosage forms with an expectation that this faster absorption will lead to improved efficacy and faster onset of action with the convenience and acceptability of an oral product[19, 20,21, 22].

3 Technical requirements for Surge Dose®

In Surge Dose® formulations, levels and ratios of pH modulating agents and water uptake agents are optimized for each drug or drug combination. This provides a pH-controlled activated dissolution system to 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 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 MMC. 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 absorption is more dependent on MMC gastric emptying often producing multiple peaks.

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 present

[19] 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

[20] Hinz B, Chevts J, Renner B, Wuttle H, Rau T, Schmidt A, Szelenyi I, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. Br J Clin Pharmacol (2005) 59(1):80-4

[21] Colberg K, Hettich M, Sigmund R, Degner FL. The efficacy and tolerability of an 8-day administration of intravenous and oral meloxicam: a comparison with intramuscular and oral diclofenac in patients with acute lumbago. Curr Med Res Opin (1996) 13(7):363-77

[22] Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration before operation suppress post-operative pain. Anaesth (1990) 45:763-66

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 at which pH they demonstrate minimum aqueous solubility.

No major capital investment is required and use of conventional ingredients should not present any regulatory hurdles. Surge Dose® formulations use approved GRAS excipients and traditional manufacturing equipment for direct compression or wet granulation. Film coatings can be selected to have minimal impact on dissolution either *in vitro* or *in vivo.* 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 provide maximum stability and an acceptable shelf life of 2 years. Small scale Surge Dose® batches of many different drugs have been manufactured, and to date three have been successfully scaled-up for commercial manufacture.

A range of highly discriminating *in vitro* dissolution methods is used as a development rather than a QC tool, with standard dissolution 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:

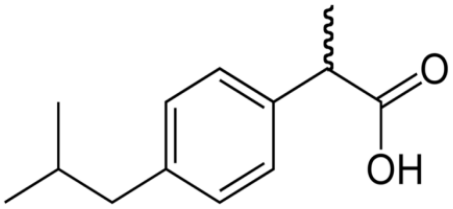
- 900 mL 0.05 M HCl at 30 rpm where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.3, contains the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo,* and is used to characterise Surge Dose® formulations
- 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

4 Effect of Surge Dose® on ibuprofen dissolution

4.1 Physicochemical properties and permeability

Ibuprofen is a chiral 2-arylpropionic acid derivative with the formula $C_{13}H_{18}O_2$, a molecular weight of 206.28, and the chemical structure shown in Figure 2.

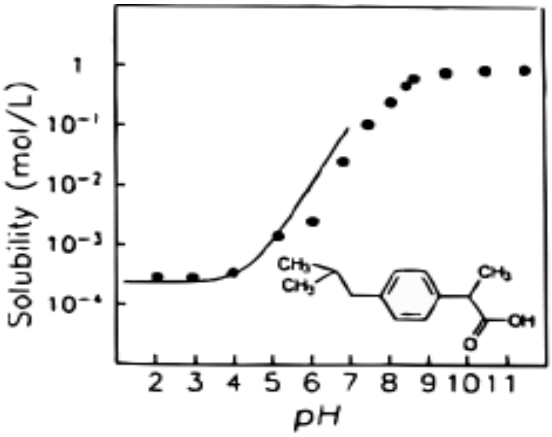
Figure 2 Chemical structure of ibuprofen



The S-enantiomer has greater biological activity (~160 times the potency *in vitro*) than the R-form which is considered clinically inactive. Although the single enantiomer was approved in Austria in 1994, the racemic mixture continues to be widely used[23]. *In vitro* the R-form is slowly and incompletely (~60 %) converted to the active S-form[24].

Ibuprofen has a pKa of 4.4 and pH dependent solubility as seen in Figure 3[25].

Figure 3 Solubility – pH profile for ibuprofen (from Avdeef et al 2000)



[23] Tan SC, Patel BK, Jackson SHD, Swift CG, Hutt AJ. Ibuprofen stereochemistry: double the trouble? *Enantiomer* (1999) **4**:195-203

[24] Cheng H, Rogers JD, Demetriades JL, Holland SD, Seibold JR, Depuy E. Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans. *Pharm Res* (1994) **11**(6):824-30

[25] Avdeef A, Berger CM, Brownell C. pH-metric solubility 2: correlation between the acid-base titration and the saturation shake-flask solubility-pH methods. *Pharm Res* (2000) **17**(1):85-9

Ibuprofen has a solubility around 78 μg/mL at pH 4, increasing to 291 mg/mL at pH 8, and 4.13 mg/mL in simulated intestinal fluid without enzymes at pH 6.8. Based on these solubility data, only 7.8 % of the dose would be expected to dissolve in 200 mL of dissolution medium at pH 4, and around 35 % of a 200 mg dose in 900 mL under the same conditions. Therefore complete dissolution would not be expected in typical acidic dissolution media. However the full dose would be freely soluble at pH 6.8, where 200 mL would dissolve 826 mg which exceeds the dose of 200 mg. Thus at neutral pH, the solubility of ibuprofen complies with the BCS criterion for high solubility with a dose:solubility ratio less than 250 mL.

The sodium salt is more soluble in water and its solubility also increases with increasing pH. The highest permeability coefficient for ibuprofen sodium occurs at pH 4 when more than 50 % of the drug is unionized which form is readily absorbed. Increasing the pH of the liquid available for dissolution, whether *in vivo* or *in vitro*, will increase the solubility of the drug but will also increase the proportion of the less permeable ionized form. However *in vitro* diffusion studies[26, 27] indicate that for ibuprofen and its sodium salt the lower permeability of the ionized species at higher pH is more than compensated for by the increased solubility at higher pH. The steady-state flux of ibuprofen sodium is greater at higher pH despite the higher permeability coefficient at lower pH where the fraction of the readily absorbed unionized species is greater. At pH 4, solubility is 0.028 mg/mL with a permeability coefficient of 38,300 x 10^{-6} cm/s, whereas at pH 6, solubility is 1.0 mg/mL with a permeability coefficient of 3,100 x 10^{-6} cm/s. At pH 7 where solubility is greatest at 340.5 mg/mL, the permeability coefficient is down to 13.5 x 10^{-6} cm/s which is still above the limit of 10 x 10^{-6} cm/s generally accepted as the lower limit for well absorbed drugs.

Based on its high permeability and pH dependent solubility, ibuprofen is classified as a BCS class II drug with predicted dissolution rate limited absorption. In light of the drug's usage, its high therapeutic index and uncomplicated PK, a biowaver for immediate release tablets has been justified[28]. It is suggested that ibuprofen fits in the proposed "intermediate solubility class" for drugs with high solubility at either pH 1.2 or 6.8 which are both physiologically relevant. However such products must contain only listed excipients which do not include alkaline agents such as hydroxides, bicarbonates, antacids or amino acids that will increase drug solubility.

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26 Sarveiya V, Templeton JF, Benson HAE. Ion-pairs of ibuprofen: increased membrane diffusion. *J Pharm Pharmacol* (2004) **56**:717-24

27 Levis KA, Lane ME, Corrigan OI. Effect of buffer media composition on the solubility and effective permeability coefficient of ibuprofen. *Int J Pharmac* (2003) **253**:49-59

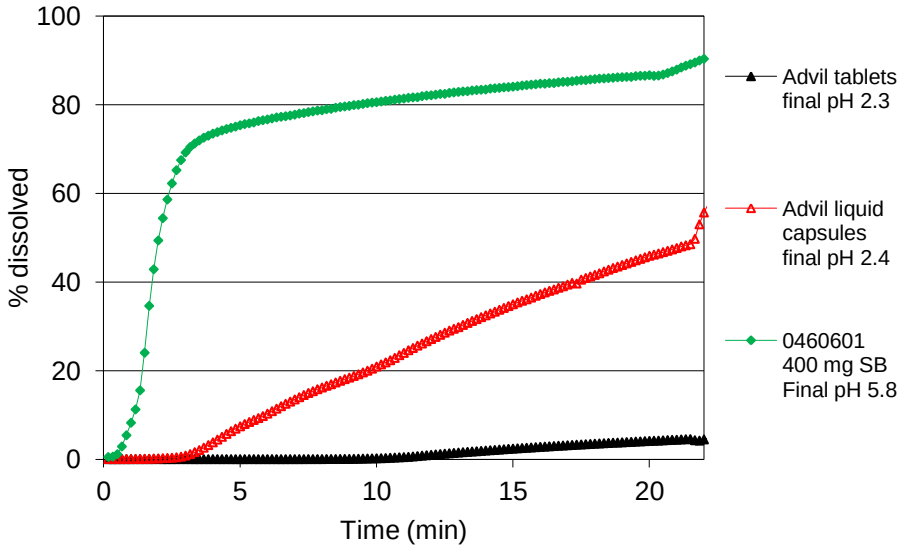
28 Potthast H, Dressman JB, Juninger HE, Midha KK, Shah VP, Vogelpoel H, Barends DM. Biowaver monographs for immediate release solid oral dosage forms: ibuprofen. *J Pharm Sci* (2005) **94**(10):2121-2131

4.2 Fast dissolving Surge Dose® tablets

Imaginot has shown that experimental Surge Dose® tablets containing 200 mg ibuprofen as the free acid or sodium salt with 400 mg sodium bicarbonate demonstrate significantly faster dissolution than commercial Advil® and Nurofen® tablets and liquid filled softgel capsules under a range of conditions that simulate adverse physiological conditions[29,30]. Although formulations were not optimized, *in vitro* dissolution exceeding 80 % within 3 minutes was achieved.

Figure 4 compares the dissolution of the Surge Dose® tablet compared with Advil® tablets and liquid capsules in 900 mL 0.0033 M HCl.

Figure 4 Dissolution Surge Dose® ibuprofen compared with Advil® tablets and liquid capsules in 900 mL 0.0033 M HCl at 30 rpm



Dissolution from the Surge Dose® tablet exceeds 70 % within 3 min compared with negligible dissolution from the Advil® tablet. The Advil® liquid filled capsule shows steady dissolution after a lag time of around 4 min as the solubilized drug is released from the capsule after rupture. The Surge Dose® tablet increases the final pH to 5.8 which is sufficient to increase the drug solubility and increase its rate and extent of dissolution.

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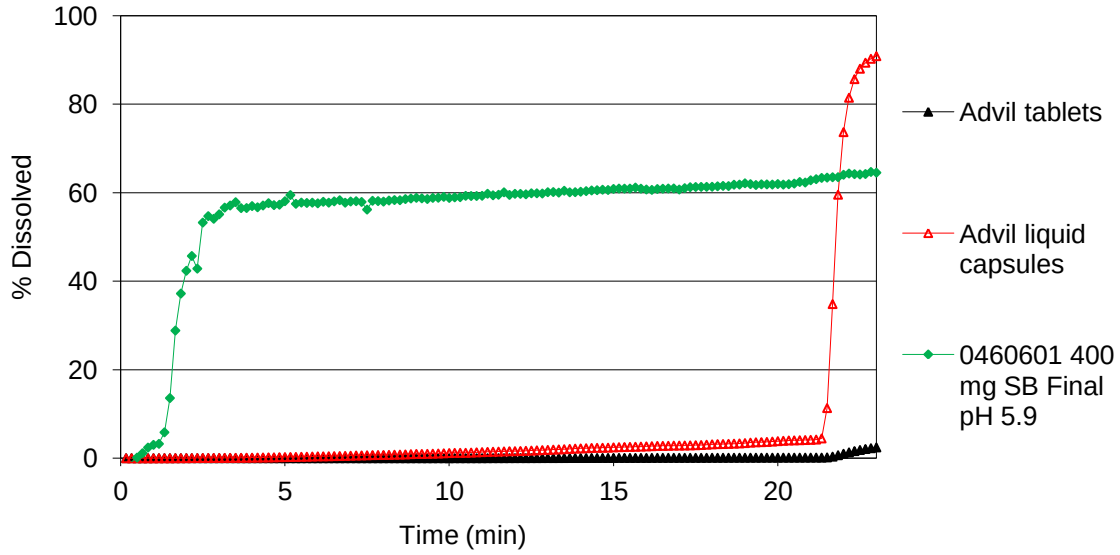
29 Imaginot Pty Ltd. DR 04-02-01 Fast dissolving swallow tablets containing ibuprofen 200 mg as the free acid, ibuprofen sodium and mixtures thereof. 28 July 2006

30 Imaginot Pty Ltd. DR 04-02-02 Dissolution of ibuprofen tablets in neutral conditions. 24 October 2006

Figure 5 shows the effect of reducing the test volume to 200 mL which better simulates physiological volumes when a tablet or capsule is swallowed with a glass of water.

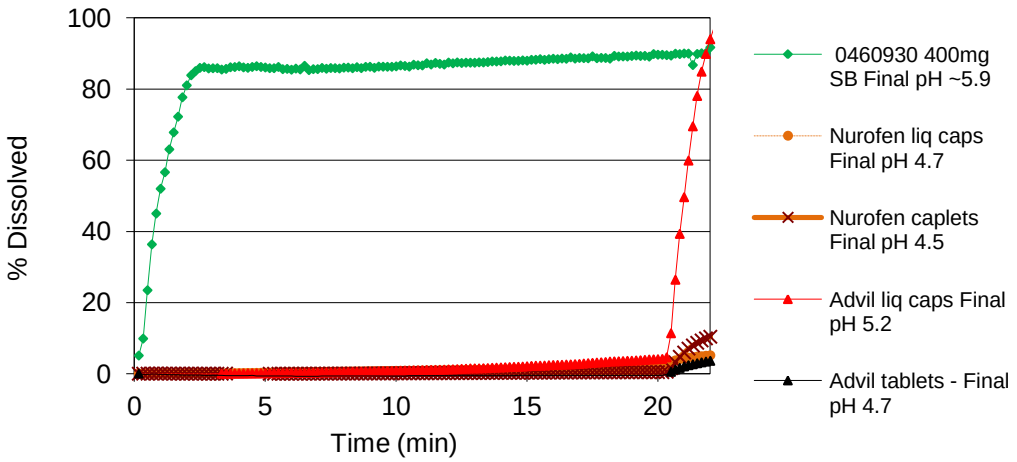
Figure 5 Dissolution Surge Dose® ibuprofen compared with Advil® tablets and liquid capsules in 200 mL 0.015 M HCl at 30 rpm



Here the acid is stronger and the lower pH depresses the solubility slowing dissolution for the two commercial products. Once the stirring speed is increased after 20 min the solubilized drug in the liquid filled capsule is totally released. The result for the Surge Dose® formulation highlights the need for further formulation development to optimize the level and composition of the pH modulating agents to better control the pH in the micro-environment around dissolving drug particles, maximizing solubility and dissolution.

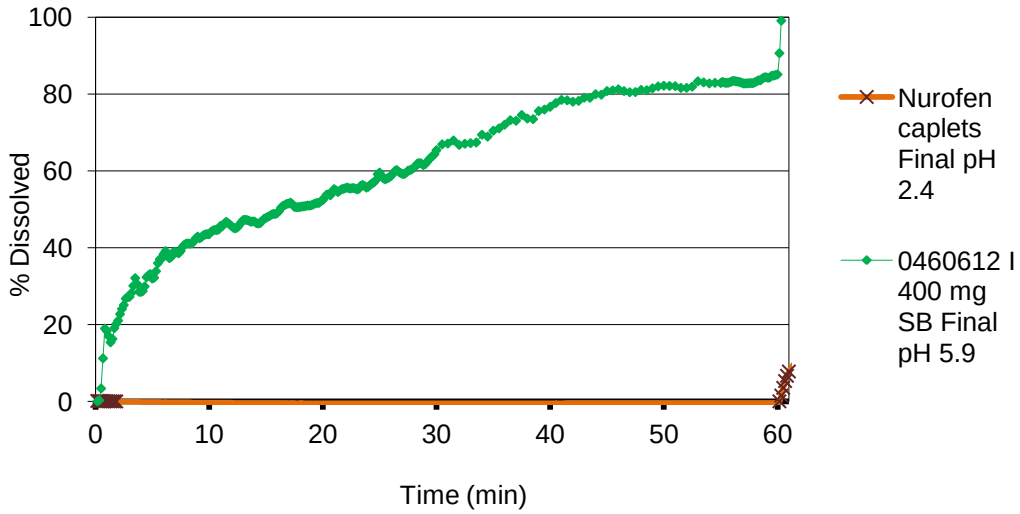
Figure 6 comparative dissolution profiles in water, a neutral pH medium that also simulates, but underestimates, the fed state as a result of the lack of buffering. In the absence of acid, the Surge Dose® formulation demonstrates its fastest and most extensive dissolution exceeding 80 % in 3 min. By comparison, the commercial caplets and the liquid filled capsules show negligible dissolution highlighting the value of the pH-controlled activated Surge Dose® dissolution. The only commercial product that demonstrated significant dissolution when the stirring speed was increased to 200 rpm after 20 min was the Advil® liquid capsules. These contain solubilised ibuprofen which remains dissolved and disperses in the water once the capsule ruptures. With the suspension in the Nurofen® liquid capsules, the suspension does not readily disperse with the water even when the stirring speed increases which has little impact on the extent of dissolution and dissolution of drug still needs to occur.

Figure 6 Dissolution of Surge Dose® ibuprofen compared with Advil® and Nurofen® tablets and liquid capsules in 200 mL water at 30 rpm



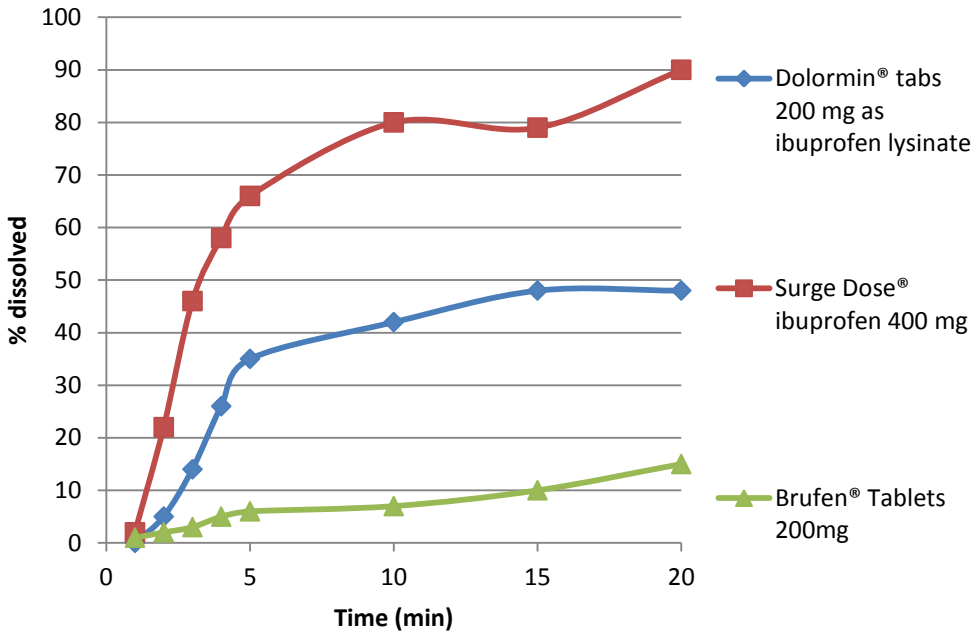
The intrinsic activated dissolution features of the Surge Dose® formulations are shown in Figure 7 exceeding 20 % dissolution in 3 minutes compared with Nurofen® caplets that show negligible dissolution even after 1 hour. Testing was conducted in 900 mL 0.0033 M HCl without stirring (0 rpm) simulating gut stasis as a result of migraine, pain and other pharmacological or physiological effects.

Figure 7 Dissolution from Surge Dose® ibuprofen tablets containing 400 mg sodium bicarbonate (0460612) and Nurofen® caplets in 900 mL 0.0033 M HCl at 0 rpm



The *in vitro* dissolution of a Surge Dose® ibuprofen tablet containing 400 mg ibuprofen free acid has been compared with that of the commercial product Dolormin® containing 200 mg ibuprofen as the lysine salt and the brand leader Brufen® 200 mg tablets. Comparative dissolution profiles in 900 mL 0.0033 M HCl at 30 rpm are shown in Figure 8. Dissolution of the ibuprofen lysinate from the Dolormin® tablets is slower and less extensive than from the Surge Dose® tablets containing double the dose of drug under conditions that reflect non-sink conditions that exist *in vivo*. The standard Brufen® tablet shows very limited dissolution under these acidic conditions.

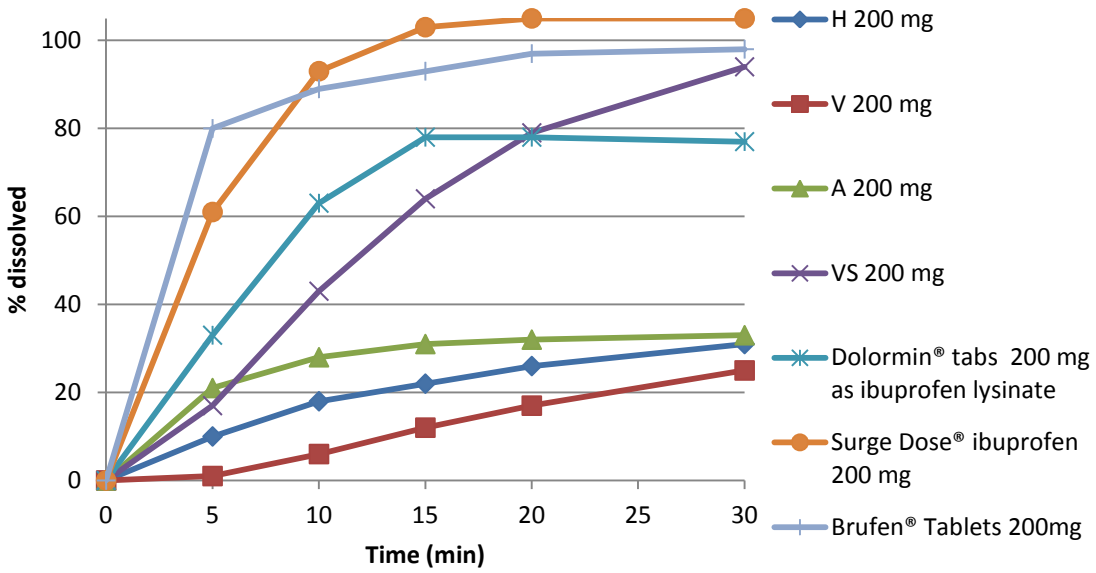
Figure 8 In vitro dissolution profiles for Surge Dose® ibuprofen 400 mg compared with 200 mg Dolormin® tablet containing ibuprofen lysinate and Brufen® standard 200 mg tablet in 900 mL 0.0033 M HCl at 30 rpm



When the same tablets are tested under more favourable conditions in 900 mL USP phosphate buffer pH 7.2 at the higher stirring speed of 50 rpm, the Brufen® tablet performs far better, comparable with Surge Dose®. Both dissolve faster than the ibuprofen lysinate product and achieve higher levels of dissolution. Despite the higher solubility of ibuprofen lysinate, this offers no advantage over tablets containing the less soluble free acid such as used in Surge Dose®. The Dolormin® tablets show slower and less extensive dissolution reaching a plateau around 80 % compared with the Surge Dose formulation which reaches around 60 % dissolution in 5 minutes in both acidic and neutral dissolution media.

These profiles are shown in Figure 9 with dissolution data for 4 other generic ibuprofen tablets which show very variable disslution.

Figure 9 In vitro dissolution profiles of Surge Dose® ibuprofen 200 mg compared with 200 mg Dolormin® (ibuprofen lysinate, Brufen® 200 mg and other generic tablets in 900 mL USP phosphate buffer 7.2 at 50 rpm



In all cases, the optimized Surge Dose® tablet formulations containing ibuprofen outperform all commercial products under a wide range of different *in vitro* test conditions that will better approximate to *in vivo* conditions.

5 Ibuprofen as a potential Surge Dose® candidate

5.1 Pharmacokinetics (PK)

Ibuprofen is a BCS class II drug with high membrane permeability which is rapidly and completely absorbed by passive diffusion approaching 100 % oral bioavailability. Plasma concentration – time profiles are best described by an open two compartment model with first order absorption for solutions and suspensions[31]. However absorption is dissolution rate limited as a result of the pH dependent solubility of this weakly acidic drug as shown by zero order

[31] Davies NM. Clinical pharmacokinetics of ibuprofen- the first thirty years. *Clin Pharmacokinet* (1998) **34**(2):101-15

kinetics (constant absorption rate) with conventional tablets, This is suggestive of dissolution rate limitation given the absence of carrier-mediated transport systems for ibuprofen[32].

At therapeutic concentrations, ibuprofen is 90 - 99 % bound to plasma proteins with an elimination half life ($t_{1/2}$) of about 2 h. Unbound ibuprofen distributes rapidly into synovial fluids where the drug exhibits longer T_{max}, lower C_{max} and longer $t_{1/2}$ than in plasma. In adults there is a lag of around 150 min before synovial fluid concentrations exceed those in plasma. In children, T_{max} in synovial fluids is 5 – 6 h, after which synovial concentrations remain higher than plasma.

Ibuprofen is absorbed quickly from solution with T_{max} around 15 min compared with 1 – 2 h for tablets, indicating delayed absorption from tablets as a result of *in vivo* disintegration and dissolution. Effervescent tablets dissolved before administration also demonstrate fast absorption with T_{max} values of 15 – 40 min. As pre-dispersed tablets in 240 mL water and orange juice had similar mean T_{max} values to tablets of 1.0 – 1.9 h, dissolution rather than disintegration appears to be absorption rate limiting[33]. In this study, the AUC in the first 2.5 h was consistently higher for the swallow tablets than the pre-dispersed tablets which were also found to cause greater gastric irritation probably as a result of greater dissolution and availability of unionized drug at low pH allowing absorption by gastric mucosal cells.

Food reduces C_{max} by around 20 % delaying T_{max} to 1.5 – 3 h. A study in 38 healthy volunteers showed a standardised continental breakfast delayed median T_{max} for ibuprofen tablets from 1.38 (0.5 – 4.0) h in the fasted state to 1.63 (0.75 – 4.0) h[34]. The range remained wide in both fed and fasted states again indicative of dissolution rate limited absorption from tablets.

5.2 IVIVC

The BCS class II assessment is supported by reported *in vitro in vivo* correlations (IVIVC) which are predicted for such drugs as shown in Figures 10 and 11[35]. Dissolution was performed using the USP rotating basket method in 900 mL phosphate buffer pH 7.2 at 150 rpm which conditions

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[32] Wagner JG, Albert KS, Szpunar GJ, Lockwood GF. Pharmacokinetics of ibuprofen in man IV: absorption and disposition. *J Pharmacokinet Biopharm* (1984) **12**(4):381-99

[33] Friedman H, Seckman C, Lanza F, Royer G, Perry K, Francom S. clinical pharmacology of predisintegrated ibuprofen 800 mg tablets: an endoscopic and pharmacokinetic study. *J Clin Pharmacol* (1990) **30**:57-63

[34] Kleuglich M, Ring A, Scheurer S, Trommehauser D, Schuijt C, Liepold B, Berndl G. Ibuprofen extrudate, a novel rapidly dissolving ibuprofen formulation: relative bioavailability compared to ibuprofen lysinate and regular ibuprofen and food effect on all formulations. *J Clin Pharmacol* (2005) **45**:1055-61

[35] Hannula AM, Marvola M, Rajamaeki M, Ojantakanen. Effects of pH regulators used as additives on the bioavailability of ibuprofen from hard gelatin capsules. *Eur J Drug Metab Pharmacokinet* (1991) **Spec No 3**:221-7

are unlikely to be highly discriminating due to the alkaline pH favouring solubility and the high stirring speed. Using sodium bicarbonate or calcium carbonate as the filler significantly increased the dissolution rate of ibuprofen from hard gelatin capsules compared with aluminium hydroxide or tartaric acid as a result of higher solubility at higher pH facilitating dissolution.

Figure 10 ***Dissolution of ibuprofen 200 mg from hard gelatin capsules containing aluminium hydroxide (□), calcium carbonate (△), tartaric acid (○) and sodium bicarbonate (●) (from Hannula et al 1991)***

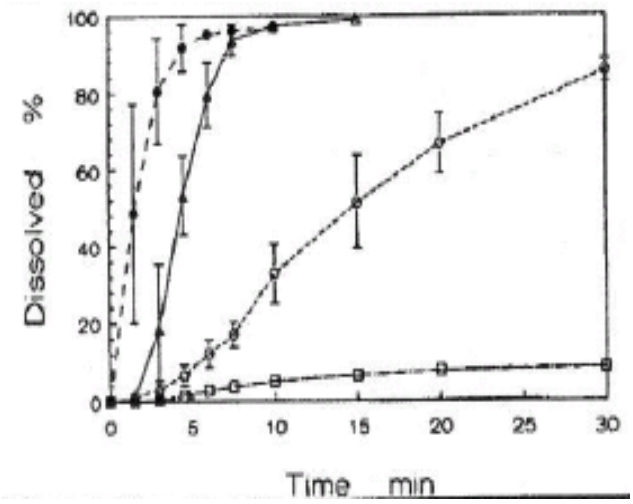
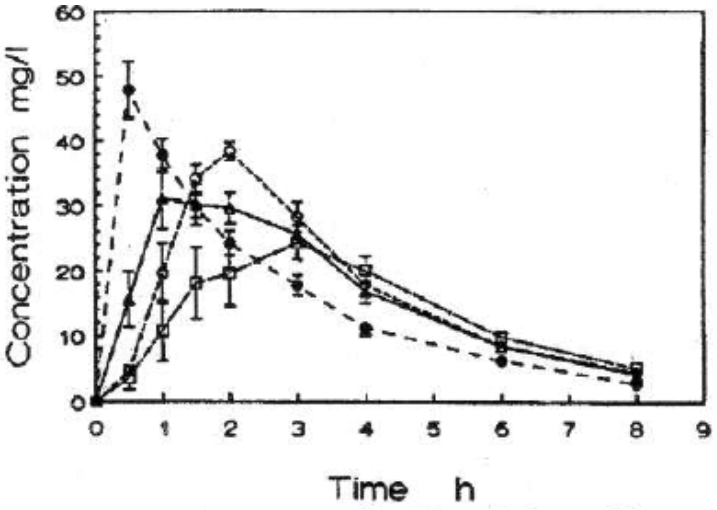


Figure 11 ***Mean plasma concentrations ± SE for ibuprofen 400 mg administered as hard gelatin capsules with aluminium hydroxide (□), calcium carbonate (△), tartaric acid (○) and sodium bicarbonate (●) (from Hannula et al 1991)***



Sodium bicarbonate had the greatest effect on both *in vitro* dissolution and *in vivo* absorption, with a mean T_{max} of 0.4 ± 0.3 h which correlated with faster *in vitro* dissolution.

Although capsules containing 400 mg ibuprofen with 264 mg sodium bicarbonate, 222 mg dicalcium phosphate or 195 mg lactose as a filler showed differences in absorption profiles (Figure 12) but did not show any marked differences in *in vitro* dissolution in pH 7.2 phosphate buffer at 150 rpm (Figure 13)[36].

Figure 12 ***Mean plasma concentrations ± SE for ibuprofen 400 mg administered as hard gelatin capsules with lactose (○), dicalcium phosphate (●) and sodium bicarbonate (▼) (from Ojantakanen et al 1990)***

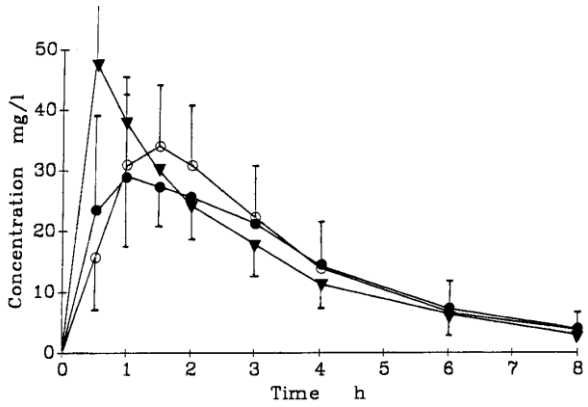
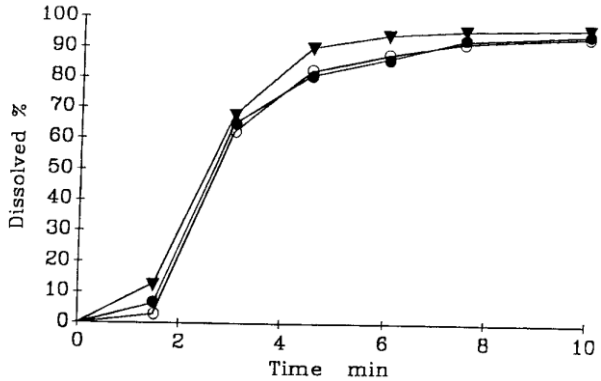


Figure 13 ***Dissolution profiles for ibuprofen 400 mg in hard gelatin capsules with lactose (○), dicalcium phosphate (●) and sodium bicarbonate (▼) in 900 mL pH 7.2 phosphate buffer at 150 rpm (from Ojantakanen et al 1990)***



[36] Ojantakanen S, Hannula aM, Marvola M. Bioavailability of ibuprofen from hard gelatin capsules containing sodium bicarbonate, lactose or dicalcium phosphate. Acta Pharm Fenn (1990) 99:119-26

In both studies, individual subject absorption profiles shoed a high degree of variability with some evidence of double peaks that could be explained by gastric emptying patterns as seen in Figures 14 and 15.

Figure 14 ***Individual plasma concentration time profiles for 4 subjects receiving ibuprofen 400 mg as hard gelatin capsules with lactose (○), dicalcium phosphate (●) and sodium bicarbonate (▼) (from Ojantakanen et al 1990)***

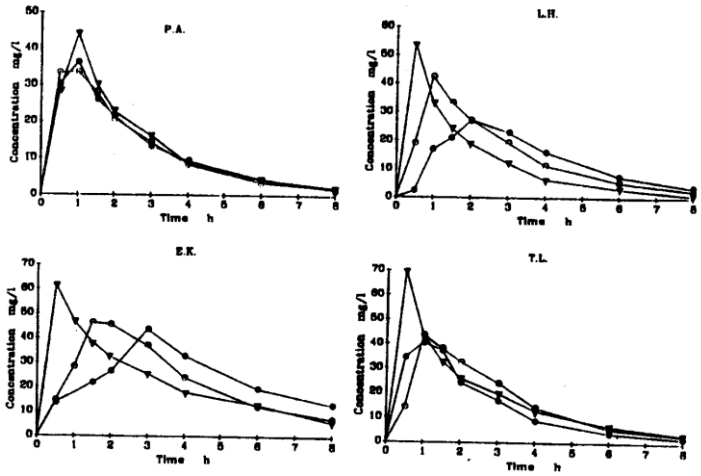
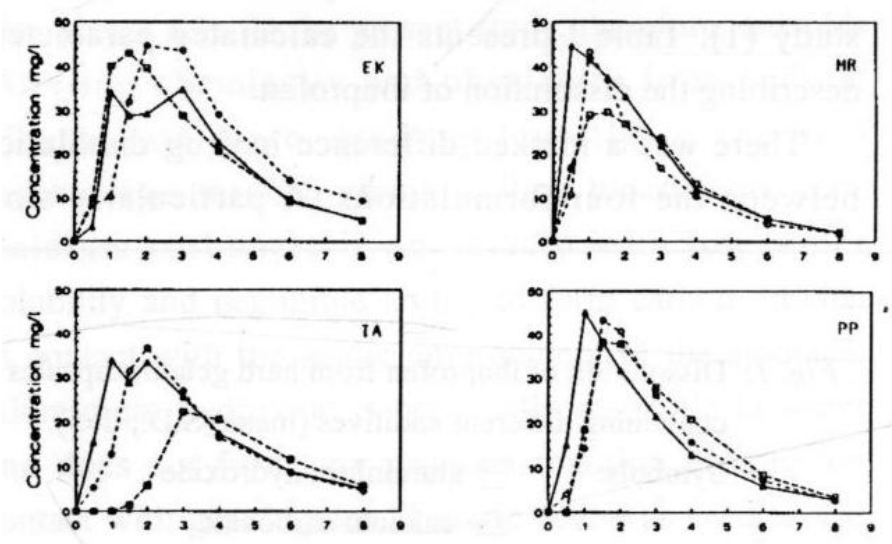


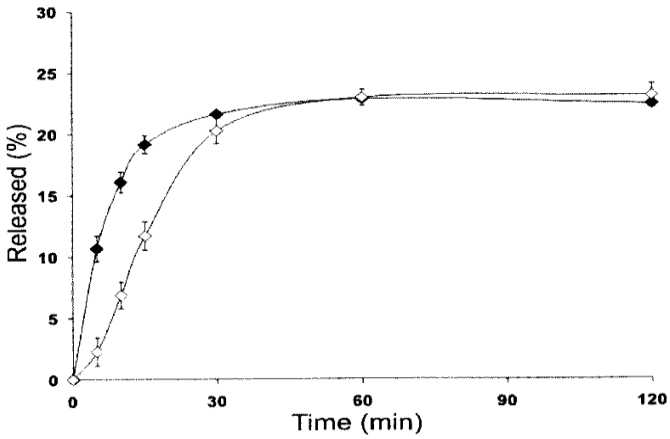
Figure 15 ***Individual plasma concentration time profiles for 4 subjects receiving ibuprofen 400 mg as hard gelatin capsules with aluminium hydroxide (□), calcium carbonate (△), tartaric acid (○) and sodium bicarbonate (●) (from Hannula et al 1991)***



Fast *in vitro* dissolution under acidic conditions has been shown to be correlated with fast absorption in both rats and humans[37]. Dissolution profiles are shown in Figure 16 with both products showing similar limited dissolution at 20 – 25 %.

In fasted healthy subjects, similar C_{max} values were obtained for the faster dissolving and the regular formulation at 43.1 ± 6.77 µg/mL and 43.5 ± 8.31 µg/mL respectively. However the rates of absorption were very different with mean T_{max} for the fast dissolving tablet of 1.26 ± 0.49 h compared with 2.19 ± 1.45 h for the regular tablet. Of note is the reduced variability for the faster dissolving tablet which has a lower standard deviation.

Figure 16 Dissolution profiles for a fast and regular dissolving formulation of ibuprofen in 900 mL simulated gastric fluid at pH 1.2 at 50 rpm and 37 °C (from Jamali & Aghazadeh-Habashi 2008)



Improved *in vitro* dissolution has also been demonstrated for ibuprofen lysinate across a wider range of pH compared with the standard tablets as shown in Figure 17[38]. The ibuprofen lysinate achieves significant release at pH 4.0 whereas there is negligible release from standard tablets at this pH, only showing significant dissolution at pH 7.2 which would suggest that little dissolution occurs until the tablet reaches the small intestine contributing to the longer lag time and slower absorption in fasted and fed conditions. This improved dissolution of the lysinate is associated with faster absorption and faster onset of action.

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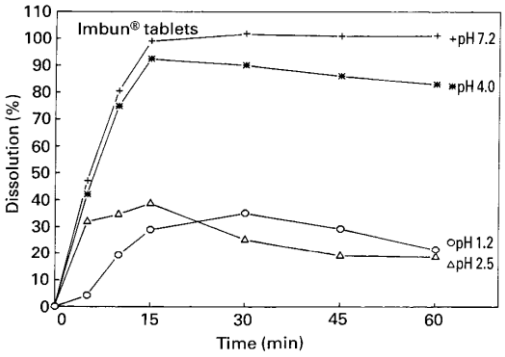
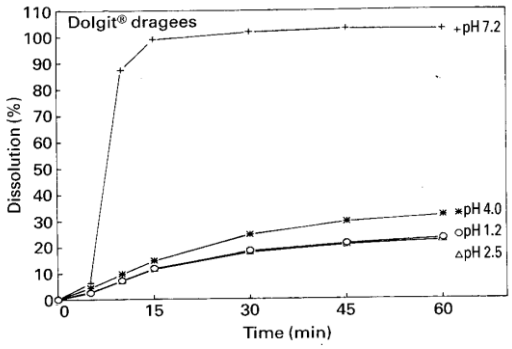
[37] Jamali F & Aghazadeh-Habashi A. Rapidly dissolving formulations for quick absorption during pain episodes: ibuprofen. Int J Clin Pharmacol Ther (2008) 46(2):55-63

[38] Geisslinger G, Dietzel K, Bezler H, Nuernberg B, Brune K. Therapeutically relevant differences in the pharmacokinetical and pharmaceutical behaviour of ibuprofen lysinate as compared to ibuprofen acid. Int J Clin Pharmacol Ther Toxicol (1989) 27(7):324-8

Figure 17 In vitro dissolution profiles for standard ibuprofen tablets and ibuprofen lysinate tablets in different dissolution media (from Geisslinger et al 2005)

Lysine ibuprofen tablets	Standard ibuprofen tablets
	

Based on the significantly faster and more extensive dissolution demonstrated by Surge Dose® formulations which exceed 50 % dissolution at 5 min under acidic conditions at pH 1.7, shorter T_{max} and higher C_{max} would be expected *in vivo*.

Based on this comparative *in vitro* dissolution data, it would be expected that a Surge Dose® ibuprofen tablet would achieve faster and more extensive dissolution under *in vivo* conditions with resultant faster absorption particularly as the improved dissolution still occurs under acidic conditions.

5.3 Pharmacodynamics (PD)

5.3.1 Mechanism of action

Ibuprofen has analgesic, antipyretic and anti-inflammatory activity as a result of inhibition of peripheral cyclo-oxygenase enzymes (COX 1 and COX 2) thus inhibiting the release of prostaglandins and related substances. It also reduces neutrophil activity and acts on leukocytes to prevent inflammatory oedema which add to its anti-inflammatory effects. Ibuprofen also has a central action inhibiting COX 2, preventing spinal release of excitatory amino acids involved in nociception and down regulating nitric oxide production.

5.3.2 PK-PD correlation

The therapeutic window for plasma levels of ibuprofen is 10 – 50 mg/L with toxicity occurring at plasma concentrations above 100 mg/L. Published studies show C_{max} values well within this therapeutic window with plasma levels of 11 – 30 µg/mL being associated with complete pain

relief in 50 % of patients after third molar extraction[39]. The EC_{50} plasma concentration for ibuprofen at which 50 % of the maximum analgesic effect is achieved, is reported as 24.4 ± 1.15 µg/mL (23.2 – 25.5), achieved within the first 20 min post dose with fast acting formulations[40]. For antipyresis, the EC_{50} is estimated to be lower at 6.16 µg/mL[41].

Good correlation has been demonstrated between plasma concentrations of ibuprofen and clinical analgesic response with reports that analgesic effects are stronger the faster the drug is absorbed[42]. In postoperative dental pain evaluating the effect of 400, 600 and 800 mg ibuprofen increased plasma levels were associated with increased analgesia[43]. 54 % of subjects had no pain at1 h and no reports of severe pain were associated with C_{max} values greater than 30 µg/mL. At levels of 26 µg/mL there was an even chance of subjects reporting no pain, and at 48 µg/mL the chances of reporting no pain increased to 3:1. The plasma concentration - dose distribution showed significant overlap with a high degree of intersubject variability. This contributed to the lack of correlation between C_{max} and the fact that a different tablet with different dissolution characteristics was used for the 600 mg dose compared with the tablets used for the 400 and 800 mg doses. However there was correlation between high plasma levels and analgesia in the first 2 hours post dose.

In fever, peak effects are reported 2.5 - 3 h after administration of ibuprofen suspensions to febrile children with T_{max} of 54 min compared with 183 min for maximum temperature reduction[44]. For products with T_{max} values of 1.9 h (soluble effervescent granules) and 0.9 h (suspension), a delayed effect was also reported in adults with maximum antipyresis measured at around 3 h.

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39 Oldfield V & Perry CM. Oxycodone/ibuprofen combination tablet: A review of its use in the management of acute pain. Drugs (2005) 65(16):2337-54

40 Sorgel F, Fuhr U, Minic M, Siegmund M, Maares J, Jetter A, Kinzig-Schippers M, Tomalik-Scharte D, Szymanski J, Goeser T, Toex U, Schiedel B, Lehmacher W. Pharmacokinetics of ibuprofen dihydrate and gastrointestinal tolerability of short-term treatment with a novel, rapidly absorbed formulation. *Int J Clin Pharmacol Ther* (2005) **43**(3):140-9

41 Troconiz IF, Armenteros S, Planelles MV, Benitez J, Calvo R, Dominguez R. Pharmacokinetic-pharmacodynamic modelling of the antipyretic effect of two oral formulations of ibuprofen. *Clin Pharmacokinet* (2000) **38**(6):505-18

42 Davies NM. Clinical pharmacokinetics of ibuprofen- the first thirty years. *Clin Pharmacokinet* (1998) **34**(2):101-15

43 Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen an clinical analgesic response. *Clin Pharmacol Ther* (1986) **40**(1):1-7

44 Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther* (1992) **52**:181-9

5.4 Assessment against Surge Dose® criteria

There is clear evidence that ibuprofen absorption is dissolution rate limited with good correlation between *in vitro* dissolution and *in vivo* absorption. An optimised Surge Dose® ibuprofen tablet will provide faster *in vivo* dissolution than other products currently available under a wide range of favourable and unfavourable conditions. This leads to the prediction that faster absorption will occur with T_{max} values in the same range as solutions of 15 – 30 min with an associated increase in C_{max} without changing the total exposure based on $AUC_{0-\infty}$.

Earlier T_{max} and increased C_{max} levels with a Surge Dose® ibuprofen tablet are expected to result in improved efficacy with more patients reaching therapeutic levels earlier. As increased C_{max} values are achieved without changing the total exposure it is likely that doses could be reduced without compromising efficacy as a result of the more consistent absorption.

The fact that ibuprofen levels in the CNS remain high after plasma levels have dropped add to the potential for extended duration of action through the central effects of this drug.

6 Improved performance products

6.1 Liquid filled soft gelatin capsules

With increasing OTC use of ibuprofen, product innovation has provided an opportunity for differentiation in a highly competitive market. Soft gelatin capsules, first approved for OTC use in 1995, deliver solubilized ibuprofen in a convenient portable, ready to swallow unit dosage form. Unlike oral disintegrating tablets (ODTs) or liquid formulations, swallow tablets and capsules present no taste and palatability issues. However unlike tablets which use conventional manufacturing equipment and processing, soft gelatin capsules are a more expensive unit dosage form requiring major capital investment or contract manufacture.

In the USA, Advil® Liquigels (Wyeth Consumer Health) containing ibuprofen free acid and ibuprofen potassium have been registered for mild to moderate migraine as a new indication demonstrating bioequivalence with a 20 mg/mL ibuprofen suspension as the reference listed drug (RLD)[45]. In fasted subjects when administered with 240 mL water, mean T_{max} was 0.77 h (CI 48.1) for Migraine Liqui-gels containing 400 mg ibuprofen compared with 0.71 h (CI 53.7) for the suspension. In two other studies with Liqui-gels, mean T_{max} values were 0.70 ± SD 0.25 and

[45] FDA NDA Drug approval package for Advil Migraine Liqui-gels http://www.fda.gov/cder/foi/nda/2000/20-402-s005_Advil.htm

0.81 ± SD 0.39 h compared with 0.81 ± SD 0.50 and 0.74 ± SD 0.49 h for the suspension. It is concluded that the rupture time for the capsules has no effect on the rate of absorption.

Liqui-gels contain polyethylene glycol, potassium hydroxide, water, simethicone, sorbitan and sorbitol as well as the active ibuprofen. The alkali will convert at least some, if not all the ibuprofen to the more soluble salt, ibuprofen potassium, and the sorbitan, a non-ionic surfactant, will act as a solubliser and emulsifier. Both excipients would rationally be used at levels which will dissolve most or all of the drug in the liquid contents. Hence the capsules deliver the drug in solution into the small intestine whence absorption can occur rapidly by passive diffusion. It is interesting that the variability of the T_{max} values for the suspension is greater than for the Liqui-gels suggesting that there may be some variability in dissolution of the suspended ibuprofen particles depending on the gastric pH.

In post-operative dental pain, ibuprofen liqui-gels demonstrated faster onset of action than other analgesics with median time to meaningful relief of 24.2 min compared with 25.5 min for 25 mg ketoprofen and 29.9 min for 100 mg paracetamol. These relatively small differences were statistically significant [46]. In the same model, 400 mg ibuprofen liqui-gels provided greater peak and overall analgesia compared with 100 mg paracetamol caplets[47]. Formulations were administered with ~240 mL water. Mean times to meaningful relief were between 28.8 and 30.0 min, with subjects reporting perceptible relief in 10.2 – 14.4 min.

6.2 Ibuprofen arginate

This highly soluble ibuprofen salt is formed by combining the racemic ibuprofen with the naturally occurring amino acid L-arginine to increase solubility and facilitate absorption[48]. In tablet formulations, this achieves T_{max} of 15 - 30 min compared with 1 – 2 h for conventional tablets with similar overall bioavailability (AUC). Higher mean C_{max} values of 56.4 ± 13.6 µg/mL are reported for 400 mg ibuprofen administered as the arginate compared with 43.0 ± 8.5 µg/mL for regular tablets[49].

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[46] Olson NZ, Otero AM, Marrero I, Tirado S, Cooper S, Doyle G, Jayawardena S, Sunshine A. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 100 mg, ketoprofen 25 mg and placebo in the treatment of postoperative dental pain. *J Clin Pharmacol* (2001) **41**:1238-1247

[47] Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D, Hong D, Secreto SA. Ibuprofen for oral surgery pain. *Clin Ther* (200) **22**(11):1306-1318

[48] Black P, Max MB, Desjardins P, Norwood T, Ardia A, Pallotta T. A randomized, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action and tolerability of ibuprofen arginate and ibuprofen in postoperative dental pain. *Clin Ther* (2002) **24**(7):1072-1089

[49] Cattaneo D & Clementi E. Clinical pharmacokinetics of ibuprofen arginine. Curr Clin Pharmacol (2010) 5:239-45

When administered as soluble granules, T_{max} values were 16.9 and 24.4 min for 200 and 400 mg respectively compared with 90.0 and 63.7 min for regular ibuprofen tablets[50]. C_{max} values for soluble granules were correspondingly higher associated with quicker and greater analgesia in osteo-articular pain compared with tablets.

In 498 patients with postoperative dental pain, earlier onset of action was found for ibuprofen arginate tablets compared with regular ibuprofen tablets. For 200 and 400 mg doses respectively, median times to meaningful relief were 29 and 28 min for ibuprofen arginine compared with 52 and 44 min for regular tablets. Another study in 266 patients with postoperative dental pain found median times to meaningful relief of 24 and 45 min for ibuprofen arginate and ibuprofen tablets respectively[51].

In 40 patients with migraine, ibuprofen arginate showed an improvement in pain relief at 15 min compared with placebo consistent with reported faster absorption[52].

Tablets containing ibuprofen arginate were first launched in Europe and would be expected to appear in other markets as a fast acting alternative to liquid filled soft gelatin capsules. Formulations are covered by a US patent assigned to the Zambon Group SpA, Milan and include wet granulation of ibuprofen, arginine and a linear PVP combined with 5 – 10 % of an alkaline bicarbonate relative to the weight of the drug[53]. Examples contain 15 – 40 mg sodium bicarbonate per tablet which is lower than the levels used in the Surge Dose® technology when applied to acidic drugs.

6.3 Ibuprofen sodium dihydrate

Tablets containing this soluble salt of ibuprofen show faster dissolution at pH 1.2, 3.5 and 7.2 in 900 mL buffer using a dissolution apparatus with paddles rotating at 50 and 100 rpm.

Ibuprofen sodium dihydrate tablets showed similar C_{max} and T_{max} values to ibuprofen lysinate tablets and liquigels, better than regular tablets. Although all products were bioequivalent, plasma concentrations were significantly higher at 10 min post dosing. Mean T_{max} values for

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50 Monti NC, Gazzaniga A, Gianesello V, Stroppolo F, Lodola E. Activity and pharmacokinetics of a new oral dosage form of soluble ibuprofen. *Arzneim Forsch/Drug Res* (1992) **42**(I) Nr 4:556-9

51 Desjardins P, Black P, Papageorge M, Norwood T, Shen DD, Norris L, Ardia A. Ibuprofen arginate provides effective relief from postoperative dental pain with a more rapid onset of action than ibuprofen. *Eur J Clin Pharmacol* (2002) **58**:387-94

52 Sandrini G, Franchini S, Lafranchi S, Granella F, Manzoni GC, Nappi G. Effectiveness of ibuprofen arginine in the treatment of acute migraine attacks. *Int J Clin Pharm Res* (1998) **XVIII**(3):145-50

53 Grassano A, Marchiorri M, Di Toro M, Castegini F. Fast dissolving compositions having analgesic activity. US Patent 6,197,336 filed 26 March 1999

regular tablets were 1.4 ± 1.1 h, for liquigels 0.73 ± 0.3 h and 0.56 ± 0.26 h, for ibuprofen lysinate 0.73 ± 0.3 h and 0.72 ± 0.46 h, and for the ibuprofen sodium dihydrate 0.6 ± 0.3 h and 0.7 ± 0.55 h[54].

6.4 Ibuprofen lysinate

Ibuprofen lysinate is a soluble salt currently approved by the US FDA, marketed as Neoprofen®, a sterile solution for intravenous injection by Ovation Pharmaceuticals[55].

Published absorption data from a coated ibuprofen lysinate tablet indicate fast absorption with a mean T_{max} value of 45 min[56]. A recent paper from Boehringer Ingelheim Pharma GmbH reports faster oral absorption of ibuprofen lysinate in both fed and fasted states compared with regular ibuprofen tablets administered with 150 mL water. This study also investigated a novel ibuprofen extrudate which performed similarly to the ibuprofen lysinate with both better than the regular tablets. For ibuprofen lysinate tablets, median T_{max} and ranges were reduced from 0.75 (0.5 – 1.5) h to 1.5 (1.00 – 3.00) h by a standardized continental breakfast which was still faster and more consistent than fed values of 1.63 (0.75 – 4.00) h for regular ibuprofen tablets.

The geometric mean C_{max} values and CVs are summarised in Table 1 for fasted and fed subjects for 400 mg doses of ibuprofen in these three different formulations and comparative PK profiles for the three products under fasted and fed conditions shown in Figure 18[57].

Table 1 Geometric mean C_{max} (CV %) values following administration of 400 mg ibuprofen as regular tablets, extrudate and lysinate (from Klueglich et al 2005)

Geom mean (CV %) C_{max} µg/mL	Regular tablets	Extrudate	Lysinate
Fasted	33.5 (17.8)	41.1 (21.3)	41.2 (16)
Fed	26.0 (27.6)	26.2 (26.0)	29.6 (17.4)

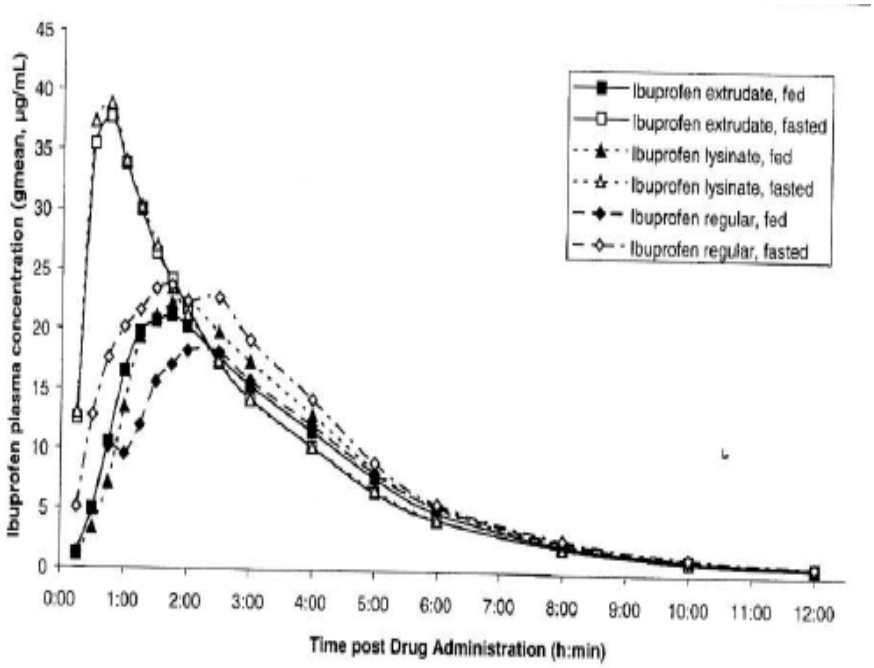
[54] Sorgel F, Fuhr U, Minic M, Siegmund M, Maares J, Jetter A, Kinzig-Schippers M, Tomalik-Scharte D, Szymanski J, Goeser T, Toex U, Schiedel B, Lehmacher W. Pharmacokinetics of ibuprofen dihydrate and gastrointestinal tolerability of short-term treatment with a novel, rapidly absorbed formulation. *Int J Clin Pharmacol Ther* (2005) **43**(3):140-9

[55] Drug approval package NDA 021903 Neoprofen® http://www.fda.gov/cder/foi/nda/2006/21-903s000TOC.htm

[56] Martin W, Koselowske G, Toberich H, Kerkmann TH, Mangold B, Augustin J. Pharmacokinetics and absolute bioavailability of ibuprofen after oral administration of ibuprofen lysine in man. *Biopharm Drug Dispos* (1990) **11**:265-78

[57] Kleuglich M, Ring A, Scheurer S, Trommehauser D, Schuijt C, Liepold B, Berndl G. Ibuprofen extrudate, a novel rapidly dissolving ibuprofen formulation: relative bioavailability compared to ibuprofen lysinate and regular ibuprofen and food effect on all formulations. *J Clin Pharmacol* (2005) **45**:1055-61

Figure 18 Geometric mean ibuprofen plasma concentrations following oral administration of 400 mg ibuprofen extrudate (■), ibuprofen lysinate (▲) and a regular (◆) under fed (filled) and fasted (open) conditions (from Klueglich 2005)



Similar results showing faster absorption and higher blood levels with ibuprofen lysinate have been reported compared with regular tablets as shown in Table 2[58].

Table 2 Median (min, max) values for PK parameters for 585.2 mg ibuprofen as lysinate (A fasted, C fed) and 600 mg regular ibuprofen tabs (B fasted, D fed) in healthy subjects (from Geisslinger et al 2005)

Parameter	Treatment A	B	C	D
Lag-time (h)	0.05 (0.01, 0.18)*	0.11 (0.04, 0.35)	0.22 (0.08, 0.57)*	0.58 (0.12, 0.89)
t_{max} (h)	0.55 (0.41, 0.72)*	0.89 (0.66, 4.90)	1.18 (0.49, 2.26)	1.55 (0.99, 5.50)
c_{max} (µg/ml)	69.1 (50.6, 80.5)*	50.8 (32.9, 57.2)	50.3 (31.7, 76.7)	44.6 (29.8, 58.0)
AUC (µg · h/ml)	174.3 (140.5, 218.4)	205.5 (137.0, 247.0)	169.7 (117.9, 197.9)	169.0 (139.0, 223.0)

[58] Geisslinger G, Dietzel K, Bezler H, Nuernberg B, Brune K. Therapeutically relevant differences in the pharmacokinetical and pharmaceutical behaviour of ibuprofen lysinate as compared to ibuprofen acid. Int J Clin Pharmacol Ther Toxicol (1989) 27(7):324-8

7 Fixed-dose combinations containing ibuprofen

There is good clinical rationale for combination products to provide multimodal analgesia using two analgesics with different mechanisms of action[59]. Potent interactions have been shown for NSAIDs and opiates in animal models and there is the potential for reduced dosage to minimise side effects without compromising efficacy particularly for long term use[60]. Several fixed dose combinations containing ibuprofen have now been registered aimed at increasing the analgesic spectrum as well as reducing the gastrotoxicity of this NSAID.

It is important to consider the relative effects of pH on the solubilities are these combinations and the resultant impact on dissolution, absorption and efficacy. None of the formulations registered appear to have been optimized for ultra-fast dissolution of both components such as could be achieved for Surge Dose® formulations as exemplified for a fixed combination of paracetamol and tramadol[61]. Also the combinations generally show only additive effect compared with the monotherapy and in some cases little of no difference.

7.1 Ibuprofen plus famotidine

Duexis® (Horizon Pharma) was approved registered in the US on 23 Apr 2011 containing 800 mg ibuprofen with 26.6 mg famotidine, a competitive inhibitor of histamine H_2 receptors which suppresses both acid concentration and volume of gastric secretions.

Two patents are listed in the Orange Book, US 8,067033 and US 8,067,451 both with priority of 18 Jul 2006 expiring 18 Jul 2026. With data exclusivity on this new combination until 23 Apr 2014, there are no generic approvals and if Horizon conduct the paediatric studies requested by the FDA, they are likely to be awarded a period of 6 months paediatric exclusivity which effectively extends the patent life.

Both Orange Book patents relate to the chemical incompatibility between ibuprofen and famotidine:

- US 8,067,033 covers formulations containing 800 mg with 26.6 mg famotidine where the surface area of direct physical contact between the two drugs is limited to no more than130

[59] Barkin RL. Acetaminophen, aspirin or ibuprofen in combination analgesic products. Amer J Therap (2001) 8:433-42

[60] Zelcer S, Kolesnikov Y, Kovalyshyn I, Pasternak DA, Pasternak GW. Selective potentiation of opioid analgesia by nonsteroidal anti-inflammatory drugs. Brain Res (2005) 1040:151-6

[61] DR 02-01-01 Effect of Surge Dose® on dissolution of tramadol HCl in combination with paracetamol. Imaginot Pty Ltd. 20 Dec 2005

mm^2, the formulation contains no more than 1 % of the sulfamide degradant after storage at 40 °C and 75 % RH for 1 month, fast release of both drugs occurs at the same time, the formulation is immediate release with no enteric coating, sustained release or delayed release, and is used three times daily with the benefit of reduced ibuprofen related gastrotoxicity due to the higher gastric pH.

- US 8,067,451 covers dosage forms that are not enteric coated, delayed or sustained release and both drugs are rapidly released at the same rate, administered three times daily for rheumatoid and osteo-arthritis pain containing 800 mg ibuprofen and 26.6 mg famotidine where the two drug are separated by a barrier layer of hydroxypropyl methyl cellulose 2910, polyoxyethylene glycol 400, polysorbate 80 and titanium oxide such that the famotidine is stable.

Duexis® was approved under a 505(b)(2) application based on PK data for the combination product compared with Pepcid® (40 mg famotidine) and Motrin® (ibuprofen) as shown in Table 3[62]. It was noted that the C_{max} for ibuprofen increased by 15.6 % for the combination product, and for famotidine C_{max} increased by 22 % and $AUC_{0-\infty}$ by 16 %.

Table 3 Data showing lack of effect interaction between ibuprofen and famotidine when administered together (from NDA 22-519)

Parameter	Ibuprofen		Famotidine	
	Alone	With Famotidine	Alone	With Ibuprofen
t_{max} (hr)	2.25 ± 1.89	1.58 ± 0.49	2.08 ± 1.02	1.75 ± 0.42
C_{max} (*)	51.9 ± 7.8	60.0 ± 10.9	136 ± 36.6	166 ± 41.0
AUC (**)	244 ± 63.5	242 ± 69.1	866 ± 234	1006 ± 215
$t_{1/2}$ (hr)	2.49 ± 0.54	2.33 ± 0.74	3.73 ± 0.35	3.92 ± 0.35

* ng/mL for famotidine; µg/mL for ibuprofen
** ng-h/mL for famotidine; µg-h/mL for ibuprofen

The increase in famotidine values are consistent the observed faster and more consistent absorption from the combination, down from 2.08 ± 1.02 h to 1.75 ± 0.42 h.

Overall these differences between the basic drug famotidine (pKa of 10.5) alone and in combination with the acidic drug ibuprofen are consistent with the effect of ibuprofen on the solubility and hence dissolution of the famotidine. Famotidine is more soluble at low pH increasing the extent and rate of dissolution allowing more drug to be absorbed. Although *in vitro* dissolution data submitted to the FDA in phosphate buffers at pH 4.2, 5.8, 6.8 and 7.2

[62] NDA 22-519 Summary review Duexis®
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022519Orig1s000SumR.pdf

stirring at 75 rpm suggested that the dissolution of famotidine was independent of pH, it must be noted that the conditions used are not very discriminating, namely 900 mL alkaline buffer and a relatively fast stirring speed of 75 rpm.

Based on solubility data, a 40 mg dose of famotidine will require only 73 mL water for complete dissolution[63] which means that in an excess test volume of 900 mL at 75 rpm, effects of solubility on dissolution will not be seen. However the *in vivo, the* volumes of fluid available for dissolution are far less more in the region of 100 – 200 mL when considering co-administered water and residual gastric contents in fasted subjects. Therefore the dissolution data submitted to the FDA are inadequately discriminating to explain the increases in famotidine C_{max} of 22 % and $AUC_{0-\infty}$ of 16 % based on the PK data.

Additional PK data in renally impaired subjects summarised in Table 4 [64] indicate slower absorption of famotidine from the combination tablet compared with a suspension which is consistent with solubility and dissolution rate limited absorption of this drug. Renal impairment significantly slows elimination with higher $AUC_{0-\infty}$ values but little effect on ibuprofen PK.

Table 4 PK data showing the effect of renal impairment on the PK of the combination of ibuprofen 800 mg and famotidine 26.6 mg compared with a 800 mg ibuprofen dose as Motrin® tablets and Pepcid® suspension containing 26.6 mg famotidine (from NDA 22-519)

Parameter	Ibuprofen		Famotidine	
	HZT-501[1]	Motrin[2]	HZT-501[1]	Pepcid[3]
t_{max} (hr)	2.10 ± 1.27	2.47 ± 3.11	5.30 ± 2.11	3.60 ± 1.52
C_{max}[4]	45.1 ± 24.9	48.1 ± 21.1	110 ± 44.9	101 ± 40.1
$t_{1/2}$ (hr)	2.47 ± 0.850	2.61 ± 0.975	11.4 ± 3.20	13.6 ± 6.28
AUC[5]	178 ± 98.2	198 ± 79.8	1674 ± 689	1790 ± 951

[1] tablet containing ibuprofen 800 mg and famotidine 26.6 mg
[2] tablet containing ibuprofen 800 mg
[3] suspension containing famotidine 26.6 mg
[4] µg/mL for ibuprofen; ng/mL for famotidine
[5] µg.h/mL for ibuprofen; ng.h/mL for famotidine

[63] IM 03-19-01 Application of Surge Dose® fast dissolution technology to famotidine. Imaginot Pty Ltd. 27 March 2012

[64] NDA 22-519 Clinical Pharmacology and Biopharmaceutics Review Duexis® http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022519Orig1s000ClinPharmR.pdf

In all cases assessing the primary end point of upper gastrointestinal ulcers and the secondary end point of gastric ulcer development, Duexis® showed a benefit over ibuprofen alone, reducing the former from 20.0 % to 10.5 % and the latter from 17.9 – 9.7 %,

Based on this review of available PK and efficacy data of ibuprofen in a fixed dose combination with famotidine, an optimised Surge Dose® would be expected to demonstrate superior performance. Faster and more consistent absorption of both components could allow the use of a much lower level of ibuprofen say 400 mg without compromising analgesic efficacy. Reduced systemic exposure from the lower dose with the shorter gastric residence time resulting from the ultra-fast activated dissolution is likely to lead to reduced gastrotoxicity overall.

7.2 Ibuprofen plus paracetamol

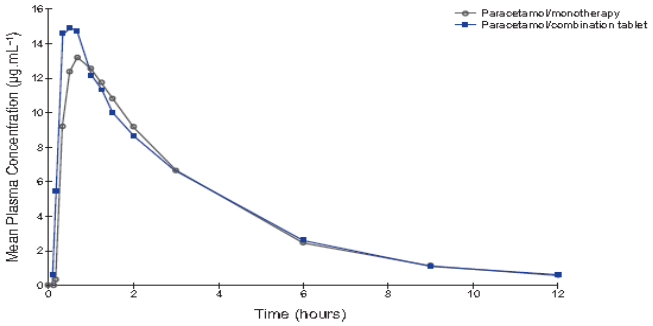
Reckitt Benckiser's fixed dose combination product of paracetamol and ibuprofen marketed as Nuromol® in the UK has also been approved in New Zealand as an OTC product for analgesia. However as studies to date do not demonstrate any improved efficacy or synergistic effects over and above the two agents used separately, it appears to be proving difficult to gain approval in some countries.

This formulation containing 200 mg ibuprofen with 500 mg paracetamol utilises Synchro-Tech™ technology to achieve fast dissolution of both drugs. WO 2077/034135 with a priority date of 22 Sep 2005 discloses a melt granulation process for a combination of NSAID and paracetamol such that both drugs achieve 89 % after 10 min when the resultant tablets are tested in 900 mL USP buffer at pH 7.2 at 50 rpm, increasing to over 90 % at 20 minutes. WO 2006/043025 discloses the same melt granulation process used with combinations of COX inhibitors.

The combination product results in faster absorption of paracetamol compared with the monotherapy and C_{max} values for both actives were higher for the combination in fasted volunteers as shown in Figures 19 for paracetamol and Figure 20 for ibuprofen[65]. These differences highlight formulation effects on both paracetamol and ibuprofen with the combination product offering faster dissolution which in turn results in faster absorption. The combination product provides release of both paracetamol and ibuprofen in the stomach within 9 minutes of ingestion compared with 20 minutes for paracetamol tablet and 30 minutes for ibuprofen tablets.

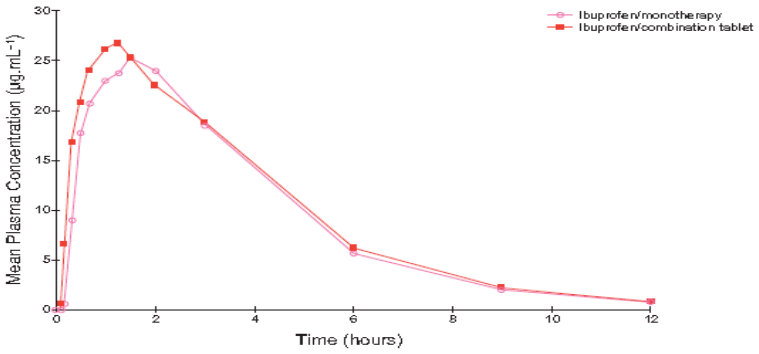
[65] Tanner T, Aspley S, Munn A, Thomas T. The pharmacokinetic profile of a novel fixed-dose combination tablet of ibuprofen and paracetamol BMC Clin Pharmacol (2010) 10(10)

Figure 19 PK profiles for paracetamol from monotherapy and combination product (from Tanner et al 2010)



For paracetamol mean plasma concentrations at 10 and 20 min post-dose were 5.43 and 14.54 µg/mL for the combination compared with 0.33 and 9.9 µg/mL for the monotherapy. Given an EC_{50} of around 15 µg/mL for paracetamol, these levels are likely to result in different clinical response based on the different absorption profiles and the degree of intersubject variability.

Figure 20 PK profiles for ibuprofen from monotherapy and combination product (from Tanner et al 2010)



For ibuprofen, plasma concentrations were 6.64 and 16.81 µg/mL at 10 and 20 min post-dose respectively from the combination product compared with lower levels of 0.58 and 9.00 µg/mL for the monotherapy. Again with an EC_{50} around 25 µg/mL for ibuprofen, differences in clinical response might be expected based on these levels.

A study in 892 patients with knee pain from arthritis comparing 400mg ibuprofen alone, 1,000 mg paracetamol alone and the combination product taken three times daily showed

haemoglobin losses similar for all groups indicating an additive effect for the ibuprofen and paracetamol combination[66].

7.3 Ibuprofen plus oxycodone

Combunox® (Forest Labs) was the first fixed dose combination of ibuprofen 400 mg and oxycodone 5 mg approved by the FDA on 26 Nov 2004[67] for the short-term management of acute moderate to severe pain. With no unexpired patents or exclusivities, there are three generic combination products marketed by Barr Labs, Watson Labs and Actavis Elizabeth.

Differences in absorption profiles between the combination product and monotherapies are shown in Table 5 and Figures 21 and 22. Absorption of the ibuprofen from the combination product is slower with a significantly lower C_{max} than from the monotherapy whereas PK profiles for oxycodone are similar for the combination product and monotherapy.

Table 5 Key PK data for Combunox® and monotherapies of ibuprofen 400 mg and oxycodone 5 mg (from NDA 21-378)

Total Ibuprofen				Oxycodone			
PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI	PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI
C_{max} (µg/mL)	30.4 ± 11.3	37.7 ± 9.4	67 - 91	C_{max} (ng/mL)	9.9 ± 2.2	9.4 ± 2.1	100 - 110
AUC_{0-t} (µg•hr/mL)	129.5 ± 35.6	144.6 ± 33.2	84 - 93	AUC_{0-t} (ng•hr/mL)	51.0 ± 12.7	47.4 ± 10.6	102 - 112
$AUC_{0-\infty}$ (µg•hr/mL)	132.4 ± 34.9	147.0 ± 32.6	85 - 94	$AUC_{0-\infty}$ (ng•hr/mL)	55.9 ± 13.3	52.3 ± 10.8	102 - 110

Note: For oxycodone, the reference product is with Roxicodone™ (oxycodone) 5 mg, not Nuprin®.

[66] Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, Reader S. A randomized controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis (2011) 70:1534-41

[67] NDA 21-378 Combunox®
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021378s000_Combunox_%20biopharmr.pdf

Figure 21 Comparative PK profiles for ibuprofen 400 mg as monotherapy and in Combunox® with 5 mg oxycodone (from NDA 21-378)

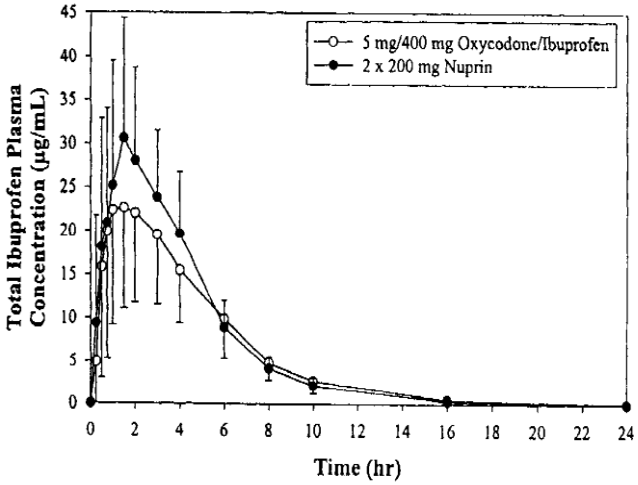
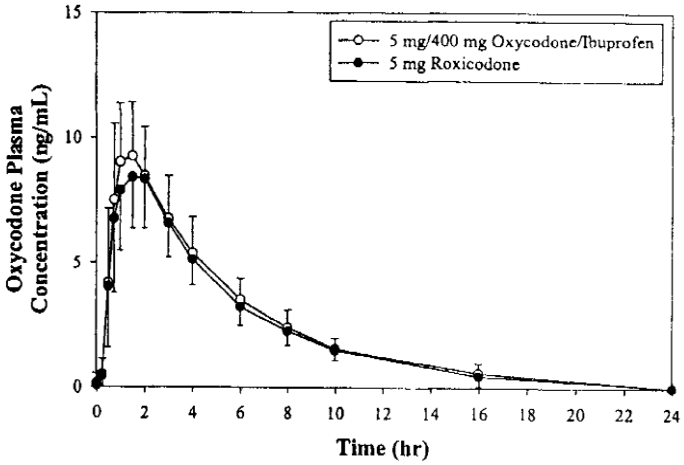


Figure 22 Comparative PK profiles for oxycodone 5 mg as monotherapy and in Combunox® with 400 mg ibuprofen (from NDA 21-378)



The efficacy of the combination compared with monotherapy of either ingredient has been well documented demonstrating additive rather than synergistic effects [68]. In oral surgery (n=118), 2.5 mg and 5 mg oxycodone each in combination with 400 mg ibuprofen were inadequate to provide acceptable levels of pain relief compared with 10 mg oxycodone which produced adequate analgesia with ibuprofen but with increased adverse events such as vomiting and

[68] Oldfield V & Perry CM. Oxycodone/ibuprofen combination tablet: A review of its use in the management of acute pain. Drugs (2005) 65(16):2337-54

drowsiness[69]. In abdominal and pelvic surgery (n = 456), the combination was superior to the individual monotherapies although the total side effects were higher with the combination and ibuprofen (61 % and 60 %) compared with only 22 % for the oxycodone alone compared with 30 % for the placebo[70]. With ibuprofen and the combination 22 and 24 % respectively were related to nausea and gastrointestinal symptoms. With all treatments onset of pain relief occurred within 15 minutes with fewer patients on the combination therapy requiring rescue medication, and those that did waiting longer. However in orthopaedic injury related pain in children the combination was shown to be no better than the corresponding monotherapies[71].

Similar C_{max}, T_{max} and $AUC_{0-\infty}$ values for the combination product and monotherapies have been demonstrated in another study comparing fasted and fed healthy subjects[72]. 400 mg ibuprofen achieved Cmax around 32 µg/mL with around 25 % intersubject variability. Food delayed T_{max} for ibuprofen from 1.8 to 2.1 h and for oxycodone from 1.5 to 2.0 h consistent with the effect of food on gastric emptying.

The combination has been shown to have superior efficacy compared with oxycodone 5 mg with 325 mg paracetamol and 7.5 mg hydrocodone with 500 mg paracetamol in 249 patients with moderate – severe post-operative pain following removal of impacted third molars[73]. Time to onset was 30 min and 89 % of patients achieved 50 % pain relief. Another study in the same dental model with 498 patients showed that efficacy of the combination was superior to either monotherapy with 28 % of patients achieving faster pain relief with the combination than with ibuprofen alone[74]. Of note was that the combination had slower absorption of both components

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69 Dionne RA. Additive analgesic effects of oxycodone and ibuprofen in the oral surgery model. J Oral Maxillofac Surg 919990 57:673-8

70 Singla N, Pong A, Newman K. Combination oxycodone 5 mg / ibuprofen 400 mg for the treatment of pain after abdominal or pelvic surgery in women: A randomized, double-blind, placebo- and active-controlled parallel-group study. Clin Ther (2005) 27(1):45-57

71 Koller Dm, Myers AB, Lorenz D, Godambe SA. Effectiveness of oxycodone, ibuprofen ot the combination in the initial management of orthopaedic injury-related pain in children. Ped Emerg Care (2007) 23(9):627-33

72 Kapil R, Nolting A, Roy P, Fiske W, benedek I, Abramowitz W. Pharmacokinetic properties of combination oxycodone plus racemic ibuprofen: Two randomized, open-label, crossover studies in healthy adult volunteers. Clin Ther (2004) 26(12) 2015-25

73 Litowsky LJ, Christensen SE, Adamson DN, Van Dyke T, Han S-H, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/ acetaminophen 325 mg and hydrocodone 7.5 mg / acetaminophen 500 mg in patients with moderate to severe post-operative pain: a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. Clin Ther (2005) 2794):418-29

74 Van Dyke T, Litkowski LJ, Kiersch TA, Zarringhalam NM, Zheng H, Newman K. Combination oxycodone 5 mg/ ibuprofen 400 mg for the treatment of post-opreative pain: A double-blind, placebo- and active-controlled parallel-group study. Clin Ther (2004) 26(12):2003-14

compared to the monotherapies with lower C_{max} values but longer T_{max} values as shown in Table 6. In all cases the combination showed higher variability than the corresponding monotherapy. Mean C_{max} levels around the EC_{50} highlight the potential for a less than optimal clinical response with some subjects experiencing sub-therapeutic levels of ibuprofen.

Table 6 Key PK data for Combunox® and monotherapies of ibuprofen 400 mg and oxycodone 5 mg (from Van Dyke et al 2004)

Mean (SD)	C_{max}	T_{max} (h)	$AUC_{0-\infty}$
Ibuprofen 400 mg	24.6 (6.4) µg/mL	2.4 (1.0)	72.7 (20.7)
400 mg /5 mg combination	18.5 (8.1) µg/mL	3.1 (1.6)	58.7 (26.6)
Oxycodone 5 mg	13.6 (4.2) ng/mL	1.1 (0.4)	35.9 (3.7)
5 mg / 400 mg combination	11.6 (6.3) ng/mL	2.1 (1.0)	35.8 (10.6)

7.4 Ibuprofen plus hydrocodone

In the US, Abbott's ibuprofen 200 mg + hydrocodone bitartrate 7.5 mg tablet Vicoprofen® approved by the FDA on 23 Sep 1997 has two Orange Book patents in the name of Knoll Pharmaceutical Co listed, US 6,348,216 and 6,599,53, both expiring on 10 Jun 2017:

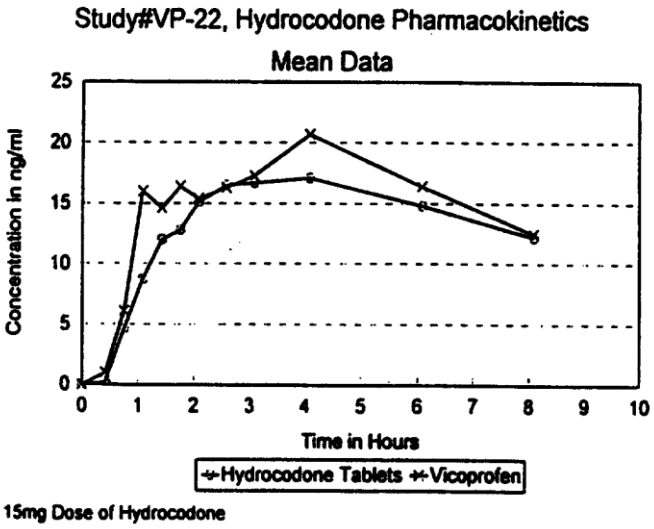
- US 6,348,216 with priority of 10 Jun 1996, claims a wet granulated compressed tablet formulation free of lactose and polyvinylpyrrolidone (PVP), containing ibuprofen (25 – 63 %), hydrocodone (0.6 – 3.8 %) colloidal silicon dioxide (0.5 – 3 %), microcrystalline cellulose (10 – 42 %) disintegrant 4 – 10 % and starch (10 – 20 %) with good disintegration, dissolution and compressibility properties
- US 6,599,531 a CIP with priority of 12 Jun 1997 claiming a combination of ibuprofen and narcotic analgesic with superior disintegration, dissolution and compression characteristics made by (a) making a wet granulation of both drugs, colloidal silicon dioxide, disintegrant, filler and starch, (b) blending granules with lubricants and at least one excipient substantially free of lactose and PVP and (c) compressing the blend.

Despite the Orange Book patents there are four generic products already approved with a range of hydrocodone levels 2.5, 5. 7.5 and 10 mg to Amneal Pharm NY (Reprexan®), Teva, Vintage Pharms and Watson Labs Florida. These may well be formulations that do not fall within the claims of the Orange Book patents such as those containing lactose or PVP, or not prepared by wet granulation.

PK and PD data submitted to the FDA[75] on this drug combination indicate highly variable absorption of both components that would be expected to impact efficacy data in relation to extent of analgesia and time to onset. The dissolution conditions used to characterise the product, 900 mL USP phosphate buffer pH 7.2 at 150 rpm, does not reflect in vivo conditions and is not discriminating achieving 98 – 103 % dissolution in 15 min.

In PK/PD study in post-operative dental pain, Vicoprofen® was compared with 15 mg hydrocodone as tablets, 400 mg ibuprofen as a suspension, and placebo tablets and suspension. Despite a high level of inter-subject variability, the combination tablets interestingly showed faster absorption of hydrocodone than from the single drug tablets as seen in the mean absorption profiles in Figure 23.

Figure 23 Effect of the acidic drug ibuprofen on the absorption of hydrocodone in the combination product Vicoprofen® compared with 15 mg hydrocodone as single ingredient tablets (from NDA 20-716)



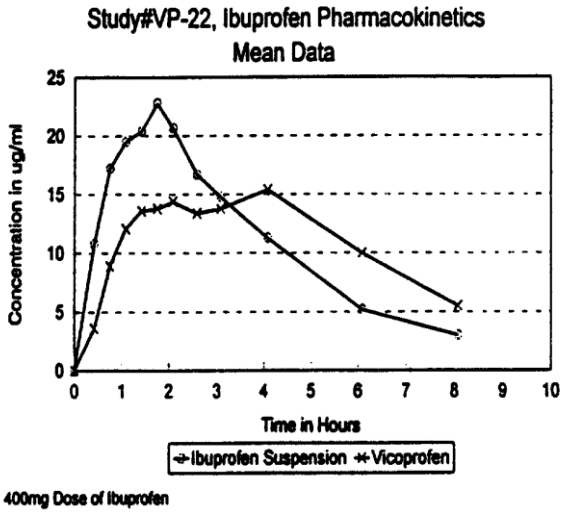
The wide absorption peak is characteristic of basic drugs with limited solubility which decreases in the alkaline environment of the small intestine whence absorption occurs. Even if the drug is solubilised in the acidic gastric environment, re-precipitation may occur in the small intestine which then requires re-dissolution before absorption can occur.

[75] NDA 20-716 Knoll Pharmaceutical Co Vicoprofen
http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020716ap_Vicoprofen_clinphrmr.pdf

Based on experience with Surge Dose® formulations, this change in absorption profile is not unexpected. Hydrocodone is a base with a pKa of 8.9 and as such will exhibit pH dependent solubility, being more soluble under acidic conditions. As ibuprofen is acidic and is present in the combination product at a level of 200 mg compared with 7.5 mg hydrocodone, it could be reasonably expected that the solubility of hydrocodone will be enhanced and its dissolution rate will increase. In the conventional tablets, there is no pH effect in the vicinity of the dissolving drug particles to enhance dissolution. These results are quite consistent with expectations based on the faster absorption of hydrocodone from a solution with median T_{max} of 0.7 – 0.9 h compared with absorption from a tablet with T_{max} of 1.3 h[76]. Such results indicate that the absorption of hydrocodone is absorption rate limited.

Similar dissolution rate limited absorption is clearly demonstrated for ibuprofen where the combination product was compared with ibuprofen suspension from which the ibuprofen was absorbed more rapidly reaching higher C_{max} as seen in Figure 24.

Figure 24 Dissolution rate limited absorption of ibuprofen from the combination product Vicoprofen® compared with 400 mg ibuprofen administered as a suspension (from NDA 20-716)



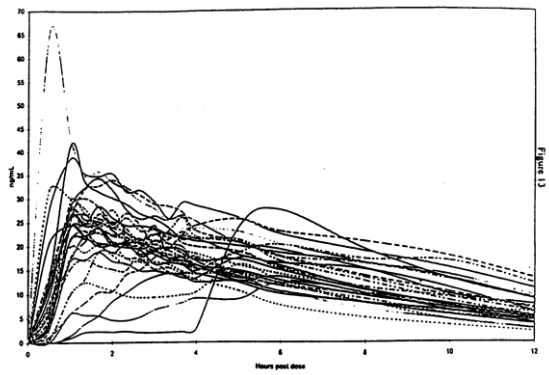
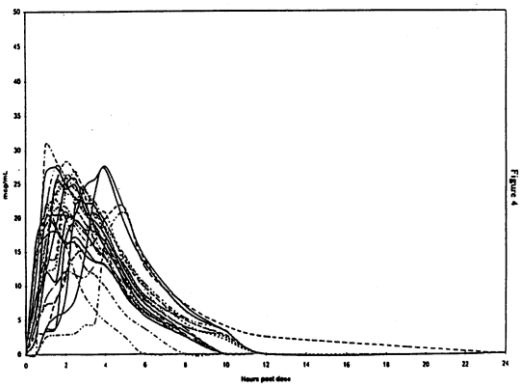
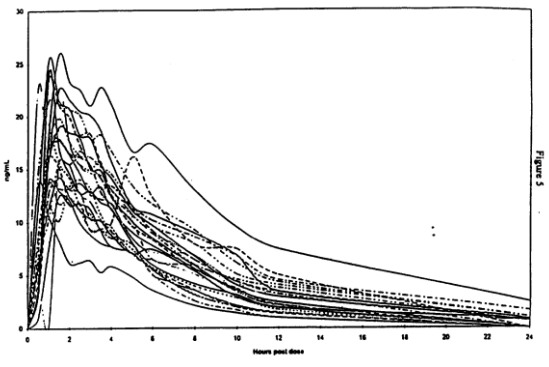
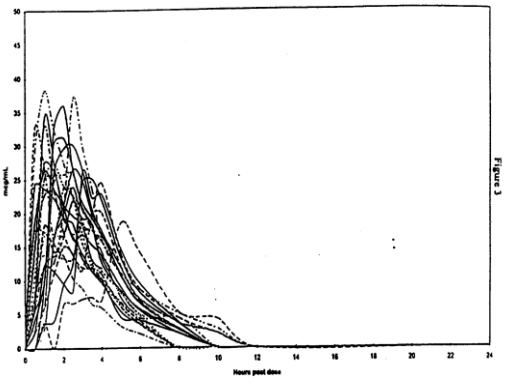
During examination, reanalysis of data from some of the studies was requested to better understand the differences between the combination and individual drugs particularly given the high level of inter-subject variability. While all individual subject data were redacted, the

[76] TQ 03-17-00 TetraQ Physicochemical Properties, Pharmacokinetics and Pharmacodynamics of Hydrocodone in Humans IMG01-FR – Part 8 30 Jun 2006

graphical representations were retained all indicating a high level of variability and multiple peaks all consistent with dissolution rate limited absorption of both drugs significantly impacted by the MMC gastric emptying cycle. Sample graphs are shown in Figure 25.

Figure 25(a) clearly shows the impact of the ibuprofen in reducing the variability in the hydrocodone absorption as a result of its pH effect on hydrocodone solubility. The variability in Figure 25(A) is much greater. With those subjects showing delayed absorption and very slow absorption, C_{max} values may well be sub-therapeutic. Unfortunately it is not possible to compare the absorption profiles of each drug for each subject to ascertain the effects of dissolution and gastric emptying. The profiles for ibuprofen show little difference in distribution between Figure 25(B) and Figure 25 (b).

Figure 25 Individual subject PK profiles from Study VP-02 for hydrocodone and ibuprofen from single component tablets and the combination tablet Vicoprofen® (from NDA 20-716)

(A) Hydrocodone absorption from hydrocodone tablets	*(B) Ibuprofen absorption from ibuprofen tablets*
	
(a) Hydrocodone absorption from Vicoprofen® tablets	*(b) Ibuprofen absorption from Vicoprofen® tablets*
	

Such variability would explain the lack of efficacy seen with the hydrocodone tablets compared with placebo in the PK-PD study where only 50 % subjects reported a positive response with acceptable pain relief compared with 67 % receiving placebo. Ibuprofen suspension achieved a 100 % response and Vicprofen® 83 % positive leading to the conclusion that the ibuprofen was the major contributor to pain relief. Both ibuprofen and Vicoprofen® had a similar median time to onset of 20 minutes compared with 50 minutes for placebo and 100 minutes for hydrocodone tablets alone. In this study the faster absorption of ibuprofen from the suspension would explain its improved efficacy compared with the combination tablet Vicoprofen®.

This analysis highlights the potential for improved release of both drugs from a combination product such that fast dissolution of both components can be achieved. Variable absorption with sub-therapeutic levels in some subjects will negatively impact efficacy results and foregoes the opportunity to achieve and to demonstrate any synergistic effect by the combined use of different therapeutic agents which is a requirement of some regulatory authorities for combination products. An optimised Surge Dose® ibuprofen-hydrocodone combination would be designed to achieve fast *in vitro* dissolution of both components such that variability would be reduced with more T_{max} individual values for both ibuprofen and hydrocodone of 1 hour or less compared with the Vicoprofen® medians in the region of 1.7 – 2.9 hours. Faster absorption will result in higher C_{max} levels which will reduce the frequency of sub-therapeutic dosing with either or both drugs which in turn will improve efficacy and may lead to a demonstrable synergy.

Efficacy studies comparing with other combinations show:

- two tablets each containing 7.5 mg hydrocodone and 200 mg ibuporofen were equivalent to two tablets each containing 375 mg paracetamol with 5 mg oxycodone and both were better than placebo in post-operative pain following obstetric or gynecoloigical procedures[77]
- two tablets each containing 7.5 mg hydrocodone and 200 mg ibuporofen were equivalent to two tablets each containing 375 mg paracetamol with 5 mg oxycodone in acute low back pain (n = 147)[78]
- two tablets each containing 7.5 mg hydrocodone and 200 mg ibuprofen were more effective than a single tablet in chronic pain (n = 469), and more effective than two

[77] Palangio M, Wideman GL, Keffer M, Landau CJ, Morris E, Doyle RT, Jiang JG, Damask M, de Padova A. Combination hydrocodone and ibuprofen versus combination oxycodone and acetaminophen in the treatment of postoperative obstetric or gynaecologic pain. Clin Ther (2000) 22(5):600-12

[78] Palangio M, Morris E, Doyle RT, Dornseif BE, Valente TJ. Combination hydrocodone and ibuprofen versus combination oxycodone and acetaminophen in the treatment of moderate or severe acute low back pain. Clin Ther (2002) 24(1):87-99

tablets each containing 30 mg codeine with 300 mg acetaminophen which was comparable with one tablet of the hydrocodone/ibuprofen combination[79]

8 Conclusions

This review confirms that faster absorption of ibuprofen can be achieved from improved oral dosage forms relative to conventional tablets and that faster dissolution is associated with improved therapeutic outcomes with faster onset of action and improved efficacy. With fast dissolving, highly soluble and solubilized ibuprofen formulations such as liquid filled soft gelatin capsules, mean T_{max} values are achieved in the region of 15 – 45 minutes compared with 1 – 2 hours for regular tablets.

There is good correlation between faster absorption and onset of analgesia such that fast absorbed products achieve meaningful pain relief in around 30 min compared with 45 – 60 min for regular tablets. Improved products offer faster onset of perceptible relief with onset of action reported within 15 min in placebo-controlled studies.

A number of commercially available fast dissolving products are covered by patents, and the manufacture of liquid filled capsules requires either capital investment in equipment or use of specialised contract manufacturers. Therefore the ultra-fast activated dissolution Surge Dose® technology provides a convenient and relatively cost effective option as well as a protected IP position for an improved differentiated product in this highly competitive market.

Ibuprofen appears to be a suitable candidate for application of Imaginot's Surge Dose® technology using pH modulating agents containing sodium bicarbonate and an organic acid. The composition and levels of this component and the level of water uptake agents would be optimized during the development process. This formulation approach maximises the extent and rate of *in vivo* dissolution under the wide range of physiological conditions, leading to faster delivery of the drug in solution into the small intestine whence absorption occurs by passive diffusion. Faster absorption into plasma drives faster distribution into effect compartments resulting in faster onset of action than conventional tablets.

Application of the Surge Dose® technology to ibuprofen would be expected to reduce T_{max} to around 15 - 30 min with a corresponding shorter time to meaningful analgesia of 15 - 30 min.

[79] Palangio M, Damask MJ, Morris E, Doyle RT, Jiang JG, Landau Cj, de Padova A. Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. Clin Ther (2000) 22(7):879-92

The Surge Dose® technology can also be considered to improve the dissolution and hence absorption of fixed dose combinations of ibuprofen with other drugs. None of the existing products demonstrate superior PK or PD performance with clinical responses generally being additive rather than synergistic compared with the monotherapies. There is evidence that the acidic nature of ibuprofen enhances the absorption of basic drugs in combination products. This indicates that an optimized Surge Dose® combination product designed to maximise the dissolution rate of both drugs is likely to provide enhanced fast absorption of both drugs. This increases the probability of improving efficacy capturing any potential synergies through faster and more consistent delivery of both drugs. A Surge Dose® combination product is also more likely to allow reduction of dosage to minimise side effects without compromising efficacy.