

IM 04-06-02



Application of Surge Dose[®] to montelukast sodium

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Issued 05 March 2007

Updated 29 January 2012

Reissued 03 October 2012

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1 Executive Summary

Imaginot has evaluated the potential for application of its Surge Dose[®] ultra-fast activated dissolution technology to the leukotriene receptor antagonist, montelukast sodium. This drug is marketed as Singulair[®] (Merck) swallow tablets, chewable tablets and oral granules, used once a day for the chronic treatment of asthma and allergic rhinitis in children and adults. Its relatively slow and variable absorption with peak plasma concentrations achieved in 2 – 4 hours currently limits its application to chronic rather than acute indications.

Montelukast sodium is an acidic drug which is freely soluble in water. However, its solubility is reduced under acidic conditions as generally occur in the stomach where the sodium salt is converted to the less soluble acid form. The resultant layer will slow *in vivo* dissolution of the underlying sodium salt. The drug is more soluble at higher pH, such as in saliva which has a pH of 6.5 – 6.9, albeit that any dissolved drug may re-precipitate in acidic gastric conditions, and also in the small intestine where absorption occurs.

Although there is OATP transporter mediated absorption of montelukast, published PK (pharmacokinetic) data suggest some level of solubility and dissolution rate limitation of absorption for this drug:

- Compared with an oral solution, swallow tablets show around 80 % relative bioavailability
- T_{max} (time to peak plasma concentrations, C_{max}) values increase with increasing dose from 5 to 800 mg consistent with progressively limited solubility in the constant volume of co-administered water and gastric contents available for dissolution
- T_{max} values for chewable tablets around 2 – 2.5 h are faster than for swallow tablets around 3 – 4 h consistent with the higher solubility of this drug under the less acidic conditions in saliva compared with gastric acidity and demonstrating the effect of eliminating *in vivo* disintegration time
- Food has little effect on the absorption of the slowly absorbed tablets but has a greater effect on the absorption of the chewable tablet, reducing the bioavailability to that seen for the tablets, with lower C_{max} and T_{max} reduced to those reported for the swallow tablets

Any drug that dissolves in the stomach will empty rapidly into the small intestine, where high drug concentrations will provide high driving forces for absorption by passive diffusion across the intestinal wall. If there is minimal drug dissolution under acidic conditions, then passage of drug into the small intestine will be dependent on the gastric emptying MMC

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and lower drug concentrations will provide lower driving forces for absorption. Slow absorption is associated with lower C_{max} which in some cases can be sub-therapeutic below 120 ng/mL the reported minimum effective level for montelukast.

Surge Dose[®] tablet formulations provide faster and more consistent drug absorption resulting in faster and more reliable onset of action. Mean and median T_{max} values are significantly reduced with Surge Dose[®] and are less variable. This has been demonstrated in human PK studies for paracetamol (acetaminophen, APAP) and two acidic NSAIDs (non-steroidal anti-inflammatory drugs) lornoxicam and diclofenac. 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.

A preliminary unoptimized Surge Dose[®] montelukast sodium 10.4 mg formulation has demonstrated significantly faster in *in vitro* dissolution in 900 mL 0.0033 M HCl (hydrochloric acid) at 37 °C using USP dissolution apparatus 2. Each tablet contained 600 mg sodium bicarbonate with 76 mg anhydrous citric acid. Dissolution exceeded 80 % in the first 5 min at 30 rpm and 60 % in the first 5 min in the absence of stirring (0 rpm) demonstrating the intrinsic activated dissolution of this technology. By comparison, Singulair[®] achieved no more than 10 % dissolution even with increased stirring.

Based on published IVIVC (in vitro in vivo correlation) data and the higher oral bioavailability of montelukast in solution, a fast dissolving Surge Dose[®] tablet would be expected to demonstrate faster *in vivo* dissolution and absorption, resulting in faster onset of action. A Surge Dose[®] montelukast sodium tablet with fast *in vitro* dissolution would be expected to have a significantly shorter mean and median T_{max} in the region of 1 – 2 h with a higher proportion of subjects having a T_{max} in this range with a reduced frequency of slow absorption occasions greater than 3 h. Food effects would be expected to be reduced as the Surge Dose[®] activated dissolution will allow the rapid delivery of dissolved drug to the small intestine reducing the effect of gastric emptying.

Additionally, faster dissolution and faster absorption may also result in a reduction in slow absorption occasions providing more consistent and less variable absorption which may reduce sub-therapeutic dose failure. This could improve the efficacy of montelukast sodium in the treatment of both acute and chronic conditions.

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1 Introduction

1.1 Technology overview

The Surge Dose[®] formulation technology for fast dissolution and fast absorption of oral drugs has been developed by Imaginot Pty Ltd <Imaginot>, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] formulations are designed to achieve ultra-fast activated dissolution even under unfavourable physiological conditions so that fast and consistent absorption and efficacy are 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 which should not present any major regulatory challenges.

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

- a requirement for fast and reproducible onset of action when taken 'on demand' for acute episodic indications such as pain, migraine, allergy, nausea and erectile dysfunction
- high passive absorption without significant intestinal metabolism or active efflux
- evidence of variable absorption associated with gastric emptying and/or *in vivo* dissolution when comparing absorption from 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 solutions and liquid formulations which provide faster drug absorption compared with conventional solid dosage forms. Disadvantages of liquids and solutions include stability issues, the need for extensive 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 also offer benefits over newer heavily promoted second generation fast acting formulations such as liquid filled soft capsules, orally disintegrating tablets

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(ODTs) and absorption enhanced formulations. These do not always deliver the promised rapid onset of action required for drugs taken 'on demand'.

Surge Dose[®] tablets are designed to act more like a solution, causing the drug to rapidly dissolve in the co-administered water and 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.

This report highlights the improved *in vitro* dissolution that can be achieved with Surge Dose[®] montelukast sodium tablets compared with Singulair[®] tablets¹ and considers published data on montelukast sodium to determine if faster *in vivo* dissolution is likely to lead to improved and more consistent absorption and therapeutic outcomes.

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 drugs claiming priority from 28 Nov 2005. Montelukast sodium is one of the acidic drugs exemplified in this patent and has been specifically claimed. This patent has been granted in Australia and is in examination in the US under the PPH and in Japan.
- 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 US, Japan and India.
- iii. PCT/AU 2005/00758 (WO/2005/115344) covering paracetamol and combinations. The patent has been granted in Australia, Canada and the US and 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.

There are a number of patents on montelukast oral formulations but none describe the compositions or dissolution performance covered by the Surge Dose[®] patents:

¹ Imaginot Pty Ltd DR 04-06-01 Fast dissolving montelukast sodium tablets. 26 Feb 2007

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- US 8,048,449 (Jubilant Organosys Ltd, India, priority 27 Dec 2005) claims compressed ODT formulations with good organoleptic properties and fast disintegration containing 42 – 72 % of a filler with an average particle diameter greater than 150 µm coated with silicon dioxide 10 – 30 % by weight of the tablet. The optional inclusion of an effervescent couple is claimed which would react together in the saliva and so be dissipated before the contents of the mouth were swallowed. Montelukast is not exemplified but is named as a suitable active in Claim 3.
- WO 2009/153305, EP 2009/057593 (Sandoz AG, priority 19 Jun 2008) claims a process for spray drying montelukast sodium solution onto a sugar substrate to produce granules with low sulfoxide levels < 0.5 %. This is the major degradant as montelukast is prone to oxidation. None of the formulations contain any pH modulating agents.
- US 2009/0124657 (Dr Reddy's Laboratories, priority 14 Aug 2007) claims tablet formulations with good stability where the relative humidity of the tablet is < 25 %. None of the formulations contain any pH modulating agents.
- WO 2008/014175 (Dr Reddy's Laboratories, priority 28 Aug 2006) claims granules
- US 2007/0184101 (Teva Pharmaceutical Industries Ltd, priority 09 Feb 2006) claims tablet formulations where the levels of the major oxidative degradant sulfoxide do not exceed 1 % after storage at 55 °C for 48 hours. None of the formulations contain any pH modulating agents. US 2010/0120848 derives from the same provisional, covering the process for making these stable tablets. US 2007/0184108, EP 2158911 and EP 1818057 also derive from the same provisional and covers stable table formulations where microcrystalline cellulose is not one of the excipients. WO 2007/092031 claims such formulations with sulfoxide levels below 1 % after storage at 40 °C and 75 % RH for 3 months.
- WO 2007/077135, EP 2005 0113112 (Krka Tovarna Zdravil DD, priority 30 Dec 05, 05 Jul 06) describes a direct compression process for tablet formulations containing montelukast or its salts with a small particle size with 90 % of particles have a diameter below 250 µm ($D_{90} < 250 \mu\text{m}$). Tablets have good content uniformity and stability with an easier process than wet granulation.
- WO 2003/035036 (Merck Frost Canada, priority 26 Oct 2001) describes a free flowing granule where an aqueous solution of montelukast is spray coated onto a sugar substrate such as mannitol, lactose or sucrose. The granules are swallowed or mixed with food.

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1.3 Commercialization

Imaginot is now seeking partners to commercialize its Surge Dose[®] technology. To date, three deals have been completed involving a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA) and India's largest pharmaceutical company (Abbot India). Imaginot has an agreement with Piramal Healthcare Ltd. in India for the contract development and manufacture of Surge Dose[®] formulations. Piramal can undertake formulation optimisation, scale, up, stability studies and Phase I studies comparing a SD formulation to an existing formulation to demonstrate the improved kinetics, at low cost for companies interested in exploring the use of the SD technology for their drugs.

Surge Dose[®] formulations demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions. The first Surge Dose[®] product was launched in 2011 with the second planned for 2012. Other drugs are under development in optimized Surge Dose[®] formulations.

1.4 The opportunity for an improved oral montelukast tablet

Montelukast sodium is one of a new class of orally active leukotriene receptor antagonists (LTRA). Cysteinyl leukotrienes (CysLT₁s) are associated with symptoms of asthma and allergic rhinitis including oedema, smooth muscle contraction and cellular inflammation, and are released from the nasal mucosa in response to allergens during both the early and the late phase reactions. Cysteinyl leukotriene receptors occur in the lungs and bronchial tubes and on pro-inflammatory cells such as eosinophils and certain myeloid stem cells. Montelukast binds to these receptors such that their activity is blocked for an extended period reducing leukotriene-induced bronchoconstriction and resulting in less inflammation, oedema and mucous secretion. High affinity and selective binding of montelukast means that the therapeutic effect continues in the absence of circulating blood levels of the drug, and that the faster the drug reaches the receptors, the faster will be the onset of action.

Montelukast sodium was approved by the FDA in 1998² covered by US Patent 5,565,473 expiring 03 Feb 2012 with paediatric exclusivity granted until 03 Aug 2012³. It is marketed as Singulair[®] in US and many other countries by Merck & Co Inc, available as 5 and 10 mg oral tablets, 4 and 5 mg chewable tablets for children, and 4 mg oral granules for

² NDA 020829
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=SINGULAIR>

³ US FDA Orange Book <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>

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dissolution in 5 mL of liquid before administration to infants⁴. Initially approved for the management and chronic treatment of asthma in adults and children 6 years and over, indications have since been extended to children of 6 months and over, acute prevention of exercise-induced bronchoconstriction, and symptomatic relief of seasonal and perennial allergic rhinitis in patients as young as 2 years and 6 months old respectively.

Montelukast is well tolerated and is typically used as an add-on therapy in chronic asthma as part of accepted asthma management guidelines⁵. Clinical studies show that once daily usage in chronic treatment of asthma is associated with reduced 'on demand' usage of beta-agonists and reduced nocturnal waking. Concomitant use of montelukast with inhaled corticosteroids demonstrates better therapeutic outcomes than either drug used alone.

Despite the rapid onset of action of IV montelukast sodium and its extended duration of action of around 24 h with improved pulmonary function, oral administration results in lower bioavailability around 64 % with slower and more variable absorption⁶. Current oral formulations do not show adequate speed of onset or efficacy for use in acute asthma and allergic attacks. Faster absorption with faster onset of action could improve the therapeutic profile of montelukast for use in acute asthma and allergic attacks. This opportunity for improved oral montelukast delivery is highlighted by the lack of efficacy reported as the principal reason for discontinuing treatment in one third of 1351 patients with mild to moderate asthma⁷.

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 oral PK studies with solid dosage forms and solutions. MMC effects are significant and can mask differences between formulations and other variables particularly in fasted PK studies.

⁴ Prescribing Information Sheet. Singulair[®], Merck & Co Inc, Whitehouse Station, NJ 08889, USA. Issued September 2006. 16 pages

⁵ Kuitert LM & Barnes NC. Leukotriene receptor antagonists: useful in acute asthma? *Thorax* (2000) 55(4): 255-256

⁶ Dockhorn RJ, Baumgartner RA, Leff JA, Noonan M, Vandormael K, Stricker W, Weinland DE, Reiss TF. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* **55**: 260-265 (2000)

⁷ Barnes N, Thomas M, Price D, Tate H. The national montelukast survey. *J Allergy Clin Immunol* 115:47-54 (2005)

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

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half life in the region of 20 min during Phase I, reduced to 12 and 5 min respectively in Phase II and Phase III⁸.

When a drug is administered to a fasted subject, they may be in any phase of the MMC. Thus, for the same formulation, a subject in Phase I will absorb the drug slower than if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III. This means that even a slow dissolving product can result in fast absorption occasions as well as slow absorption occasions according to the phase of the MMC. However the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Gastric emptying effects are responsible for the double or multiple absorption peaks often seen during the first two hours in individual subject PK profiles particularly where there is frequent plasma sampling. These are well documented for a variety of different drugs^{9,10,11,12,13,14,15,16,17,18} and differ from later peaks due to entero-hepatic recycling.

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- ⁸ Oberle RL, Chen T-Z, Lloyd C, Barnett JL, Owyang C, Meyer J, Amidon GL. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroent* (1990) **99**:1275-82
- ⁹ Mummaneni V, Amidon GI, 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
- ¹⁰ 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
- ¹¹ 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
- ¹² 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
- ¹³ 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
- ¹⁴ Marathe PH, Sandefer EP, Kolli 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
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Multiple peaks are reported for the acidic NSAID diclofenac¹⁹ which has low solubility at under acidic gastric conditions but higher solubility under the alkaline pH of the small intestine.

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

In addition to the MMC, GI motility can be influenced by other factors, and where slowing occurs, this will have an impact on gastric emptying and subsequent drug absorption. Delayed absorption and reduced variability in fed studies result from interruption of the underlying MMC by food which triggers Phase I MMC²⁰. 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

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- ¹⁵ 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
- ¹⁶ 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
- ¹⁷ 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
- ¹⁸ 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
- ¹⁹ 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
- ²⁰ Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. Gut (1979) **20**(Nov):963-970
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2.1.2 Gastric pH

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

- A significant proportion of the population has low gastric acidity such as those with achlorhydria where gastric pH does not drop below pH 4, and hypochlorhydria which affects up to 50 % of the population increasing with age or pathology such as diabetes mellitus and autoimmune conditions
- Patients taking drugs such as antacids and proton pump inhibitors will experience relatively high gastric pH most of the time
- Food increases gastric pH and patients using 'on demand' medication will often be in the post-prandial or partial prandial state where gastric pH will be less acidic

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

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

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

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

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

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2.2 Clinical rationale

Drug absorption following oral administration is influenced by:

- i. the rate at which the drug dissolves 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.

Dosage forms will not change physiological conditions but strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*. Surge Dose[®] tablets achieve ultra fast activated dissolution under the wide range of conditions occurring in the general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

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

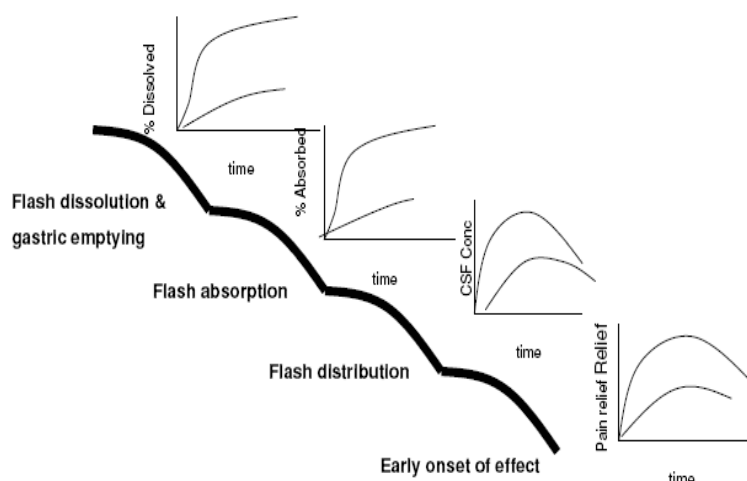
Dissolved drug will reach the small intestine quickly independent of gastric motility. The higher the drug concentration, the greater will be the driving force across the intestinal mucosa for rapid absorption and high C_{max} . Total dissolution of the drug from a solid dosage form into the co-administered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

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

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

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



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

2.3 Surge Dose[®] proof of concept

2.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects²¹ demonstrated significantly faster absorption with two fast dissolving preliminary Surge Dose[®] paracetamol formulations that

²¹ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

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

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

PK-PD modelling to quantify pain relief following oral administration predicted more rapid onset and greater analgesia with Surge Dose[®] paracetamol than Tylenol[®] tablets²². Improved clinical efficacy was predicted for Surge Dose[®] formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol[®]. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

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

²² Green B, Chandler S, Macdonald G, Elliott G, Roberts MS. Quantifying pain relief following administration of a novel formulation of paracetamol (acetaminophen) J. Clin. Pharmacol. (2010) Online First doi 10.1177/0091270009359181

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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 tablet²³. Surge Dose[®] tablets significantly reduced T_{max} and resulted in significantly higher C_{max} levels similar to parenteral administration²⁴. Faster and more consistent absorption has the potential to improve efficacy. Absorption from Surge Dose[®] lornoxicam tablets was twice as fast as from the reference commercial product:

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

2.3.3 Diclofenac

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

²³ 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

²⁴ Radhofer-Welte S, Dittrich P, Simin M, Branebjerg PE. Comparative bioavailability of lornoxicam as single doses of quick release tablet, standard tablet and intramuscular injection – a randomized, open-label, crossover Phase I study in healthy volunteers. Clin Drug Invest. (2008) 28(6): 345-51

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

- Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min) indicating fewer slow absorption profiles with a high T_{max} . Voveran[®]-D showed slower and more variable absorption with a median T_{max} of 1.5 h (15 min – 4 h) indicating a tail of slow absorption profiles.
- Surge Dose[®] produced significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. Surge Dose[®] C_{max} values were comparable with those obtained following IV^{25,26} or IM^{27,28} administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets²⁹.
- With Surge Dose[®], 76 % subjects had a T_{max} equal to or less than 20 min and 100 % reached T_{max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{max} equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{max} , with 6 (30 %) waiting at least 2 h.

3 Montelukast sodium

3.1 Physicochemical properties

Montelukast sodium has the chemical formula $C_{35}H_{35}ClNaO_3S$, molecular weight of 608.18 and the chemical structure shown in Figure 2³⁰.

Montelukast is highly lipophilic with a logP of 8.79 and, being amphoteric, has pKa at 2.7 and 5.8 which are both within the physiological range³¹.

²⁵ Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* (2005) 59(1):80-84

²⁶ Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur J Clin Pharmacol* (1979) 16:405-10

²⁷ Auler JO, Espada EB, Crivelli E, Quintavalle TBG, Kurata A, Stolf NAG, Issy AM, Paschoa OED, Danhof M, Breimer DD, Chamone DAF, Santos SRCJ. Diclofenac plasma protein binding: PK-PD modelling in cardiac patients submitted to cardiopulmonary bypass. *Braz J Med Biol Res* (1997) 30:369-74

²⁸ 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

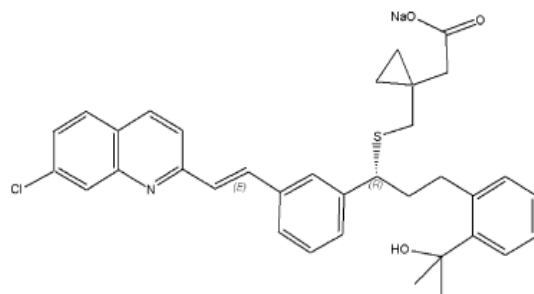
²⁹ Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arznein-Forsch/Drug Res* (2001) 51(11): 885 – 890

³⁰ Drug Bank DB00471 Montelukast sodium <http://www.drugbank.ca/drugs/DB00471/>

³¹ Okumu A, DiMaso M, Lobenberg R. Dynamic dissolution testing to establish in vivo/in vitro correlations for montelukast sodium, a poorly soluble drug. *Pharm Res* (2008) 25(12):2778-2785

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Figure 2 Molecular structure of montelukast sodium



Montelukast is sensitive to light being converted to the cis-isomer and loses up to 20 % potency in the solid state when exposed to daylight for 1 week³². Similar loss of potency has been reported for chewable tablets exposed to light. Although it degrades rapidly under acidic and in the presence of hydrogen peroxide to the S-oxide, it is stable under alkaline conditions in sodium hydroxide solutions at 65 °C as demonstrated by a selective reverse phase HPLC method.

3.1.1 Permeability considerations

Montelukast is absorbed from the small intestine, even though poor oral bioavailability would be predicted based on Lipinski's rule of five which does not account for any active intestinal wall transporter mechanisms^{33,34}. The high molecular weight > 500 and ClogP > 5 would predict poor absorption although the number of hydrogen-bond donors (-OH and -NH groups) are < 5 and hydrogen-bond acceptors (sum of O and N atoms) are < 10 both favouring permeability. The rotational bond count of 12 being > 7 does not favour oral absorption³⁵. The polar surface area (PSA) is 70.42 Å² which favours cell permeability (< 140 Å²) but not blood brain barrier permeability (< 60 Å²).

Recent Caco-2 cell studies have demonstrated the role of major intestinal transport proteins OATP1A2 and OATP2B1 in the absorption of montelukast which are inhibited by components in orange and grapefruit juice³⁶. Permeability is saturable at high

³² Al Omari MM, Zoubi RM, Hasan EI, Khader TZ, Badwan AA. Effect of light and heat on the stability of montelukast in solution and in its solid state. *J Pharm Biomed Anal* (2007) 45:465-71

³³ Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* (2001) 46(1-3):3-26

³⁴ Gimenez, BG, Santos MS, Ferrarini M, Fernandes JPS. Evaluation of blockbuster drugs under the rule-of-five. *Pharmazie* (2010) 65(2):148-52

³⁵ Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem* (2002) 45:2615-2623

³⁶ Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenetics Genomics* (2009) 19:129-138

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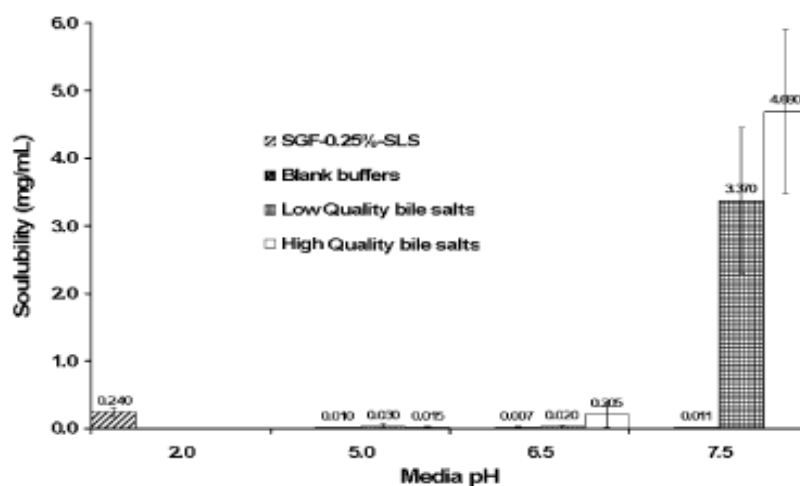
concentrations of montelukast following Michaelis-Menten kinetics. Cell lines expressing OATP2B1 showed increased montelukast permeability. The activation of energy of 13.7 kcal/mol is consistent with carrier mediated transport mechanisms with activation energy in the range 7 – 25 kcal/mol. It is postulated that the residual 30 % permeability seen at maximal inhibition by citrus juice results from passive permeability or diffusion associated with activation energies below 4 kcal/mol, or other transport proteins unaffected by citrus juice.

3.1.2 Solubility considerations

Montelukast sodium is freely soluble in water at 25 °C to the extent of 0.15 mg/mL so that around 67 mL water will be required for complete dissolution of a 10 mg dose. Therefore 10 mg as the sodium salt has the potential to completely dissolve when taken with 100-200 mL co-administered water. The sodium salt is much more soluble than the free acid which, with a predicted water solubility of 0.0082 mg/mL, would require 1220 mL water for complete dissolution of a 10 mg dose.

Although montelukast sodium is more soluble under alkaline conditions, Figure 3 shows that pH alone does not increase solubility as a result of poor wetting of this highly lipophilic molecule³⁷. In simulated gastric fluid at 37°C, 0.25 % sodium lauryl sulphate (SLS) increased the solubility of montelukast sodium to 0.24 mg/mL and at pH 7.5, the addition of bile salts increased its solubility to 3.4 – 4.7 mg/mL. Hence in intestinal fluid *in vivo*, rapid and complete dissolution of an adult dose would be expected.

Figure 3 Solubility of montelukast sodium in different dissolution media showing the effect of a surfactant (SLS) and bile salts



³⁷ Okumu A, DiMaso M, Lobenberg R. Dynamic dissolution testing to establish *in vivo/in vitro* correlations for montelukast sodium, a poorly soluble drug. *Pharm Res* (2008) **25**(12):2778-2785

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It is noted that montelukast is surface active and at concentrations below 5 mg/mL, there is less self association resulting in precipitation of the free acid form³⁸. Therefore when the montelukast sodium is administered orally, it is likely that under the acidic conditions of the stomach the less soluble acid form of montelukast will precipitate out. This has the potential to coat the surface of the undissolved sodium salt thus impairing dissolution of this more soluble form. Hence dissolution will be limited in acidic gastric contents, delaying complete dissolution until the drug reaches the small intestine as a result of gastric emptying. Although alkaline conditions in the small intestine favour dissolution and hence absorption, there will be a variable lag time reflecting the MMC cycle before this occurs.

3.2 Pharmacokinetics (PK)

A linear three-compartment population PK model has been proposed to describe the disposition of montelukast after intravenous (IV) administration in both adults and children³⁹. Oral bioavailability is 60 – 70 % relative to IV administration with extensive CYP3A4 and CYP2C9 metabolism in hepatic microsomes⁴⁰. The metabolites have little overall contribution to the activity of montelukast and are excreted exclusively in the bile. PK are approximately linear for oral doses up to 50 mg, and there is little accumulation of the parent drug in plasma. Montelukast is more than 99% bound to plasma proteins.

Typical PK parameters for IV administration of 3 – 18 mg montelukast sodium are clearance of 45 ml/min, volume of distribution (V_d) of 8 – 11 L and elimination half life ($t_{1/2}$) of 4 – 5 h. Oral and IV absorption profiles are shown in Figure 4⁴¹ and oral PK data showing no gender differences in Table 1. The first 5 sampling points in this study were 0.5, 1, 2, 4, and 6 h. Oral bioavailability of the 10 mg tablets administered with 150 mL co-administered water was 58 – 66 % of the IV dose.

³⁸ FDA NDA 020829 Clinical Pharmacology Biopharmaceutics Review p 3
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020829s000_SingulairTOC.cfm

³⁹ Ramakrishnan R, Migoya E, Knorr B. A population pharmacokinetic model for montelukast disposition in adults and children. *Pharm Res* (2005) **22**(4):532-540

⁴⁰ Balani SK, Xu , Pratha V, Koss MA, Amin RD, Dufresne C, Miller RR, Arison BH, Doss GA, Chiba M, Freeman A, Holland SD, Schwartz JI, Lasseter KC, Gertz BJ, Isenberg JI, Rodgers JD, Lin JH, Baillie TA. Metabolic profiles of montelukast sodium (Singulair), a potent Cysteinyl leukotriene₁receptor antagonist, in human plasma and bile. *Drug Metab Disp* (1997) **25**(11):1282-87

⁴¹ Cheng H, Leff JA, Amin R, Gertz BJ, De Smet M, Noonan N, Rogers JD, Malbecq W, Meisner D, Somers G. Pharmacokinetics, bioavailability and safety of montelukast sodium (MK-0476) in healthy males and females. *Pharma Res* (1996) **13**(3):445-448

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Figure 4 Mean plasma concentration – time profiles for IV and oral administration of montelukast sodium

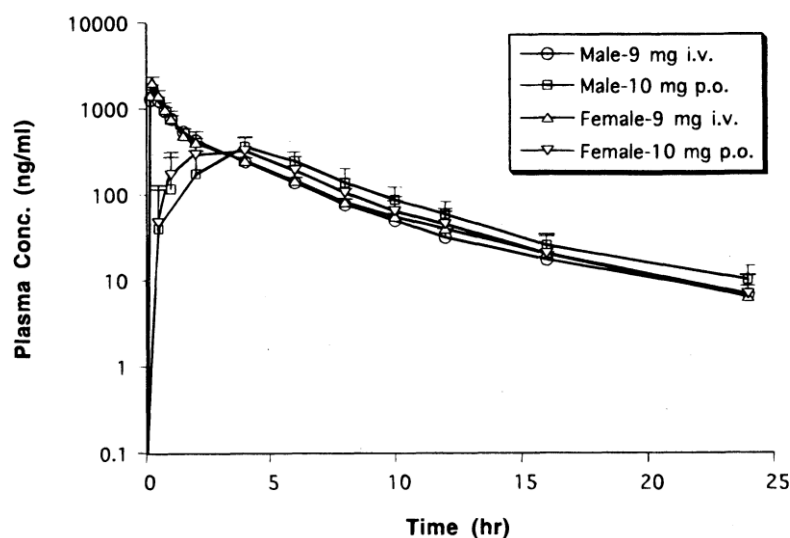


Table 1 Comparative mean (\pm SD) PK parameters for 10 mg oral administration of montelukast sodium for fasted male and female subjects

Parameter	Oral (male)	Oral (female)
Elimination half life $t_{1/2}$ (h)	4.9 ± 0.4	4.4 ± 0.7
MRT (h)	7.3 ± 1.3	6.2 ± 1.0
MAT (h)	3.4 ± 1.0	2.6 ± 0.7
C_{max} (ng/mL)	385 ± 85	350 ± 161
T_{max} (h)	3.7 ± 0.8	3.3 ± 1.0
$AUC_{0-\infty}$ (ng.h/mL)	2441 ± 441	2270 ± 919

3.2.1 Oral absorption

Although Caco-2 studies suggest that montelukast absorption involves active intestinal transport proteins OAT P1A2 and OATP2B1⁴², published PK data suggest that this is not the only absorption rate limiting factor. Both transport mediated absorption and passive diffusion will be affected by any dissolution or solubility rate limitation in the formulations. Faster drug dissolution and delivery to the small intestine will ensure drug reaches transport carriers quickly and maximizes passive diffusion across the mucosa.

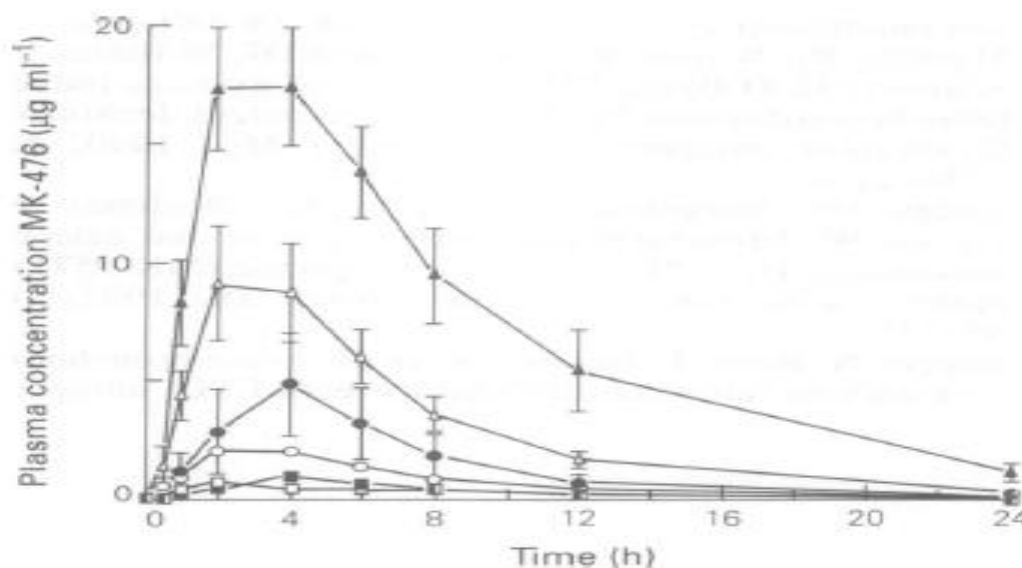
⁴² Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenetics Genomics* (2009) **19**:129-138

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Systemic exposure and C_{\max} show high variability, with mean total AUC values of 2689 ng.hr/mL in the range 1521 to 4595, and mean C_{\max} values of 353 ng/mL in the range 180 to 548 for a 10 mg tablet. Reported T_{\max} values also show a high degree of variability with evidence of a non-normal distribution with mean values being longer than median values indicating a proportion of subjects experiencing slow absorption. In many cases, comparative values are not discriminating as a result of the infrequent sampling schedule. However in some studies, plasma samples were taken at 30 minute intervals out to 4 hours to characterise the absorption phase, and with less frequent samples to 24 h to characterise the elimination, showing T_{\max} values of 3 – 4 h in fasted subjects.

Mean absorption profiles in a dose ranging study are shown in Figure 5 for doses of 20 – 800 mg administered to healthy subjects as a single dose in capsules⁴³.

Figure 5 Mean plasma concentrations \pm SD for montelukast sodium after single dose of 20 – 800 mg in capsules to healthy volunteers



Median T_{\max} values around 2 hour are reported with sampling times at 30 min, 1, 2, 4, 6, 12 and 24 hours as shown in Table 2. With the exception of the solution, doses of montelukast were administered as 10 and 50 mg capsules with an unspecified volume of co-administered water.

⁴³ Schoors DF, De Smet M, Reiss T, MargolskeeD, Cheng H, Larson P, Amin R, Somers G. Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene D₄-receptor antagonist, in healthy volunteers. Br J Clin Pharmacol (1995) 40:277-280

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Table 2 Mean PK data \pm SD for doses of 20 – 800 mg montelukast sodium to fasted healthy volunteers compared with 200 mg administered as a solution in the fasted state and 200 mg capsule in the fed state (T_{max} median and range)

Capsule dose (mg)	AUC ($\mu\text{g ml}^{-1} \text{ h}$)	C_{max} ($\mu\text{g ml}^{-1}$)	t_{max} (h)	$t_{1/2}$ (h)*
Panel A				
20	5.8 \pm 1.5	0.84 \pm 0.22	2.0 (2.0, 4.0)	4.51 \pm 1.70
100	16.0 \pm 8.5	2.21 \pm 0.98	2.0 (2.0, 4.0)	4.96 \pm 1.03
400	68.7 \pm 19.1	10.04 \pm 3.20	3.0 (2.0, 4.0)	4.94 \pm 0.67
Panel B				
50	6.4 \pm 3.90	1.02 \pm 0.56	4.0 (2.0, 4.0)	4.08 \pm 1.65
200	29.3 \pm 14.0	4.89 \pm 2.18	4.0 (2.0, 4.0)	4.18 \pm 0.40
200†	38.0 \pm 11.0	5.54 \pm 1.31	4.0 (2.0, 4.0)	4.38 \pm 0.42
200‡	71.3 \pm 27.5	6.38 \pm 2.03	8.0 (6.0, 12.0)	3.79 \pm 0.57
800	172.8 \pm 38.2	19.53 \pm 3.13	3.0 (2.0, 4.0)	5.19 \pm 0.82

*Harmonic mean, \pm Jackknife s.d.

†200 mg administered as oral solution under fasting conditions.

‡200 mg administered as capsules after a standard breakfast.

The investigators conclude that there is no evidence for dissolution rate limited absorption based on a statistical analysis of the T_{max} data. However the results are limited by the infrequent sampling frequency which provides little discrimination between doses. T_{max} data indicate a tail of slow absorption events with an apparent increase in the median value as the dose increases.

In addition, C_{max} values become more variable as the dose increases indicative of more variable absorption. Dose dependent absorption could be associated with dissolution limited absorption due to the limited solubility of this drug, and is consistent with the faster mean T_{max} of 2.3 h reported for 5 mg dose montelukast sodium compared with 3.0 h for a 10 mg dose in the fasted state⁴⁴.

The lower AUC for the 200 mg tablet which is 76 % of that for the solution in fasted subjects suggests dissolution rate limited absorption. This is consistent with the reported 82 % relative oral bioavailability of a 50 mg tablet compared with a solution under fasted conditions⁴⁵.

For tablets, mean T_{max} values derived from half hourly sampling are consistently reported in the range of 3 – 4 h with coefficients of variation around 30 – 40 %. This indicates that some values will be as short as 1 h and the longest will be over 5 h assuming a normal distribution of results. Typically T_{max} data show a non-normal distribution with a tail of slow

⁴⁴ FDA NDA 020829 Clinical Pharmacology Biopharmaceutics Review p 9
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020829s000_SingulairTOC.cfm

⁴⁵ FDA NDA 020829 Clinical Pharmacology Biopharmaceutics Review p 7
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020829s000_SingulairTOC.cfm

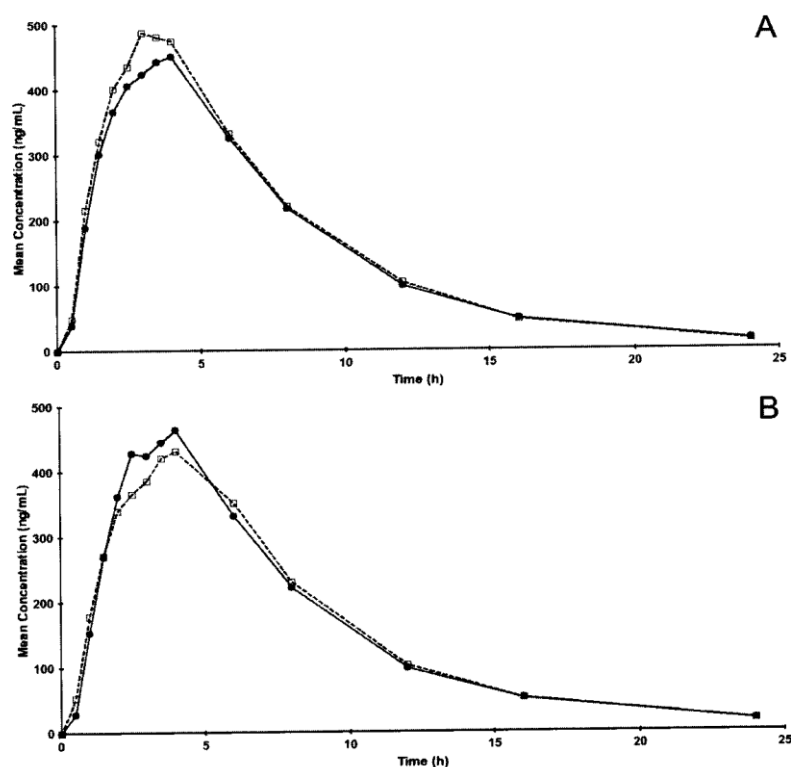
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absorbers such as indicated by the data in Table 2 where the median of 2 h is the same as the lower end of the range.

In patients with cystic fibrosis similar PK to healthy subjects have been reported with mean T_{max} values of 3.3 ± 0.8 h and 3.5 ± 1.0 h respectively⁴⁶. However C_{max} and AUC values were higher in the cystic fibrosis patients although very variable in both groups; 606.7 ± 237.8 and 448.9 ± 165.3 ng/mL and $3,976.1 \pm 2,073.4$ and $2,680.0 \pm 693.6$ ng.min/mL.

Two generic tablets were bioequivalent to Singulair as the reference product⁴⁷. Mean plasma concentration – time curves are shown in Figure 6 where ● is the reference product, with the corresponding PK data in Table 3. Although dissolution studies were conducted on the three products, no methods or data are published. As these tablets are bioequivalent, it is assumed that dissolution profiles would be similar.

Figure 6 Mean plasma concentrations – time curves for two generic montelukast 10 mg tablets (□) compared with Singulair (●) in fasted healthy Thai males



⁴⁶ Graff GR, Weber A, Wessler-Starman D, Smith AL. Montelukast pharmacokinetics in cystic fibrosis. J Pediatr (2003) 142:53-6

⁴⁷ Sripalakit P, Maphanta S, Saraphanchotiwithaya A. Bioequivalence of two generic formulations of 10 mg montelukast tablets in healthy Thai male volunteers. Int J Clin Pharmacol Ther (2010) 48(9):628 - 32

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Table 3 PK parameters for two generic tablets of montelukast 10 mg (□) compared with Singulair (●) in fasted healthy Thai males

Pharmacokinetic parameters		Study A		Study B	
		Montek [®]	Singulair [®]	Tomont [®]	Singulair [®]
C _{max} (ng/ml)	Mean	543.32	530.85	526.27	540.60
	SD	129.09	117.39	178.24	190.83
	C.V. (%)	23.76	22.11	33.87	35.30
	T/R point estimate	1.02		0.97	
	90% C.I.	0.96 – 1.09		0.93 – 1.01	
AUC _{0-t} (ng·h/ml)	Mean	3,859.16	36,91.36	3,734.07	3,733.46
	SD	834.15	753.96	1247.39	1248.14
	C.V. (%)	21.61	20.43	33.41	33.43
	T/R point estimate	1.04		1.00	
	90% C.I.	0.98 – 1.11		0.96 – 1.04	
AUC _{0-∞} (ng·h/ml)	Mean	3,950.43	3,775.93	3,837.01	3,833.83
	SD	854.47	781.25	1294.98	1289.03
	C.V. (%)	21.63	20.69	33.75	33.62
	T/R point estimate	1.05		1.00	
	90% C.I.	0.98 – 1.11		0.96 – 1.04	
t _{max} (h)	Mean	3.4	3.4	3.7	3.8
	SD	1.1	1.2	1.5	1.3
	C.V. (%)	32.5	34.2	39.1	34.3

3.2.2 Formulation effects

Faster absorption from chewable tablets than swallow tablets is reported with mean T_{max} values around 2 hours and SD 0.3 – 0.7 h as shown in Table 4⁴⁸.

Table 4 Mean PK data ± SD for chewable and swallow tablets of montelukast sodium in fasted healthy adults

Pharmacokinetic Parameter	Dose and Formulation of Montelukast (N = 16 ^a)			
	2 mg CT	5 mg CT	10 mg CT	10 mg FCT
Potency-normalized AUC _{0-∞} ng·h/mL ^b	575 ± 109	1417 ± 313	2938 ± 583	2448 ± 779
Potency-normalized C _{max} ng/mL ^b	92 ± 15	232 ± 50	494 ± 83	333 ± 110
t _{max} hour	2.1 ± 0.7	1.9 ± 0.3	1.9 ± 0.3	3.9 ± 1.4
t _{1/2} hour	3.8 ± 0.7	4.4 ± 0.8	4.8 ± 0.3	4.6 ± 0.6

CT, chewable tablet; FCT, film-coated tablet. Values shown are the geometric mean ± back-transformed standard deviation for AUC_{0-∞} and C_{max}; the arithmetic mean ± standard deviation for t_{max}, and the harmonic mean ± jackknife standard deviation for t_{1/2}.

a. Seventeen patients enrolled; only 16 patients completed the study.

b. Potency normalized for tablet content.

⁴⁸ Knorr B, Larson P, Nguyen HH, Holland S, Teiss TF, Chervinsky P, Blake K, van Nispen CHM, Noonan G, Freeman A, Haesen R, Michiels N, Rodgers JD, Amin RD, Zhao J, Xu X, Seidenberg BC, Gertz BJ, Spielberg S. Montelukast dose selection in 6 to 14 year olds: comparison of single dose pharmacokinetics in children and adults. J Clin Pharmacol (1999) **39**(8):786-93

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Reported differences in absorption with the swallow and chewable tablets are consistent with expectations for an acidic drug where it becomes increasingly soluble as the pH increases. The pH of saliva is generally in the range 6.5 – 6.9, much higher than the acidic pH of 1-2 which occurs in the stomach, particularly in the fasted state. Therefore, if an acidic drug is chewed in the mouth before swallowing a much higher proportion is likely to be present in solution and likely to empty from the stomach with any co-administered liquids. Rapid gastric emptying leads to higher driving forces across the GI wall and rapid absorption. This would explain the higher bioavailability and shorter T_{max} compared with the swallow tablet.

Mean population estimates of T_{max} with SEM and 95 % confidence intervals based on 3 plasma samples from 1 – 3 month old infants administered montelukast 4 mg as granules mixed with infant formula⁴⁹ were longer than for the same dose mixed with applesauce in 3 - 6 months old children⁵⁰ as shown in Table 5. Again mean T_{max} values are around 2 h.

Table 5 Mean C_{max} and T_{max} data \pm SEM (95 % confidence intervals) for paediatric patients following a single dose of 4 mg montelukast as oral granules

Population Age, mo	N	C_{max} , ng/mL	T_{max} , hr	$t_{1/2}$, hr	Cl/F, mL/min
1-3	12	1234.6 \pm 196.4 (754.1-1715.1)	3.2 \pm 0.6 (1.7-4.6)	1.20 \pm 0.48 (0.02-2.39)	5.1 \pm 0.9 (2.9-7.2)
3-6 ^a	14	561.1 \pm 78.0 (381.3-741.0)	2.1 \pm 0.4 (1.1-3.1)	0.94 \pm 0.38 (0.05-1.82)	18.3 \pm 2.4 (12.7-23.9)
3-24 ^b	42	582.3 \pm 47.4 (486.2-678.4)	1.9 \pm 0.3 (1.3-2.5)	0.75 \pm 0.20 (0.34-1.17)	18.4 \pm 1.2 (15.9-20.9)

Values are mean \pm standard error (95% confidence interval).

Based on T_{max} data and the proof of concept study with the acidic NSAID lornoxicam, a Surge Dose[®] montelukast sodium tablet would be expected to result in more fast absorption occasions towards the lower end of the range as a result of fast *in vivo* dissolution. Table 4 indicates that the shortest T_{max} values are around 1.1 – 1.3 h. Therefore a Surge Dose[®] montelukast would have more T_{max} values at the lower end of this range, so that the median T_{max} approaches or is shorter than that seen with the chewable tablets and granules. It would be significantly faster than T_{max} reported for film coated tablets around 3 - 4 h.

⁴⁹ Kearns GL, Lu S, Maganti L, Li X, Migoya E, Ahmed T, Knorr B, Reiss TF. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* (2008) **48**:502-511

⁵⁰ Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Kearns G. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* (2006) **46**(6):620-627

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3.2.3 Food effects

Table 2 in section 3.2.1 shows significantly a higher AUC for 200 mg montelukast after food than in the fasted state. Mean AUC values after food are $71.3 \pm 27.5 \mu\text{g/mL}\cdot\text{h}$ compared with $29.3 \pm 14.0 \mu\text{g/mL}\cdot\text{h}$ in fasted subjects. The mean T_{max} is doubled from 4 to 8 h consistent with delayed gastric emptying as food triggers Phase I MMC.

This increased bioavailability by food is postulated to be explained by delayed gastric emptying so that in the less acidic conditions in the fed stomach there is more time and more favourable conditions for more drug to dissolve and be available for absorption once gastric emptying occurs. Food may also increase the extent of absorption by increased mesenteric blood flow with associated reduced hepatic metabolism.

However different food effects have been reported for lower doses in the therapeutic range comparing the 10 mg film coated tablet with the 5 mg chewable tablet⁵¹. For the 10 mg tablet, food had no significant effect on mean total AUC (around 64 %), C_{max} or T_{max} which was delayed from 3.0 to 3.4 h. However oral bioavailability for the 5 mg chewable tablet dose was reduced from 73 % to 63 % when administered with a standard meal, mean C_{max} was reduced and T_{max} delayed from 2.3 h to 4 h.

These differences are consistent with the solubility and dissolution effects discussed in the previous section with the 10 mg tablet showing more dissolution limited absorption than the chewable 5 mg tablet. As the chewable tablet is absorbed to a greater extent, food will have a greater delaying effect.

3.3 Pharmacodynamics (PD)

Reduction of LTD₄-induced bronchoconstriction is evident following doses of montelukast sodium as low as 5 mg, with a minimum effective plasma level of 120 ng/mL⁵².

Figure 7 shows the significant 10-fold differences in total exposure (AUC) and plasma concentrations that have been reported between subjects following the oral administration of 10 mg montelukast sodium attributed to genetic phenotypes. It is notable that in one patient, plasma concentrations do not reach the reported minimum effective plasma level of 120 ng/mL which would contribute to the observed heterogeneity in response to this class of drugs⁵³.

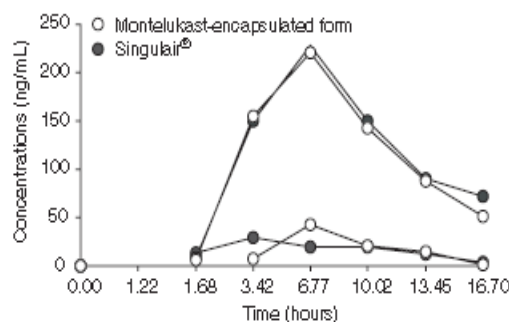
⁵¹ FDA NDA 020829 Clinical Pharmacology Biopharmaceutics Review p 9
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020829s000_SingulairTOC.cfm

⁵² FDA NDA 020829 Clinical Pharmacology Biopharmaceutics Review p 19
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020829s000_SingulairTOC.cfm

⁵³ Lima JJ. Treatment Heterogeneity in Asthma: Genetics of Response to Leukotriene Modifiers
Mol Diag Ther (2007) 11 (2): 97-104

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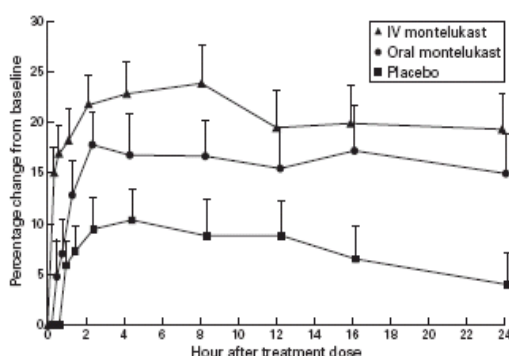
Figure 7 Plasma concentration – time curves for two subjects after oral administration of 10 mg montelukast sodium showing the potential for sub-therapeutic dosing



Although the efficacy of montelukast is apparent after the first dose, with the effects lasting throughout the 24 h dosing interval, lack of efficacy is reported to be the principle reason for withdrawal for one third of patients ($n = 1351$) being treated with montelukast for mild to moderate asthma⁵⁴.

Compared with placebo, IV montelukast (7 mg) shows a statistically significant faster increase in the forced expiratory volume in one second (FEV_1) than 10 mg tablets administered with 150 mL water to 50 asthma patients as shown in Figure 8⁵⁵. Both routes of administration produce a similar effect on the FEV_1 over 24 hours. Based on these results, the authors suggest investigating the use of a fast acting form of montelukast in acute severe asthma where fast onset of action is required.

Figure 8 Percentage change from baseline in FEV_1 over the 24 hours following treatment with IV and oral montelukast sodium compared with placebo



⁵⁴ Barnes N, Thomas M, Price D, Tate H. The national montelukast survey. *J Allergy Clin Immunol* 115:47-54 (2005)

⁵⁵ RJ Dockhorn, RA Baumgartner, JA Leff, M Noonan, K Vandormael, W Stricker, DE Weinland, TF Reiss. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 55: 260-265 (2000)

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In seasonal allergic rhinitis, phase III trials of 10 mg montelukast daily (n = 1350) showed self-rated improvements in symptoms on day 1 with 70 % of the maximum response reported by day 2⁵⁶. Again faster and more consistent absorption of the drug could provide faster onset of action and improved efficacy by day 2.

While genetic polymorphisms are thought to contribute to impaired absorption and variable and poor clinical response to montelukast and other LTRAs in some patients⁵⁷, there will still be some effect of slow and variable absorption. In Korean children with exercise-induced bronchoconstriction, 55 % with IL-13-1112C/T polymorphism were responders to montelukast compared with 25 % non-responders and the remainder intermediate responders⁵⁸. A fast dissolving montelukast tablet could improve the clinical outcome.

4 Surge Dose[®] montelukast sodium

4.1 Improved dissolution

Limited experimental work was conducted by Imaginot to demonstrate significantly improved dissolution of montelukast sodium using the Surge Dose[®] ultra-fast activated dissolution technology. As no montelukast sodium raw material was available, Singulair[®] tablets each containing 10.4 mg montelukast sodium were reformulated as detailed in Table 6 where √ indicates unquantified named excipients in the commercial product.

Table 6 Experimental formulations of uncoated montelukast sodium tablets compared with the film coated commercial tablet Singulair[®]

Ingredients (mg)	0521310	0521311	0521710/11	Singulair [®]
Montelukast sodium	10.4	10.4	10.4	10.4
Sodium bicarbonate	40	400	600	0
Citric acid anhydrous	0	0	76	0
Microcrystalline cellulose *	√	√ + 70	√ + 100	√
Croscarmellose sodium *	√	√ + 30	√ + 40	√
Lactose *, magnesium stearate	√	√	√	√
Total tablet weight	240	700	1016	204

⁵⁶ Weinstein SF, Philip G, Hampel FC, Malice M-P, Swern AS, Balachandra Dass S, Reiss TF. Onset of efficacy of montelukast in seasonal allergic rhinitis. *Allergy Asthma Proc* 26:41-46 (2005)

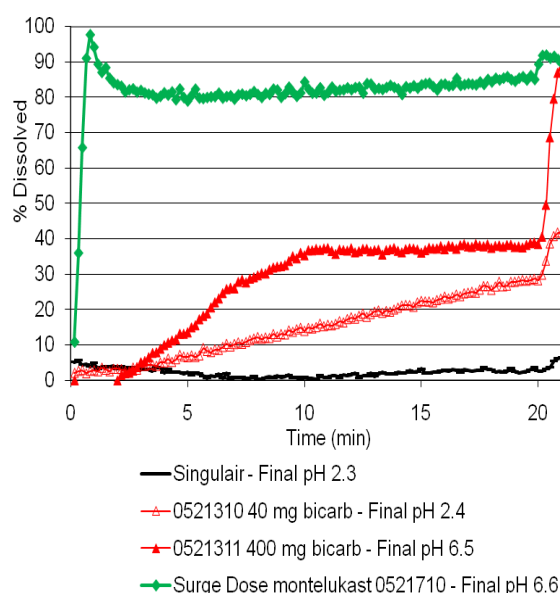
⁵⁷ Langmarck EL & Martin RJ. Heterogeneity of response to asthma controller therapy: clinical implications. *Curr Opin Pulmon Med* (2010) **16**:13-18

⁵⁸ Kang M-J, Lee S-Y, Kim H-B, Yu J, Kim B-J, Choi W-A, Jang S-O, Hong S-J. Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. *Pharmacogenet Genom* (2008) **18**(7):551-558

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In vitro dissolution profiles in 900 mL 0.0033 M HCl in USP dissolution apparatus II at 30 rpm and 37 °C are shown in Figure 9 for tablets containing 40 and 400 mg sodium bicarbonate, an unoptimized Surge Dose[®] formulation containing 600 mg sodium bicarbonate with 76 mg citric acid anhydrous and the commercial Singulair[®] tablet. The stirring speed was increased to 200 rpm after 20 min to maximize the extent of dissolution at the final pH.

Figure 9 *Dissolution profiles for montelukast sodium tablets demonstrating the effect of a Surge Dose[®] formulation, and two different levels of sodium bicarbonate compared with the commercial product Singulair[®] in 900 mL 0.0033 M HCl in USP dissolution apparatus II at 30 rpm and 37 °C*



Singulair[®] tablets consistently demonstrated less than 10 % dissolution and no change in the pH of the dissolution medium during the test period. Also there was some evidence of a decrease in % dissolved with time as the inherently soluble montelukast sodium was converted to the less soluble acid form of the drug. When the stirring speed was increased, the % dissolved reached original levels.

40 mg sodium bicarbonate (0521310) slightly increased the pH of the dissolution medium allowing a slow but steady increase in dissolution over time, which was further increased when the stirring rate was increased. At the final pH, some 40 % of the drug was dissolved compared with less than 10 % for Singulair[®].

400 mg sodium bicarbonate (0521311) provided a faster dissolution rate after an initial lag reaching a plateau around 40 % in the first 10 min once the reaction between the sodium

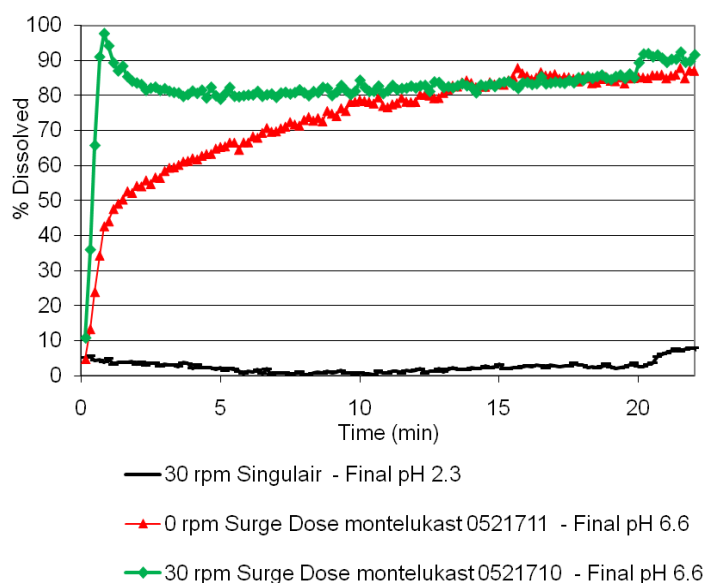
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bicarbonate and the acid in the dissolution medium was exhausted. Thereafter, dissolution was dependent on the external mixing energy provided. Maximal dissolution when the stirring speed was increased reached 90 % reflecting the higher final pH 6.5 of the dissolution medium. The initial lag in the first minute is likely to result from the high level of sodium bicarbonate effectively masking drug particles from dissolution and competing for water with disintegrating agents and other soluble ingredients.

The unoptimized Surge Dose[®] formulation (0521710) showed the fastest and most extensive dissolution reaching around 80 % dissolution within the first 3 min. This demonstrates the synergistic effect of the reaction between the bicarbonate and acid in the formulation and the pH in the microenvironment around the dissolving drug particles. When the stirring rate was increased there was a slight increase in % consistent with the final pH at 6.6 which was similar to that achieved with 400 mg bicarbonate alone. The initial high peak is thought to result from high concentrations of drug solution reaching the detector until the bulk solution becomes homogenous.

Figure 10 demonstrates the intrinsic activated dissolution of the Surge Dose[®] formulations where the extent of dissolution reaches 60 % dissolution in 5 min in the absence of stirring. This simulates Phase I MMC such as in the fed state where there is little gastric motility such that dissolution can still occur in available liquids which will empty rapidly from the small intestine.

Figure 10 Dissolution profiles for a Surge Dose[®] montelukast sodium tablet formulation at 30 rpm and 0 rpm demonstrating the intrinsic activated Surge Dose[®] dissolution compared with the commercial product Singulair[®] in 900 mL 0.0033 M HCl in USP dissolution apparatus II at 37 °C

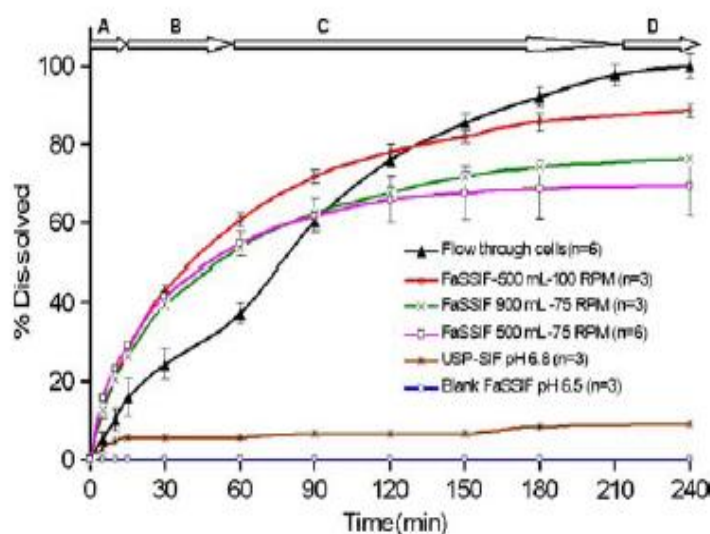


Application of Surge Dose[®] to montelukast sodium

4.2 IVIVC predictions for faster absorption

Recognizing the poor solubility of montelukast sodium and the need for consistent dissolution to reduce absorption variability, the effect of different biorelevant dissolution media on dissolution has been investigated⁵⁹. As seen in Figure 11, dissolution profiles obtained even at relatively high stirring speeds of 75 and 100 rpm and with progressive increases in pH, do not show such rapid dissolution as the Surge Dose[®] formulations. The fastest dissolution reaches only 40 % in 30 min in alkaline dissolution media compared with 80 % in the first minute in an initially acidic dissolution medium where precipitation of the less soluble free acid form of this drug would occur..

Figure 11 *Dissolution profiles for commercial montelukast sodium tablets 10 mg in flow through cells with a dynamic pH change protocol (A = pH 2, B = pH 6.5, C = pH 7.5, D = pH 5.0) and USP dissolution apparatus II with different dissolution media and stirring rates*



These *in vitro* dissolution data were used to predict absorption profiles shown in Figure 12 indicating good correlation with the observed absorption profile when a 38 % first pass extraction was applied for hepatic metabolism. Profiles were a little faster than the observed profile suggesting that 75 and 100 rpm provide more agitation and mixing energy than occurs *in vivo*. T_{max} values were in the region of 2 – 3 h corresponding to 60 – 80 % dissolution in the *in vitro* testing.

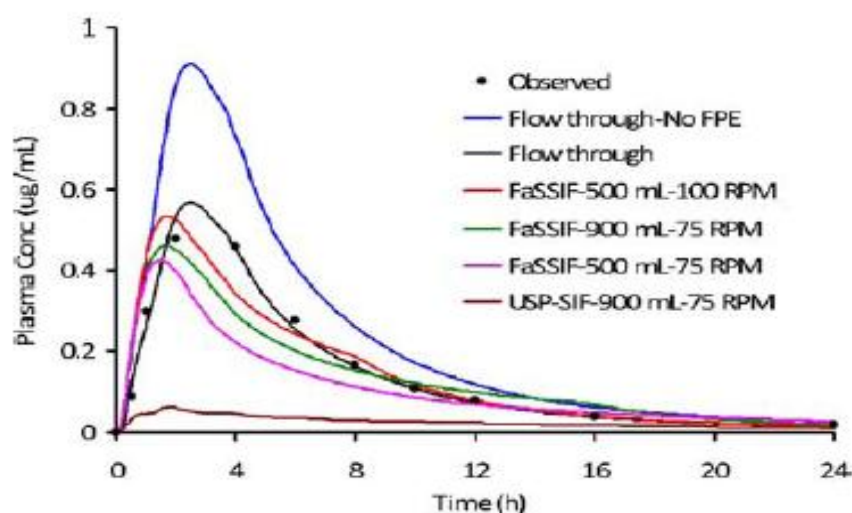
The Surge Dose[®] formulation achieved 80 % dissolution in the first minute at slower stirring speeds that might be more representative of the *in vivo* conditions, and with a change in

⁵⁹ Okumu A, DiMaso M, Lobenberg R. Dynamic dissolution testing to establish *in vivo/in vitro* correlations for montelukast sodium, a poorly soluble drug. *Pharm Res* (2008) **25**(12):2778-2785

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pH from 2.3 to 6.5 during the course of the test. Therefore, it would be expected that Surge Dose[®] tablets would result in faster and more reproducible absorption of montelukast sodium *in vivo*.

Figure 12 Observed absorption profile for commercial montelukast sodium tablets compared with simulated profiles from Fig 10 data with 38 % first pass extraction applied to USP dissolution data only



Based on PK-PD clinical evidence⁶⁰, faster absorption of an oral form of montelukast sodium will be associated with an earlier onset of action. This could potentially extend the current therapeutic use of this drug to acute asthma and provide earlier onset of action and relief of symptoms in allergic rhinitis.

5 Conclusions

Based on this analysis of available data, montelukast sodium appears to be a good candidate for the application of Imaginot's Surge Dose[®] ultra-fast activated dissolution technology. There is evidence of some *in vivo* dissolution rate limitation reducing the rate and extent of absorption of montelukast sodium following oral administration. This will contribute to the slow and variable absorption of this drug with T_{max} values in the range 2 – 4 h and relatively low oral efficacy with slow onset of action.

Long T_{max} values around 3 – 4 h for the film coated tablet suggest relatively slow *in vivo* dissolution. This proposition is reinforced by the faster absorption and improved

⁶⁰ RJ Dockhorn, RA Baumgartner, JA Leff, M Noonan, K Vandormael, W Stricker, DE Weinland, TF Reiss. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* **55**: 260-265 (2000)

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pharmacokinetics of a solution, and chewable tablets with T_{\max} values in the region of 2 h where more drug will be dissolved in the neutral saliva before swallowing. Individual subject T_{\max} values may be as short as 1 h based on published distribution data.

An optimized Surge Dose[®] montelukast sodium tablet could be developed based on the preliminary formulation that provides significantly faster and more extensive dissolution than Singulair[®] tablets. Levels of pH modulating agents and water uptake agents would be optimized to maximize the rate and extent of dissolution under a wide range of acidic and alkaline *in vitro* test conditions. It is expected that levels of sodium bicarbonate would be in the range 400 – 600 mg with the addition of an organic acid up to 100 mg per tablet.

Based on published IVIVC and the improved oral bioavailability of this drug in solution, a fast dissolving Surge Dose[®] montelukast sodium tablet would be expected to demonstrate faster *in vivo* dissolution and faster *in vivo* absorption, resulting in faster onset of action.

Based on this improved dissolution, a Surge Dose[®] montelukast sodium tablet would be expected to have a significantly shorter mean and median T_{\max} in the region of 1 – 2 h with a higher proportion of subjects having a T_{\max} in this range with a reduced frequency of slow absorption occasions greater than 3 h. Food effects would be expected to be reduced as the Surge Dose[®] activated dissolution will allow the rapid delivery of dissolved drug to the small intestine reducing the effect of gastric emptying.

Although used daily by oral administration for the regular management of chronic asthma, an improved Surge Dose[®] montelukast sodium tablet offers the opportunity for wider use of this drug in acute indications. Increased rate and extent of oral absorption closer to that of IV administration may provide improved clinical efficacy in acute asthma and allergic rhinitis.