

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

Imaginot Pty Ltd

ABN 34 089 023 352

Ground floor

100, Ipswich Rd

Woolloongabba

Qld 4102

Australia

Phone: +617 3392 3811

Contacts

Garth MacDonald. Managing Director

gmacdonald@imaginot.com.au

Geraldine Elliott, R&D Director

gelliott@imaginot.com.au

Issued

Geraldine Elliott

Name

R & D Director

Position

15 April 2012

Date

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

Table of Contents

1	TECHNOLOGY OVERVIEW	1
2	SURGE DOSE[®] FOR FASTER AND MORE CONSISTENT ABSORPTION	2
2.1	Paracetamol	2
2.2	Lornoxicam	3
2.3	Diclofenac	4
3	IMPROVED PK TRANSLATES TO IMPROVED PD.....	6
3.1	Paracetamol	6
3.2	Lornoxicam	9
3.3	Diclofenac	10
4	HOW DO OTHER FAST ABSORPTION TECHNOLOGIES COMPARE? ..	11
4.1	Buffered products	11
4.2	Liquid filled soft capsules.....	13
4.3	Orally disintegrating tablets (ODTs).....	14
5	SUMMARY	16

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

1 Technology overview

Gastrointestinal conditions and particularly gastric emptying are responsible for much of the intra- and inter-subject variability seen in oral drug absorption. This is important for drugs taken 'on demand' for immediate effect such as in pain, migraine, insomnia, drug addiction, allergies, nausea and erectile dysfunction where delayed absorption often results from prevailing physiological conditions. It is also important for drugs taken on a regular basis, such as in the treatment of Parkinson's disease, asthma, chronic pain and inflammatory conditions where consistent absorption from the minimum possible dose is highly desirable to reduce overall exposure and the potential for adverse events without compromising efficacy.

Throughout the day a wide range of gastrointestinal physiological conditions exists within the general population, and while this cannot be changed, 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[®] swallow tablet formulations are designed to achieve ultra-fast activated, pH-controlled dissolution under a wide range of favourable and unfavourable physiological conditions. Surge Dose[®] formulations minimise the *in vivo* drug dissolution time resulting in fast and consistent absorption *in vivo*.

Surge Dose[®] tablets are designed so that the drug absorption profile is more like an oral solution or an injection than a conventional solid oral dosage form. In a Surge Dose[®] formulation a drug will rapidly dissolve in the stomach contents after oral administration regardless of gastric pH and motility. Dissolved drug reaches the small intestine quickly independent of gastric motility. The higher the small intestinal 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, then emptying from the stomach to the duodenum, provides the maximum concentration to drive absorption and then distribution to effect compartments by passive diffusion, resulting in fast onset of action and clinical response.

Surge Dose[®] formulations are optimized for each drug or drug combination using *in vitro* dissolution test methods developed by Imaginot to simulate a range of physiological conditions. Levels and composition of pH modulating agents (pHMA) and water uptake agents (WUA) are selected to maximize any pH dependent solubility effects and achieve at least 50 % drug release in 5 min in 900 mL 0.0033 M HCl at 30 rpm.

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

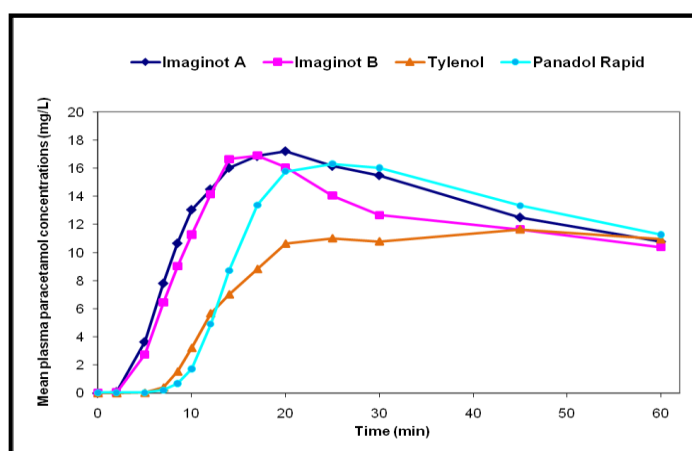
2 Surge Dose[®] for faster and more consistent absorption

Phase I pharmacokinetic (PK) studies have been conducted on three drugs in Surge Dose[®] formulations in fasted healthy subjects. These have been compared with conventional commercial tablets as well as products marketed as 'fast absorption'; Panadol[®] Rapid (GSK) a swallow tablet containing 1260 mg bicarbonate per 1,000 mg paracetamol and Voveran-D[®] (Novartis) a 50 mg diclofenac dispersible tablet mixed with water before swallowing. In all cases, Surge Dose[®] formulations demonstrated faster and more consistent absorption reaching higher C_{max} than the comparator. Surge Dose[®] formulations reduced times to C_{max} (T_{max}) with a smaller difference between mean and median values by eliminating the tail of slow absorption occasions associated with low C_{max} values.

2.1 Paracetamol

Although optimized Surge Dose[®] paracetamol tablets with improved in vitro dissolution profiles have since been developed, two early formulations (A & B) showed fast in vivo absorption compared with two marketed products claiming 'fast absorption' commercial products, Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol[®]> and Panadol[®] Rapid (GSK, Aus)¹. Panadol[®] Rapid contains 630 mg sodium bicarbonate per tablet but shows slower in vitro dissolution compared with the Surge Dose[®] tablets. Mean absorption profiles are shown in Figure 1.

Figure 1 Mean absorption profiles for 1,000 mg paracetamol administered orally as unoptimized Surge Dose formulations and two commercial 'fast absorption' tablets in 25 healthy fasted subjects



¹ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

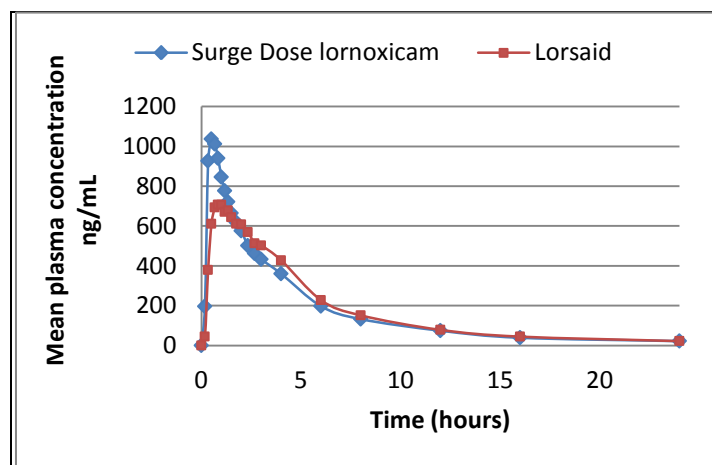
- Median T_{\max} values for Surge Dose[®] formulations were 17 and 25 min respectively and for Panadol[®] Rapid 25 min compared with 45 min for Tylenol[®]
- Mean C_{\max} values were lowest for Tylenol[®] at $19.4 \pm 10.3 \mu\text{g/mL}$ compared with 23.1 ± 9.3 and $21.8 \pm 11.2 \mu\text{g/mL}$ for the two Surge Dose[®] formulations and $24.2 \pm 9.3 \mu\text{g/mL}$ for Panadol[®] Rapid
- Although $AUC_{0-\infty}$ values were similar for all products, Surge Dose[®] formulations achieved significantly more absorption in the first 10 min

This study showed good *in vitro in vivo* correlations (IVIVC) with the best Level A correlation in 900 mL 0.0033 M HCl at 30 rpm which conditions are used to optimize Surge Dose[®] formulations.

2.2 Lornoxicam

A film coated Surge Dose[®] lornoxicam 8 mg tablet was developed containing optimized levels of pHMA and WUA to meet the Surge Dose[®] *in vitro* dissolution specifications. A Phase I PK study in 24 fasted healthy subjects showed significantly faster absorption than Lorsaid[®] (Hetero Drugs Limited) as shown in Figure 2². Compared with other generic lornoxicam tablets, Lorsaid[®] showed more extensive *in vitro* dissolution but did not meet the Surge Dose[®] specification.

Figure 2 Mean absorption profiles for 8 mg lornoxicam administered orally as a Surge Dose[®] tablet and Lorsaid[®]



² 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

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

- 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 Lorsaid[®] was 0.83 h ranging from 0.5 to 2.3 h with a longer mean T_{max} of 1.06 h indicating a tail of subjects with slow absorption
- 75 % subjects on Surge Dose[®] lornoxicam achieved T_{max} within the first 0.5 h compared with only 8 % for Lorsaid[®]
- Surge Dose[®] lornoxicam achieved C_{max} comparable with parenteral administration³, around 40 % higher than Lorsaid[®] with mean C_{max} 1,098 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 Lorsaid[®] 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 Lorsaid[®]

2.3 Diclofenac

A film coated Surge Dose[®] diclofenac sodium 50 mg tablet was developed containing optimized levels of pH modulating agents and water uptake agents to meet the Surge Dose[®] in vitro dissolution specifications. This was compared with Voveran[®]-D (Novartis), a dispersible tablet taken by dissolving in water before administration, containing 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium. This Phase I PK study in 21 fasted healthy subjects demonstrated faster and more consistent absorption of diclofenac with significantly higher C_{max} for Surge Dose[®] as shown in Figure 3⁴.

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). By comparison Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h). Surge Dose[®] tablets resulted in significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with

³ 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

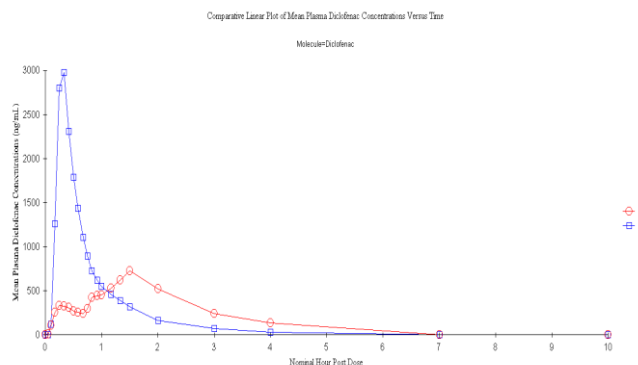
⁴ Piramal Clinical Research. Report No CR-BE-324-DICL-2011 (draft) An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose comparative pharmacokinetic study of Diclofenac Rapid Release tablets 50 mg sodium diclofenac comparing with Voveran D dispersible tablets 46.5 mg diclofenac free acid in healthy adult human subjects under fasting conditions. March 2012

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

1,042 ± 518 ng/mL for Voveran[®]-D. C_{max} values for Surge Dose[®] were comparable with those obtained following IV^{5,6} or IM^{7,8} administration whereas as those for Voveran[®]-D were lower than reported for standard tablets of 1,340 ± 627 ng/mL⁹.

Figure 3 Mean absorption profiles for 50 mg diclofenac sodium administered orally as a Surge Dose[®] tablet and a dispersible commercial tablet (Voveran[®]-D) dispersed in water before administration in 21 healthy fasted subjects



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.

Despite the marketing of the Voveran[®]-D dispersible tablets as providing faster pain relief, they 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 (migrating motility complex).

- ⁵ 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
- ⁶ 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
- ⁷ 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
- ⁸ 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
- ⁹ 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

3 Improved PK translates to improved PD

For all three drugs where Surge Dose[®] formulations have been shown to produce faster absorption, there are published studies demonstrating that faster absorption is associated with faster onset of action and improved efficacy. PK-PD modelling for paracetamol is consistent with this proposition, indicating that Surge Dose[®] formulations are likely to demonstrate superior efficacy on a par with NSAIDs.

3.1 Paracetamol

NNT (Number Needed to Treat) values determined from systematic reviews of randomised controlled trials taking into account a placebo control, provide a useful measure of analgesic efficacy for comparing different treatments. The lower the NNT value above 1, the more effective the analgesic, with NSAIDs such as diclofenac and ibuprofen, and synthetic opioids such as tramadol, being superior to paracetamol¹⁰:

- NNT of 3.8 (CI 3.4 – 4.4) for 1,000 mg oral paracetamol achieving 50 % pain relief in 46 % of subjects (n = 2,759)
- NNT of 2.7 (CI 2.4 – 3.1) for 50 mg oral diclofenac achieving 50 % pain relief in 57 % of subjects (n = 1,296)
- NNT of 2.7 (CI 2.5 – 2.9) of 200 mg oral ibuprofen achieving 50 % pain relief in 48 % of subjects (n = 3,248)
- NNT of 2.9 (CI 2.4 – 3.6) for 150 mg oral tramadol achieving 50 % pain relief in 48 % of subjects (n = 561)

PK-PD modelling has been used to quantify pain relief based on the PK study with Surge Dose[®] paracetamol¹¹. NNT estimates predict that both Surge Dose[®] formulations will achieve more rapid onset and greater analgesia with improved efficacy than the two commercial products as shown in Table 1. Not only do the Surge Dose[®] formulations reach NNT values below 4 in 30 min within the range reported for paracetamol¹², they

¹⁰ The 2007 Oxford league table of analgesic efficacy
<http://www.medicinesox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/lftab.html>
 Ideally a drug formulation will achieve an NNT of 1, which means that every patient treated achieves the measured end point

¹¹ 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

¹² Moore, A. et al. Paracetamol with and without codeine in acute pain: A quantitative systematic review. Pain (1997) 70(2-3):193-201

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

reach lower minimum levels of 2.7 – 2.9 after 45 min comparable with more effective analgesics such as the NSAIDs and tramadol.

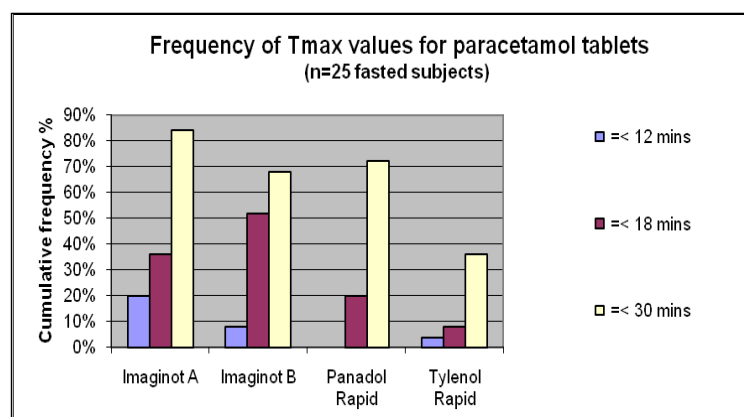
Table 1 Simulated NNT values for at least 50 % pain relief for 1,000 mg doses of four different paracetamol tablet formulations

Product	Simulated NNT Values for at least 50 % Pain Relief						
Time post-dose	10 min	15 min	30 min	45 min	1 h	2 h	4 h
Surge Dose [®] A	278	31.6	3.97	2.75	3.33	14.3	48.1
Surge Dose [®] B	250	25.5	3.71	2.88	3.53	14.1	44.6
Tylenol [®]	∞	313	9.33	4.31	4.19	13.9	44.6
Panadol [®] Rapid	2500	208	5.73	3.20	3.62	13.9	42.4

Tylenol[®] is predicted to have comparatively slow onset of action and lower efficacy than the other three products based on the lowest NNT value of 4.19 after 1 h which is at the high end of the CI reported for paracetamol. Panadol[®] Rapid with a minimum NNT of 3.2 after 45 min is predicted to be superior to Tylenol[®] but with slower onset of action and lower efficacy than the two Surge Dose[®] tablets.

Analysis of the individual subject absorption profiles reveals the likely cause of the predicted improved clinical efficacy. Surge Dose[®] formulations result in fewer slow absorption occasions resulting in sub-therapeutic C_{max} values below the reported minimum therapeutic plasma level (EC_{min}) of 10 µg/mL as shown in Figure 4 and Table 2.

Figure 4 Cumulative frequencies of different T_{max} values among the 25 fasted subjects for the four paracetamol products



IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

Table 2 *Percentage of subjects reaching paracetamol EC_{min} (10 mg/mL) by time for the four test products (* $P < 0.05$)*

Product	10 min	15 min	20 min	30 min	Ever
Surge Dose [®] A	48*	76*	88*	92*	96
Surge Dose [®] B	44*	64*	68*	80*	88
Panadol [®] Rapid	4	32	64*	88*	96
Tylenol [®]	8	20	40	52	84

The two Surge Dose[®] formulations achieved faster absorption than the two commercial products, with as many as 80% of subjects achieving T_{max} within 30 min compared with less than 40% for Tylenol[®]. Although Panadol[®] Rapid showed faster absorption than Tylenol[®], there were far fewer early absorption profiles with T_{max} less than 12 and 18 min compared with Surge Dose[®].

These results indicate statistical superiority of the Surge Dose[®] formulations over both commercial products after 10 minutes when around 50 % subjects have already reached EC_{min} resulting in a clinical response. Panadol[®] Rapid reached this 50 % response level in 15 - 20 min whereas Tylenol[®] did not achieve this response level until 30 min post-dose. Of concern is that 16 % of subjects receiving Tylenol[®] never reached EC_{min} at any time during the study which has serious implications in relation to clinical efficacy and the potential for repeat dosing. Recent moves to lower paracetamol dosing to reduce the risk of toxicity can be predicted to reduce efficacy and increase the risk of toxicity through repeat dosing with products such as Tylenol[®].

Fast dissolving paracetamol tablets have been shown to achieve faster onset of action than conventional tablets comparable with that of an effervescent solution. In sore throat, Panadol[®] Rapid analgesia was superior to placebo after 15 min with 49 % reporting onset of action within 15 min and 88 % within 30 min¹³. In dental surgery pain, an effervescent paracetamol solution and Panadol[®] Actifast[®] produced superior analgesia to placebo at 10 min and superior to conventional tablets at 10 and 40 min¹⁴.

¹³ Schachtel BP, Burnett I, Grattan TJ, Sanner KM, Bey M, Healy A, Butler A, Littlejohn SY. Onset of analgesia within 15 minutes by a novel paracetamol tablet containing sodium bicarbonate. J Clin Pharmacol (2004) 44(10):1188 #16

¹⁴ Grattan TJ, Burnett I, Sindet-Pedersen S, Desjardins PJ, Gill A, Butler A, Clark KD. PK/PD investigation of a novel paracetamol tablet containing sodium bicarbonate. J Clin Pharmacol (2004) 44(10): 1188 #15

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

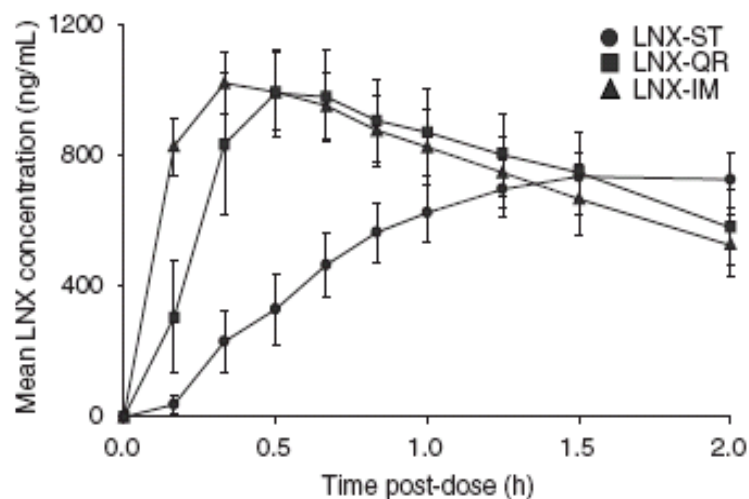
Based on the PK data, PK-PD modelling and published efficacy studies optimized Surge Dose[®] paracetamol would be expected to show:

- superior efficacy and faster onset of action than conventional tablets such as Tylenol[®]
- at least comparable, if not superior efficacy and onset of action to fast dissolving Panadol[®] Rapid or Actifast[®] tablets and effervescent soluble products.

3.2 Lornoxicam

Quick release lornoxicam tablets, marketed as Xefo[®] Rapid (Nycomed Pharma SA) utilize a fast dissolution technology and produce faster absorption and faster onset of action than standard tablets. Absorption profiles for this product (LNX-QR) were similar to those obtained with IM administration, and both were faster with higher C_{max} than standard tablets¹⁵. Mean plasma concentration profiles are shown in Figure 5 with LNX-QR achieving a T_{max} of 30 minutes compared with 90 minutes for the standard tablet. Surge Dose lornoxicam demonstrated a similar mean absorption profiles reaching a mean C_{max} of 1,098 ng/mL in 30 min.

Figure 5 Mean plasma concentration curves of lornoxicam 8 mg administered as a quick release tablet (LNX-QR), standard tablet (LNX-ST) or IM injection (LNX-IM) over the first 2 hours post dose (n=18) (Radhofer-Welte et al 2008)



Following third molar surgery in 200 patients, the median time to onset of analgesia for LNX-QR was 32 min (range 29 – 37) compared with 46 min (range 37 – 59) for standard

¹⁵ 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

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

tablets (LNX-ST)¹⁶. LNX-QR showed less variable onset as well as faster onset. Fast onset of pain relief has also been reported in 220 patients with low back pain, 30 min for a quick release diclofenac potassium tablet compared with 36 min for a standard tablet¹⁷.

Based on PK data and published efficacy studies optimized Surge Dose[®] lornoxicam would be expected to show:

- superior efficacy and faster onset of action than conventional tablets
- at least comparable efficacy and onset of action to fast dissolving tablets

3.3 Diclofenac

Diclofenac has both peripheral and local sites of action inhibiting the COX enzymes which are involved in prostaglandin production and pain. Although plasma levels of diclofenac drop away rapidly post peak as a result of metabolism, levels remain high in the synovial fluid for around 24 h. This explains the extended duration of effect of diclofenac and good response with once daily dosing despite the relatively short elimination half life of this drug.

The absorption profile of Surge Dose[®] diclofenac tablets is more similar to 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^{18, 19, 20, 21}.

The low C_{max} values achieved with Voveran[®]-D suggest that some patients may not achieve adequate plasma or synovial fluid levels for maximum analgesia which would be associated with a lower efficacy than the Surge Dose[®] formulation. Minimum plasma concentrations of diclofenac associated with onset of analgesia (MEC) are in the range 50

¹⁶ Moller P & Norholt SE. Analgesic efficacy of quick release versus standard lornoxicam in pain after third molar surgery – a randomized, double-blind, placebo-controlled, single-dose trial. Clin Drug Invest (2008) 28(12): 757 - 66

¹⁷ Yakhno N, Guekht A, Skoromets A, Spirin N, Strachunskaya E, Ternavsky A, Olsen KJ, Moller PL. Analgesic efficacy and safety of lornoxicam quick release formulation compared with diclofenac potassium. Clin Drug Invest (2006) 26(5): 267 - 77

¹⁸ 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

¹⁹ Hinz B, Chevts J, Renner B, Wuttel 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

²⁰ 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

²¹ Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration before operation suppress post-operative pain. Anaesth (1990) 45:763-66

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

– 100 ng/mL^{22,23}. EC₅₀ (50 % maximal effective plasma concentration) is reported at 559 ng/mL and EC_{max} around 600 ng/mL²⁴.

With Surge Dose[®] diclofenac 50 mg, the minimum C_{max} level was 1,032 ng/mL compared with a minimum of 384 ng/mL and a median of 946 ng/mL with Voveran[®]-D indicating that 50 % of subjects experienced C_{max} values below 1,000 ng/mL. Although all values were above the MEC of 50 – 100 ng/mL, Surge Dose[®] diclofenac would be expected to achieve faster and superior analgesia to Voveran[®]-D in light of its significantly shorter T_{max} and higher C_{max}.

4 How do other fast absorption technologies compare?

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. Surge Dose[®] uses GRAS excipients and conventional tableting equipment unlike some of the other available drug delivery technologies, but requires manufacture under controlled low RH conditions and unit packaging to protect from moisture.

4.1 Buffered products

Given that levels and composition of pHMA are optimized for each drug using the Surge Dose[®] technology to maximise in vitro dissolution, it is expected to provide at least comparable and probably improved absorption compared with other technologies based on the use of buffering agents.

As unoptimized Surge Dose[®] paracetamol tablets are superior to Panadol[®] Rapid which uses high levels of bicarbonate to promote gastric emptying and fast absorption, optimized Surge Dose formulations should demonstrate significantly faster absorption and improved efficacy by reducing the number of sub-therapeutic dosing events.

Surge Dose[®] diclofenac demonstrates superior absorption to several diclofenac potassium dosage forms including swallow tablets and drops that are based on APR's (Applied

²² Nishihata T, Keigami M, Kamada A, Fujimoto T, Kamide S, Tatsumi N. Clinical investigation of sodium diclofenac sustained release suppositories. *Int J Pharm* (1988) 42:251-6

²³ Nishihata T, Sodho M, Kamada A, Keigami M, Fujimoto T, Kamide S, Tatsumi N. Investigation of sustained release suppository of sodium diclofenac in humans. *Int J Pharm* (1986) 33:181-6

²⁴ 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

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

Pharma Research SA, Switzerland) patented Dynamic Buffering Technology (DBT)^{25,26}. Tablets are marketed in Europe as Catafast[®], Inflamac[®] Rapid, and Voltfast^{®27}. Cambia[®] an effervescent powder in sachets for solution prior to administration are now approved in the US as for migraine²⁸. Formulations contain 20 – 80 % by weight of an alkaline metal bicarbonate relative to the weight of diclofenac (10 – 40 mg per 50 mg drug). Comparative PK data for these different dosage forms and Surge Dose[®] diclofenac tablets are shown in Table 3²⁹. All tablets are film coated.

Table 3 Comparative fasted absorption parameters for diclofenac 50 mg doses in various buffered dosage forms and Surge Dose[®] tablets

	Standard tablet 50 mg	DBT Drops 50 mg	DBT Sachet 50 mg	DBT tablet 50 mg	Surge Dose [®] tablet 50 mg
C _{max} (ng/mL)	1,340 ± 627	1,679 ± 669	2,213 ± 743	1,766 ± 1,020	3,569 ± 1,515
T _{max} (min)	50.8 ± 53.2	15.0 ± 8.4	13.7 ± 2.2	29.8 ± 22.0	19.5 ± 5.0
AUC _{0-t} (ng.h/mL)	1,286 ± 351	1,392 ± 423	1362 ± 358	1,267.7 ± 356	1,833 ± 599

These data clearly show the superiority of the Surge Dose[®] technology relative to DBT with improved absorption profiles compared with the DBT tablet as well as the two soluble dosage forms. The higher AUC_{0-t} values reflect more complete dissolution of the drug in vivo as a result of the activated pH-controlled Surge Dose[®] technology driving higher C_{max} values. Absorption from the Surge Dose[®] tablets is much faster than from the standard and DBT tablets with T_{max} values closer to those found with the soluble products.

Surge Dose[®] lornoxicam demonstrates similar absorption to the quick release lornoxicam tablets (LNX-QR) described in Section 3.2. These tablets are marketed as Lorcam[®] in Japan and Xefo[®] Rapid in Europe by Nycomed Danmark AS³⁰ and use another patented buffering technology, processing the drug with low levels of sodium bicarbonate before

²⁵ US Patent Application Number 2005/0147671, Reiner A & Reiner G. Pharmaceutical compositions based on diclofenac.

²⁶ US Patent 6,974,595, Reiner A & Reiner G. Pharmaceutical compositions based on diclofenac.

²⁷ <http://medicaldevicelicensing.com/public/outlicensing/view/104/diclofenac-potassium-immediate-release-tablets-25-and-50-mg>

²⁸ NDA 22-165, Nautilus Neurosciences Inc, NJ

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 EMEA registration submission accessed 22 May 2009
http://www.emea.europa.eu/pdfs/human/referral/xefo/Xefo_annexI-III_en%20.pdf

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

use³¹. The Surge Dose[®] lornoxicam tablets have faster in vitro dissolution in 900 mL 0.0033 M HCl than Lorcam[®] tablets which may be responsible for the reduced in vivo absorption variability compared with LNX-QR as shown in Table 4.

Table 4 Comparative fasted absorption parameters for lornoxicam 8 mg in buffered oral dosage forms, IM administration and Surge Dose[®] tablets

	Standard tablet LNX-SR	IM injection LNX-IM	Quick release tablet LNX-QR	Surge Dose [®] tablet
C _{max} (ng/mL)	825 ± 151	1,065 ± 192	1,101 ± 318	1,098 ± 205
T _{max} (min)	90	20	30	30 ± 9
AUC _{0-∞} (ng.h/mL)	3,239 ± 1,054	3,219 ± 1,245	3,740 ± 2,038	4,183 ± 1,643

Although mean C_{max} values are similar, variability for LNX-QR is 29 % compared with 19 % for Surge Dose[®], while AUC variability is 55 % for LNX-QR and only 39 % for Surge Dose[®]. The higher AUC may result from the more frequent sampling schedule in the Surge Dose[®] study where these values were similar for both test and reference products.

4.2 Liquid filled soft capsules

Liquid filled capsules require specialist manufacture and have a relatively high cost compared with compressed tablets such as Surge Dose[®]. Although liquid filled capsules may contain solubilised drug, in vivo release is still limited by capsule rupture time and dispersion of contents as well as drug dissolution if not completely in solution.

Zipsor[®] (Xanodyne Pharmaceuticals), a soft gel containing 25 mg diclofenac potassium using Prosorb dispersion technology, has been approved in the US at a lower dose of 25 mg rather than 50 mg based on its improved absorption profile similar to that of a solution. The 50 % dose reduction has a significant advantage over other formulations reducing overall patient exposure which will be associated with reduced gastrotoxicity and cardiovascular risk without compromising efficacy.

Comparative PK data for 25 and 50 mg Zipsor[®], a 25 mg solution, 50 mg conventional Cataflam[®] tablet and 50 mg Surge Dose[®] tablet are shown in Table 5³². These data clearly show the superiority of the Surge Dose[®] formulation over the 50 mg Zipsor[®] with a higher C_{max} and shorter, less variable T_{max}. Such data indicate that a Surge Dose[®] 25 mg

³¹ Japanese Patent No 33491/90, Taisho

³² ANDA 22-202, Xanodyne Pharmaceuticals

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

diclofenac would offer fast onset of action and effective analgesia with reduced adverse events and could be registered using a similar strategy to that used for Zipsor[®].

Table 5 Comparative fasted absorption parameters for diclofenac 25 and 50 mg doses as Zipsor[®] soft gels, solution, conventional and Surge Dose[®] tablets

	Solution 25 mg/mL	Zipsor [®] soft gel 25 mg	Zipsor [®] soft gel 50 mg	Cataflam [®] tablet 50 mg	Surge Dose [®] tablet 50 mg
C _{max} (ng/mL)	958 ± 274	1,087 ± 274	2,365 ± 1,034	1,169 ± 528	3,569 ± 1,515
T _{max} (min)	15.0 ± 5.4	28.2 ± 10.2	30.6 ± 11.4	55.8 ± 51	19.5 ± 5.0
AUC _{0-t} (ng.h/mL)	606 ± 144	597 ± 151	1,521 ± 377	1,133 ± 297	1,833 ± 599

Although 100 mg diclofenac liquid filled soft gels showed faster absorption than conventional tablets, the faster onset of analgesia in dental extraction pain of 18 min compared with 38 min was not statistically significant³³. T_{max} for soft gels was 53 min compared with 115 min for conventional tablets, both slower than 20 min for Surge Dose[®]. Although mean C_{max} was higher for 100 mg soft gels at 1,882 ng/mL compared with 1,031 ng/mL for tablets, these are much lower than the value of 2,365 ± 1,034 for Zipsor[®] 50 mg.

Another study showed 25, 50 and 100 mg soft gels provided perceptible pain relief for around 60 % patients following third molar extraction compared with 30 % on placebo, and more than 80 % with meaningful relief compared with 17 % for placebo³⁴. Median time to onset of action was around 25 min, with meaningful relief delayed to around 50 min which is later than the T_{max} which would reflect delayed distribution into an effect compartment.

4.3 Orally disintegrating tablets (ODTs)

Whilst ODTs offer convenience without the need to take with water, a critical review of published data submitted for registration in the US on 11 ODTs indicates that they result in slower rather than faster absorption, and there is no evidence of faster onset of action or improved efficacy compared with standard tablets³⁵. These data are summarised in Table 6.

³³ Zuniga JR, Phillips CL, Shugars D, Lyon JA, Peroutka SJ, Swarbrick J, Bon C. Analgesic safety and efficacy of diclofenac sodium softgels on postoperative third molar extraction pain. J Oral Maxillofac Surg (2004) 62:806-15

³⁴ Zuniga JR, Malstrom H, Noveck RJ, Campbell JH, Christensen S, Glickman RS, Tomasetti BJ, Boesing SE. Controlled Phase III clinical trial of diclofenac potassium liquid-filled soft gelatin capsule for treatment of postoperative dental pain. J Oral Maxillofac Surg (2010) 68:2735-42

³⁵ <http://www.fda.gov/Drugs/default.htm>

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

Table 6 Summary of T_{max} values for standard solid dosage forms and ODTs

Drug (brand)	T_{max} tablet (h)	T_{max} ODT alone (h)	T_{max} ODT + water (h)	C_{max} ratio tablet : ODT
Clonazepine (Fazoclo [®])	2.0 (0.4-5)	2.0 (1-6)	-	1.04
Donezepil (Aricept [®])	3.33 ± 0.31	-	3.11 ± 0.18	0.98
Lamotrigine (Lamictal [®])	1.00 (0.5-12.0)	1.59 (0.5–4.07)	2.00 (0.75-8.0)	1.06, 1.05
Metoclopramide (Reglan [®])	1.67 ± 0.54	1.88 ± 0.71	1.65 ± 0.58	1.05, 1.06
Tramadol (Ralivia [®])	1.87 ± 0.70	2.16 ± 0.53	2.11 ± 0.52	1.05, 1.08
Prednisolone (Orapred [®]) Vs solution	0.64 ± 0.19	1.33 ± 0.55	-	1.2
Zolpidem (Tovalt [®])	1.50 (0.50-4.02)	1.75 (0.50-4.00)	1.25 (0.50-4.02)	1.13, 1.02
Ondansetron (Zofran [®])	1.3	1.6	1.2	0.82, 0.78
Zolmitriptan (Zomig [®] -ZMT)	1.5	3.0 (0.5-3.0)	-	-
Famotidine (Fluxid [®])	2.25 ± 1.03	2.62 ± 0.89	2.37 ± 0.93	0.98, 0.98
Vardenafil (Staxyn [®])	0.75 (0.5-2.0)	1.5 (0.75-3.0)	0.5 (0.5-1.0)	0.89, 0.94

Based on these comparative data, there is no evidence that ODTs offer faster absorption that conventional formulations of solid dosage forms. This means that inferior absorption would be expected with an ODT reformulation compared with an optimised Surge Dose[®] formulation where dissolution and hence availability for absorption will be maximised.

IM 00-01-04

Clinical benefits of using Surge Dose[®] ultra-fast activated pH-controlled dissolution technology

5 Summary

Surge Dose[®] is an easy to apply fast dissolution technology for unit packed swallow tablets using GRAS excipients that are easily manufactured under controlled low RH conditions.

Surge Dose[®] uses in vitro dissolution specifications to optimize formulations for each drug or drug combination so that the best formulations are selected for in vivo testing, thus reducing development times and costs.

Phase I PK studies in fasted subjects have demonstrated superior absorption of three drugs from Surge Dose[®] formulations compared with other orally administered commercial dosage forms with significant reductions in T_{max} :

- Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) containing 500 mg paracetamol
- Panadol[®] Rapid (GSK) a buffered swallow tablet containing 630 mg bicarbonate per 500 mg paracetamol
- Voveran-D[®] (Novartis) a 50 mg diclofenac dispersible tablet mixed with water before swallowing
- Lorsaid[®] (Hetero Drugs Limited) which demonstrates improved dissolution compared with other generic lornoxicam 8 mg tablets

Absorption profiles for Surge Dose[®] diclofenac and Surge Dose[®] lornoxicam are similar to those achieved following parenteral administration with the convenience and patient preference of a swallow tablet.

Significantly higher C_{max} and AUC values seen with Surge Dose[®] diclofenac supports the registration of a lower 25 mg dose for chronic use to reduce gastrointestinal and cardiovascular risks of this NSAID without compromising efficacy.

There is good evidence that faster absorption is associated with:

- faster onset of action and maximum clinical response
- improved efficacy where slow absorption leads to sub-therapeutic dosing

Based on available published data and PK evaluation, Surge Dose[®] formulations are expected compared favourably with other drug delivery technologies:

- comparable to solution oral products and IM administration
- superior to liquid filled capsules and ODTs
- superior or at least equal to other buffered drug delivery technologies