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Application of Surge Dose[®] fast dissolution technology to diclofenac

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Table of Contents

1	EXECUTIVE SUMMARY	1
2	SURGE DOSE[®] DRUG DELIVERY FORMULATION TECHNOLOGY.....	2
2.1	Physiological basis of Surge Dose [®]	2
2.2	Surge Dose [®] IP status	4
2.3	Commercialization.....	5
2.4	Application of Surge Dose [®] to diclofenac.....	5
3	RATIONALE FOR SURGE DOSE[®] DICLOFENAC	6
3.1	Mechanism of action and therapeutic use.....	6
3.2	Products.....	6
3.3	Physicochemical Properties.....	7
3.4	Permeability	8
3.5	Pharmacokinetics (PK) and pharmacodynamics (PD).....	9
3.6	Suitability as candidate for Surge Dose [®] technology	14
4	PERFORMANCE OF SURGE DOSE[®] DICLOFENAC.....	14
4.1	In vitro dissolution	14
4.2	PK simulations based on dissolution data.....	15
4.3	PK performance of Surge Dose [®] diclofenac.....	16
4.4	Comparison of Surge Dose PK with other diclofenac products	17
5	CONCLUSIONS	19

Application of Surge Dose[®] fast dissolution technology to diclofenac

1 Executive Summary

Diclofenac is a widely used nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties used in prescription and OTC products for the treatment of a range of acute and chronic conditions. A review of published physicochemical, pharmacokinetic (PK) and pharmacodynamic (PD) data has concluded that faster in vitro dissolution is likely to result in faster in vivo absorption and faster onset of action, desirable features for this drug particularly in acute usage. This prediction has been confirmed in vivo with an optimised film coated Surge Dose[®] tablet that shows improved absorption profiles more comparable with injectable dosage forms compared with a commercial dispersible Voveran-D.[®]

Diclofenac is a weak acid with a pKa of 4.15 with pH dependent aqueous solubility ranging from 17.8 mg/L at neutral pH to less than 1 mg/L at acidic pH. It is frequently used as the more soluble salts rather than the free acid form; the sodium salt has a solubility of 1,113 mg/L in water compared with the more soluble potassium salt 2,430 mg/L where around 20 mL of water will dissolve a 50 mg dose of diclofenac potassium. Diclofenac acid is classified as a BCS Class 2 drug based on its high permeability and low solubility.

Imaginot Pty Ltd <Imaginot> has developed its patented Surge Dose[®] drug delivery technology providing ultra-fast pH-controlled activated dissolution with resultant fast absorption of drugs from swallow tablets. In vitro, Surge Dose[®] has been shown to significantly increase the dissolution rate of more than 30 commonly used drugs classified as acidic, basic, amphoteric and unionized molecules including diclofenac. Surge Dose[®] formulations using customised levels of pH modulating agents (pHMA) and water uptake agents (WUA) are designed to achieve fast dissolution under both favourable and unfavourable in vitro test conditions that reflect the wide range of physiological conditions existing within the general population. These include gut stasis in migraine and neutral gastric conditions as in the fed state and in patients with impaired gastric function or those taking proton pump inhibitors or antacids. Faster in vivo dissolution particularly under less favourable conditions will also reduce inter- and intra-patient variability in absorption seen with many drugs that can result in sub-therapeutic plasma concentrations. Reduced variability can potentially result in increased efficacy.

Fast Surge Dose[®] dissolution has been shown to be associated with significantly faster and more consistent absorption in man for paracetamol and two NSAIDs, lornoxicam and diclofenac compared with commercial products. PK-PD modeling of individual subject PK profiles for paracetamol predicts faster onset of action and improved efficacy.

Application of Surge Dose[®] fast dissolution technology to diclofenac

Simulations using a modeling technique to generate plasma profiles from dissolution data, suggest that the faster dissolution demonstrated for a preliminary Surge Dose[®] tablet formulation should result in at least comparable PK to marketed fast absorbing tablets and soluble products. This formulation containing diclofenac potassium 50 mg diclofenac with pH modulating agents (pHMA) and water uptake agents (WUA) demonstrated very fast in vitro dissolution in tests simulating adverse in vivo conditions exceeding 95 % dissolution after 5 minutes in 900 mL 0.0033 M HCl at 30 rpm. Based on this dissolution profile, times to peak plasma concentration (T_{max}) in the range 15 – 30 minutes were predicted for Surge Dose[®] formulations compared with around 1 hour for conventional tablets.

Formulation optimization and process development have since been undertaken producing film coated tablets containing 50 mg diclofenac sodium which demonstrate both fast in vitro dissolution and significantly improved absorption PK in man consistent with the predicted performance. PK data for these Surge Dose[®] diclofenac tablets are superior to published data for all other orally administered diclofenac products, with peak plasma concentrations (C_{max}) comparable with those following IM administration. Such results suggest that a reduction in dosage may be possible to reduce side effects without compromising efficacy, particularly as faster gastric emptying and solubilized ionized drug in the stomach will reduce the potential for local damage.

Improve absorption kinetics are likely to lead to improved efficacy for Surge Dose[®] diclofenac allowing approval of this drug for more severe pain indications such as migraine.

2 Surge Dose[®] drug delivery formulation technology**2.1 Physiological basis of Surge Dose[®]**

Imaginot's Surge Dose[®] technology was developed based on in vitro dissolution testing and in vivo evaluation of paracetamol tablet formulations in fasted subjects. Paracetamol is a marker of gastric emptying and in vivo results demonstrate the effect of the different phases of gastrointestinal motor activity known as the Migrating Motility Complex (MMC) on the PK profile. Fast in vitro dissolution was associated with fast in vivo absorption.

The results from Imaginot's proof of concept clinical trial in 25 fasted subjects showed good correlation between in vitro dissolution and in vivo absorption (IVIVC). Generally, products with fast in vitro dissolution produced a higher frequency of fast absorption occasions as demonstrated by plasma concentration time - profiles. Each fast absorption occasion was associated with higher C_{max} compared with slow absorption occasions. As such, Surge Dose[®] formulations are predicted to achieve improved therapeutic outcomes with faster onset of action and greater efficacy as a result of more consistent absorption exceeding

Application of Surge Dose[®] fast dissolution technology to diclofenac

minimum effective plasma concentrations¹. Imaginot has demonstrated that slow absorption leads to a high proportion of low C_{max} which may be so low as to be sub-therapeutic.

For fast absorption, a drug contained in a solid dosage form needs to dissolve rapidly and completely in the available gastric contents and any co-administered fluid. Liquids empty exponentially from the stomach independently of solids with a half life of around 10 – 12 minutes, and so will rapidly transfer the drug in solution into the small intestine whence absorption can occur. The higher the drug concentration, the higher will be the driving force across the intestinal mucosa resulting in rapid absorption with high C_{max} . High plasma concentrations drive distribution throughout the body and into the CNS so that drug rapidly reaches all sites of actions with rapid onset of action and achievement of peak effect.

Conversely, slow dissolution of drug in the stomach will produce relatively low drug concentrations in solution, providing a low driving force across the intestinal wall. This results in slow absorption and lower C_{max} .

Higher solubility favours faster dissolution so any formulation changes that enhance solubility and promote dissolution will have a favourable effect on absorption. However a competing consideration is the degree of ionization of a drug as the unionized form is the more readily absorbed form of a drug even though this is the least soluble form. Acidic drugs are more soluble at high pH but the proportion of the readily absorbed unionized species is lower. Conversely, basic drugs are more soluble in acidic conditions where the proportion of readily absorbed unionized species will be lower. Hence when formulating for fast absorption, both solubility and degree of ionization must be considered.

While gastric contents are acidic in the fasted healthy state, there is significant variability in inter- and intra-subject gastric pH and gastric emptying patterns. Conditions can be less acidic or neutral such as in the fed or partial prandial state, and in patients with hypochlorhydria, impaired gastric function or on concurrent proton pump inhibitor or antacid medication. Hence when a drug is taken under normal therapeutic conditions, gastric pH is not always acidic. This highlights the importance of optimizing drug formulations to ensure adequate solubility and fast dissolution under a wide range of physiological conditions.

If only a proportion of the drug dissolves in the co-administered liquid, the concentration will be lower providing a lower driving force for absorption. Where any drug remains undissolved, particles are held within the mucosal folds of the stomach in contact with

¹ 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

Application of Surge Dose[®] fast dissolution technology to diclofenac

limited volumes of liquid for dissolution. These and any dissolved drug will remain in the stomach until emptied into the small intestine during the active emptying phase III MMC gastric emptying. This results in double or multiple peaks with associated longer T_{max} values as reported for a number of drugs including diclofenac^{2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12}.

2.2 Surge Dose[®] IP status

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

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- ² 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
 - ³ 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
 - ⁴ 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
 - ⁵ 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
 - ⁶ 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
 - ⁷ Marathe PH, Sandefer EP, Kollia GE, Greene DS, Barbhैया RH, Lipper RA, Page RC, Doll WJ, Ryo UY, Digenis GA. In vivo evaluation of the absorption and gastrointestinal transit of avitriptan in fed and fasted subjects using gamma scintigraphy. *J Pharmacokinet Biopharm* (1998) **26**(1):1-20
 - ⁸ 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
 - ⁹ 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
 - ¹⁰ 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
 - ¹¹ 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
 - ¹² 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

Application of Surge Dose[®] fast dissolution technology to diclofenac

- i. PCT/AU 2006/001798 covering acidic and unionized, basic and amphoteric therapeutic agents claiming priority from three Australian provisionals, one on acids and unionized drugs filed on 28 Nov 2004, and two others on 13 May 2005. During examination the claims have been restricted to acidic and unionised drugs. Granted in Australia, this patent is under examination in US (PPH) and in Japan.
- ii. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. This has been granted in Australia and Canada without limitation and is under examination elsewhere.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations has been assigned to a third party in Australia (granted), Europe, India and Japan. The patent is granted in US and Canada.

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

2.3 Commercialization

Imaginot is now seeking partners to commercialize its Surge Dose[®] technology. To date, deals involve a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA), India's largest pharmaceutical company (Abbott Healthcare Pvt Ltd) and Piramal Healthcare Ltd <Piramal>, an international drug delivery technology contract development and manufacturing company. Piramal can undertake formulation development, biostudies and contract manufacture of products based on the Surge Dose[®] technology for interested parties.

Surge Dose[®] formulations have been developed for a number of drugs which demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low humidity conditions. The first Surge Dose[®] product containing lornoxicam was launched in 2010 with the second product diclofenac to be launched in late 2012.

2.4 Application of Surge Dose[®] to diclofenac

Diclofenac is a weak acid exemplified in the Imaginot patent covering acidic drugs. Although its solubility is lower under acidic gastric conditions (low pH) which will not favour dissolution, the higher proportion of the drug in the unionized form will favour absorption under such conditions. At higher pH, the solubility will be increased and dissolution enhanced, but more drug will be present in the less readily absorbed ionized form.

Application of Surge Dose[®] fast dissolution technology to diclofenac

This report describes the potential for Surge Dose[®] diclofenac to provide faster in vivo dissolution and absorption, with improved and more consistent therapeutic outcomes.

3 Rationale for Surge Dose[®] diclofenac

A comprehensive literature review was conducted by an independent CRO concluding that diclofenac is a suitable candidate for the application of Surge Dose[®] technology to produce faster absorption from a swallow tablet than conventional tablet formulations¹³.

3.1 Mechanism of action and therapeutic use

Diclofenac inhibits cyclo-oxygenase isoenzymes (COX-1 and COX-2) which results in decreased prostaglandin production in tissue and fluids. As with other COX inhibitors, usage is limited by its gastro-intestinal (GI) toxicity with high risk of ulceration, bleeding and perforation. Although local gastric damage can be reduced by the use of enteric coating and use of ionized solution products which reduce the extent of absorption into gastric mucosal cells, GI damage is evident with long term usage as a result of systemic effects.

Diclofenac is mainly used for the relief of mild – moderate pain and inflammation in various conditions where fast onset of action is desirable. These include musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendonitis; soft tissue disorders such as sprains and strains; other painful conditions such as renal colic, acute gout, primary dysmenorrhoea, and following surgery. There are an increasing number of studies demonstrating its efficacy in the treatment of migraine^{14, 15}.

3.2 Products

Diclofenac was first approved as Voltaren[®] and Cataflam[®] (Novartis) and is now available in a number of branded and generic prescription and OTC products. Immediate release oral products use diclofenac potassium which is the most soluble of the available diclofenac salts. To minimise GI toxicity, particularly in the long term use of diclofenac for chronic conditions, the drug is available as the sodium salt in delayed release (enteric coated) and

¹³ Tetra Q IMG01-FR-Part 6 Physicochemical properties, pharmacokinetics and pharmacodynamics of diclofenac in humans. 30 June 2006

¹⁴ Engindeniz Z, Demircan C, Karli N, Armagan E, Bulut M, Aydin T, Zarifoglu M. Intramuscular tramadol versus diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised double blind study. *J Headache Pain* (2005) **6**:143-8

¹⁵ Diclofenac K / sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a non-steroidal anti-inflammatory drug, diclofenac potassium, in comparison to oral sumatriptan and placebo. *Cephalgia* (1999) **19**:232-40

Application of Surge Dose[®] fast dissolution technology to diclofenac

extended release tablets. It is also available as a tablet in combination with a synthetic PGE (misoprostol) to protect the gastric mucosa (Arthrotec[®], GD Searle).

Fast absorbed diclofenac potassium products have been approved as tablets and sachets for solution (Volfast[®], Catafast[®], Cambia[®]) based on a Dynamic Buffering Technology¹⁶ patented by APR (Applied Pharma Research SA, Switzerland)¹⁷. This technology has been licensed by ProEthic Pharmaceuticals Inc who announced on 02 July 2007 that they had submitted a NDA based on Phase III trials for the use of their PRO-513 fast dissolving diclofenac potassium tablets in the treatment of migraine.

The APR patents have been reviewed in detail in relation to the Surge Dose[®] technology¹⁸. In the formulations disclosed by APR, potassium bicarbonate is the preferred buffering agent used at a level of 20 – 80 % by weight of the diclofenac or its salt. Thus for a 50 mg tablet this equates to 10 – 40 mg sodium bicarbonate which levels are lower than those found by Imaginot to have the desired effect in achieving fast dissolution in in vitro tests that simulate a wide range of in vivo conditions.

More recently on 16 June 2009, Zipsor[®] liquid filled capsules (ANDA 22-202, Xanodyne Pharmaceuticals) were approved in the USA based on a 505(b)(2) submission referencing Cataflam[®] IR diclofenac potassium tablets (NDA 20-142, Novartis)¹⁹. This included four Phase 1 PK studies, one Phase 2 PK/PD study in post-operative bunionectomy, one paediatric and six adult Phase 3 safety and efficacy studies in post-operative pain following bunion, dental and knee surgery. Compared with the normal dose of 50 mg diclofenac potassium in IR products, Zipsor[®] offers a lower dose equipotent alternative containing 25 mg drug solubilized in PEG 400, glycerine, sorbitol solution, povidone and polysorbate.

3.3 Physicochemical Properties

Diclofenac has an empirical formula of $C_{14}H_{10}Cl_2NO_2$ and is frequently used as the more soluble potassium salt with a molecular weight of 332.24 g/mol and the chemical structure shown in Figure 1²⁰.

¹⁶ US Patent Application Number 2005/0147671, Reiner A & Reiner G. Pharmaceutical compositions based on diclofenac.

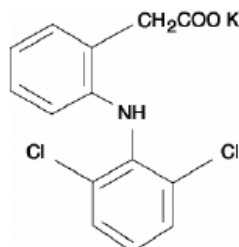
¹⁷ US Patent 6,974,595, Reiner A & Reiner G. Pharmaceutical compositions based on diclofenac.

¹⁸ Imaginot Pty Ltd. IM 04-01-02 CP Fast dissolving swallow tablets containing diclofenac potassium 50 mg in relation to Reiner & Reiner disclosures. 14 July 2006

¹⁹ ANDA 22-202, Zipsor[®] soft capsules, Xanodyne Pharmaceuticals

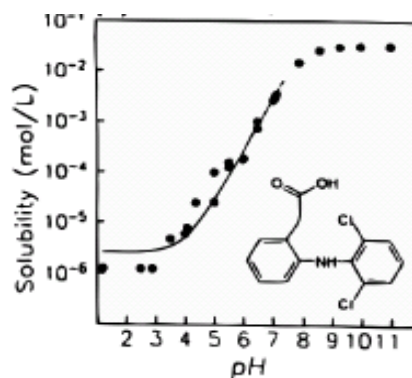
²⁰ Budavari, S. The Merck Index: An encyclopaedia of chemicals, drugs and biologicals. 13th ed. 2001 Merck Research Laboratories

Figure 1 Chemical structure of diclofenac potassium



Diclofenac is a weak acid with reported pKa values of 4.15. The free acid is relatively insoluble (0.82 µg/ml). As it is an acid, the solubility is pH dependent, and increases significantly as the pH increases as shown in Figure 2²¹.

Figure 2 Diclofenac solubility as a function of pH (Avdeef et al 2000)



3.4 Permeability

Diclofenac is completely absorbed from the gastrointestinal tract with a log P of 4.0. It is classed as a BCS Class 2 drug based on its low solubility and high permeability.

With a pKa of 4.15, diclofenac will be 50 % ionized at this pH, with less ionization at lower pH where it is less soluble, and more ionization at higher pH where it is more soluble. This means that the alkaline conditions of the small intestine will be less favourable for absorption by passive diffusion pathways, where higher levels of unionized drug would be expected to provide a higher driving force for faster absorption.

To optimise the dissolution rate of diclofenac and achieve fast absorption, the two opposing pH effects on solubility and ionization need to be considered. Solubility and dissolution will be impaired at low pH but absorption of the unionized species will be enhanced under such

²¹ Avdeef A, Berger CM, Brownell C. pH-metric solubility. 2: Correlation between the acid-base titration and the saturation shake-flask solubility-pH methods. *Pharm Res* 2000 **17**(1): 85-89

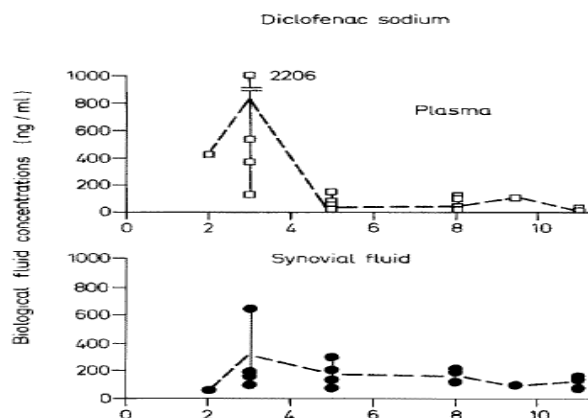
Application of Surge Dose[®] fast dissolution technology to diclofenac

conditions. A high pH will be advantageous in getting the drug into solution, but a lower pH will be advantageous to drive absorption in the unionized form.

3.5 Pharmacokinetics (PK) and pharmacodynamics (PD)

Despite its complete absorption, the oral bioavailability of diclofenac is around 50 – 60 % as a result of first pass metabolism. Around 65 % of the dose is excreted in the urine, and 35 % in bile. It is 99 % bound to plasma proteins, primarily albumen, over the therapeutic concentration range. Diclofenac is rapidly distributed into the synovial fluid, a peripheral compartment where levels are maintained for an extended period after plasma levels have fallen below detectable limits. In healthy volunteers, high synovial plasma levels persisted for 25 hours despite negligible plasma concentrations 8 hours after a single dose²². Similar distribution has been shown for rheumatoid arthritis patients on three times daily dosing as shown in Figure 3 for 16 rheumatoid arthritis patients where T_{max} values are similar for plasma and synovial fluid²³.

Figure 3 Mean plasma and synovial fluid levels of diclofenac following a single dose of 50 mg diclofenac sodium in 16 rheumatoid arthritis patients on chronic three times daily dosing (from Fowler et al 1983)



Extended synovial fluid concentrations cannot be explained by entrapment of the diclofenac as the synovium allows rapid two way transport of unionized and ionized molecules. Since synovial fluid has lower protein levels and lower pH than plasma, reduced levels in synovial fluid compared with plasma would be expected. Whatever the mechanism that results in

²² Fowler PD, Dawes PT, John VA, Shotton PA. Plasma and synovial fluid concentrations of diclofenac sodium and its hydroxylated metabolites during once daily administration of a 100 – mg slow –release formulation. *Eur J Clin Pharmacol* (1986) 31:469-72

²³ Fowler PD, Shadforth MF, Crook PR, John VA. Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol* (1983) 25:389-94

Application of Surge Dose[®] fast dissolution technology to diclofenac

these extended levels of diclofenac in the synovial fluid, this distribution explains the efficacy of once daily dosing with diclofenac despite the lower plasma levels and relatively rapid elimination by hepatic metabolism.

Typical T_{max} data for different dosage forms and diclofenac salts are shown in Table 1.

Table 1 Typical T_{max} values for different formulations of diclofenac

Substance	T_{max}	Reference
Diclofenac (fasted, capsule, acid)	0.8 ± 0.5 h	Terhaag et al 1991 ²⁴
Diclofenac (Fed, capsule, acid)	2.4 ± 0.9 h	
Sodium diclofenac (dissolved effervescent tablet)	30 min	Terhaag et al 2000 ²⁵
Potassium diclofenac (tablet)	53.1 min	Marzo et al 2000 ²⁶
Potassium diclofenac (dissolved sachet)	13.68 ± 3 min	
Potassium diclofenac (25 and 50 mg tablets with buffer)	21.2, 29.8 min	Reiner et al 2001 ²⁷ .
Potassium diclofenac (dissolved sachet)	13.7	

Overall diclofenac is absorbed faster from soluble products and tablets with bicarbonate with T_{max} values around 15 - 30 minutes compared with around 1 hour for conventional solid dosage forms swallowed intact. Overall total oral bioavailability (AUC) is similar for all oral dosage forms.

Swallow film-coated tablet formulations containing low levels of sodium bicarbonate as disclosed in the Reiner patents are reported to have mean T_{max} values of 21.2 and 29.8 minutes for the 25 mg and 50 mg tablets respectively.

Of note is the slower T_{max} of 30 minutes reported for the effervescent solution by Terhaag et al (2000) attributed to 15 of the 24 subjects exhibiting double peaks. This indicates two

²⁴ Terhaag B, Gramatte T, Hrdlcka P, Richter K, Feller K. The influence of food on the absorption of diclofenac as a pure substance. *Int J Clin Pharmacol Ther Toxicol* (1991) **29**(10):418-21

²⁵ Terhaag B, Hoffmann A, Barkworth M, Vens-Cappell B. Bioavailability of a new effervescent tablet of diclofenac. *Int J Clin Pharmacol Ther* (2000) **38**(11):546-51

²⁶ Marzo A, Dal Bo L, Verga F, Monti NC, Abbondati G, Tettamanti RA, Crivelli F, Uhr MR, Ismaili S. Pharmacokinetics of diclofenac after oral administration of its potassium salt in sachet and tablet formulations. *Arznein-Forsch/Drug Res* (2000) **50**(1):43 – 47

²⁷ 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

Application of Surge Dose[®] fast dissolution technology to diclofenac

absorption phases dependent on the MMC such as reported for many drugs where there is dissolution rate limited absorption including diclofenac²⁸.

Double peaks with an effervescent solution could be explained by re-precipitation of the solubilised drug in the acidic gastric environment of fasted subjects which is retained in the stomach until phase 3 of the MMC. Effervescent products typically contain high stoichiometric levels of acid and base which react so that there is limited buffering capacity and no excess alkalinity to keep the drug dissolved in the stomach. Initial peaks result from absorption from solution which empties exponentially from the stomach and the later peaks reflect absorption of residual drug retained in the gastric contents and emptied as a bolus in phase III of the MMC.

Differences in the variability of the absorption of these formulations are also noted as demonstrated by the standard deviations of the T_{max} values. The sachet solution is the least variable, the standard tablet the most variable and the tablet with sodium bicarbonate as the dynamic buffering agent is intermediate.

The effect of formulation on absorption has been clearly demonstrated noting the difference in C_{max} levels from the different absorption profiles²⁹. For a 75 mg dose, the enteric coated tablet produced the highest mean C_{max} , double that of the buffered solution and four times that of the sustained release tablet as shown in Table 2.

Table 2 Comparative absorption for 75 mg diclofenac sodium from a buffered solution (BAS), enteric coated tablet (EC) and sustained release tablet (SR) in fasted healthy subjects (from Chen et al 1990)

Parameter	Mean (SD)		
	Treatment A (BAS)	Treatment B (EC)	Treatment C (SR)
Gastric residence time (GRT), hr	2.00 (0.45)	1.89 (1.16)	2.00 (0.89)
Lag time (T_{lag}), hr	0.00 (0.00)	[1.00 (0.00)] ^a	1.06 (0.86)
Median	0.00	[1.00]	2.00
Range	—	[—]	0.00–2.00
Peak time (T_{max}), hr	0.43 (0.65)	[1.83 (0.26)]	2.69 (1.16)
Median	0.17	[2.00]	3.00
Range	0.08–2.00	[1.50–2.00]	0.50–4.00
Adjusted peak time (Adj T_{max}), hr	0.43 (0.65)	[0.83 (0.26)]	1.63 (1.22)
Median	0.17	[1.00]	1.00
Range	0.08–2.00	[0.50–1.00]	0.50–4.00
Peak concentration (C_{max}), ng/ml	1175.8 (835.0)	2074.1 (1412.1)	694.2 ^b (247.38)
AUC-inf, ng·hr/ml	1906.9 (508.1)	2362.9 (867.8)	2163.5 ^b (494.9)
Half-life ($T_{1/2}$), hr	1.52 (0.37)	1.56 (0.37)	2.53 (1.87)

²⁸ 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

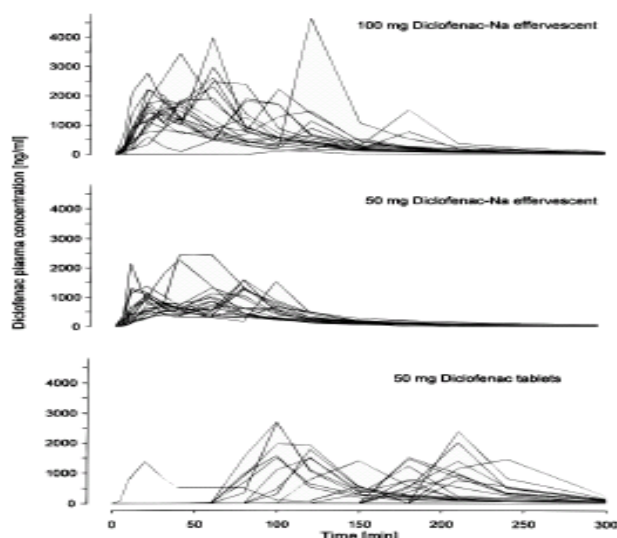
²⁹ Chan KKH, Mojaverian P, Ziehmer BA, John VA. Application of radiotelemetric technique in evaluating diclofenac sodium absorption after oral absorption of various dosage forms in healthy volunteers. *Pharm Res* (1990) **7**(10):1026-32

Application of Surge Dose[®] fast dissolution technology to diclofenac

Although all products showed a similar mean gastric residence time of 2 h, the solution had the shortest median T_{max} of 10 min with a longer mean of 26 min indicating a non-normal distribution with a tail of slow absorbers as indicated by the range of 5 – 120 min. The enteric coated product had a T_{max} of 2 h reflecting the delay in the dosage form reaching the small intestine where the drug is released, dissolves readily in the alkaline intestinal fluid and is absorbed resulting in the higher C_{max} driven by higher concentrations of dissolved drug. In contrast the sustained release tablet releases drug slowly with the longest T_{max} of 0.5 – 4 h such that the lower concentration of dissolved drug produce lower peak plasma levels, albeit sustained over a longer period. This sustained release is associated with the longer elimination half life.

Similar high variability has been reported in a population PK assessment which focussed on the PD implications using stimulation of nasal nociceptors with gaseous carbon dioxide as a pain model³⁰. Individual PK profiles are shown in Figure 4 for two fast release effervescent formulations containing 50 and 100 mg diclofenac sodium compared with an enteric coated Voltaren[®] tablet. These data are similar to those reported for an effervescent sodium diclofenac tablet dissolved in water before administration³¹.

Figure 4 Individual plasma concentration for fasted subjects following oral administration of absorption following administration of two buffered fast release formulations and enteric coated Voltaren[®] (Lötsch et al 2000)



³⁰ Lötsch J, Kettenmann B, Renner B, Drover D, Brune K, Geisslinger G, Kobal G. Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: Relation to pharmacodynamics in an experimental pain model. *Pharm Res* (2000) **17**(1):77-84

³¹ Terhaag B, Hoffmann A, Barkworth M, Vens-Cappell B. Bioavailability of a new effervescent tablet of diclofenac. *Int J Clin Pharmacol Ther* (2000) **38**(11):546-51

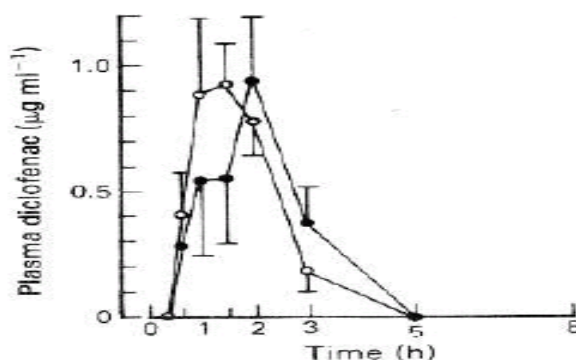
Application of Surge Dose[®] fast dissolution technology to diclofenac

Median T_{max} values and ranges for the 50 mg and 100 mg effervescent products and the enteric coated Voltaren were 60 (10 – 102), 40 (20 – 150) and 165 (20 -242) minutes respectively. There was higher variability with the enteric coated tablet compared with the fast release effervescent products which showed more consistent and reproducible PK.

The Lötsch study found a short delay between PK and PD in the pain model used associated with the time for the drug to reach the effect site from the plasma. Despite the high variability in PK and PD, results at 30 minutes indicated a faster onset of analgesia with the effervescent product compared with the enteric coated tablet.

Absorption of diclofenac is delayed by food by around 1.5 hours and is more variable^{32, 33, 34}. When 850 mg magnesium hydroxide was administered in fasted subjects to neutralise gastric contents immediately after a 50 mg enteric coated tablet of diclofenac sodium, faster absorption was reported although the total bioavailability was unchanged as seen in Figure 5³⁵. These results are consistent with premature rupture of the enteric coat in the neutral conditions and then solubilisation of the diclofenac at the higher pH favouring dissolution and subsequent absorption. This mean absorption profile does not show the biphasic double peak seen with the enteric coated tablet alone.

Figure 5 Diclofenac absorption following administration of a 50 mg enteric coated tablet alone (●) and followed by 850 mg magnesium hydroxide (○) (Neuvonen 1991)



- ³² Terhaag B, Gramatte T, Hrdlcka P, Richter K, Feller K. The influence of food on the absorption of diclofenac as a pure substance. *Int J Clin Pharmacol Ther Toxicol* (1991) **29**(10):418-21
- ³³ Willis JV, Kendall MJ, Jack DB. The influence of food on the absorption of diclofenac after single and multiple oral doses. *Eur J Clin Pharmacol* (1981) **19**:31-7
- ³⁴ Willis JV, Jack DB, Kendall MJ, John VA. The influence of food on the absorption of diclofenac as determined by the urinary excretion of the unchanged drug and its major metabolites during chronic administration. *Eur J Clin Pharmacol* (1981) **19**:39-44
- ³⁵ Neuvonen PJ. The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac. *Br J Clin Pharmacol* (1991) **31**:263-6

Application of Surge Dose[®] fast dissolution technology to diclofenac

3.6 Suitability as candidate for Surge Dose[®] technology

Diclofenac is a weakly acidic molecule with a pKa of 4.15 and is classed as a BCS Class 2 low solubility drug with high permeability. However its solubility is pH dependent such that under acidic conditions it is less soluble, with its solubility increases significantly as the as the pH increases. Diclofenac is absorbed from the small intestine by passive diffusion with no evidence of active transport and there is a close PK-PD correlation.

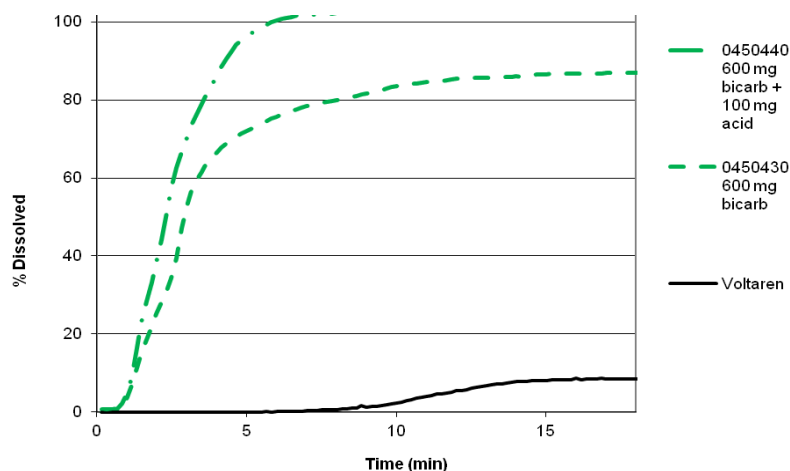
Such properties make diclofenac a suitable candidate for the application of Surge Dose[®] technology because the levels of bicarbonate and acidic components can be optimized for the drug to achieve fast and complete dissolution in the stomach. This allows the dose administered to empty from the stomach dissolved in the co-administered water into the small intestine whence fast absorption can occur.

4 Performance of Surge Dose[®] diclofenac

4.1 In vitro dissolution

An experimental screening program to determine the effects of different pH modulating agents (pHMA) and water uptake agents (WUA) on the dissolution rate of diclofenac potassium 50 mg from tablets was conducted by Imaginot during 2005³⁶. The extent of improvement in in vitro dissolution profiles of a preliminary Surge Dose[®] formulations compared with Voltaren[®] tablets is shown in Figure 6 with a mixture of 600 mg sodium bicarbonate and 100 mg citric acid providing the fastest and most extensive dissolution..

Figure 6 Dissolution profiles in 900 mL 0.0033 M HCl at 30 rpm for Voltaren[®] and Surge Dose[®] tablets



³⁶ Imaginot Pty Ltd. DR 04-01-01 Fast dissolving swallow tablets of diclofenac potassium. 11 July 2006

Application of Surge Dose[®] fast dissolution technology to diclofenac

4.2 PK simulations based on dissolution data

A simulation of the anticipated PK was performed for a preliminary Surge Dose[®] formulation containing 600 mg sodium bicarbonate with 100 mg citric acid (0450440) using the in vitro dissolution data in 900 mL 0.0033 M HCl at 30 rpm³⁷. These were compared with the PK profiles for the dissolved effervescent granules and two buffered tablets scanned from the paper by Reiner³⁸.

While the levels of sodium bicarbonate in these two buffered tablets are not disclosed, it is likely that they are based on the levels of 20 – 80 % of the weight of diclofenac claimed in the Reiner patents. At the top of the patented range, this equates to 40 mg bicarbonate for a 50 mg diclofenac tablet and 20 mg for a 25 mg diclofenac tablet which is less than the 600 mg used in the Surge Dose[®] formulation.

The PK profile for an enteric coated Voltaren[®] tablet was also estimated using population PK (PPK) without the long and highly variable lag phase³⁹. It was assumed that once the enteric coat had been dissolved, release kinetics of the drug would be similar to a tablet without the enteric coat.

As shown in Figure 7, these simulated profiles predict a T_{max} of 15 minutes for the Surge Dose[®] tablets (0450440), compared with 13.7 minutes for the dissolved effervescent granules, 21.2 minutes for the 25 mg tablet with bicarbonate, and 29.8 minutes for the 50 mg tablet with bicarbonate reported by Reiner et al (2001).

While the simulated PK profile for Voltaren[®] Rapid tablets based on the dissolution data in 900 mL 0.0033M HCl at 30 rpm indicates slightly slower absorption than that predicted by PPK for enteric coated Voltaren[®] without the lag time, the profiles would be quite similar if the dissolution lag time had also been eliminated. Since the in vitro dissolution test did not demonstrate any change in pH with the Voltaren[®] Rapid tablets, dissolution results would tend to underestimate in vivo results where there is an increase in pH from the stomach into the small intestine which dissolves the enteric coat and also increases the solubility of the drug.

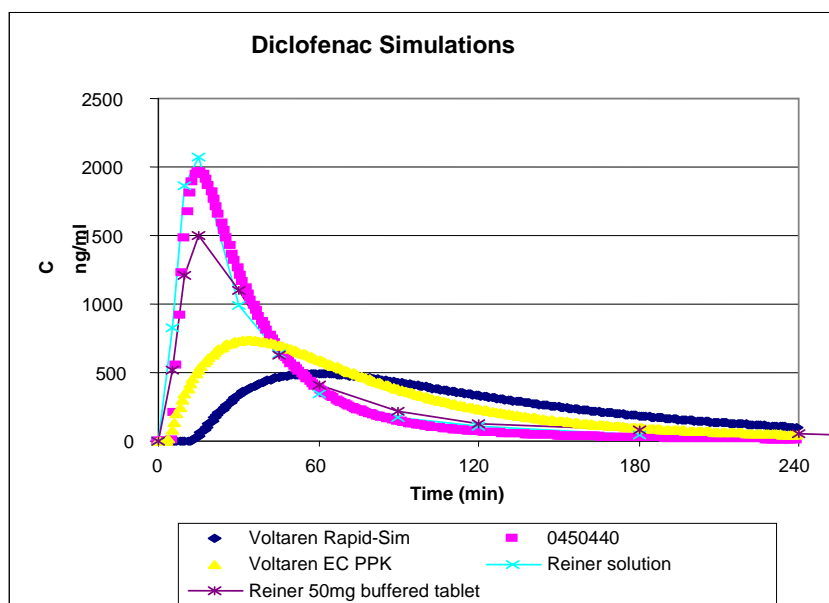
³⁷ Imaginot Pty Ltd. DR 04-01-03 Simulated plasma profiles of fast dissolving diclofenac potassium tablets. 11 July 2006

³⁸ 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

³⁹ Lötsch J, Kettenmann B, Renner B, Drover D, Brune K, Geisslinger G, Kobal G. Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: Relation to pharmacodynamics in an experimental pain model. *Pharm Res* (2000) **17**(1):77-84

Application of Surge Dose[®] fast dissolution technology to diclofenac

Figure 7 Simulated plasma levels of diclofenac from Voltaren[®] Rapid and Surge Dose[®] tablets (0450440) compared with population data for Voltaren[®] enteric coated tablets (Lötsch et al 2000) and scanned data for dissolved effervescent solution and a 50 mg buffered tablet (Reiner et al 2001)



Of note is that the PK profiles for the two swallow tablets were consistently slower than those for the effervescent solution and the fast dissolving tablets containing sodium bicarbonate. If the dissolution measured in vitro which is associated with a pH change is replicated in vivo, it is likely that the absorption rate from the Surge Dose[®] formulation will be similar to the solution product and better than the tablet with bicarbonate reported by Reiner et al (2001). The absorption profile will be significantly faster than that from Voltaren[®] Rapid higher peak plasma concentrations in around half the time.

Based on this simulation it would be expected that an optimized Surge Dose[®] tablet formulation of diclofenac potassium would demonstrate at least equivalent clinical performance to the fast absorbing formulations and better than conventional tablets.

4.3 PK performance of Surge Dose[®] diclofenac

A film coated Surge Dose[®] diclofenac sodium 50 mg tablet with optimized levels of pHMA and WUA meeting the Surge Dose[®] in vitro dissolution specifications has been developed and was compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration. This commercial product promoted as a fast absorbed product contained 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium.

Application of Surge Dose[®] fast dissolution technology to diclofenac

Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (± 5.0) and 19.5 min (range 5 – 30 min) indicating fewer slow absorption profiles with a high T_{max} . Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 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^{40,41} or IM^{42,43} administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets⁴⁴.

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).

4.4 Comparison of Surge Dose PK with other diclofenac products

Absorption of diclofenac from immediate release (IR) oral dosage forms is dissolution rate and gastric emptying dependent and published PK data for different products are summarized in Table 3 in descending order of C_{max} values. As can be seen, the Surge Dose[®] PK data are superior to those reported for soluble Cambia[®] sachets and Zipsor[®] liquid filled capsules which have recently been approved in the US with C_{max} values similar to those obtained following injection but provided in a more convenient and more patient-friendly dosage form.

⁴⁰ 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

⁴¹ 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

⁴² 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

⁴³ 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

⁴⁴ 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

Application of Surge Dose[®] fast dissolution technology to diclofenac

Table 3 Comparative PK data for Surge Dose diclofenac and other diclofenac products and dosage forms

Dosage form	C _{max} (ng/mL)	T _{max} (min)	AUC ng.h/mL
IV injection 50 mg diclofenac sodium (Willis et al)	7,800 ± 1,200	5	3,290 ± 690
Surge Dose [®] swallow tablet 50 mg diclofenac sodium (Abbott India)	3,569 ± 1,515	20 (15 – 30)	1, 883 ± 599
IM diclofenac sodium 75 mg (Voltaren 75 [®]) (Derendorf et al)	2,730 ± 810	25.3 ± 10.6	4,933 ± 1,061
Dissolved sachet 50 mg (Cambia [®] , APR DBT)	2,213 (444 – 4,273)	14 (10 – 16)	1,362 (690 – 2,173)
IM diclofenac sodium (Voltaren 75 [®]) 1 mg/kg (Auler et al)	2,167	30	4,440
Enteric coated tablets 50 mg (Voltaren [®])	2,000 ± 700	150 ± 66	1,670 ± 440
IV infusion 22.5 mg diclofenac potassium (Hinz et al)	1,892 ± 439	17 ± 0	873 ± 197
Buffered swallow tablet 50 mg (APR DBT technology)	1,766 (317 – 4.517)	21 – 30 (10 – 90)	1,267 (682 – 2,123)
Drops 50 mg (APR DBT technology)	1,679 (806 – 3,330)	15 (5 – 45)	1,392 (845 – 2,570)
Effervescent dispersible tablet 50 mg	1,111 (628 – 2,455)	60 (10 – 102)	1,396 (889 – 3,140)
Liquid filled capsule 25 mg (Zipsor [®] 25 mg)	1,087 ± 419	28 ± 10	517 ± 151
IR swallow tablet 50 mg	1,071 (454 – 2,421)	53 (15 – 240)	1,214 (831 – 2,092)
Voveran-D dispersible tablets 46.5 mg diclofenac free acid	1042 ± 518	90 (15 – 240)	1471 ± 499* * 0-t as late 2 nd peaks precluded estimates of 0-∞

Overall Surge Dose[®] diclofenac is absorbed as fast as from products where the drug is completely dissolved when administered such as drops and Cambia[®] sachets for solution where T_{max} values are around 15 minutes. This compares with around 1 hour for standard IR tablets.

Although the drug is solubilized in the Zipsor[®] liquid filled capsules, T_{max} values around 30 minutes are longer as the capsule must rupture and contents disperse before the drug can be absorbed⁴⁵. Despite the slower absorption, this solubilized formulation produces C_{max} values for a 25 mg dose equivalent to those from a standard IR 50 mg diclofenac tablet. This potentially allows a 50 % dose reduction with similar efficacy but reduced exposure

⁴⁵ ANDA 22-202, Zipsor[®] soft capsules, Xanodyne Pharmaceuticals

Application of Surge Dose[®] fast dissolution technology to diclofenac

providing an improved safety profile. The buffered swallow tablets based on the APR technology show the fastest absorption of the swallow tablets comparable with liquid filled capsules offering the same potential for reduced dosage and improved safety profile without compromising efficacy.

Voveran[®]-D, the dispersible tablet showed slower absorption with a longer T_{max} at 90 minutes compared with standard IR tablets around 1 hour despite the drug being dispersed in water before ingestion. This is likely to be attributable to limited dissolution of the drug in water or precipitation of dissolved drug in the stomach as there is no buffering to keep it in solution. This results in more variable absorption with a much wider range of T_{max} values as long as 4 hours.

Faster absorption with resultant higher C_{max} values for Surge Dose[®] diclofenac offers the same potential benefits of the Zipsor[®] liquid filled capsule, where a reduction in dosage can reduce exposure and risks of gastrointestinal and cardiovascular side effects without compromising efficacy with once daily dosing. Surge Dose[®] diclofenac should offer an advantage in relation to local gastric irritancy as the drug is in solution and in the unionized form in the stomach which will minimise absorption by gastric mucosal cells.

Faster absorption will result in faster onset of action whether central or local, as high plasma concentrations will drive distribution into peripheral tissues and synovial fluid for rapid onset of local and central effects.

The level of sodium used in the Surge Dose[®] diclofenac tablet to be taken once daily is well below the normal total daily intake limits recommended the US Food and Drug Administration of 2,300mg, or 1,500 mg for people with high blood pressure.

5 Conclusions

A review of published physicochemical, PK and PD data on diclofenac, suggests that this NSAID is an excellent candidate for the application of Imaginot's Surge Dose[®] technology providing ultra-fast, pH-controlled activated dissolution independent of physiological conditions. This has been confirmed by a PK study in man comparing an optimised film coated Surge Dose[®] diclofenac tablet formulation with a commercial dispersible tablet. A Surge Dose[®] tablet containing 50 mg diclofenac potassium formulated with 600 mg sodium bicarbonate and 100 mg citric acid demonstrated significantly improved in vitro dissolution. Based on a correlation between in vitro dissolution data and published PK data, times to peak plasma concentration (T_{max}) in the range 15 – 30 minutes were predicted for Surge Dose[®] formulations compared with around 1 hour for tablets.

Application of Surge Dose[®] fast dissolution technology to diclofenac

This performance projection was confirmed in a subsequent PK study in fasted subjects conducted on an optimised film coated tablet formulation containing 50 mg diclofenac sodium with 500 mg sodium bicarbonate and 100 mg fumaric acid. The Surge Dose[®] tablet showed fast absorption with T_{max} values in the range 15 – 30 minutes for individual subjects, with mean and median values the same at 20 minutes indicating a more consistent and tighter distribution of results. Absorption was significantly faster than from the dispersible tablet Voveran[®]-D (Novartis) containing 46.5 mg diclofenac free acid was dispersed in water before swallowing. Voveran[®]-D showed slower and more variable absorption with a median T_{max} of 90 minutes ranging from 15 minutes to 4 hours.

It was notable that faster absorption was associated with higher C_{max} values, $3,569 \pm 1,515$ ng/mL comparable with values reported for IM injections. Higher plasma concentrations will more effectively drive distribution to peripheral and central receptors which should lead to faster onset of action and time to peak effect.

These higher plasma concentrations also provide a clinical opportunity to reduce the dose of drug used without compromising efficacy which should reduce the incidence of side effects. Faster dissolution and gastric emptying of the drug reduces the time for gastric exposure which should result in reduced local gastric damage with Surge Dose[®] diclofenac tablets. Faster and more consistent absorption may also allow approval for Surge Dose[®] diclofenac in more severe indications such as migraine when compared with triptans as the gold standard treatment.