

**Application of Imaginot's technology to increase the in vitro dissolution of
a range of different therapeutic agents**

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

Written	Greg Davey, Pharmaceutical R & D Scientist	05 January 2006
Approved	Geraldine Elliott, R & D Director	05 January 2006
Reissued		02 August 2012

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

Table of Contents

1	Executive Summary.....	1
2	Scope.....	3
3	Background.....	3
4	Experimental	4
4.1	Active ingredients	4
4.2	Formulations	4
4.3	Comparator commercial products.....	6
4.4	Dissolution.....	6
5	Results and discussion.....	7
5.1	Analgesics	8
5.2	Non-steroidal anti-inflammatory drugs (NSAIDs).....	9
5.3	Anti-migraine (Selective 5-HT ₁ agonists)	9
5.4	Anti-histamines	10
5.5	Hypnotics.....	11
5.6	Anti-emetics.....	11
5.7	Phosphodiesterase inhibitors for erectile dysfunction	12
5.8	Anti-inflammatory agents (leukotriene inhibitors)	12
5.9	Diuretic agents	12
5.10	Lipid lowering agents	13
6	Conclusions	13
Appendix 1	Formulations and dissolution profiles	15
A1.1	Paracetamol 500mg tablets.....	15
A1.2	Paracetamol 325mg / tramadol HCl 37.5 mg tablets	17
A1.3	Tramadol HCl 37.5 mg tablets	19
A1.4	Ibuprofen 200 mg tablets.....	20
A1.5	Naproxen 250 mg tablets.....	21
A1.6	Naproxen sodium 275 mg tablets	22
A1.7	Diclofenac potassium 50 mg tablets	23
A1.8	Sumatriptan 50 mg tablets	24
A1.9	Zolmitriptan 2.5 mg tablets.....	25
A1.10	Eletriptan 40 mg tablets.....	26
A1.11	Rizatriptan 10 mg tablets.....	27
A1.12	Cetirizine dihydrochloride 10 mg tablets	28
A1.13	Temazepam 10 mg tablets.....	29
A1.14	Zolpidem tartrate 10 mg tablets.....	30
A1.15	Ondansetron hydrochloride 10 mg tablets	31
A1.16	Sildenafil 100 mg tablets	32
A1.17	Montelukast sodium 10 mg tablets.....	33
A1.18	Furosemide 40 mg tablets	34
A1.19	Gemfibrozil 600 mg tablets.....	35

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

1 Executive Summary

Imaginot has developed an ultra-fast activated dissolution drug delivery technology based on the use of pH modulating agents for swallow tablets. These are designed to achieve rapid pH-controlled in vitro dissolution under test conditions simulating the wide range of physiological conditions encountered in vivo among healthy fed and fasted individuals, as well as patients with impaired gastric function or on concurrent medication to reduce gastric acidity.

This technology was developed using paracetamol as a marker drug for gastric emptying and subsequently has been evaluated in vitro and in vivo with paracetamol and two NSAIDs (non-steroidal anti-inflammatory drugs), lornoxicam and diclofenac. Imaginot formulations demonstrated increased in vitro dissolution rates compared with conventional tablets and significantly faster absorption compared with leading commercial products claiming rapid dissolution and rapid action.

In the PK (pharmacokinetic) studies in fasted healthy subjects it was notable that all products showed some fast absorbing occasions and some slow absorbing occasions. However more fast absorbing occasions occurred with the Imaginot formulations even compared with a pre-dispersed diclofenac product. From a clinical perspective, the improved absorption profile of rapidly dissolving formulations will lead to earlier distribution, earlier onset of action, and more consistent achievement of therapeutic levels.

The in vitro dissolution methodologies developed by Imaginot demonstrated good IVIVC (in vitro in vivo correlation) in the paracetamol PK study in 25 healthy fasted subjects. Therefore these methods are used to optimise tablet formulations for maximum dissolution rates that will be indicative of fast absorption in vivo. Some 20 drugs, including a combination product of paracetamol and tramadol, have now been assessed to determine the effect of Imaginot's formulation technology and methodology on dissolution rates. These drugs cover a wide range of therapeutic classes, and include acidic, basic, amphoteric and unionised molecules. This report summarises dissolution results for Imaginot formulations compared with the corresponding commercial tablets, including any with fast dissolution or fast absorption claims. Drug concentrations were measured continuously in 900mL 0.0033 M HCl (hydrochloric acid) using USP dissolution apparatus II with paddles at 30 rpm and 37°C with the % drug dissolved compared at 3 and 15 minutes.

In all cases, drug dissolution rates can be increased using the Imaginot formulation approach, confirming its potential application as a platform technology with the levels and composition of the pH modulating agents and water uptake agents optimised for each drug.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

As demonstrated for the combination of paracetamol and tramadol, the levels of bicarbonate and acid need to be optimised, since the levels from the individual optimisations did not achieve the fastest dissolution when combined. However once the combination formulation was optimised, dissolution exceeded 90 % in 3 minutes for both actives, significantly faster than the commercial combination product.

In general, this preliminary screen work showed that:

- For acidic drugs where the solubility is low in acidic conditions, 400 - 600mg sodium bicarbonate per tablet will maximise in vitro dissolution which in some cases can be further increased by the addition of an organic acid. Typically, up to 90 % dissolution in 3 minutes was achieved, often reaching concentrations more than 100 times higher than those seen with conventional commercial products.
- For basic drugs where the solubility is lower under alkaline conditions, lower levels of sodium bicarbonate per tablet were effective, with the addition of an organic acid often further increasing the dissolution rate. Typically, dissolution exceeded 80 – 90 % in 3 minutes, reaching concentrations 10 - 100 times higher than conventional commercial products. Compared with a fast absorbing commercial sumatriptan product, the Imaginot formulation showed comparable in vitro dissolution, both being faster than the conventional commercial tablet.
- For unionised drugs where solubility is not pH dependent, maximum dissolution was usually achieved with a mixture of sodium bicarbonate and an organic acid. Optimised paracetamol tablet formulations containing sodium bicarbonate with fumaric acid exceeded 80 % dissolution after 3 minutes compared with those containing sodium bicarbonate alone that achieved around 70 % dissolution. These formulations demonstrated faster dissolution than those used in the paracetamol PK study which showed faster absorption in vivo than conventional tablets. It is therefore expected that the optimised paracetamol formulations reported here would result in faster absorption in vivo.

Based on these in vitro results, the IVIVC established for paracetamol, and in vivo PK data for paracetamol, lornoxicam and diclofenac, ultra-fast dissolving Imaginot formulations of other drugs are expected to show improved in vivo absorption providing their absorption is not limited by intestinal permeability. This is further supported by the correlation between the in vitro dissolution of the Imaginot sumatriptan formulation and an approved fast absorbing formulation of this drug. Hence Imaginot's fast dissolving drug delivery technology is expected to provide faster absorption for a wide range of therapeutic agents which will be associated with faster onset of action.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

2 Scope

The work covered by this report was designed to investigate the application of Imaginot's formulation approach developed using paracetamol as a marker for gastric emptying to a range of other drugs. The objective was to determine if in vitro drug dissolution could be significantly improved relative to commercially available products. Therapeutic categories of particular interest were pain, migraine, allergy, insomnia, nausea and vomiting, and erectile dysfunction where fast absorption and a fast onset of action are desirable.

Typical in vitro dissolution results using Imaginot test methods are summarised for preliminary swallow tablet formulations of a wide range of different therapeutic agents formulated using the Imaginot drug delivery technology. Comparative data are presented for corresponding commercial products, including any with fast absorption claims. Separate development reports are available for each drug detailing the full scope of work undertaken. This report contains formulations, specific manufacturing methods and comparative dissolution profiles in Appendix 1.

With limitations on raw material, most experimental formulations in this screening program were not optimised and data presented are for the fastest dissolving preliminary formulations for each drug. Where raw material was not available, preliminary screening was undertaken using reformulated commercial tablets to demonstrate the effect of the Imaginot technology. Hence a comprehensive development program should be undertaken to optimise formulations for maximum dissolution using the Imaginot test methods for any drug of interest.

3 Background

Imaginot conducted an extensive research program to develop ultra-fast dissolving swallow tablet formulations that demonstrate rapid in vivo absorption. This involved the investigation of in vitro dissolution kinetics, in vivo gastric emptying and PK of different oral formulations containing paracetamol. As this drug is recognised and used as a marker for gastric emptying and for the absorption of soluble drugs where intestinal permeability is not rate limiting, the results from the in vivo paracetamol studies were expected to translate to other drugs that are not solubility or intestinal absorption limited.

The use of pH modulating agents was found to significantly enhance in vitro dissolution of paracetamol from swallow tablet formulations. In vivo, this was consistently associated with faster absorption, which in turn would lead to earlier distribution, faster onset of action and improved efficacy. Sodium bicarbonate was found to be effective in achieving this faster dissolution and faster absorption over a defined concentration range, used alone or

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

in combination with an organic acid such as citric, tartaric or fumaric acid. Compared with conventional paracetamol tablets, Imaginot formulations containing various levels and combinations of pH modulating agents, showed improved early absorption of paracetamol based on partial AUC values at 10 (AUC_{10}) and 20 minutes (AUC_{20}).

Based on the results of a 25 subject PK study, an IVIVC was established between the AUC_{10} ($R^2 = 0.91$) and AUC_{20} ($R^2 = 0.87$) for paracetamol and the in vitro % drug dissolved in 300 seconds in USP apparatus II with 900 mL 0.0033 M HCl at 30 rpm and 37°C. This quantity of dissolution medium contains 3 millimoles HCl approximating the finite amount of acid present in the fasted human stomach.

4 Experimental

4.1 Active ingredients

Therapeutic class/Indication	Drug
Analgesics	Paracetamol, Tramadol HCl
Non-steroidal anti-inflammatory drugs (NSAIDs)	Diclofenac potassium, Ibuprofen, Ibuprofen sodium, Naproxen, Naproxen sodium
Anti-migraine (Selective serotonin 5-HT ₁ agonists)	Eletriptan hydrobromide, Rizatriptan benzoate, Sumatriptan succinate, Zolmitriptan
Anti-histamines	Cetirizine diHCl
Hypnotics	Temazepam, Zolpidem tartrate
Anti-emetics	Ondansetron HCl
Erectile dysfunction (Phosphodiesterase inhibitors)	Sildenafil citrate
Anti-inflammatory agents (leukotriene inhibitors)	Montelukast sodium
Diuretics	Furosemide
Lipid lowering agents	Gemfibrozil

4.2 Formulations

While paracetamol formulations have been extensively studied, only preliminary screening has been conducted on other drugs. Two swallow tablets formulations have been optimised for paracetamol 500 mg, one containing 200 mg sodium bicarbonate, and the other containing sodium bicarbonate and fumaric acid. Both formulations dissolve rapidly under the acid conditions normally encountered in the stomach but the latter formulation is designed to dissolve rapidly even under low acid conditions such as in the fed state or in subjects with reduced gastric acid function. The optimisation process resulted in

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

formulations which achieved faster in vitro dissolution than the two formulations in the PK study which had demonstrated faster absorption.

To date, paracetamol formulations have been optimised with respect to manufacturability on small scale equipment for batch sizes up to 5 kg considering compression properties, flow, uniformity of weight and friability, as well as stability and uniformity of content issues. Similar work has been undertaken for the paracetamol / tramadol combination identifying an optimised formulation suitable for scale up.

In general, formulation development is based on the following approach using 900 mL 0.0033 M HCl at 37 °C in USP dissolution apparatus II at 30 and 0 rpm:

1. Assess the effect of different levels of sodium bicarbonate on drug dissolution and select the level that provides maximum dissolution
2. Assess the impact of different levels of citric acid on the dissolution rate using the selected level of sodium bicarbonate
3. If citric acid enhances dissolution, test other acids and optimise levels
4. Optimise levels and type of disintegrants and other water uptake agent
5. Assess the impact of wet granulation to provide a robust and easy to manufacture tablet whilst maintaining disintegration and dissolution performance
6. Optimise the granule size for flow properties and dissolution characteristics
7. Optimise the moisture content for processing and stability

Tablets were prepared either by direct compression or wet granulation, compressed on a single punch BT 50 tablet press or a 16 station rotary Cadmach CMD3B-16 tablet press using appropriate size tooling. Direct compression powder blends were prepared by screening all excipients through a 280 µm screen to remove agglomerates and mixing all except the lubricant magnesium stearate which was added last.

Wet granulation was conducted in a laboratory scale planetary mixer with specific processing instructions detailed in Appendix 1. Fluid bed drying was performed in a Yamato Pulvis GB22 laboratory scale fluid bed drier. Water contents were conducted on a Mettler Toledo DL32 Karl Fischer Coulometer or a Sartorius MA30 Moisture analyzer.

For patented drugs with limited availability the effect of the Imaginot technology was assessed by reprocessing commercial products. Tablets were ground using a mortar and pestle and passed through a 280 µm screen to remove any coating. The sodium bicarbonate and any acid were passed through a 280 µm screen and any microcrystalline cellulose and magnesium stearate added and blended before compression.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

4.3 Comparator commercial products

Drug	Brand Product (Supplier)
Paracetamol	Panadol™ Rapid 500 mg caplets - Lot 100384 (GlaxoSmithKline) Tylenol™ Extra Strength Rapid Release 500 mg gelcaps - Lot JMA383 (McNeil, USA)
Paracetamol / tramadol HCl	Ultracet™ 325 mg / 37.5 mg tablets - Lot 5CG872 (Ortho McNeil, USA)
Tramadol HCl	Ultram™ 50mg tablets - Lot 5CG905 (Ortho McNeil, USA)
Ibuprofen	Nurofen™ 200 mg tablets - Lot 47WW (Boots)
Naproxen	Naprosyn™ 250 mg tablets - Lot E6053 (Roche)
Naproxen sodium	Naprogesic™ 275 mg tablets - Lot D06598 (Roche)
Diclofenac	Voltaren™ Rapid 50 mg tablets - Lot T4041 (Novartis)
Sumatriptan succinate	Imigran™ 50 mg tablets - Lot EA9064 (GlaxoSmithKline) Imitrex™ 50 mg tablets - Lot 5ZP3584A (GlaxoSmithKline, USA)
Zolmitriptan	Zomig™ 2.5 mg tablets - Lot CK014 (Astra Zeneca)
Eletriptan hydrobromide	Relpax™ 40 mg tablets - Lot 0623K05A (Pfizer, USA)
Rizatriptan	Maxalt™ 10 mg tablets - Lot R7124 (Merck)
Cetirizine	Zyrtec™ 10 mg tablets - Lot 41111 (Pfizer)
Temazepam	Temtabs™ 10 mg tablets - Lot 57209 (Sigma)
Zolpidem tartrate	Stilnox™ 10 mg tablets - Lot 24580 (Sanofi)
Ondansetron HCl	Zofran™ 10 mg tablets - Lot DZ9116 (GlaxoSmithKline)
Sildenafil citrate	Viagra™ 100 mg tablets - Lot 414834432 (Pfizer)
Montelukast sodium	Singulair™ 10 mg tablets - Lot G2121 (Merck)
Furosemide	Uremide™ 40 mg tablets - Lot 5J037 (AlphaPharm)
Gemfibrozil	Jezil™ 600 mg tablets - Lot B514285201 (AlphaPharm)

4.4 Dissolution

Test media based on 0.1 M HCl are frequently used for QC dissolution methods, approximating the acidity of gastric fluids. However, recognising that greater discrimination can be achieved by using lower concentrations of acid and slower stirring speeds (Handbook of Dissolution Testing, 3rd edition, R Hanson & V Gray, Dissolution Technologies Inc, 2004), Imaginot dissolution test methods use 0.015 and 0.0033 M HCl

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

with stirring speeds of 30 and 0 rpm. This allows better characterisation of the dissolution profile for fast dissolving formulations particularly when there is limited point sampling.

0.015 M HCl simulates in vivo conditions based on an estimate of approximately 30 mL residual gastric acid in a fasted subject, diluted with 170 mL water co-administered with the formulation. When 200 mL dissolution medium is used, the pH may be changed by the pH modulating agents in the Imaginot formulations which is important where drug solubility is pH dependent. However, when testing is conducted in 900 mL dissolution medium, there is excess acid preventing any significant pH change.

0.0033 M HCl achieves a pH change in 900mL of medium which contains the same absolute amount of acid as 200mL 0.015 M HCl. This concentration mimics low gastric acid conditions such as in fed patients or those with low gastric acid secretion.

Dissolution media were prepared by adding 32 % v/v concentrated HCl (AR quality from Rowe Scientific) to purified water from an in-house Millipore Elix[®] reverse osmosis system, filtered and degassed before use.

USP dissolution apparatus II with 900mL and 200 mL 0.0033 M HCl at 37°C and paddle stirrers at 30 rpm used to perform the dissolution testing comprised a VanKel VK 7010 dissolution bath, VanKel VK 750 D Heater/Circulator and Gilson Minipuls peristaltic pump for automatic continuous sampling. The stirring speed was increased to 250 rpm after 20 minutes to achieve maximum dissolution for the calculation of % dissolved. Dissolution results were based on the mean of 2 replicates.

For single drug formulations, drug concentrations were measured using a Varian Cary 50 UV-Vis Spectrophotometer set at an appropriate wavelength selected by running UV scans in the different media. Drug concentrations were measured continuously using the flow through cell. For the tramadol and paracetamol combination tablets, HPLC analysis was used to assay filtered samples taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 30 minutes.

5 Results and discussion

Formulations and dissolution profiles are detailed in Appendix 1 using the designations <Imaginot> for formulations containing sodium bicarbonate alone and <Imaginot Plus> for those containing sodium bicarbonate with an organic acid.

Dissolution enhancement ratios compare the % dissolved from the Imaginot formula to the % dissolved from the commercial comparator at the same time point. Where the extent of dissolution is negligible, the % dissolved is assumed to be 0.1 % to allow calculation of a ratio. However, where the ratio exceeds 100, it is not quantified but expressed as >100.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

5.1 Analgesics

Dissolution results are summarised in Table 1 for paracetamol, tramadol HCl and a combination of both drugs. Despite the rapid action claims of Panadol™ Rapid and Tylenol™ Extra Strength Rapid Release gelcaps, both Imaginot formulations demonstrate faster dissolution. Imaginot Plus shows that the addition of citric acid enhances dissolution compared with bicarbonate alone. These optimised formulations contain 200 mg sodium bicarbonate, and demonstrate significantly faster in vitro dissolution than the two Imaginot formulations evaluated in the PK study. As these earlier formulations which achieved around 40% dissolution in 180 seconds, showed faster absorption than both commercial products, it is expected that both optimised formulations will demonstrate faster absorption.

Table 1 Dissolution data for paracetamol 500 mg, tramadol HCl 37.5 mg and a combination of paracetamol 325 mg with tramadol HCl 37.5 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Paracetamol	Imaginot	71	2.4 ^a / 4.4 ^b	93	1.2 ^a / 1.5 ^b
	Imaginot Plus	82	2.8 ^a / 5.1 ^b	95	1.2 ^a / 1.6 ^b
	Panadol™ Rapid ^a	29	-	77	-
	Tylenol™ RR ^b	16	-	61	-
Tramadol HCl	Imaginot Plus	100	16.7	101	1.8
	Ultram™	6	-	56	-
Paracetamol ^c with tramadol HCl ^d	Imaginot Plus	89 ^c / 105 ^d	89 ^c / 35 ^d	92 ^c / 106 ^d	3.2 ^c / 2.4 ^d
	Ultracet™	1 / 3	-	29 / 44	-

Tramadol HCl is a base and exhibits higher solubility at low pH. The Imaginot Plus formulation contains sodium bicarbonate with acid maintaining a low pH around the dissolving drug particles to significantly enhance dissolution compared with Ultram™.

After extensive optimisation of the paracetamol / tramadol combination tablet, the fastest dissolution was achieved with 100 mg sodium bicarbonate and 34 mg fumaric acid. Table 1 shows this formulation provides significantly improved dissolution compared with Ultracet™, achieving 90 – 100 % dissolution of both actives in 3 minutes. The commercial product Ultracet™ achieves only 30 – 40 % dissolution of the two actives after 15 minutes.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

The dissolution for the combination products was conducted in 200 mL vessels which provide the most discriminating conditions. In 900 mL vessels as used for all the other products, faster results would be expected for both products but with similar differences.

5.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are acidic molecules with greater solubility at high pH than low pH such that higher levels of sodium bicarbonate are required to maximise dissolution.

Table 2 shows the improved performance of the Imaginot formulations compared with commercial products.

Table 2 *Dissolution data for ibuprofen 200 mg, naproxen 250 mg, naproxen sodium 275 mg and diclofenac potassium 50 mg*

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Ibuprofen	Imaginot	85	> 100	91	18.2
	Nurofen™	0	-	5	-
Naproxen	Imaginot	78	78	100	10
	Naprosyn™	1	-	10	-
Naproxen Sodium	Imaginot Plus	37	6.2	93	4.4
	Imaginot	27	4.5	76	3.6
	Naprogesic™	6	-	21	-
Diclofenac potassium	Imaginot	57	> 100	85	10.6
	Voltaren™ Rapid	0	-	8	-

Voltaren™ Rapid which claims to be fast acting, shows negligible dissolution under these test conditions, reaching only 8 % after 15 minutes compared with 57 % within the first 3 minutes for the Imaginot formulation. Although the commercial tablets are film coated, dissolution of the Imaginot formulations is still 4 - 10 times higher after 15 minutes, by which time any film coating will have completely dissolved.

5.3 Anti-migraine (Selective 5-HT₁ agonists)

The anti-migraine “triptan” drugs are basic compounds or salts of basic compounds which exhibit higher solubility in acidic solutions.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

Table 3 shows that Imaginot Plus formulations provide relatively fast dissolution compared with the commercial products. Notably the Imaginot Plus sumatriptan formulation achieves comparable dissolution to the fast dissolving, fast absorbed commercial product Imitrex™ both showing significantly faster dissolution than the standard product, Imigran™.

Table 3 Dissolution data for sumatriptan succinate 70 mg, zolmitriptan 2.5 mg, eletriptan hydrobromide 48.5 mg and rizatriptan benzoate 14.53 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Sumatriptan	Imaginot Plus	90	3.3 ^e / 0.94 ^f	93	1.0 ^e / 0.9 ^f
	Imigran™ ^e	27	-	94	-
	Imitrex™ ^f	96	-	98	-
Zolmitriptan	Imaginot Plus	84	7	96	1.0
	Zomig™	12	-	93	-
Eletriptan	Imaginot Plus	94	13.4	97	2.3
	Relpax™	7	-	42	-
Rizatriptan	Imaginot Plus	96	2.0	96	1.2
	Maxalt™	48	-	77	-

5.4 Anti-histamines

Cetirizine is an amphoteric molecule, exhibiting basic characteristics when used as the HCl salt with higher solubility in low pH conditions. Fastest dissolution was achieved by using a small amount of sodium bicarbonate alone.

Table 4 shows that only 6mg sodium bicarbonate is sufficient to enhance the dissolution of the drug to 3 times that of the commercial product Zyrtec™ after 3 minutes.

Table 4 Dissolution data for cetirizine diHCl 10 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Cetirizine	Imaginot	92	3.2	99	1.1
	Zyrtec™	29	-	90	-

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

5.5 Hypnotics

The hypnotic class of drugs is exemplified by temazepam, an amphoteric basic drug, and zolpidem tartrate, the salt of a basic drug which require a low pH environment for maximum solubility.

Table 5 shows that the Imaginot Plus formulations of both drugs provide significantly enhanced dissolution compared with the commercial products Temtabs™ and Stilnox™ at both 3 and 15 minutes.

Table 5 Dissolution data for temazepam 10 mg and zolpidem tartrate 10 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Temazepam	Imaginot Plus	62	62	88	22
	Temtabs™	1	-	4	-
Zolpidem	Imaginot Plus	91	45.5	92	1.2
	Stilnox™	2	-	80	-

5.6 Anti-emetics

Ondansetron is an anti-emetic drug used as the HCl salt of the base which has its highest solubility and hence fastest dissolution at low pH. As with other basic drugs, the dissolution is enhanced by maintaining a low pH micro-climate surrounding the dissolving particles.

In this case, the amino acid glycine was surprisingly found to provide faster dissolution than other organic acids. Table 6 shows that faster dissolution is achieved compared with Zofran™ after 3 minutes. However the relatively high solubility of ondansetron HCl allows the commercial product to reach 77 % dissolution after 15 minutes, compared with 83 % achieved in the first 3 minutes for the Imaginot Plus formulation.

Table 6 Dissolution data for ondansetron HCl 10 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Ondansetron	Imaginot Plus	83	10.4	99	1.3
	Zofran™	8	-	77	-

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

5.7 Phosphodiesterase inhibitors for erectile dysfunction

Sildenafil citrate is an acid salt of a basic drug used for erectile dysfunction.

Table 7 shows the citrate salt has sufficient acidic character to react with the sodium bicarbonate without the need for additional acid providing significant dissolution enhancement for the Imaginot product compared to Viagra™ at both 3 and 15 minutes. Even after 15 minutes, the dissolution of the commercial product reaches only 24 % compared with 97 % after 3 minutes for the Imaginot formulation.

Table 7 Dissolution data for sildenafil citrate 140 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Sildenafil	Imaginot	97	8.8	99	4.1
	Viagra™	11	-	24	-

5.8 Anti-inflammatory agents (leukotriene inhibitors)

Montelukast sodium is the salt of an acidic compound with higher solubility at a higher pH. Its low solubility means that dissolution is very pH sensitive.

Table 8 shows significantly enhanced dissolution with the Imaginot Plus formulation. The commercial product showed negligible dissolution even after 15 minutes whereas the Imaginot Plus formulation achieved the plateau dissolution of around 80 % in 3 minutes.

Table 8 Dissolution data for montelukast sodium 10.4 mg

Drug name	Formulation	% Dissolution			
		3 min	Ratio	15 min	Ratio
Montelukast	Imaginot Plus	81	27	82	27
	Singulair™	3	-	3	-

5.9 Diuretic agents

Furosemide is a widely used diuretic agent with once daily dosage. It is an acidic drug with higher solubility at higher pH.

Table 9 shows the Imaginot formulation containing 400 mg sodium bicarbonate exceeds 80 % dissolution in 3 minutes compared with negligible dissolution of Uremide™ 40 mg tablets even after 15 minutes.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

Table 9 Dissolution data for furosemide 40 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Furosemide	Imaginot	86	> 100	88	44
	Uremide™ 40	0	-	2	-

5.10 Lipid lowering agents

Gemfibrozil is a lipid lowering agent which is used at a relatively high dosage of 600 mg. It is an acid and has higher solubility at neutral or alkaline pH than under acidic conditions. The low solubility and high dose of this drugs means than dissolution is very pH sensitive.

Table 10 shows that the Imaginot formulation with 500 mg sodium bicarbonate increases the dissolution to 45 % in 3 minutes which is significantly better than Jezil™ showing negligible dissolution even after 15 minutes.

Table 10 Dissolution data for gemfibrozil 600 mg

Drug name	Product	% Dissolution			
		3 min	Ratio	15 min	Ratio
Gemfibrozil	Imaginot	45	> 100	78	> 100
	Jezil™	0	-	0	-

6 Conclusions

This work has demonstrated the applicability of Imaginot's ultra-fast pH controlled activated dissolution technology to a wide range of drugs and drug classes significantly enhancing the in vitro dissolution rate relative to currently available commercial products under discriminating test conditions. Hence this formulation approach provides a platform technology that can be applied to any drug or drug combination using the Imaginot dissolution test methodology to optimise formulations in relation to the levels of pH modulating agents and water uptake agents.

This technology is suitable for unionised, acidic and basic drugs that have high intestinal permeability and are sufficiently soluble such that dissolution does not significantly limit absorption. As has been now demonstrated with paracetamol, lornoxicam and diclofenac, in vivo absorption is enhanced by the use of products demonstrating faster in vitro

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

dissolution. Consequently, the significant dissolution differences seen between the Imaginot and commercial formulations of these exemplar drugs, are expected to result in faster absorption in vivo.

As a general principle to maximise the rate of in vitro dissolution:

- acidic drugs will require higher levels of bicarbonate and sometimes the addition of a low level of organic acid
- basic drugs will require lower levels of bicarbonate often with additional organic acid
- unionised drugs will require an intermediate level of bicarbonate usually with additional organic acid

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

Appendix 1 Formulations and dissolution profiles

A1.1 Paracetamol 500mg tablets

Formulation	Imaginot	Imaginot Plus
Paracetamol, micronised (mg)	500	500
Sodium bicarbonate (mg)	200	200
Citric acid (mg)	0	75
Microcrystalline cellulose (mg)	0	0
Povidone K30 (mg)	40	34
Crospovidone (mg)	100	100
Starch 1500 (mg)	50	50
Magnesium stearate (mg)	0	0
Stearic acid (mg)	9	9
Total (mg)	899	968

Methods

Imaginot (wet granulation)

- Granulate the paracetamol, starch 1500, povidone K30 and 40% crospovidone with 170 mg deionised water per tablet.
- Screen wet mass through 1.7 mm mesh and dry to less than 2% w/w moisture content.
- Screen dry granules through 355 µm mesh and blend with sodium bicarbonate and magnesium stearate prior to compression.

Imaginot Plus (double granulation)

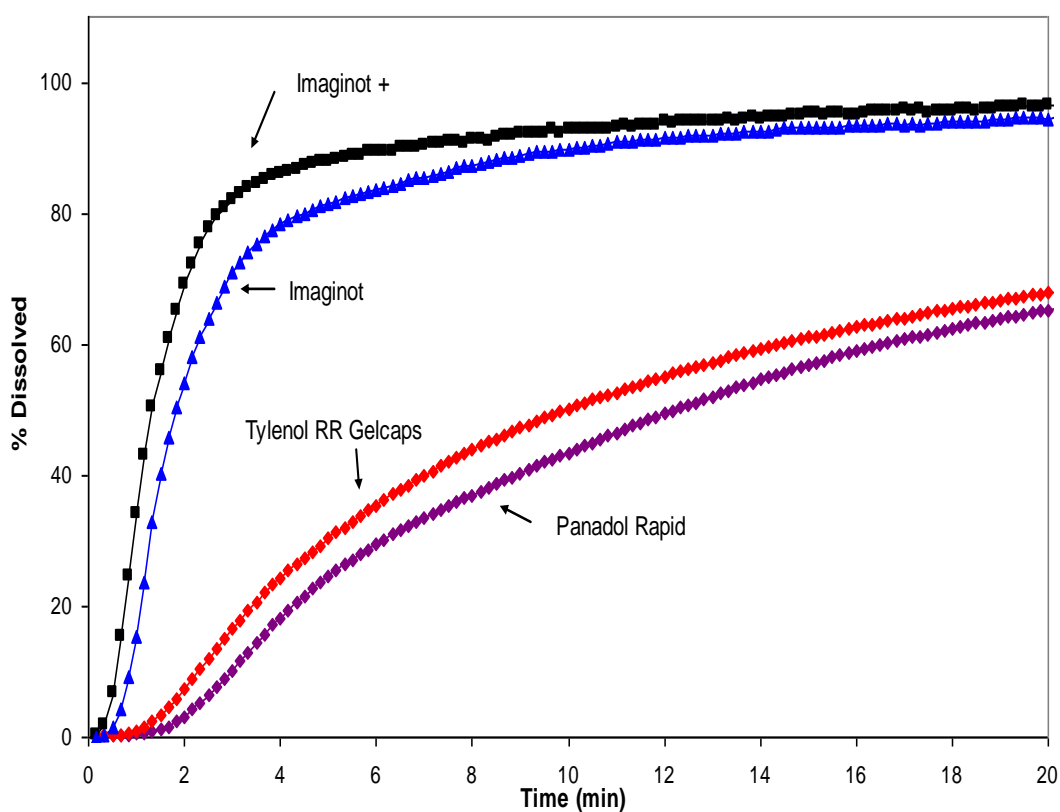
- Granule A - 250 mg paracetamol, 75 mg citric acid, 25 mg starch 1500, 20 mg povidone K30 and 20 mg crospovidone granulated with 50 mg deionised water per tablet.
- Granule B - 250 mg paracetamol, 25 mg starch 1500, 14 mg povidone K30 and 20 mg Crospovidone granulated with the equivalent of 125 mg deionised water per tablet.

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

- iii. Both wet screened through 1.7 mm mesh and dried to less than 2% w/w moisture content.
- iv. Dry granules screened through 1 mm mesh and blended proportionally with the equivalent of 60 mg Crospovidone and 9 mg stearic acid per tablet prior to compression.

Dissolution Profiles

Paracetamol dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.2 Paracetamol 325mg / tramadol HCl 37.5 mg tablets

Formulation	Imaginot Plus	Ultracet™
Paracetamol, micronised (mg)	325	325
Tramadol hydrochloride (mg)	37.5	37.5
Sodium bicarbonate (mg)	100	0
Fumaric acid (mg)	34	0
Microcrystalline cellulose (mg)	100	0
Povidone K30 (mg)	12.3	0
Crospovidone (mg)	85	0
Powdered cellulose, Pregelatinised corn starch, Sodium starch glycolate, Starch, Opadry light yellow, Carnauba wax	0	√
Magnesium stearate (mg)	7	√
Total (mg)	700.8	441

√ indicates unquantified presence of ingredients detailed in Product Information

Method (double granulation)

- Granule A - 162.5 mg paracetamol, 34 mg citric acid, 37.5 mg tramadol HCl, 12.5 mg crospovidone, 50 mg microcrystalline cellulose and 5 mg povidone K30 granulated with the equivalent of 33 mg deionised water per tablet.
- Granule B - 162.5 mg paracetamol, 100 mg sodium bicarbonate, 7.3 mg povidone K30 and 12.5 mg crospovidone granulated with the equivalent of 50 mg deionised water per tablet.
- Both granules wet screened through 1.7 mm mesh and dried to less than 2% w/w moisture content.
- Dry granules screened through 1 mm mesh and blended proportionally with the equivalent of 60 mg crospovidone, 50 mg microcrystalline cellulose and 7 mg magnesium stearate acid per tablet prior to compression.

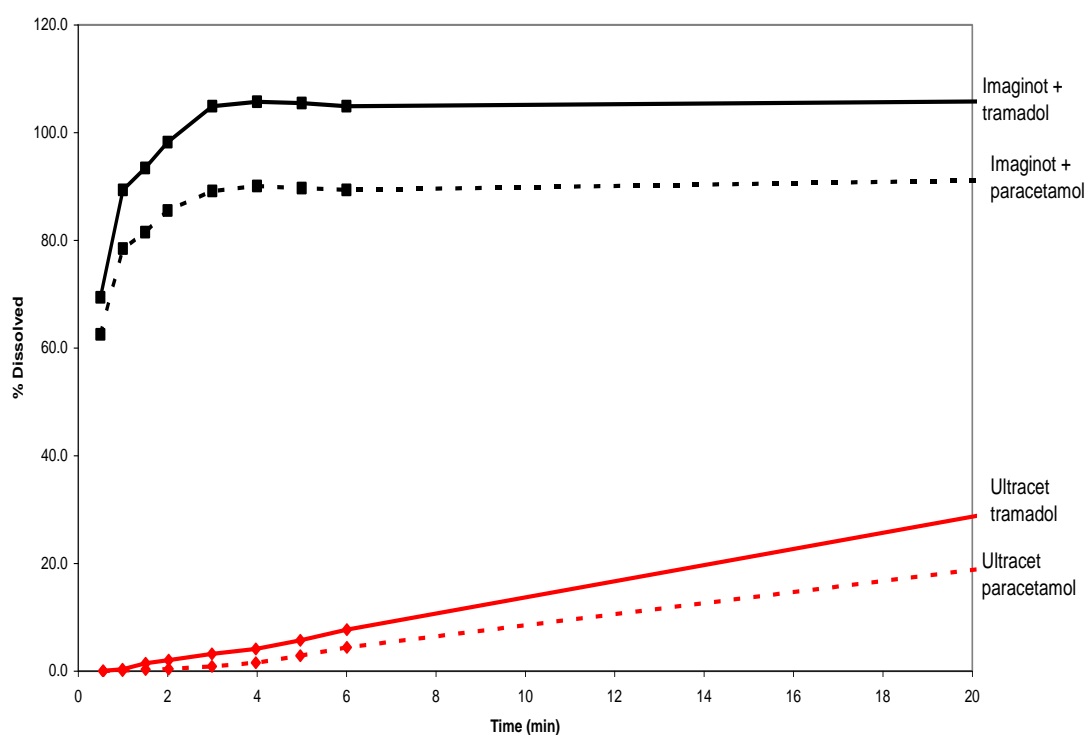
Dissolution Profiles

While all other testing was conducted in 900mL dissolution vessels, the dissolution testing on the combination product which required point sampling and HPLC analysis of the two actives, was conducted using the 200mL vessels. Overall this is a more discriminating test method, and generally shows slower dissolution than in 900 mL vessels although the

Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

relative order of different products is the same. If this testing was repeated in 900 mL, slightly faster results would be expected for both actives in both products as a result of the larger volume available for dissolution.

Paracetamol/Tramadol dissolution in 200 ml of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

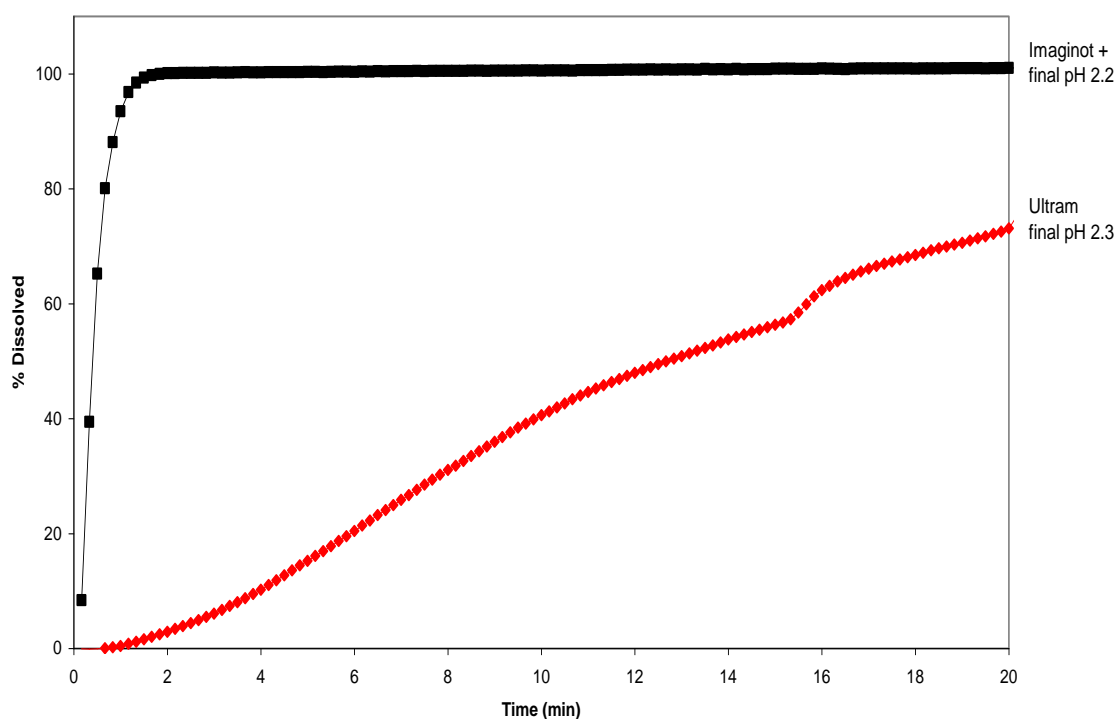
A1.3 Tramadol HCl 37.5 mg tablets

Formulation	Imaginot Plus	Ultram™
Tramadol hydrochloride (mg)	37.5	37.5
Microcrystalline cellulose (mg)	79.5	√
Sodium bicarbonate (mg)	40	0
Citric acid anhydrous (mg)	31	0
Crospovidone (mg)	10	0
Corn starch, Hypromellose, Lactose, Sodium starch glycolate, PEG, Polysorbate 80, titanium dioxide & wax	0	√
Magnesium stearate (mg)	2	√
Total (mg)	200	229

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Tramadol dissolution in 900 ml of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

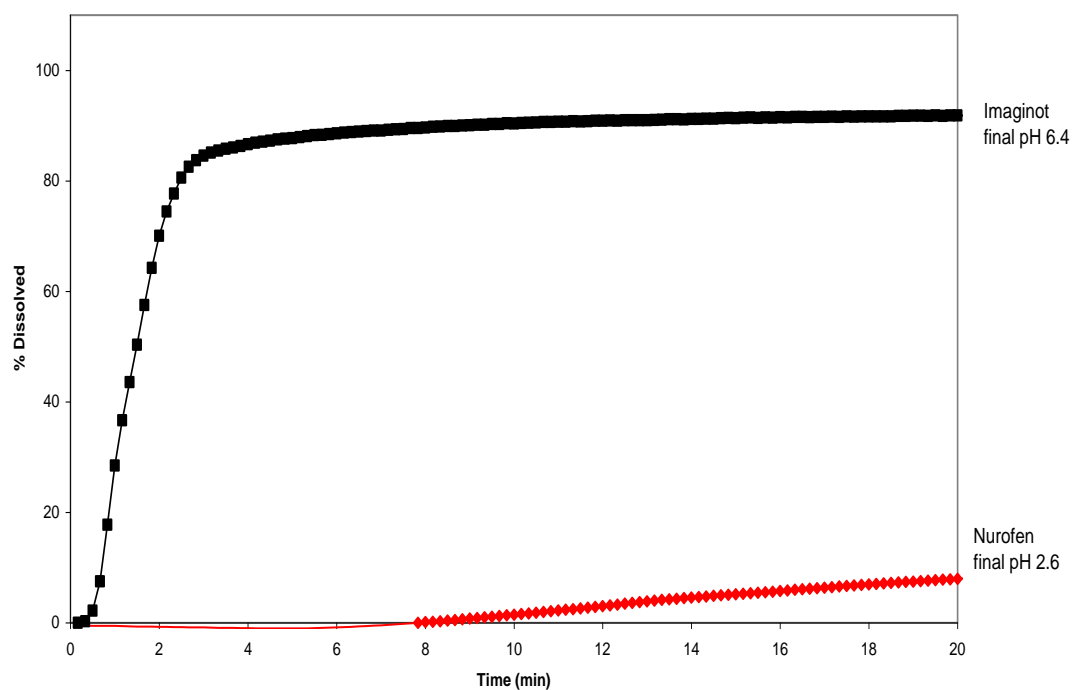
A1.4 Ibuprofen 200 mg tablets

Formulation	Imaginot Plus	Nurofen™
Ibuprofen (mg)	200	200
Sodium bicarbonate (mg)	600	0
Microcrystalline cellulose (mg)	540	0
Croscarmellose sodium (mg)	50	0
Sucrose	0	√
Magnesium stearate (mg)	10	√
Total (mg)	1400	442

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Ibuprofen dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



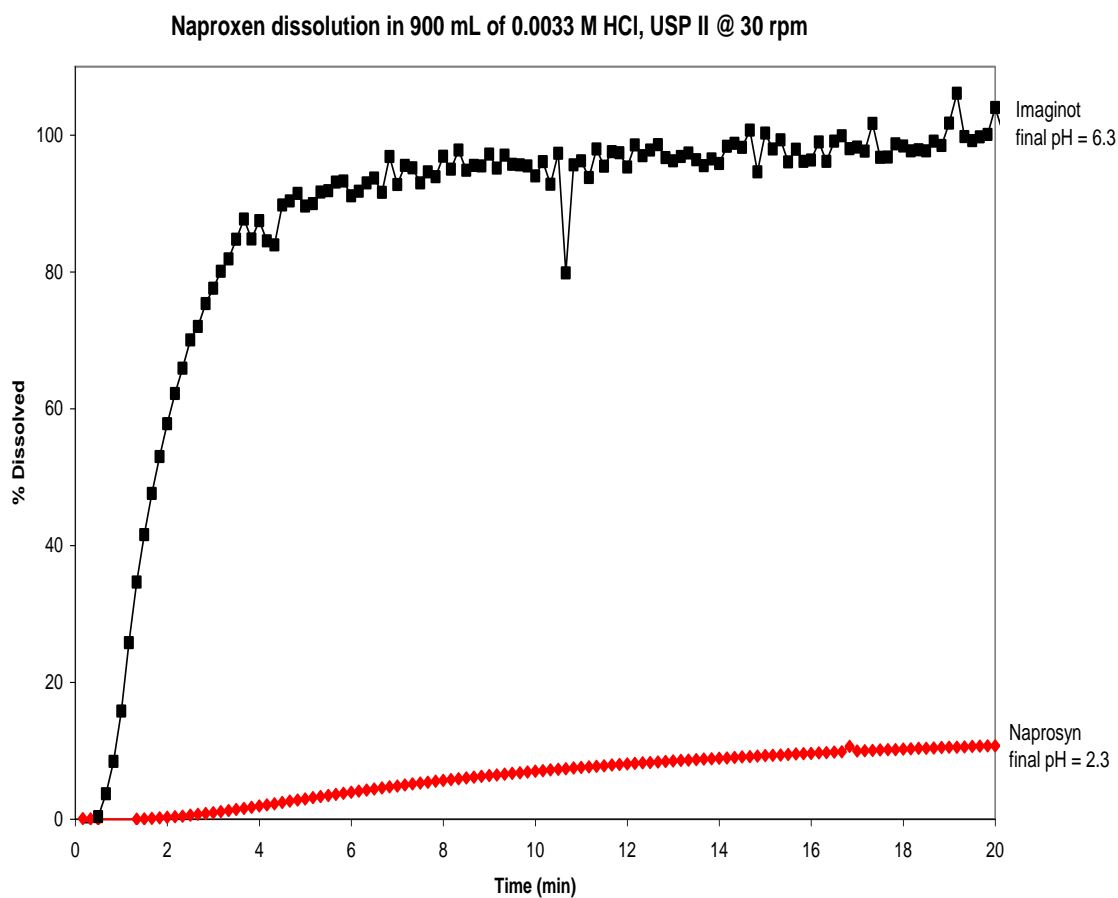
Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.5 Naproxen 250 mg tablets

Ingredients	Imaginot	Naprosyn™
Naproxen (mg)	250	250
Sodium bicarbonate (mg)	400	0
Microcrystalline cellulose (mg)	242	0
Croscarmellose sodium , Povidone K30, Magnesium stearate, Iron oxide yellow	√	√
Total (mg)	950	268

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

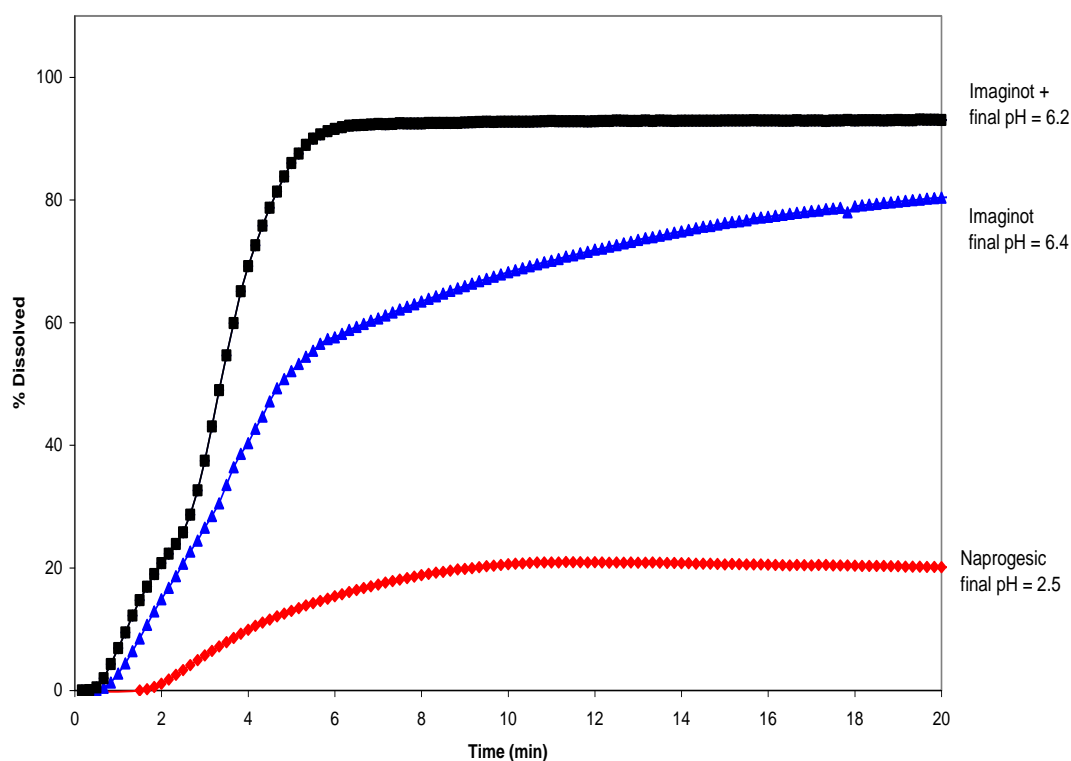
A1.6 Naproxen sodium 275 mg tablets

Ingredients	Imaginot	Imaginot Plus	Naprogesic™
Naproxen sodium (mg)	275	275	275
Sodium bicarbonate (mg)	500	500	0
Crospovidone (mg)	50	50	0
Citric acid anhydrous (mg)	0	76	0
Microcrystalline cellulose, Talc, Povidone K30, Magnesium stearate	√	√	√
Total (mg)	1050	1126	400

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Naproxen sodium dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



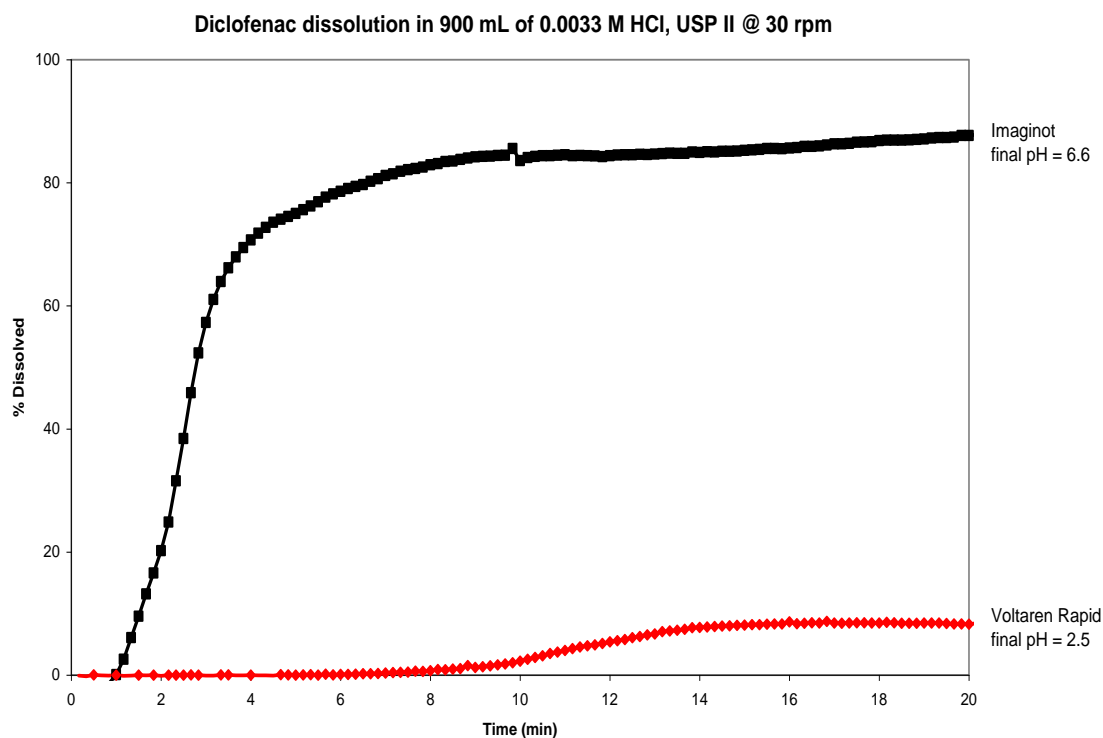
Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.7 Diclofenac potassium 50 mg tablets

Formulation	Imaginot	Voltaren™ Rapid
Diclofenac potassium (mg)	50	50
Sodium bicarbonate (mg)	600	0
Microcrystalline cellulose (mg)	290	√
Sodium starch glycolate (mg)	50	√
Colloidal anhydrous silica, Calcium phosphate, Maize starch, Povidone, Iron oxide, Macrogol 8000, Sucrose, Purified talc, Titanium dioxide	0	√
Magnesium stearate (mg)	10	√
Total (mg)	1000	318

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

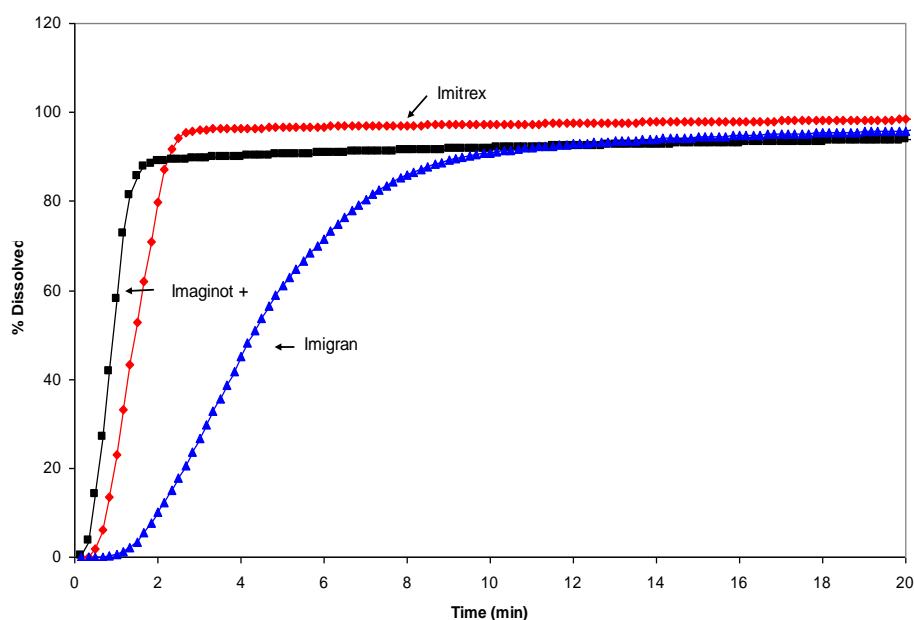
A1.8 Sumatriptan 50 mg tablets

Formulation	Imaginot Plus	Imigran™	Imitrex™
Sumatriptan succinate (mg)	70	70	70
Microcrystalline cellulose (mg)	248.5	√	√
Croscarmellose sodium (mg)	17.5	√	√
Citric acid anhydrous (mg)	9	0	0
Sodium bicarbonate (mg)	10.5	0	√
Dibasic calcium phosphate, Hypromellose, Iron oxide, Titanium dioxide, Triacetin	0	0	√
Lactose, Opadry YS-1-1441-G	0	√	0
Magnesium stearate (mg)	3.5	√	√
Total (mg)	359	307	350

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Sumatriptan dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

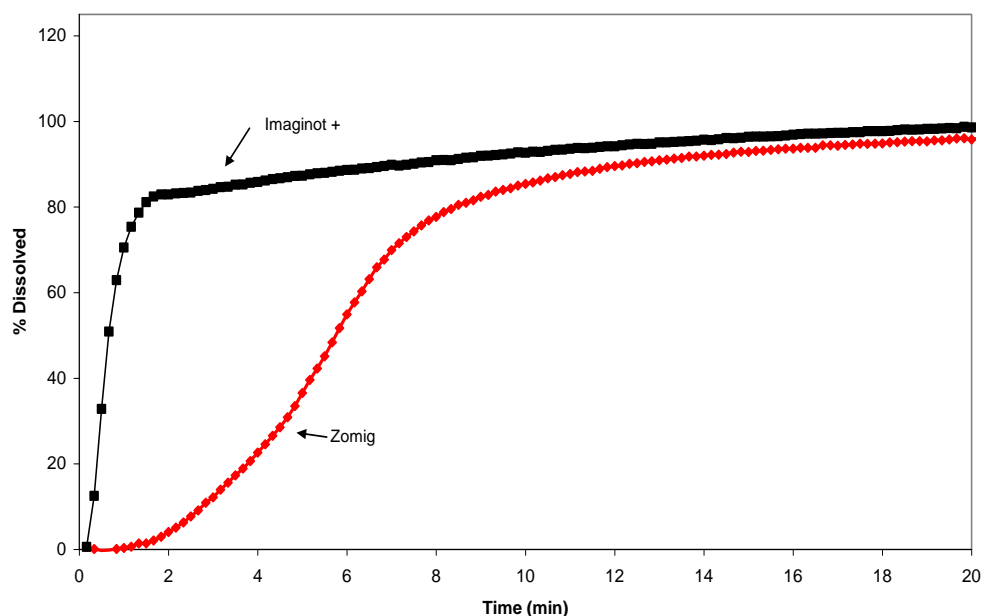
A1.9 Zolmitriptan 2.5 mg tablets

Formulation	Imaginot Plus	Zomig™
Zolmitriptan (mg)	2.5	2.5
Microcrystalline cellulose (mg)	97.1	√
Sodium starch glycolate (mg)	10	√
Citric acid anhydrous (mg)	38.4	0
Sodium bicarbonate (mg)	50	0
Lactose, Hydroxypropyl methylcellulose, Titanium dioxide, PEG 400 & 8000, Iron oxide (yellow & red)	0	√
Magnesium stearate (mg)	2	√
Total (mg)	200	126

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Zolmitriptan dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

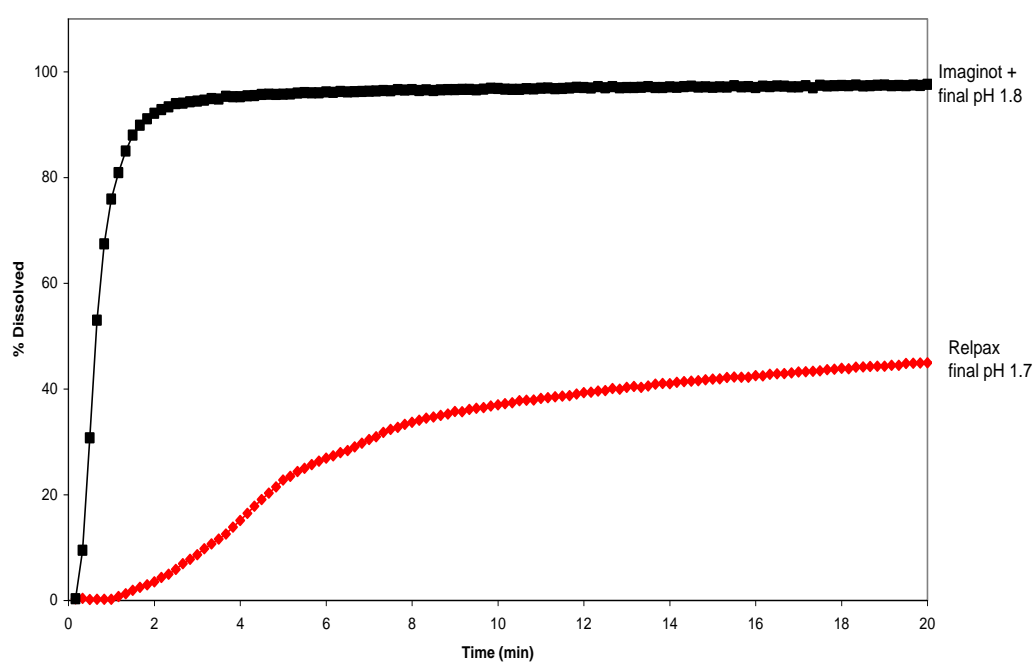
A1.10 Eletriptan 40 mg tablets

Formulation	Imaginot Plus	Relpax™
Eletriptan hydrobromide (mg)	48.5	48.5
Microcrystalline cellulose (mg)	√	√
Lactose (mg)	√	√
Fumaric acid (mg)	28	0
Sodium bicarbonate (mg)	40	0
Croscarmellose sodium (mg)	10	0
Magnesium stearate, Film coating	√	√
Total (mg)	348	204

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Eletriptan dissolution in 900 ml of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

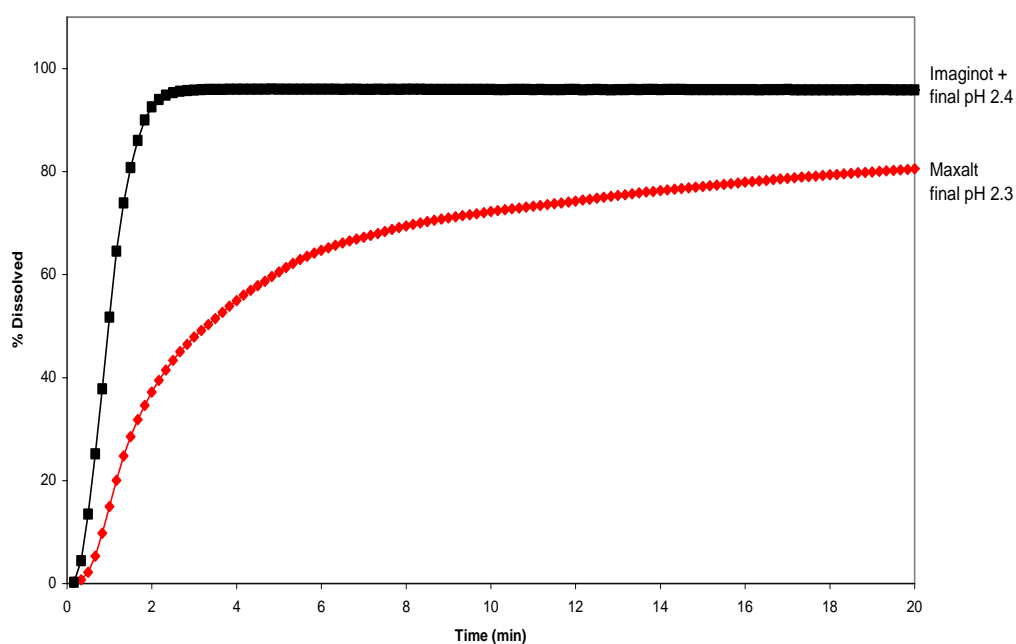
A1.11 Rizatriptan 10 mg tablets

Formulation	Imaginot Plus	Maxalt [™] (uncoated)
Rizatriptan benzoate (mg)	14.53	14.53
Microcrystalline cellulose (mg)	51.27	√
Citric acid (mg)	30.7	0
Sodium bicarbonate (mg)	40	0
Crospovidone (mg)	12	0
Lactose monohydrate, Pregelatinised starch, Iron oxide	0	√
Magnesium stearate (mg)	1.5	√
Total (mg)	150	190

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Rizatriptan benzoate dissolution in 900 ml of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

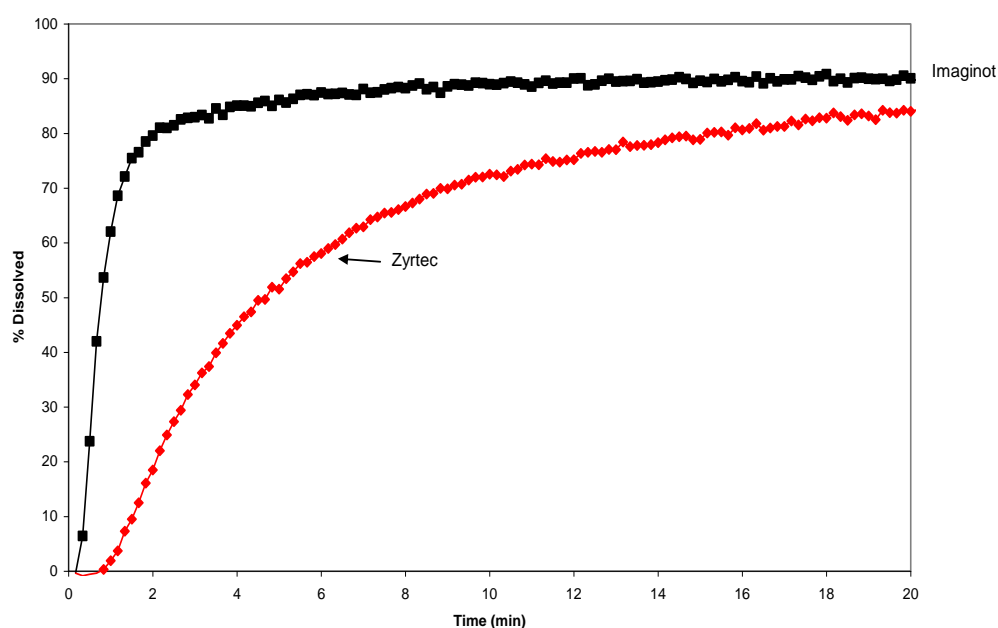
A1.12 Cetirizine dihydrochloride 10 mg tablets

Formulation	Imaginot	Zyrtec™
Cetirizine dihydrochloride (mg)	10	10
Microcrystalline cellulose (mg)	172	√
Sodium bicarbonate (mg)	6	0
Crospovidone (mg)	10	0
Lactose, Colloidal anhydrous silica, Titanium dioxide, PEG 400, talc	0	√
Magnesium stearate (mg)	2	√
Total (mg)	200	119

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Cetirizine dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

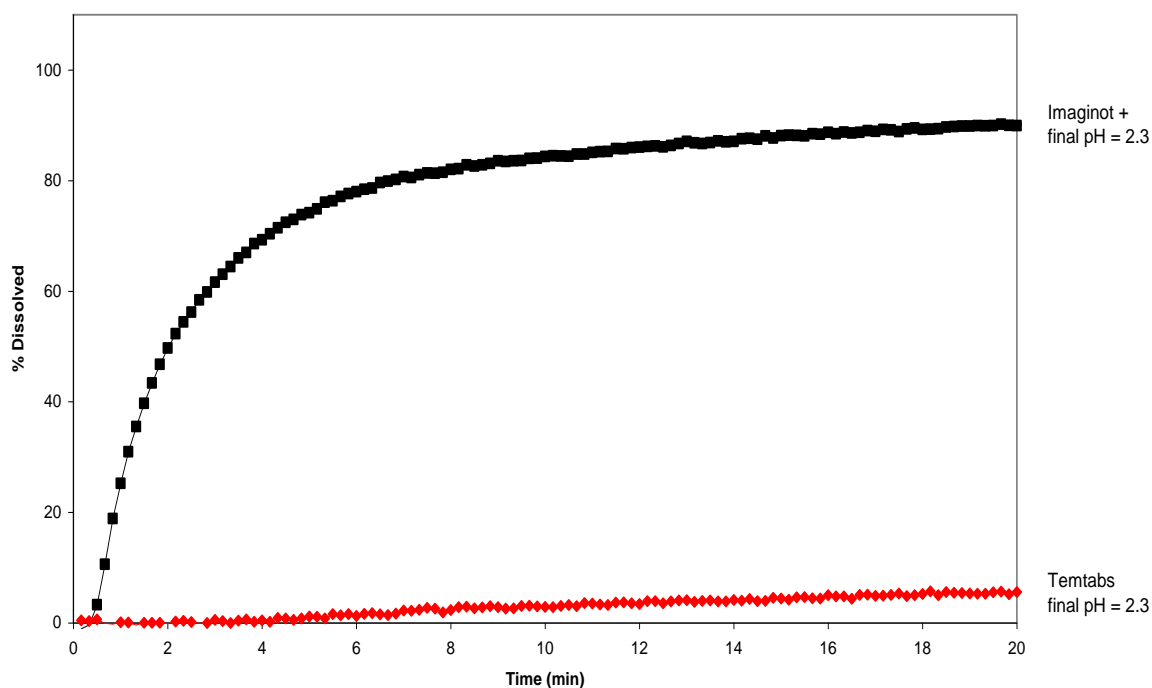
A1.13 Temazepam 10 mg tablets

Formulation	Imaginot Plus	Temtabs™ (uncoated)
Temazepam (mg)	10	10
Sodium bicarbonate (mg)	20	0
Citric acid (mg)	10	0
Crospovidone (mg)	10	0
Microcrystalline cellulose, Lactose, Maize starch, Sunset yellow lake, Magnesium stearate	√	√
Total (mg)	218	178

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Temazepam dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



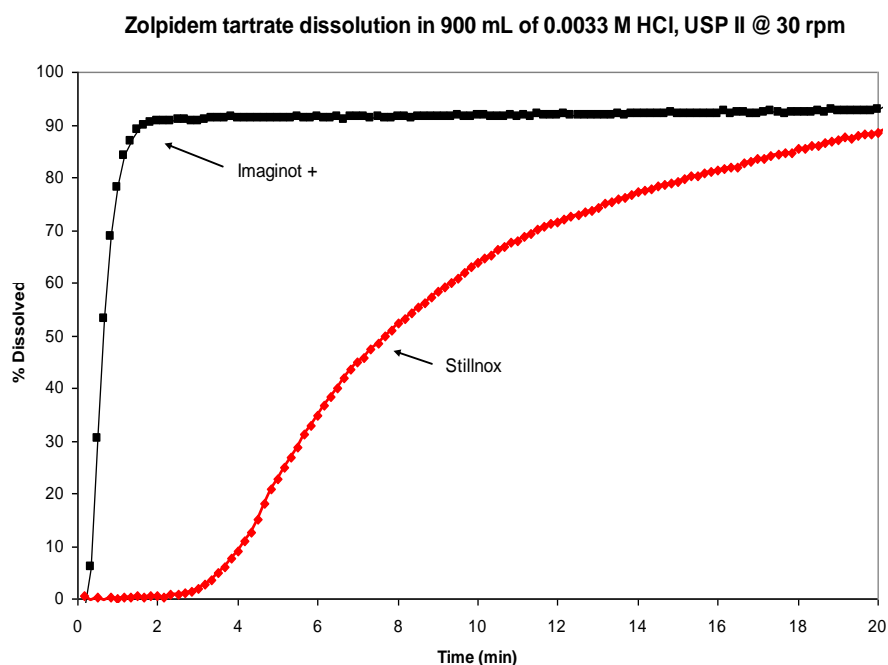
Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.14 Zolpidem tartrate 10 mg tablets

Formulation	Imaginot Plus	Stilnox™
Zolpidem tartrate (mg)	10	10
Microcrystalline cellulose (mg)	86	√
Sodium bicarbonate (mg)	50	0
Citric acid anhydrous (mg)	42	0
Sodium starch glycolate (mg)	10	√
Lactose, Hypromellose, titanium dioxide, PEG 400	0	√
Magnesium stearate (mg)	2	√
Total (mg)	200	126

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

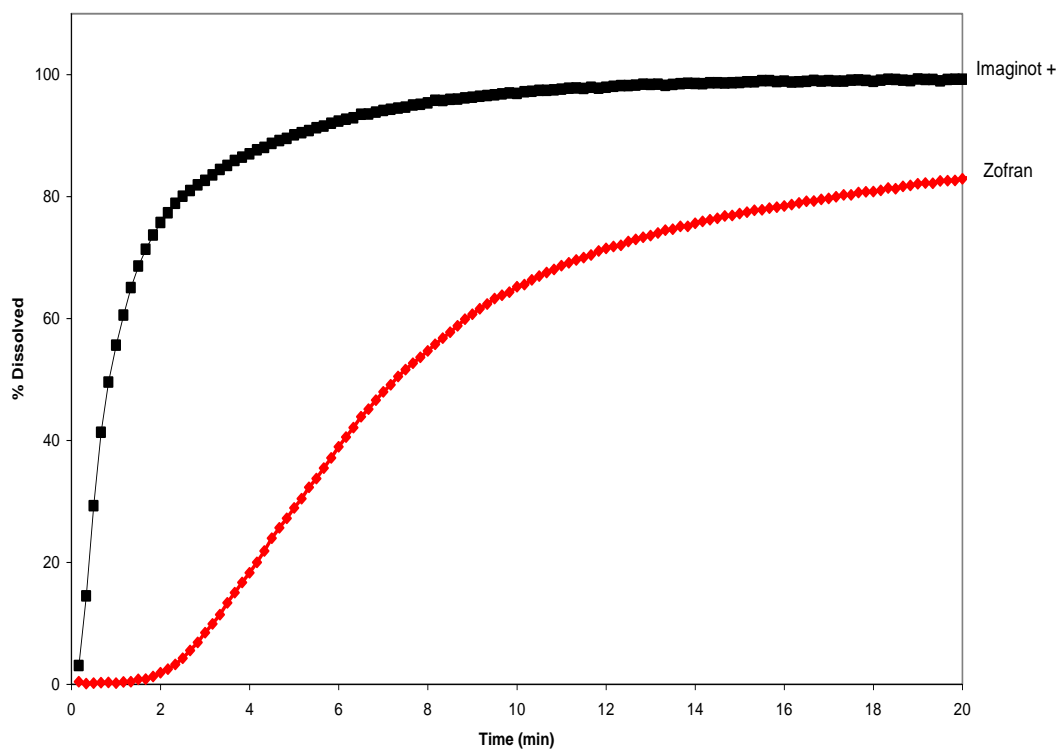
A1.15 Ondansetron hydrochloride 10 mg tablets

Formulation	Imaginot Plus	Zofran™
Ondansetron hydrochloride (mg)	10	10
Microcrystalline cellulose (mg)	140	√
Sodium bicarbonate (mg)	20	0
Glycine (mg)	18	0
Crospovidone (mg)	10	0
Lactose, Starch, Hypromellose, Opaspray yellow	0	√
Magnesium stearate (mg)	2	√
Total (mg)	200	259

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Ondansetron dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.16 Sildenafil 100 mg tablets

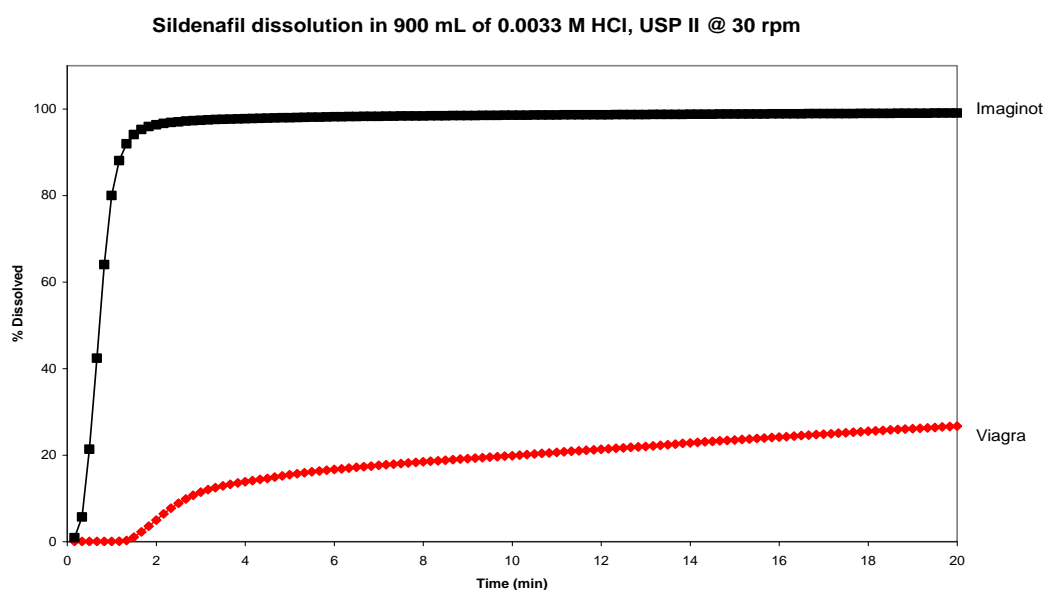
Formulation	Imaginot	Viagra™
Sildenafil citrate (mg)	140	140
Microcrystalline cellulose (mg)	263	√
Sodium bicarbonate (mg)	50	0
Croscarmellose sodium (mg)	25	√
Povidone K30 (mg)	8	0
Anhydrous calcium hydrogen phosphate, Hypromellose, Lactose, Titanium dioxide, Glyceryl triacetate, Indigo carmine aluminium lake	0	√
Magnesium stearate (mg)	5	√
Total (mg)	491	623

√ indicates unquantified presence of ingredients detailed in Product Information

Method

- Granulate the sildenafil citrate, microcrystalline cellulose, povidone K30 and croscarmellose sodium with 590 mg deionised water per tablet.
- Screen the wet mass through 1.7 mm mesh and dry to 3.1% w/w moisture content.
- Screen dry granules through 850 µm mesh and blend with sodium bicarbonate and magnesium stearate.

Dissolution Profiles



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

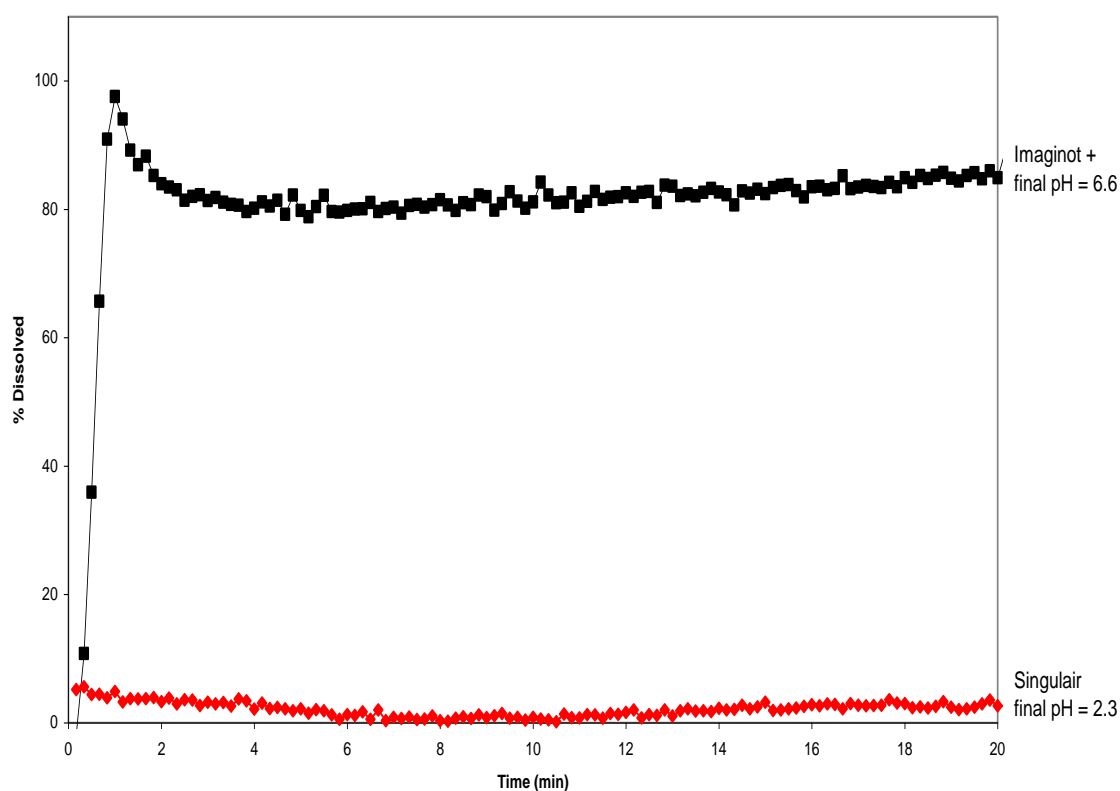
A1.17 Montelukast sodium 10 mg tablets

Ingredients	Imaginot Plus	Singulair™
Montelukast sodium (mg)	10.4	10.4
Sodium bicarbonate (mg)	600	0
Citric acid anhydrous (mg)	76	0
Microcrystalline cellulose, Croscarmellose sodium, Lactose, Magnesium stearate, Film coating	√	√
Total (mg)	1016	204

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Montelukast sodium dissolution in 900 ml 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

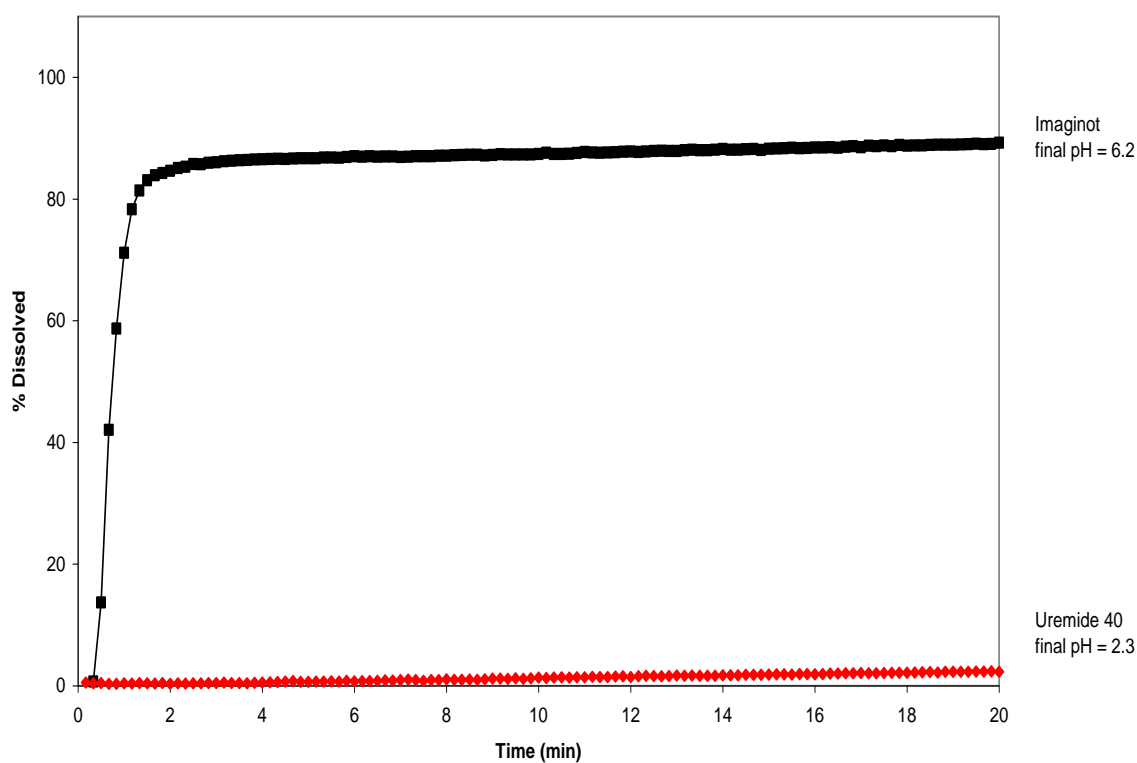
A1.18 Furosemide 40 mg tablets

Ingredients	Imaginot	Uremide™ (uncoated)
Furosemide (mg)	40	40
Sodium bicarbonate (mg)	400	0
Microcrystalline cellulose (mg)	300	0
Crospovidone (mg)	50	0
Lactose, Maize starch, Pregelatinised maize starch, Magnesium stearate	√	√
Total (mg)	910	160

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Furosemide dissolution in 900 mL of 0.0033 M HCl, USP II @ 30 rpm



Application of Imaginot's technology to increase the in vitro dissolution of a range of different therapeutic agents

A1.19 Gemfibrozil 600 mg tablets

Ingredients	Imaginot	Jezil™
Gemfibrozil (mg)	600	600
Sodium bicarbonate (mg)	500	0
Microcrystalline cellulose, Silica, Calcium stearate, Pregelatinised maize starch, Hydroxy propyl cellulose, Macrogol 3350, Polysorbate 80, Methylhydroxybenzoate, Hypromellose, Candelilla wax, Opaspray white	√	√
Crospovidone (mg)	50	0
Total (mg)	1420	870

√ indicates unquantified presence of ingredients detailed in Product Information

Dissolution Profiles

Gemfibrozil dissolution in 900 ml of 0.0033 M HCl, USP II @ 30 rpm

