BIOCOMPATIBLE MATRIX FOR CONTROLLED DRUG

CONFIDENTIAL Presentation

Matripharm International Inc.

A privately held pharmaceutical company based in Montreal (Canada) specialized in the development of novel drug delivery platforms aiming to reduce the side effects of current platform delivery systems while also improving on and extending the duration of therapeutic coverage.

Matripharm

Matripharm has 4 patents submitted in the field of drug-delivery and has access from a sister company (B-Organic Corp.) to a 5th patent for drug solubility and an increased bioavailability

Heighten safe aAll of its Intellectual Property are based on proprietary functionalized starch and other components that have already been cleared by FDA to be used in humans and improve efficacy profile

Backed by more than 20 years of research and technical expertise, Matripharm monolithic matrix technology improves the efficiency of sustained-release drug delivery by a factor of 80%.

What Is The Importance of Our Proprietary Technologies?

- Allow an extension of existing patents for block-buster drugs with a newly formulated API that is more efficient either by reducing dosage (increased bioavailability) or by extending the release of the compound over a longer period of time
- Allow the formulation of High Soluble Compounds that are poorly bio-availability
- Easier formulation of newly discovered molecules sometimes rejected before pre-clinical trials, despite their in vitro efficacy, because of poor solubility and bio-availability
- Reduce or eliminate side effects
- Heighten safe and improve efficacy profile
- Increase patient compliance
- Compatible with many APIs in today`s market

Main Properties of Our Excipients

1. Excipient based mainly on starch glycolate (already approved by FDA and currently used in the market)
2. Easy to manufacture
3. Inexpensive components
4. Possibility to have a monolithic tablet with dual-release of the active drug (API) that can be modulated (immediate release or extended release)
5. Already cleared by FDA for human use
6. High drug loading
7. Compatible with large range of APIs

Two speed monolithic system for controlled release of drugs (2RR)

Dual-rate release formulation with high drug loading (DRR)

Monolithic tablets based on carboxyl polymeric complexes for controlled drug … (HSDER)

Monolithic composition for dual-rate release with high drug loading (DRR)

Our Technology

The new platform described herein a process consists in converting insoluble APIs to water soluble (WS) or dispersible (WD) APIs. One of the unique and important aspects of our Technology is that the conversion processing is operated under mild conditions and without modification of APIs. Consequently, there is no alteration of API structure or of its biological activity.

In addition, the converted API is mechanically resistant in biological fluids (i.e. gastric acid) and stable at high temperatures able to protect effectively certain sensitive APIs against to oxidation and to light enhancing thus its shelf-life.

Our Technology

The converted API in powder forms can obtain under homogenous liquid form by dispersing in an aqueous medium or under tablet forms by direct compaction. It is of interest to mention that these different dosage forms could be formulated with our excipients for immediate release (rapid action) or controlled release (delayed or longer action) including, when it may be necessary, targeted colon delivery.

One of key feature of the our Technology is not only to improve the availability and effectiveness of APIs, but also to reduce their undesirable secondary effects. Additionally, the simplicity, compatibility and versatility of our Technology confers to new formulations with WS-API a high competitiveness compared with that of its initial insoluble

Advantages of Our Technology

Inexpensive and 100 % GRAS (Generally Recognized As Safe) raw materials

Broad portfolio of applications for almost common dosage forms;

Stable and resistant in gastric acidity;

Simple to manufacture;

easy to formulate with any drugs under oil, liquid or solid forms;

able to protect against oxidation and light for sensible APIs;

Unparalleled performance and safety;

Simple to formulate for immediate or controlled delivery;

Possible to open ways to enable intravenous and intramuscular administrations for certain APIs, etc.

How our technologies can be immediately applied to existing products?

- Formulate double rate-release in a monolithic tablet easy to manufacture and with the possibility of formulate the release
- Extend the patent of existing products by accelerating the patent protection of newly formulated molecules
- Formulate High Soluble Drugs in a time-release situation
- Increase the bio-availability of poorly soluble drugs in pre-clinical development

Business Models for An Industrial Collaboration

Formulate new API by combing two molecules using our know-how.

Using our proprietary technologies and trade secret we are willing to re-formulate existing API (active pharmaceutical ingredients) that need a better and simpler delivery systems in order to restart again a patented life-cycle

Formulate new API that are currently at the discovery stage using our know-how.

Matripharm Products (Started Registration with Health Canada)

- Paracetamol (DRR)
- Metformin (HSDER)
- Ibuprofen (2RR)
- Paracetamol/Caffeine (DRR)

Examples of Existing Products that Can Be Improved by Matripharm Technologies

- Atorvastatin (Lipitor)
- Norvasc (Amlodipine)
- Diflucan (Fluconazole)
- Pregabalin(Lyrica)
- Sertraline (Zoloft)
- Nilutamide
- Dolasetron Mesylate
- Irbesartan
- Leflunomide
- Meperidine hydrocholoride
- Metformin hydrochloride
- Fludarabine phosphate
- Zopiclone
- Furosemide
- Dronedarone
- Sodium Cromoglycate

Hydrocodone Bitartrate/ Phenylephrine HCl

- Clopidogrel (possible combined with or without ASA)

Sevelamer hydrochloride, Acebutolol hydrochloride

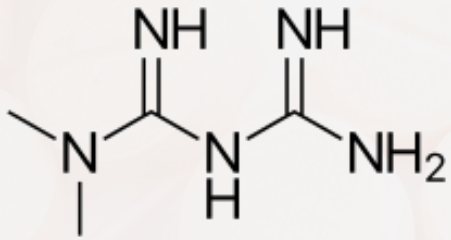
Highly Soluble Drug Extended Release (HSDER) Technology

(Applicable Example: Metformin Extended Release)

Matripharm International INC

HSDER

HSDER Technology was developed for controlled release of high soluble drugs such as Metformin (~ 300 mg/mL)

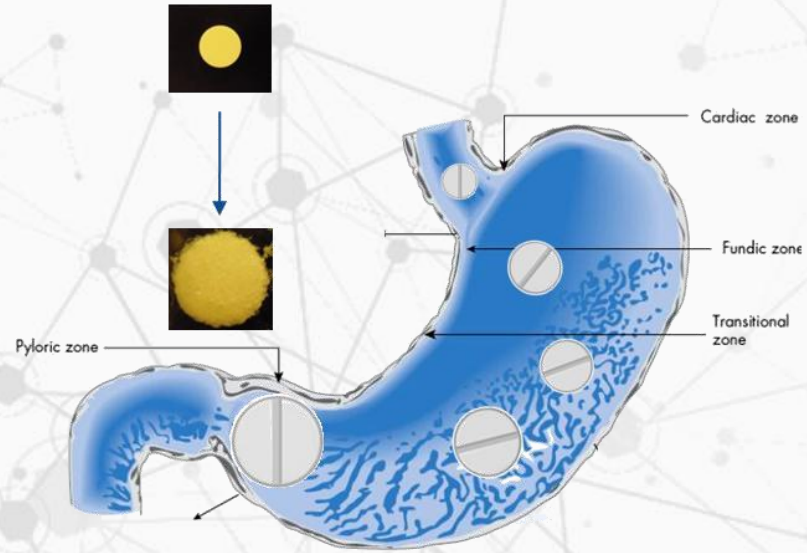


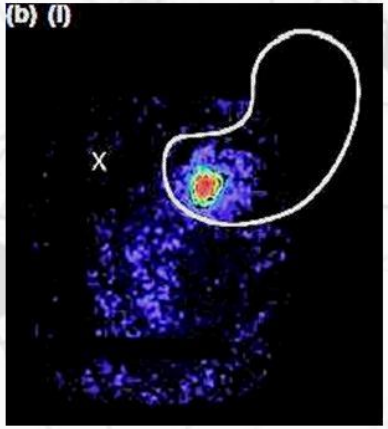
This HSDER system appears as unique, being able to limit the saturation or bio-accumulation phenomena

The technology concept is widely differing from the systems currently commercialized (Gastroretentive Dosage Form)

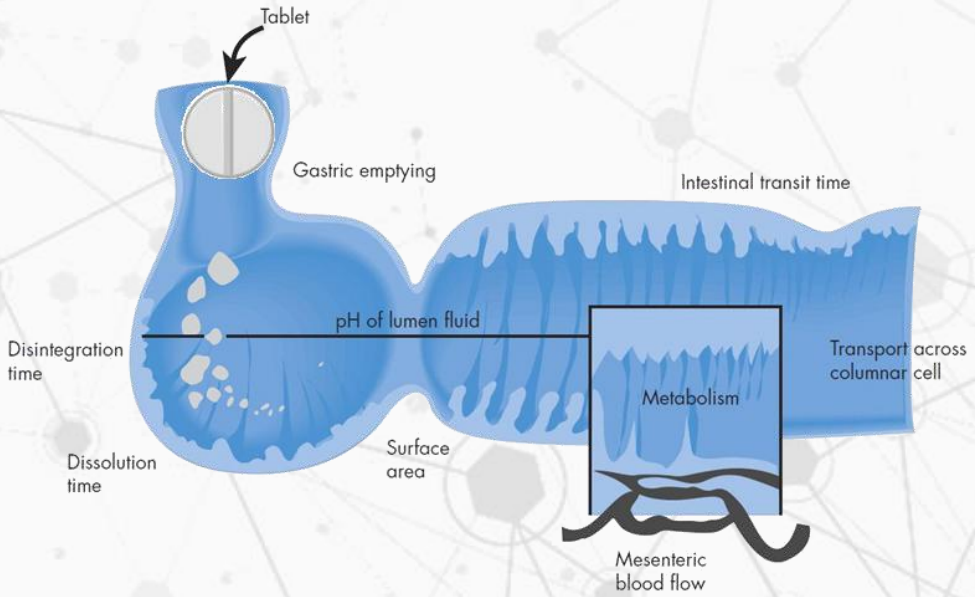
HSDER

Gastroretention Technology
Glucophage SR (MERCK SERONO) – Glumetza (DEPOMED)





High swelling dosage forms



HSDER

Comparison of Cost between Immediate and Extended Release Formulation

Metformin (Non-proprietary) PoM

Tablets, coated, metformin hydrochloride 500 mg, net price 28-tab pack = 93p, 84-tab pack = £1.37; 850 mg, 56-tab pack = £1.34. Label: 21

Oral solution, sugar-free, metformin hydrochloride 500 mg/5 mL, net price 100 mL = £62.06. Label: 21

Brands include *Metsol®*

Glucophage® SR (Merck) PoM

Tablets, m/r, metformin hydrochloride 500 mg, net price 28-tab pack = £3.07, 56-tab pack = £6.14; 750 mg, 28-tab pack = £3.20, 56-tab pack = £6.40; 1 g, 28-tab pack = £4.26, 56-tab pack = £8.52. Label: 21, 25

Dose initially 500 mg once daily, increased every 10–15 days, max. 2 g once daily with evening meal; if control not achieved, use 1 g twice daily with meals, and if control still not achieved change to standard-release tablets

Note Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of *Glucophage® SR*; not suitable if dose of standard-release tablets more than 2 g daily

The *Scottish Medicines Consortium* (p. 3) has advised (December 2005) that *Glucophage® SR* is not recommended for the treatment of type 2 diabetes

HSDER

In Canada

Glumetza® was excluded from the Non-Insured Health Benefits (NIHB) Program as recommended by the Common Drug Review (CDR) and the Federal Pharmacy and Therapeutics Committee, because

1

«… published evidence does not support the clinical value or cost of the drug relative to existing therapies…»

2

«In a phase III trial, the occurrence of GI adverse events was comparable between all treatment groups (immediate vs. extended-release form), but all GLUMETZA treatment groups reported fewer occurrences of diarrhea and nausea in comparison to immediate release»

HSDER

After studies conducted by Matripharm for GRDF system, no evident improvement of metformin side effects could be probably due to:

Retention time of tablet in the stomach is too long

Metformin release occurs locally and continually in the stomach (saturated absorption)

High dose of drug required to achieve beneficial effects

Incomplete release due to the interactions of Metformin with Matrix (croscarmellose sodium)

Impairment of the digestive system

HSDER

The new system HSDER releases Metformin in the whole gastrointestinal system including:

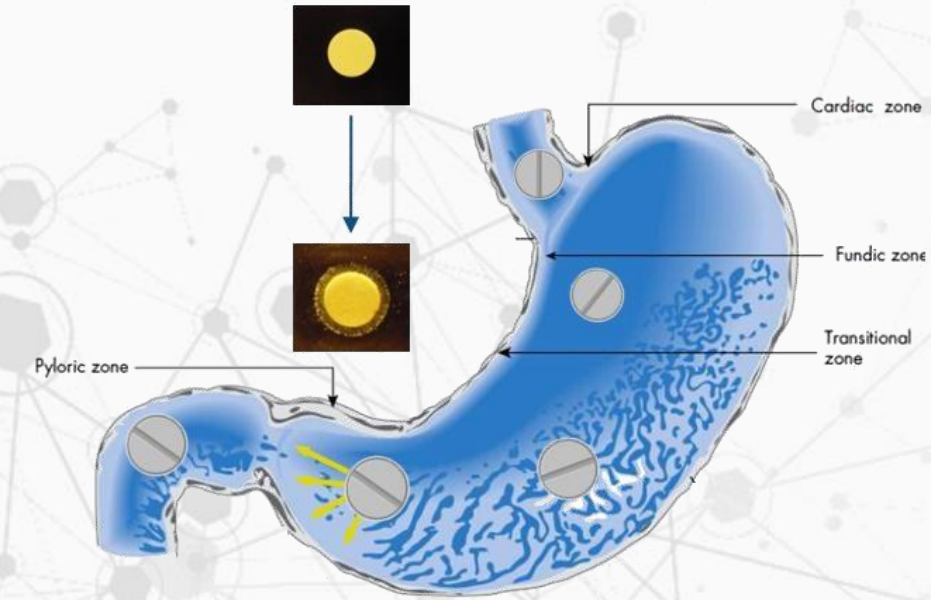
in the stomach

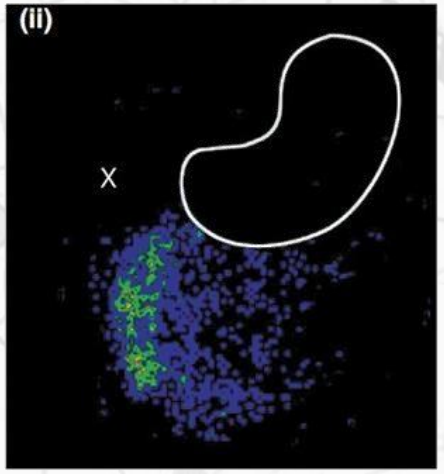
in upper intestine

including the colon
and others

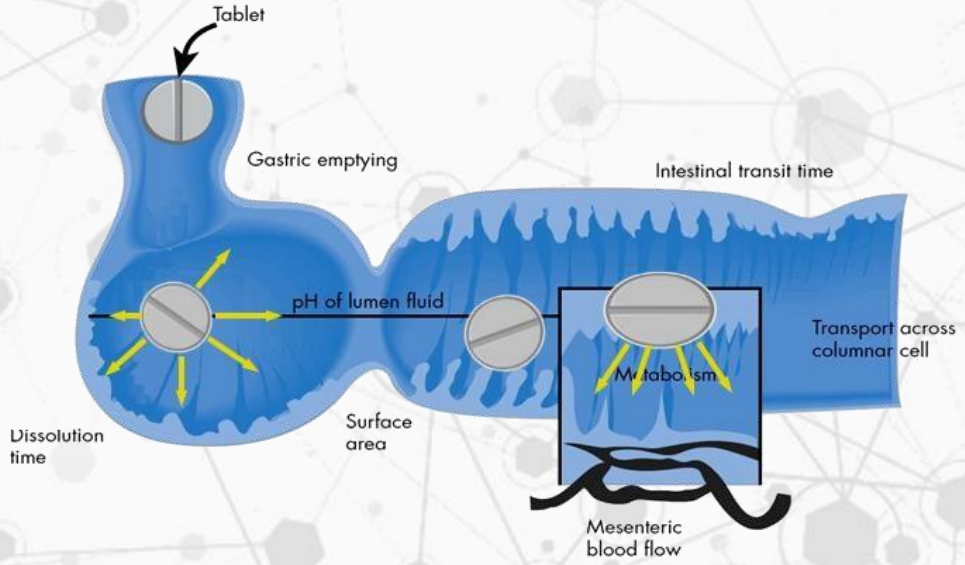
HSDER

MATRIPHARM Technology



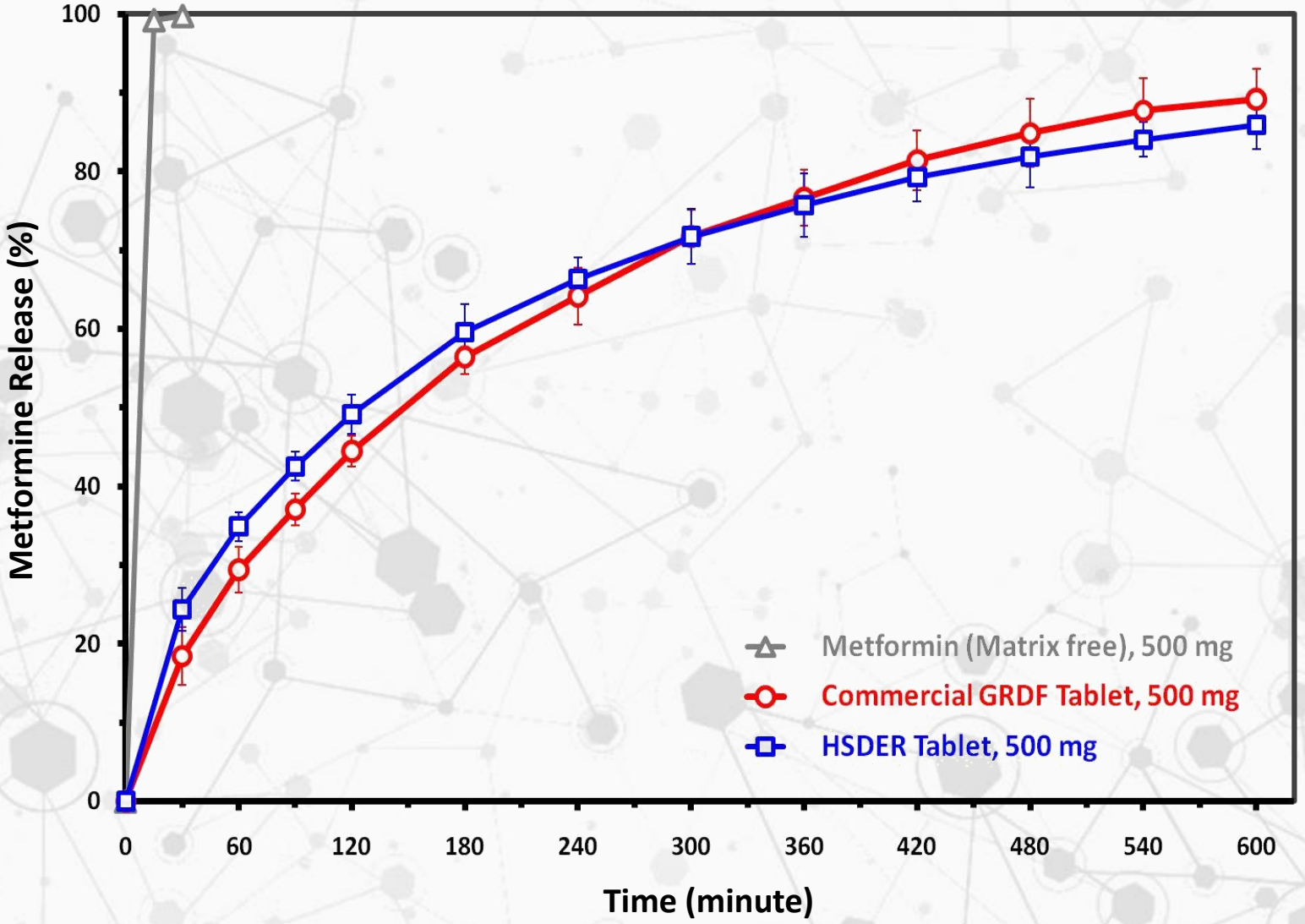


Low swelling dosage forms



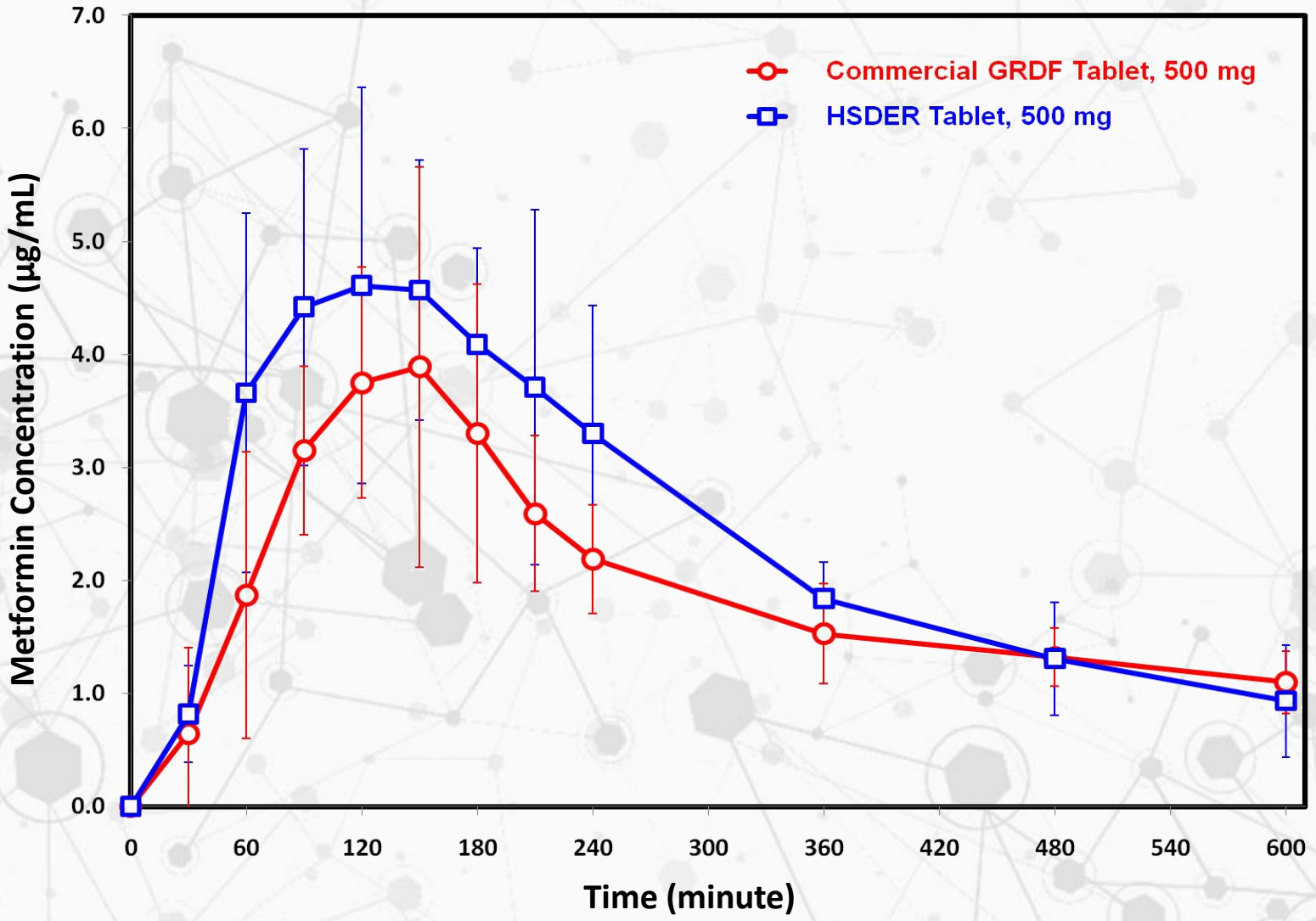
HSDER

In vitro Dissolution Assay



HSDER

In vivo Study (Beagle Dogs)



HSDER

In vivo Study (Beagle Dogs)

Metformin Hydrochloride Biphasic Tablet

Manufacturing Directions

1. 25 g of ethylcellulose N10 NF is dissolved/dispersed in 100 mL of 95% ethanol.
2. This dispersion is gradually added to 500 g of metformin hydrochloride in a planetary mixer to produce a uniform damp granulation.
3. The granulation is dried at 55°C for 1 hour and passed through a 0.8 mm aperture screen to break down agglomerates.
4. The metformin–ethylcellulose granules (541 g) are blended with 351.5 g of hydroxypropyl methylcellulose 2208 USP (100,000 cps grade), 10 g of hydroxypropyl methylcellulose 2910 USP (5 cps grade), and 100.5 g of microcrystalline cellulose in a planetary mixer for 10 minutes.
5. Finally this mix is lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500 mg of metformin hydrochloride.

Matripharm Formulation
Metformin Hydrochloride Extended Release Monolithic Tablet (500 mg)

Manufacturing Directions
Metformin-HCl (500 mg) are blended with Matripharm Excipient (330 mg) and compressed into capsule shaped tablet

HSDER

Metformin Biphasic Tablet (Commercial Formulations)	Metformin Monolithic Tablet (Matripharm Technology)
High cost to manufacture	**Low** cost to manufacture
Preparation implied **several** steps	Preparation in **one** step
Special equipment required	**No** require special equipment
Requiring the use of solvent (alcohol)	**No** solvent required
Low loading tablet (max. 50 %)	**High** loading tablet (max 60 %)
No versatile excipient	Versatile excipient
Requires a **new formulation** process for each drug	**Compatible** with a large range of drugs

Two-Rate Release or «2RR» Monolithic Excipient Technology

useful for drugs with short half-life
Non-steroidal anti-inflammatory drugs NSAID

(Applicable Example Ibuprofen 2RR)

Matripharm International INC

2RR

Motrin®

Ibuprofen Tablets, USP

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).
- MOTRIN tablets are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

2RR

In order to reduce side effect, it is desirable to reduce the dose…

Two Rate Release (2RR) system is conceived to release API such as to provide:

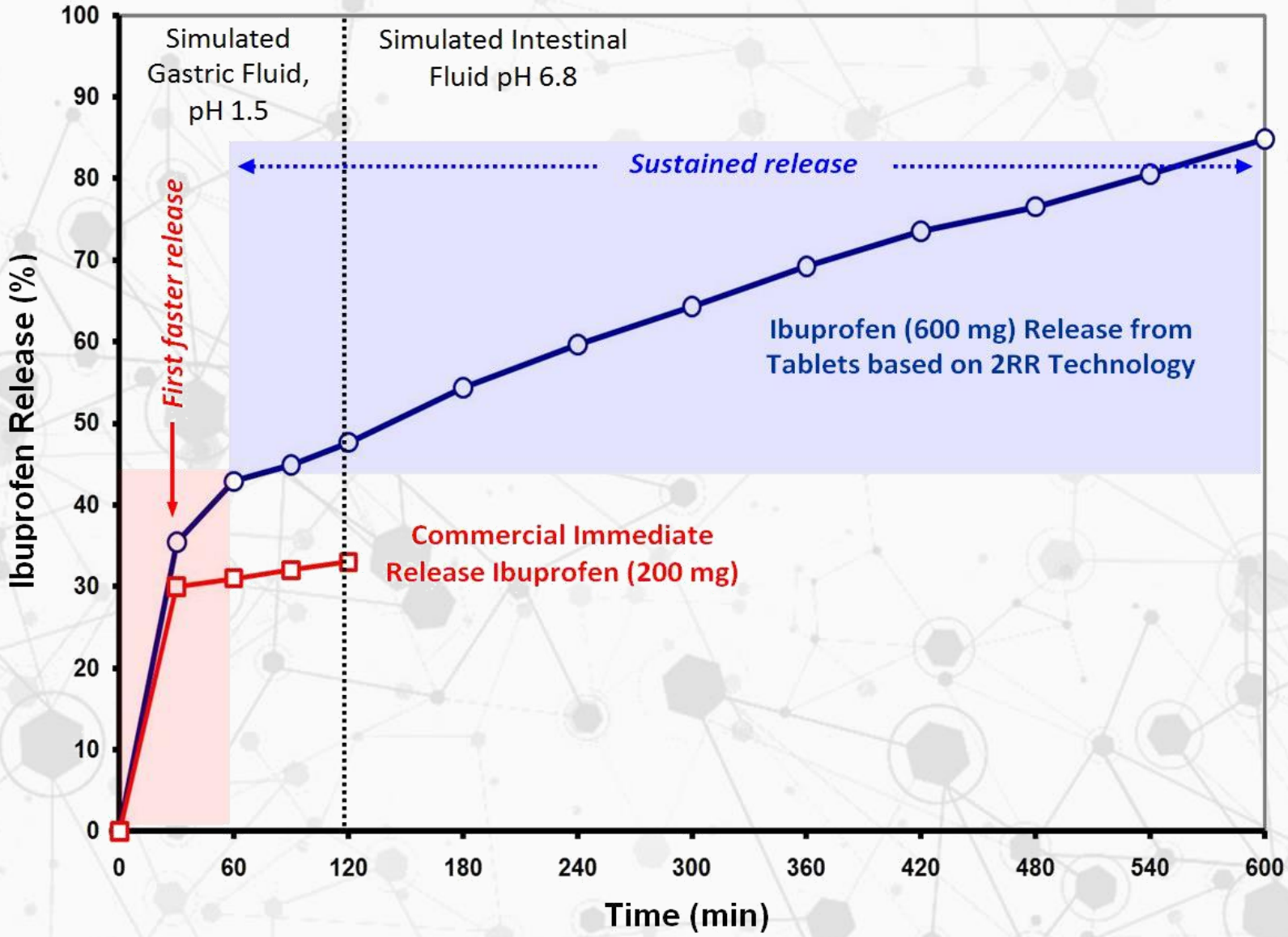
First, a rapid therapeutic effect (an initial dose effective required for immediately pain relief)

Followed by a sustained release (maintain the effective concentration in therapeutic window for a longer period of time)

- useful for subjects (e.g. Alzheimer) unable to follow frequent administrations
- Useful for Anti-imflamatories

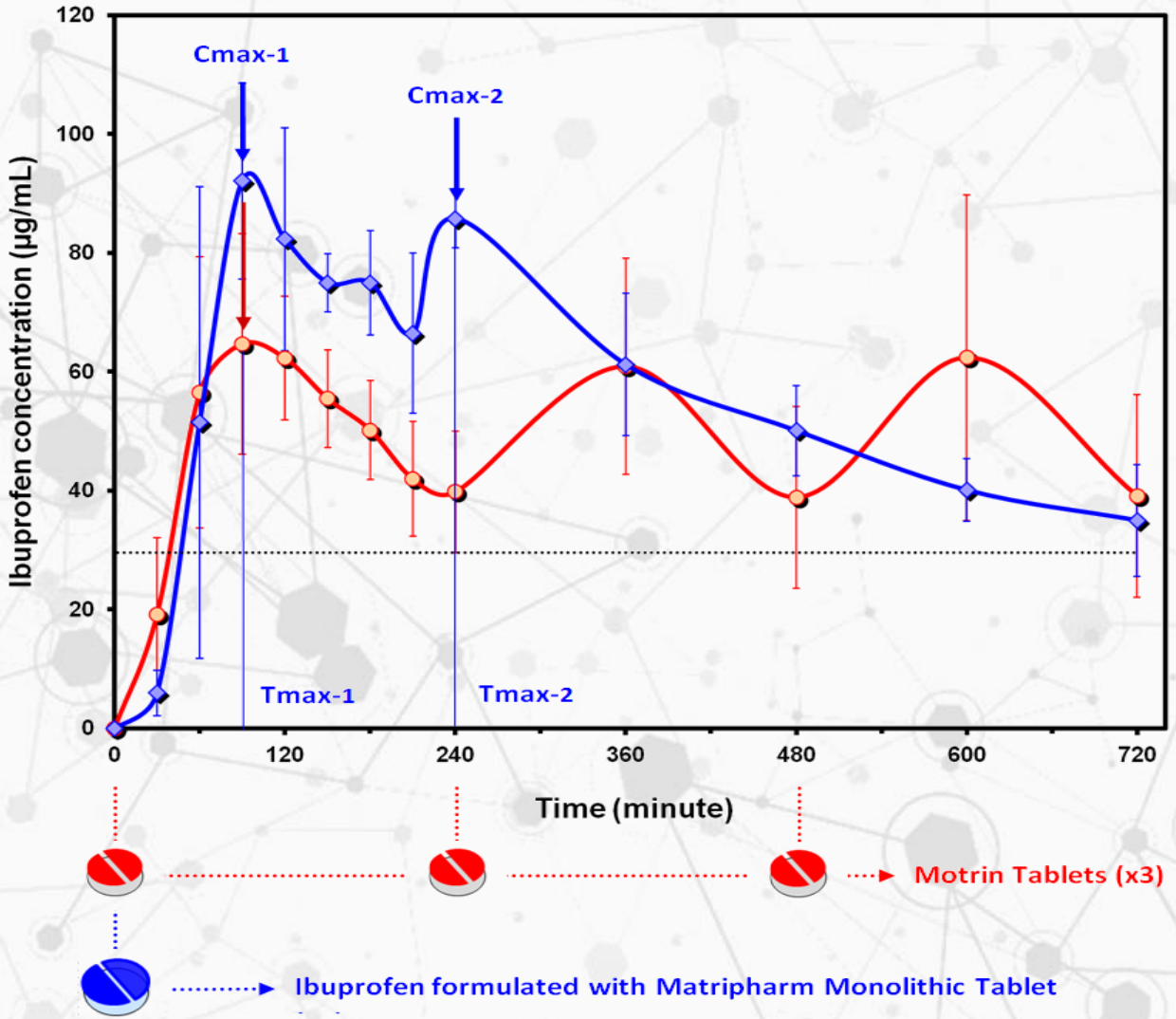
2RR

In vitro Dissolution Assay



2RR

In vivo Study (Beagle Dogs)



2RR

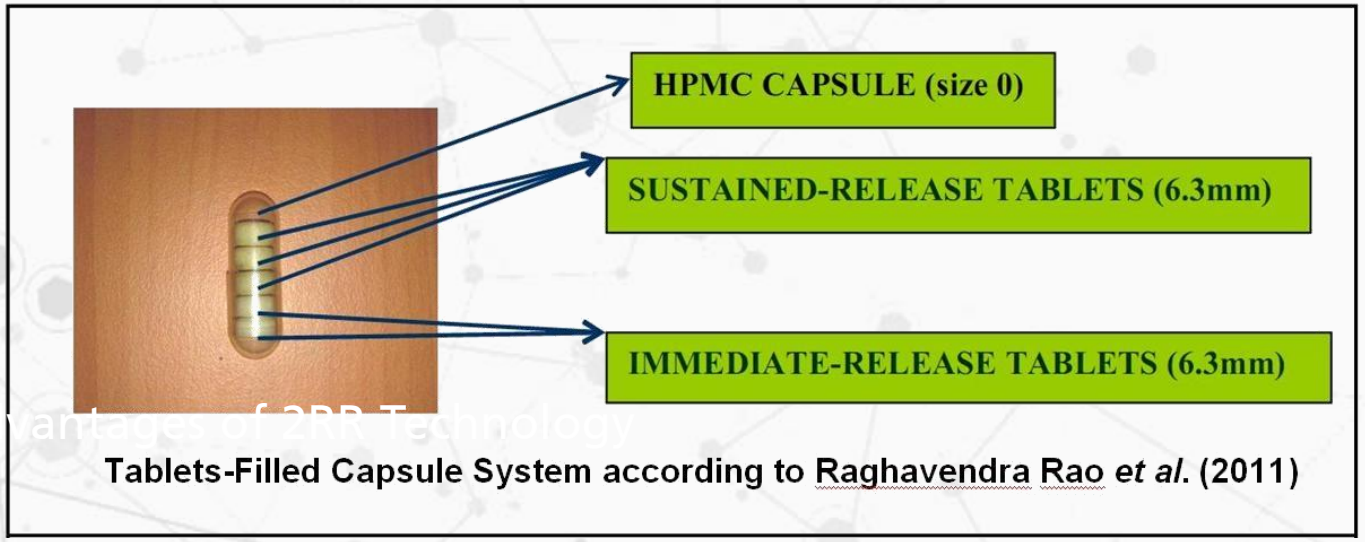
Ibuprofen Pharmacokinetic Parameters in Dogs from 2RR Monolithic Tablets vs Conventional Form Motrin®

	Ibuprofen Monolithic Tablet formulated with 2RR Technology	Conventional Dosage Form
Test or Control Articles	2RR-400	Motrin®
Dose (mg)	400	200
Number of Dose	1 (x 400 mg)	3 (x 200 mg) (*every 4 h, at t_0, t_4 & t_8*)
Route of Administration	Oral	Oral
Cmax-1 (µg/mL) Immediate Release	92	65
Cmax-2 (µg/mL) Sustained Release	86	-
Tmax-1 (h) Immediate Release	1.5	1.5
Tmax-2 (h) Sustained Release	4.0	-
AUC_{0-24h} (µg.h/mL)	981	899
$T_{1/2}$ (h)	9.9	4.8

Cmax = maximal concentration; Tmax = time at maximal concentration; AUC_{0-24} = area under the concentration-time curve from time zero to 24 h; $T_{1/2}$ = elimination half-life.

Comparison of Dosage Forms

Matripharm Monolithic Tablet

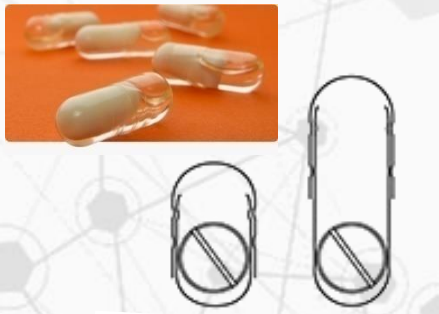


Advantages of 2RR Technology

Tablets-Filled Capsule System according to Raghavendra Rao *et al.* (2011)

Biphasic Tablets

Biphasic Tablets



Over-encapsulation

2RR

Advantages of 2RR Technology

Reduced frequency of administration;

Diminished common side effects caused by NSAIDs;

Increased compliance for patients requiring long-term NSAID therapy

Moreover

- Monolithic tablet easy to manufacture by direct compaction;
- High loading of APIs;
- Compatible with a large rang of APIs;
- Raw material «generally recognized as safe» (GRAS)

2RR

"Commercial brand names and photos are for reference only"

Dual-Rate Release (DRR)

Technology MI-755

Matripharm International INC

DRR

Dual-Rate Release (DRR) Technology MI-755

The DRR matrix present the same 2RR kinetic profile, but used for a combination of APIs (e.g. Caffeine + acetaminophen)

This matrix (composed polysaccharide complexed with amphionic molecules) is mildly disintegrated in gastric fluid, but stable in intestinal fluid

required lower excipient (active principle/excipient 80:20);

Easy and simple to manufacture: no heating and no spray-drying;

No required disintegrating agents in the formulation

useful for Combination of different APIs

DRR

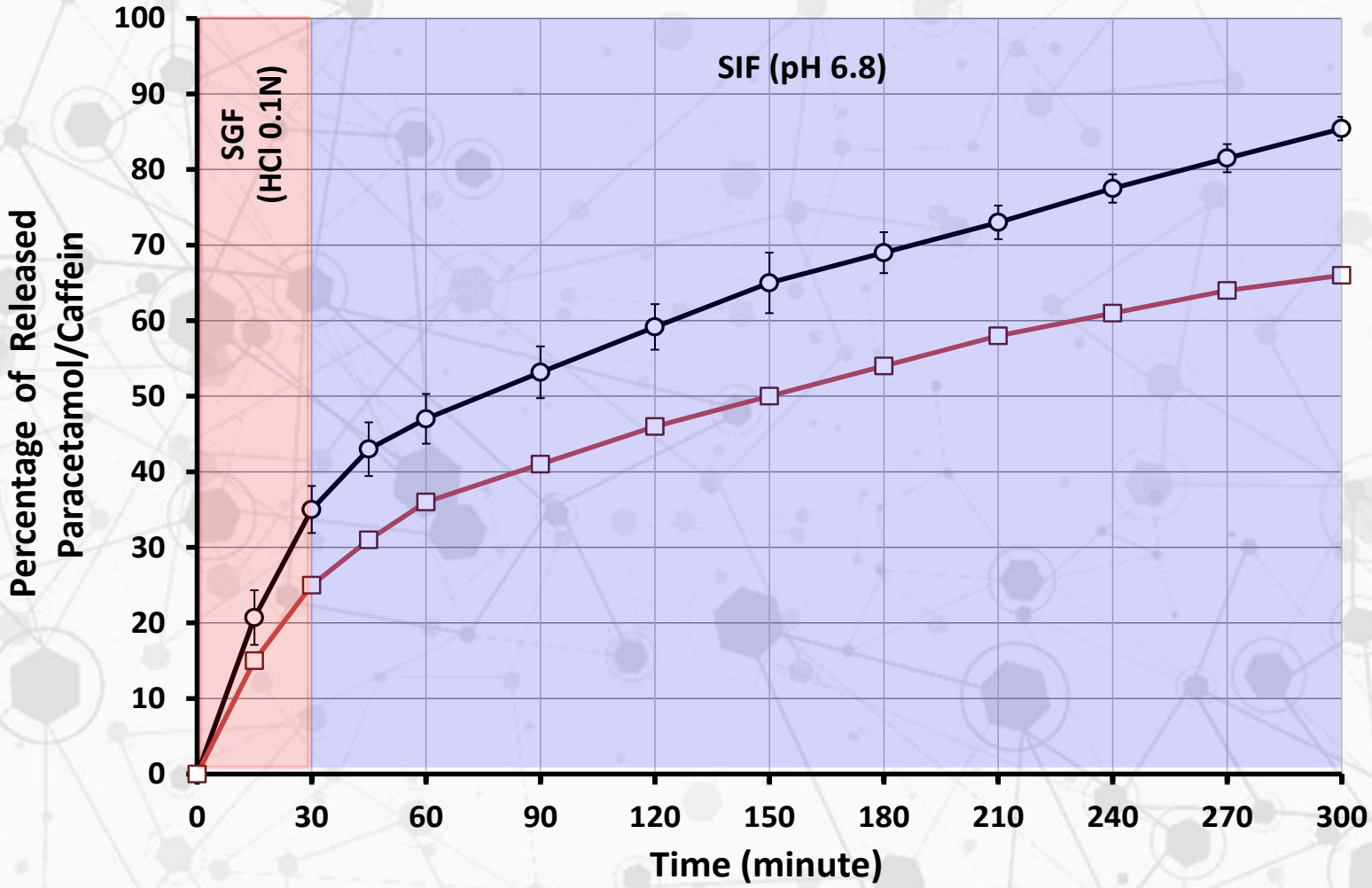
Dual-Rate Release (DRR) Technology MI-755

Ingredient	Quantity (mg)	Percentage (%)
Paracetamol	**900**	**68.2**
Caffeine	**160**	**12.1**
Carboxymethyl-Starch	**130**	**9.8**
Carboxymethylcellulose/Arginine-Cacium	**30**	**2.3**
Hydroxypropyl methylcellulose (E5)	**60**	**4.6**
Arginine	**20**	**1.5**
Magnesium Stearate	**20**	**1.5**
Total	**1320**	**100.0**

Ratio Paracetamol/Excipient 80:20

DRR

Release Kinetic Profile of Paracetamol/Caffeine in Simulated Gastric (SGF) and Intestinal (SIF) Fluids



Contact Us

nael@matripharm.com

shafik@matripharm.com

max@matripharm.com

2550 boul Daniel Johnson, bureau 220 Laval (Québec) Canada H7T 2L1

Matripharm International Inc.