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.

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%.

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.
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 bioavailability.
- 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 Intellectual Property Portfolio
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.
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
- Simple to manufacture;
- Unparalleled performance and safety;

- Broad portfolio of applications for almost common dosage forms;
- Easy to formulate with any drugs under oil, liquid or solid forms;
- Simple to formulate for immediate or controlled delivery;

- Stable and resistant in gastric acidity;
- Able to protect against oxidation and light for sensible APIs;
- Possible to open ways to enable intravenous and intramuscular administrations for certain APIs, etc.
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.

How our technologies can be immediately applied to existing products?
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)
- Sodium Cromoglycate
- Hydrocodone Bitartrate/ Phenylephrine HCl
- Nilutamide
- Dolasetron Mesylate
- Irbesartan
- Leflunomide
- Meperidine hydrochloride
- Metformin hydrochloride
- Fludarabine phosphate
- Zopiclone
- Furosemide
- Dronedarone
- Clopidogrel (possible combined with or without ASA)
- Sevelamer hydrochloride, Acebutolol hydrochloride
Highly Soluble Drug Extended Release (HSDER) Technology

(Applicable Example: Metformin Extended Release)
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).
Gastroretention Technology
Glucophage SR (MERCK SERONO) – Glumetza (DEPOMED)

High swelling dosage forms
Comparison of Cost between Immediate and Extended Release Formulation

**Metformin** (Non-proprietary) [PoM]

Tablets, coated, metformin hydrochloride 500 mg, net price 28-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 Metso®

**Glucophage® SR** (Merck) [PoM]

Tablets, m/r, metformin hydrochloride 500 mg, net price 28-tab pack = £1.20, 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
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

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

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

- in the stomach
- in upper intestine
- including the colon and others
MATRIPHARM Technology

Low swelling dosage forms
In vitro Dissolution Assay

Metformine Release (%)

Time (minute)
In vivo Study (Beagle Dogs)

Metformin Concentration (μg/mL) vs. Time (minute)

- Commercial GRDF Tablet, 500 mg
- HSDER Tablet, 500 mg
In vivo Study (Beagle Dogs)

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.
<table>
<thead>
<tr>
<th>Metformin Biphasic Tablet (Commercial Formulations)</th>
<th>Metformin Monolithic Tablet (Matripharm Technology)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong> cost to manufacture</td>
<td><strong>Low</strong> cost to manufacture</td>
</tr>
<tr>
<td>Preparation implied <strong>several</strong> steps</td>
<td>Preparation in <strong>one</strong> step</td>
</tr>
<tr>
<td>Special equipment required</td>
<td><strong>No</strong> require special equipment</td>
</tr>
<tr>
<td>Requiring the use of solvent (alcohol)</td>
<td><strong>No</strong> solvent required</td>
</tr>
<tr>
<td><strong>Low</strong> loading tablet (max. 50 %)</td>
<td><strong>High</strong> loading tablet (max 60 %)</td>
</tr>
<tr>
<td><strong>No</strong> versatile excipient</td>
<td>Versatile excipient</td>
</tr>
<tr>
<td>Requires a <strong>new formulation</strong> process for each drug</td>
<td><strong>Compatible</strong> with a large range of drugs</td>
</tr>
</tbody>
</table>
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)
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 perioperative 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).
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
In vitro Dissolution Assay

Simulated Gastric Fluid, pH 1.5
Simulated Intestinal Fluid pH 6.8

Sustained release
Ibuprofen (600 mg) Release from Tablets based on 2RR Technology

First faster release
Commercial Immediate Release Ibuprofen (200 mg)
In vivo Study (Beagle Dogs)

![Graph showing ibuprofen concentration over time for the study on beagle dogs. The graph includes points for Cmax-1, Cmax-2, Tmax-1, and Tmax-2, along with markers for ibuprofen formulated with Matripharm Monolithic Tablet and Motrin Tablets (x3).]
**Ibuprofen Pharmacokinetic Parameters in Dogs from 2RR Monolithic Tablets vs Conventional Form Motrin®**

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen Monolithic Tablet formulated with 2RR Technology</th>
<th>Conventional Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test or Control Articles</td>
<td>2RR-400</td>
<td>Motrin®</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>Number of Dose</td>
<td>1 (x 400 mg)</td>
<td>3 (x 200 mg) (every 4 h, at t0, t4 &amp; t8)</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Cmax-1 (µg/mL) Immediate Release</td>
<td>92</td>
<td>65</td>
</tr>
<tr>
<td>Cmax-2 (µg/mL) Sustained Release</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>Tmax-1 (h) Immediate Release</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Tmax-2 (h) Sustained Release</td>
<td>4.0</td>
<td>-</td>
</tr>
<tr>
<td>AUC0–24h (µg.h/mL)</td>
<td>981</td>
<td>899</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>9.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Cmax = maximal concentration; Tmax = time at maximal concentration; AUC0–24h = area under the concentration-time curve from time zero to 24 h; T1/2 = elimination half-life.
Comparison of Dosage Forms

Matripharm Monolithic Tablet

Biphasic Tablets

Biphasic Tablets

Over-encapsulation

Advantages of 2RR Technology

Tablets-Filled Capsule System according to Raghavendra Rao et al. (2011)
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 range of APIs;
- Raw material «generally recognized as safe» (GRAS)
“Commercial brand names and photos are for reference only”
Dual-Rate Release (DRR)

Technology MI-755
**Dual-Rate Release (DRR)**

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

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**Technology MI-755**

- 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

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useful for Combination of different APIs

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<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>900</td>
<td>68.2</td>
</tr>
<tr>
<td>Caffeine</td>
<td>160</td>
<td>12.1</td>
</tr>
<tr>
<td>Carboxymethyl-Starch</td>
<td>130</td>
<td>9.8</td>
</tr>
<tr>
<td>Carboxymethylcellulose/Arginine-Cacium</td>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (E5)</td>
<td>60</td>
<td>4.6</td>
</tr>
<tr>
<td>Arginine</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1320</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

**Ratio Paracetamol/Excipient**: 80:20
Release Kinetic Profile of Paracetamol/Caffeine in Simulated Gastric (SGF) and Intestinal (SIF) Fluids

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