CHEMIUM
EFFICIENT CHEMISTRY

Mg *Flow* ®

WHITEPAPER

SOLVING BATCH-MODE SPECIFIC CHALLENGES WHILE PRODUCING **BEST QUALITY GRIGNARD REAGENTS**

ABSTRACT

CHEMIUM's **Mg*Flow*** Technology is the next evolution step in industrial scale Grignard reagents production. **Mg*Flow*** not only solves the serious process safety issues associated to batch-mode Grignard reagents production, but also enables faster kinetics and much tighter control of reaction conditions, hence resulting in better and constant product quality.

INTRODUCTION

Grignard reagents, originally reported in the early 20th century, have become one of the most useful tools for creating carbon-carbon bonds in the chemical industry. They find application in pharma, agrochemicals, perfumes, electronics, materials science, energy storage, …

Simultaneously, organomagnesium reagents remain a very active area in research. Yet, their synthesis mode hasn't evolved much and most of large-scale Grignard production campaigns are carried out in batch mode. As a result, the chemical industry faces significant safety and quality issues when it comes to producing Grignard reagents.

CHEMIUM has designed the **Mg*Flow*** Technology in order to by-pass these obstacles, making safe and efficient Grignard production accessible to any chemical industry. As its name suggests, **Mg*Flow*** relies on Flow Chemistry principles to tackle most of Grignard related challenges.

SETUP DESCRIPTION

Mg*Flow* units are basically composed of a reactor column that is continuously fed with magnesium, organohalide and a solvent under inert atmosphere. The product is continuously withdrawn from the unit and directed to the next step's reactor or optionally to a storage container (Figure 1).

The process is continuously monitored by several probes that collect temperature, pressure, flow rates data and others. A Process Analytical Tool (PAT) is additionally used to closely examine chemical information and the instantaneous products quality as the Grignard solution exits the **Mg*Flow*** unit. These data support the exceptional stability of the **Mg*Flow*** process and are valuable tools to prevent any safety issue or out-of-specification production (See Stable process parameters section).

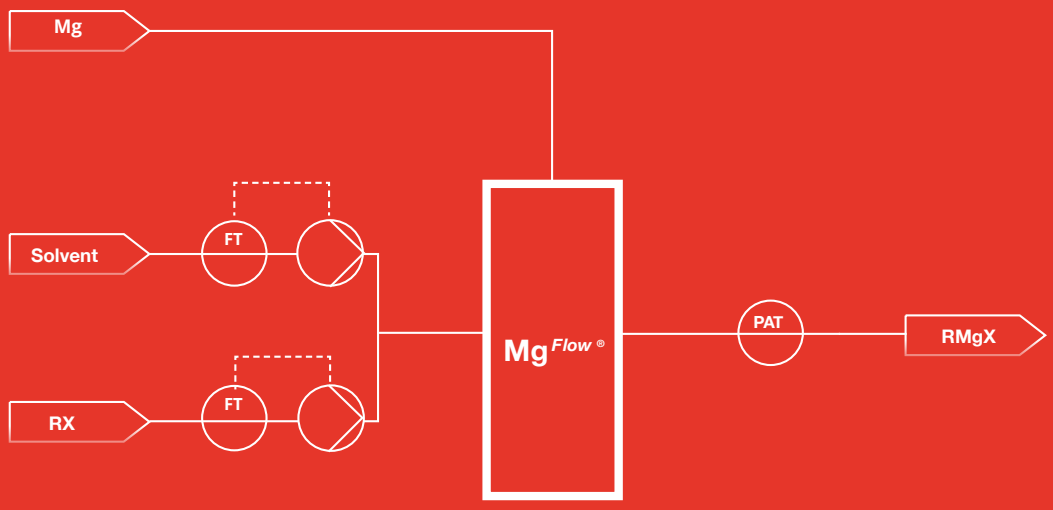

Figure 1 Schematic view of the **Mg*Flow*** *Technology.*

IMPROVED KINETICS

The synthesis of Grignard reagents is well known for more than a century. Many methodologies have been discovered to access these compounds. Yet, the main method remains the reaction between metallic magnesium and an organic halide in an ethereal solvent. This reaction yields the desired compound in high yields along with variable amounts of the Wurtz by-product (Figure 2).

In traditional Grignard production, limited by safety and economical reasons, the stoichiometry between the magnesium and organohalide is typically set around a 1:1 ratio. As a result, the formation rate of the target Grignard compound often competes with the Wurtz by-product, the latter being sometimes formed in significant quantities.

Where
R= organic side chain
X= halogen

Figure 2 Formation of Grignard reagent and Wurtz by-product from magnesium and organic halides in ethereal solvents.

Most often, Grignard kinetic equations show a first order behaviour of the magnesium (Equation 1). As a result, the more magnesium engaged in the reaction, the fastest the Grignard reagent formation, in turn leading to a drastically decreased or even suppressed Wurtz by-product formation.

$$\text{Rate} = k\,[Mg]^{1}[RX]^{n}$$

Equation 1 Kinetic equation of Grignard reagent's formation rate.

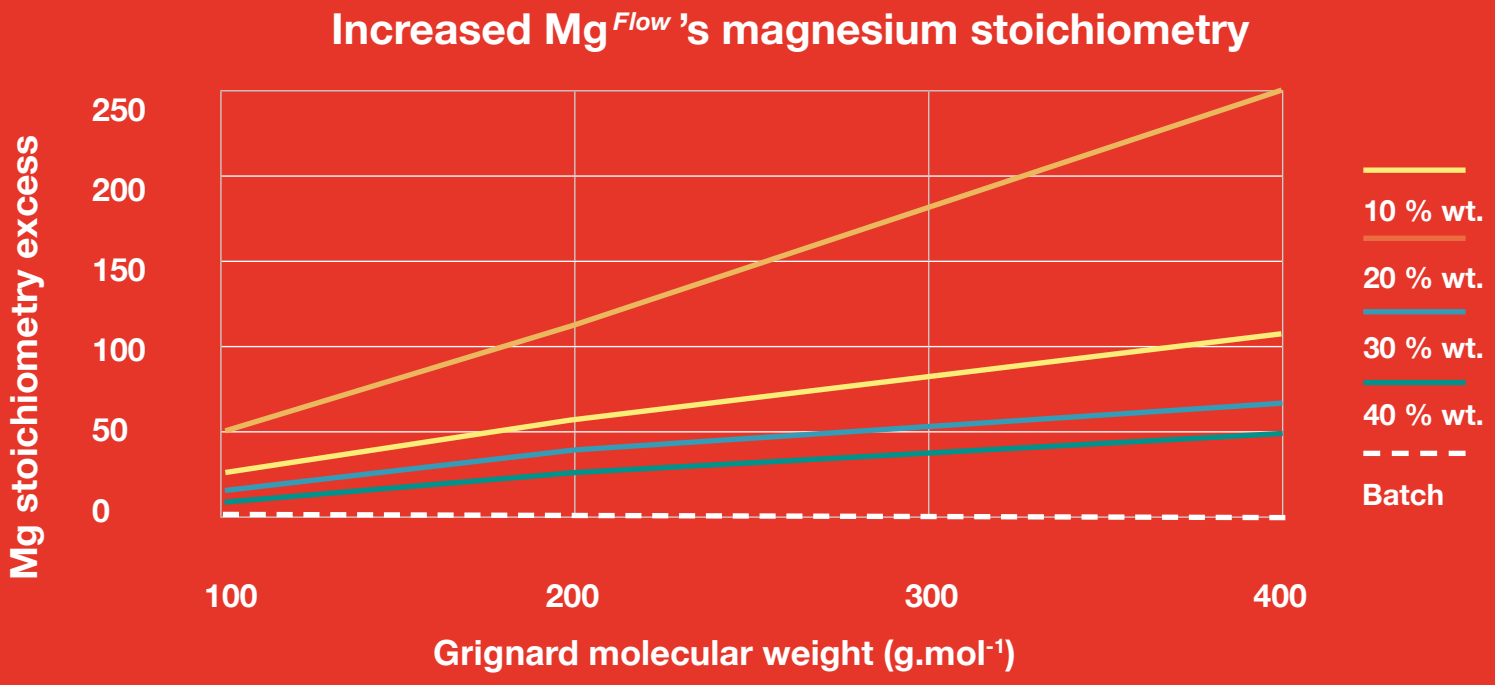

Figure 3 Increased magnesium stoichiometric excess in **Mg** *Flow compared to typical batch processes.*

The **Mg** *Flow* design strives to this goal as the reactor is constantly filled with a high excess of magnesium (Figure 3).

As can be read from the above graph (Figure 3), any common Grignard reagent will benefit from increased conversion kinetics resulting from the large excess of magnesium when produced using **Mg** *Flow*.

Even low molecular weight targets will experience at least 14-fold rate increase at high concentrations, *i.e.* 40 % wt., compared to batch processes.

These benefits are presented below in terms of their impact on the Wurtz by-product formation (Table 1). On average, the by-product formation is

Project	Wurtz content (% wt.)	
	Batch	Mg *Flow*
Aliphatic proprietary Grignard compound	5	<1
n-Butylmagnesium chloride	0.07	0.01 - 0.02
Cyclohexylmagnesium chloride	0.14	0.03

Table 1 Suppression of Wurtz by-product formation in **Mg** *Flow production units.*

divided by 5 when using **Mg**^{Flow} production units. This improved impurity profile facilitates subsequent step's purification.

Furthermore, the use of magnesium excesses is not accompanied with economical losses anymore since excess magnesium will react with organohalide streams to come, or will be used in next production campaigns after thorough cleaning. More importantly, the safety concern of using massive excesses of magnesium does not exist under **Mg**^{Flow} conditions thanks to the efficient heat removal capacities and small instantaneous reaction volumes of the developed technology.

STABLE PROCESS PARAMETERS

Mg^{Flow} production units are designed to deliver Grignard solutions at constant quality. Unlike batch processes, **Mg**^{Flow} allows easy and efficient temperature control throughout the reaction *via* excellent mixing performances and limited instantaneous reaction volume coupled with optimised internal heat exchange.

The graph hereafter shows a typical temperature profile in an **Mg**^{Flow} production unit delivering 40 kg of Grignard solution per hour (Figure 4).

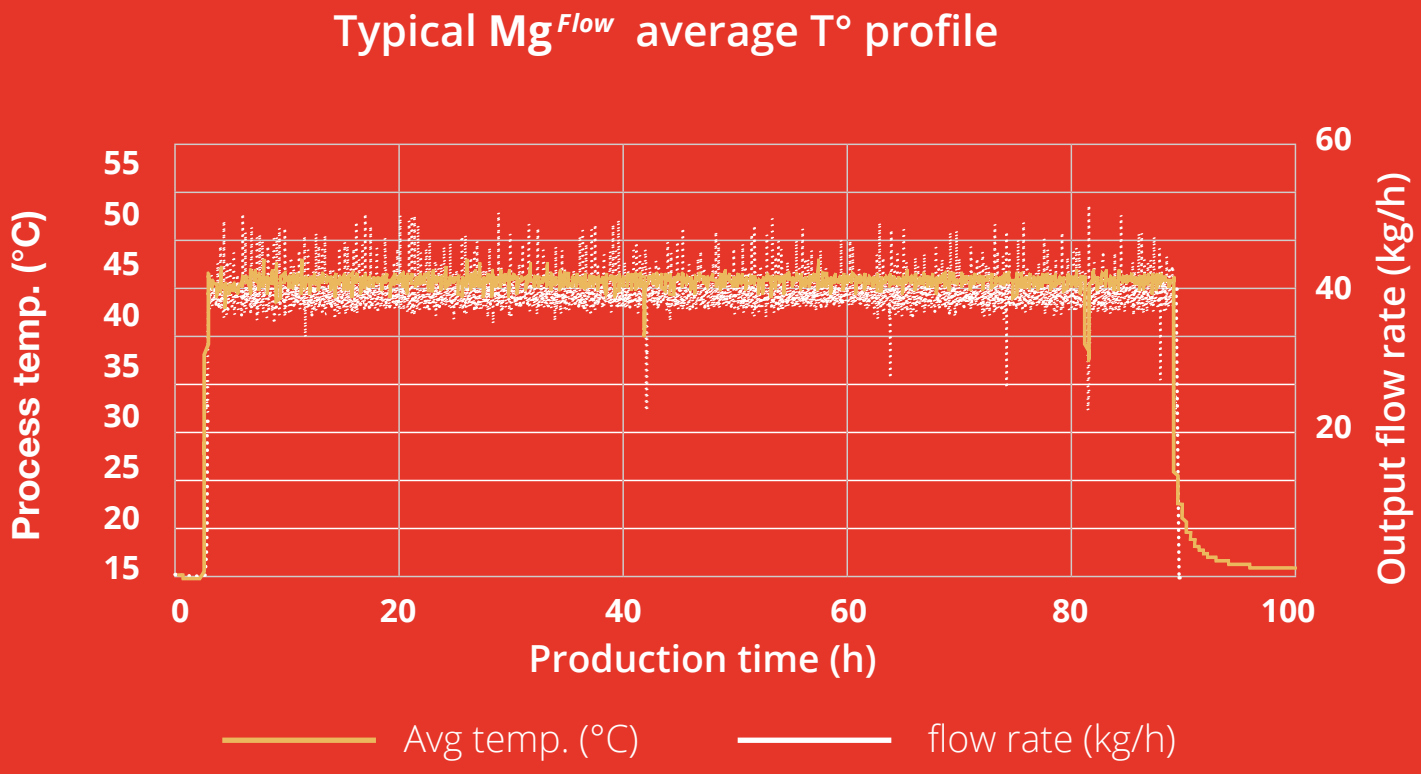

Figure 4 Average **Mg**^{Flow}*'s temperature and flow rate profiles.*

As evidenced by the graph (Figure 4), apart from the production phase's start up (reaction initiation) and its shut down, the reaction temperature remains stable for prolonged productions campaigns. This clearly supports the thermal efficiency of the **Mg*Flow*** design that prevents any unexpected hotspot, erratic temperature profile or even reaction runaway.

Graph hereafter (Figure 5) shows a detailed monitoring of individual temperature probes across the **Mg*Flow*** unit that again demonstrates the stable thermal profile in several reaction zones.

This trend is also reflected in the online analysis curve. Indeed, well controlled process temperatures means optimal and constant product quality. As exhibited by the PAT and density values displayed (Figure 6), the production unit delivered the target Grignard reagent, 24/7 within the specification range with virtually no variation.

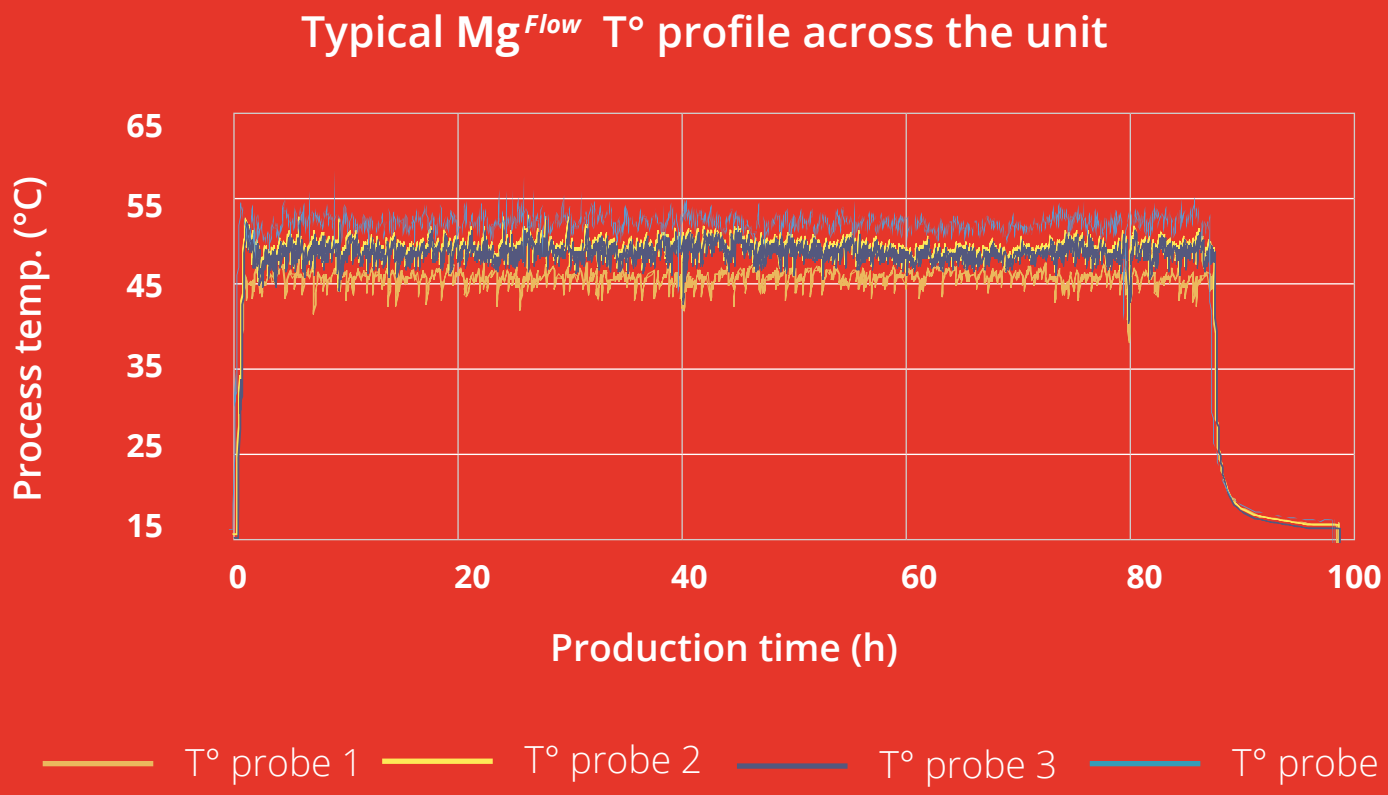

Figure 5 **Mg*Flow***'s temperature profile across the reactor.

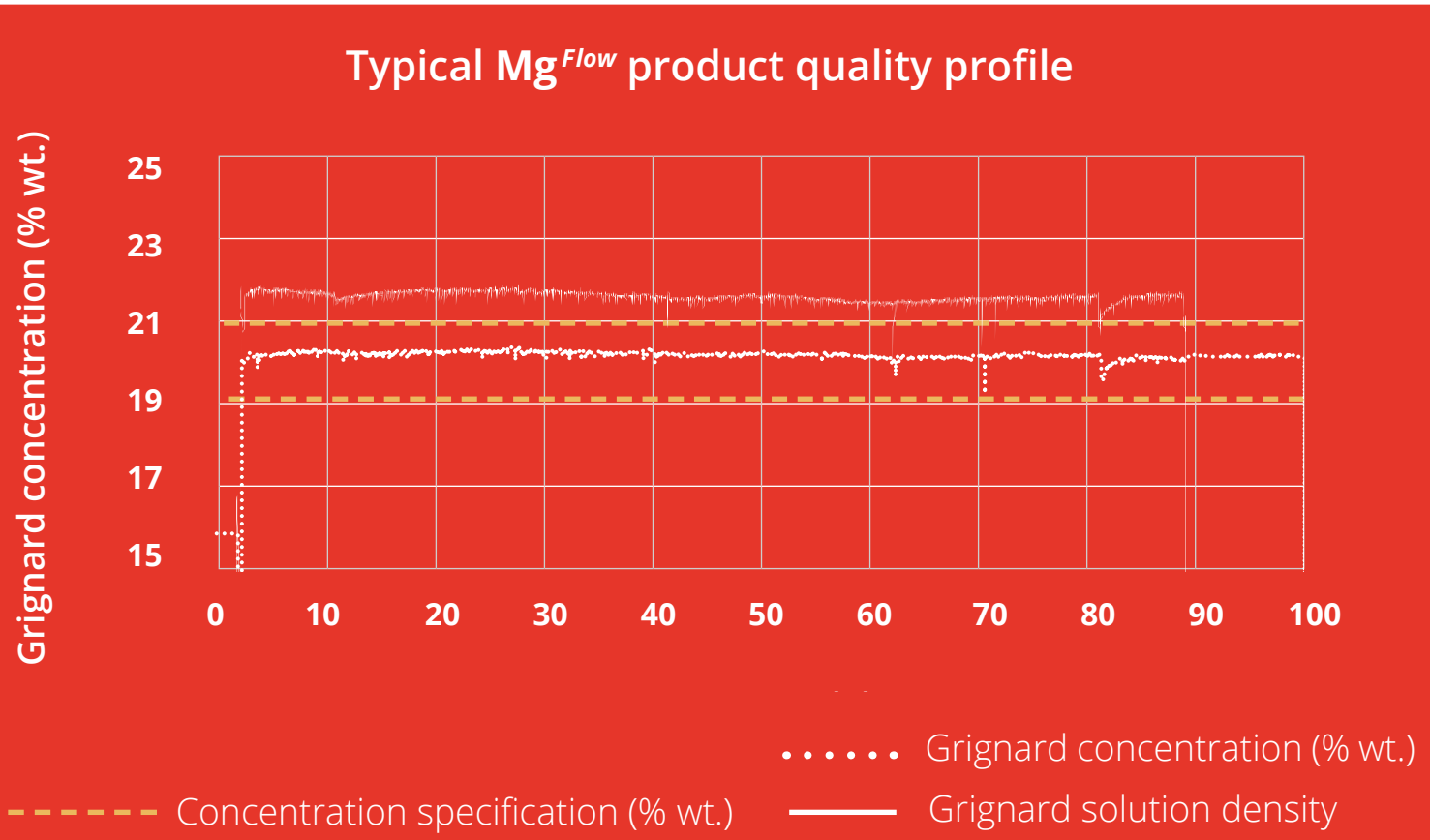

Figure 6 **Mg** ***Flow*** *'s product online quality control via concentration and density monitoring.*

CONCLUSION

Mg ***Flow*** Technology brings significant improvements to industrial scale Grignard manufacturing. Taking advantage of the flow chemistry concepts, excellent temperature control is achieved suppressing process safety and product quality concerns. Moreover, exceptional stoichiometric reagent ratios are systematically applied and result in superior product formation kinetics and strong decrease of by-product formation compared to typical batch processes.

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