



Development of a once-a-month formulation of Semaglutide from an innovative injectable and biodegradable hydrogel

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Abstract

AdoGel® is an injectable hydrogel platform consisting of degradable polymers that allows sustained release of soluble peptides tailored to at least one month. We leveraged this technology to develop a one month-long semaglutide drug product.

AdoGel® Semaglutide formulations were optimized *in vitro* by engineering drug release and hydrogel degradation kinetics.

AdoGel® Semaglutide was evaluated in a rat model, following subcutaneous injection either as an *in situ* forming gel (ISFG) or microgel suspension. The pharmacokinetic profile showed limited burst and flat release profile for both approaches. The product is well tolerated with no local reaction during the study period.

AdoGel® Semaglutide can be presented either in a dual-chamber (*in situ* forming gel approach) or in a ready to use device (microgel suspension).

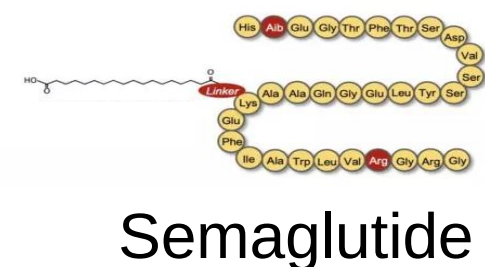
The results showed that a sustained release of semaglutide over one month is achievable and could be a real benefit for people with Type 2 Diabetes and overweight by limiting injection frequencies and reducing side effects.

Introduction & Background

The prevalence of obesity in the general population worldwide is 14% in 2023 and is expected to increase to 24% in 2035. Two billion people are expected to be obese in 2035[1]. The associated impact on health-related complications and quality of life give rise to a large medical and economic burden. Today, medical treatment options comprise bariatric surgery, a highly invasive technique with irreversible secondary effects, that can lead to weight loss of 20 to 30%.

Recent advances based on weekly treatment with incretin hormones, namely semaglutide and tirzepatide, are approved for obesity treatment with or without type 2 diabetes. Weight loss of up to 15 % from baseline have been obtained in clinical trials.

However, a relatively high discontinuation rate has been observed with incretin treatment; 48% at 12 months and 70% at 24 months [2]. A treatment with a once-a-month injection or less could enhance patient adherence and thus improve efficacy.



Semaglutide

Aim

To develop formulations for extended release of semaglutide, compatible with a monthly injection regime. Two approaches have been evaluated based either on *in situ* forming hydrogel (ISFG) or microgel suspension, both are based on biocompatible polymers that degrade by both hydrolysis and enzymatic cleavage. The target product profile for semaglutide is defined as follows:

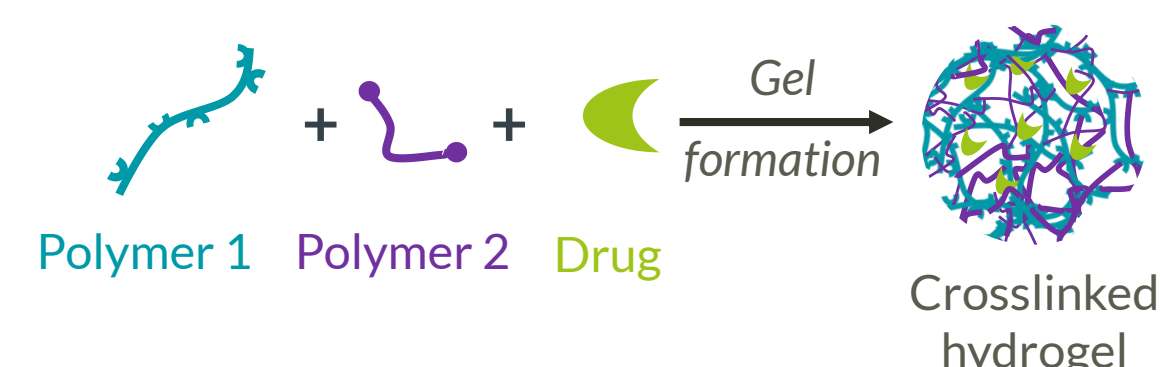
- ✓ Semaglutide loading: at least 8 mg
- ✓ Limited early release
- ✓ Release duration of at least one month
- ✓ Injectable with 25G needle or thinner

[1] World Obesity Atlas 2023

[2] Weiss T et al. Real-World Adherence and Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists Therapy in Type 2 Diabetes Mellitus Patients in the United States. Patient Prefer Adherence. 2020 Nov 27;14:2337-2345.

AdoGel® platform

Figure 1 Hydrogel preparation



AdoGel® Sema product presentations

Figure 2 In Situ Forming Gel (ISFG)

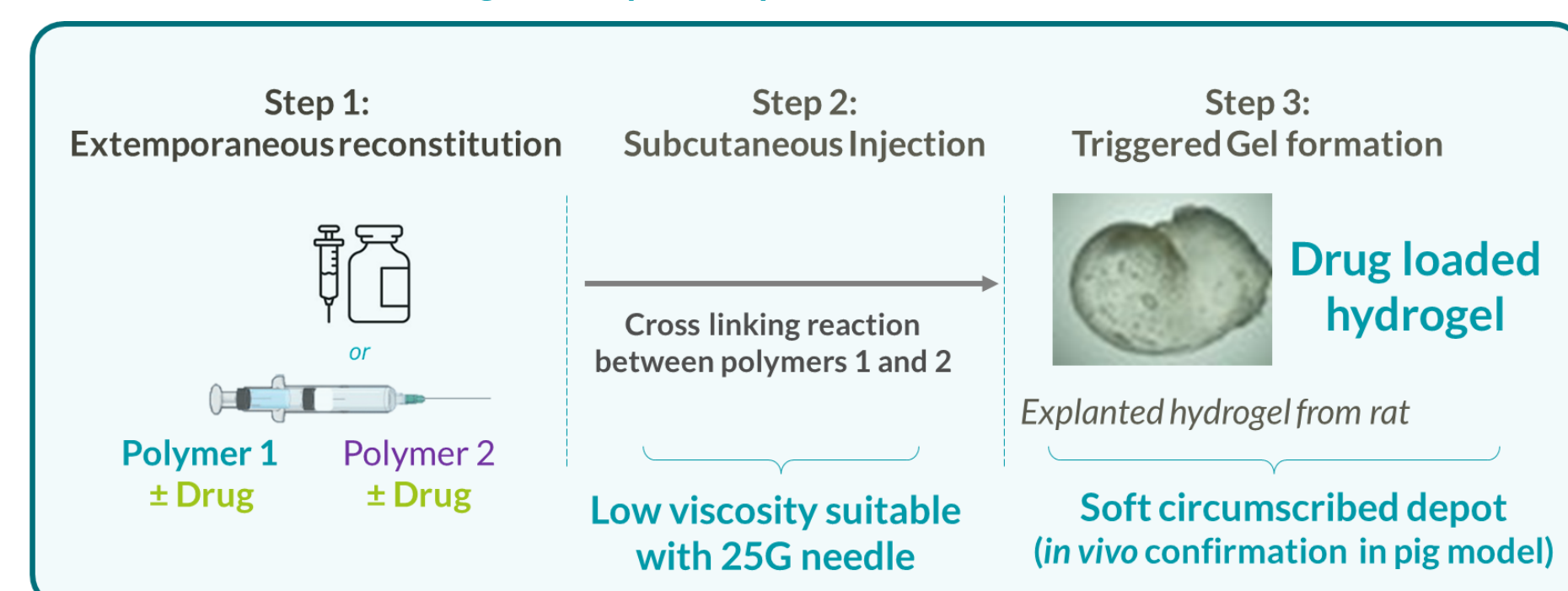
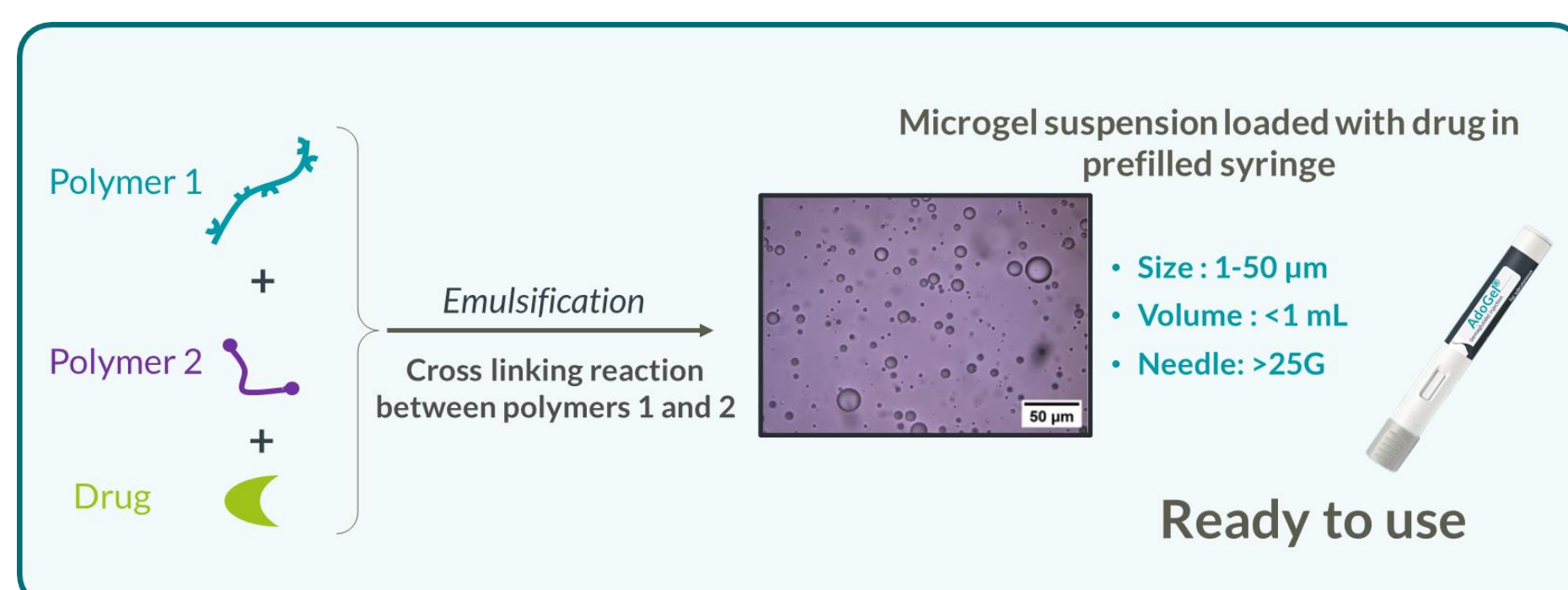


Figure 3 Microgel suspension



Methods

o In vitro studies

- o AdoGel® Sema are prepared by mixing polymers solution and drug (Figure 1). Gel disks of 100 µL (mimicking *in situ* forming gel) were molded by pouring the premix in a mold of 9 mm in diameter. Microgels were formed by emulsification of the premix (Figure 3).
- o Release assay: gel disks or microgel suspension were immersed in PBS at 37°C. Semaglutide released from the hydrogels was quantified over time by RP-HPLC.
- o Biodegradability: hydrogel swelling and degradation were studied at 37°C in PBS and in enzymatic bath (mix of peptidases) by weighing the discs (ISFG) or microscopic observation (microgel).

o In vivo studies

- o Wild-type Wistar Han male rats (n=6), weighing between 250 to 300 g, received a single subcutaneous administration of ISFG or microgel in the interscapular area. Animals were kept in collective cages.
- o Animals were monitored for local reaction and blood was regularly collected to assess the plasmatic semaglutide concentration up to 56 days. Semaglutide concentration in plasma samples was quantified by LC-MS/MS.

In vitro release kinetics

Semaglutide release from AdoGel® was investigated by *in vitro* release assessment. Release rate as a function of semaglutide loading show smooth release over a period of 2 months in a concentration dependent manner (Figure 4). The daily release rate is proportional to the gel volume as shown in Figure 5. Similar release profiles are observed with both product presentations (Figure 6). Regardless of semaglutide concentration, gel volume and presentation (disk vs microgel) a full release of semaglutide from the hydrogel is demonstrated.

Figure 4 Semaglutide dose effect

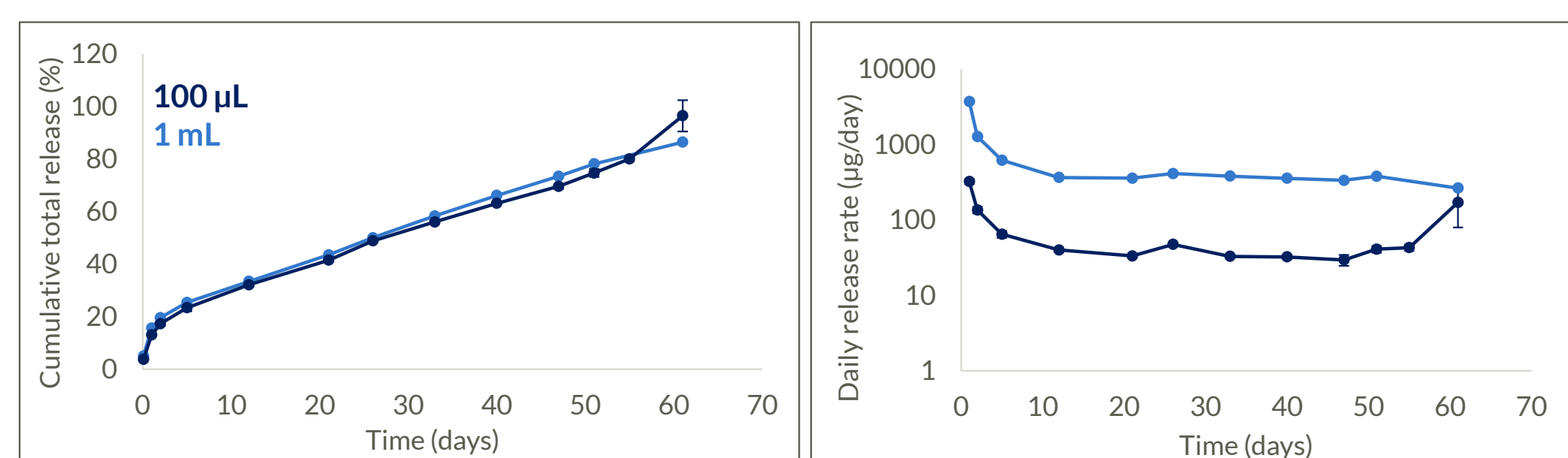


Figure 5 Gel volume effect

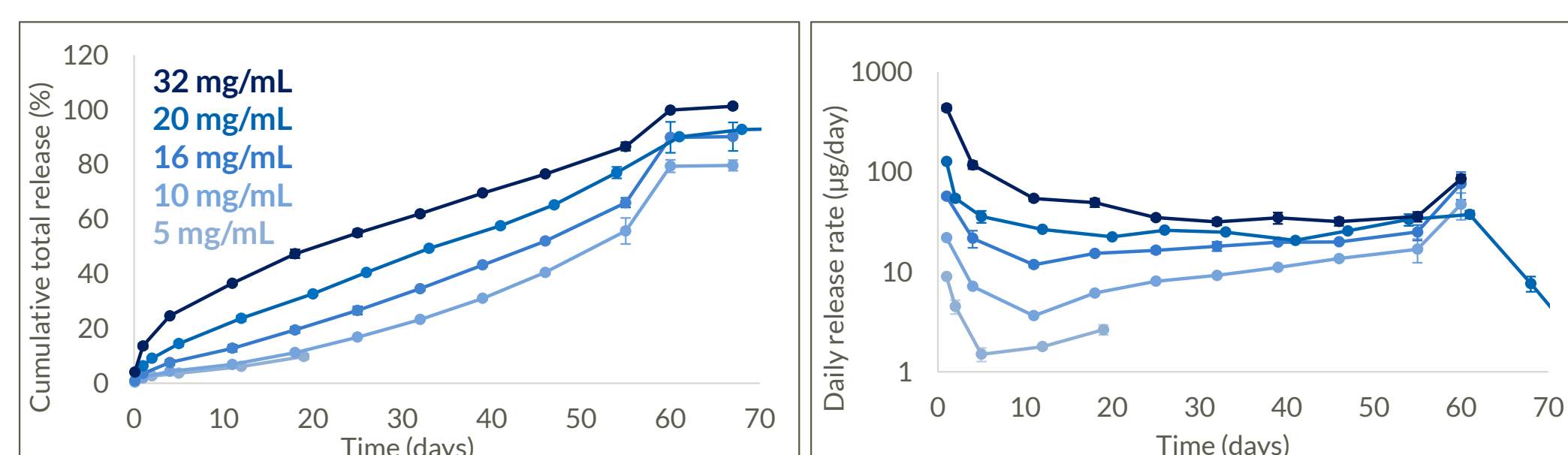
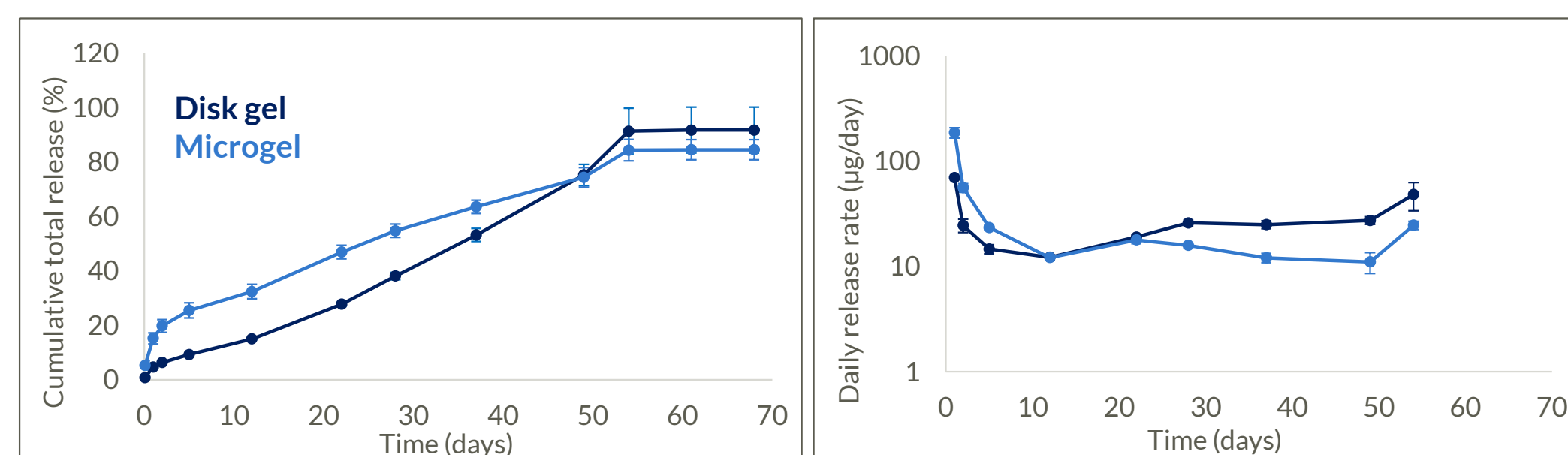


Figure 6 Gel disk vs microgel



In vitro hydrogel degradation

Figure 7 demonstrates the tunability of the AdoGel® degradation kinetic from weeks to months in physiological conditions at 37°C. AdoGel® can also be degraded by enzymes as shown in Figure 8. These results confirm the biodegradable behavior of AdoGel®.

Figure 7 Gel swelling in PBS 37°C

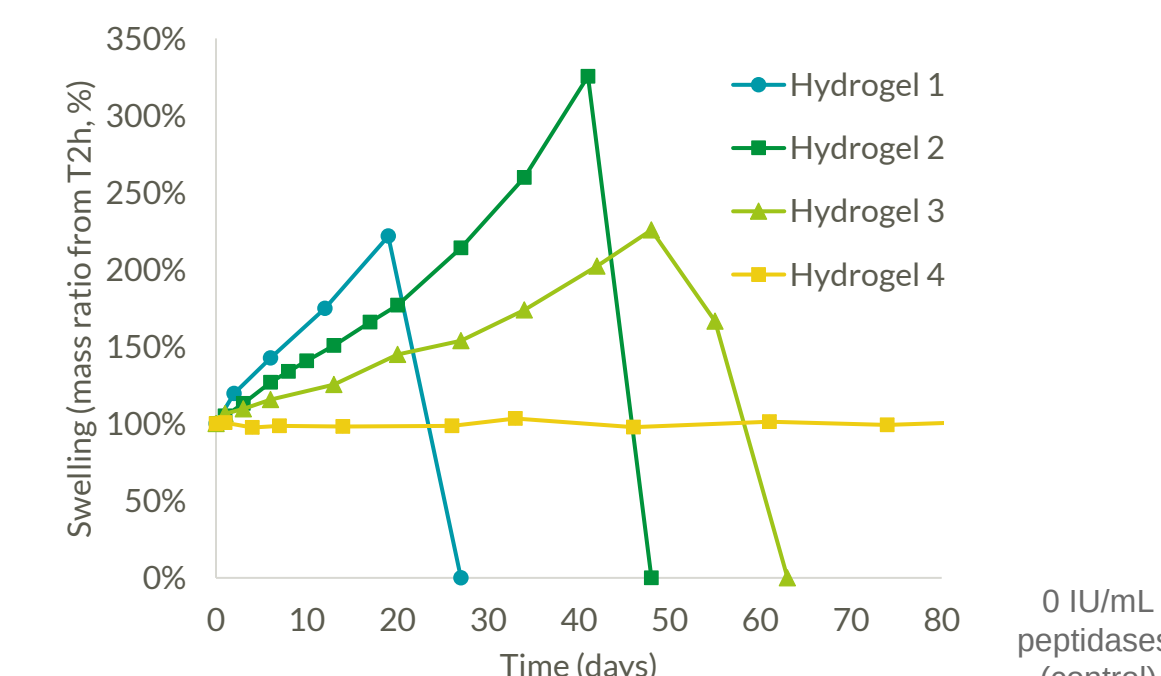
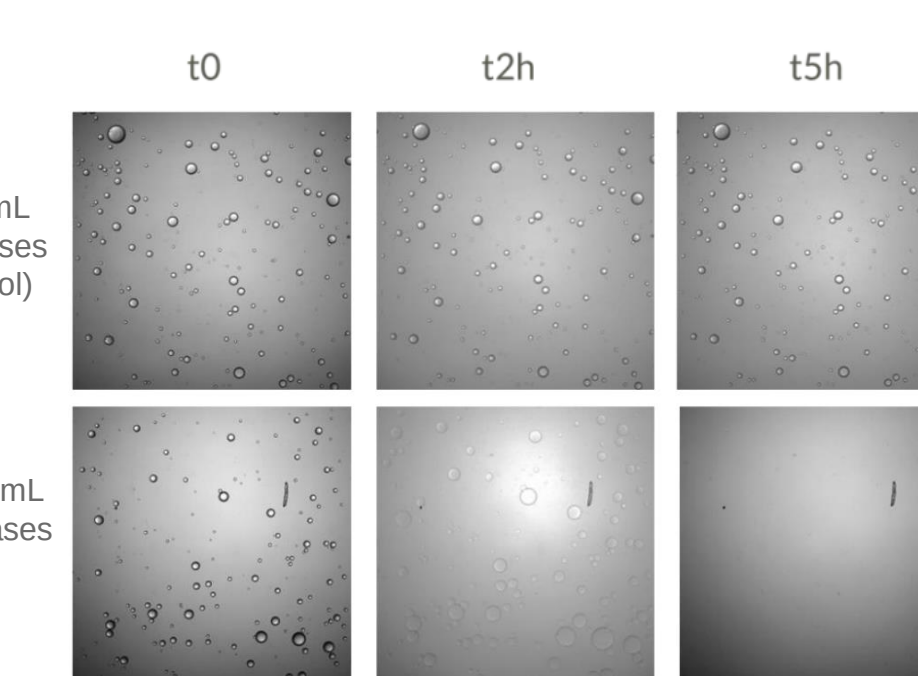


Figure 8 Accelerated enzymatic degradation (microgel)



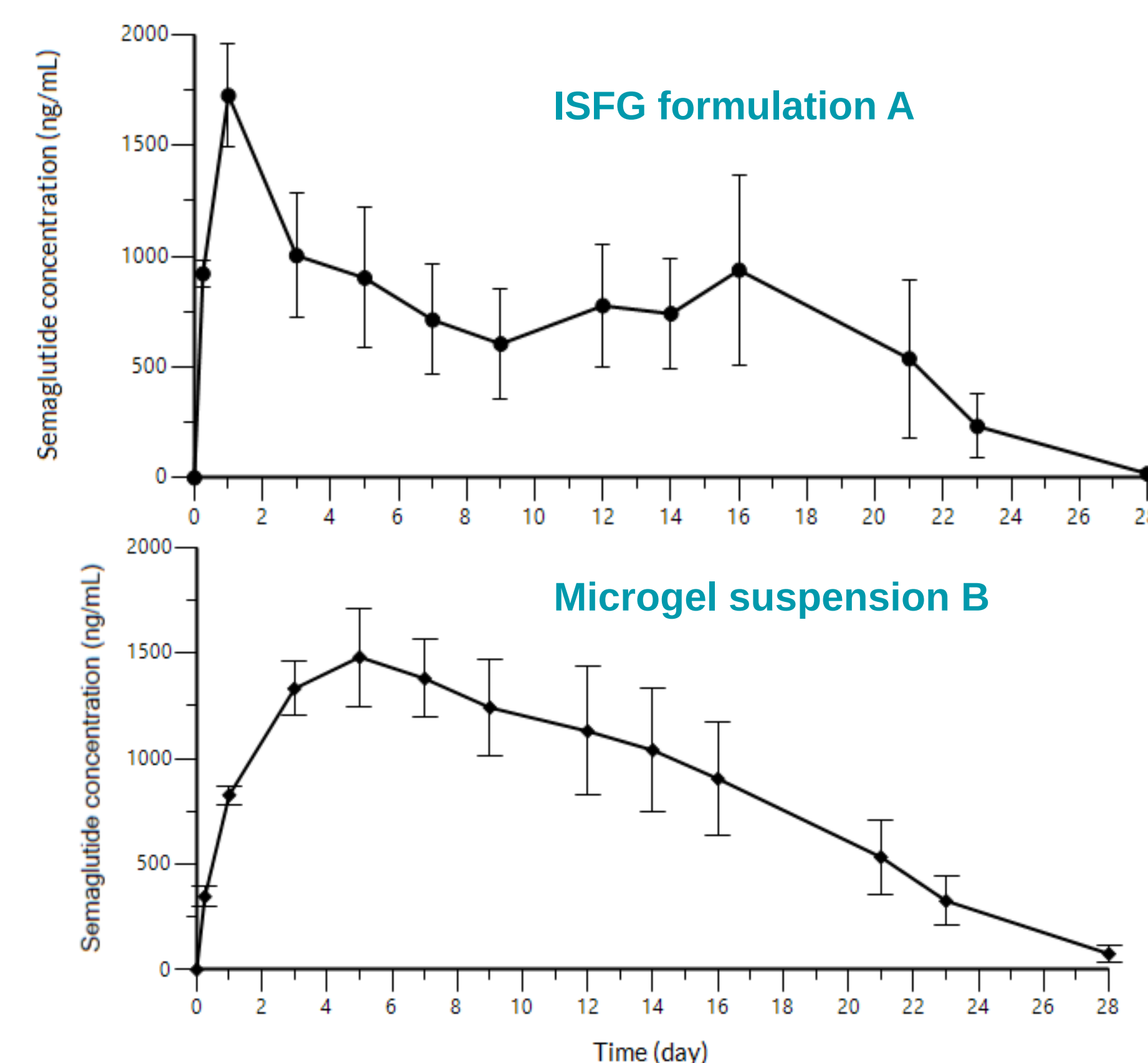
Pharmacokinetics in rats

Both ISFG and microgels AdoGel® Sema were administered in rats showing good tolerance (no oedema nor inflammation over the 56 days period). Both ISFG and microgel led to sustained-release PK profile characterized by a low Cmax and an exposure for 28 days.

Two types of sustained release PK profiles have been observed. Figure 9-A shows an example of flat plateau after a rapid low Cmax (reached at day 1). In this example obtained for an ISFG formulation, Cmax is less than 2.5 times the concentration of the plateau.

Figure 9-B shows an example of a delayed low Cmax (reached at day 5) followed by a slow decrease of concentration until day 28. In this example obtained for a microgel suspension, terminal half-life is about 2.2 days (vs 12h after Semaglutide SC in rat).

Figure 9 Mean (± SE) PK profile of semaglutide in rats, n=6



Conclusions

- ✓ AdoGel® is a biodegradable and biocompatible hydrogel technology with unique properties designed for the extended release of peptides and proteins.
- ✓ AdoGel® Sema, administrated in rats as an *in situ* forming gel or as microgel particles, has demonstrated sustained release of the peptide with exposure over one month and no initial burst. Based on PK parameters, it is expected that in human, the exposure will be further extended to at least one month.
- ✓ Both hydrogels presentation (ISFG & microgel) showed excellent local tolerance.
- ✓ AdoGel® Sema once-a-month has the potential to improve the quality of life of treatment for patients with T2D or overweighted.