

Development of a Solubilised Capsule Formulation Using Co-Micronisation and Precipitation Inhibition

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PURPOSE

An extremely poorly soluble compound was developed to improve thermodynamic solubility (Drug A). However, the resultant solubilized form (Drug A) remained dissolution rate limited, and also had a propensity to precipitate once in solution. In vivo bioavailability is limited by the dissolution rate for oral administration.

There are many developed techniques used to improve the solubility of poorly soluble drugs, it is critical right technique to be selected and sometimes a combination of techniques is required.

For this study, micronisation by jet-milling was adopted to reduce the particle size of the drug for rapid dissolution. The impact of additional functional excipients such as wetting agent, dispersion agent and precipitation inhibitor (PI) on the drug dissolution via co-micronisation or post mill blending process.

METHODS

Micronisation was carried out using MCOne Jet mill with the aim to produce a particle size of $d_{50} < 10\mu\text{m}$. The blend particle size was assessed by laser diffraction (Sympatec). The venturi and ring valve pressures were adjusted to 6 and 2 bar, respectively. For initial assessment of Drug A and micronized Drug A, non-sink dissolution testing was performed using USP Apparatus II in FaSSIF v2 media.

Co-micronisation of Drug A and functional excipients was then explored. Formulation prototypes were prepared by jet-milling Drug A with one excipient after blending on a Turbula mixer. Milling parameters were adjusted in order to achieve a particle size of $D_{50} < 10\mu\text{m}$ with single pass. A variety of excipient at different ratios (Drug A :excipient) were investigated such as Microcrystalline cellulose (Avicel PH101) (2:1 and 1:1), Sodium Lauryl Sulphate (SLS) (99:1/90:10), Lactose Monohydrate 312 (1:1), Nesulin US2 (7:30) and Hydroxypropyl cellulose (HPC) (83:17).

To assess the impact of additional filler, wetting agent or PI on the drug dissolution the co-micronised material was also blended with a candidate excipient at different ratios using a Turbula mixer before dissolution testing.

The resultant formulation prototypes were assessed using single stage dissolution testing in biorelevant media. Additional 2-stage biorelevant dissolution studies were also performed using FaSSGF and FaSSIF media to further characterise preferred formulations. Dissolution conditions can be seen below in Table 1.

Table 1: Biorelevant dissolution conditions

Medium:	FaSSGF then FaSSIF v2
Dissolution type:	USP II (Paddles)
Paddle Speed:	100 rpm
Volume of Medium:	450 mL FaSSGF, at 30 minutes add 450mL pre-heated FaSSIF v2 (double strength)
pH adjustment:	Adjust to ~6.5 with 10M NaOH
Temperature:	37.0°C ± 0.5
Sampling Time Points:	10, 20, 30 (before switch), 35, 45, 60 and 90 minutes
Sampling Type:	Manual with filtration through a 10 µm filter and a 0.45 µm PTFE syringe filter
Sampling Volume:	5 mL

RESULTS

Jet milling was able to achieve a particle size of $< 5\mu\text{m}$ for all investigated with single pass. The results of dissolution test in Figure 1 show that the non-micronised Drug A alone has an extremely slow dissolution rate. The micronised Drug A has a slightly higher release rate compared to the non-micronised form. However, it still showed less than 4% release over 60 minute dissolution test, indicating the micronised drug alone gave limited improvement in the drug dissolution due to poor wettability or very rapid precipitation or combined effect and therefore formulation development efforts were focussed on addressing these observations.

Therefore, functional excipients were screened by blending a binary mixture at different ratios with Drug A followed by co-micronisation as per the process described in the method section. The excipients investigated were Microcrystalline cellulose PH101, SLS, Lactose Monohydrate 312 and HPC. The results in Figure 1 show that, by co-micronising Drug A with a functional excipient, there was an improvement to the dissolution rate with a fast onset on drug release to achieve the supersaturation state. At the same time, precipitation of the solubilised metastable drug solution occurred rapidly after reaching supersaturation. Drug A co-micronised with precipitation inhibitor HPC (Drug A: HPC at 83:17 ratio) was the most promising co-micronisation combination as 6.2 % of the drug was released within the first 10 minutes in FaSSIF dissolution media. Therefore, it is selected for further development.

In the further optimization the co-micronised Drug A and HPC was then blended with wetting agent SLS to form the final formulation. Table 2 shows the composition of the co-micronised Drug A formulation. The results of 2-stage, biorelevant dissolution profiles in Figure 2 show a significant improvement of the final formulation over the co-micronised Drug A:HPC. Figure 2 shows the dissolution rate is further enhanced with the incorporation of the wetting agent SLS (via Turbula mixing with the co-micronised blend). This allowed rapid dispersion of the formulation, and the precipitation inhibitor (via co-micronising with Drug A) imposed a parachute effect on the metastable solution.

Table 2: Composition and Batch Formula of Co-micronised Drug A Formulation

Components	%w/w	g/50g blend
Co-micronised Drug A: PI (83:17)	66.67	33.34
Sodium Dodecyl Sulfate	33.33	16.66
Total	100.00	50.00

CONCLUSIONS

Both micronisation and co-micronisation can improve the rate and extent of drug dissolution. However, co-micronisation of Drug A with a precipitation inhibitor HPC and further blending with a wetting agent SLS could significantly increase the drug dissolution to achieve a supersaturated state for Drug A. In the presence of a precipitation inhibitor, the solubilized drug was maintained in the metastable over a period of time with a slow precipitation rate. The addition of precipitation inhibitor has successfully maintained Drug A in the solubilized form for an extended period allowing greater potential for drug absorption. In vivo studies will be conducted to evaluate the bioavailability of the final formulation. The final results demonstrate the co-micronisation process manage to improve the bioavailability of the poorly soluble drug investigated.

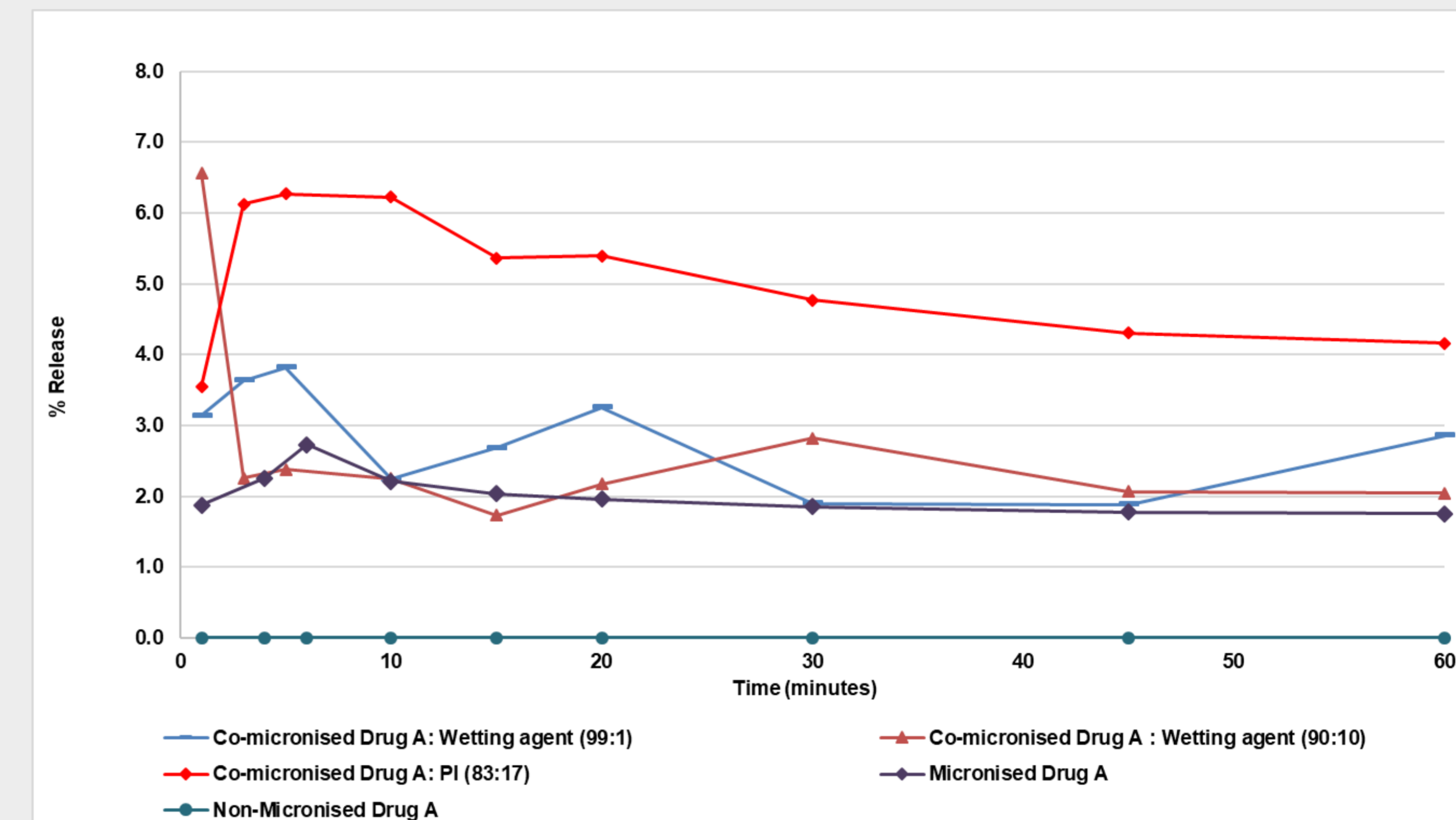


Figure 1: Dissolution Profiles of Co-micronised Samples and Micronised Drug A tested in FaSSIF (single stage dissolution)

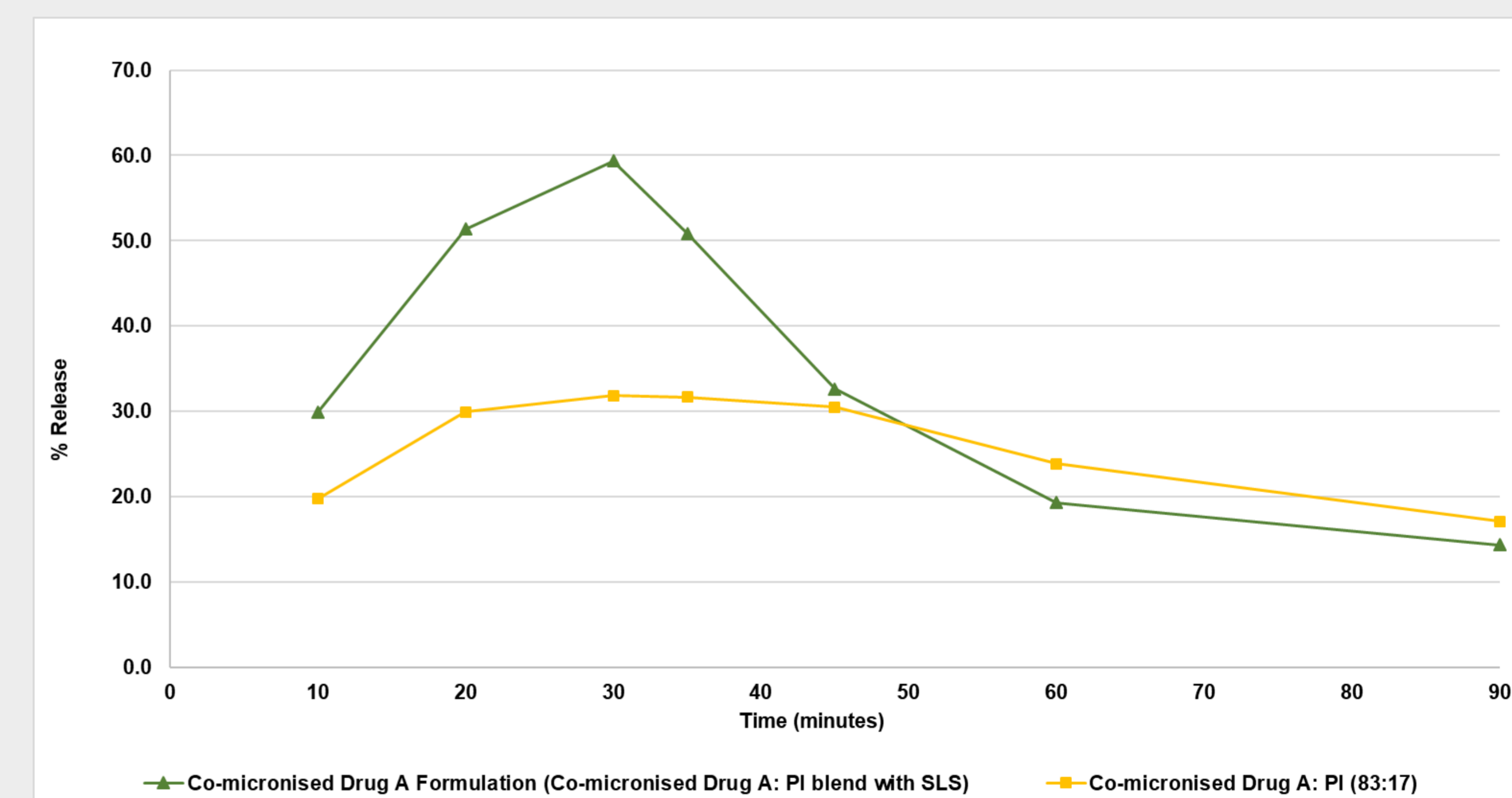


Figure 2: Dissolution Profiles of a 2 stage biorelevant dissolution using FaSSGF and FaSSIF

REFERENCES

Markus, V et al., Co-grinding enhances the oral bioavailability of EMD 57033 a poorly water soluble drug, in dogs. Eur. J. Pharma. Biopharm. 86 (2008) 338-345.