High-throughput Agrochemical Formulation: Easing the Route to Commercial Manufacture

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HTFS III
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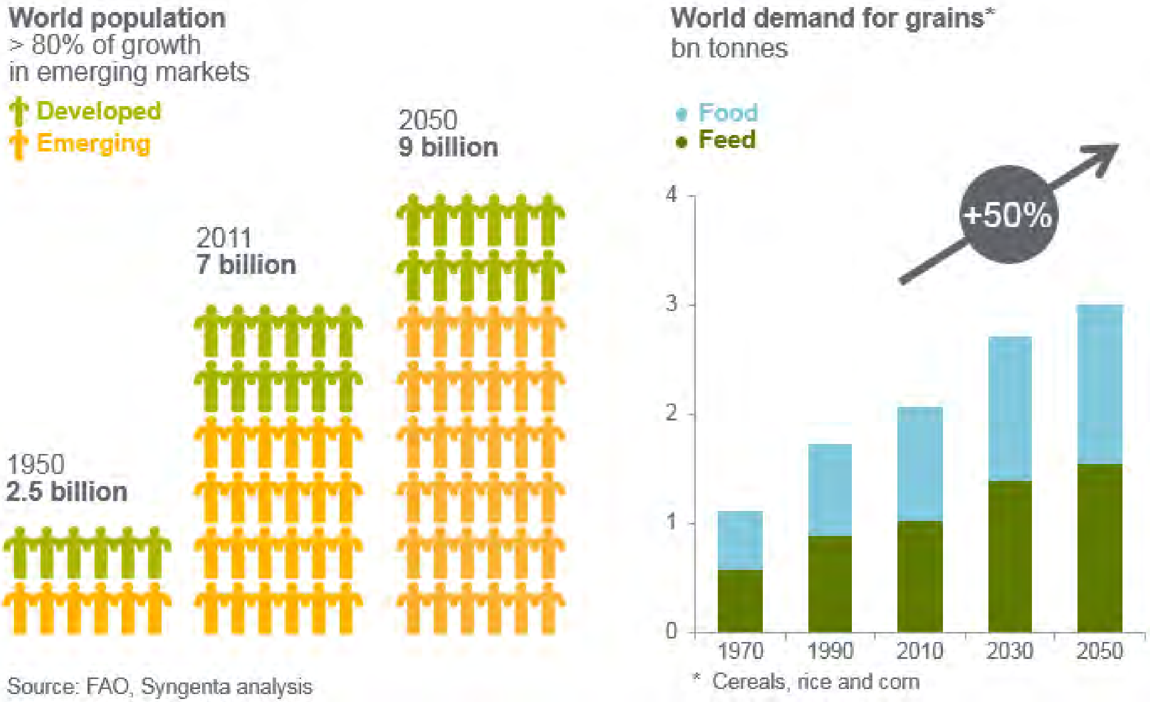
Classification: PUBLIC

Agribusiness – an essential industry

By **2050**, global population will rise by about a third to **9 billion** people but global food demand will increase by **70%**



40% of the world's food would not exist without crop protection products.

Land scarcity, limited water supplies and climate change will all impact crop yields unless we have new innovative solutions.

Source: UN, FAO, World Bank statistics, Syngenta (link)

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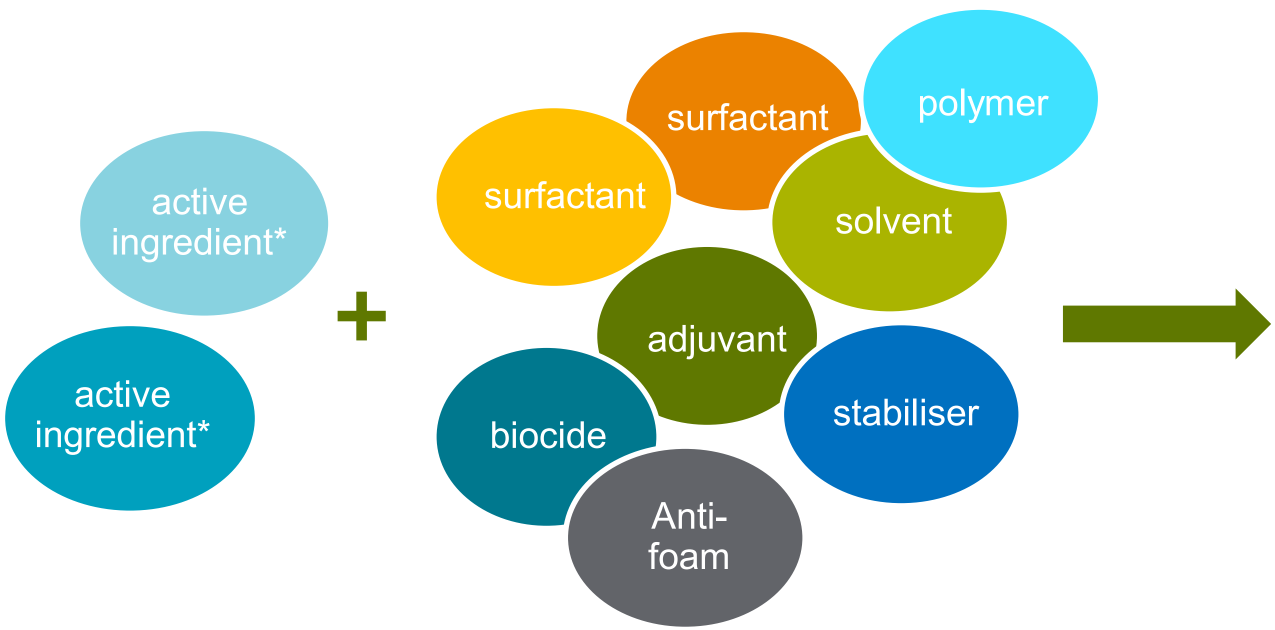
Good Growth Plan: One Planet, Six Commitments

Source: Syngenta Annual Report 2016 (link)

Formulation in Syngenta – designing and producing crop protection products



Highly active compounds – low application rates
Application by dilution into water and spraying

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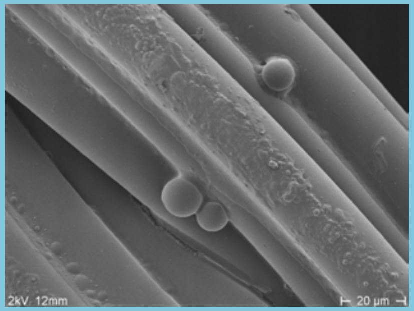
Agricultural formulations are growing more sophisticated

Then

Application of wettable powder formulations in Egypt (1980s)

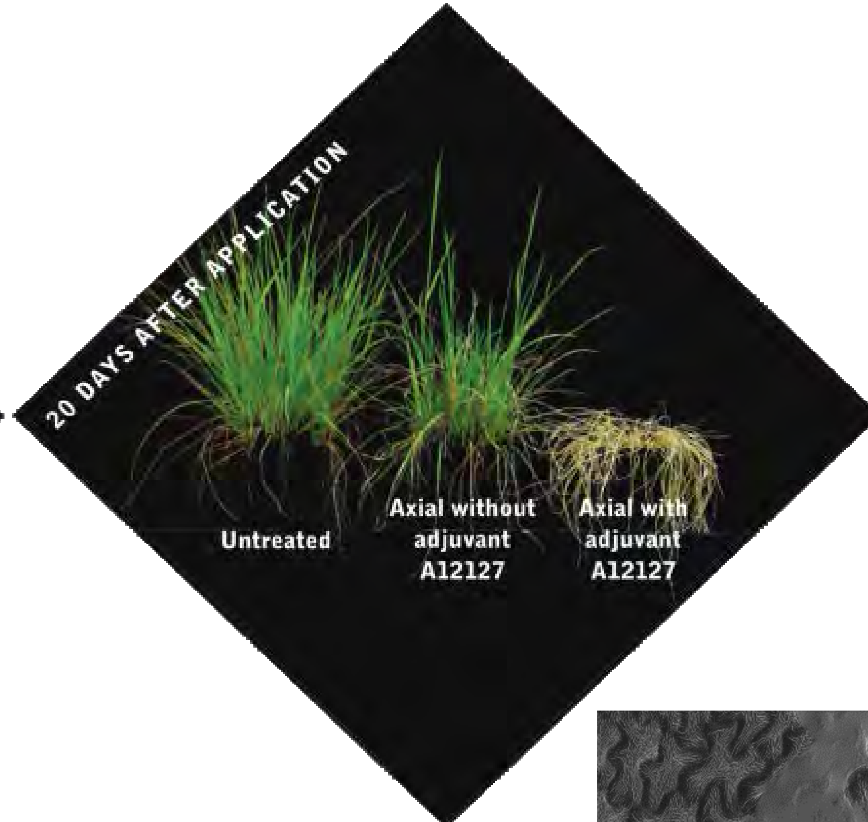
Now

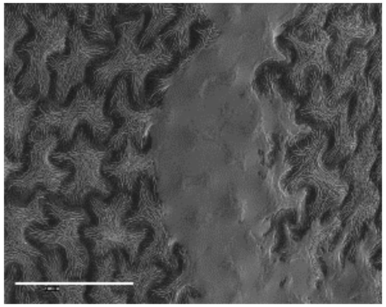
Encapsulated formulations provide improved performance and increased operator safety



Opportunities for immediate, slow, delayed or triggered release

Unlocking Potential - maximising efficacy with adjuvants





Adjuvant deposit on leaf surface

Axial ® is a registered trademark

Product requirements

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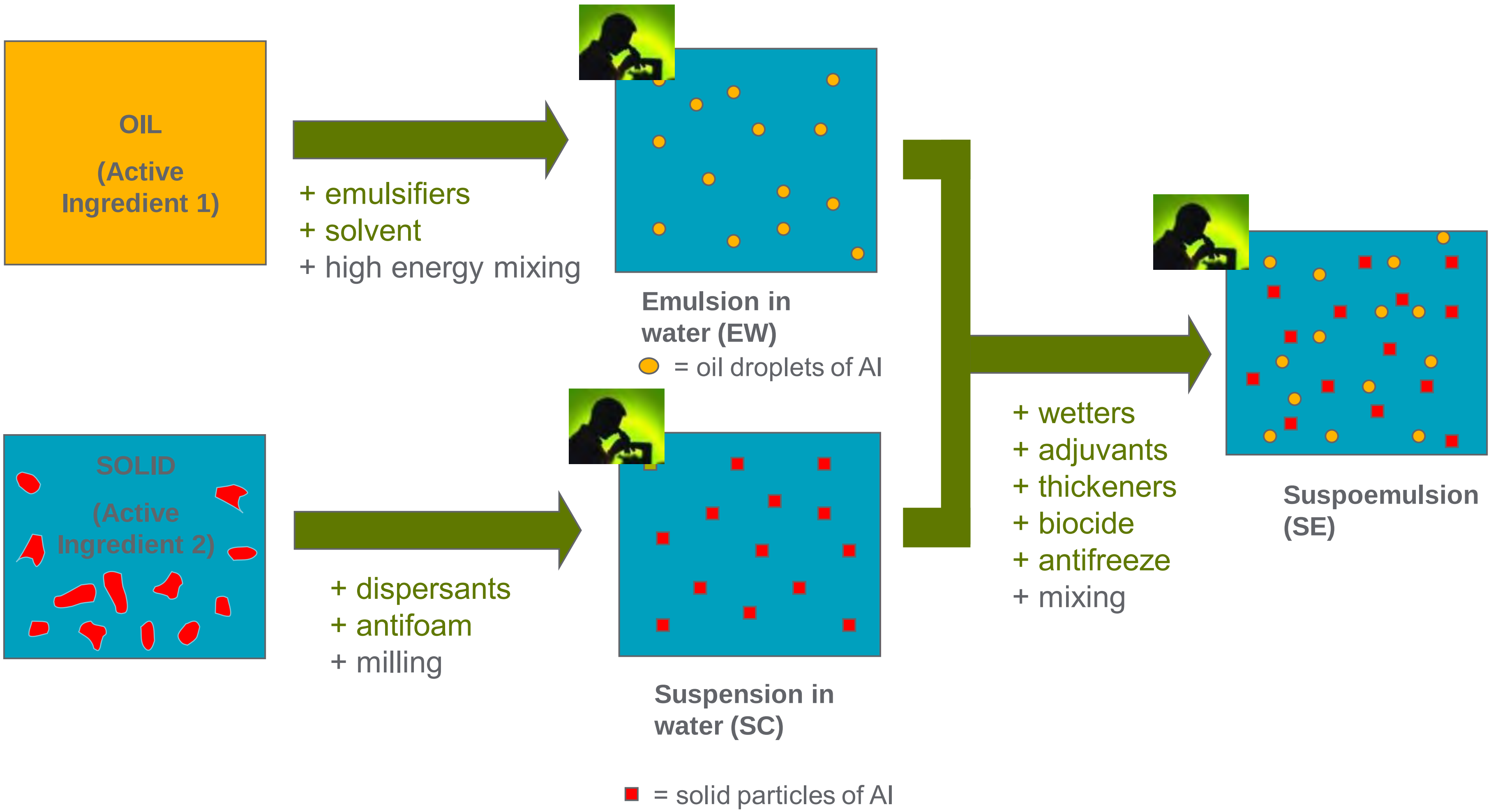
Reality is complex mixtures: e.g. suspoemulsions (SE)



Formulation Trends

- Increasing **complexity**.
  - mixtures, AI properties, novel technology.
- **Regulatory pressure** on active ingredients and other components
- **Fast track** projects
- Supply chain **cost** pressures - especially raw materials costs
- Professional Products markets growing.
- Formulation **differentiation** increasingly important to business.

Importance of formulation has grown

Why high throughout formulation screening?

E.g. Emulsifier screening for formulations

No. of ingredients	1:1 blends	1:1:1 blends	3-way blends (+ ratios)
20	190	1,140	12,371
50	1,225	19,600	202,176
100	4,950	161,700	1,641,851

No need for huge libraries to generate significant sample numbers.
Diversity introduced through non-linear interactions.

Discriminating tests - It’s (usually) clear when it goes wrong!

Opportunities for high-throughput formulation

- Challenges:
  - complexity of composition
  - process variables important
  - responses often non-linear

- Rewards:
  - larger, complete data sets
  - reduce repetitive and tedious labour requirements
  - cost and process optimisation
  - improved product performance

Syngenta's High-Throughput Formulation System

Syngenta's High-Throughput Formulation System

- Sample Preparation:
  - Accurate Dispensing – powders, viscous liquids, suspensions, waxes
  - Controlled addition / mixing /milling / pH adjustment steps
  - Representative scale

- Sample Characterisation
  - Visual analysis – of concentrated products and dilutions
  - Particle size measurement
  - High shear viscosity / rheology
  - Compatibility testing (residue evaluation)

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Case Study: Background

- Significant cost saving opportunity identified if a specific emulsifier could be replaced with an alternative in a commercialised formulation.
- Lab study identified a group of feasible alternatives, but an optimal, stabilised formulation could not be generated.
- High-throughput technology used to determine if these alternative chemistries / suppliers could be optimised to work within the formulation.

Case Study: The Variables

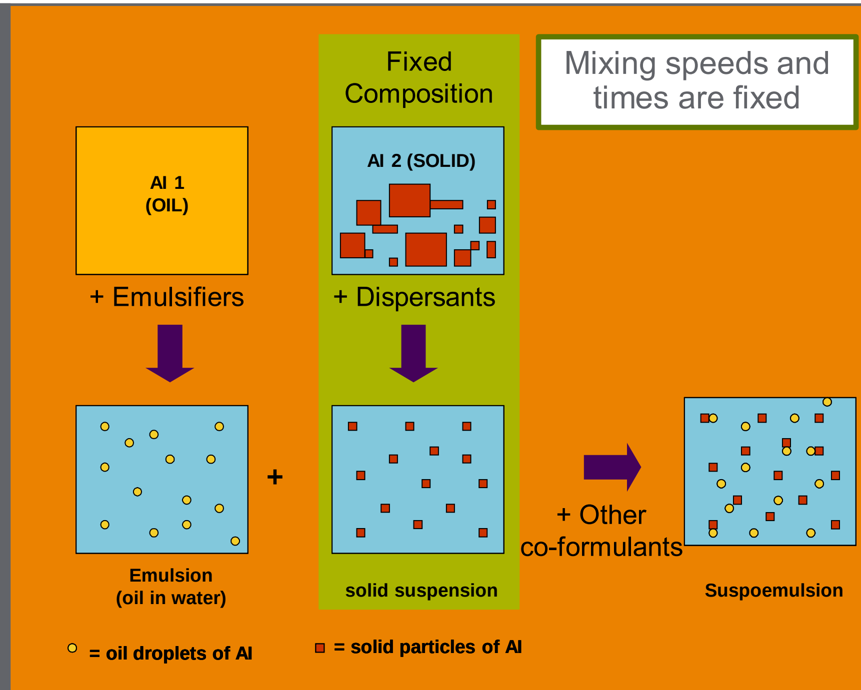
Composition

Component	Increment
AI 1 (oil phase)	Fixed
AI 2 (solid phase)	Fixed
Oil/Solvent	Fixed
Emulsifier 1	Variable
Emulsifier 2	Variable
Emulsifier 3	Variable
Emulsifier 5	Variable
Dispersants	Fixed
Thickeners	Fixed
Antifreeze	Fixed
Antifoam	Fixed
Biocide	Fixed
Water	To 100%

The chosen experimental design uses two total emulsifier loadings; high or low

Emulsifiers 1 and 5 are different sources of the same chemistry and so are not used together in this design.

Preparation



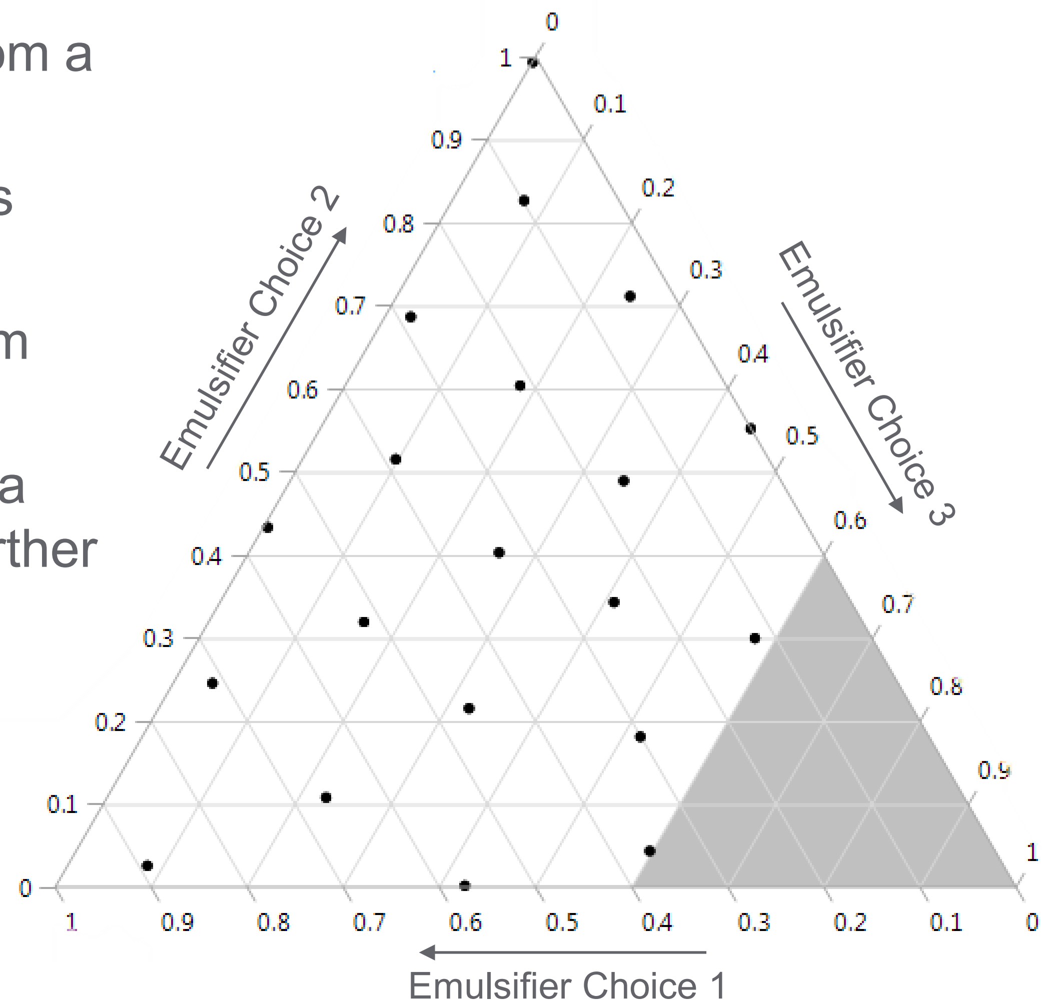
Testing

- Product Stability (shelf-life)
- Dilution Stability (visual)
- Rheology / viscometry
- Particle size
- Surface Properties (DST etc)
- AI chemical stability

Not Used in this experiment

Case Study : The Experimental Design

- Three emulsifiers selected from a group of four*
- Total emulsifier content set as either "high" or "low".
- Emulsifier set determined from initial lab screening work.
- Lab screening also identified a clear area of failure, which further constrains the design.
- Design replicated to evaluate two categorical levels for Emulsifier Choice 3.



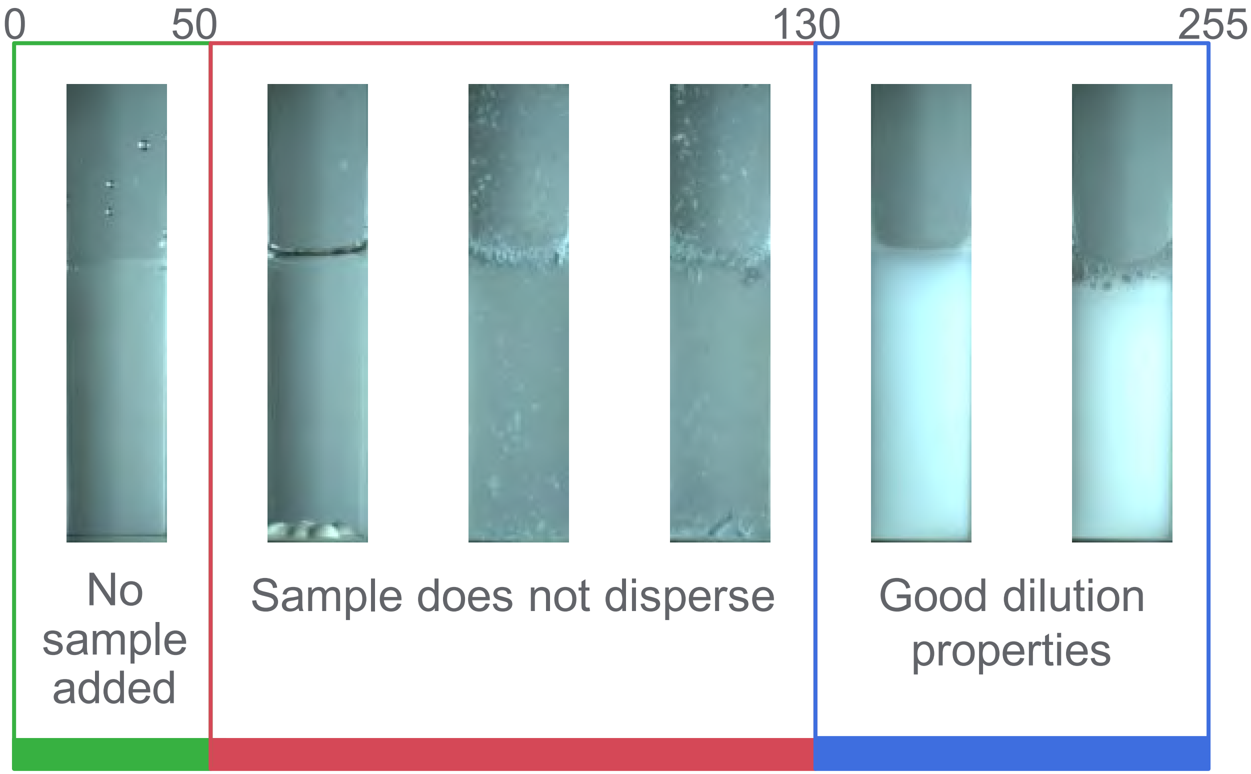
* Two of these are different versions of the same chemistry and so would not be used together in the same design.

Measurements Taken (Responses)

- Lab work indicated two known failure modes for this formulation:
  - Phase inversion (where an oil-in-water emulsion inverts to a water-in-oil emulsion)
  - Irreversible sample thickening
- Measurements taken during the experiment:
  - Rheological properties (neat sample)
  - Visual analysis (neat sample)
  - Dilution characteristics (1% dilution in tap water)
- These measurements were taken immediately after preparing the samples and again after 7 days storage at 50°C

Image Analysis: Turning Pictures into Data

- The prepared samples were diluted 1%v/v in cold tap water and evaluated for their dilution properties.
- By using laser reflection information, the quality of the dilution can be quantified:



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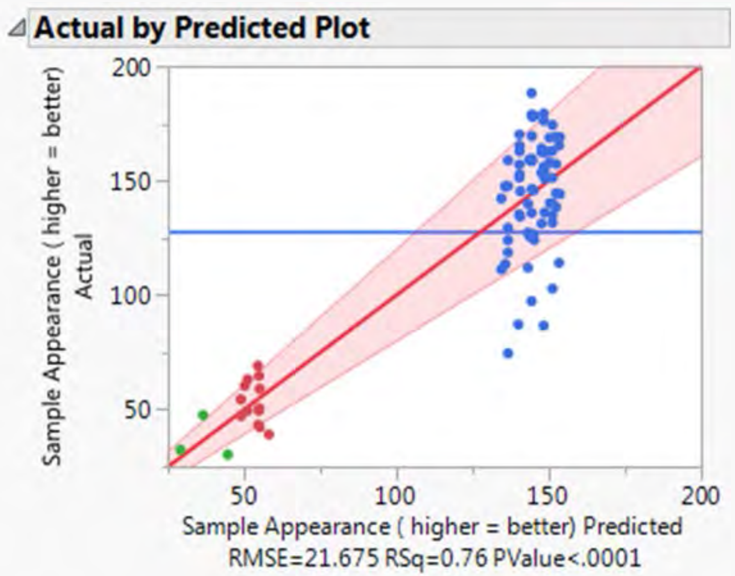
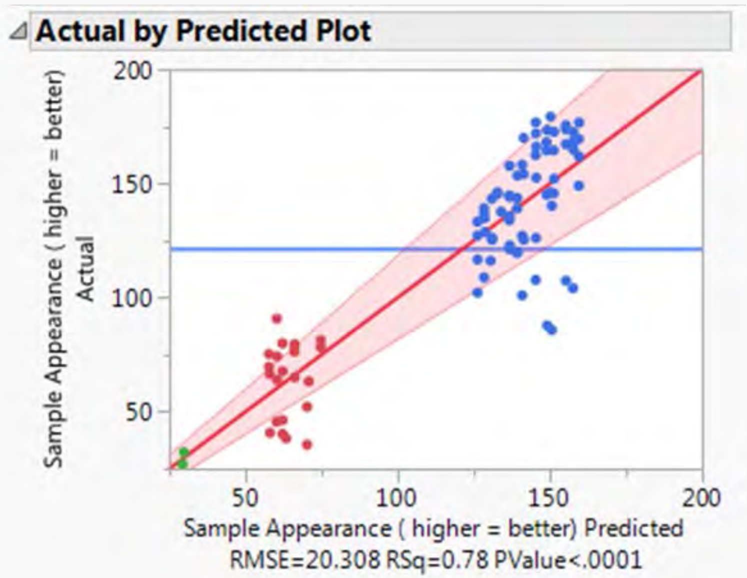
Modelling the Image Data

- A statistical data package was utilised to fit a model to the quantitative image data:

System 1: Emulsifiers 1,2 and 3



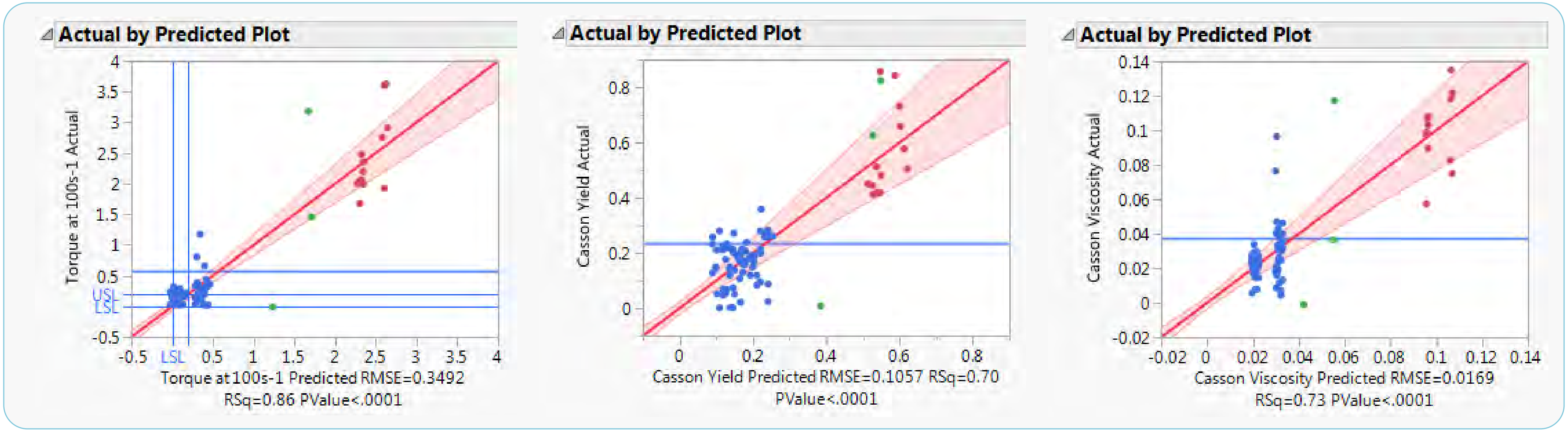
System 2: Emulsifiers 2, 3 and 5



- Three clear data groups can be seen, which correlate with no sample added (green dots), samples that do not disperse (red) and good dilution (blue).

Rheology Data

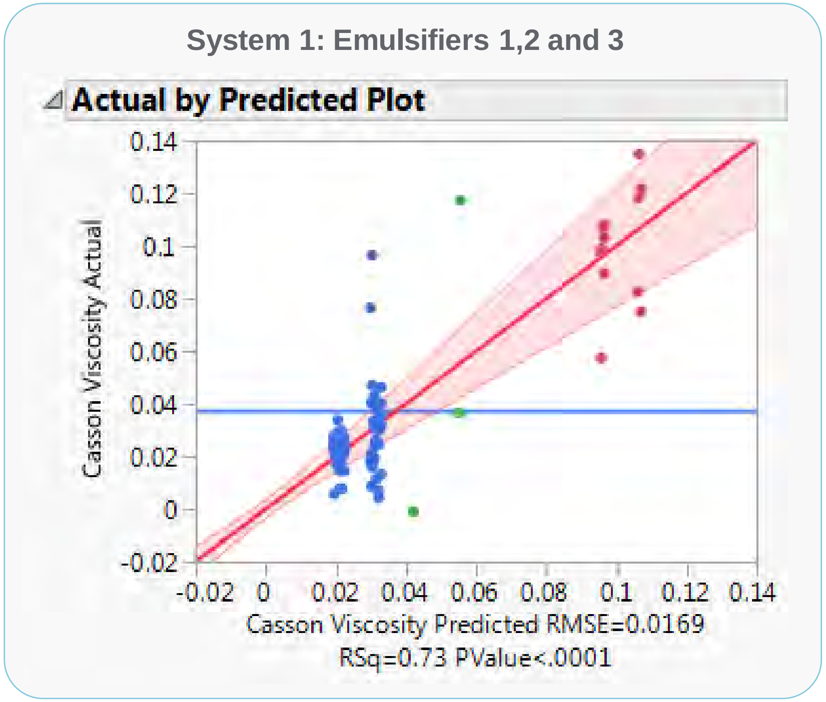
- The rheological properties of the samples were assessed by measuring the torque value over a range of vane rotational speeds.
  - Experience has shown acceptable samples usually have a torque value measured at $100s^{-1}$ of 0.2 or lower.
  - Applying the Casson model to the torque data results in an estimated Casson viscosity and an estimated Casson yield stress.
  - These three parameters can also then be modelled:



Plots shown relate to System 1: Emulsifiers 1,2 and 3

Rheology Data: Interpretation

- Samples with poor dilution (emulsification) properties (red dots) also have high Casson viscosities.



- Samples with low Casson viscosities have good emulsification properties.

Mixture Profiling: System 1

- The models generated were then used to evaluate where both acceptable dilution properties and desirable rheology properties overlap:

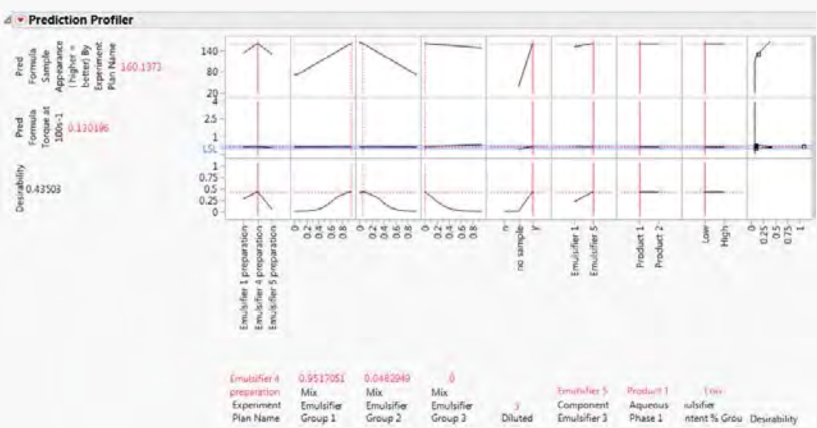
System 1: Emulsifiers 1,2 and 3

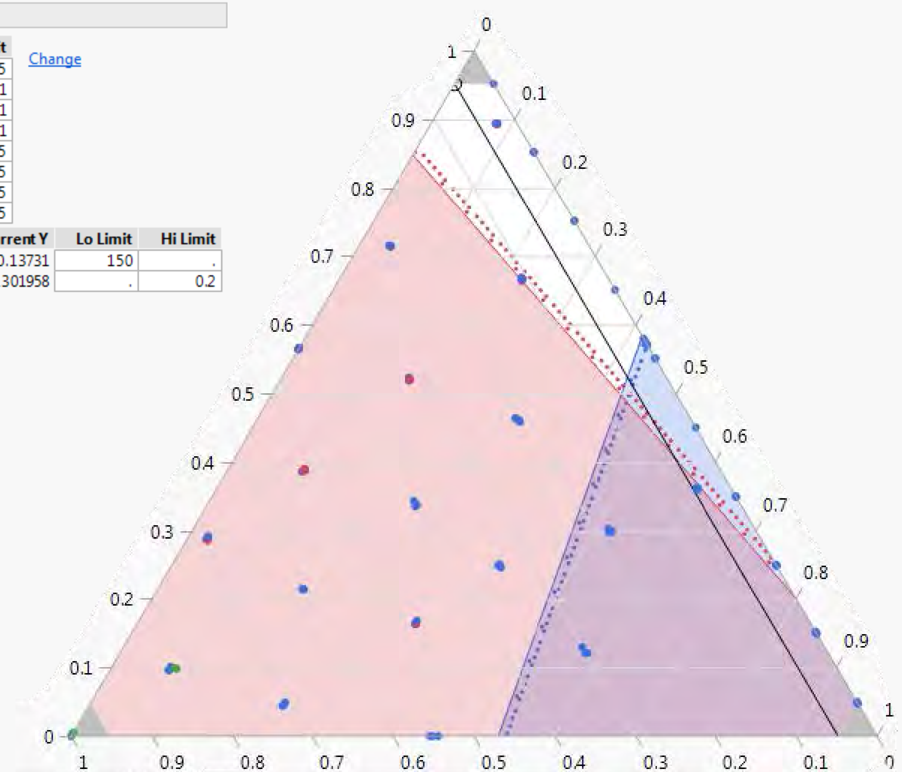
Mixture Profiler

T	L	R	Factor	Current X		Lo Limit	Hi Limit
○	○	○	Experiment Plan Name	1	Emulsifier 4 preparation	-0.5	2.5
◉	○	○	Mix Emulsifier Group 1	0.9517051		0	0.9517051
○	◉	○	Mix Emulsifier Group 2	0.0482949		0	0.9517051
○	○	◉	Mix Emulsifier Group 3	0		0	0.9517051
○	○	○	Diluted	2	y	-0.5	2.5
○	○	○	Component Emulsifier 3	1	Emulsifier 5	-0.5	1.5
○	○	○	Aqueous Phase 1	0	Product 1	-0.5	1.5
○	○	○	Emulsifier Content % Groups	0	Low	-0.5	1.5

Change

Response	Contour	Current Y	Lo Limit	Hi Limit
Pred Formula Sample Appearance (higher = better) By Experiment Plan Name	150	160.13731	150	.
Pred Formula Torque at 100s-1	0.2	0.1301958	.	0.2

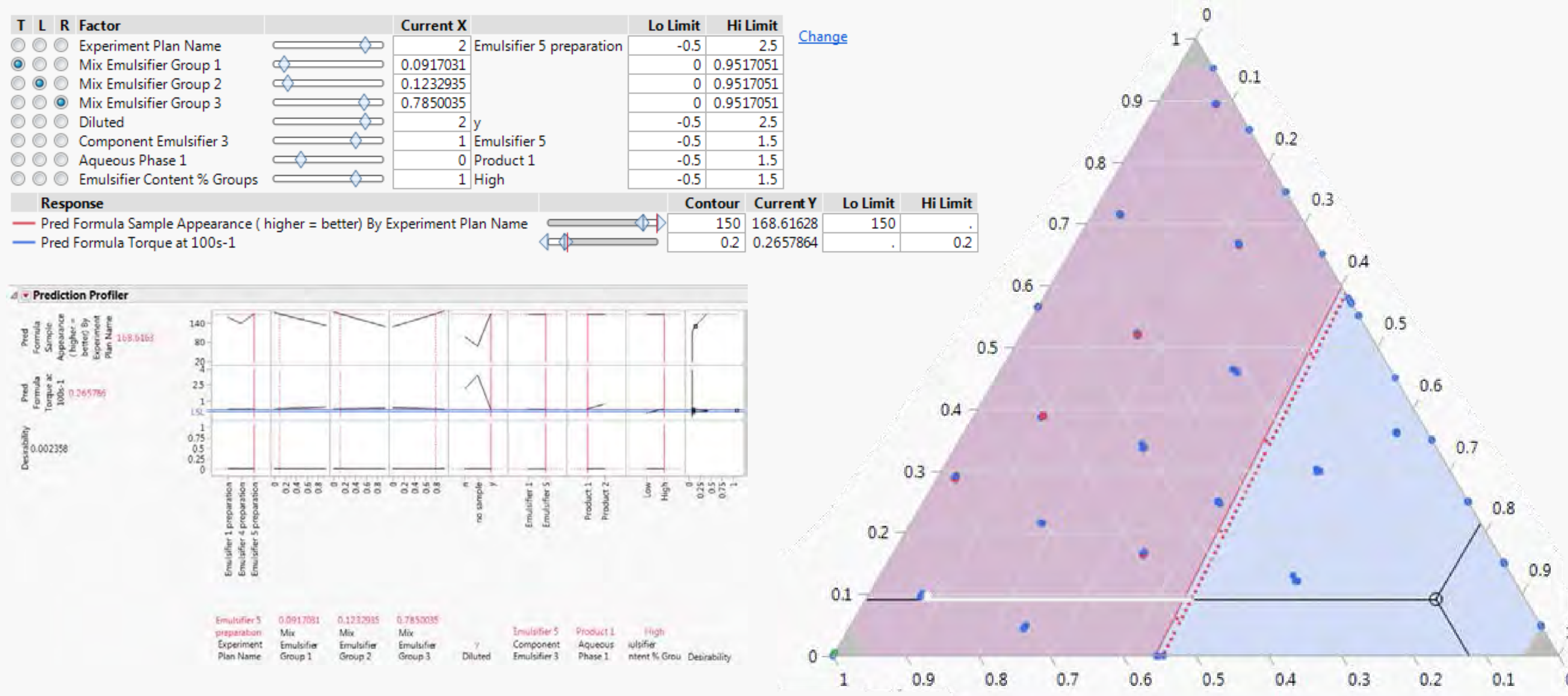




Mixture Profiling: System 2

- For System 2, the models predict that there is no area where both acceptable dilution properties and desirable rheology properties overlap:

System 2: Emulsifiers 2,3 and 5



T	L	R	Factor	Current X		Lo Limit	Hi Limit
			Experiment Plan Name	2	Emulsifier 5 preparation	-0.5	2.5
●			Mix Emulsifier Group 1	0.0917031		0	0.9517051
	●		Mix Emulsifier Group 2	0.1232935		0	0.9517051
		●	Mix Emulsifier Group 3	0.7850035		0	0.9517051
			Diluted	2	y	-0.5	2.5
			Component Emulsifier 3	1	Emulsifier 5	-0.5	1.5
			Aqueous Phase 1	0	Product 1	-0.5	1.5
			Emulsifier Content % Groups	1	High	-0.5	1.5

Response	Contour	Current Y	Lo Limit	Hi Limit
Pred Formula Sample Appearance (higher = better) By Experiment Plan Name	150	168.61628	150	.
Pred Formula Torque at 100s-1	0.2	0.2657864	.	0.2

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Study Conclusions

- System 1 (Blends of emulsifiers 1, 2 and 3) showed potential compositions that were predicted to be stable.
  - Lab and field work is now underway to confirm these lead compositions meet all of our requirements.
- System 2 (blends of emulsifiers 2, 3 and 5) showed no areas where acceptable optimisation was achievable.
  - No further work conducted on this system.
- Over 350 samples of a complex formulation were prepared and evaluated:
  - Completed with 15 days of system time
  - Large dataset builds confidence that the chosen composition is robust and will scale-up successfully.
- We find the most successful projects are those where there is a strong interaction between traditional lab work and modern HTFS methods.

Thank you