Machine Learning-Driven Quality by Design Framework for Predicting Dose Recovery in Enteral Feeding Tube Administration

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1 Introduction

- **Enteral feeding tubes (EFTs)** deliver essential medicines to children with a compromised swallowing function[1]
- Effective delivery is challenging, as outcomes depend on a **complex interplay of tube characteristics, formulation properties, and administration conditions**[1].
- **Quality by Design (QbD)** link these variables to key delivery outcomes, such as dose recovery. However, establishing design spaces using traditional approaches are **labour-intensive and time-consuming**[2].
- This pilot study tests **machine learning (ML) to predict dose recovery and clogging risk**, supporting EFT design space development.

2 Aims and objectives

- **Integrate ML within a QbD framework to build an interpretable design space for rheological parameters governing EFT delivery performance.**
- Identify rheological and tube-related drivers of EFT delivery performance and clogging risk.
- Support risk-based, evidence driven EFT formulation design.

3 Methods

1. Prepare 15 glycerol formulations with varying viscosity for **ML training**;
2. Select and characterise marketed oral solutions for **ML validation**;
3. Characterise all formulations via **rheological profiling** and gravimetric dose recovery testing through 4, 6, and 8 Fr NG tube
4. Train and evaluate ML models **predicting dose recovery and clogging risk** from viscosity, flow behaviour, and tube size
5. **Identify viscosity and flow behaviour thresholds** for EFT delivery performance

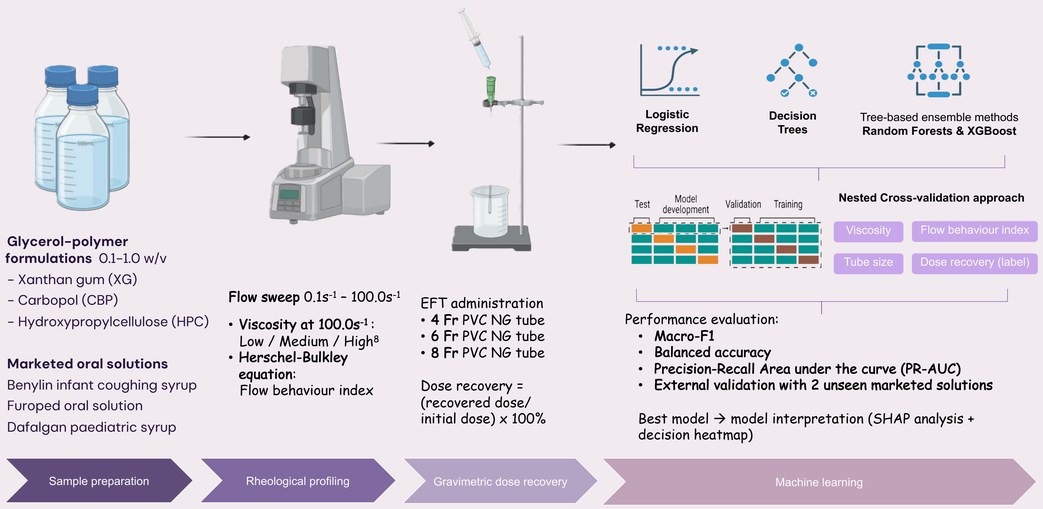

Figure 1. Methods workflow — sample prep → rheological profiling → gravimetric dose recovery → ML

Bibliography

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4 Results: In vitro Evaluation

2.19 mPa.s to 18 445.27 mPa.s at 100 s^{-1} Viscosity range tested

n = 0.45 – 1.02 shear-thinning to near-Newtonian

Tube size effect

- Glycerol-control, glycerol-HPC, XG/CBP formulations were largely insensitive to tube size.. CBP4-5 and XG5 showed reduced dose recovery (< 90%), with 4Fr blockage observed (Figure 2)

Rheology effect

- Low-viscosity formulations recovred consistentely well (~ 94 to 97%), regardless of tube size. High-viscosity: CBP4-5, XG5 showed no/partial recovery in 4 Fr tubes and reduced recovery in larger tubes (<90%; p <0.05) (Figure 2)

Key finding: Dose recovery is driven by the interplay of tube size, formulation composition, and polymer-specific properties, not viscosity alone.

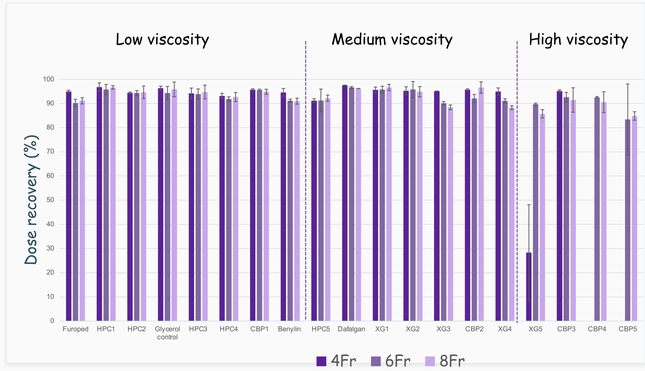

Figure 2. Mean dose recovery (%) across formulations, grouped by viscosity tier (n=3)

5 Machine Learning Predictions

- All models discriminated low- vs high-risk formulations effectively.
- **Random Forest (RF) was best-performing** viewed as a feasibility-level decision-support tool (Table 1).
- SHAP analysis confirms high viscosity + strong shear-thinning drive administration risk. (Figure 3)

ML model	Macro F1	Balanced accuracy	PR-AUC	External validation False flags (n = 6)
RF	0.78 (0.76-0.80)	0.81 (0.79-0.83)	0.78 (0.75-0.81)	No False flags
LR	0.75 (0.73-0.76)	0.84 (0.82-0.86)	0.80 (0.77-0.82)	3 False flags
XGB	0.74 (0.73-0.76)	0.82 (0.80-0.83)	0.72 (0.69-0.75)	3 False flags
DT	0.76 (0.74-0.77)	0.82 (0.80-0.84)	0.60 (0.56-0.63)	No False flags

Table 1: External validation on 2 unseen marketed solutions, n=6 total predictions.

6 ML-Driven Design Space

RF-derived decision boundaries revealed a **two-zone risk structure** within the risk-informed region; translating model predictions into practical formulation design criteria for QbD risk management (Figure 4).

Parameter	Low Risk	Medium Risk	High Risk
Flow behaviour index (n)	> 0.70	0.55 – 0.65	< 0.55
Viscosity @ 100 s^{-1}	< 500 mPa·s	< 500 mPa·s	> 500 mPa·s
Failure probability	0 – 30%	30 – 70%	70 – 100%

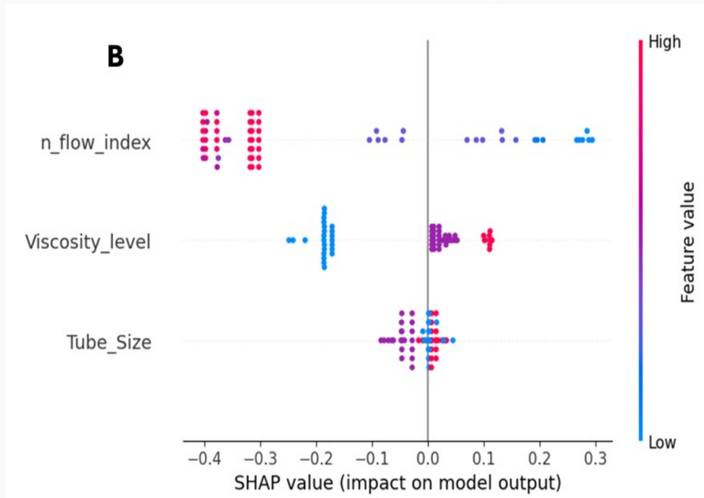

Figure 3. SHAP beeswarm plot — feature contributions to RF model output

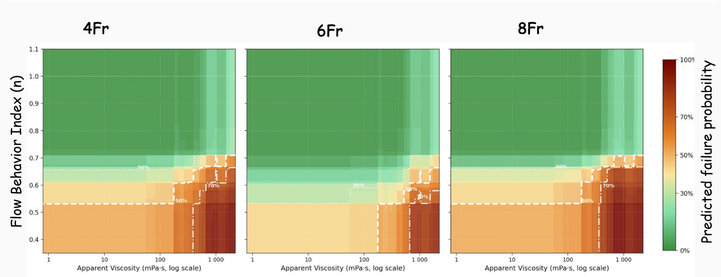

Figure 4. EFT decision boundary heatmaps — risk zones by viscosity & flow behaviour

Limitations: data limited to gravimetric dose recovery, oral solutions only.
Future work: expand features/models toward dosage forms with insoluble components.

6 Conclusion

First ML-driven QbD framework for EFT formulation design enabling the prediction of dose recovery and clogging risk during EFT administration. Potential to accelerate formulation development