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Ethanol Solubility of Rate Controlling Polymer in Modified Release Formulation Can Impact Alcohol Dose Dumping: An Assessment Through Principal Component Analysis

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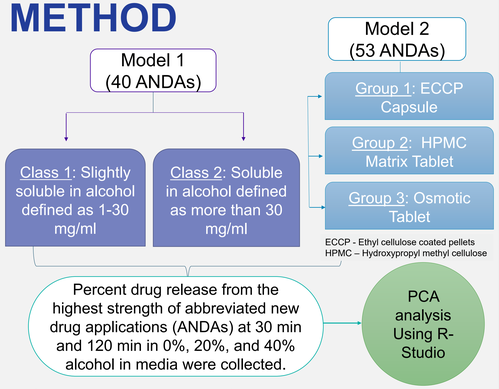
PURPOSE

- In vitro alcohol dose dumping (ADD) testing is a quality tool used to predict the potential of accidental dose dumping from modified release (MR) formulations when mixed with alcoholic beverages.
- To understand the driving force for ADD in MR formulation, we developed a sequential analysis using principal component analysis (PCA).

OBJECTIVE

To investigate the impact of active pharmaceutical ingredient (API) solubility in alcohol and formulation designs with different rate controlling (RC) polymers on ADD of MR products.

METHOD



- PCA is applied to identify similarities and dissimilarities among the independent factors: model 1 and 2.
- Percent drug release was used as numerical data.
- PCA score plots were used to evaluate the data structure and identify clusters, outliers, and trends.
- PCA loading plots determines which variables demonstrated the most impact on each component.

RESULTS

Figure 1: PCA score plot and PCA loading plot from Model-1 – Impact of API solubility on ADD using alcohol concentrations as variables and two dissolution time points, i.e., 30 minutes and 120 minutes.

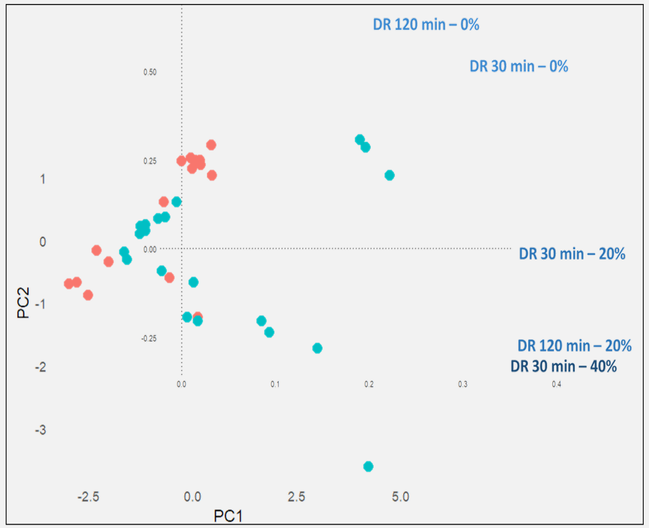
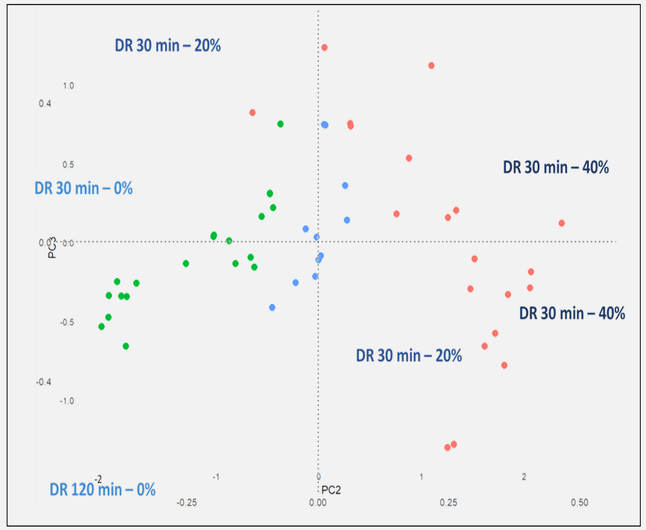


Figure 2: PCA score plot and PCA loading plot from Model-2 – Impact of formulation design on ADD using alcohol concentrations as variables and two dissolution time points, i.e., 30 minutes and 120 minutes.



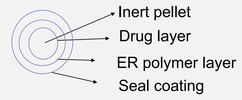
- Model-1 contains two classes of categorical data based on solubility. It appears PC2 represents the variability in data based on the alcohol concentration in the dissolution media. There was no apparent trend observed for PC1. The score plot for Model-1 did not reveal any distinct clusters with respect to API solubility (figure 1).
- The score plot and loading plot for Model-2 (figure 2) show that HPMC matrix data points are clustered around the center of PC3 with little variability in the quadrant represented by low alcohol concentrations (i.e., 0% and 20%) at 30 min.
- This suggests that the HPMC matrix tablets are largely unaffected by higher concentrations of alcohol (i.e., 40%) and may preferentially release the maximum percent of drug in 20% alcohol.
- The cluster for ECCP capsules is spread across and predominantly located in the right half of the PC space which represents data collected in 40% alcohol media. This suggests that the ECCP capsules experience maximum drug release in 40% alcohol.
- As expected, release from osmotic tablets does not appear to be influenced by alcoholic media or time as evidenced by the centered clustering of this group in the PCA space. This aligns with our current understanding that osmotic tablets release drug at a rate that is independent of dissolution hydrodynamics.
- HPMC is insoluble in alcohol, ethyl cellulose is soluble in alcohol and therefore, ADD of these formulations appears to be dependent on RC polymer solubility.

CONCLUSION

- Model-1 results suggest that the API solubility in alcohol appears not to impact ADD.
- Model-2 results suggest that formulation design and solubility of RC polymer are critical factors affecting ADD in MR formulations.

What Happens to ER Mechanism of These Formulations

ECCP Capsule



In Presence of Alcohol

- Destruction of ER layer leading to exposure of drug to dissolution media

HPMC Matrix Tablet

– RC polymer not soluble in alcohol

Formation of gel layer around matrix which controls drug release through HPMC matrix

Presence of alcohol in dissolution medium did not impact the gel layer and hence ER mechanism is retained

Osmotic Tablet

The osmotic tablets release drug at a rate that is independent of dissolution hydrodynamics.

DISCLAIMER

This work reflects the views of the authors and should not be construed to represent FDA's views or policies

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