PHYSICOCHEMICAL PARAMETERS AS A PREDICTIVE TOOL FOR OPTIMUM DISPERSION OF ACTIVE PHARMACEUTICAL INGREDIENTS

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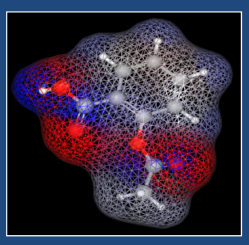
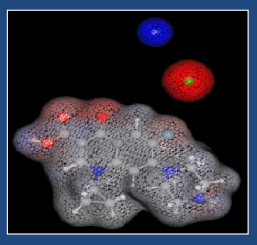
Introduction

Particle size analysis of active pharmaceutical ingredients (API) using wet dispersion is by far the most widespread method in the pharmaceutical industry. However, despite this being a well established procedure, there are still no hard-and-fast rules which give an indication of which dispersing conditions may be most effective at dispersing the API particles prior to their application. Usually, the analyst takes a system specific approach, and tries a number of different dispersing liquid and surfactant combinations until the desired degree of dispersion is achieved.

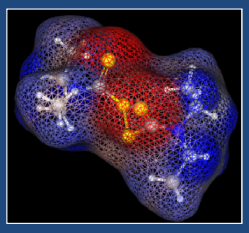
This study addressed the possibility of constructing a **predictive model that may give an indication as to the effectiveness of a specific set of dispersion conditions prior to their application**, particularly for **dispersions in hydrophobic media**.



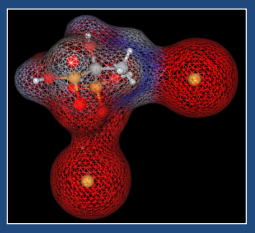
acetylsalicylic acid



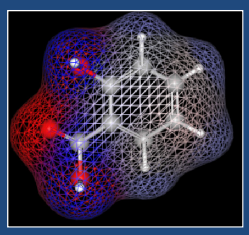
ciprofloxacin HCl



disulfiram



etidronate disodium



salicylic acid

Methodology

The preparation of a wet dispersion required the API particles to be in a physical state where the physicochemical affinity between the dispersing liquid and the dispersing agent was not high so as to produce a molecular dispersion, but not lacking affinity such that the dispersing agent favoured interfaces other than the solid-liquid one, resulting in aggregation of the particulates.

Five APIs were analysed: **acetylsalicylic acid**, **ciprofloxacin hydrochloride**, **disulfiram**, **etidronate disodium** and **salicylic acid**. Dispersions were prepared in dispersing media with different **physicochemical properties**, notably *density*, *surface tension* and *kinematic viscosity*.

- The **dispersion stability** was evaluated by using a method analogous to that employed when using a turbidimeter. The propensity of the primary particles to settle to the bottom of the containing vessel was monitored as a function of time by quantifying optical density in terms of the absorbance of the particulate sample at 600 nm.
- The **wetting profile of each API** was characterised by monitoring the rate of permeation of each dispersing solution into the pores of the solid powder, and the relative efficacy with which each dispersing solution wetted the active ingredient particles was statistically analysed

Correlations between the API physicochemical properties and the adequate choice of dispersion medium were statistically computed.

Results and Discussion

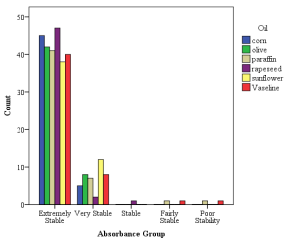
Physicochemical Properties of Dispersing Media

	ethanol	methanol	n-propyl acetate	isopropyl acetate	Vaseline Oil
Kinematic Viscosity (mm^2/s)	1.421	0.681	0.640	0.569	145.955
Density (g/mL)	0.675	0.677	0.861	0.785	0.861
Surface Tension (dynes/cm)	22.015	21.680	23.450	20.745	30.785

	sunflower oil	corn oil	rapeseed oil	olive oil	paraffin oil	Vaseline Oil
Kinematic Viscosity (mm^2/s)	64.125	63.011	70.605	75.571	140.376	145.955
Density (g/mL)	0.845	0.840	0.834	0.836	0.772	0.804
Surface Tension (dynes/cm)	32.580	32.645	32.580	32.250	31.005	30.785

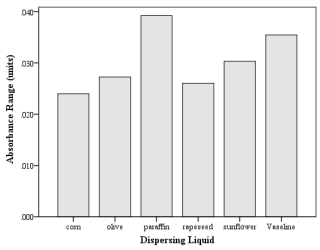
The study was initiated with a set of *five dispersing liquids*. It was observed that enhanced dispersions were afforded by the more ***viscous dispersing liquids***. Five other dispersing liquids were selected for analysis.

API Powder Dispersion Stability



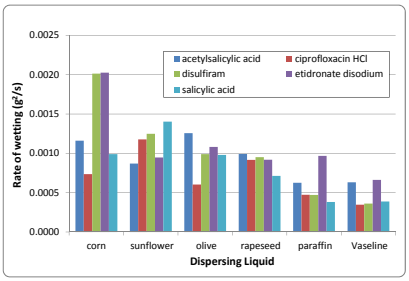
The use of oils as dispersing liquids resulted in ***extremely stable dispersions***. These dispersing liquids were taken to provide the framework for *extended dispersion stability.*

However, the *API dispersion stability in paraffin and Vaseline Oil was not infinite.* Rather oils with lower viscosities exhibited more extended dispersion stabilities.



API Powder Wettability

Powder wettability results indicated that as the attractive forces between molecules increased in magnitude, the *more viscous oils were impeded from flowing freely and penetrating into the API powder bed*. Thus, the rate of wetting of the powder surfaces was relatively slower in the case of Vaseline Oil and paraffin oil, and particle settling could have commenced prior to complete wetting.



Conclusions

1. In terms of the ***dispersing medium***, the optimised sample preparation was related to the interplay between the dispersing medium's ability to affect powder wetting in a relatively short period of time and to confer resistance to settling, both processes significantly dependent on viscosity.
2. While **surfactants** are usually chosen because of their stabilising effects on the dispersion stability, the study indicated that differences in the *hydrophilic-lipophilic balance* of these surface active agents were related above all to the rate of wetting of the API, rather than to the rate of settling.
3. As regards the ***active pharmaceutical ingredients***, the physicochemical property *percentage polarity* was the only parameter which was correlated to dispersion stability. This was taken to be indicative of the strength of intermolecular forces of attraction between API molecules.

References

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