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Advanced imaging, detection and prediction of initial gel formation and swelling of hypromellose compacts

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PURPOSE

The purpose of this work was to combine the Alicona® infinite focus microscope (IFM) with the new Sirius surface dissolution imaging system (SDi2) to detect similarities or potential differences in the initial gel formation of HPMC CR and DC2 (K100M grades) pure polymer compacts.

OBJECTIVE(S)

The objectives for this work were:

- To develop a method for the analysis of tablet surfaces using the IFM and focus variation.
- To identify a number of surface metrology parameters to describe key surface features necessary for behaviour prediction.
- To develop a method of analysing whole polymer tablets with the SDi2.
- Combine data from the IFM and the SDi2 to provide a complete analysis of the initial swelling behaviour of the polymer tablets.

METHOD(S)

Compact Manufacture

Polymers of the CR and DC2 grades with a target weight 250mg were compacted using the Piccola 10 station automated tabletting machine with SMI software (Riva, Argentina). All tablets were compressed at a force of15kN.

Focus Variation Analysis (Alicona IFM)

10 tablets from each batch were profiled using a 20x magnification. The 3D data sets were analysed further using the Surfstand software (Taylor-Hobson, UK).

Surface Dissolution Imaging (Sirius SDi2)

Swelling experiments were performed using the SDi2 whole dosage flow cell and a wavelength of 520 nm. The swelling of the polymer compacts were measured in water at a temperature of37 ± 0.5 °C for 2 hours. Width measurements were conducted using the bespoke SDi2 software. Statistical analysis of the data was performed using IBM® SPSS® Statistics.

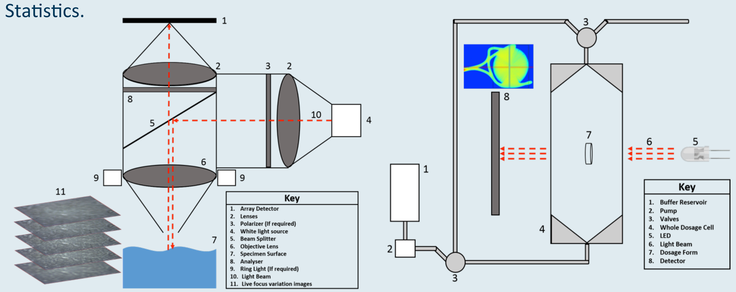


Fig 1. Schematic representation of A) IFM and B) SDI2

RESULT(S)

Focus Variation Analysis

The FVI showed that the surfaces of both the CR and DC2 tablets were different. This appeared to be primarily as a result of the morphology of the individual particles; spherical in the DC2 polymer and ribbon like in the CR polymer. A number of key surface metrology parameters were selected to describe the differences on the surface of the compacts. These were; Sq to determine the vertical scale and mean area of the surface, Sal to determine the lateral scale of the surface and confirm accurate filtration, Str to determine texture uniformity, Sdr to calculate the area gained by the surface as a result of its texture and Vvv to determine the fluid retention ability of the surface. Percentage lubrication availability was also calculated for the surface.

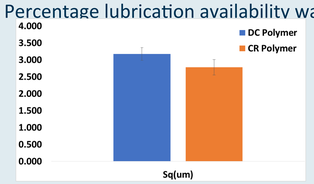
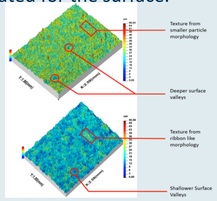


Fig 2: Focus Variation Parameters and an Areal Data Plot



The DC2 polymer compacts were found to be greater in value for Sq (3.177µm), Sdr (8.078 %) and Vvv. This indicates that the DC2 polymer has a higher vertical scale, larger surface area as a result of its surface texture and greater fluid retention. This indicated that the DC2 compacts should wet quicker than the CR tablets under dissolution and as a result swell at a quicker rate. The CR compacts had a higher Sal value of 0.067 mm indicating that the CR surfaces have a larger lateral scale. Both polymers produced surfaces with a Str value >0.5 indicating that the surface texture is uniform in all directions and thus represents the whole surface of the tablet. The null hypothesis (i.e. both surfaces are the same) was rejected for; Sq ($p = 0.001$), Sal ($p<0.001$), Sdr ($p < 0.001$) and Vvv ($p < 0.001$). Indicating that the surfaces are statistically different.

Swelling Analysis (SDi2)

The SDi2 was very capable of monitoring and detecting small changes in the polymer compacts. The system also produces a real time dissolution video that provides further insight into the behaviour of the dissolving compacts. The DC2 polymer formed a swelled to a greater width between 2 and 20 minutes. After this point, at 60 minutes, the CR polymer swelled to a similar size as the DC2 polymer. At 120 minutes the CR polymer swelled to a slightly greater size than the DC2 polymer. The swelling data plot also confirmed this observation.

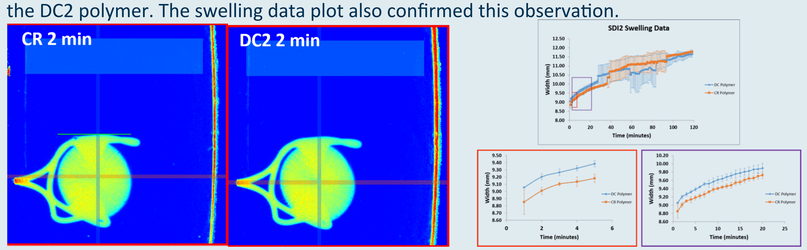


Fig 3. SDi2 Swelling images of CR and DC2 with Plot

RESULT(S)

Combination of the two techniques

The SDi2 data correlated with the results from the FVI that surface topography had an influence on the swelling behaviour of the tablets during the initial wetting and dissolution. After 20 minutes, with the gel layer formed, surface topography is no longer a contributing factor to the swelling of the polymers. Instead the chemistry of the polymer is a controlling factor and with both polymers having the same K100M chemistry it is expected that they should be similar. The null hypothesis (swelling profiles are the same) could be rejected at 5 and 20 minutes ($p = 0.046$ and $p = 0.012$ respectively) however, the null hypothesis was retained for the experiment as a whole DC2 at 120 minutes ($p = 0.743$).

CONCLUSION(S)

The novel combination of the SDI2 and FVI showed a number of key differences between the surfaces of DC2 and CR compacts. FVI showed that the DC2 polymer had a larger vertical scale, larger fluid retention capability and a larger surface area as a result of its topography. The FVI data led to an initial hypothesis that the DC2 polymer compacts will wet and swell initially better than the CR polymer. The SDI2 then tested this hypothesis and found that initially the swelling of the DC2 polymer was indeed greater than that of the CR polymer at both the 5 minute and 20 minute points of the experiment. This difference was also found to be statistically significant. The SDI2 also detected other differences in the gel layers formed by both the DC2 and CR polymers that casts doubt on the ability of the DC2 polymer to effectively manage and control drug release. This work highlights the potential of the FVI to be used within pharmaceutics as prediction tool for the behaviour of compacts under dissolution and also as a tool to help guide formulation. This work also displays the new capabilities of the Sirius SDi2 and the system's ability to monitor swelling of whole dosage forms in real-time with high levels of detail.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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