Development and characterization of microcapsules containing acetylsalicylic acid for long term suspension in acidic aqueous environment

S.S, Kuang[a], J.C., Oliveira[a], , A. M, Crean.[b]
[a] Department of Process and Chemical Engineering
[b] School of Pharmacy
University College Cork, Cork, Ireland (s.kuang@mars.ucc.ie)

Introduction

Beverages can be an excellent delivery medium for active pharmaceutical ingredients (API), providing a pleasant and easy form of ingestion. If the API can be protected from dissolution in the aqueous environment of the beverage by a coating, it can also be protected from the even more aggressive environment of the stomach, and be released only in the intestinal tract. The result would be an easy-to-take medicine (even for elderly who may have difficulties swallowing pills), with the potency of a suppository, as it is released only in the gut and protected from the digestive fluids.

Microencapsulation has been widely used in both pharmaceutical and food industries and has the potential to develop particles with delayed release characteristics controlled by pH.

In this study, acetylsalicylic acid (ASA) crystals were microencapsulated by direct coating with different levels of enteric polymer (EUDRAGIT® L 30 D-55) using fluidized-bed coating technology. The release of the drug from the microcapsules was analysed using a full factorial experimental design to ascertain the influence of different levels of coating (50, 60 and 70%), temperature (storage, 25^{o}C, and human body temperature, 37^{o}C), and pH (mimicking the human stomach, pH 1.3, typical juice drinks, pH 3.8 and mimicking the human gut, pH 7).

Materials and methods

An enteric coating suspension was prepared by pre-mixing Tween 80, dibutyl sebacate, and talc and homogenizing for 10-30 minute. The suspension was then poured in the EUDRAGIT® L 30 D-55 (provided by Röhm GmbH, Germany) while stirring gently. All chemicals used were Ph. Eur. grade.

200g ASA crystals (Sigma-Aldrich) were film coated using a fluidized-bed coater, top spray (Glatt WSG 2). The settings for the operating variables were based on previous work: inlet temperature, 28-40^{o}C, exhaust air temperature, 25-30^{o}C, inlet air volume, 265 m^{3}/h, liquid flow rate (average), 10.5 g/min, atomizing air pressure, 2 bar. 50g samples each were collected after the required coating level of polymer was applied. The coated products were cured at 40^{o}C in an oven for 1 hour, and sieved to remove the agglomerates (>1.25mm).

The characteristics of the uncoated and coated crystals were examined by scanning electron microscopy (SEM). The crystals were cracked with a needle for the cross section images and coated with gold prior to observation with a scanning electron microscope (Jeol, JSM-840A, Germany).

Dissolution of the coated ASA crystals was conducted in 500ml of dissolution media. 1 ml of samples were withdrawn and filtered at pre-determined time intervals. The amount of ASA released was determined using the HPLC method described in the British pharmacopoeia for enteric-coated aspirin tablets.

A full factorial experimental design was applied, that is, all possible combinations of the 2 or 3 settings considered for each variable were tested.

Statistical analysis was done using Statistica 7.1 (StatSoft, Inc., USA).

Results and Discussion

ASA microcapsules with a thick polymer coating were produced. Figure 1a shows the final microcapsules formed consisted of aggregates of individually coated particles that had subsequently stuck to each other and had been over coated with the coating suspension. Figure 1b shows a cross-section of coated ASA crystal with 70% w/w polymer. The coating was applied as a thick and distinct layer. The coating thickness achieved was 74.94±13.77µm.

The ASA release from the microcapsules coated with different levels of EUDRAGIT® L 30 D-55 coating was tested at different temperatures and pH values. Figures 2 and 3 show the release profiles of ASA from the microcapsules in the acidic media at 25°C and 37°C, respectively. Cumulative ASA release was increased for all microcapsules at 37°C compared to 25°C. In acidic media (pH1.3 and pH3.8) the release of ASA was primarily diffusion-controlled, and therefore slow. The coating polymer is in an unionized form, thus insoluble. The insoluble polymer coat results in a long diffusion-path for the drug to diffuse through.

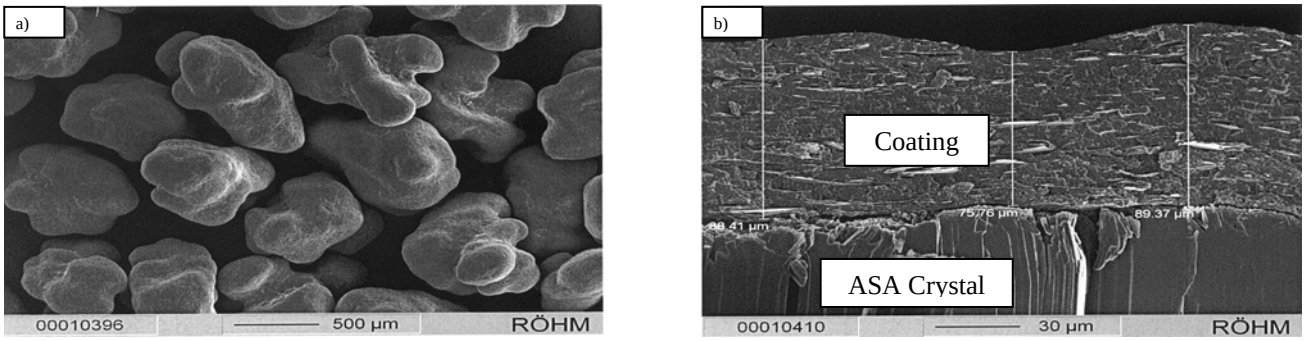

Figure1 : SEM picture of a) coated ASA with 70% polymer (w/w) (magnification 30X); b) cross section of coated ASA with 70% polymer (w/w) (magnification 500X)

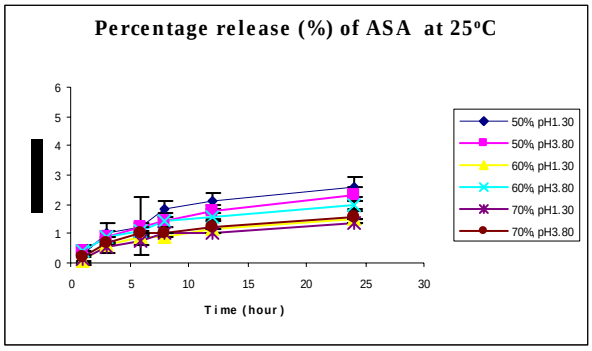

Figure 2 Cumulative release of ASA at 25°C (n=4)

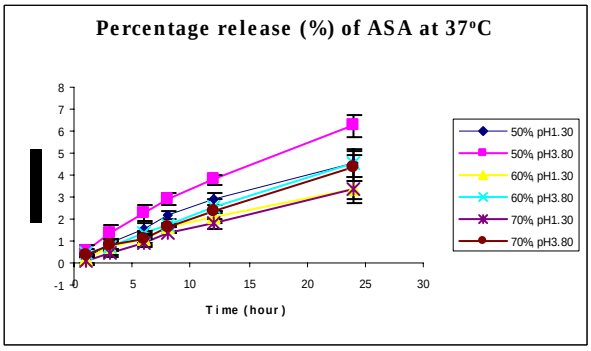

Figure 3 Cumulative release of ASA at 37°C (n=4)

At pH 7.0 the drug release was considerable faster (Figure 4). At this pH, the coating polymer is ionized; and therefore the release was dissolution controlled. The carboxylic groups in EUDRAGIT® L 30 D-55 begin to ionize in aqueous media at pH5.5 and above, consequently the polymer is resistant to acidic environment but soluble at neutral or alkaline pH (Bruce et al., 2003). The lower percentage release in pH 7.0 at 37°C compared to 25°C is due to degradation of ASA to salicylic acid and acetic acid in solution. As expected the rate of this reaction is greater at higher temperatures. Degraded ASA is not accounted for in the percentage release values shown.

Statistical analysis was applied in order to identify the relationship between the independent variables studied (level of coating, pH and temperature) and the dissolution characteristics. The data for pH 7 were removed, as the effect of pH in this region is so significant that it would dominate all other effects. The analysis is therefore valid for the pH range 1.3 to 3.8, temperature 25 to 37 °C, and coating level from 50 to 70%, only. The data was very well fitted by a quadratic model, with a coefficient of variation R^2 of 98.9%, which is very high and therefore gives good confidence on the conclusions. Figure 5 shows the statistical significance of all effects in a Pareto chart. Effects that are statistically significant are those whose bars go over the p=0.05 vertical dashed line. It can be seen that all 3 factors are significant, as well as the interaction between temperature and pH. The only quadratic effect that was analysed was that of the coating level, which was negligible.

The response surfaces are shown in figures 6 and 7. The former shows that the nature of the interactive effect between pH and temperature is that the effect of pH is significant at the highest temperature, and not really at the storage temperature.

At 25°C, only the 50% and 60% coating level show significant difference on ASA release, there is no significant difference between 60% and 70%.

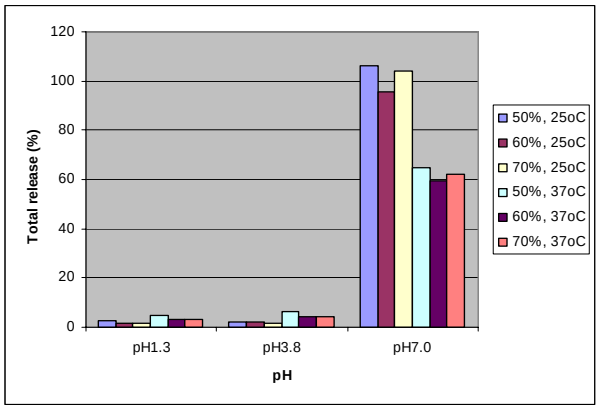

Figure 4. The average of cumulative ASA release (%) at pH1.30, pH3.80, and pH7.0 after 24 hour at 25°C and 37°C

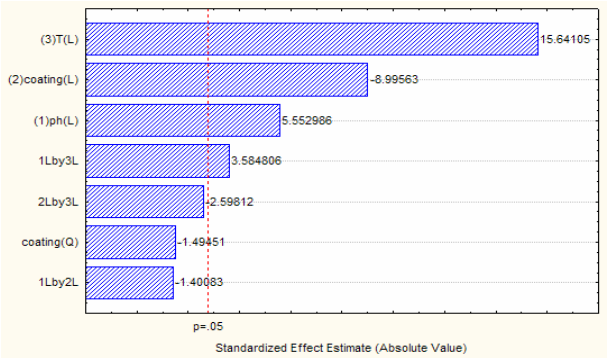

Figure 5. Pareto chart of the effects of T, pH and coating level on the release after 24 hours. The vertical line indicates the 95% confidence level of statistical significance

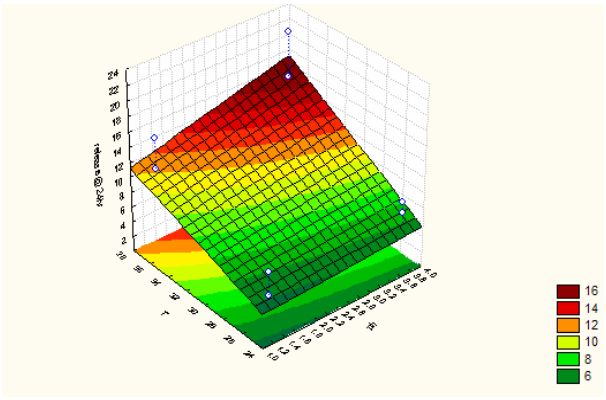

Figure 6. Average accumulated release at 24 hours for 60% coating as a function of pH and temperature (T, ^{o}C)

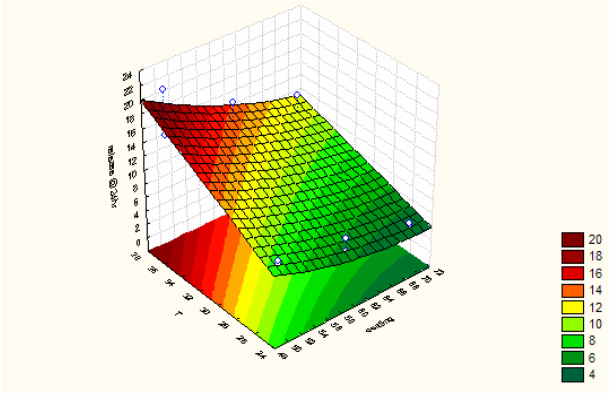

Figure 7. Average accumulated release at 24 hours as a function of temperature (T, ^{o}C) and coating level (%)

Conclusions

This study shows promising results by applying thick coating of Eudragit L-30 D-55 to protect the active ingredient in acidic drinks for long shelf life at room temperature. Statistical analysis show that temperature, pH and coating level all have significant effects on the release of ASA. At 25^{o}C, only 50% and 60% coating level show significant difference on ASA release, there is no significant difference observed between 60% and 70%. In conclusion, the ASA coated with high coating levels (60% and 70%) showed slower release at the desired drink storage conditions (pH 3.8 and 25^{o}C) and stomach environment (pH1.3 and 37^{o}C), but fast release in the intestine (pH5 to over 7, 37^{o}C). 60% coating level is concluded to be the best of three tested.

Acknowledgements

This work was supported by the Department of Agriculture and Food, Ireland, under the National Development Plan 2000-2006. The authors would like to thank Röhm Pharma, Darmstadt, Germany for providing the coating polymer and for their technical help.

Reference

Bruce, L.D. et al. (2003). The influence of polymeric subcoats and pellet formulation on the release of chlorpheniramine maleate from enteric coated pellets. *Drug Development and Industrial Pharmacy, 29 (8), 909-924*.