

Preparation of Sustained-Release Matrix Tablets of Aspirin with Ethylcellulose, Eudragit RS100 and Eudragit S100 and Studying the Release Profiles and their Sensitivity to Tablet Hardness

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Abstract

A sustained-release tablet formulation should ideally have a proper release profile insensitive to moderate changes in tablet hardness that is usually encountered in manufacturing. In this study, matrix aspirin (acetylsalicylic acid) tablets with ethylcellulose (EC), Eudragit RS100 (RS), and Eudragit S100 (S) were prepared by direct compression. The release behaviors were then studied in two counterpart series of tablets with hardness difference of three Kp units, and compared by non-linear regression analysis. The release pattern for both the S-containing and RS-containing formulations fitted best in Higuchi model, and the proper equations were suggested. In the EC-containing formulation, Higuchi and also zero-order models were probable models for the release, and a combination equation for the release was suggested. In the S-containing formulation, the release profile was completely sensitive to the hardness change. In RS-containing series, the slope of the release graph did not change due to the hardness decrease, but the y-intercept or the lag time in release was decreased. In EC-containing matrix tablets, both the slopes and the y-intercepts did not change by the decrease in hardness. In conclusion, EC with an amount as little as 10 percent in formulation could make sustained-release aspirin tablets in which the release profile is not sensitive to moderate changes in hardness.

Keywords: Aspirin; Ethylcellulose; Eudragit; Matrix tablet; Sustained-release; Release rate; Hardness.

Introduction

Aspirin (acetylsalicylic acid) is one of the oldest drugs known at present, which is still the most common. The main adverse effects associated with it, are the gastrointestinal disturbances and ulcers. Sustained-release tablets of aspirin not only could provide a more constant plasma concentration with less frequent administration, but also could help decrease the side effects to some extent. This could extend its safe administration and improve patient compliance. In sustained-release technology, directly compressed matrix tablets are the most attractive

both scientifically and economically. Among the different polymers used for this purpose, some Eudragits have been used successfully to obtain appropriate sustained-release matrix formulations of different active materials (1-3). Ethylcellulose has also been successfully used in preparing matrix-type sustained-release tablets of different drugs (4-9).

The usual diffusion-controlled mechanism of release in matrix tablets represents a release profile of the Higuchi model, in which the release rate is decreased with time. This is in contrast with the ideal constant release rate, i.e. zero-order model. In most studies, matrix tablets containing ethylcellulose, Eudragit RS and Eudragit S have been reported to show a

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Higuchi release model (4-5, 10-11), while in another study a release profile resembling the zero-order model has been reported for an ethylcellulose matrix tablet (8).

In manufacturing tablets, considering the behavior of the powders or granules to be compressed is of great importance. It has been observed that by increasing compaction force, hardness value increases. Usually an increase in hardness of a tablet is accompanied by a decrease in release rate, due to a decrease in porosity of the tablet (5, 6). This sensitivity of the release profile to the tablet hardness is of great importance in industrial production of sustained-release tablets. This is due to the likely changes in hardness values of the compressed tablets, which could cause non-uniformity of the release profile in different batches produced or even in individual tablets within a production batch.

In this study, sustained-release aspirin tablets with different amounts of ethylcellulose, Eudragit RS100 and Eudragit S100 were prepared by direct compression. They were then studied with regard to their release behavior. The appropriate formulations from the three series were chosen and the best-fitted equations for their release were suggested. Then, the effect of tablet hardness on the release rate from these formulations was evaluated and results compared to each other.

Experimental

Materials

The main materials used in this study, were aspirin (acetylsalicylic acid) crystals (Temad Pharmaceutical Manufacturing Company, Iran), ethylcellulose powder with ethoxyl content of 48% and viscosity grade of 22 cps (Aldrich Chem. Co. Ltd., England), Eudragit RS100 and Eudragit S100 (Rohm-Pharma, Germany).

Methods

Preparation of polymeric matrix tablets of aspirin

Different formulations of aspirin matrix tablets with different amounts of the polymers ethylcellulose (5%, 10%, and 20%), Eudragit RS100 (10%, 20%, and 30%), and Eudragit

S100 (10%, 20%, and 30%) were designed and prepared by direct compression. All the materials were weighed accurately and passed through a 35-mesh sieve. The mixing was performed in a cubic mixer (Erweka, Germany). All formulations (containing 400 mg aspirin) were compressed into flat 12 mm diameter tablets, by EKO model single-punch tablet machine (Erweka, Germany). The compression force was adjusted separately for each formulation so that the corresponding crushing strengths of tablets were at maximum.

Determination of hardness and friability of the tablets

Ten tablets from each series of the compressed tablets were tested for the diametrical crushing strength using the Erweka TBH 28 hardness tester. The crushing strengths (hardness values) were determined and reported as mean \pm 1SD. The friability of the tablets was also tested by an Erweka TA Roche-type friabilator at a speed of 25 rpm for 4 minutes. The acceptable formulations from these tests were then promoted towards the dissolution tests.

Dissolution test

Dissolution test was performed on six tablets from the formulations accepted by friability and hardness (crushing strength) tests. The USP apparatus 2 (Erweka DT6R Dissolution Tester) at a speed of 30rpm, with 1000 ml distilled water as the dissolution medium was used, and samples were taken after 1, 2, 4, and 8 hours. The amounts of dissolved aspirin were then determined by spectrophotometry at 265 nm, using filtered portions of the samples. The release in any time was obtained by calculating the mean cumulative percent release of the 6 tablets tested. These test conditions were according to test 2 in the monograph of aspirin extended-release tablet in USP XXIV (12). The percent drug release was then graphed against time and the release profiles studied. Three different Pharmacokinetic models, i.e. Higuchi, zero-order, and first-order models were studied using non-linear regression analysis performed by the SPSS computer program, and the best equations were suggested.

Studying the effect of tablet hardness on release profile

After performing the dissolution test on the best formulations obtained from the three polymers investigated, another series of tablets with a hardness value of 3 KP units lower was compressed from the same formulations. The tablets were then tested for their release behavior the same way as above. The slopes and y-intercepts of the release graphs for the two counterpart series with different hardness values were compared by non-linear regression analysis performed by the SPSS computer program (p values of less than 0.05 were considered significant).

Results and Discussion

An ideal matrix formulation should contain polymers and diluents at amounts as little as possible, as well as releasing its content in a sustained release profile over a reasonable length of time, and preferably with a zero-order kinetic. The results of the release studies are summarized in figures 1-3. There have been reports that lower viscosity grades of ethylcellulose have higher fragmentation rates and plasticity which results in harder tablets with lower porosity and a more sustained release pattern (5-7, 10). Also, even in constant hardness, low viscosity grades have shown more sustained release pattern, which may be due to extensive plastic deformation of these grades of ethylcellulose even at low compression pressures (5). Therefore, in this study the 22-cps grade of ethylcellulose was selected. As it has previously been reported for the water-soluble diphenhydramine hydrochloride (7), increasing the amount of the polymer in this study extended the release process of aspirin to a higher degree (Figure 1). As the figure shows, the 20% ethylcellulose matrix tablets (EC series) showed a very much sustained profile of release, which was not suitable, while the 5% formulation could not decrease the release rate to an acceptable level. The 10% formulation, with a hardness value of 8.0 ± 0.7 KP, showed the desired release profile over the test period (Figure 1). In this selected formulation, the calculated regression coefficients for Higuchi, zero-order, and first-order models were 0.9980, 0.9874, and 0.9375

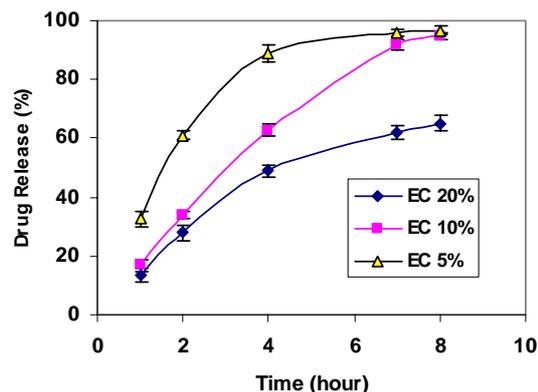


Figure 1. Aspirin release profiles from different percent EC-containing matrices (n=6, mean \pm SD)

respectively. Therefore, the release seems to fit in the Higuchi model. This has also previously been reported for ethylcellulose matrix tablets containing other drugs (5, 10 and 13). The Higuchi model is usually considered to be applicable up to about 75-80% of the drug released (5), or 75-80% of the time needed for complete release (10). Therefore, the regression coefficients for the first part of the release process (up to 4 hours) were also calculated as being 0.9989 and 0.9990 for the Higuchi and zero-order models, respectively. Therefore, both of these models could be applicable, although the Higuchi model seems to fit better, since it had a higher "r" value for the whole release process. In our study, the best curve for the release process according to the Higuchi model has the following equation:

$$\text{Drug Released (\%)} = 44.14 t^{1/2} - 27.31$$

The equation has a negative y-intercept, which represents a lag time of about 20 minutes in release. However, the zero-order model has also a high regression coefficient, i.e. 0.9874 for the full length of time and 0.9990 for the initial period, which makes it a probable model for the release. Ethylcellulose has a tendency to erode slowly, which could be promoted by the presence of erosion-promoting ingredients (8). The erosion of the tablet could gradually reduce the diffusion path length, which in turn attenuates the decreasing of the release rate in Higuchi model, making the pattern to resemble zero-order model. In a previous study, the release of theophylline from ethylcellulose matrix tablets showed a zero-order model from the 1st to 10th hour (8). A combination equation

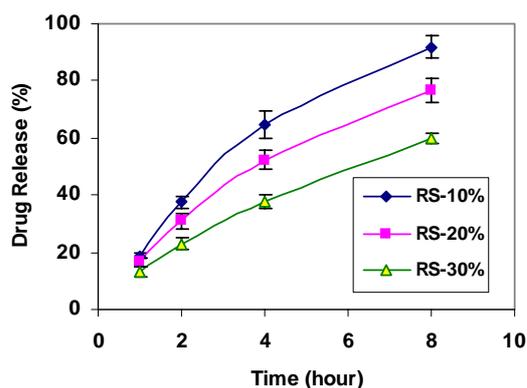


Figure 2. Aspirin release profiles from different percent RS-containing matrices (n=6, mean±SD)

taking into account the both mechanisms, i.e. diffusion and erosion, would best represent the dissolution profile. The following equation was calculated and suggested for the present release process ($r = 0.9985$):

$$\text{Drug Released (\%)} = 55.26 t^{1/2} - 2.87 t - 36.67$$

This equation has also a negative y-intercept, which is related to a lag time of about 28 minutes. The lag time could be related to the time required for the erosion to begin.

The 10% and also 20% Eudragit RS100 matrix tablets (RS series) showed a desired release profile (Figure 2). In a previous study, an appropriate release pattern has been reported for a 12.4% matrix of the same polymer (14), while in another study only 3% of the polymer was sufficient to produce an acceptable release rate (3). The formulation with the lower amount of polymer (i.e. 10%) which had a hardness value of 8.3 ± 0.7 KP was selected as the desirable one. In this selected formulation, the calculated regression coefficients for Higuchi, zero-order and first-order models were 0.9963, 0.9197, and 0.9060 respectively. The Higuchi model is usually considered to be applicable up to about 75-80% of the drug released (5), or 75-80% of the time needed for complete release (10). The calculated regression coefficient for this model during the first part of the release process (up to 4 hours) was 0.9999. From these results, the Higuchi model seems the best-fitted model, which indicates a diffusion-controlled mechanism of release. On the contrary, in a previous study release of the water-soluble quinine hydrochloride from matrices of the same polymer was observed to fit to first-order

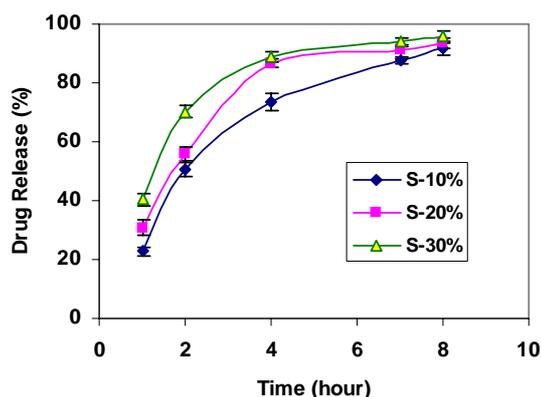


Figure 3. Aspirin release profiles from different percent S-containing matrices (n=6, mean±SD)

kinetic in the first part and Hixon-Crowell equation in the last part (1). This could be due to the fact that they used a water-soluble active compound and also polyvinylpyrrolidone as an excipient in their formulation, which would impart other mechanisms into the release process. Our suggested equation for the release from this matrix is as follows ($r = 0.9963$):

$$\text{Drug Released (\%)} = 40.03 t^{1/2} - 19.30$$

The equation has a negative y-intercept and represents a lag time of about 14 minutes in release. This could be explained as the required time for the polymer to absorb water and swell.

The 10% Eudragit S100 matrix tablets (S series), with a hardness value of 9.9 ± 0.6 KP showed the desired release profile over the 8h-experiment period (Figure 3). It is interesting to note that, increasing the polymer content in this series of formulations (up to 30%) increases the dissolution rate. This may be due to the fact that above the dissolution pH of this polymer, its matrix structure completely dissolves hence increases the available aspirin surface for dissolution. In a previous study, 3% of this polymer has been reported to be sufficient to produce a sustained release profile of aspirin (8). In this selected formulation, the calculated regression coefficients for Higuchi, zero-order and first-order models were 0.9720, 0.9236, and 0.8854 respectively. The calculated regression coefficient for the Higuchi model during the first part of the release process (up to 4 hours) was 0.9872. From these results, the Higuchi model seems the best fitted model and the equation is suggested as follows:

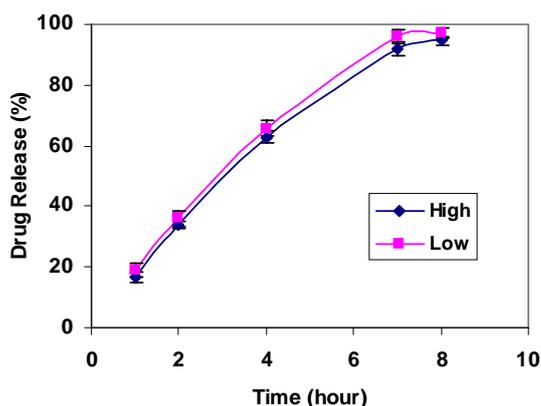


Figure 4. Aspirin release profiles from EC (10%)-containing matrices with different hardnesses (n=6, mean±SD)

$$\text{Drug Released (\%)} = 33.28 t^{1/2}$$

In the present study, the release profiles were studied in three counterpart matrix tablets with a hardness value of about 3 KP units lower than the selected formulations with maximum hardness values. The release graphs were then statistically compared to the graphs for the formulations with the maximum hardness values, by non-linear regression analysis performed by the SPSS computer program.

Changing the hardness could affect the release rate through changing the porosity of tablet (5, 6). However, in selected ethylcellulose matrix formulation in this study, lowering the hardness value of 3.0 KP units did not cause a prominent difference in the release profile (Figure 4). The non-linear regression analysis showed that both the slopes and the intercepts are the same. This shows that the formulation is not sensitive to moderate changes in hardness, with regard to the release rate. Of course in low compression forces and hardness values, changing the hardness of ethylcellulose matrix tablets has been reported to result in a significant change in dissolution rate (8). However, since ethylcellulose has plastic deformation properties and a tendency to coat the drug particles, high compression forces result in hard tablets with low porosities. In high compression forces, a continuous matrix is formed and the change in tablet hardness causes relatively small change in porosity and therefore the release rate (5, 10). In the release graph of RS-containing matrix tablets (Figure 5), the non-linear regression analysis showed that the slopes are the same, but the intercepts have statistically significant difference. Therefore, the release rate of the

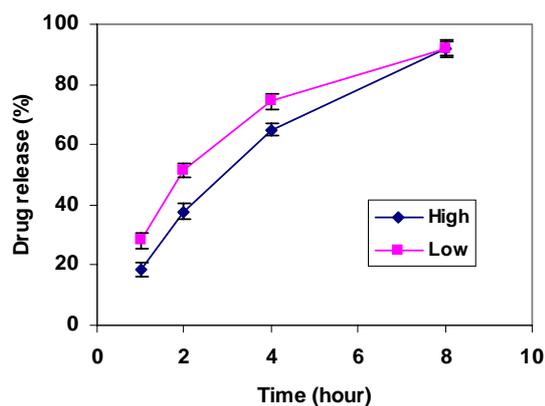


Figure 5. Aspirin release profiles from RS (10%)-containing matrices with different hardnesses (n=6, mean±SD)

Eudragit RS series was not so much sensitive to this change in hardness (Figure 5), but the lag time was reduced due to the decrease in hardness. The Eudragit S formulation was completely sensitive to the above-mentioned change in tablet hardness, with regard to release (Figure 6).

Conclusion

Ethylcellulose could make sustained-release aspirin tablets, with amounts as little as 10 percent in formulation. Its pharmacokinetic model of release is not absolutely the Higuchi model and the decreasing in release rate, characteristic of the Higuchi model, is attenuated. The release profile has a zero-order like component and could be explained by the combination equation suggested. Also, both the slope and the y-intercept of the release graph would not change due to moderate changes in tablet hardness. This change in hardness may be encountered during the industrial production of

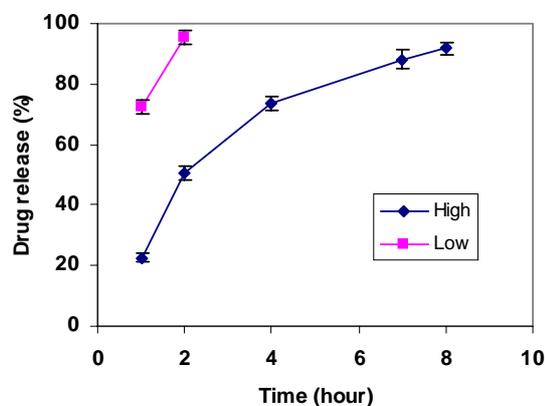


Figure 6. Aspirin release profiles from S (10%)-containing matrices with different hardnesses (n=6, mean±SD)

the tablets, and this insensitivity of the release profile to moderate changes in hardness would be of great importance in industrial production. Therefore, ethylcellulose is suggested as an ideal candidate for production of directly compressed matrix sustained-release aspirin tablets.

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