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Research Article

Effect of compression force, humidity and disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant

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Abstract

Purpose: *The effect of compression force, relative humidity and disintegrant concentration on furosemide dissolution in directly compressed furosemide/Avicel®-tablets was studied.*
Methods: *Mixtures of furosemide (12.5% w/w), Ac-Di-Sol® (0, 0.625% to 10% w/w) and Avicel® PH200 (qs to 100% w/w) were prepared in a Turbula® mixer at 69 rpm for 10 min. Tablets were stored for 6 months under conditions similar to the four climatic zones recognized by ICH. Tablet hardness, disintegration time and dissolution were measured.*
Results: *At the same compression force, disintegration time decreased as the disintegrant concentration increased above 0.625% w/w but an increase in compression force resulted in increased tablet crushing strength and apparent density, both of which prolonged the disintegration time. This effect was less significant when the disintegrant concentration was above 1.25%. However, storage under high relative humidity conditions (mediterranean or subtropical, hot and humid climate) caused softening of tablets leading to the spontaneous disintegration of tablets containing high concentrations of Ac-Di-Sol®.*
Conclusion: *Fast disintegration of tablets within 1-2 min is a prerequisite for improving the dissolution of furosemide. This was attributed to an increase in the speed at which the maximum surface area of the sparingly water-soluble drug is exposed to the dissolution medium. Ac-Di-Sol® was an efficient disintegrant for furosomide tablets at low concentrations of 1.25% - 10% because it rapidly released the hydrophobic drug particles from tablets. However, tablets containing 10 % disintegrant must be protected from atmospheric moisture because storage at 60-70 % relative humidity led to softening of tablets.*

Keywords: *Disintegration; Furosemide dissolution; Tablets; Compression Force; Relative Humidity; Croscarmellose sodium*

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Introduction

For tablets containing sparingly water-soluble drugs, the start of dissolution is often delayed by the poor wettability of the tablet surface and/or slow liquid penetration into the tablet matrix. This property causes increased disintegration time and retarded drug release that can be overcome by the addition of a disintegrant[1]. Various compounds have been employed as disintegrants in tablet formulations[1-3]. Direct compression as a method of tablet manufacture, however, puts many of the traditional disintegrants at a disadvantage due to: (1) high concentrations needed for optimum disintegrating efficiency, (2) poor disintegration in insoluble systems, (3) susceptibility to high compression forces which decreases the efficiency of a disintegrant, (4) poor compression properties and (5) decreased disintegration efficiency in hydrophobic formulations[1-8]. A group of fast or super disintegrants, including croscarmellose sodium type A (Ac-Di-Sol®), sodium starch glycolate (Primojel® and Explotab®), and cross-linked polyvinyl-pyrrolidone (Polyplasdone® XL), alleviate most of these problems.

The effect and efficiency of some super disintegrants have been studied in both wet granulated[4, 5] and directly compressed formulations[6-8]. The mechanism of action of these disintegrants is that of water uptake (liquid penetration) into the tablet which cause the disintegrant particles to swell[9, 10]. This results in a significant disintegrating force inside the tablet, causing rupture of the tablet structure[11, 12]. Factors affecting disintegrant efficiency include tablet solubility[5, 7, 13-16], tablet hygroscopicity[5, 7], method of incorporation into wet granulated formulations[4, 13, 14], compression force[15-17], and storage under high relative humidity[18, 19]. All of these factors are related to the accessibility of liquid molecules to disintegrant particles inside the tablet[20].

The purpose of this study was to determine the effect of the disintegrating efficiency of croscarmellose sodium (Ac-Di-Sol®) in directly compressed Avicel® (PH200), on the dissolution rate of furosemide, a sparingly water-soluble drug, as a function of disintegrant concentration, compression force and storage under different climatic conditions. Furosemide was chosen because the work of several researchers has shown that excipients and processing factors significantly affect its dissolution and bioavailability[21-25]. The correlation between disintegrant concentration and compression force and two dissolution parameters - the initial dissolution rate and extent of dissolution was also investigated.

Materials and Methods

Materials

Furosemide (lot 14859, Adcock Ingram Ltd, Wadeville, South Africa), Avicel® PH200 (lot M439C, FMC International, Wallingstown, Ireland) and Ac-Di-Sol® (lot T124, FMC Corporation, Philadelphia, Pennsylvania, USA) were used.

Mixture Composition and Preparation

Thirty-two gram mixtures, consisting of furosemide (12.5% w/w), Ac-Di-Sol® (0, 0.625%, 1.25%, 5% or 10% w/w) and Avicel® PH200 (qs to 100% w/w) were prepared in a Turbula® mixer (model T2C, WA Bachofen, Basle, Switzerland) at 69 rpm for 10 min.

Tablet Preparation

Flat-faced tablets weighing approximately 160 mg were prepared from each mixture. The mixture powder was placed manually into a stainless steel die with an inner diameter of 8 mm and compressed for 15 seconds at 77, 154, 231 and 203 Mpa, respectively, on an automated hydraulic press (Carver Inc., Wabash, In., USA). Figure 1 is a schematic of the die set-up used in this study. The tablets used for determination of crushing strength were manually pushed out from the die. In the

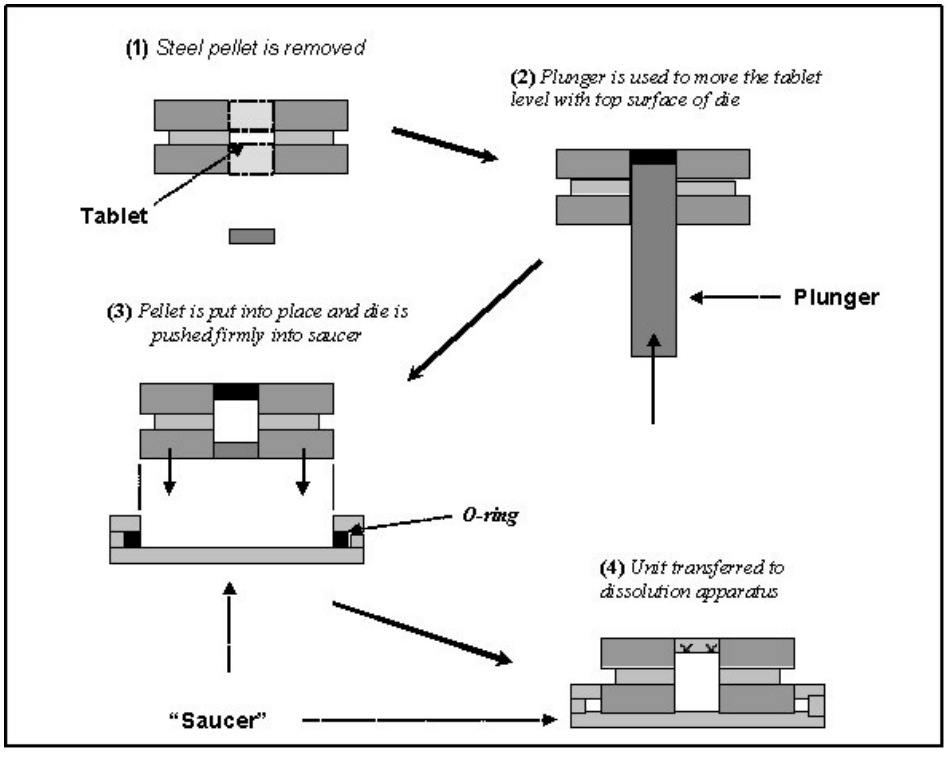

Figure 1: Presentation of the "cup" and "saucer" system used for compressing the tablets and for determination of drug dissolution from tablets

dissolution studies the tablets were leveled with the surface of the die. The open bottom of the die was sealed with a stainless steel pellet. The die was then firmly pushed down in a stainless steel "saucer", which fitted tightly around the die.

Tablet Storage

The International Conference on Harmonization (ICH) is developing stability standards guidelines[26]. According to these guidelines, manufacturers, when conducting "real time" product stability studies, will use actual packaging and storage conditions according to the climatic zone in which the product will be marketed. The four worldwide Climatic Zones recognized by ICH are based on observed temperatures and relative humidities, both outside and inside rooms, from which mean temperatures and average humidity values are calculated[26]. Zone I (21°C/45% relative humidity, RH), Temperate - includes the United Kingdom, Northern Europe, Canada, and Russia. Zone II (25°C/60% RH), Mediterranean or Subtropical - includes the United States, Japan, and Southern Europe. Zone III (30°C/35% RH), Hot and Dry - includes Australia, Argentina, and Egypt. Zone IV (30°C/70% RH), Hot and Humid - includes Brazil, Ghana, Indonesia, Nicaragua, and the Philippines. In this study tablets were stored for up to six months under these conditions in climatic chambers (Hot Pack Temperature/Humidity Chamber, MOD, 435314). Tablets were stored uncovered in glass Petri-dishes similar to the conditions described as the "open dish" method for stability testing[27].

Dissolution Studies

Dissolution studies were performed in a six-

station Erweka® dissolution apparatus (model DT6R, Erweka, Heustenstamm, Germany) fitted with a thermostat and a variable speed synchronous motor. The standard USP-paddles were removed from the rods and replaced with stainless steel clips to accommodate the tablet dies shown in Figure 1.

The single tablet surface was exposed to 900 mL 0.1 M HCl at 37 ± 1°C and rotated at 50 rpm. At t = 0, the rods were pushed down so that the bottom clearance was 5 cm. At t = 1, 2, 4, 5, 6, 10, 20, 30, 45 and 60 minutes, 5 mL samples were withdrawn through Millipore® pre-filters (Millipore, Milford, MA., USA) and transferred to 10 mL glass containers. An equal volume of fresh, preheated dissolution medium was added to compensate the medium lost through sampling. The samples were assayed at 274 nm against 0.1 M HCl as blank with a Unicam spectrophotometer (model Helios α, Unicam Ltd, Cambridge, UK). Dissolution curves, the amount of drug dissolved (mg/mL) versus time (min), were constructed. Dissolution profiles presented are the mean of at least four USP dissolution test (6 flasks per test). For all tests sink conditions were maintained.

Physical Properties and Disintegration Time of Tablets

The physical properties (crushing strength, thickness, and diameter) of 10 tablets of each formulation at each compression force were determined with a model PTB-311 Pharma Test tablet-test unit (Pharma Test, Switzerland). The disintegration time of the tablets was determined as the time necessary for the tablets to be completely released from the dies. The apparent density of the tablets (mg/mm^3) was calculated from the powder weight (mg), the tablet radius (mm) and the tablet thickness (mm).

Calculation of Dissolution Parameters

The initial dissolution rate (DR_i, mg/mL/min) represented the slope of the dissolution curve between t_0 and t_6. The slope was determined through linear regression analysis. The area under the dissolution curve (AUC, mg·min/mL) between t_0 and t_{60} was considered as an indication of drug dissolution extent and was calculated using the trapezoidal rule[28].

Statistical Evaluation of Data

Statistical analysis was performed using the statistical option available in Microsoft Excel 2000 for Windows (Microsoft® Corporation, Seattle, Washington, USA). A 99% confidence level ($p < 0.01$) was considered satisfactory for indicating significant differences. The mean values of the various parameters determined, i.e., initial dissolution rate (DRi), normalized area under the dissolution curve (AUC), crushing strength (CS) and disintegration time (DT), were compared for significant differences using one-way or two-way analysis of variance (ANOVA) for single factor and two factor comparisons respectively.

Results and Discussion

Table 1 summarizes the results for initial dissolution rate (DR_i), area under the dissolution curve (AUC), disintegration time (DT), and crushing strength (CS) of different formulations at different compression forces. Tables 2 and 3 list these results for tablets stored under conditions simulating the environmental conditions of the four climatic zones defined by Grimm[26].

Effect of Storage under Increased Relative Humidity on the Physical Properties of the Tablets

The crushing strength (CS) and density of all formulations increased with an increase in compression force, but levelled off above 154 MPa (Figure 2). The Ac-Di-Sol® concentration had little effect on crushing strength and the disintegration time of the tablets at different disintegrant concentrations reflected the effect of compression force (Figure 2). At each

Table 1: The initial dissolution rate (DR_i), area under the dissolution curve (AUC), disintegration time (DT) and crushing strength (CS) of furosemide tablets containing increasing concentrations of Ac-Di-Sol® and compressed at 77-308 MPa. The values in parenthesis are the percentage relative standard deviation (% RSD)

Ac-Di-Sol (% w/w)	Compression Force (MPa)	Parameters			
		$DR_i x10^{-5}$ (mg/mL/min)	$AUC_i x10^{-2}$ (mg.min/mL)	DT (min:sec)	CS (N)
0	77	4.8 (5.9)	8.8 (13.2)	n/d	97.1 (5.1)
	154	3.8 (15.1)	5.9 (32.2)	n/d	189.5 (4.3)
	231	3.4 (36.1)	4.8 (18.6)	n/d	231.4 (3.7)
	308	2.0 (7.2)	2.4 (17.2)	n/d	239.5 (3.5)
0.625	77	9.4 (23.7)	13.5 (17.9)	n/d	106.7 (7.0)
	154	8.1 (37.9)	13.0 (23.9)	n/d	196.0 (6.6)
	231	6.9 (15.8)	11.8 (17.9)	n/d	236.2 (5.4)
	308	1.7 (19.0)	3.1 (33.2)	n/d	249.8 (2.5)
1.25	77	32.4 (4.0)	38.4 (5.1)	0:27 (7.7)	113.2 (6.2)
	154	24.6 (12.0)	30.7 (5.9)	1:42 (3.2)	198.3 (7.3)
	231	16.0 (15.3)	23.1 (11.4)	3:24 (3.4)	237.9 (4.5)
	308	10.0 (10.6)	16.6 (9.5)	4:06 (3.5)	239.7 (3.3)
2.5	77	37.8 (2.6)	40.6 (2.3)	0:22 (6.7)	102.2 (2.9)
	154	26.4 (8.4)	32.3 (6.7)	1:34 (3.3)	190.7 (6.9)
	231	18.1 (5.2)	24.7 (5.0)	2:49 (3.0)	219.7 (4.4)
	308	13.3 (12.5)	20.9 (17.5)	3:34 (1.4)	230.5 (5.3)
10	77	60.4 (4.8)	52.7 (4.2)	0:14 (4.2)	105.1 (3.4)
	154	40.5 (17.0)	42.2 (10.6)	0:35 (13.6)	197.8 (1.4)
	231	26.5 (6.2)	24.9 (2.5)	0:55 (5.2)	236.0 (2.6)
	308	26.1 (3.9)	36.9 (3.5)	1:06 (2.5)	no data

n/d, no disintegration

compression force, tablets containing 0% to 0.625% Ac-Di-Sol® did not disintegrate during dissolution. However, when the disintegrant concentration was increased to above 1.25%, rapid disintegration occurred at all applied forces. This meant that disintegration times (DT) increased with an increase of compression force at each disintegrant concentration, but decreased as the disintegrant concentration increased at a specific compression pressure.

The increase in DT with an increase of compression force could be attributed to the reduced liquid penetration into the tablet structure and hence the increased tablet strength and density as shown in Figure 3. This increase in tablet density hampered liquid penetration and access to disintegrant particle and the development of an effective disintegrating force inside the tablets. When tablets were stored under relatively high relative humidities of 60 and 70 % (results for climatic zones II and IV listed in Table 2 and 3) disintegration times decreased with time because moisture from the environment penetrated the tablets and softened them. Results for CS and DT listed in Tables 2 and 3 showed that storage at low relative humidities at 21°C and 30°C (Zone I and II) did not significantly change the disintegration time and hardness of the tablets. In contrast when exposed to humidities of 60 % and 70 % the tablets became softer and after 3 months those tablets containing 2.5 % and 10.0 % Ac-Di-Sol® disintegrated in the Petri-dishes in which it was stored.

Table 2: The initial dissolution rate (DR_i), area under the dissolution curve (AUC), disintegration time (DT) and crushing strength (CS) of furosemide tablets containing increasing concentrations of Ac-Di-Sol®, compressed at 154 MPa and stored for 1 month under conditions simulating the four climatic zones. The values in parenthesis are the percentage relative standard deviation (% RSD)

Ac-Di-Sol (% w/w)	Climatic Zone	Parameters			
		$DR_i x10^{-5}$ (mg/mL/min)	$AUC_i x10^{-2}$ (mg.min/mL)	DT (min:sec)	CS (N)
0	I	5.2 (3.8)	9.1 (12.1)	n/d	181.2 (3.6)
	II	8.6 (5.2)	15.2 (11.2)	n/d	125.3 (5.3)
	III	4.3 (16.1)	7.8 (8.6)	n/d	178.3 (4.2)
	IV	9.2 (6.8)	13.4 (16.2)	n/d	118.6 (4.7)
1.25	I	8.2 (15.1)	15.4 (11.8)	1:51 (5.4)	201.3 (4.1)
	II	16.1 (9.3)	18.3 (9.2)	6:28 (7.2)	128.6 (4.2)
	III	9.3 (11.2)	12.9 (8.6)	2:11 (4.6)	194.2 (3.8)
	IV	17.8 (6.8)	20.6 (6.2)	5:06 (6.2)	119.8 (5.1)
2.50	I	27.6 (5.9)	39.4 (6.8)	2:16 (6.2)	201.6 (7.6)
	II	28.4 (11.2)	36.8 (8.9)	1:09 (7.1)	127.8 (8.6)
	III	25.4 (8.1)	40.1 (6.2)	1:49 (3.8)	211.2 (9.2)
	IV	30.6 (7.9)	36.3 (12.2)	1:11 (4.8)	136.3 (4.2)
10.0	I	40.2 (11.1)	48.3 (9.2)	1:19 (3.6)	189.5 (2.7)
	II	58.6 (7.7)	53.6 (10.1)	0:51 (4.2)	114.4 (3.2)
	III	49.6 (12.7)	50.8 (12.3)	1:21 (5.1)	188.4 (5.2)
	IV	52.4 (9.8)	51.4 (8.9)	0.56 (6.2)	118.6 (4.6)

Zone I (21°C/45% relative humidity, RH), temperate - includes the United Kingdom, Northern Europe, Canada and Russia. Zone II (25°C/60% RH), mediterranean or subtropical - includes the United States, Japan and Southern Europe. Zone III (30°C/35% RH), hot and dry - includes Australia, Argentina and Egypt. Zone IV (30°C/70% RH), hot and humid - includes Brazil, Ghana, Indonesia, Nicaragua and the Philippines; n/d, no disintegration.

Effect of Disintegrant Concentration, Compression Force and Storage on DR_i and AUC

Figures 4 - 6 show the influence of storage conditions on the release of furosemide from the tablets. At all compression forces increasing Ac-Di-Sol® concentration resulted in increased furosemide dissolution (Figure 4). At each disintegrant concentration, however, dissolution decreased with an increase in compression force (Figure 5).

Since compression force and disintegrant concentration influenced the DT of the tablets as well as the dissolution of furosemide, it was expected that changes in DT would be reflected in the dissolution profiles of furosemide. The results in Figure 6 confirmed the relationship between DT and the dissolution parameters. A decreased DT with increased disintegrant concentrations resulted in an increase in the DR_i and AUC at all compression forces. This result indicates that the dissolution of furosemide from tablets containing Ac-Di-Sol® mainly depended on the DT of the formulations. Hence, for furosemide/Ac-Di-Sol® formulations, DT was an indication of the initial dissolution rate of the drug. Because higher Ac-Di-Sol® concentrations improved the rate and extent of liquid uptake and penetration into the tablets, tablets broke up quicker and thus exposed the drug particles to the dissolution medium very quickly, improving the contact between drug particles and solvent molecules. Rapid tablet disintegration thus optimized the drug surface area available to the medium,

Table 3: The initial dissolution rate (DR_i), area under the dissolution curve (AUC), disintegration time (DT) and crushing strength (CS) of furosemide tablets containing increasing concentrations of Ac-Di-Sol®, compressed at 154 MPa and stored for 3 months under conditions simulating the four climatic zones. The values in parenthesis are the percentage relative standard deviation (% RSD)

Ac-Di-Sol (% w/w)	Climatic Zone	Parameters			
		$DR_i x10^{-5}$ (mg/mL/min)	$AUC_i x10^{-2}$ (mg.min/mL)	DT (min:sec)	CS (N)
0	I	6.5 (5.4)	14.5 (11.2)	n/d	209.8 (5.7)
	II	27.8 (8.3)	39.8 (4.5)	1:12 (5.5)	117.8 (9.5)
	III	7.4 (10.7)	12.6 (4.3)	n/d	221.3 (3.1)
	IV	23.9 (11.2)	41.4 (7.5)	1:06 (6.7)	107.9 (12.3)
1.25	I	7.9 (11.9)	13.5 (7.6)	1:20 (4.4)	197.2 (4.1)
	II	22.1 (5.4)	24.5 (12.3)	0:52 (6.2)	106.7 (5.1)
	III	11.2 (8.7)	12.1 (11.2)	1:32 (4.3)	201.9 (3.2)
	IV	19.4 (5.6)	26.7 (6.5)	0:41 (3.4)	103.6 (4.0)
2.50	I	32.1 (12.3)	41.3 (6.5)	2:54 (4.8)	189.5 (3.5)
	II	50.4 (8.7)	55.6 (9.2)	0:32 (2.1)	56.2 (10.9)
	III	37.1 (8.7)	48.9 (8.7)	2:01 (5.1)	192.5 (6.1)
	IV	dis	dis	dis	dis
10.0	I	42.3 (12.3)	46.5 (15.2)	1:11 (2.8)	179.8 (2.1)
	II	dis	dis	dis	dis
	III	47.6 (11.3)	54.3 (9.8)	0.57 (4.3)	187.5 (5.0)
	IV	dis	dis	dis	dis

Zone I (21°C/45% relative humidity, RH), temperate - includes the United Kingdom, Northern Europe, Canada and Russia. Zone II (25°C/60% RH), mediterranean or subtropical - includes the United States, Japan and Southern Europe. Zone III (30°C/35% RH), hot and dry - includes Australia, Argentina and Egypt. Zone IV (30°C/70% RH), hot and humid - includes Brazil, Ghana, Indonesia, Nicaragua and the Philippines; n/d, no disintegration; dis, tablets disintegrated during storage.

resulting in increased DR_i and AUC of furosemide. For tablets stored at relatively high relative humidities it was evident that the decrease in hardness and disintegration time, results listed in Table 2 and 3, increased the dissolution rate of furosemide from tablets and that this effect was more pronounced for tablets containing more than 1 % of Ac-Di-Sol®.

These results indicate that the good water uptake and effective swelling by Ac-Di-Sol® were dominant in ensuring fast drug dissolution. In disintegrating systems (≥1.25% Ac-Di-Sol®), a maximum contact area of the drug was quickly exposed to the dissolution medium resulting in more rapid dissolution of furosemide. For example, at 77 MPa and 10% Ac-Di-Sol®, the DR_i was approximately 12.5 times higher compared to the rate at 0% disintegrant. The problem with higher concentrations of disintegrant is that when tablets were exposed to environments where the relative humidity is quite high, Zone II and IV, it lead to softening and eventual disintegration of the tablets. Therefore, tablets containing high concentrations of super disintegrants should be probably packaged and labelled to protect them from atmospheric moisture.

Correlation between DR_i and AUC

For disintegrating systems, Ac-Di-Sol® concentrations above 1.25%, the DR_i and AUC increased linearly with disintegrant concentration. In this study this quantitative

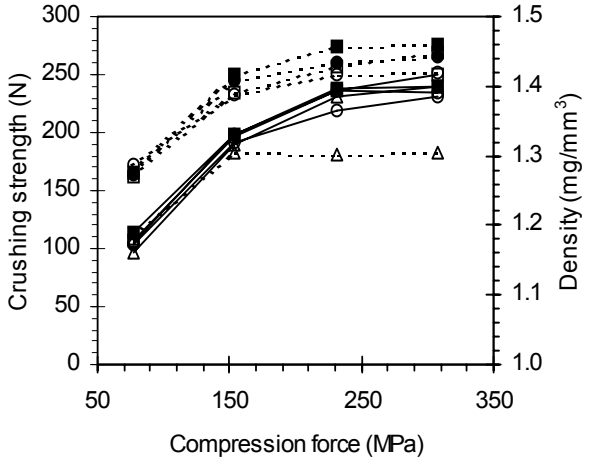

Figure 2: The effect of compression force on the crushing strength (solid lines) and density (dashed lines) of the tablets at different concentrations of Ac-Di-Sol®. △, 0%; □, 0.625%; ■, 1.25%; ○, 2.5%; ●, 10%.

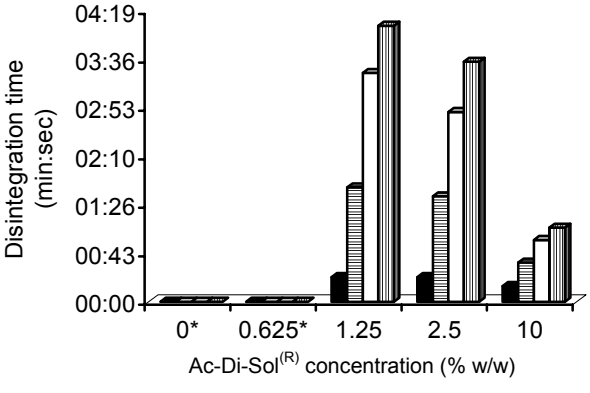

Figure 3: The effect of compression force on the disintegration times of formulations containing various concentrations of Ac-Di-Sol®. *, no disintegration occurred.

■, 77 MPa; ▤, 154 MPa; □, 231 MPa; ▥, 308 Mpa.

relationships between Ac-Di-Sol® concentration and the DR_i and AUC provided a means to estimate these parameters at any concentration within the concentration range. Figure 7 shows the effect of the initial dissolution rate of furosemide on the extent of dissolution (AUC). The AUC increased linearly with the initial dissolution rate of the drug. This indicated that faster initial dissolution rates lead to more furosemide going into solution but the slopes of the lines decreased with an increase in disintegrant concentration, indicating that at the lowest disintegrant concentration, 0.625%, compression force had the most pronounced effect on the dissolution of furosemide. At this disintegrant concentration, the DR_i and AUC of furosemide decreased by 81% and 77%, respectively, with an increase in force from 77 to 308 MPa, compared to a decrease of only 56 and 30% at 10% Ac-Di-Sol®. These results suggested that at lower Ac-Di-Sol® concentrations, an increase in compression force opposed and suppressed the swelling mechanism of the disintegrant. At the highest concentration (10%), the disintegration mechanism was the dominating force in determining both the rate and extent of dissolution. Between the lowest and highest concentrations, the dissolution of furosemide depended on both disintegrant concentration and compression force.

The DR_i versus AUC relationship held true for tablets stored up to 6 months under conditions simulating climatic Zone I and III. At higher relative humidities, Zone II and IV, the softening of tablets with time led to unpredictable changes in tablet disintegration and the quantitative relationship between Ac-Di-Sol® concentration and the DR_i and AUC no longer applied.

Conclusion

The results confirmed that fast disintegration of tablets is a prerequisite for improving the dissolution of furosemide because drug dissolution improved significantly when tablets rapidly disintegrated within 1-2 minutes. This could be attributed to an

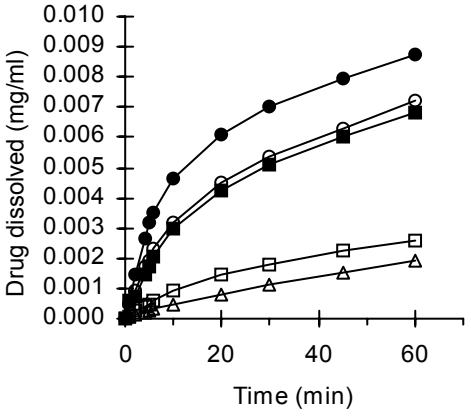

Figure 4: The effect of disintegrant concentration on the dissolution of furosemide from tablets compressed at 77 MPa. △, 0%; □, 0.625%; ■, 1.25%; ○, 2.5%; ●, 10%.

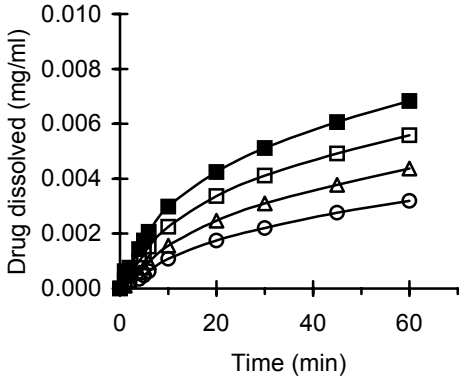

Figure 5: The effect of compression force on the dissolution profile of furosemide tablets containing 1.25% w/w Ac-Di-Sol®. ■, 77 MPa; □, 154 MPa; △, 231 MPa; ○, 308 MPa.

increase in the speed at which the maximum surface-area of the sparingly water-soluble drug is exposed to the dissolution medium.

Using two novel indicators, the initial dissolution rate (DR_i) and extent of dissolution (*AUC*) it was shown that for directly compressed furosemide tablets disintegration times correlated well with these two parameters and could be used to predict the overall dissolution behaviour of the drug. The linear relationship between the DR_i and *AUC* confirmed that the extent of dissolution was almost entirely dependent on the initial dissolution rate of the drug. This relationship was used to determine the rate and extent of drug dissolution at any concentration within a range of 1.25 to 10% Ac-Di-Sol®.

Although an increase in compression force increased the disintegration times of tablets Ac-Di-Sol® proved to be an efficient disintegrant at relatively low concentrations of 2.5-10 % because it has the ability to rapidly release hydrophobic drug particles from tablets. However, tablets containing high concentrations of this disintegrant must be protected from atmospheric moisture because storage at high relative humidities lead to the softening of tablets. This effect must be taken into account by formulators in countries where tablets will be exposed to high relative humidities, climatic zones II and IV. Tablets manufactured and distributed in these regions must be adequately protected against moisture.

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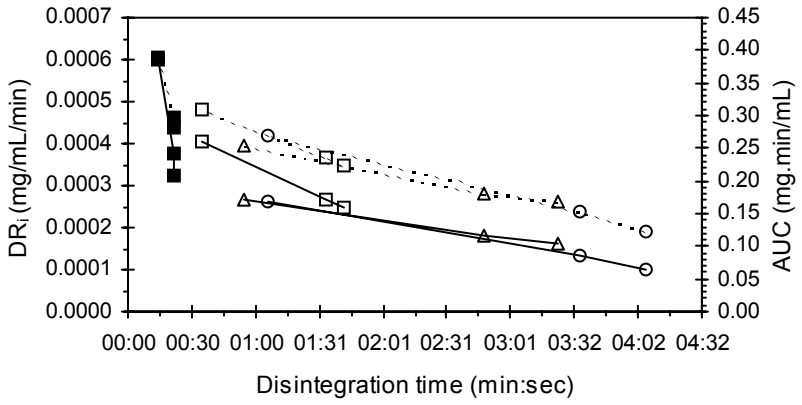

Figure 6: The effect of tablet disintegration times on the initial dissolution rate (DR_i, solid lines) and extent of dissolution (AUC, dashed lines) of furosemide at various compression forces. [At each compression force the disintegrant concentration decreased from top-left (1.25%) to bottom-right (10%)]. ■, 77 MPa; □, 154 MPa; △, 231 MPa; ○, 308 MPa.

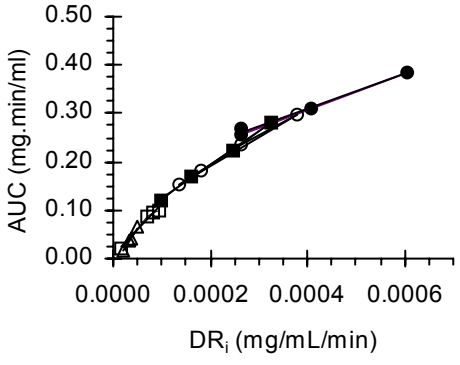

Figure 7: The correlation between the initial dissolution rate and extent of dissolution for furosemide at various disintegrant concentrations over a compression range of 77 to 308 MPa. [For each concentration the compression force decrease from bottom-left (308 MPa) to top-right (77 MPa)]. △, 0%; □, 0.625%; ■, 1.25%; ○, 2.5%; ●, 10%.

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