DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(18), 2047-2056 (1995)

THE EFFECT OF MIXING VARIABLES ON THE DISSOLUTION PROPERTIES OF DIRECT COMPRESSION FORMULATIONS OF FUROSEMIDE

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ABSTRACT

The particles of a number of poorly water soluble drugs, for instance furosemide, tend to agglomerate spontaneously and as a result decrease the drug's dissolution properties. This phenomena is undesirable when the drug is to be formulated in a direct compressible formulation. Interactive or ordered mixing with a filler usually rectifies this problem but the drug load is limited to a maximum of ± 5 % of the mixture. This is well below the formulation requirements of furosemide (25 %) and below the maximum drug load which can be handled in direct compression formulations (± 35 %). The effect of two types of mixers, the mixing time and drug load were investigated for a direct compression formulation of furosemide tablets. A Turbula and a V mixer, both with a volume of 720 ml, were used. The drug was formulated with Ludipress (a commercial direct compression filler, BASF, Germany) at two drug loadings of 20 and 25 %. Magnesium stearate (1 %) was added as a lubricant. A mixture was prepared for each experimental condition. After mixing the whole mixture (120 gram) was tabletted on a Korsch single punch machine producing ± 500 tablets. The crushing strength, mass and disintegration time of ten tablets and the dissolution of six tablets were measured. Dissolutions were done according to the USP XXII - method 2^1 - in 0,1 M HCl and a phosphate buffer with pH = 5.8. The intrinsic dissolution rates of some of the mixtures were also determined in the two dissolution media. The dissolution properties of the formulations were compared with the properties of Lasix®, a commercially available furosemide product, which is not manufactured by direct compression. The dissolution rates of the formulations mixed in the Turbula mixer were significantly higher than those mixed in the V mixer. The area under the dissolution curves increased as a function of mixing time for both mixers. The best dissolution results were obtained for formulations with a 20 % drug load and mixed for 120 minutes in the Turbula mixer. The dissolution curves for these formulations compared well with the curves for the commercial tablets. Intrinsic dissolution rates were also a function of mixing time, which indicates that the

increase in dissolution properties is probably a result of the deagglomeration of the agglomerated furosemide particles. The Turbula mixer, which can develop more shear force, breaks the agglomerates quicker and to a larger extend than the V mixer. It can be concluded that the type of mixer, mixing time and drug load control the dissolution properties of direct compression formulations of poorly water soluble drugs in which the drug particles form agglomerates.

INTRODUCTION

Furosemide, a widely used diuretic, is not completely absorbed from peroral tablets. Hammerlund-Udenaes & Bennett[2] reported in a review on the pharmacokinetics and pharmacodynamics of the drug that the absolute bioavailability in plasma of healthy volunteers ranged between 43 and 71 % in 15 different studies. The bioavailability is also characterised by a large inter- and intra-subject variation. The intra-subject variation in AUC, as determined by repeat administration, of two brands of furosemide was 18.6 and 21.5 %.[3]

The incomplete absorption and the variation in response are attributed to the absorption process.[2] The absorption rate is the highest in the stomach and increases with decreasing pH.[4] Factors which influence the solubility and the dissolution rate, especially at low pH-values would probably influence the bioavailability of the drug.

Furosemide is a poorly water soluble drug which particles tend to agglomerate spontaneously and as a result decrease the drug's dissolution properties.[5] This phenomena is undesirable if the drug is to be formulated in a direct compressible formulation. Interactive or ordered mixing of these drugs with a filler usually rectifies this problem but the drug load is limited to a maximum of ± 5 % of the mixture. This is well below the formulation requirements of furosemide (25 %) and below the maximum drug load which can be handled in direct compression formulations (± 35 %).

The effect of two types of mixers, the mixing time and drug to filler ratio on the dissolution properties are reported.

EXPERIMENTAL SECTION

Mixing operations were carried out in a Turbula and a V mixer. Ludipress, a commercial direct compression filler, was used and the effect of mixer, drug loading and mixing time on tablet properties were investigated.

Formulation and mixing

Mixtures containing furosemide (Laboratori Mag, Milan, Italy, Lot number 92K29808), Ludipress (BASF, Ludwigshaven, Germany, Lot number 06-2521) and magnesium stearate (Breyer Chemi, Hamburg, Germany, Lot number BI-1863/H) were formulated according to the concentrations in table 1. The formulations differ in their drug load. The drug load, calculated as the ratio of drug to exipients, was 25 and 20 % respectively. The experimental lots were prepared by mixing a formulation (120 gram for 500 tablets) for each experimental condition. Mixtures were mixed with a Turbula mixer

TABLE 1
The composition of the two formulations with variable drug loads (dl).

Ingredient	Composition (%)	
	dl = 25 %	dl = 20 %
Furosemide	20.0	16.7
Ludipress	79.0	82.3
Magnesium Stearate	1.0	1.0

(model T2C) at 90 r.p.m. in a 720 ml stainless steel, cylindrical vessel for 15, 30, 60 and 120 minutes. The V mixer had the same volume, was made from stainless steel and revolved at a speed of 60 r.p.m. Mixtures were prepared at mixing times of 15, 30, 60 and 120 minutes. After mixing the mixtures were tabletted on a Korsch single punch machine equiped with 8 mm flat beveled punches.

Tablet properties

The crushing strength (Pharma Test), mass, disintegration time[6] and furosemide content[1] of ten tablets and the dissolution of six tablets were measured. Dissolutions were done according to the USP XXII - method 2[1] - using a six station apparatus (Erweka, Model 6DTR). The dissolution medium was 0.1 M HCl or a phosphate buffer with pH = 5.8. Samples of 10 ml were extracted through a Sartorius pre-filter at time intervals of up to 60 minutes. The loss through sampling was immediately replaced with fresh medium at 37 °C. The amount of furosemide dissolved in the samples were determined by UV absorption at 271 nm and the amount of furosemide dissolved calculated as a percentage of the mean content of tablet lot. The percentage dissolved was plotted against time and the areas under the curves were calculated by the trapezium rule. The dissolution properties of Lasix® tablets (Hoechst, South Africa, Lot number H407/A), a commercially available product, were determined accordingly. The intrinsic dissolution rates of the mixtures, mixed for 15 and 60 minutes in the Turbula, were determined in the phosphate buffer and in 0.1 M HCl by employing the propeller-driven stirrer apparatus of Singh *et al.*[7] Tablets with a diameter of 13 mm were compressed with an IR press at 7 MPa. The amount dissolved were determined with UV absorption. Sampling losses were immediately replaced with fresh medium at 37 °C. The amount dissolved was plotted against time and the intrinsic dissolution rate calculated from the slope of the least square straight line through the data points. Two tablets from both mixtures were tested.

Statistical calculations

All the calculations were done with CSS, a statistical software package (Statsoft Inc., Tulsa, USA). Anova/manova routines were executed and the significance of differences were calculated according to the Newman-Keuls test.

TABLE 2

Crushing strength, tablet weight and disintegration time for the experimental lots.

Mixing Time (min)	Crushing Strength (Newton)		Weight (mg)		Disintegration (seconds)	
Turbula Drug Load : 25 %						
15	22.5	(9.8)*	196.7	(1.5)	61.9	(28.4)
30	16.7	(23.2)	194.4	(2.1)	77.5	(5.6)
60	15.9	(19.0)	194.5	(1.4)	71.8	(9.2)
120	34.0	(10.7)	199.3	(0.8)	56.5	(20.7)
Turbula Drug Load : 20 %						
15	39.2	(14.5)	246.0	(0.7)	48.8	(8.6)
30	27.8	(13.6)	241.6	(0.7)	66.8	(3.7)
60	38.2	(11.8)	243.9	(0.8)	71.2	(3.2)
120	31.1	(15.2)	240.7	(1.4)	79.0	(11.4)
V-mixer Drug Load : 25 %						
30	24.7	(20.3)	198.9	(2.0)	33.2	(34.2)
60	32.8	(12.0)	201.7	(0.9)	33.8	(33.1)
90	35.7	(12.3)	199.1	(0.6)	30.2	(39.7)
120	36.9	(17.0)	207.4	(1.5)	30.2	(38.5)

* coefficient of variation ; n = 10

TABLE 3

Furosemide content and coefficient of variation for ten tablets from each lot and for Lasix® Lot number 407/A.

Mixing Time (min)	Furosemide Content (mg/tablet)	CV Content (%)
Turbula Drug Load : 25 %		
15	36.24	3.30
30	34.86	2.35
60	36.40	4.32
120	36.90	2.74
Turbula Drug Load : 20 %		
15	38.10	5.12
30	36.88	3.02
60	39.03	1.81
120	36.18	2.26
V-mixer Drug Load : 25 %		
30	38.06	6.89
60	38.10	5.54
90	36.78	5.12
120	37.60	5.53
Lasix® Lot H407/A		
	39.20	2.22

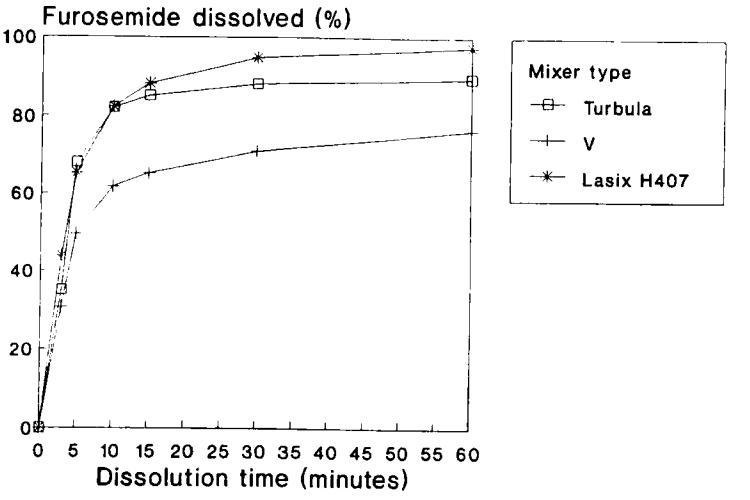

FIGURE 1

Dissolution of tablets (USP XXII - method 2[1]) in pH 5.8 phosphate buffer as function of mixer type.

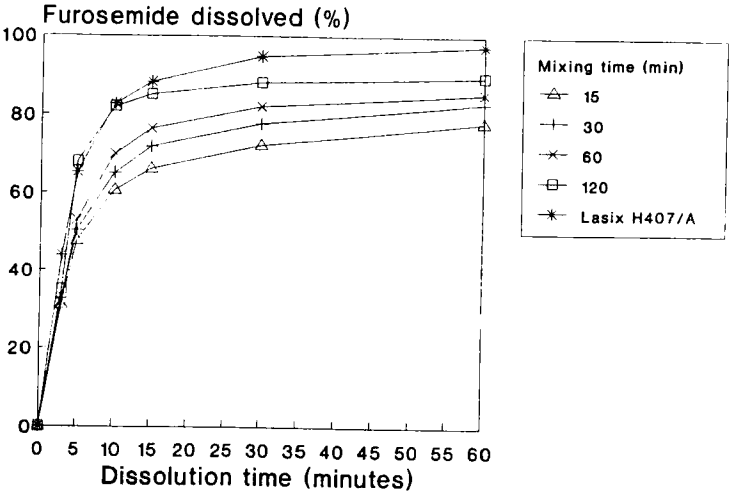

FIGURE 2

Dissolution of tablets (USP XXII - method 2[1]) in pH 5.8 phosphate buffer as function of mixing time in the Turbula mixer.

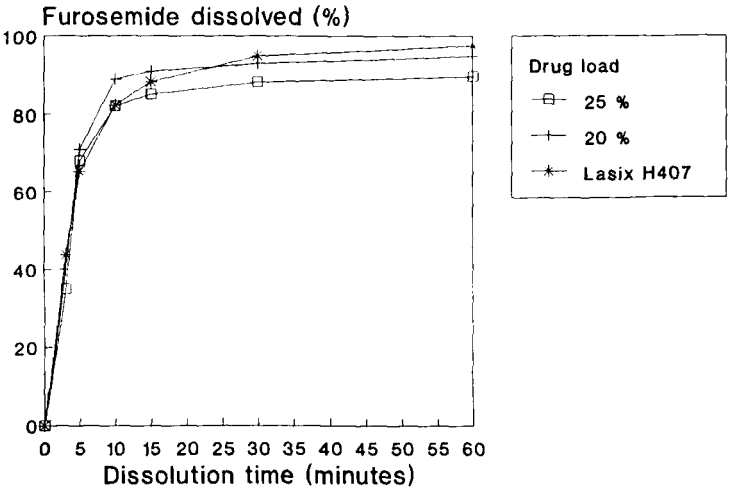

FIGURE 3

Dissolution of tablets (USP XXII - method 2[1]) in pH 5.8 phosphate buffer as function of drug load mixed in Turbula mixer.

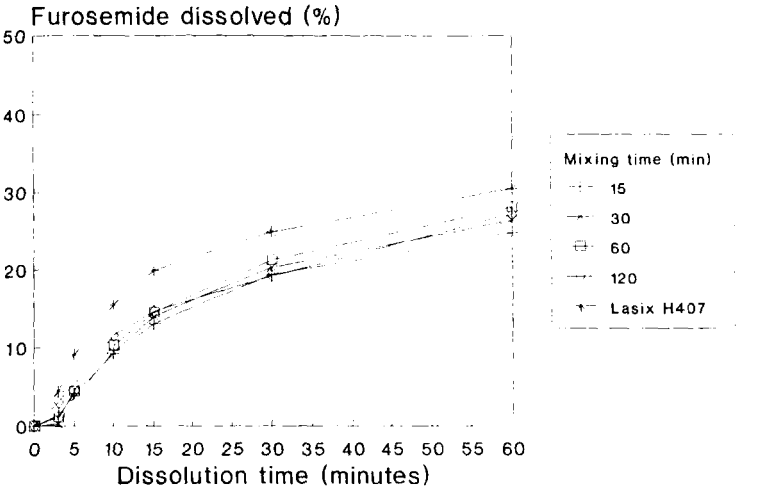

FIGURE 4

Dissolution of tablets (USP XXII - method 2[1]) in 0.1 M HCl as function of mixing time in the Turbula mixer.

TABLE 4
Intrinsic dissolution rates.

Mixing Time (min)	Dissolution Rate ($\mu gcm^{-2}.min$) pH 5.8 Buffer		0.1 M HCl	
Turbula Drug Load : 20 %				
15	1.51	(0.18)*	0.13	(0.60)
30	1.78	(0.04)	0.14	(0.01)

* coefficient of variation ; n = 2

RESULTS AND DISCUSSION

The results are reported as a function of drug load, mixer type and mixing time. The mean values for crushing strength and disintegration time for all experimental lots (table 2) were within narrow limits so that neither of these properties could have an effect on the dissolution properties. The content uniformity of the lots, as judged by the coefficient of variation (CV) of ten tablets (table 3), was acceptable for Turbula mixtures after long mixing times. The CV of the lot mixed in the Turbula for 120 minutes with a drug load of 20 % was 2.26. This value compares well with the 2.22 obtained for Lasix® tablets.

Dissolution curves in phosphate buffer are shown in figures 1 - 3 and those in 0.1 M HCl in figure 4. The intrinsic dissolution rates are given in table 4 and the areas under the dissolution curves[8] in table 5. The statistical significance of differences are given in table 6 and 7. The AUC of the dissolution curves, obtained in the buffer for the lots mixed in the Turbula mixer, were significantly higher than those mixed in the V mixer. The AUC increased as a function of mixing time for both mixers. The best dissolution results were obtained with a 20 % drug load mixed for 120 minutes in the Turbula mixer. The dissolution properties of this experimental lot compared well with the those of the commercial tablets. The Turbula mixer which can develop more shear force, probably breaks up the agglomerates quicker and to a larger extend than the V mixer.

The increase in dissolution properties at the lower drug load is probably the result of an increase in the available surface area of the filler and an increase in the flowability of the mixture. Both these factors favour the mixing process in which agglomerated furosemide particles must be broken down into more primary particles. No significant statistical difference in the AUC's of the dissolution curves obtained in the 0.1 M HCl, as a function of mixer, mixing time or drug load could be indicated (table 8). This might be due to the low solubility of the drug in the acid, which made the maintenance of sink condition in the 900 ml dissolution flask difficult. The AUC for Lasix, however, was significantly higher than any value of the experimental lots. This may be the result of

TABLE 5
Dissolution characteristics - AUC from 0 to 60 minutes.

Mixing Time (min)	AUC (%.min) pH 5.8 Buffer		0.1 M HCl	
Turbula Drug Load : 25 %				
15	3948	(7.2)*	843	(7.2)
30	4073	(7.7)	874	(13.6)
60	4411	(4.9)	963	(15.0)
120	4930	(4.0)	964	(7.8)
Turbula Drug Load : 20 %				
15	4152	(2.1)	na	na
30	4878	(4.2)	919	(4.2)
60	5041	(4.4)	901	(7.3)
120	5260	(3.4)	1052	(9.9)
V-mixer Drug Load : 25 %				
30	3431	(2.9)	859	(11.0)
60	3536	(5.7)	785	(19.2)
90	3912	(3.4)	851	(14.0)
120	3927	(4.1)	919	(2.7)
Lasix® Lot H407/A				
	5211	(2.6)	1189	(8.9)

* coefficient of variation ; n = 6

TABLE 6
Probabilities for significance of differences between AUC's in pH = 5.8 buffer according to the Newman-Keuls test.

Mixing Time (min)	Mixer	Drug Load	AUC (%.min)	p
Effect of Mixer				
120	Turbula	20	4930	
120	V-mixer	20	3927	*< 0.001*
Comparison with Lasix®				
120	Turbula	20	5259	
Lasix® Lot H407/A			5212	0.9070
Effect of Drug Load				
120	Turbula	20	5259	
120	Turbula	25	4930	*0.0235*

* *Significant differences at a 5 % level of confidence, $p < 0.05$, are printed in italics.*

TABLE 7

The effect of mixing time. Probabilities for significance of differences between AUC's in pH = 5.8 buffer according to the Newman-Keuls test.

Turbula Drug Load : 20 %					
AUC	4152	4878	5041		5259
Mixing Time (min)	15	30	60	90	120
15	-	*0.002**	*0.001*		*< 0.001*
30	-	-	0.249		*0.034*
60	-	-	-		0.132
120	-	-	-		-
Turbula Drug Load : 25 %					
AUC	3948	4073	4411		4930
Mixing Time (min)	15	30	60	90	120
15	-	0.451	*0.026*		*< 0.001*
30	-	-	*0.050*		*< 0.001*
60	-	-	-		*0.005*
120	-	-	-		-
V-mixer Drug Load : 25 %					
AUC		3481	3611	3869	3951
Mixing Time (min)	15	30	60	90	120
30	-	-	0.112	*0.003*	*0.002*
60	-	-	-	*0.027*	*0.019*
90	-	-	-	-	0.495
120	-	-	-	-	-

* *Significant differences at a 5 % level of confidence, $p < 0.05$, are printed in italics.*

TABLE 8

Probabilities for significance of differences between AUC's in 0.1 M HCl according to the Newman-Keuls test, for Lasix® and experimental lots.

AUC	1189	1052	964	919
Lot	Lasix®	Turbula 20 % Load	Turbula 25 % Load	V-mixer 20 % Load
Lasix®	-	*0.013*	*< 0.001*	*<0.001*
Turbula 20 % Load	-	-	0.098	0.649
Turbula 25 % Load	-	-	-	0.067
V-mixer 20 % Load	-	-	-	-

* *Significant differences at a 5 % level of confidence, $p < 0.05$, are printed in italics.*

unknown formulation factors in the commercial tablet. Intrinsic dissolution rates (table 5) were also a function of mixing time which indicates that the increase in dissolution properties is probably a result of the deagglomeration of the agglomerated furosemide particles.

CONCLUSIONS

The type of mixer, mixing time and drug load influenced the dissolution properties of a direct compression formulation of furosemide, a poorly water soluble drug with particles that form agglomerates. The Turbula mixer which can develop more shear force, probably breaks up the agglomerates quicker and to a larger extend than the V-mixer, which results in better dissolution properties.

A decrease in the drug load probably increases the available surface area of the filler and an increase in the flowability of the mixture. Both these factors favour the mixing process in which agglomerated furosemide particles must be broken down into more primary particles.

The dissolution and content uniformity properties of the best experimental lot compare favourable with the results obtained from a commercial product.

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