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PREPARATION and PROPERTIES of TABLETS PREPARED from FUROSEMIDE-PVP SOLID DISPERSION SYSTEMS

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ABSTRACT

Tablets were prepared from the solid dispersion of furosemide: PVP by using different techniques such as direct compression and double compression. The results were compared with similar tablets prepared by physical mixture. Direct compression was much prefered, as it provided tablets with acceptable mechanical and physical qualities. On the other hand, the choice of disintegrant is very important in the formulation of furosemide: PVP solid dispersed tablets. With Kollidon CL, the best result was obtained. Disintegration

mechanism of this system was also discussed. The other effective factor is the particle sizes of coprecipitates. Fine particle exhibited compression difficulty. The drug release from these tablets was 17 times greater than that from tablets prepared from physical mixture.

INTRODUCTION

The solubility and the dissolution increase of poorly water-soluble drugs by solid dispersion systems is well established (1,2). However, up to date only a few formulations have been marketed and a few reports on the formulations of these systems have appeared (3-7) because of the formulation problems.

The furosemide-polyvinylpyrrolidone (PVP) solid dispersion systems exhibited higher dissolution rates compared with physical mixtures and pure drug (8,9).

This paper describes the formulation and the properties of tablets prepared from furosemide: PVP solid dispersion systems and the effect of process variables, the type of disintegrant and particle sizes, on tablet properties.

EXPERIMENTAL

Materials

Furosemide (Hoechst A.G., Frankfurt, F.R.G.), polyvinylpyrrolidone (Kollidon K-30, BASF,

D-Ludwigshafen, F.R.G.), Avicel PH 101, Avicel PH 102 (F.M.C. Corp. Philadelphia, USA).

Primojel (Avebe BA, Foxhol, The Netherlands), Kollidon CL (Crospovidone, BASF, D-Ludwigshafen, F.R.G.), methanol (Riedel-de-Haen A.G, Seelzo-Hannover, F.R.G.). Corn starch, talc and magnesium stearate were pharmaceutical grade.

Moisture contents of ingredients; furosemide: PVP solid-dispersion system, Primojel, Kollidon CL and corn starch were 15.0, 6.0, 2.5 and 4.2 % respectively.

Preparation of Solid dispersion System

Furosemide-PVP solid dispersion systems were prepared as previously mentioned (8). With PVP the solid-dispersion system was prepared by coprecipitation of two components which were dissolved in methanol and evaporating off the solvent in vacuo. In tablet studies, 80-mesh and 100-mesh of particle sizes were used.

Particle size (mechanical sieve shaker, Retsch, Haan, F.R.G.) tapping density (Volumeter, J.Engelsmann A.G, F.R.G.) and true density (air pycnometer, Gerhard, F.R.G.) of solid dispersion systems were determined.

Preparation of Tablets

Tablet formulations containing furosemide-PVP solid dispersion systems and physical mixture were

TABLE 1
Tablet Formulations

Ingredients	mg tablet								
	F-I	F-II	F-III	F-IV*	F-V	F-VI	F-VII	F-VIII	F-IX**
Furosemide	40	40	40	40	40	40	40	40	40
PVP	240	240	240	240	240	240	240	240	240
Avicel PH101	140	140	140	140	70	70	-	-	-
Avicel PH102	-	-	-	-	-	-	-	70	-
Corn starch	140	-	-	-	35	-	-	-	58.8
Primojel	-	140	-	-	-	-	-	-	-
Kollidon CL	-	-	140	-	-	35	-	35	-
Talc	5.88	5.88	5.88	5.88	3.46	3.46	3.46	3.46	3.04
Magnesium stearate	1.47	1.47	1.47	1.47	0.38	0.38	0.38	0.38	0.33

* Physical mixture
** Solvent deposition

shown in Table 1. Before the compression, all the additives were dried at 60° for 4 hrs and sieved through a 120-mesh. Tablets were compressed on an Englar tablet machine at constant pressure, using 9.8 mm diameter flat-faced punches.

For tablet preparation, two different techniques such as double compression and direct compression were used and a formulation was evaluated from solvent deposited dispersion.

For double compression technique (F-I, F-II and F.III); the weighted powders were mixed in a plastic bag and compressed into slugs and then broken and sieved and dry-mixed with magnesium stearate and talc prior to the second compression.

For direct compression (F-IV, F-V, F-VI, F-VII and F-VIII); the lubricant was added to the powder mixture and tablets were compressed.

Compression of solvent-deposited dispersion (F-IX); furosemide-PVP solution in methanol was used to wet throughly the corn starch then methanol was removed in a rotary evaporator and by the addition of lubricant, the dried mixture was compressed.

Tablet Properties

All properties of the tablets were evaluated in the course of 24 hrs after compaction. The crushing

strength (Schleuniger-2E) was the mean of 10 tablets. The friability tests were carried out in a friabilator and the avarage of 3 values was reported. Disintegration times of tablets were measured by the USP XXI method. Dissolution test was performed according to the paddle method of USP XXI. O.IN HC1 was used as a medium and rotating rate was 100 rpm/min. Drug content was spectrophometrically assayed at 272 nm. (Varian Techtron Series 634 Spectrophotometer).

Porosity of tablets was calculated from the weight, volume and density of the material with an air pycnometer. The liquid penetrability of the tablets was assayed by dropping 5 µl of distilled water from a "volupette" disposable pipete onto the face of a tablet and measuring with a stopwatch the time for all of the water to be taken up by the tablet (10). Values are the means of 5 determinations.

RESULTS AND DISCUSSION

Powder characteristics of furosemide-PVP solid dispersion systems were given in Table 2.

Tablet Preparation

Since aqueous solution would break down the solid dispersion system, wet granulation technique was not used for tablet preparation.

TABLE 2

Physical Properties of Solid dispersion systems before Compression

Physical Property	80-mesh	100-mesh
Particle Size		
d_{gw} (μm)	281	182
Bulk density (g/ml)	0.613	0.595
Tapped density (g/ml)	0.687	0.694
True density (g/ml)	1.265	1.381
Porosity (%)	51.55	56.93
Compressibility (%)	10.77	14.26
Hausner ratio	1.12	1.16

Table 3 summarizes the properties of freshly prepared tablets. Two different Avicel PH 101 concentrations were used in tablet formulations. After the addition of high proportion of Avicel PH 101 and disintegrants to the powder mixtures, it was impossible to apply direct compression, therefore double compression technique was used for the preparation of F-I, F-II and F-III tablets. However, double compression caused a significant reduction in tablet strength and highly friable tablets such as 6.13-6.28 % values were obtained (Table 3). After addition of small proportion of Avicel PH 101, by using direct compression, harder and less friable tablets produced. (F-V and F-VI).

Tablet properties of the same formulations compressed in different techniques were given in Table

TABLE 3
Tablet Properties

Formulation	Crushing strength (N)*	Friability %	Disintegration time (min)*	Drug content (mg)*	Weight (g)*
F-I	21.5 (0.29)	6.21	15.00 (1.92)	26.50 (0.05)	0.4873 (0.01)
F-II	20.5 (0.37)	6.28	8.66 (1.15)	32.50 (1.61)	0.4933 (0.01)
F-III	23.5 (0.24	6.13	0.38 (19.59)	27.40 (0.04)	0.4487 (0.02)
F-IV**	35.0 (0.47)	2.22	12.50 (3.00)	43.75 (0.02)	0.4989 (0.006)
F-V	39.1 (2.54)	0.75	46.60 (3.80)	42.00 (2.31)	0.3914 (0.01)
F-VI	35.5 (2.44)	0.53	12.14 (0.53)	40.00 (0.03)	0.3720 (0.009)
F-VII	33.3 (2.01)	1.68	29.50 (3.14)	42.50 (0.02)	0.3032 (0.006)
F-VIII	48.0 (3.84)	0.96	19.72 (7.71)	39.75 (0.01)	0.3338 (0.004)

* Mean values ± s.d
**Physical mixture

4. As seen in this table,more friable tablets formed by the double compression. On the contrary of expecting, re-work did not increase the tablet crushing strength. Furthermore, a remarkable decrease in the dissolution rates of the double-compressed tablets was observed. Therefore direct compression was prefered for the other formulations.

On the other hand, compression of solvent deposited dispersion (F-IX) which was prepared by direct deposition of furosemide onto excipient, was found impossible.

Effect of Disintegrants

Between three disintegrants such as corn starch, Primojel and Kollidon CL, lowest disintegration time and highest dissolution were obtained by the addition of Kollidon CL. For that reason, at the further step of this study, Kollidon CL was used as a disintegrant (F-VI and F-VIII) and the results were compared with the tablets prepared by corn starch, by physical mixture (F-IV) and tablets without additives (F-VII) Since the physical properties of tablets were not satisfactory, Primojel was omitted in the further study.

When the dissolution patterns of solid-dispersed tablets (F-VI) were compared with the tablets prepared by the physical mixtures of furosemide-PVP(F-IV);

TABLE 4
Effect of Tabletting Techniques on Tablet Properties

Formula	Technique	Crushing strength N*	Friability (%)	Disinteg-ration time (min)*	Weight (g)*	Dissolution Parameters t_{50} min	k - min
FVI	Direct com	35.5 (2.44)	0.53	12.14 (0.53)	0.3720 (0.009)	5.30	0.1305
	Double com	32.1 (3.56)	2.90	21.60 (6.69)	0.3986 (2.12)	19.81	0.0349
FVIII	Direct com	48.0 (3.84)	0.96	19.72 (7.71)	0.3338 (0.004)	22.33	0.0310
	Double com	47.6 (0.65)	2.90	27.20 (6.45)	0.3888 (0.01)	28.00	0.0247

*Mean values ± s.d

TABLE 5
Dissolution Parameters of Tablets

Formulation	k - min	t_{50} (min)	t_{100}** (min)	$A_{30\%}$*
F-I	0.0101	68.24	>90.00	16.66
F-II	0.0129	53.63	>90.00	34.24
F-III	0.1752	3.95	56.00	87.59
F-IV***	0.0076	90.30	>90.00	25.10
F-V	0.0122	56.47	>90.00	39.92
F-VI	0.1305	5.30	45.00	83.75
F-VII	0.0260	26.57	>90.00	69.55
F-VIII	0.0310	22.33	>60.00	62.47

* The amount dissolved in 30 min
** Time necessary for complete dissolution
***Physical mixture

seventeen fold increase was observed with solid-dispersed tablets containing Kollidon CL (Table 5). On the other hand, by the addition of starch (F-V), only two fold increase in drug dissolution was seen. Disintegrant is the main factor in the dissolution of solid-dispersed tablets. As shown in Table 5, comparison of solid-dispersed tablets without disintegrant (F-VII) and tablets prepared from physical mixtures(F-IV), only three fold increase was found by solid-dispersed tablets without disintegrants. Briefly, it could be stated that the choice of the disintegrant in furosemide-PVP tablet formulation has an importance.

Kollidon CL was found superior as a disintegrant for this kind of solid dispersed tablets. When the dissolution profiles of the solid dispersed tablet and the tablet prepared by physical mixtures were compared, it was observed that solid dispersion could be used to provide rapid complete drug release from tablets. Tablets containing solid-dispersed furosemide had lower t_{100}'s than tablets of those containing physical mixtures (F-IV).

As given in Table 3, by the addition of corn starch and Kollidon CL, harder tablets with low friability values were obtained (F-V and F-VI). As a conclusion physical properties of these tablets such as friability and crushing strength were satisfactory, but as it is shown in Tables 3 and 5, tablets formulated by corn starch exhibited a poor disintegration and also slow dissolution profiles (t_{50} > 56.47 min).

On the other hand, according to our observation, solid-dispersed tablets did not disintegrate during the test, but slowly broke up by surface erosion. This is reflected in Tables 3 and 5 where the disintegration times of tablets prepared by direct compression are equal or greater than the values of t_{50} (dissolution half-life). Similar observations have been noted previously (4,7).

A poor correlation was obtained between the disintegration time and dissolution half-lives of the tablets ($r<0.5$).

On the other hand as seen in Table 6, porosity values of these tablets are very variable. A relationship was not found between the disintegration time and the porosity of tablets. The delayed disintegration times were expected from the low porosity tablets, but the fast disintegration was observed. Therefore the rate limiting step in the disintegration of solid-dispersed tablets is not related only to porosity.

It is considered that film formed subtances such as PVP, fill the pores and prevent further capillary flow if the formulation of tablet is not convenient. As seen in Table 6, during the Liquid penetration test, film formation was observed in the tablets containing Primojel and the tablets without disintegrant.

Moreover, a relation was not observed between the porosities and penetration times (Table 6).

It has been noted that the pore structure of the tablet and the wetting capacity of powders in the tablet are responsible for liquid penetration (11, 12). Since no relation was found between the porosity and penetration time, wetting of the powders in the tablet might be more important for water penetration into

TABLE 6
Porosity and Liquid Penetration times of Tablets

Formulation	Porosity %	Penetration time (s)
F-I	40.80	1463
F-II	17.92	film formed
F-III	8.8	61.6
F-IV*	52.34	3045
F-V	24.93	8050
F-VI	36.30	140
F-VII	43.45	film formed
F-VIII	20.11	1200

*Physical mixture

solid-dispersed tablets. The water penetration times of F-III and F-VI were faster than the others.

The fastest dissolution rates were observed with F-III and F-VI which were containing Kollidon CL as a disintegrant. (Table 1). Those tablets with faster penetration rate had an increased dissolution. In solid-dispersed tablets, water penetration also reflected the dissolution behavior of tablets (r=0.526). As seen in Tables 5 and 6, when the water penetration time reduced, tablets indicated increased dissolution profiles.

Effect of Particle Size

The properties of tablets (F-VI) prepared by furosemide-PVP solid-dispersion system at different

TABLE 7
Effect of Particle Sizes of Solid-dispersion Systems on Tablet Properties

Particle size (μm)	Crushing strength (N)***	Friability (%)	Disintegration time (min)***	Weight (g)***	Dissolution Parameters		
					t_{50min}	k_{min}	$A_{30\%}$
281*	35.5 (2.44)	0.53	12.14 (0.53)	0.3720 (0.009)	5.3	0.1305	83.75
182**	39.5 (5.49)	0.72	19.16 (3.76)	0.3842 (0.006)	26.65	0.0260	63.16

* 80-mesh size
** 100-mesh size
*** Mean values ± s.d.

particle sizes (particle sizes in 80-mesh or 100-mesh) were given in Table 7. No difference was found between the crushing strength, disintegration time and friability values of tablets prepared with different particle sizes, but furosemide-PVP solid dispersion system in 100-mesh particle size was less compressible. When the dissolution rates of two mesh sizes tablets were compared, dissolution rate of tablets produced by 80-mesh particle sizes was five fold faster than the tablets produced from fine particles.

As a conclusion, tablets can be prepared with furosemide-PVP solid dispersion systems. However, technique used for preparation, choice of disintegrant and particle size of solid dispersion system are effective factors for tablet properties. Kollidon CL is the best disintegrant for furosemide-PVP solid dispersed tablets. By using direct compression technique, tablets with satisfactory properties could be obtained. The dissolution of furosemide in acidic medium was increased seventeen fold. Although rapid and complete dissolution was achieved from tablets containing the solid dispersed drug, the factors mentioned above must be considered. A study is going on for the stability of furosemide-PVP solid dispersed tablets in different conditions.

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