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Physical properties and dissolution profiles of tablets directly compressed with β-cyclodextrin

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Summary

In this study, β-CD was evaluated as a direct compression vehicle either singly or in blends with spray-dried lactose (sp.d.l.) for preparing tablets containing either phenobarbitone, diazepam, prednisolone or spironolactone. These drugs are examples of slightly soluble drugs forming inclusion complexes with β-CD in different molar ratios. Generally, it was found that β-CD and its combinations with sp.d.l. produced tablets having very good mechanical properties and higher dissolution rate. The uniformity of weight and thickness were good (coefficient of variation, c.v., less than 2%) for all formulations containing up to 60% β-CD, after which the c.v. exceeds 2%. In each drug formulation, the dissolution rate was progressively increased with the increase in β-CD concentration up to a certain limit after which the dissolution rate was not significantly changed or only slightly decreased. The dissolution rate of the selected drugs was improved by about 6–10-fold compared to that of tablets prepared by wet granulation or those containing 100% sp.d.l. The optimum formulation was found to vary from one drug to another depending upon its nature, dose and molar ratio of inclusion complex with β-CD.

Introduction

β-Cyclodextrins and their derivatives have been used in pharmaceutical formulations to enhance the solubility (Cohen and Lach, 1963; Uekama et al., 1982), dissolution rate (Corrigan and Stanley, 1982; Uekama et al., 1983; Chow and Karara, 1986), membrane permeability (Uekama et al., 1985a; Okamoto et al., 1986), bioavailability (Nambu et al., 1978; Iwaoku et al., 1982; Vila-Jato et al., 1986) of slightly soluble drugs, through the formation of inclusion complexes with the drugs. Solid inclusion complexes have been prepared by coprecipitation (Si-Nang et al., 1985), solid dispersion (Fukuda et al., 1986), freeze-drying (Erden and Celebi, 1988), heating in a sealed container (Nakai et al., 1987) and co-grinding (Nakai et al., 1980).

The introduction and successful application of the direct compression technique especially for low and medium dosage ranges of drugs can be regarded as a major advance in the field of tablet formulation. Much effort has been devoted to the development of new and special direct compression vehicles (Ondari et al., 1983; Elsabbagh and ElShaboury, 1984).

The objective of the present study was to evaluate β-CD as a direct compression vehicle either singly or in blends with spray dried lactose (sp.d.l.) (co-vehicle and bulking agent) for preparing tablets containing either phenobarbitone, di-

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azepam, prednisolone, or spironolactone. These drugs were selected to represent a model of slightly soluble drugs which form solid complexes with β-CD in different molar ratios: 1 : 1 (Koizumi et al., 1980), 2 : 3 (Uekama et al., 1983), 1 : 2 (Uekama et al., 1985b) and 1 : 3 (Yusuff and York, 1988), respectively. The possibility of improving the release of these drugs via complexation was also investigated.

Materials and Methods

Materials

The following materials were used: β-cyclodextrin (β-CD, Fluka, Buchs, Switzerland), spray-dried lactose (sp.d.l., Foremost-McKesson, San Francisco, CA), diazepam (Hoffmann La Roche, Switzerland), prednisolone (Hoechst, Frankfurt, F.R.G.), spironolactone (Searle Pharmaceuticals, U.K.), corn starch (Best Foods, New York, NY), phenobarbitone, lactose monohydrate and magnesium stearate (BDH, Poole, U.K.).

Methods

Direct compression. In the case of phenobarbitone, diazepam or spironolactone the tablet matrix consisted of 10 parts drug and 90 parts β-CD-sp.d.l. at the following ratios: 0 : 100, 10 : 90, 20 : 80, 30 : 70, 40 : 60, 50 : 50, 60 : 40, 70 : 30, 80 : 20, 90 : 10 and 100 : 0.

For prednisolone, the tablet matrix consisted of 5 parts prednisolone and 95 parts β-CD-sp.d.l. at the same ratios as mentioned above.

Each of the matrix materials was mixed with 5% corn starch (disintegrant) and 1.0% magnesium stearate (lubricant) in a twin-shell blender (Patterson-Kelley) for 10 min.

Wet granulation. In wet granulation, lactose monohydrate was used instead of β-CD and sp.d.l. Drugs and other substances were used in the same proportions as in direct compression. PVP (6% w/v) was used as a binder. The drug and lactose mixture was kneaded with the binder solution for 10 min using a Kenwood kneader. The wet mass was forced through a no. 12 sieve and dried at 50 °C in a hot-air oven for 12 h. The dried granules were re-sieved through a no. 20 sieve. The granules were then mixed with corn starch and magnesium stearate.

The formulations were compressed in a single-punch Erweka tablet press (EKO, F.R.G.). For each drug formulation, the machine settings were adjusted to produce tablets having approximately the same hardness and weight. A minimum of 500 tablets were prepared per patch. The nominal weight was: 315 mg for phenobarbitone tablets, 265 mg for spironolactone tablets and 105 mg for diazepam or prednisolone tablets.

Tablet properties

The following properties were measured: uniformity of weight and thickness, hardness, friability, disintegration time and dissolution. A sample of 20 tablets was used for weight, thickness and hardness determinations. Friability was determined by using a Roche friabilator with 20 tablets for 4 min (100 revolutions). The disintegration time was determined for six tablets with a USP disintegration apparatus (Erweka, ZT-6-1-D) without discs at 37 °C, in water.

Dissolution studies were determined according to the USP XX paddle method in 600 ml of 0.1 N HCl at 37 ± 0.5 °C. The stirring rate was 60 rpm. At appropriate intervals, the solution was sampled and filtered rapidly through a filter paper (Whatman 40). Each sample was diluted and analysed spectrophotometrically (UV-260 Shimadzu spectrophotometer) at 255, 243, 240 and 245 nm for phenobarbitone, diazepam, prednisolone and spironolactone, respectively. A correction was applied for the cumulative dilution caused by replacement of the samples by equal volumes of the original medium. All measurements were made in triplicate, at least, and the results given are the means of several determinations.

Results and Discussion

Uniformity of weight and thickness

The results summarized in Tables 1–4 show that a good degree of uniformity of weight and thickness was achieved for all formulations. The uniformity of thickness was found to be more or less parallel to that of weight. Tablets containing

TABLE 1

Physical properties and dissolution profiles of spironolactone tablets

Percentage		Weight (g)		Thickness (mm)		Hardness (K_P)	Friability (%)	Disintegration time (min)	Dissolution profiles		
β-CD	Sp.d.l.	Mean	c.v. (%)	Mean	c.v. (%)				$T_{30\%}$	$T_{60\%}$	$T_{90\%}$
0	100	267.1	1.41	3.75	1.30	9.10	0.83	6.95	19.5	44.5	–
10	90	266.7	1.50	3.73	1.33	10.00	0.47	6.60	14.0	31.5	78.5
20	80	264.3	1.63	3.70	1.71	10.15	0.41	6.25	11.0	23.5	60.5
30	70	266.7	1.70	3.71	1.73	10.25	0.38	6.45	8.5	18.5	39.0
40	60	264.6	1.81	3.69	1.77	10.00	0.38	6.55	7.0	13.0	30.0
50	50	264.1	1.87	3.69	1.81	10.25	0.36	6.50	5.5	10.5	23.5
60	40	263.7	1.92	3.66	1.85	10.10	0.33	6.75	4.5	8.5	19.0
70	30	264.3	2.31	3.68	2.21	10.35	0.33	6.75	4.0	7.5	16.5
80	20	265.1	3.05	3.69	2.96	10.50	0.31	6.95	4.0	6.5	13.5
90	10	266.2	4.75	3.71	4.33	10.50	0.32	6.80	3.5	5.5	11.5
100	0	267.2	7.13	3.72	6.55	10.6	0.29	6.95	4.0	7.0	13.0
Wet granulation		268.1	1.45	3.72	1.51	9.65	0.34	8.75	26.5	58.5	–

TABLE 2

Physical properties and dissolution profiles of diazepam tablets

Percentage		Weight (g)		Thickness (mm)		Hardness (K_P)	Friability (%)	Disintegration time (min)	Dissolution profiles		
β-CD	Sp.d.l.	Mean	c.v. (%)	Mean	c.v. (%)				$T_{30\%}$	$T_{60\%}$	$T_{90\%}$
0	100	107.7	1.36	2.62	1.41	7.05	0.57	4.25	9.5	19.0	29.5
10	90	107.1	1.55	2.60	1.45	7.45	0.34	4.00	8.0	15.5	24.0
20	80	106.7	1.78	2.60	1.66	7.55	0.34	4.10	6.0	11.5	20.0
30	70	104.5	1.77	2.58	1.81	8.00	0.30	4.30	5.0	8.5	15.5
40	60	106.2	1.81	2.59	1.78	7.75	0.32	4.25	4.0	7.0	12.0
50	50	104.4	1.84	2.56	1.91	7.80	0.30	4.15	3.0	6.0	9.5
60	40	104.1	1.97	2.57	1.93	7.75	0.28	4.35	2.5	4.5	7.0
70	30	103.7	2.76	2.55	2.45	7.90	0.26	4.45	2.0	3.5	5.5
80	20	104.5	3.66	2.55	3.45	7.80	0.28	4.65	3.0	4.0	5.5
90	10	103.7	5.70	2.53	5.37	8.00	0.24	4.65	3.0	5.0	6.5
100	0	103.3	7.80	2.52	7.56	7.90	0.23	4.75	3.0	6.0	8.0
Wet granulation		106.4	1.43	2.59	1.39	7.25	0.33	5.90	13.0	22.5	36.5

up to 60% β-CD complied with the pharmacopoeial requirements. The coefficient of variation did not exceed 2%, indicating excellent uniformity of weight and thickness. The variation in weight for the formulations containing more than 60% β-CD was relatively high (c.v. > 2%). This may be attributed to the fact that sp.d.l. has superior flow properties compared to β-CD.

Mechanical properties

All tablets exhibited good mechanical properties with regard to both hardness and friability (Tables 1–4). No significant differences in hardness values within each of the drug formulations were observed, while the friability was decreased as the concentration of β-CD increased. Tablets containing 100% sp.d.l. (0% β-CD) showed the highest friability values, while those containing 100% β-CD displayed the lowest values. This may be due to the greater binding strength of β-CD (Fenyvesi et al., 1984).

Disintegration time

Generally, it was evident that all tablets disintegrated within the USP limits, where the disintegration time for all tablets was less than 10 min

TABLE 3

Physical properties and dissolution profiles of prednisolone tablets

Percentage		Weight (g)		Thickness (mm)		Hardness (K_P)	Friability (%)	Disintegration time (min)	Dissolution profiles		
β-CD	Sp.d.l.	Mean	c.v. (%)	Mean	c.v. (%)				$T_{30\%}$	$T_{60\%}$	$T_{90\%}$
0	100	107.1	1.65	2.57	1.54	7.00	0.53	4.65	11.5	20.0	34.5
10	90	106.3	1.72	2.54	1.63	7.60	0.41	4.25	7.5	15.0	22.5
20	80	106.9	1.78	2.54	1.66	7.70	0.41	4.20	5.0	10.5	14.5
30	70	104.2	1.81	2.51	1.77	7.50	0.41	4.10	3.0	6.0	7.5
40	60	106.6	1.88	2.51	1.83	7.65	0.34	4.30	2.5	4.0	6.0
50	50	106.3	1.91	2.53	1.87	7.70	0.33	4.50	3.0	5.0	6.5
60	40	103.9	2.04	2.48	1.94	7.90	0.33	4.50	3.5	6.0	8.0
70	30	104.2	3.21	2.49	2.97	7.80	0.30	4.65	3.5	6.5	8.5
80	20	104.5	4.45	2.50	4.31	7.75	0.30	4.65	4.0	6.5	9.5
90	10	104.5	6.37	2.48	6.07	7.75	0.31	4.75	5.0	7.5	11.0
100	0	106.1	8.88	2.50	8.31	7.90	0.28	4.75	5.5	8.5	11.5
Wet granulation		107.5	1.61	2.54	1.57	7.50	0.31	6.15	17.0	28.5	39.5

TABLE 4

Physical properties and dissolution profiles of phenobarbitone tablets

Percentage		Weight (g)		Thickness (mm)		Hardness (K_P)	Friability (%)	Disintegration time (min)	Dissolution profiles		
β-CD	Sp.d.l.	Mean	c.v. (%)	Mean	c.v. (%)				$T_{30\%}$	$T_{60\%}$	$T_{90\%}$
0	100	316.7	1.45	4.46	1.52	8.75	0.61	6.75	12.5	24.5	38.5
10	90	314.8	1.62	4.43	1.54	9.75	0.47	6.25	9.0	16.5	30.0
20	80	314.3	1.68	4.41	1.72	9.80	0.41	5.90	6.5	12.0	22.0
30	70	315.1	1.84	4.42	1.73	9.75	0.39	6.35	5.5	9.0	17.5
40	60	313.4	1.82	4.39	1.71	10.10	0.38	6.45	4.0	8.0	13.5
50	50	314.7	1.89	4.39	1.90	9.95	0.35	6.50	3.5	6.0	10.0
60	40	316.2	1.97	4.40	1.93	10.15	0.36	6.65	3.0	5.5	6.5
70	30	314.5	2.98	4.38	2.65	9.95	0.31	6.65	3.0	6.0	7.5
80	20	313.6	3.87	4.36	3.75	10.25	0.31	6.75	3.5	5.5	9.5
90	10	313.2	4.75	4.34	4.44	10.00	0.29	6.90	3.5	6.0	10.5
100	0	314.4	6.88	4.35	6.45	10.30	0.28	6.90	4.0	7.0	11.5
Wet granulation		316.6	1.54	4.41	1.49	9.50	0.33	8.25	17.5	30.5	46.0

(Tables 1–4). For each drug formulation prepared by direct compression, the disintegration times did not vary significantly. This may be due to the approximately equal hardness of these tablets; in addition, the disintegrant and lubricant concentrations were the same in each drug formulation.

Dissolution profiles

The time necessary for 30, 60 and 90% dissolution was used to represent the dissolution profiles of the prepared tablets. Wet granulation yields tablets of slower dissolution rate than those prepared by direct compression irrespective of the vehicle used (Tables 1–4). This can be explained by the fact that for tablets prepared by direct compression, the drug is readily available to the dissolution medium thus not requiring the splitting time for granules in the case of wet granulation. The $T_{90\%}$ of spironolactone tablets prepared by wet granulation or direct compression with 0% β-CD (100% sp.d.l.) could not be determined, since only about 70% of the dose was maximally dissolved.

In the case of tablets prepared by direct compression, the dissolution rate of each of the selected drugs was markedly improved in the presence of

β-CD in the formulations. In each drug formulation, the amounts of drug, disintegrant and lubricant were constant. In addition, the mechanical properties and disintegration time did not vary significantly. Therefore, this marked increase in dissolution rate arose from the presence of β-CD in the formulations. It was found that a progressive increase occurred in the percentage of drug release, corresponding to the increase in β-CD concentration. However, in each drug formulation, β-CD showed its maximum effectiveness at a certain concentration after which the dissolution rate was not significantly changed or only slightly decreased. In the case of prednisolone tablets, the maximum increase in dissolution rate was observed at 40% β-CD, while with phenobarbitone, diazepam and spironolactone the maximum dissolution rate was 60, 80 and 90%, respectively. As can be seen, β-CD up to these concentrations results in an approx. 6–10-fold greater rate of dissolution than that of tablets prepared by wet granulation or those containing 100% sp.d.l. The enhanced dissolution rate is probably due either to the improved wettability and increased solubility which arose from interaction between the drug and β-CD molecules during compression or to complex formation in the test solution.

The results of this study indicate that β-CD could be a useful direct compression vehicle for preparing tablets of good mechanical properties and higher dissolution characteristics which in turn would improve the bioavailability and stability of drugs. The optimum formulation varied from drug to drug depending upon the nature, dose and molar ratio of the inclusion complex with β-CD.

Further investigations are in progress to determine the bioavailability and stability of the prepared tablets.

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