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PHYSICAL PROPERTIES AND STABILITY OF DIAZEPAM AND PHENOBARBITONE SODIUM TABLETS PREPARED WITH COMPACTROL

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ABSTRACT

Compactrol as a newly introduced direct compressible vehicle was used for the preparation of Diazepam and phenobarbitone sodium tablets. Spray dried lactose and wet granulation technique were also employed to prepare these tablets for comparison. The effect of storage at 75% RH, at two temperature levels (25° and 45°) on the physical properties of these tablets was studied for 6 weeks. It was found that, there were an increase in tablet weight, thickness and friability per cent, while a significant decrease in hardness was observed. Tablets prepared with compactrol showed no significant changes in both disintegration and dissolution times, while tablets prepared with spray dried lactose showed a marked decrease in disintegration and dissolution times. On the other hand,

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tablets prepared by wet granulation showed a pronounced in crease in both disintegration and dissolution times.

INTRODUCTION

Direct compression offers many advantages of improved physical and chemical stability of tablets compared with those prepared by the conventional granulation methods (1). It is for these reasons, much efforts have been put into the modification of dry binders to make them suitable for direct compression and for the development of special and new direct compression vehicles. Compactrol is one of the newly introduced vehicle in the formulation of direct compression tablets (2). It is a specially-processed grade of calcium sulfate dihydrate, non-hygroscopic, white and free-flowing. The particle size distribution of compactrol is within the range of a great majority of active ingridients, where, less than 5% retained on 60 mesh screen and less than 50% through 200 mesh screen.

The aim of this work is to evaluate compactrol as a new direct compressible vehicle for the preparation of diazepam and phenobarbitone sodium tablets. Spray dried lactose was used as a traditional vehicle. Wet granulation technique was also employed to prepare these tablets for comparison. The drugs were selected on the basis of their difference in the incorporated ratios and represent a model for drugs that are greatly affected by moisture and heat (3). Thus, the effect of ageing at 75% RH, at two temperature levels (25 and 45°), on the physical properties and dissolution characteristics of the formulated tablets were also studied.

MATERIALS AND METHODS

Tablet Formulations :

Ingredients	Diazepam Tablets		Phenobarbitone Tablets	
	A	B	C	D
Diazepam[1]	20	20	-	-
Phenobarbitone[1]	-	-	60	60
Compactrol or[2] Spray d. Lactose[3]	244	-	204	-
Lactose[1]	-	244	-	204
Corn Starch[1]	30	30	30	30
Talc[1]	6	6	6	6
Total weight (gm)	300	300	300	300

A,C: Direct compression
B,D: wet granulation with 10% w/v aqueous gelatin solution.
1 From, El Nile Pharm. Chem. Co., A.R.E.
2 From, Edward Mendel Co., Carmel, N.Y., U.S.A.
3 Foremost-Mckesson, San Francisco, California, U.S.A.

Tableting was carried out on a single punch Erweka tablet press (EKO). About 2000 tablets were prepared for each batch. The tablet weight was nominally 150 mg.

Evaluation of the Physical Properties of the Tablets:

The tablets were evaluated for uniformity of weight (USP), uniformity of thickness (micrometer), hardness (Erweka Hardness tester), friability (Roche Friabilator) and disintegration time (USP). The dissolution rate was also determined using USP-XIX-NFXIV dissolution apparatus.

Accelerated Storage Conditions :

Two sets of stress storage conditions 75% RH, at two temperature levels 25° and 45° were employed using

desiccators containing salt solution of sodium chloride (4). Each batch of tablets was subdivided into two groups placed in petri-dishes, and stored under the selected stress conditions.

The tablets were evaluated weekly for their physical standards and dissolution characteristics as mentioned before.

RESULTS AND DISCUSSION

Physical Characteristics of Tablets :

All tablets were found to satisfy the USP requirements for weight uniformity and thickness. They exhibited good mechanical properties as regards both hardness and friability. The disintegration time of all tablets was found to be within the USP limits.

Effect of Ageing on the Physical Characteristics of Tablets :

Tablet Weight and Thickness :

From the results obtained (Tables 1,4), it was found that there is a slight increase in tablet weight and thickness. This increase is more pronounced at 45° than that at 25°. Tablets prepared with spray dried lactose and wet granulation showed a marked increase in weight and thickness than those prepared with compactrol. On the other hand, phenobarbitone sodium tablets prepared with spray dried lactose and wet granulation, stored at 75% RH and 45° were moistened and their colour changed to brown, after 4 weeks.

The increase in tablet weight and thickness may be due to the absorption of moisture from the surrounding humid atmosphere (5). The brown colouration of phenobarbitone tablets may be due to the formation of shiffs base resulted from the interaction of lactose and

Table (1): Physical Characteristics of Diazepam Tablets, Stored at 75% RH and 25°.

Time in weeks	Weight gm	C.V. %	Thickness mm	C.V. %	Hardness kg	Friability %	Disinteg. min.	Dissolut. T90
				Using Compactrol				
0	0.14251	0.82	2.77	0.78	4.75	0.30	0.16	5.00
1	0.14305	0.97	2.77	0.92	4.25	0.41	0.16	5.00
2	0.14465	1.18	2.80	1.10	4.10	0.49	0.13	5.00
3	0.14536	1.17	2.81	1.13	3.90	0.52	0.13	4.75
4	0.14540	1.21	2.81	1.16	3.75	0.58	0.13	5.00
5	0.14590	1.33	2.82	1.28	3.25	0.71	0.13	4.75
6	0.14610	1.28	2.83	1.26	3.10	0.83	0.13	5.00
				Using Spray dried lactose				
0	0.14851	1.25	4.00	1.14	4.85	0.33	0.42	6.50
1	0.14960	1.29	4.05	1.22	4.25	0.37	0.25	3.00
2	0.14990	1.37	4.07	1.33	3.75	0.45	0.25	3.00
3	0.15120	1.32	4.10	1.30	3.25	0.49	0.33	3.00
4	0.15360	1.41	4.13	1.36	3.10	0.57	0.33	3.50
5	0.15430	1.38	4.16	1.31	2.50	0.89	0.40	3.50
6	0.15638	1.28	4.18	1.31	2.00	0.96	0.33	3.00
				Using Wet granulation				
0	0.15125	1.09	4.02	1.01	4.75	0.22	4.50	18.50
1	0.15250	1.20	4.06	1.17	4.00	0.27	5.33	20.00
2	0.15335	1.17	4.10	1.14	3.80	0.33	6.00	25.00
3	0.15495	1.22	4.12	1.19	3.50	0.38	7.25	28.50
4	0.15550	1.31	4.14	1.27	3.30	0.52	9.50	33.66
5	0.15580	1.33	4.17	1.36	2.75	0.57	10.33	35.00
6	0.15690	1.29	4.20	1.31	2.60	0.53	13.50	38.50

hydrolysed products of phenobarbitone sodium at high temperature and humidity levels (6,7).

Mechanical Properties :

It was found that, all tables showed a marked decrease in their hardness (Tables 1-4). However, this decrease was less pronounced in case of tablets prepared with compactrol. The decrease in hardness may be due to the weakening of interparticulate bonding between the particles of tablets resulted from moisture uptake. These results are in coordination with those reported by several investigators (4,5,8-10).

Table (2): Physical Characteristics of Diazpam Tablets, Stored at 75% RH 45°.

Time in weeks	Weight gm	C.V. %	Thickness mm	C.V. %	Hardness kg	Friability %	Disinteg. min.	Dissolut. T90
				Using Compactrol				
0	0.14251	0.82	2.77	0.78	4.75	0.30	0.16	5.00
1	0.14365	1.11	2.79	0.96	4.50	0.51	0.12	5.00
2	0.14500	1.15	2.82	1.13	4.00	0.62	0.12	5.00
3	0.14595	1.19	2.83	1.16	3.50	0.68	0.16	5.00
4	0.14610	1.21	2.86	1.17	3.30	0.83	0.16	5.00
5	0.14595	1.28	2.90	1.31	2.60	1.07	0.12	5.00
6	0.14675	1.40	2.93	1.33	2.10	1.28	0.12	5.00
				Using Spray dried lactose				
0	0.14851	1.25	4.00	1.14	4.85	0.33	0.42	6.50
1	0.14980	1.31	4.04	1.26	4.25	0.37	0.33	4.50
2	0.15175	1.28	4.09	1.22	3.60	0.48	0.33	4.00
3	0.15315	1.20	4.13	1.18	3.20	0.62	0.25	3.00
4	0.15500	1.31	4.20	1.28	3.00	0.75	0.25	3.00
5	0.15710	1.34	4.26	1.31	2.60	1.15	0.13	3.00
6	0.15825	1.27	4.30	1.28	2.00	1.36	0.13	3.00
				Using Wet granulation				
0	0.15125	1.09	4.02	1.01	4.75	0.22	4.50	18.50
1	0.15240	1.19	4.05	1.15	4.50	0.26	6.25	21.66
2	0.15360	1.21	4.08	1.19	4.00	0.31	7.50	28.50
3	0.15510	1.29	4.12	1.23	3.10	0.35	9.33	31.00
4	0.15680	1.37	4.16	1.31	2.70	0.45	11.50	37.00
5	0.15795	1.27	4.20	1.25	2.20	0.74	13.50	41.50
6	0.15950	1.25	4.25	1.19	1.75	0.92	17.33	47.00

The friability percent of tablets was found to be increased gradually as the time of storage increased. These results were found to be correlated well with the decrease in tablet hardness.

Disintegration Time :

The effect of ageing on the disintegration time of tablets was variable (Tables 1-4). Tablets prepared by wet granulation showed a marked increase in disintegration time. On the other hand, the reverse effect was observed in case of tablets prepared by direct compression. The increase in disintegration time may be due to the

Table (3): Physical Characteristics of Phenobarbitone Sodium Tablets Stored at 75% RH and 25°.

Time in weeks	Weight gm	C.V. %	Thickness mm	C.V. %	Hardness kg	Friability %	Disinteg. min.	Dissolut. T90
					Using Compactrol			
0	0.14904	1.06	3.18	0.91	4.25	0.42	3.33	25.50
1	0.15045	1.13	3.21	1.02	4.10	0.56	3.83	26.50
2	0.15125	1.09	3.24	1.04	3.75	0.68	2.66	25.00
3	0.15165	1.16	3.30	1.12	3.20	0.73	2.75	22.50
4	0.15275	1.21	3.34	1.15	2.70	0.73	2.16	22.50
5	0.15300	1.34	3.39	1.31	2.40	0.82	2.00	22.50
6	0.15495	1.31	3.40	1.25	2.40	1.25	2.33	22.50
					Using Spray dried lactose			
0	0.14658	1.14	3.93	0.99	4.80	0.38	1.00	3.50
1	0.14795	1.21	3.97	1.16	4.25	0.49	0.66	2.50
2	0.14925	1.37	4.02	1.32	3.50	0.58	0.66	2.50
3	0.15150	1.24	4.10	1.21	2.60	0.82	0.50	2.50
4	0.15360	1.22	4.18	1.19	1.50	1.07	0.33	2.00
5	0.15500	1.28	4.24	1.27	1.30	1.03	0.50	2.00
6	0.15695	1.35	4.29	1.33	1.10	0.96	0.66	2.00
					Using Wet granulation			
0	0.15885	0.96	4.58	0.88	5.20	0.15	9.50	45.00
1	0.16025	0.99	4.61	1.01	4.50	0.28	19.60	60.00
2	0.16125	1.20	4.63	1.13	3.75	0.47	33.50	75.00
3	0.16250	1.26	4.66	1.22	2.75	0.54	36.50	75.00
4	0.16350	1.21	4.66	1.22	1.75	0.65	40.25	83.50
5	0.16495	1.35	4.70	1.29	1.00	0.52	38.50	76.50
6	0.16590	1.29	4.72	1.25	1.00	0.45	39.50	81.25

loss of disintegrant efficiency resulted from moisture uptake. In addition the binder within these tablets may swell, forming a gel which prevents or blocks the pass of disintegrating liquid into the tablets (5,11,12).

In case of tablets prepared by direct compression the decrease in disintegration time, may be attributed to the decrease of hardness and the increase of friability percent of these tablets.

Dissolution Rate (T_{90})

A significant increase in dissolution time (T_{90}) was observed in case of tablets prepared by wet granula-

Table (4): Physical Characteristics of Phenobarbitone Sodium Tablets Stored at 75% RH and 45°.

Time in weeks	Weight gm	C.V. %	Thickness mm	C.V. %	Hardness kg	Friability %	Disinteg. min	Dissolut. T90
				Using Compatrol				
0	0.14904	1.06	3.18	0.91	4.25	0.42	3.33	25.50
1	0.15205	1.18	3.22	1.11	4.00	0.67	3.66	25.50
2	0.15325	1.21	3.28	1.13	3.60	0.84	2.25	24.50
3	0.15400	1.28	3.32	1.22	3.10	0.92	2.33	25.00
4	0.15485	1.35	3.37	1.31	2.50	1.07	2.66	25.00
5	0.15510	1.41	3.41	1.37	2.00	2.72	3.00	25.00
6	0.15600	1.43	3.42	1.40	1.80	3.35	3.00	25.00
				Using Spray dried lactose				
0	0.14658	1.14	3.93	0.99	4.80	0.38	1.00	3.50
1	0.14800	1.37	3.98	1.32	4.00	0.42	0.66	3.00
2	0.15160	1.42	4.11	1.37	3.10	0.37	1.00	3.00
3	0.15460	1.51	4.22	1.47	2.10	0.25	0.50	3.00
4	0.15895	1.55	4.32	1.52	1.00	0.28	0.33	2.50
5	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-
				Using wet granulation				
0	0.15885	0.96	4.58	0.88	5.20	0.15	9.50	45.00
1	0.16195	1.33	4.63	1.27	3.75	0.46	16.00	52.00
2	0.16300	1.43	4.64	1.36	2.25	0.27	15.50	52.00
3	0.16665	1.61	4.67	1.57	1.50	0.22	16.50	53.50
4	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-

tion, while a noticeable decrease in dissolution time occurred with spray dried lactose tablets. Tablets prepared with compactrol showed no significant changes. These results may be due to the increase or decrease in the disintegration time of the corresponding tablets (5,8,11,12).

CONCLUSION

In this report, it was found that there are significant changes in the physical and mechanical properties of diazepam and phenobarbiton sodium tablets prepared

by spray dried lactose and wet granulation method when stored under the selected stress conditions. However, less marked changes were observed for those prepared with compactoral.

In general these changes can affect the physical and chemical stability of the formulated tablets, which in turn will modify directly or indirectly the biological availability of these tablets.

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