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SOME EFFECTS OF RELATIVELY LOW LEVELS OF EIGHT TABLET DISINTEGRANTS ON A DIRECT COMPRESSION SYSTEM

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Abstract

Eight common tablet disintegrants (Amberlite IRP-88, Corn Starch U.S.P. CLD, Explotab, Ac-Di-Sol, Sta-RX 1500 Starch, Polyplasdone XL, and Guar Gum) were used in concentrations of 0, 0.25, 0.5, 1 and 2% (w/w) in a direct compression system of 75:25 Unmilled Calcium Phosphate Dihydrate/Anhydrous Lactose. Using a Recording Powder Flowmeter (RPF) it was noticed that linearity of flow was relatively unaffected while g/sec. flow rate decreased with increasing concentrations. Each system was then lubricated and tableted keeping the applied pressure relatively constant. Evaluation of the resulting tablets showed that even at very low disintegrant concentrations, significant reduction in disintegration time took place. At the same time, very few detrimental effects often seen with tablet disintegrants, were noticed.

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It has been generally recognized that disintegration time will decrease as the disintegrant concentration increases (1-3). However, it has been noticed that the disintegration time can actually increase with increasing disintegrant concentration (4). Although this is an unusual case, it has been generally accepted that very high concentrations of tablet disintegrant can cause untoward effects on the performance of the tablet. It has been purported that many formulators employ an "overkill" approach when formulating tablet disintegrants, thereby allowing their product to be more susceptible to the adverse effects of disintegrants. Thus, it was deemed important to study the effects of relatively low concentrations of various disintegrants on a pharmaceutical system.

Experimental

Unmilled Calcium Phosphate Dihydrate and Anhydrous Lactose were mixed[1] in a 75:25 ratio, respectively for 15 minutes. This mixture was used as the excipient system throughout the study. Eight tablet disintegrants (Corn Starch U.S.P., Amberlite IRP-88 Resin, CLD, Explotab, Ac-Di-Sol, Sta-RX 1500 Starch, Polyplasdone XL, and Guar Gum) were added to this system in concentrations of 0%, 0.25%, 0.5%, 1% and 2% (w/w) by mixing the appropriate amount of disintegrant with the excipient system and 0.5% (w/w) Magnesium Stearate[2] for 15 minutes.

Each disintegrant/excipient system was then tableted utilizing a computer-instrumented single-punch tablet press[3]. The applied compression force was kept relatively constant (± 200 lbs.) for each system. The resulting tablets were tested for weight[4], thickness[5], hardness[6] and disintegration time[7]. These are reported as mean values[8].

In addition, each disintegrant was evaluated for its effect on powder flow utilizing a recording powder flowmeter (RPF). The RPF was similar in design to that described by Jordan and Rhodes (5) and

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[1] Twin Shell Blender, Patterson-Kelley Co.
[2] First passed through #60 mesh screen
[3] Stokes Model F Press
[4] Mettler Model H 12
[5] Ames Thickness Guage
[6] Heberlein Hardness Tester
[7] U.S.P. Apparatus with discs
[8] n = 10

Rudnic, et al (6), in that it was comprised of a stainless-steel funnel[9], analog balance[10], and single pen recorder[11]. Disintegrants were added in concentrations of 0, 0.25, 0.5, 1 and 2% (w/w) to the excipient system by mixing[1] for 15 minutes. One kilogram of each disintegrant system was run through the flowmeter to produce a flowgram characterizing flow. This procedure was carried out three times and both parameters of flow rate and linearity were reported as mean values. The parameters of powder flow evaluation were the same as previously reported (6) for the RPF in that mass flow was reported as g/sec (avg.) while linearity was determined by altering the least squares correlation coefficient of the flowgram as follows: fl = $(r^2 - 0.8) \times 100$.

Results and Discussion

Tables I-VIII list the results of tablet evaluation and powder flow for each concentration tested for each disintegrant. Examination of each disintegrant/concentration profile revealed that while low levels of tablet disintegrant have relatively little effect on such parameters as weight, weight variation, thickness and hardness; disintegration times were reduced significantly. In fact, even at such a low concentration as 0.25% (w/w), one disintegrant reduced disintegration time from greater than 120 minutes to 1.2 minutes. At a concentration of 1% (w/w), seven of the disintegrants showed greater than a ten-fold decrease in disintegration time. One half of the disintegrants reduced the disintegration time to under one minute at a concentration of 2% (w/w).

For the parameter of powder flow, it was noticed that, although there might have been a general trend to decrease linearity of the flowgram with increase in concentration of disintegrant, it was not overly significant for low levels of disintegrant. The mass flow (g/sec.) rate of the powder, in all cases, decreased slightly with increasing concentration, even though only low levels of disintegrant were used.

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[9] Hopper of Stokes Model F Single Punch Tablet Press
[10] Mettler Model PR 1200
[11] Linear Single Pen Recorder

TABLE I

Amberlite IRP-88 Concentration Profile

	W/W Concentration				
Parameter	0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.6	19.4	19.3	18.9
Flow Rate (g/sec.)	241	234	223	211	201
Tablet:					
Weight(mg.)	402.3	404.5	405.2	402.6	407.3
R.S.D.	0.708	0.412	0.403	0.341	0.246
Thickness(mm)	3.308	3.349	3.333	3.344	3.376
R.S.D.	0.814	0.387	0.430	0.395	0.386
Hardness(kg)	8.75	8.65	8.80	8.60	8.90
R.S.D.	12.71	9.459	11.74	10.54	11.48
Disintegration Time (min.)	120+	22.75	8.25	2.67	0.39
Range	-	16.2-29.3	5.3-11.2	2.8-3.5	0.3-0.5
Applied Pressure (lbs.)	3600.9	3553.4	3588.9	3640.9	3603.1
R.S.D.	1.899	1.728	2.139	1.695	1.749

1. see Experimental Section

TABLE II

Corn Starch U.S.P. Concentration Profile

	W/W Concentration				
Parameter	0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.3	19.4	19.2	19.1
Flow Rate (g/sec.)	241	238	227	212	206
Tablet:					
Weight(mg)	402.3	403.0	403.4	404.2	403.5
R.S.D.	0.708	0.287	0.429	0.436	0.578
Thickness(mm)	3.308	3.318	3.310	3.309	3.333
R.S.D.	0.814	0.353	0.383	0.548	0.656
Hardness(kg)	8.75	8.50	8.35	9.05	8.60
R.S.D.	12.71	7.337	9.799	11.18	10.54
Disintegration Time (min.)	120+	55.83	54.20	16.48	11.98
Range	-	28.6-63.2	38.0-70.4	12.2-20.8	10.2-13.8
Applied Pressure(lbs)	3600.9	3557.2	3735.0	3826.4	3590.3
R.S.D.	1.399	1.554	2.309	1.663	2.233

1. see Experimental Section

TABLE III

CLD Concentration Profile

Parameter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.6	18.9	19.2	19.0
Flow Rate (g/sec.)	241	234	226	212	204
Tablet:					
Weight(mg)	402.3	406.1	406.7	403.1	397.0
R.S.D.	0.708	0.472	0.376	0.379	1.042
Thickness(mm)	3.308	3.356	3.337	3.328	3.308
R.S.D.	0.814	0.444	0.571	0.515	0.776
Hardness(kg)	8.75	8.80	9.00	8.85	8.85
R.S.D.	12.71	12.33	10.14	12.79	11.32
Disintegration Time(min.)	120+	1.20	0.75	0.33	0.31
Range	-	0.5-1.9	0.6-0.9	0.3-0.4	0.28-0.33
Applied Pressure(lbs)	3600.9	3544.1	3841.6	3740.9	3491.1
R.S.D.	1.899	1.982	1.650	1.692	3.673

1. see Experimental Section

TABLE IV

Explotab Concentration Profile

Parameter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.4	19.6	19.4	19.5
Flow Rate (g/sec.)	241	233	228	222	217
Tablet:					
Weight(mg)	402.3	399.4	401.0	397.8	400.3
R.S.D.	0.708	0.277	0.424	0.543	0.343
Thickness(mm)	3.308	3.265	3.292	3.273	3.327
R.S.D.	0.814	0.498	0.697	0.551	0.494
Hardness(kg)	8.75	9.60	9.10	10.10	8.20
R.S.D.	12.71	14.06	14.37	9.56	10.44
Disintegration Time(min.)	120+	14.46	4.62	2.55	0.98
Range	-	9.8-11.2	3.2-6.1	2.1-3.0	0.9-1.3
Applied Pressure(lbs)	3600.9	3821.6	3693.8	3768.9	3595.2
R.S.D.	1.899	1.362	1.388	1.565	1.687

1. see Experimental Section

TABLE V

Ac-Di-Sol Concentration Profile

Paramter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.5	19.6	19.2	19.2
Flow Rate (g/sec.)	241	234	223	219	211
Tablet:					
Weight(mg)	402.3	402.1	404.9	402.4	401.4
R.S.D.	0.708	0.342	0.302	0.249	0.275
Thickness(mm)	3.308	3.272	3.296	3.289	3.311
R.S.D.	0.814	0.622	0.497	0.473	0.358
Hardness(kg)	8.75	9.90	9.70	9.10	8.40
R.S.D.	12.71	10.16	9.16	12.09	12.16
Disintegration Time(min.)	120+	4.75	1.89	0.56	0.45
Range	-	3.1-5.5	0.9-2.1	0.5-0.7	0.4-0.5
Applied Pressure(lbs.)	3600.9	3767.7	3783.8	3852.9	3662.3
R.S.D.	1.899	1.911	2.423	1.547	1.819

1. see Experimental Section

TABLE VI

STA-RX 1500 Starch Concentration Profile

Parameter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.4	19.6	19.2	19.1
Flow Rate (g/sec.)	241	231	220	212	201
Tablet:					
Weight(mg)	402.3	410.1	411.4	405.2	410.9
R.S.D.	0.708	0.398	0.388	0.520	0.538
Thickness(mm)	3.308	3.366	3.366	3.281	3.392
R.S.D.	0.814	0.726	0.592	0.601	0.635
Hardness(kg)	8.75	8.30	8.80	10.45	7.85
R.S.D.	12.71	9.92	11.42	8.57	11.65
Disintegration Time(min.)	120+	34.54	21.29	10.33	5.75
Range	-	31.6-53.5	28.6-34.0	8.8-11.8	3.8-7.8
Applied Pressure(lbs.)	3600.9	3636.4	3745.0	4092.0	3512.0
R.S.D.	1.899	1.606	1.599	5.648	2.458

1. see Experimental Section

TABLE VII

Polyplasdone XL Concentration Profile

Parameter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.4	19.4	19.6	19.5
Flow Rate (g/sec.)	241	244	240	232	219
Tablet:					
Weight(mg)	402.3	406.0	403.0	395.8	387.5
R.S.D.	0.708	0.260	0.468	1.525	1.006
Thickness(mm)	3.308	3.343	3.306	3.292	3.246
R.S.D.	0.814	0.353	0.586	0.635	0.606
Hardness(kg)	8.75	8.80	8.95	7.70	8.35
R.S.D.	12.71	12.04	15.23	17.64	5.68
Disintegration Time(min.)	120+	17.79	6.5	2.67	0.40
Range	-	17.2-18.4	5.2-7.8	1.4-3.9	0.38-0.42
Applied Pressure(lbs.)	3600.9	3676.4	3729.7	3594.1	3543.4
R.S.D.	1.899	2.294	5.68	5.16	4.96

1. see Experimental Section

TABLE VIII

Guar Gum Concentration Profile

Parameter	W/W Concentration 0%	0.25%	0.5%	1%	2%
Flow:					
Linearity[1]	19.5	19.2	19.4	18.9	18.9
Flow Rate (g/sec.)	241	238	233	218	196
Tablet:					
Weight(mg)	402.3	405.3	403.6	408.5	409.2
R.S.D.	0.708	0.539	0.734	0.637	0.382
Thickness(mm)	3.308	3.339	3.333	3.359	3.368
R.S.D.	0.814	0.665	0.720	0.685	0.451
Hardness(kg)	8.75	8.15	8.05	8.55	8.65
R.S.D.	12.71	15.59	12.91	13.35	10.92
Disintegration Time(min.)	120+	9.71	7.50	3.37	2.22
Range	-	7.3-12.2	4.3-10.7	2.7-4.1	1.8-2.7
Applied Pressure(lbs.)	3600.9	3571.9	3668.9	3754.8	3714.3
R.S.D.	1.899	3.713	3.298	1.724	3.289

1. see Experimental Section

It has been generally recognized that an increase in tablet disintegrant concentration can be detrimental to such tablet parameters as weight variation, powder flow, hardness and thickness specifications. Often it has been found that a large increase in disintegrant concentration has had only a minor effect on lowering disintegration times, and in fact, can even increase disintegration time. This study has shown that by using lower levels of tablet disintegrants, it was possible to alleviate some of the detrimental effects of these disintegrants, while still effecting significant disintegration with no modification of formulation.

It is also possible that extremely rapid disintegration can be detrimental in specific cases, and therefore, it is the task of each formulator to evaluate disintegrants at low levels in his tablet system. The most important conclusion in this work is that disintegration, which can be masked at higher levels, can be effectively evaluated at low disintegrant levels.

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