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DATE: 17-Apr-03
TO: Hurter, P.; Gandek, T.; Palkar, S.
FROM: Ney, J.
CONTRIBUTORS: Meyer, R.; Wang, L.
RE: L-000224715 Monohydrate Evaluation
CC: L-224715 Formulation Team

Summary

This memorandum describes the preliminary evaluation of L-224715 monohydrate. Details on formulation sticking tendency, tablet hardness, and content uniformity are included.

The following conclusions were drawn from the formulation development :

- *L-224715 monohydrate shows less sticking to the punch surface than the anhydrous drug.*
- *The monohydrate is less compactable than the anhydrous drug. This is reflected in lower tablet hardness.*
- *The content uniformity percent claim variation was impacted mostly by the tablet weight variation.*
- *The content uniformity normalized % RSD values for monohydrate formulations are acceptable.*

Monohydrate Formulation Development

L-224715 monohydrate (25g NB66839-125) was obtained from CERD for formulation analysis and development. Four formulations were produced using this material to evaluate its performance and compare it to formulations previously produced using L-224715006F024. The first two DC blends were based on the Phase IIB clinical formulation. The grade of Avicel was changed from PH101 to Ph102. This change was made in order to facilitate satisfactory flow with the large rod-like crystals of the monohydrate. The compositions for formulations DL612 and DL613 are shown compared to the Phase IIB clinical formulation (0431FCT002C001) in Table 1.

Table 1. Phase IIB Formulation Comparison

	0431FCT002C001	DL612	DL613
Component	**Percentage (%)**		
L-224715006F024*	31.00	31.00	0.00
L-224715 Monohydrate**	0.00	0.00	32.10
Avicel PH 101	32.50	0.00	0.00
Avicel PH 102	0.00	32.50	31.95
Mannitol SD100	32.50	32.50	31.95
Dical Phosphate	0.00	0.00	0.00
Cros Carm Na	2.00	2.00	2.00
Mg St.	2.00	2.00	2.00
Talc	0.00	0.00	0.00
Cab-O-Sil	0.00	0.00	0.00

*25% x 1.24 (conversion factor) = 31%
**25% x 1.284 (conversion factor) = 32.1%

Blends (20g) were prepared in a turbula blender and 100mg images were compressed on the Korsh tablet press using 8/32” standard concave tools. The press was set-up with one embossed and one plain upper punch. Tablets were compressed at approximately 9kN. Pictures of the punch faces were taken before and after each run. Figures 1-4 show a punch face comparison of the Phase IIB formulation

(0431FCT002C001) and DL612 after the run. Figures 1 and 2 show a uniform haze over the tool surface. However, figures 3 and 4 show severe sticking in the embossing. The formulation containing Avicel PH102 (DL612) shows greater sticking than the clinical formulation (0431FCT002C001) containing Avicel PH101.

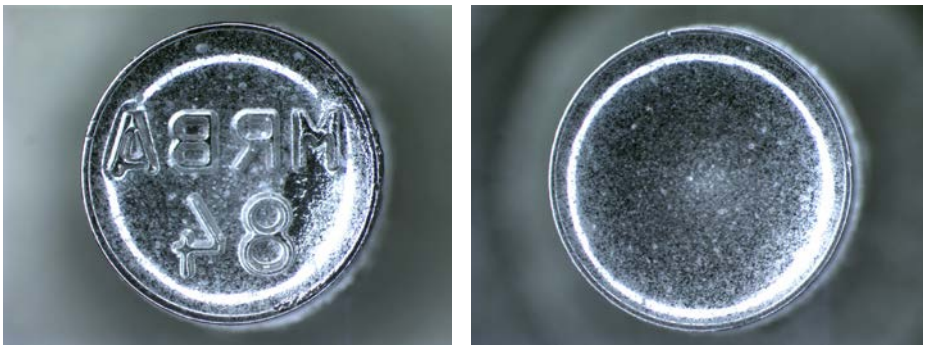
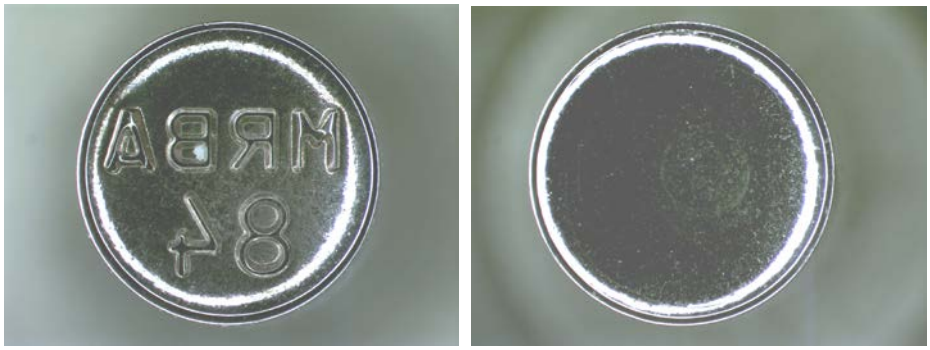


Figure 1 and 2. Phase IIB Clinical Formulation Upper Punches– 0431FCT002C001

Figure 3 and 4. DL612 Upper Punches (Clinical Formulation with Avicel PH102)

Replacing L-224715006F024 with monohydrate, as in DL613, shows a decrease in adherence to the punch face (Figure 5 and 6).



Figures 5 and 6. DL613 Upper Punches

Monohydrate "Best Case" Comparison

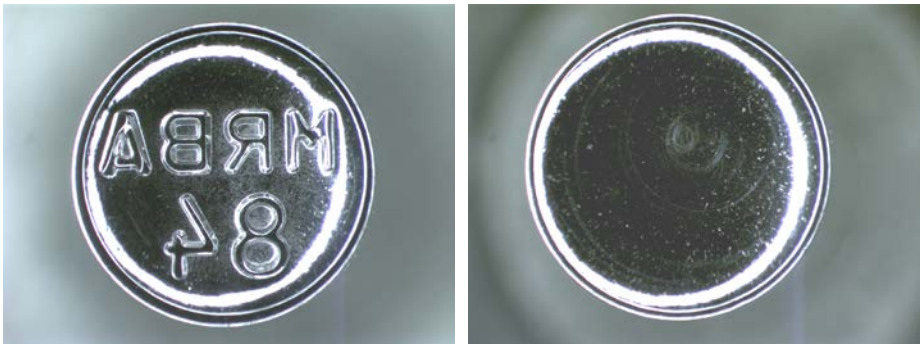
Two monohydrate formulations (DL614 and RC21) were prepared based on formulations that were seen to reduce sticking with L-224715006F024 (anhydrous). These blends included dicalcium phosphate in place of the mannitol. The formulation ratio of dicalcium phosphate to mannitol was 2.5:1. DL614 (20g) was a DC blend prepared in the turbula blender. RC21 (60g) was roller compacted on the Vector TF-mini roller compactor. The resulting ribbons were milled on the Alexanderwork roller compactor RFGs. The compositions are shown in Table 2.

Table 2. "Best Case" Monohydrate Formulations

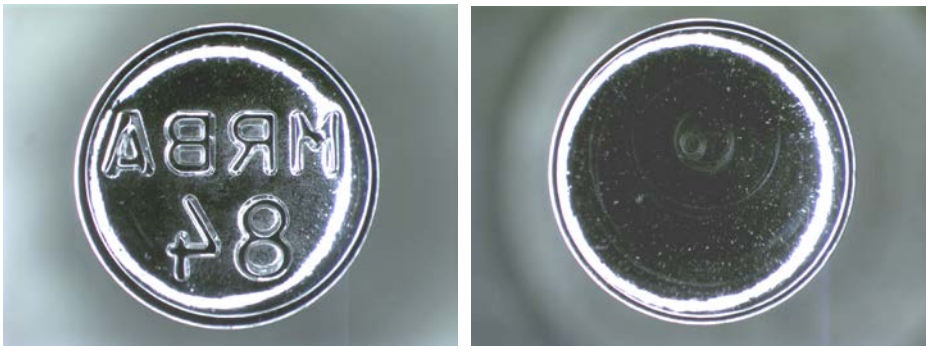
	DL614	RC21
Component	**Percentage (%)**	
L-224715006F024	0.000	0.000
L-224715 Monohydrate**	21.404	21.404
Avicel PH 101	0.000	0.000
Avicel PH 102	20.884	20.884
Mannitol SD100	0.000	0.000
Dical Phosphate	52.211	52.211
Cros Carm Na	2.000	2.000
Mg St.	3.000	3.000
Talc	0.000	0.000
Cab-O-Sil	0.500	0.500

**16.67% x 1.284 (conversion factor) = 21.404%

Tablets (100mg) were compressed on the Korsh press using one embossed and one plain 8/32" standard concave tool. Compacts were compressed at approximately 9kN. Figures 7-10 show the upper punches after compression. Both DL614 and RC21 show almost no sticking.



Figures 7 and 8. DL614 – DC "Best Case" with Monohydrate Upper Punches



Figures 9 and 10. RC21 – Roller Compacted "Best Case" with Monohydrate Upper Punches

Monohydrate Tablet Hardness

A reduction in tablet hardness was observed for the monohydrate formulations as compared to the anhydrous drug formulations (DL612 and DL613). This reduction is greater for the DC formulations. Table 3 shows the average tablet hardness achieved for each formulation.

Table 3. Average Tablet Hardness

Formulation	Description	Tablet Hardness
0431FCT002C001	Phase IIB Clinical	6.80
DL612	Phase IIB Clinical with Avicel 102	7.74
DL613	DL612 with monohydrate drug	5.40
DL505	DC "Best Case"	5.97
RC20	RC "Best Case"	4.2
DL614	DC "Best Case" with monohydrate and Avicel 102	4.75
RC21	RC "Best Case" with monohydrate and Avicel 102	4.13

Monohydrate Content Uniformity

Table 4 shows content uniformity for 10 random tablets from formulation DL613. The RSD is higher than was typically seen for formulations containing the anhydrous drug. Given that the monohydrate prefers to stay agglomerated, it may be difficult to blend at small scale. It is unsure if increasing the batch size will improve this problem. The added shear in larger batches may be helpful in breaking agglomerates. High shear blending could also be used.

Table 4. Content Uniformity- DL613

Samples	Weight (mg)	%Claim	% Normalized Claim
1	99.23	102.0	102.8
2	107.47	105.5	98.2
3	105.98	107.9	101.8
4	107.27	103.3	96.3
5	108.78	107.6	98.9
6	104.07	99.2	95.3
7	99.08	97.6	98.5
8	108.61	107.9	99.3
9	103.33	101.0	97.7
10	107.55	109.2	101.5
Ave.	**105.1**	**104.1**	**99.0**
%RSD	**3.4**	**3.9**	**2.4**

Table 5 shows content uniformity results for RC21. Despite the lower drug loading as compared to DL613 (16.67% vs. 25%), the roller compaction process yields better uniformity.

Table 5 Content Uniformity – RC21

Samples	Weight (mg)	%Claim	% Normalized Claim
1	104.69	103.1	98.5
2	101.03	98.4	97.4
3	102.39	100.7	98.3
4	99.44	97.6	98.1
5	101.04	100.2	99.2
6	99.49	97.2	97.7
7	100.34	98.4	98.1
8	101.06	98.4	97.4
9	106.83	103.3	96.7
10	101.32	99.0	97.7
Ave.	**101.8**	**99.6**	**97.9**
%RSD	**2.3**	**2.2**	**0.7**