W4231

Application Of A Dissolution Test Using Crescent-Shaped Spindle (CSS) To Evaluate Assay And Uniformity Of Dosage Units Parameters

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ABSTRACT

Purpose: To evaluate the use of the CSS to assess the quality parameters from a dissolution test.

Methods: Acetaminophen (7) and prednisone (3) tablet products were tested. The dissolution test conditions (USP): 900 mL phosphate buffer (pH 5.8) for acetaminophen and 500 mL water for prednisone; 50 rpm; test duration=60 min with sampling every 10 min. Assay and UDU were evaluated as per respective USP monographs. In the case of testing using the CSS, all tests were conducted using spindle at 25 rpm with 900 mL of water. The results of the last sampling time (60 min) from the dissolution tests were used for the assessment of assay and UDU parameters.

Results: The use of both spindles provided complete dissolution and similar dissolution profiles. The results obtained using CSS showed a trend of significantly lower variability in the dissolution results at the beginning of the tests. For example, % dissolved (min/max) results using paddle spindle at 10 minutes were 30/101 (acetaminophen) 61/108 (prednisone) and at 20 minutes results were 62/103 (acetaminophen) and 72/110 (prednisone). The corresponding results using CSS were 70/106 (10 min) and 94/112 (20 min) for acetaminophen and 96/105 (10 min) and 101/108 (20 min) for prednisone tablets. Assay (99 to 107%) and UDU (95 – 111%) results were similar from both approaches.

Conclusion: The assay and UDU data may be obtained using CSS from dissolution tests rather than separate testing as currently required.

BACKGROUND

Like any other product evaluation, pharmaceutical products are also evaluated using various analytical tests. For solid oral pharmaceutical products such as tablets and capsules, these tests include: (1) Assay or Potency; (2) Uniformity of Dosage Units; (3) Drug Dissolution/Release.

These tests are usually conducted separately. One common aspect of these tests is that they all usually require an extraction step followed by quantitation using chromatographic or spectrophotometric method. Drug dissolution testing by itself is an extraction-based test in which the drug from the product is extracted in an aqueous based solvent (e.g. water or buffer having a pH between 5 and 7) maintained at 37 ºC. However, these apparatuses are not considered as extractors because of the poor stirring and mixing environment within the apparatuses, in particular Paddle and Basket. To address this artifact of poor stirring and mixing within a dissolution tester, recently a modified stirrer (Figure 1), known as a crescent-shaped spindle (CSS), has been suggested [1]. With this modification, the apparatus may also be utilized as any other extractor and may be used for the above mentioned tests [2]. Thus, all these tests can be conducted using a dissolution tester/extractor with the modified spindle or stirrer.

This presentation provides results from a study where assay, uniformity of dosage units (UDU) and dissolution results were obtained based on a single method using CSS and compared with the results obtained using multi-method approach as suggested in the pharmacopeias.

Figure 1

EXPERIMENTAL

MATERIALS: In total ten tablet products were tested: seven of 325 mg strength acetaminophen and three (two of 5 and one of 1 mg strength) of prednisone. The products were obtained from the Canadian market.

APPARATUSES: The dissolution tests were conducted using a Hansen system (SR8-Plus) which met the required mechanical and operational specifications. Two stirring approaches were used: (1) USP Paddle spindles and; (2) the Crescent-shape spindle (CSS).

TESTS CONDUCTED: Assay, uniformity of dosage units (UDU) and dissolution.

1. **As per USP Monographs:**
   Test Conditions for dissolution tests were as follows:
   Acetaminophen: Medium: pH 5.8 phosphate buffer (900 mL).
   Prednisone: Medium: water; 500 mL.
   Apparatus: USP Paddle, spindle rotation speed set at 50 rpm.

   Assay and UDU tests were performed as described in the respective Acetaminophen and Prednisone USP Monographs.

2. **Using CSS:**

   All tests were conducted using 900 mL of distilled water with spindle rotation speed of 25 rpm. No further tests were conducted for Assays and UDU which were derived from the dissolution results. A repeat dissolution test was conducted to obtain results for 10 tablets so that the results may appropriately be compared with those obtained as per USP.

Prior to use, the dissolution media were equilibrated at 37 °C to deaerate the medium to avoid bubble formation due to the escape of dissolved gases.

SAMPLING TIMES: The dissolution tests were conducted for 60 minutes with sampling at every 10 minutes.

QUANTITATION: Ultraviolet absorbance at 243 nm, for acetaminophen, and 242 nm, for prednisone, of the filtered portions of the solution under test, in comparison with a reference solution having a known concentration of acetaminophen and prednisone standards.

DETERMINING ASSAY AND UDU VALUES FROM DISSOLUTION RESULTS USING CSS: The results of the last sampling time (60 min) of the dissolution tests were used as the Assay and UDU. The mean values from the dissolution results are considered as Assay results while the individual values would represent UDU.

RESULTS

Figure 2: Dissolution profiles of the products

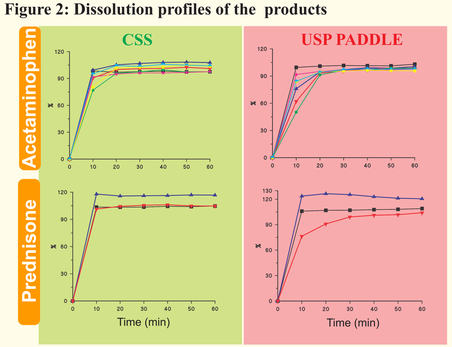

Table 1: Summary of dissolution results of the products tested.

Acetaminophen		PARAMETERS			
Time (min)	METHOD	MIN	MAX	MEAN	CV(%)
10	CSS	70.15	105.69	90.42	10.69
	USP	30.90	100.89	72.76	26.93
20	CSS	94.00	111.67	99.95	4.38
	USP	61.73	103.12	93.05	7.51
30	CSS	95.83	109.31	100.82	3.75
	USP	90.58	106.87	96.73	2.99
40	CSS	94.75	110.90	101.69	4.11
	USP	91.09	103.18	97.88	2.63
50	CSS	95.33	116.51	101.91	4.82
	USP	94.74	103.17	98.25	2.07
60	CSS	95.38	110.57	101.33	3.98
	USP	94.84	106.35	98.68	2.96

Prednisone		PARAMETERS			
Time (min)	METHOD	MIN	MAX	MEAN	CV(%)
10	CSS	96.36	122.44	107.59	7.41
	USP	61.42	141.24	101.97	20.83
20	CSS	100.64	119.95	107.85	5.77
	USP	72.46	147.11	108.07	15.63
30	CSS	102.31	119.10	108.39	5.61
	USP	91.86	146.46	110.49	11.70
40	CSS	102.86	118.98	108.91	5.31
	USP	95.24	126.27	110.58	8.91
50	CSS	101.90	121.53	108.62	5.93
	USP	97.93	126.21	110.33	7.99
60	CSS	101.30	121.53	108.73	5.75
	USP	99.87	123.29	111.17	6.75

Table 2: The assay and UDU results as per USP approach and based on the dissolution testing using CSS. Here, Mean should considered as Assay and range (Min Max) and CV be considered as UDU.

Acetaminophen		PARAMETERS			
PRODUCT	METHOD	MIN	MAX	MEAN	CV(%)
A	CSS	95.49	101.88	98.76	1.91
	USP	102.71	105.26	103.74	0.76
B	CSS	95.70	110.57	104.28	5.19
	USP	92.23	101.64	98.75	2.60
C	CSS	99.52	104.55	101.33	1.43
	USP	99.52	101.41	100.46	0.73
D	CSS	95.38	100.33	97.91	1.64
	USP	93.72	102.34	97.74	2.29
E	CSS	97.03	102.91	98.98	1.98
	USP	97.64	100.26	99.03	0.77
F	CSS	100.99	107.57	104.76	2.03
	USP	97.68	99.77	99.01	0.78
I	CSS	103.40	107.43	105.24	1.5
	USP	89.05	90.41	89.71	0.49

Prednisone		PARAMETERS			
PRODUCT	METHOD	MIN	MAX	MEAN	CV(%)
A	CSS	104.06	114.24	108.11	4.09
	USP	101.08	108.74	102.47	0.89
B	CSS	111.62	121.53	115.87	2.55
	USP	95.30	98.90	97.38	1.20
C	CSS	101.30	124.37	109.49	6.76
	USP	97.54	107.88	101.67	3.57

- Both approaches, using USP Paddle and CSS, provided complete dissolution within 60 minutes (Figure 2).
- The use of CSS offers simplicity, requiring simple and common experimental conditions, thus provides improved comparison of dissolution (product) characteristics not only within products but also between products.
- At earlier sampling times, the USP approach showed significantly higher variability in dissolution results. This may be attributed to the positioning/settling effect of the tablets as commonly described in literature [3]. Such variability in results was not observed using CSS, thus leads to improved product characterization.
- The values obtained from the last sampling point to represent Assay and UDU using CSS are presented in the Table 2, along with the values obtained using Pharmacopeial (USP) methods.
- Both approaches of USP and the dissolution based using CSS, provide very similar Assay and UDU results. Therefore, it appears that there is no need to perform extra tests as is currently required.

Advantages Of The CSS-based Approach

1. It provides significant cost savings as only one vs. three tests would be needed.
2. Testing (product evaluations) will be completed significantly faster, thus, time saving.
3. As Assay, UDU and dissolution results using CSS are obtained from the same units (tablets), therefore, the approach provides improved overall evaluation of product quality.
4. The experimental conditions employed were water as the medium and an rpm of 25, thus, offers significant experimental simplicity and physiological relevancy [4].
5. The testing will be more physiologically relevant as the test conditions (medium or stirring) mimics the common GI tract environment. Presently, tests are usually conducted without concern to the physiological aspect, e.g., use of organic solvents, high pH aqueous solvents, high impact processes (crushing, extracting at high rpms in blenders or using a mortal and pastel).
6. Experimental conditions are product independent which would provide simplifications and cost saving. In addition, only the use of common experimental conditions, as employed in this study, can provide comparison of quality within and between products.

CONCLUSION

The assay and UDF data may be obtained from dissolution tests using CSS rather than separate testing as is currently required. This approach provides a simpler, physiologically relevant, cost effective and improved alternate to current practices.

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