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A HPLC assay for coating integrity of topiramate sprinkle formulation

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Abstract

A HPLC method has been developed for the determination of coating integrity of topiramate sprinkle formulation. This method determines the completeness of the sprinkle coating and, indirectly, the completeness of taste masking of the product. This method utilizes a sample preparation where the sprinkles are placed in a specially designed stainless steel basket equipped with a screen, 25-mesh size, at the bottom. Water is used to solubilize any incompletely coated drug. The aqueous solution is analyzed for topiramate using a phenyl column in the reversed-phase mode, isocratic elution, and refractive index detection. This analytical method, for recovered topiramate, provides an indirect measure of drug taste-masking in the sprinkle formulation. It was also used in formulation selection by screening sprinkles beads that contained different amounts of coating to see which formula can best mask the taste with an acceptable level of exposed topiramate drug substance. This method has been validated to meet FDA validation guidelines.

Keywords: Coating integrity; Reversed-phase HPLC; Sprinkle formulation; Refractive index detection; Taste masking

1. Introduction

Topiramate (structure in Fig. 1) is a anticonvulsant drug developed by The R.W. Johnson Pharmaceutical Research Institute [1,2] and marketed by Ortho-McNeil Pharmaceutical in the United States, and Janssen Research Foundation world wide. In order to make it easier to administer the drug to children, a pediatric oral formulation was developed. This formulation consists of a sugar bead coated with active drug and a polymeric outer coating, which serves to mask the bitter taste of topiramate. Generally speaking, a more thorough coating of topiramate provides for a better taste-masked dosage form.

This paper describes a reversed-phase HPLC method that utilizes a unique sample preparation

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procedure to evaluate the integrity of the polymeric outer coating and to provide an indirect measurement of the extent of taste masking. Refractive Index (RI) detection was employed for this method because topiramate lacks a UV chromophore.

Other techniques have been used to study the integrity of coated pharmaceuticals [3–8]. These techniques primarily rely on surface analysis of the coating. Scanning electron microscopy (SEM), microscopic observation of the distribution of marker dyes, which can leak through defects in the coating, and other microscopic techniques are all qualitative tools. Dissolution testing, while a quantitative technique, is usually designed to evaluate the extent of drug released from a dosage form over time, and is not intended to evaluate the level of coating integrity. Our main goal was to develop a new method that could mimic the process of orally dosing the sprinkle formulation and then quantitate the amount of drug that might be tasted. In this way we can analyze whether or not the polymeric coating has been applied effectively to mask the bitter taste of drug and also the effect of encapsulation on the integrity of the coated beads. This method is used after coating and then again after encapsulation. Encapsulation where the beads come in contact with moving machine parts can be a cause for bead fracture. The data was used during formulation development to optimize settings for the encapsulation process that would result in the least bead breakage. In the initial stages of formulation development the difference in assay values before and after encapsulation was a very clear indication of breakage during encapsulation. After continued adjustment of the equipment parameters, the difference between pre-encapsulation and post-encapsulation assay values was minimized. If encapsulated beads are to be tested the capsules will be emptied first and then the beads analyzed. The beads are encapsulated for dosage reasons (50 mg active per capsule). Usually the capsules are emptied onto food for consumption and the capsule shells are not digested.

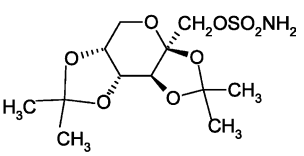
Identity	Structure
Topiramate	

Fig. 1. Structure of topiramate.

2. Experimental

2.1. Chemicals and reagents

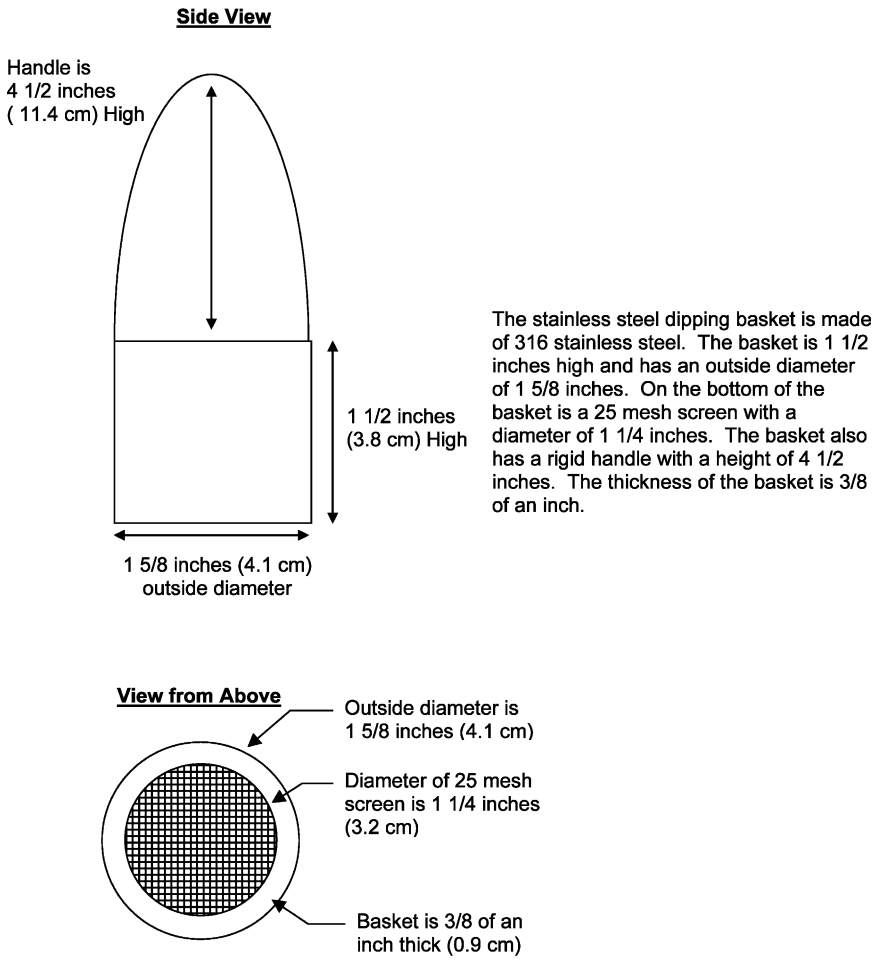
Acetonitrile was HPLC grade (Fisher Scientific, Fair Lawn, NJ, USA). Methanol was HPLC grade (Fisher Scientific, Fair Lawn, NJ, USA). Water was deionized or distilled, 18 mega ohms or better (pH 5–7.5). Topiramate reference standard (solubility of the drug substance is approximately 10 mg/ml in water and over 100 mg/ml in acetonitrile) was available from The R.W. Johnson Pharmaceutical Research Institute (Spring House, PA, USA).

2.2. Solutions

Mobile Phase: Methanol–water, 20:80, v/v (Premixed).
Sample Solvent: Acetonitrile–water, 20:80, v/v.

2.3. Sample preparation

A sample equivalent to 1 g of topiramate was transferred into the stainless steel dipping basket (Scheme 1). This basket is placed on a glass funnel (60°, 2 1/4 in. diameter) inserted into a 100 ml volumetric flask. Tap the basket against the sides of the funnel for 30 s to pass the loose powder into the flask. Move the basket into a 100 ml beaker and rinse the beads by pouring



Scheme 1. Diagram of the stainless steel dipping basket.

35 ml of water through the basket into the beaker. Dip the basket up and down into the beaker six times. Remove the basket from the beaker and transfer this solution into the volumetric flask by way of the funnel. Repeat this rinsing procedure with 15 ml of water and then again with 10 ml of water. All the rinsing should be completed within 1 min this will help insure dissolving of coating is not taking place. Rinse the beaker with 20 ml of acetonitrile. Transfer the rinsing through the funnel to the 100 ml volumetric flask and repeat beaker rinse with 10 ml of water. Sonicate the volumetric flask for 10 min then shake for 30 min. Fill to the mark with water and mix sample well. This is the sample solution.

2.4. Procedures

The instrumentation used was a Waters liquid chromatographic system (Model 600E pump, model 715 autosampler, model 410 refractive index detector) (Waters Corporation, Milford, MA, USA). The detector was operated with an internal temperature of 35 °C. The operating parameters described below were validated to determine the level of topiramate in the sample.

The analytical column was a Phenyl/B, 5 μm, 25 cm × 4.6 mm stainless steel column (Keystone Scientific, Bellefonte, PA, USA). The flow rate was 2.0 ml/min isocratic, column temperature was 35 °C, and injection volume was 100 μl. The RI

detector was operated with a temperature setting of 35 °C. The retention time for topiramate was 28.2 min. An overlay chromatogram of a typical placebo and topiramate sprinkle sample is presented in Fig. 2.

3. Results and discussion

3.1. Precision

The injection repeatability was determined by making 10 injections of a topiramate sprinkle sample (containing approximately 0.35% topiramate) and a spike topiramate (spike with ~4% topiramate) sprinkle sample. Peak areas were used, and the relative standard deviations (R.S.D.) calculated. The repeatability was 0.17% R.S.D. for the spike sample and 1.61% R.S.D. for the sprinkle sample.

The analysis repeatability was determined by analyzing four preparations of a topiramate sprinkle sample and four preparations of a spiked sample (spiked with ~4% topiramate). The R.S.D. of the spiked samples was 2.15% while the R.S.D. of the sprinkle sample was 9.57% (Table 1).

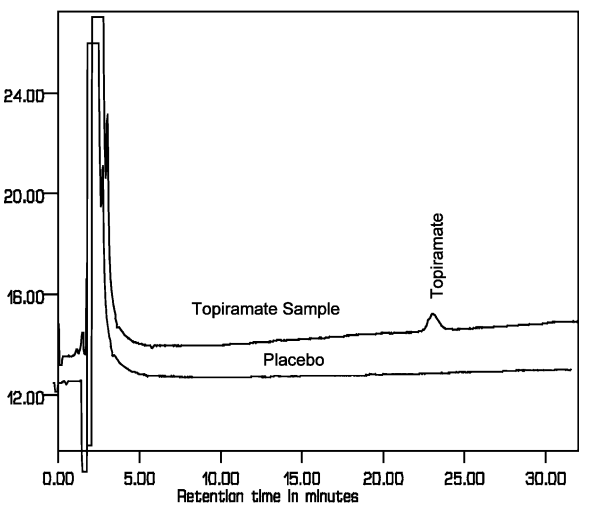


Fig. 2. Overlay of chromatogram of a placebo and topiramate sprinkle bead sample.

Table 1
Analysis repeatability

Injection	% Topiramate in Beads batch A	(%) Recovery from topiramate-spiked beads
1	0.3510	101.5
2	0.3058	96.3
3	0.3476	99.0
4	0.2886	99.0
Average	0.3233	99.0
% R.S.D.	9.57	2.15

For day to day precision a total of six topiramate samples and six spiked topiramate samples were prepared and analyzed on two different days and run on two different instruments. The intermediate precision of the method was 2.40% R.S.D. for spiked sprinkle samples and 13.40% R.S.D. for sprinkle samples (Table 2). This precision was judged acceptable for the low level of topiramate found in these samples.

3.2. Linearity

The plot of peak area vs. micrograms topiramate injected (3–60.23 μg which is equal to 0.3–6% of the sample) is linear with a coefficient of determination of 1.0000.

Table 2
Day to day precision

Injection	% Topiramate in Beads batch A	(%) Recovery from spiked beads
Replicate 1, Instrument 1	0.42	95.6
Replicate 2, Instrument 1	0.38	95.8
Replicate 1, Instrument 2	0.35	101.5
Replicate 2, Instrument 2	0.31	96.3
Replicate 3, Instrument 2	0.35	99.0
Replicate 4, Instrument 2	0.29	99.0
Minimum	0.29	95.6
Maximum	0.42	101.5
Average	0.35	97.9
% R.S.D.	13.40	2.40

Table 3
Accuracy at the limit of quantitation (LOQ)

Injection	% Topiramate
1	0.0996
2	0.0946
3	0.0964
4	0.1003
5	0.0970
6	0.0907
% R.S.D.	3.64
Average % assay	0.0964
Theoretical %	0.1005
% Accuracy	95.9
% Bias	4.1

3.3. Sensitivity

The limit of detection was determined experimentally ($S/N = 3$) to be 0.07% (w/w) (equivalent to 0.7 μg topiramate injected). The experimentally verified limit of quantitation (defined as having an accuracy of better than 85% with a precision of 15% or better for 6 replicate injections) was 0.1% (w/w) (equivalent to 1 μg topiramate injected) (Table 3).

3.4. Accuracy

The accuracy of this analytical procedure expresses the closeness of agreement between the theoretical value and the assay value. The accuracy for determination of uncoated topiramate in the presence of topiramate sprinkles was determined by assaying topiramate sprinkles spiked with topiramate at the 4% level ($n = 6$). The results ranged from 95.6 to 101.5% as shown in Table 4.

3.5. Wash procedure

Several procedures were evaluated for effectiveness in collecting uncoated drug. Data for these alternative collection procedures are presented in Table 5. Initially a two-part water wash was attempted. This gave unsatisfactory recovery from spiked samples. In a subsequent procedure a wash using 20% acetonitrile in water (topiramate is more soluble in acetonitrile) was followed by a 100% water wash. This procedure gave inconsistent results and appeared to dissolve the beads giving artificially high values. The optimal wash procedure, consisting of a three-part wash with water, gave the most consistent results.

Table 4
Accuracy from spiked samples

Spiked sprinkle sample	% Theoretical	% Actual	% Accuracy
Sample 1	3.982	3.805	95.6
Sample 2	3.997	3.831	95.8
Sample 3	3.983	4.043	101.5
Sample 4	4.006	3.857	96.3
Sample 5	3.979	3.941	99.0
Sample 6	4.023	3.984	99.0
Average			97.9
%R.S.D.			2.40

The basket was designed based on the specification for beads. The bead specification for size is between 16 and 20 mesh, therefore, the 25 mesh screen in the bottom of the basket is the largest mesh that can be used that will retain intact beads. This design allows for the collection and quantitation of broken beads, while allowing for the rinsing of any loose particles on the beads.

Table 5
Precision using other washing procedures

Extraction	% Topiramate in Beads batch A	(%) Recovery from spiked beads
Two water washes	0.15	94.3
Two water washes	0.20	92.3
One wash 20% AcN, One water wash	1.55	117.5
One wash 20% AcN, One water wash	1.81	108.0
One wash 20% AcN, One water wash	Not done	83.3
One wash 20% AcN, One water wash	Not done	87.7
Three water washes	0.42	95.6
Three water washes	0.38	95.8

Table 6
Effect of encapsulation on coating integrity

Sample	% Topiramate before encapsulation	% Topiramate after encapsulation
9% coated sprinkles	1.9	2.3
11% coated sprinkles	0.41	0.44
13% coated sprinkles	0.21	0.20

3.6. Formulation selection

Sprinkles were manufactured with various amounts of polymeric coating in order to identify the optimal coating for the formulation. This analytical method was then used to determine the integrity of the coating. Three coating levels of 9, 11 and 13% were evaluated. The average level of uncoated topiramate found for these formulations was 1.93% topiramate for the 9% coating, 0.41% topiramate for the 11% coating, and 0.21% topiramate for the 13% coating. As seen from the previous data this method can easily differentiate between the different coating levels on the sprinkles, with the higher the level of coating correlating to a lower level of topiramate detected. Using the data generated by this method, and dissolution data obtained on the same samples, it was determined that the 11% coating level would be adequate in terms of taste masking, while allowing adequate release of the drug for delivery, and so this was chosen as the target formula.

3.7. Encapsulation effect

Beads with three different levels of coating were analyzed before and after encapsulation and the data presented in Table 6. This data was used to optimize the settings on the encapsulation equipment. The data illustrates the effect encapsulation can have on the integrity of the bead coating.

4. Conclusion

The results of these studies demonstrate that this method is suitable for the determination of the coating integrity for topiramate sprinkles. This method was successfully used to support optimization of the proper coating level during formulation development and is still being used to gather information of the coating process.

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