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Rapid screening of guar gum using portable Raman spectral identification methods

Hirsch K. Srivastava, Steven Wolfgang, Jason D. Rodriguez*

Division of Pharmaceutical Analysis, Center for Drug Evaluation and Research, US Food and Drug Administration, 645 S. Newstead Ave., St. Louis, MO 63110, United States

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ABSTRACT

Guar gum is a well-known inactive ingredient (excipient) used in a variety of oral pharmaceutical dosage forms as a thickener and stabilizer of suspensions and as a binder of powders. It is also widely used as a food ingredient in which case alternatives with similar properties, including chemically similar gums, are readily available. Recent supply shortages and price fluctuations have caused guar gum to come under increasing scrutiny for possible adulteration by substitution of cheaper alternatives. One way that the U.S. FDA is attempting to screen pharmaceutical ingredients at risk for adulteration or substitution is through field-deployable spectroscopic screening. Here we report a comprehensive approach to evaluate two field-deployable Raman methods—spectral correlation and principal component analysis—to differentiate guar gum from other gums. We report a comparison of the sensitivity of the spectroscopic screening methods with current compendial identification tests. The ability of the spectroscopic methods to perform unambiguous identification of guar gum compared to other gums makes them an enhanced surveillance alternative to the current compendial identification tests, which are largely subjective in nature. Our findings indicate that Raman spectral identification methods perform better than compendial identification methods and are able to distinguish guar gum from other gums with 100% accuracy for samples tested by spectral correlation and principal component analysis.

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1. Introduction

Guar gum is a water-soluble polysaccharide composed of the sugars galactose and mannose and is based on a β 1,4-linked mannose backbone to which galactose residues are 1,6-linked at every second mannose [1]. Guar gum produces a highly viscous, thixotropic solution and is obtained from the grinding of endospores of the seed of the leguminous tree Cyamopsis tetragonlubus located mostly in the Indian subcontinent. In tablet manufacturing guar gum is used as a binder and disintegrating agent and in micro-encapsulation of drugs [2].

Since 2009, FDA has applied a working definition of economically-motivated adulteration (EMA) as "the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain [3]". Documented incidents of EMA involve a common vulnerability, i.e., the substitutes possess similar physical and/or chemical properties and are thus difficult to detect by non-specific compendial and conventional tests used by industry [4–9]. Recent high profile cases of EMA include the 2008 heparin crisis due to contamination of raw heparin stock imported from China [4] and the 2007–2008 melamine contaminations of pet food, milk and infant formula. Guar gum's use as a chemical additive for a rapidly expanding petroleum gas fracking industry in the US may have contributed to a recent guar gum shortage and an observed 500% price increase during a period of 15 months beginning in 2012 [10,11]. These events have further raised concerns about vulnerability towards possible substitution of guar gum by cheaper gum alternatives.

In 2012, the U.S. FDA alerted the United States Pharmacopeia (USP) that guar gum was one of 12 excipients considered at elevated risk of adulteration due to an ambiguous identification (ID) test. The ID test lacks specificity, and analysis of a sample from a container labeled guar gum could result in a false positive identification for a mixture containing guar gum.Shortly after being notified by FDA, USP initiated a project to revise the ID test for guar gum NF to include a qualitative determination of presence of the main sugar components, galactose and mannose, by thin layer chromatography [12]. This improvement in the ID test still leaves

* Corresponding author. Fax: +1 314 539 2113.
E-mail address: Jason.Rodriguez@fda.hhs.gov (J.D. Rodriguez).

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some uncertainty about the total composition and whether other galactomannans are present [13].

Manufacturers of finished pharmaceuticals are generally accustomed to relying on a supplier certificate of analysis and performing an ID test in order to release incoming shipments of excipients such as guar gum. However, most ID tests lack the specificity and sensitivity to be effective in screening for possible adulteration. In addition, many of the analytical ID test methods are time consuming, require complex sample preparation and are designed for use in the laboratory setting [14]. There are currently two compendial tests to confirm the identity and purity of guar gum: a colorimetric ID testan appearance test (Test A) and a thin-layer chromatography test (Test B). The current USP/NF compendial method for ID of guar gum (ID Test A) has an acceptance criteria that includes an "appreciable" change in viscosity and a change to produce an "opalescent" solution [15]. Using such a subjective and qualitative test, however, has well-known limitations in differentiating guar gum from locust bean gum, gellan gum, and other galactomannans due to the similarity in their compositions [9]. More specific analytical methods based on differences in galactomannan composition remain viable for identification of guar gum and differentiation from similar galactomannans. These include chromatography or electrophoresis and hydrolysis [16] with subsequent determination of the monosaccharide composition; the latter is the new USP ID Test B [12]. These analytical methods are destructive to the sample, time-consuming, and are relegated to the laboratory setting. Thus, these methods are not amenable to tests designed to rapidly screen ingredients and identify those which are either falsely labeled or which possibly contain an adulterant.

In this paper we propose an improved ID test that is based on spectral library based methods. Spectroscopic methods are non-destructive, require minimal sample preparation, and can be carried out on portable instruments at the pharmaceutical product manufacturing facility by non-experts. Previous studies have indicated that they are capable of screening for and detecting adulterant [17] levels which are in the 5–25% range [18]. Raman spectroscopic techniques are often used to acquire the unique vibrational molecular signature of substances. Until recently, Raman was regarded as primarily a laboratory method due to the large footprint required for traditional Raman spectrometers. Today, miniaturization of the optical and electronic components used to craft these instruments has led Raman to be commonly available in portable/handheld platforms from a variety of commercial vendors [19]. One of the greatest benefits of using these instruments is their ability to perform rapid interrogation of the sample under study, often in its original packaging, without any additional sample preparation [18]. Raman instruments can be programmed with methods ranging from correlation-based spectral library tests [20] to more rigorous multivariate-based tests such as principle component analysis (PCA) [21,22]. Both approaches were used in this study to evaluate the ability of spectroscopic methods to provide unambiguous ID of guar gum versus monograph methods.

2. Material and methods

2.1. Sample preparation

The gum samples used to in this work were taken from commercially-available samples from various manufacturers and lots without further purification. A total of 18 different samples were used for method development—ten guar gum samples and eight other gums.The samples are listed in Table 1.

Table 1
Commercial gum samples used for method development.

Sample	Grade	Manufacturer	Lot designation	Type
Guar gum	NF	Spectrum	Lot 1	Library[a]
Guar gum	Research	Sigma Life Sciences	Lot 1	Library[a]
Guar gum	Research	MP Biomedicals	Lot 1[b]	Library
Guar gum	NF	Spectrum	Lot 2	Library
Guar gum	Research	MP Biomedicals	Lot 1[b]	Library
Guar gum	Research	Fisher Science Education	Lot 1	Library
Guar gum	Research	Sigma Life Sciences	Lot 2	Library
Guar gum	NF	Spectrum	Lot 3	Library
Guar gum	Research	Aqua Solutions	Lot 1	Library
Guar gum	Research	Fisher Science	Lot 2	Library
Gellan gum	Research	Alfa Aesar	Lot 1	Test
Xanthan gum	Research	Sigma Life Sciences	Lot 1	Test
Karaya gum	Research	Sigma Life Sciences	Lot 1	Test
Arabic gum	Research	Sigma Life Sciences	Lot 1	Test
Rosin gum	Research	MP Biomedicals	Lot 1	Test
Tamarind gum	Research	Tokyo Chemical Industry	Lot 1	Test
Locust bean gum	FCC	Spectrum	Lot 1	Test
Ghatti gum	Research	Pfaltz & Bauer	Lot 1	Test

[a] Guar gum control used for compendial ID test.
[b] Samples received under different containers.

Table 2
Results of compendial tests for different types of gums.

Sample	Compendial ID	Spectral Based ID		
		Raman		Raman
	Decision	SC	Decision[a]	PCA ID
Arabic	Fail	0.890	Fail	Fail
Gellan	Pass	0.873	Fail	Fail
Karaya	Fail	0.897	Fail	Fail
Tamarind	Fail	0.819	Fail	Fail
Xanthan	Fail	0.879	Fail	Fail
Locust Bean	Fail	0.924	Fail	Fail
Rosin	Fail	n/a	n/a	n/a
Ghatti	Fail	n/a	n/a	n/a

[a] A 0.95 threshold used for pass.

2.2. Compendial identification tests

The different gum samples were tested according to the ID Test A compendial identification test for guar gum [15]. Briefly, approximately 2 g of sample were placed into a 400 mL beaker and moistened with 4 mL of isopropyl alcohol. Next, 200 mL of cold water were added to the sample and stirred vigorously until the sample was uniformly dispersed. An authentic guar gum sample prepared in this manner should result in in an opalescent (off white) viscous solution. A 100 mL portion of the solution is then heated in a bath of boiling water for about 10 min. Authentic guar gum samples should exhibit no appreciable increase in viscosity.

2.3. Spectral collection

All Raman spectra were collected through clear polyethylene bags. Spectra were acquired on an EZ-Raman I Raman spectrometer (Enwave Optronics Inc.) using the output of a 785 nm laser (340-mW). The TE-cooled CCD detector was operated at −50 °C with variable acquisition times. The resolution of the spectrometer is ~6 cm^{-1} and uses a sampling spot size ~200 μm. Each sample bag was measured 15 times using random sampling at different locations on the bag. Raman spectra for all guar gum and gum samples were collected in the spectral range of 250–2400 cm^{-1}. The spectral range used for method development, described in the next section, was 300–2000 cm^{-1}.