

The Potential of Raman Spectroscopy as a Process Analytical Technique During Formulations of Topical Gels and Emulsions

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Purpose. The primary objective of this study is to investigate the possibility of using Raman spectroscopy as a process analytical technique (PAT) for quality control during manufacturing of topical dosage forms.

Methods. A fiber-optic Raman probe was used to monitor the formulation of pharmaceutical gel and emulsion in laboratory scale. Raman shifts of typical commercial raw materials used in topical dosage forms were measured to ascertain the potential of this technique for monitoring and analyzing topical products. Spectra of some well-characterized topical gels manufactured in our laboratory were also measured.

Results. Commercial raw materials were found to be Raman sensitive. Due to the difference in chemical composition, raw materials exhibit characteristic peaks that can be exploited to monitor formulation processes. Spectra taken during formulation of an emulsion using Carbopol Ultrez as thickener and Tefose as emulsifying agent show changes in Raman shifts immediately after major formulation steps.

Conclusions. The findings from this work suggest that Raman spectroscopy can be a valuable process analytical technique for quality control of topical gel and cream formulations.

KEY WORDS: pharmaceutical gels and emulsions; process analytical technique (PAT); Raman spectroscopy; topical formulations.

INTRODUCTION

Vibrational spectroscopic techniques are becoming increasingly popular in the pharmaceutical industry for characterizing topical dosage forms for a variety of reasons. First, the spectroscopic techniques are nondestructive in nature. Second, these techniques have the advantages of simple instrument operation, and easy sample preparation. Therefore, spectroscopic techniques have the potential of providing rapid and convenient solutions to a multitude of analytical problems (1,2). Using Fourier Transform Infrared Spectroscopy (FTIR) and Raman spectroscopic techniques, fundamental information about molecular structure of complex mixtures can easily be obtained. The measured spectra have a high information density providing opportunity for both quantitative and qualitative analyses (3).

Process analytical techniques (PATs) are becoming increasingly important in the pharmaceutical industry (4). The primary objective of PAT is to modernize quality control by

continuously monitoring processes using sensitive and sophisticated instruments at every stage of the manufacturing process (5). This will enable continuous assessment of critical quality parameters and performance attributes of raw and in-process materials and ensure acceptable end product quality.

Among the vibrational spectroscopic techniques, FTIR has long been used most widely in the pharmaceutical industry for materials identification, as a large number of molecules are IR sensitive and also extensive spectral libraries of many materials are available. In addition, reliable and straightforward methods for qualitative analysis of solid and liquid pharmaceuticals are available. However, IR spectroscopy is generally not suitable for noninvasive measurements of samples in glass or plastic containers and is difficult to interface with a remote location via fiber optics probe because mid-infrared (MIR) light is strongly absorbed by most sample containers and fiber optics (4). On the other hand, near-infrared (NIR) absorption is compatible with fiber optics and glass containers thereby enabling remote and noninvasive sampling possible. Therefore NIR can be used for quality control of raw materials and products, and for process monitoring. The principal shortcoming of NIR is that the generated spectra are primarily based on combinations and overtones of mainly C-H stretches. Hence NIR spectra are not as informative as IR spectra, which are based on fundamentals of a wider variety of molecular vibrations (3). Moreover, NIR analyses often require multivariate calibration.

On the contrary, Raman spectroscopy combines the advantages of IR and NIR although it differs fundamentally from IR and NIR in the sense that Raman response requires a polarizability change while MIR or NIR requires a dipole moment change (6). Like IR, it is based on fundamental vibrations and provides detailed and distinctive spectra of molecules. Like NIR, Raman uses light in the wavelength compatible with fiber optics and many sample containers (7,8). The vent of NIR excitation (to avoid fluorescence interference) lasers and sensitive CCD (charged coupled device) detectors provide opportunity to use reliable, integrated Raman spectrometers for routine analysis of topical dosage forms.

In this article, we investigate the possibility of using Raman spectroscopy as a potential tool for monitoring pharmaceutical and cosmetic processes. In pharmaceutical industry quality control is usually maintained by collecting sample and analyzing data which provides information only "after the fact" not during the process. Depending on the circumstance, the analysis will clear a product or release the batch for the next step. In other cases, the analysis may find that the batch needs to be reworked or dumped which results in considerable waste of time and money (9). The on-line monitoring can avoid this wastage by providing real-time feedback control of the pharmaceutical and cosmetics manufacturing processes. The non-invasive spectroscopic techniques provide ideal automation tool for establishing a successful PAT initiative (9).

In the current work, we monitored a bench-scale formulation process using a Raman probe. A topical emulsion was formulated from raw materials where one of the intermediate products was an aqueous gel. The aqueous gel was heated and mixed with an oil phase to produce the emulsion (cream). In this way we observed the time resolve Raman spectra for both

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gel and emulsion formulation processes with a fiber optic probe attached to the spectrometer.

The effectiveness of any spectroscopic technique as a process monitor depends on the existence of fingerprint spectra of the raw materials. The distinguishable spectra can be used to monitor the presence of the said materials during different steps of a formulation process. To explore this possibility, we analyzed the Raman spectra of a few raw materials typically used in topical formulations. We also measured Raman shifts of some well-characterized aqueous and anhydrous gels formulated in our lab.

MATERIALS AND METHODS

Materials

Carbopol 980 and Carbopol Ultrez 10 were obtained from Noveon (Cleveland, OH, USA). Distilled deionized water was used to prepare gels. The triethanolamine (TEA) 98% solution was obtained from Sigma-Aldrich (St. Louis, MO, USA). Anhydrous glycerol (99.9% purity) was purchased from J. T. Baker (Phillipsburg, NJ, USA), ethyl alcohol (USP absolute 200 proof grade) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY, USA), whereas propylene glycol was purchased from Sigma. Ethomeen (grade C25, trademark of Akzo-Nobel) was obtained from Garo Enterprises (Chicago, IL, USA).

Gel Formulations

Aqueous Gel

Appropriate quantities of Carbopol 980 NF were added to deionized water and mixed using Omni Mixer Homogenizer model M50 (Omni International, Inc.; Warrenton, VA, USA). These mixtures were stirred for 30 min. Then pre-weighed amounts of propylene glycol and glycerol were added to the mixture and the mixture was stirred for additional 20 min. The dispersion was allowed to hydrate and swell for 60 min. The pH of the un-neutralized sample (AQ1) was then measured. In case of neutralized samples, 98% TEA (or 0.1 N NaOH) was added to Carbopol dispersions until the desired pH value was approximately reached (5.0, 6.0, or 8.0). During neutralization, the mixtures were stirred gently with a spatula until homogeneous gels were formed. The pH values were measured in-situ and after 5 days with a digital Accumet 25 pH-meter (Fisher Scientific International, Inc., Hampton, NH, USA). All the samples were allowed to equilibrate for at least 5 days at room temperature prior to performing Raman measurements. The concentrations (weight fraction) of dif-

ferent components as well as the pH values (after 120 h) of the products are given in Table I.

Anhydrous Gel

Carbopol 980 NF was added to ethanol and mixed using Omni Mixer Homogenizer (Model M50) for 30 min. Then pre-weighed amounts of glycerol were added to the mixture and agitated for additional 20 min. The dispersion was allowed to hydrate and swell for 60 min. In a separate beaker, appropriate quantities of TEA (98%) or ethomeen were dissolved in propylene glycol. The surfactant/ neutralizer solution was subsequently added to the Carbopol dispersion. The mixtures were stirred gently with a spatula until homogeneous gels were formed. All the samples were allowed to equilibrate for at least 5 days at room temperature prior to the evaluation of their Raman shifts. The compositions of these formulations are shown in Table II.

Raman Spectroscopic Measurements

The Raman spectra of topical gel formulations were collected with Renishaw's RM spectrometer (Hoffman Estates, IL, USA). A 785 nm Renishaw High Power Diode laser was used for excitation. For performing measurements, the microscopic slide used as the sample stage was replaced with an aluminum pan. A thin film of each sample was spread directly on the pan. The pan was used as a precaution, as Raman spectra of aluminum gives smooth baseline with no characteristic peak. The laser beam was focused on the gel surface using a 20× objective lens. Because surfaces of gel samples were not smooth, use of 50× lens was difficult because of the very low working distance. In most cases, 100% laser power provided the best spectra for the samples. No other sample preparation was required. The sample could be viewed using the closed circuit video camera mounted on the microscope's trinocular head.

The instrument was controlled with the manufacturer's WiRE software, which operated in conjunction with GRAMS/32 software. A Rencam Charge Coupled Device (CCD) silicon detector was used to acquire the Raman shifts. The range for data collection was 3400 to 100 cm^{-1} shift relative to the laser line. The exposure time for data collection was 20 s per exposure and 5 exposures per sample.

Raman spectroscopic measurements of some commercial raw materials typically used in topical gel formulations were performed using Kaiser Optic's (Ann Arbor, MI, USA) Rxn system Raman spectrometer. A fiber-optic probe attached to the spectrometer was used to measure spectra of the samples inside glass containers. A 785 nm (red) stabilized diode laser

Table I. Compositions and pH of Aqueous Carbopol Gel Formulations

| Sample | Water % (wt/wt) | Glycerin % (wt/wt) | Propylene glycol % (wt/wt) | TEA % (wt/wt) | Carbopol 980 NF % (wt/wt) | pH |
|------------------|--------------------|-----------------------|----------------------------------|------------------|---------------------------------|-----|
| AQ1 | 68.5 | 1.0 | 30.0 | | 0.5 | 3.1 |
| AQ2 ^a | 68.5 | 1.0 | 30.0 | | 0.5 | 5.8 |
| AQ3 | 68.87 | 1.0 | 30.0 | 0.13 | 0.5 | 5.1 |
| AQ4 | 67.6 | 1.0 | 30.0 | 0.9 | 0.5 | 8.0 |

^a 0.1 N NaOH was added to increase pH from 3.1 to 5.8.

Table II. Compositions of Anhydrous Carbopol Gel Formulations

| Sample | Ethanol % (wt/wt) | Glycerin % (wt/wt) | Propylene glycol % (wt/wt) | TEA % (wt/wt) | Ethomeen % (wt/wt) | Carbopol % (wt/wt) |
|--------|----------------------|-----------------------|-------------------------------|------------------|-----------------------|-----------------------|
| AH1 | 60.0 | 10.0 | 27.0 | | 2.0 | 1.0 |
| AH2 | 59.5 | 10.0 | 27.0 | | 2.5 | 1.0 |
| AH3 | 59.5 | 10.0 | 28.0 | 0.5 | | 2.0 |
| AH4 | 59.0 | 10.0 | 28.0 | 1.0 | | 2.0 |
| AH5 | 60.0 | 10.0 | 28.0 | | | 2.0 |

was used. The range for data collection was 3400 to 100 cm^{-1} shift relative to the laser line. The exposure time for data collection was 20 s per sample.

RESULTS AND DISCUSSION

Raman Spectroscopic Measurements as a Process Monitor

Process monitoring was performed using Kaiser Optic's Rxn system Raman spectrometer mentioned above. The fiber-optic probe attached to the spectrometer was used to monitor the process of formulating a gel and an emulsion inside a glass container. The laser power was 400 mWatt at the source and 120 mW at the probe. The duration of each scan was 20 s. The entire process of emulsion formulation was captured in 250 scans and the steps were numbered consecutively (up to 225) in Fig. 1a. During process monitoring, the glass container along with the Raman probe was covered with a dark cloth. The cover was removed briefly during addition of raw materials. It was observed that light interferes with the spectral pattern obtained during the process. Some of the spectra obtained during these brief exposed periods were removed from Fig. 1a.

Figure 1a is dominated by the strong spectral responses obtained at Raman shifts close to 2900 cm^{-1} . Many important changes in the Raman shifts are not clearly discernible due to the preeminence of this shift. Key changes observed during important steps (i.e., immediately after addition of a raw material) are described below and plotted in Figs. 1b and 1c.

We started taking spectra as soon as the process started after 200 ml distilled deionized water was poured into the glass container (scans 1 to 15 of Fig. 1a). The spectra obtained during these steps are only due to water. Two grams of Carbopol Ultrez 10 (Noveon, Cleveland, OH, USA), a poly(acrylic acid) (PAA) polymer cross-linked with divinyl glycol, was added during scans between 14 and 15 (additional descriptions of Carbopol Ultrez 10 is discussed in detail in the subsequent section for commercial raw materials). Initially there was little change in Raman shifts pattern, as Ultrez is not solvated at this stage. Heating started during scans 47–48 up to a temperature of 68°C, which resulted in solvation of Carbopol Ultrez (i.e., PAA chains uncoil partially due to hydrogen bonding with water).

The spectrum obtained after solvation process (scan 57 in Fig. 1a) is compared with the spectrum without Ultrez in Fig. 1b. The change in Raman shift in scan 57 are characteristics of poly(acrylic acid) (PAA). However, due to the crosslink structure of the polymers, the Raman peaks are somewhat different compared to the Raman shifts for linear PAA poly-

mers as reported by Dong *et al.* (10). Assignments of some of the major peaks to corresponding possible vibrational modes are given below:

2869 and 2942 cm^{-1} → CH₂ or CH stretching; 1222, 1183, 1157 cm^{-1} → CO stretching coupled with OH in plane bending; 1098 cm^{-1} → CCH₂ stretching; 968 cm^{-1} → CH₂ rocking [1026 cm^{-1} for linear PAA (10)]; 802 cm^{-1} → CCOOH stretching [846 cm^{-1} for linear PAA (10)].

The Raman shifts of the mixture inside the beaker underwent another major change after addition of Tefose 63 (scans 58–61 in Fig. 1a). The temperature of the mixture jumped from 58°C to 74°C after this addition. At this point, the heater was turned off to prevent further rise in temperature. The emergence of the major Raman shift peaks and their assignments are given below (11,12): 1300 cm^{-1} → combinations of CH₂ in phase twist, and CH₂ twist and rock; broad peak at 1446 cm^{-1} → CH₃, CH₂ deformations of the long alkane chain of the stearic acid; 1116 cm^{-1} → CC stretch; broad peak at 843 cm^{-1} → COC stretch of the aliphatic ether group. Also addition of Tefose resulted in the suppression of 967 cm^{-1} peak and shifts of peaks in the region 1158–1222 cm^{-1} (Fig. 1b). The Raman shifts of Tefose 63 as a raw material are given in detail in a subsequent section.

Another major step during the formulation of the emulsion was observed after addition of 20 ml mineral oil (scans 73–74 with respect to Fig. 1a). During this addition temperature of the mixture slightly dropped from 74.3°C to 70°C. A typical spectrum during this period is shown as scan 80 in Fig. 1b. Because mineral oils are primarily mixtures of long chain alkanes, its addition contributed to the enhancement of the peak at 1446 cm^{-1} owing to the extra CH₃, CH₂ deformations from the long alkane chains (11). For the same reason enhancement of the 1300 cm^{-1} peak occurred due to the vibration modes corresponding to CH₂ in-phase twist, and CH₂ twist and rock. Same argument applies for the augmentation and broadening of peak at 1079 cm^{-1} . As a result of the CH₂ twisting of the alkane chain a new peak at 1346 cm^{-1} appeared (11). Addition of long alkane chain also caused enhancement as well as broadening of the peak at 1134 cm^{-1} responsible for C-CH₂ stretching.

The next significant change during the formulation process was after addition of 2.63 ml 1N NaOH at 54°C during the period represented by scans 94–95. Addition of the base ionized the carboxylic groups of the Ultrez and the repulsion of the like negative charges caused the polymer to swell and to form gel. However, there was no significant change in Raman shifts after this addition.

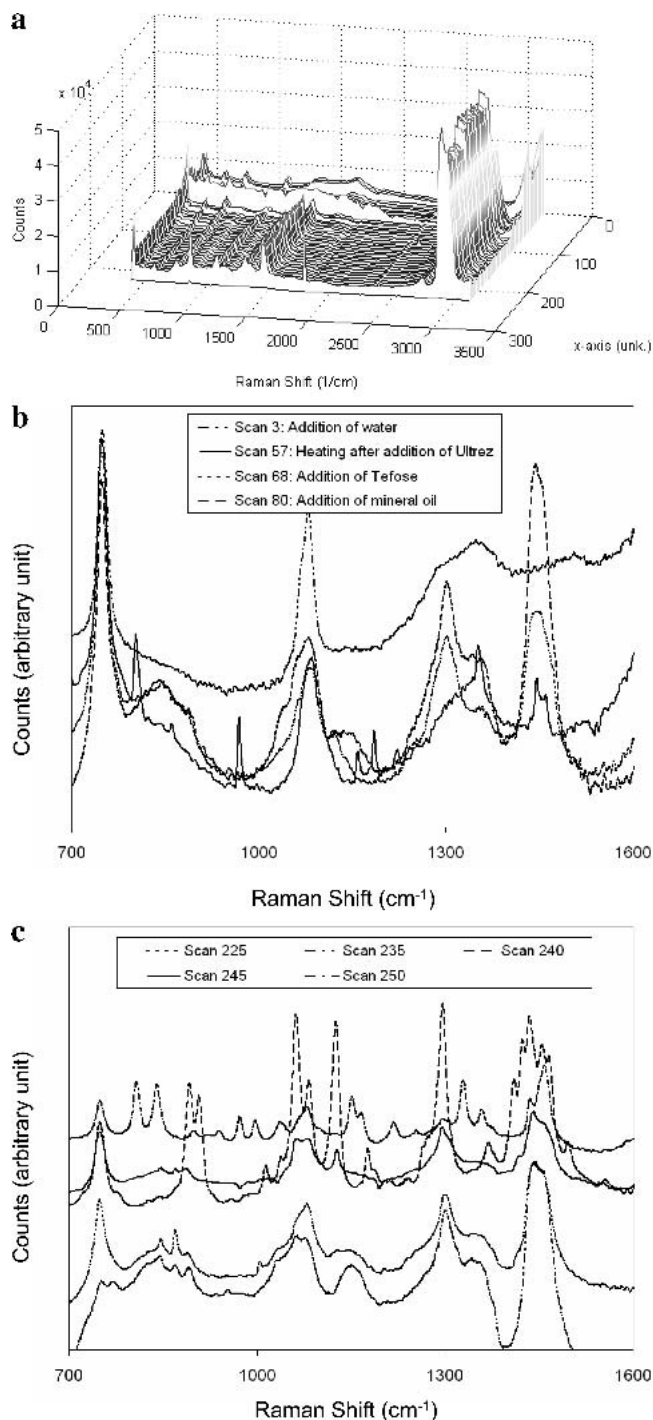


Fig. 1. Monitoring of the process of gel and emulsion formation using a Raman probe. Figure 1a shows all the spectra collected over the entire span. Figures 1b and 1c exhibit the spectra corresponding to major changes during addition of ingredients or change in operating conditions.

At this point, 33.9 g of Tefose was added further and the mixture was heated to 74°C. The formation of emulsion occurred during the scans 225–250 presented in Fig. 1c. There were phenomenal changes from scan to scan during this period. At this stage it is very difficult to assign peaks to vibration modes of individual components in this complex mixture. The key finding here is that the change in spectra can be

used to monitor the progress of gel and emulsification formation.

One notable problem during process monitoring was the need to maintain dark environment to avoid interference from outside light. One possible way to overcome this problem would be to use an NIR laser (~1000 nm wavelength) for illumination. In general, using longer wavelength lasers can reduce fluorescence. For example, a 785 nm system will exhibit fewer fluorescent samples than a 532 nm spectrometer but more than a Raman operating at 1064 nm. However, caution must be exercised since lasers at these wavelengths may generate heat and cause sample degradation. The problem would be more acute if active drug components are present in the topical products.

Raman Analysis of Topical Gels Formulated In-house

Both aqueous and anhydrous gels were formulated in our laboratory by dispersing and subsequently expanding Carbopol polymers. Carbopol is a poly(acrylic acid) (PAA) polymer cross-linked with divinyl glycol (13). Raman spectra of anhydrous gels formulated with different neutralizers/ surfactants are shown in Fig. 2a. Despite the simple structure of the PAA monomer, the correct assignment of the observed spectra of the crosslinked PAA polymer is a complex procedure. Most of the experimental and theoretical literature devoted to the vibrational spectra of different kinds of compounds is concerned with single molecule monomer form of the materials (14,15). Even in a single molecule most of the spectral bands are overlap or originate from a mixture of several vibrations. However, gel formation process is believed to be due to combinations of hydrogen bonding and/or ionic interactions. Hence, we will only discuss the spectral shifts relating to these two forms of interactions (14).

When Carbopol is dispersed in any solvent, two types of interactions are responsible for gel formation – ionization or acid-base interaction between carbopol and polar solvent, and hydrogen bonding between polymer and solvent (16). There is a competition between these two interactions. As shown in Fig. 2a, the Raman shift peak of sample AH5 (no neutralizer) at $\sim 925\text{ cm}^{-1}$ can be attributed to the ionic interaction between carbopol and polar solvents glycerol (GL) and propylene glycol (PG), whereas the peak at $\sim 880\text{ cm}^{-1}$ is due to solvent-polymer hydrogen bonding.

When a neutralizer such as triethanol amine (TEA) is used to form gel (sample AH3 and Fig. 2a), solvent soluble salt of carbopol polymer is formed. The salt formation is responsible for uncoiling into extended structure of the carbopol polymers (16). Due to the increased ionic interaction as a result of this salt formation, enhancement of the 925 cm^{-1} peak occurred whereas the peak at 880 cm^{-1} diminished.

In sample AH1, ethomeen, was used for gel formation. Being a nonionic surfactant with five or more ethoxy groups, ethomeen acted as hydroxyl donor for hydrogen bond formation. As a result, the hydrogen-bonding peak at 880 cm^{-1} dominates over the ionic-interaction peak at 925 cm^{-1} .

The potential of Raman spectroscopy as a strong process analytical tool can be inferred from Fig. 2b. In this figure, Raman shifts of two gels with different ratios of TEA and carbopol are plotted. For sample AH3 with 1:4 TEA/carbopol ratio, significant Raman shift was observed at 876 cm^{-1} although the dominant interaction was ionic (925 cm^{-1}). How-

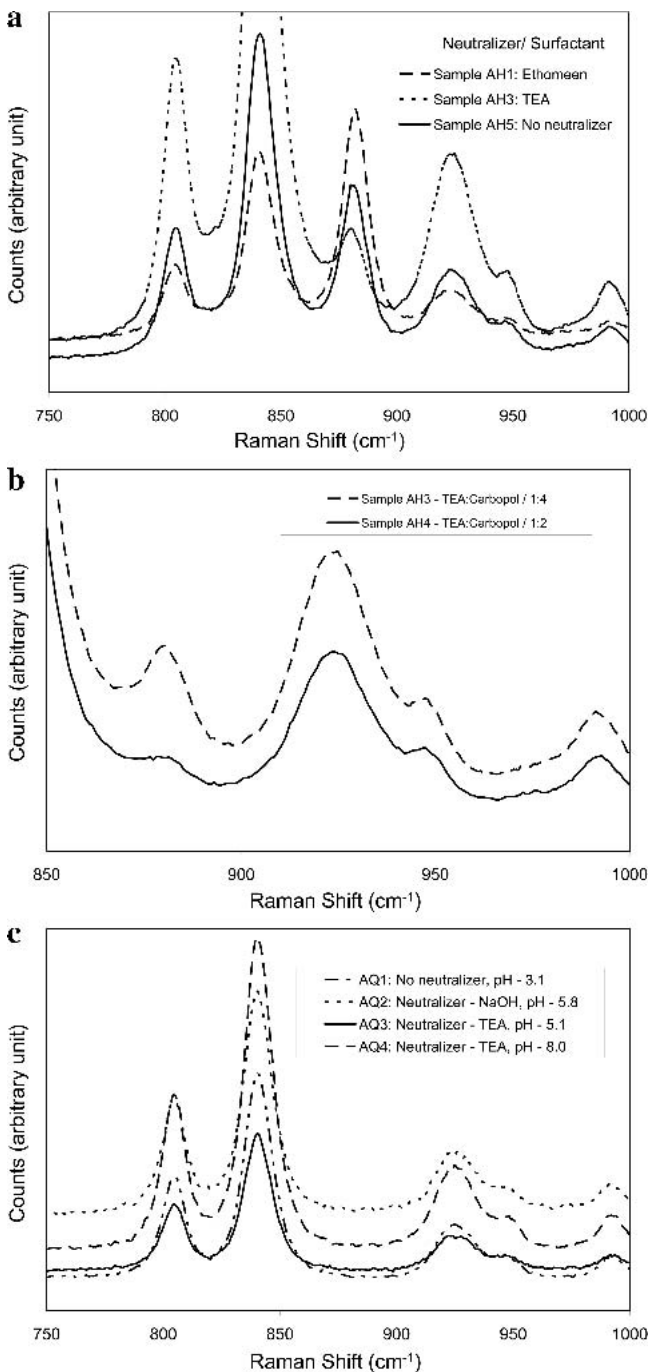
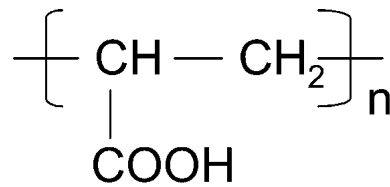


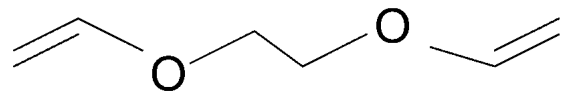
Fig. 2. (a) Raman spectra of anhydrous gels formulated with different neutralizers. (b) Spectra of anhydrous gels with different levels of neutralizers. (c) Comparison of Raman shifts of aqueous gels neutralized to different pH.

ever, as the TEA/Carbopol ratio was increased to 1:2 in case of sample AH4, the ionic peak (925 cm^{-1}) grew at the expense of the hydrogen bond peak (880 cm^{-1}). The ratio of the two peak areas or heights can be used as a quantitative tool for controlling the addition of TEA during gel formulation. Recently, Islam *et al.* (16) have demonstrated the potential of using similar peak ratios in FTIR measurements for detecting the end point during formulations of anhydrous gels.

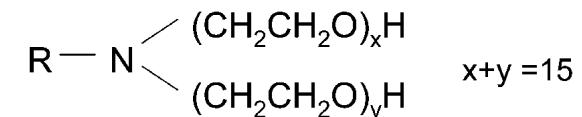
Raman spectra of aqueous gels with different extent of neutralization (measured by pH of the system) are shown in



Polyacrylic acid (PAA)

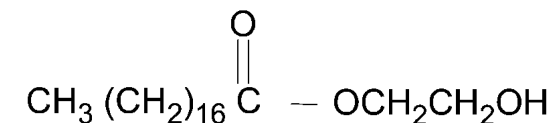


Divinyl glycol ($\text{C}_6\text{H}_{10}\text{O}_2$)



[Polyoxyethylene (15) cocoalkylamines]

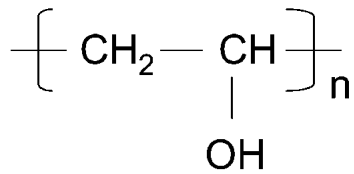
Ethomeen



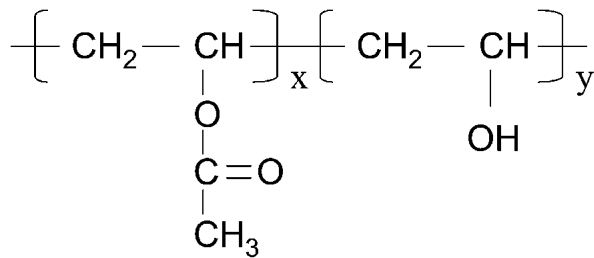
Tefose 63 (glycol stearate)

Fig. 3. Chemical structures of common raw materials used in topical formulations and discussed in this paper.

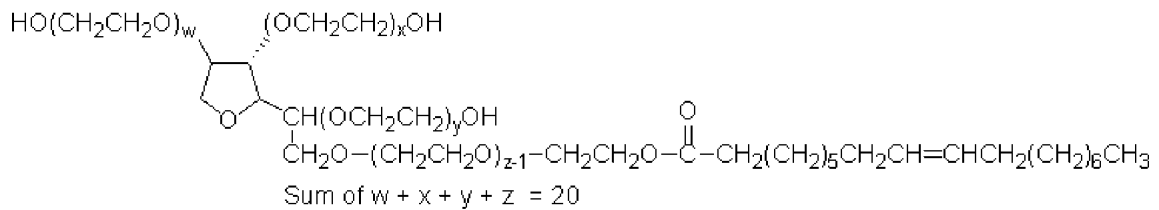
Fig. 2c. The Raman shift at 925 cm^{-1} is due to the ionic interaction between carbopol and TEA. The height of the peak at 925 cm^{-1} relative to the peak height at 845 cm^{-1} (reference peak) increased with increasing extents of neutralization as measured by pH of the systems. The ratio of the heights or areas of the two peaks can be used as a tool for controlling the amount of neutralizer during manufacturing of aqueous gels. In this case, the changes in relative



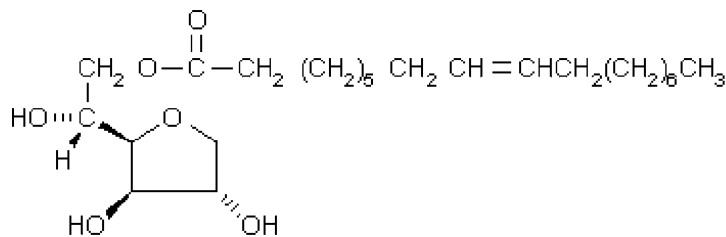
PVA(Polyvinyl Alcohol)
(Fully hydrolyzed grade)



PVA(Polyvinyl Alcohol)
(Partially hydrolyzed grade)



Tween 80



Span 80

Fig. 3. Continued

heights of the peaks are not as dramatic as in case of anhydrous gels.

Raman Analysis of Commercial Raw Materials

The Raman spectra of typical raw materials used in topical formulations were obtained using Kaiser's RXN Spectrometer. The purpose was to find out whether the raw materials exhibit distinctive spectra that can be exploited during mixing or addition of the raw materials. The chemical structures of the raw materials are shown in Fig. 3 and the Raman shifts are plotted in Figs. 4a–4c. Some of the distinctive peaks and their assignment to different vibrational modes are described below (11,12).

Ultrez 10 (Noveon, Inc., Cleveland, OH, USA). Ultrez 10 is an acrylic acid polymer cross-linked with polyalkenyl polyethers or divinyl glycol (Fig. 3). The peak observed at 1668 cm^{-1} is primarily due to the C=O stretch but it can also contain small variable amounts of other vibrations as well. The peak in the range $1649\text{--}1654\text{ cm}^{-1}$ is for symmetric C=O stretch which seems to be shifted compared to the pure PAA polymers due to the cross-linking (10). The C-C stretch of the backbone is responsible for the 1084 cm^{-1} peak.

Tefose 63 [chemical name: PEG-6-32 stearate (and) glycol stearate; USP adopted name: Pegoxol-7 stearate]: Glycol stearate is the ester of ethylene glycol and stearic acid. It conforms generally to the formula $\text{C}_{20}\text{H}_{40}\text{O}_3$. The major distinctive peaks and their assignment are as follows: $852, 891\text{ cm}^{-1}$ → aliphatic ether group (symmetric COC stretch) (11,12) modified by the CO stretch; twin peaks at 1063 and 1129 cm^{-1} → CC stretches (11), probably the two different components give rise to two peaks; $1440\text{--}1450\text{ cm}^{-1}$ → CH_3, CH_2 deformation of the long alkane chain of the stearic acid; sharp peak at 1296 cm^{-1} → combination of CH_2 in phase twist and CH_2 twist and rock.

Mineral oil: Main peak occurs at 1450 cm^{-1} as a result of CH_3, CH_2 deformations of n-alkane group of the mineral oil.

PVA (polyvinyl alcohol): 1735 cm^{-1} → C=O stretch; 858 cm^{-1} CC skeletal stretch (but different shift as compared to lauric acid where the peak is at 894 cm^{-1}); and 925 cm^{-1} → COC stretch of the side chain.

Lauric acid (synonyms: dodecanoic acid, dodecoic acid; chemical formula: $\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$): Lauric acid exhibit peaks characteristic of its long alkane chain. In addition, it exhibits a distinguishable peak at 1636 cm^{-1} due to carboxylic group (symmetric C=O stretch). The other major peaks are: 1373 cm^{-1} → CH_3 symmetric deformation of the long alkane chain; 894 cm^{-1} → CC skeletal stretch (11).

Tween 80 (synonyms: polyethylene glycol sorbitan monooleate, polyoxyethylenesorbitan monooleate, Polysorbate 80): One broad peak at 1302 cm^{-1} → vibrational modes corresponding to different types of aliphatic alkane groups combine to give the broad peak. The primary modes are CH_2 rocking and twisting and CH deformation.

Span 80 [sorbitane monooleate, fatty acid composition: oleic acid (C18:1) approximately 75%, balance primarily linoleic (C18:2), linolenic (C18:3) and palmitic (c16:0) ac-

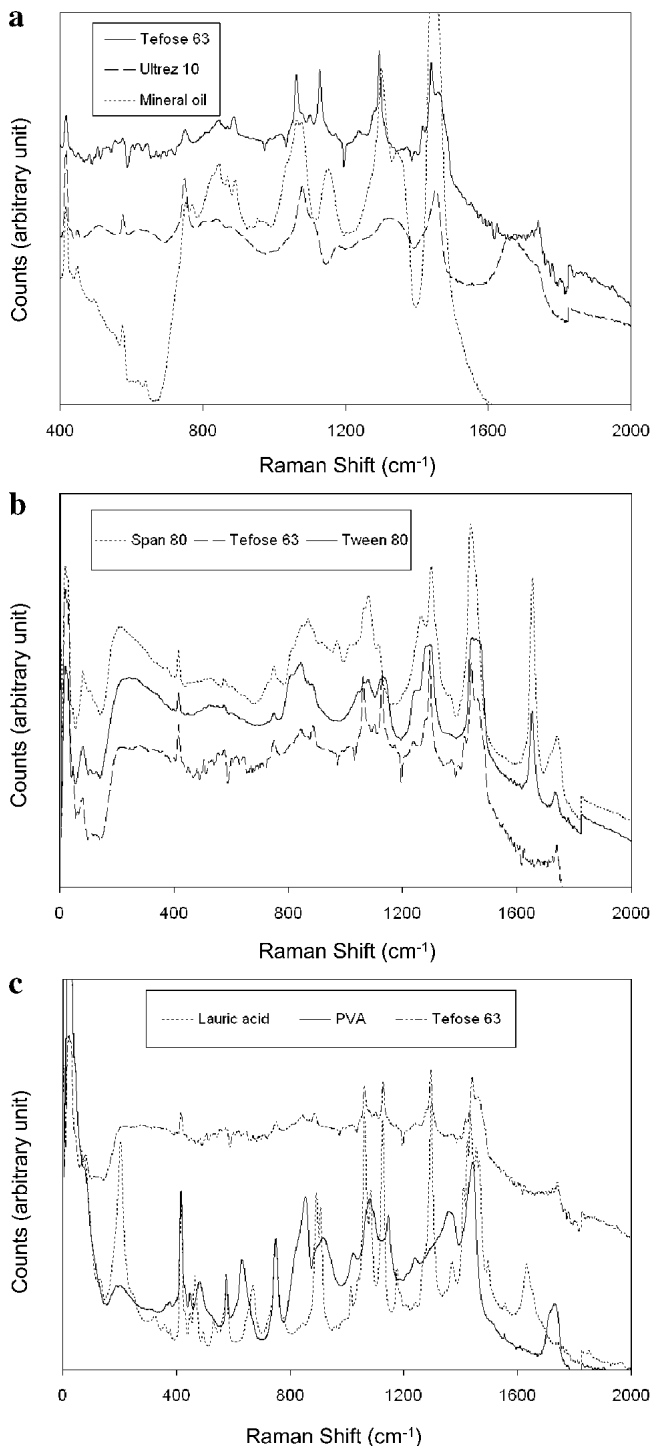


Fig. 4. (a)–(c) Raman spectra of typical raw materials used in commercial topical formulations.

ids]: Twin peaks at 1271 and 1303 cm^{-1} → CH and CH_2 deformations of two types of alkane. Although Span is very close to Tween in terms of molecular formula, it shows a distinctive peak at 975 cm^{-1} .

From the preceding discussions, we observe that the typical raw materials exhibit somewhat distinctive spectra that can be exploited during manufacturing of topical dosage forms. Also, Raman spectral library is not as common as

FTIR library. Hence the measured spectra of the raw materials can be used for comparison or quality control purpose.

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