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RESEARCH PAPER

The Composition of NF-Defined Emulsifiers: Sorbitan Monolaurate, Monopalmitate, Monostearate, Monooleate, Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80

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ABSTRACT

Using the analytical constants for sorbitan monolaurate, monopalmitate, monostearate, and monooleate given in the National Formulary *(NF), calculations were carried out that indicated that these emulsifiers are esters of sorbitol mono- and dianhydrides. Contrary to the NF description, no significant amount of sorbitol ester was calculated to be present, in agreement with recent experimental findings. Further calculations were made using the NF-defined analytical constants of polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80, which indicate that these emulsifiers are esters primarily of polyoxyethylated sorbitol monoanhydride (i.e., sorbitan), with lesser quantities of polyoxyethylated esters of sorbitol dianhydride. Since all hydroxyl groups of the polysorbates are primary, random distribution of acyl groups on the available hydroxyls can be assumed, and the likely composition of these emulsifiers can be calculated. The most abundant compounds appear to be polyoxyethylated sorbitan mono-, di-, and triesters. Although the polysorbates are stated to contain 20 moles of ethylene oxide per mole of ester, the oxyethylene contents stated in the* Food Chemicals Codex *reveal that somewhat more than 20 moles of ethylene oxide are combined.*

INTRODUCTION

Sorbitan monoesters of several fatty acids and the corresponding polyoxyethylene (POE) (20) sorbitan fatty acid esters, designated polysorbate, are widely used in pharmaceutical, cosmetic, industrial, and food applications. They are defined by monographs in the NF section of the 1995 edition, *U.S. Pharmacopeia XXIII/National Formulary XVIII* (1), and by the fourth edition of the *Food Chemical Codex* (2). The definitions and the analyt-

ical constants of these emulsifiers were used in calculations to attempt to elucidate their complex compositions. As far as I am aware, no one previously made such calculations.

PROCEDURE

Sorbitan Esters

Sorbitan fatty acid esters are prepared by reacting sorbitol with fatty acid at elevated temperatures at which both esterification and anhydrization of the sorbitol occur. Benson (3) pointed out that anhydrization of sorbitol leads to a mixture of mono- and dianhydrides, which for simplicity are usually referred to as sorbitan and sorbide. Sorbitan monolaurate, for example, is defined in the NF as "a partial ester of lauric acid with sorbitol and its mono and dianhydrides. It yields, upon saponification, not less than 55.0 percent and not more than 63.0 percent of fatty acids, and not less than 39.0 percent and not more than 45.0 percent of polyols (w/w)." The hydroxyl value is stated to be between 330 and 358, with the saponification value between 158 and 170. If one uses the median saponification value of 164 and assumes that equimolar quantities of sorbitol and lauric acid were reacted, the mole weight of sorbitan monolaurate is found to equal 56,100/164 = 342. This compares favorably with the value of 352 calculated for a mole of sorbitan (164) combined with a mole of the lauryl moiety (188).

The foregoing calculations assume that sorbitan monolaurate is made of an equimolar combination of polyol and lauric acid. The proportions actually combined can be calculated from the amounts of polyol and lauric acid recovered on saponification. Using the median values of 42% polyol and 59% lauric acid, 100 g of ester yields 42/164 = 0.256 moles polyol, and 59/206 = 0.286 moles lauric acid. The mole ratio of lauric acid to polyol is 0.286/0.256 = 1.11, and the mole weight of sorbitan monolaurate = 164 + (188 × 1.11) = 372.

Using this corrected mole weight,

Esterified hydroxyl = 372 × 164/56,100 = 1.09 moles
Free hydroxyl = 372 × 344/56,100 = 2.28 moles
Total hydroxyl = 3.37 moles

Similar calculations were performed for sorbitan monopalmitate, sorbitan monostearate, and sorbitan monooleate. Table 1 gives the analytical constants used in the calculations and also the molecular weights of the commercial fatty acids. The results determined for all four sorbitan monoesters are given in Table 2. The monoesters are determined to contain from approximately 3.4 to 3.7 hydroxyl groups, free and combined, per polyol molecule, indicating that these sorbitan esters are mixtures of mono- and dianhydrides of sorbitol containing little or no sorbitol, and that all monoesters contain more than a mole of acid per mole polyol.

A recent paper on the analysis of sorbitan esters by Wang and Fingas (4) agrees with the conclusion from these calculations, namely, that sorbitan monoesters contain no significant amount of sorbitol ester, but are mixed partial esters of anhydrized sorbitol. Wang and Fingas assume only the monoanhydride, sorbitan, whereas these calculations from analytical constants indicate the polyol also must contain dianhydride. Wang and Fingas also separated the esters from sorbitan trioleate and sorbitan tristearate and reported that, in the case of these more highly esterified compounds, that sorbitol as pentaester was present. In view of their finding, it was of interest to calculate the polyol content of sorbitan trioleate from constants given in the NF. From the yield of fatty acid and polyol on saponification, the molecular weight of ester equals 1162. Using the median saponification value of 176 and the hydroxyl value of 62.5,

Table 1

NF-Defined Analytical Constants of Sorbitan Esters

Sorbitan Ester	Hydroxyl Value	Saponification Value	Saponification Yield		Mole Weight Fatty Acid
			Polyol	Fatty Acid	
Monolaurate	330–358	158–170	39–45	55–63	206
Monopalmitate	275–305	140–150	32–38	63–71	256
Monostearate	235–260	147–157	27–34	68–76	270
Monooleate	190–215	145–160	25–31	72–78	282
Trioleate	50–75	169–183	13–19	85.5–90	282

Table 2

Calculations on Sorbitan Esters

Sorbitan Ester	Mole Weight Ester	Moles Hydroxyl/Mole Polyol			Mole Fraction Hydroxyl	
		Esterified	Free	Total	Esterified	Free
Monolaurate	372	1.09	2.28	3.37	0.32	0.68
Monopalmitate	479	1.24	2.48	3.72	0.33	0.67
Monostearate	526	1.42	2.22	3.64	0.38	0.62
Monooleate	576	1.57	2.08	3.65	0.43	0.57
Trioleate	1162	3.65	1.29	4.94	0.74	0.26

Esterified OH = 1162 × 176/56,100 = 3.65 moles
Free OH = 1162 × 62.5/56,100 = 1.29 moles

With the total of 4.9 hydroxyls per molecule, the ester obviously contains a large amount of esterified sorbitol, in agreement with Wang and Fingas finding for pentaester.

Polysorbate Esters

Polysorbate 20 is defined in NF 18 as "a laurate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides." The structural formula shows polysorbate 20 has four hydroxyl groups at the ends of POE chains, with one of the hydroxyls esterified with lauric acid. This is a very simplified representation of the emulsifier. Birkmeier and Brandner (5), Wrigley et al. (6), and others have shown that the reaction of ethylene oxide with fatty acids or esters occurs under conditions favoring rapid transesterification. Since the hydroxyl groups at the ends of the oxyethylene chains are all primary, the assumption that fatty acid groups will be distributed randomly is reasonable. Birkmeier and Brandner found that the oxyethylene chain length varied according to a Poisson distribution, as predicted by Flory (7). The ethoxyl group distribution is not a subject of this study.

The NF monograph for polysorbate 20 stipulates a hydroxyl value between 96 and 108 and a saponification value between 40 and 50. Using the median hydroxyl value of 102 and median saponification value of 45, the mole fractions of esterified and free hydroxyls can be determined:

Fraction esterified OH = 45/(45 + 102) = 0.31
Fraction free OH = 102/(45 + 102) = 0.69

These values compare favorably with calculated fractions of 0.32 and 0.68 given in Table 2 for the intermediate, sorbitan monolaurate, and demonstrates that the addition of ethylene oxide merely dilutes the free and combined hydroxyls without altering their relative proportions. The molar proportions of free polyol and mono-, di-, tri-, and tetraester in polyoxethylated sorbitan can now be determined from random distribution of the acyl groups. Thus, the chance of any hydroxyl being esterified is 0.31, and the chance of it being free is 0.69. The mole fractions of the esterified components of POE sorbitan are as follows:

Mole fraction of free polyol	$= (0.69)^4$	= 0.227
Mole fraction of monoester	$= 4(0.69)^3(0.31)$	= 0.406
Mole fraction of diester	$= 6(0.69)^2(0.31)^2$	= 0.274
Mole fraction of triester	$= 4(0.69)(0.31)^3$	= 0.083
Mole fraction of tetraester	$= (0.31)^4$	= 0.009
		0.999

The number 4 in the calculation of monoester and triester and the number 6 in the calculation of diester are the number of ways the acyl group(s) can be randomly distributed. The distribution of lauryl groups in the dianhydride, sorbide, is given below:

Mole fraction of free polyol	$= (0.69)^2$	= 0.476
Mole fraction of monoester	$= 2(0.69)(0.31)$	= 0.428
Mole fraction of diester	$= (0.31)^2$	= 0.096
		1.000

The weight percentage composition of polysorbate 20 can be determined from the mole fractions of POE sorbitan and POE sorbide esters, assuming that no POE sorbitol is present, a reasonable assumption based on calculated composition of sorbitan monolaurate. As sorbitan

monolaurate was determined to have 3.37 hydroxyls per mole and the calculated ratio of free and esterified OH groups is essentially the same for sorbitan monolaurate and for polysorbate 20, the corrected moles of ethylene oxide reacted per OH is not 20/4 but 20/3.37 = 5.94, and, on the average, sorbitan is combined with about 24 ethoxyls and sorbide with 12.

If these numbers are used in the calculations,

Mole weight POE sorbitan polyol	= (24 × 44) + 164	= 1220
Mole weight POE sorbitan monolaurate	= 1220 + 188	= 1408
Mole weight POE sorbitan dilaurate	= 1220 + 376	= 1596
Mole weight POE sorbitan trilaurate	= 1220 + 564	= 1784
Mole weight POE sorbitan tetralaurate	= 1220 + 752	= 1972
Mole weight POE sorbide	= (12 × 44) + 146	= 674
Mole weight POE sorbide monolaurate	= 674 + 188	= 862
Mole weight POE sorbide dilaurate	= 674 + 376	= 1050

The molecular weight of the POE sorbitan portion of polysorbate 20 can be determined from the molecular weights of the individual compounds and their mole fractions:

Free POE sorbitan	= 1220 × 0.227	= 277 g
POE sorbitan monolaurate	= 1408 × 0.406	= 572 g
POE sorbitan dilaurate	= 1596 × 0.274	= 437 g
POE sorbitan trilaurate	= 1784 × 0.083	= 148 g
POE sorbitan tetralaurate	= 1972 × 0.009	= 18 g
		1452 g

The molecular weight of the POE sorbide portion of polysorbate 20 can be determined similarly:

Free POE sorbide	= 674 × 0.476	= 321 g
POE sorbide monolaurate	= 862 × 0.428	= 368 g
POE sorbide dilaurate	= 1050 × 0.096	= 101 g
		790 g

The proportion of POE sorbitan and POE sorbide, both free and esterified, can now be determined using the above molecular weights and the value determined from the definition of polysorbate 20, which is that 20 moles of ethylene oxide are combined with ester containing a mole of polyol, thus (44 × 20) + 372 = 1252. If x equals the mole fraction of POE sorbitan components, and (1 − x) equals the mole fraction of sorbide components, then

$$1452x + 790\,(1-x) = 1252$$

Therefore,

$$662x = 462$$

and

$$x = 0.70 \text{ POE sorbitan esters}$$

and

$$(1 - x) = 0.30 \text{ POE sorbide esters}$$

The composition of polysorbate 20 is now determined as follows:

POE sorbitan	= 277 × 0.70 =	194 g	15.4%
POE sorbitan monolaurate	= 572 × 0.70 =	400 g	31.9%
POE sorbitan dilaurate	= 437 × 0.70 =	306 g	24.4%
POE sorbitan trilaurate	= 148 × 0.70 =	104 g	8.3%
POE sorbitan tetralaurate	= 18 × 0.70 =	13 g	1.0%
POE sorbide	= 321 × 0.30 =	96 g	7.7%
POE sorbide monolaurate	= 368 × 0.30 =	110 g	8.8%
POE sorbide dilaurate	= 101 × 0.30 =	30 g	2.4%
		1253 g	99.9%

The calculations indicate that POE sorbitan monolaurate is the most abundant compound, with substantial quantities of POE sorbitan di- and trilaurate and POE sorbide monolaurate. A substantial proportion (23%) of unesterified polyol is also estimated to be present.

The *Food Chemicals Codex* has the same analytical figures for acid value, saponification value, and hydroxyl values for polysorbates 20, 60, and 80 as the NF (see Table 3); in addition, it specifies oxyethylene content. In the case of polysorbate 20, oxyethylene content is 70% to 74%. If one uses the median value of 72%, then polysorbate 20 contains 28% sorbitan monolaurate with a mole weight 372. The mole weight of polysorbate 20 is then calculated to be 372/0.28 = 1329, and there are (1329 − 372)/44 = 21.8 moles of ethylene oxide, rather than 20, per mole of polysorbate 20. The correct moles of ethylene oxide for each of the 3.37 hydroxyls is 21.8/

Table 3

Values Used in Calculating Composition Polysorbates

Polysorbate	NF Analytical Constants		FCC Oxyethlene Content	Fraction Hydroxyls		Ethoxy Groups per OH	Calculated Mole Weight
	OH Value	Sap. Value		Esterified	Free		
20	96–108	40–50	70–74	0.31	0.69	6.4	1329
40	89–105	41–52		0.32	0.68	5.5	1359
60	81–96	45–55	65–69.5	0.36	0.64	6.6	1604
80	65–80	45–55	65–69.5	0.41	0.59	7.3	1756

3.37 = 6.4, so on the average the monoanhydride portion of polysorbate 20 contains 4 × 6.4 = ~26 ethylene oxide units, and the dianhydrides portion is 2 × 6.4 = ~13. The composition of polysorbate 20 was calculated based on this higher molecular weight and the higher ethylene oxide chain length per hydroxyl. These values are shown in Table 4. They do not differ significantly from those assuming 20 moles of ethylene oxide were reacted per mole of sorbitan monolaurate. The reason, of course, is that dilution by ethylene oxide does not alter the proportion of sorbitol mono- to dianhydride or the ratio of free to esterified hydroxyls.

Similar calculations were made using the oxyethylene content in the *Food Chemicals Codex* for polysorbate 60 and polysorbate 80. For polysorbate 40, the calculations had to be based on the assumption of 20 moles of ethylene oxide per mole of ester. The results are presented in Tables 3 and 4. It is important to note in Table 3 that sorbitol is anhydrized beyond the mono- stage in formation of the sorbitan ester, and that average oxyethylene chain length per hydroxyl is not 5, but between 6 and 7. Table 4 shows that POE sorbitan mono-, di-, and triesters are the major components of the polysorbate emulsifiers. Substantial quantities of unesterified polyols are also indicated to be present.

SUMMARY

The complex composition of the polysorbates as indicated by the foregoing calculations is presumed to be the reason they are excellent, widely used emulsifiers. The calculations ignored the possibility of POE sorbitol esters being present. The basis for this assumption is that calculations for the sorbitan esters showed that the average number of hydroxyl groups per molecule is less than four, corresponding to a mix of mono- and dianhydrized sorbitol. The agreement of the mole fractions of free and esterified hydroxyl groups in the sorbitan esters with mole fractions in the corresponding polysorbates indicates that the POE esters are also based on polyols averaging less than four hydroxyl groups. The addition of ethylene oxide does not alter the proportion of free hydroxyls to esterified hydroxyls. As previously noted, Wang and Fingas could find no sorbitol ester in the sorbitan monoesters they examined. It was not possible to calculate the distribution of acyl groups in the sorbitan esters because the relative esterifiability of the several kinds of hydroxyl groups present in mono- and dianhydrides of sorbitol is unknown. Brandner and Birkmeier (8) reported that, in the case of glycerol partial esters, the primary hydroxyl was several times more likely to be esterified than the

Table 4

Calculated Weight Percentage Composition of Polysorbates

Polysorbate	Polyoxyethylene Sorbitan as					Polyoxyethylene Sorbide as		
	Polyol	Mono-	Di-	Tri-	Tetraester	Polyol	Mono-	Diester
20	15.7	32.0	24.3	8.2	1.0	7.8	8.7	2.4
40	15.7	35.8	29.5	10.6	1.5	2.6	3.3	1.0
60	12.5	33.3	32.9	14.1	2.2	1.7	2.5	0.9
80	8.5	28.1	34.1	17.8	3.4	2.2	4.2	1.8

secondary hydroxyl. Since monoanhydrized sorbitol has a primary hydroxyl, it is reasonable to believe that this will be the most frequent site of the fatty acid moiety in the sorbitan monoesters.

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REFERENCES

1. *U.S. Pharmacopeia XXIII/National Formulary XVIII*, U.S. Pharmacopeial Convention, Rockville, MD, 1995, pp. 2306–2308, 2289–2290.
2. *Food Chemicals Codex*, 4th ed., National Academy Press, 1996, pp. 306–309, 387–388.
3. F. R. Benson, Chemistry of polyol surfactants, in *Nonionic Surfactants* (Schick, ed.), Marcel Dekker, New York, 1967, chap. 9.
4. Z. Wang and M. Fingas, J. High Res. Chrom., 17, 15–19 and 85–90 (1994).
5. R. L. Birkmeier and J. D. Brandner, J. Agr. Food Chem., 6, 471–475 (1958).
6. A. N. Wrigley, F. D. Smith, and A. J. Stirton, J. Am. Oil Chem. Soc., 34, 39–43 (1957).
7. P. J. Flory, J. Am. Chem. Soc., 62, 1561–1565 (1940).
8. J. D. Brandner and R. L. Birkmeier, J. Am. Oil Chem. Soc., 37, 390–396 (1960)