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PERSPECTIVE

Chemical Drug Stability in Lipids, Modified Lipids, and Polyethylene Oxide-Containing Formulations

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ABSTRACT To critique the stability complications seen in formulating poorly water-soluble, problematic drugs in lipids, modified lipids, and polyethylene oxide solvents and surfactants in hard and soft gelatin capsules as well as some parenterals, a literature search was performed and personal experiences, and those of colleagues, collated. The literature is replete with examples of molecules undergoing rapid oxidative degradation in the presence of polyethylene oxide based solvents and surfactants as well as in the presence of unsaturated lipids. More recently appreciated is instability caused by the reaction of amine and amide drugs, with formaldehyde, formic acid found in many of these solvents as impurities and other degradation byproducts of the solvents themselves. One would expect acylation and transacylation reactions to be more common than reported but the literature has some good examples. An added complexity is occasionally seen with the use of hard and soft gelatin capsules with these solvents. The chemical stability of drugs in liquid and semi-solid formulations in the presence of lipids, modified lipids, and polyoxyethylene oxide-based solvents and surfactants can be complex, further exacerbated by the use of gelatin capsules, and can lead to a plethora of degradation pathways often not seen when the same drugs are formulated in solid dosage forms.

KEY WORDS chemical stability · formaldehyde · lipids · oxidation · transacylation

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WHY STABILITY?

Below are some observations based on my own work, reading the literature and my experiences as a consultant for the pharmaceutical industry over the last 40 years related to the use of lipid, modified lipids, polyethylene oxide (PEO), including polyethylene glycols (PEG), and surfactant based liquid or semi-solid capsule formulations.

1. Long-term chemical stability issues (as well as physical stability) of drugs formulated in lipids, self emulsifying drug delivery systems, SEDDS, self-microemulsifying and self-nanoemulsifying drug delivery systems, SMEDDS and SNEDDS, etc. are often ignored by academicians and initially by some in industry.
2. Lipid, SEDDS, SMEDDS and SNEDDS vehicles are complex and often contain reactive molecules or impurities such as esters, formaldehyde (especially PEO based solvents), formic and acetic acid and peroxides, etc.
3. Drugs in solution degrade more rapidly than drugs in their solid state - most of the time.
4. A product cannot be developed unless it can achieve chemical and physical stability over the expected storage and use time (usually two years or greater).
5. No one wants to see unqualified degradation products at >0.1%.

About 15 years ago I visited a company in the San Diego area that had a very promising drug with extreme poor water solubility (does that sound familiar?) whose bioavailability was very significantly enhanced when formulated in a lipid based self-emulsifying system. I was asked to consult on an alternative formulation because, and I am paraphrasing, "we found 29 degradation products we formed under modest storage conditions and could not move forward with the formulation."

Table I Some Observations on the Stability of an Unidentified Drug, Drug X from an Experimental, Unidentified SEDDS Vehicle, Over a Short Exposure Time

Storage condition	Assay for Drug X	Observations
5°C, 2 days	97%	2% - mostly dimers
5°C, 8 days	90%	4% - dimers
		1.2% - epimer
		0.4% - possible hydrolysis product
Room temperature, 8 days	78%	8.5% - dimers
		5% - epimer
		1.2% - possible hydrolysis product
		2% - possible lipid adduct or lipid degradation product

In 2007 I was asked to give a talk at an AAPS lipid vehicle workshop held in Bethesda, MD. While most of the other speakers talked glowingly about the use of lipid vehicles (broadly defined), only a few of us raised the issue of some limitations, poor solubility and thus loading limitations, and poor long-term chemical stability.

In preparing for that talk I canvased some of my colleagues at various drug companies about stability issues for lipid based or other liquid or semisolid capsule based formulations. Most were reluctant to be quoted but many did provide some valuable insights. One who wished to remain anonymous said "we had developed a prototype self-emulsifying drug delivery system …and got over 600% enhancement in oral bioavailability. The lipid formulation contains a medium chain mono- and di-glycerides, Cremophor and propylene glycol with a drug loading capacity at around 20%. However, due to following [chemical] stability issues, the formulation was not carried forward."

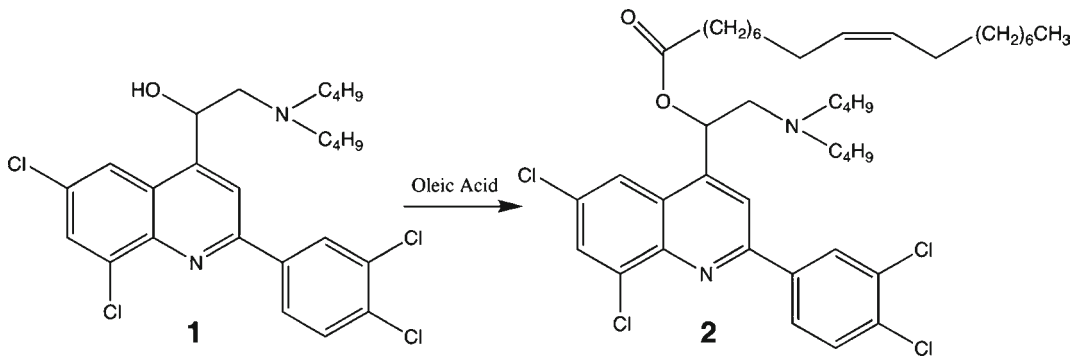
Another provided the following comment and some data, "The Drug X in SEDDS was examined for short time periods. There has been some limited LC-MS work performed so we know, in most cases, the nature of the degradation peaks observed were as following," see Table I.

Drug X was obviously very unstable. The presence of "dimers" would indicate probable oxidative dimerization while the presence of an "epimer" would indicate a particularly sensitive epimerization site in the molecule.

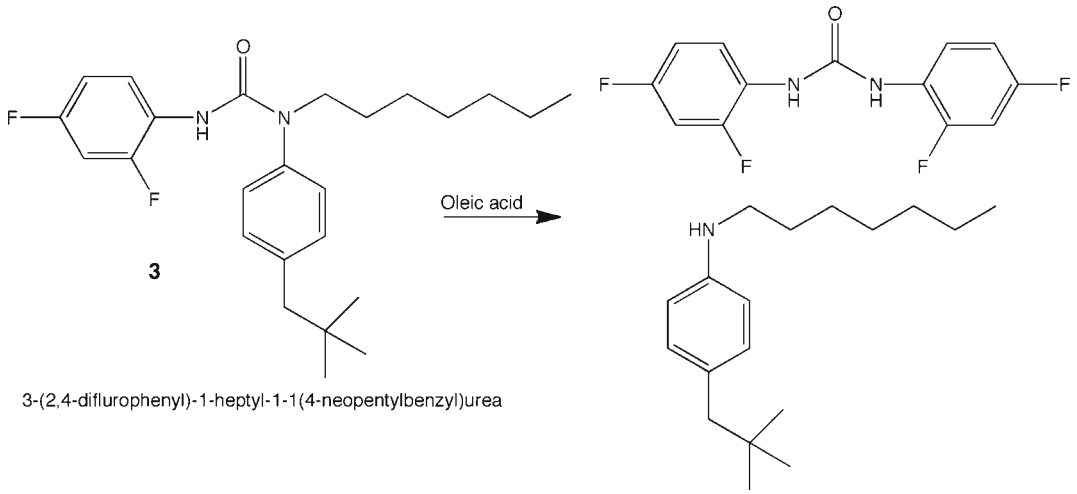
In the late 1970s I had my first personal experience in this area when asked to formulate a novel antimalarial for the Walter Reed Army Institute of Research and SRI International. We were working with a molecule, WR 30090 (**1**, see Scheme 1), an analog of mefloquine and halofantrine. We were able to get good drug exposure on oral dosing in dogs using a formulation that utilized a high purity sample of oleic acid (1) as the vehicle. WR 30090 showed considerable chemical instability at 40°C resulting in 4% formation of the Oleic acid ester (**2**) of WR 30090 within one month, but surprisingly no further degradation over longer periods of time. We speculated at the time that the equilibrium like oleic acid ester formation behavior was not due to an equilibrium but the possible presence of oleic acid anhydride in the oleic acid sample used as the source of the high purity oleic acid was prepared by fraction distillation where dehydration of oleic acid to oleic acid anhydride was possible. One might argue that **2** (and similar esters) might act as a prodrug of WR 30090, however, from a stability and regulatory authority point of view, **2** would be an impurity and thus subject to scrutiny.

A second experience was while consulting with a New York pharmaceutical company on an experimental lipid-lowering agent, 3-(2,4-difluorophenyl)-1-heptyl-1-(neopentylbenzyl)urea (**3**), also formulated with oleic acid. On storage **3** rapidly degraded to a complex mixture with two of the degradation products identified shown in Scheme 2. One could speculate as to the reaction involved here but sometimes the mechanism/s are just not obvious (2).

More recently, we observed the dimerization (see Scheme 3), through a methylene group, of O^6-benzylguanine (**4**) in the presence of polyoxyethylene 400 (PEG 400) due to the presence of formaldehyde in aged PEG samples (3). Scheme 3 also shows a later product seen when one of the products of the hydrolysis of O^6-



Scheme I Reaction pathway for the degradation of WR 30090 in an oleic acid vehicle (1), possibly due to oleic acid anhydride in the purified oleic acid sample.

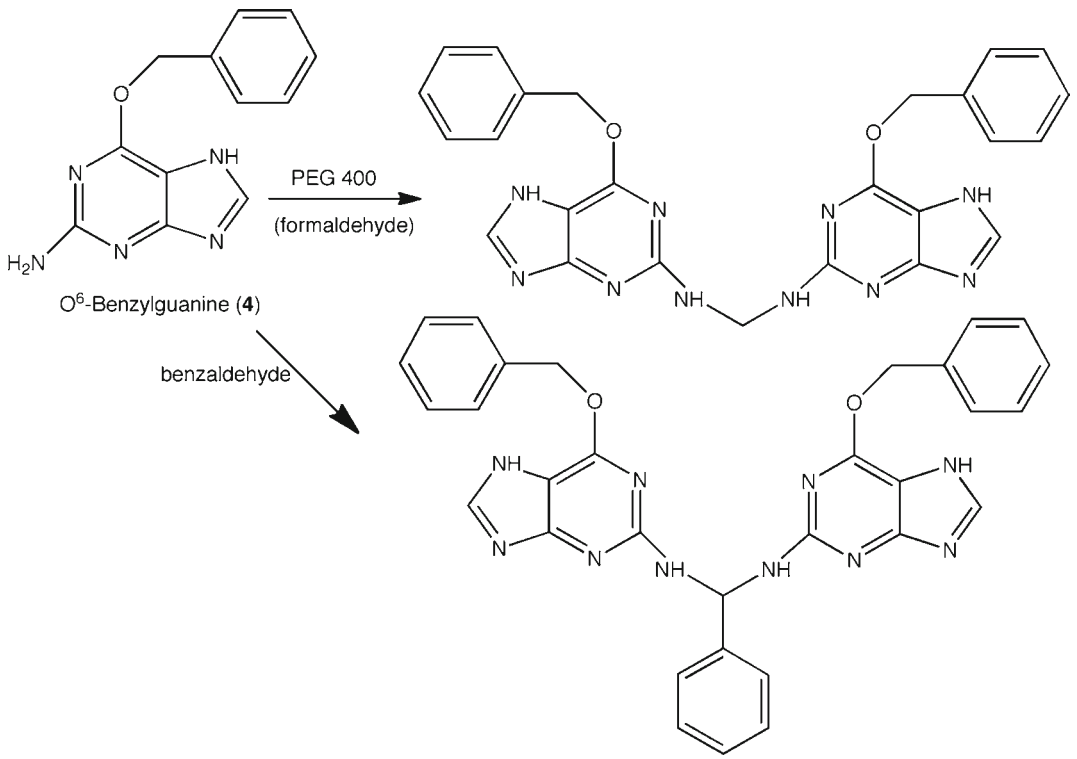


Scheme 2 Some degradation products seen when 3-(2,4-diflurophenyl)-1-heptyl-1-(neopentylbenzyl)urea (**3**) was formulated with oleic acid (2).

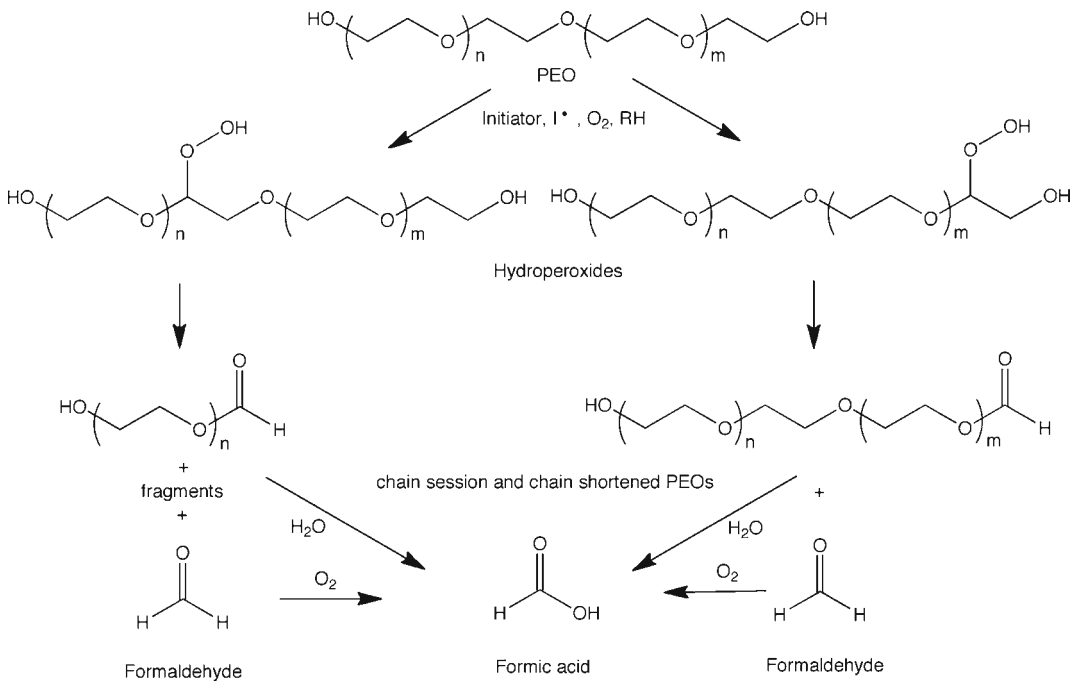
benzylguanine to benzyl alcohol is oxidized to benzaldehyde resulting in a second dimerization product (unpublished results). Formaldehyde and other aldehydes are formed in a number of vehicles use in liquid and semi-solid capsule formulations. Li *et al.* analyzed various such vehicles for aldehydes (formaldehyde through octanal) and found formaldehyde and acetaldehyde as the only two detectable aldehydes in the 30 vehicles studied (4).

The formation of formaldehyde from polyethylene oxide-based solvents is presumably *via* the normal free radical based autoxidation of ethers resulting in the formation of hydroperoxides, which breakdown to formaldehyde, formate esters and formic acid (5–8). The proposed reaction pathway by Yang *et al.*, (8) is shown in Scheme 4. A similar facile breakdown is seen with polypropylene oxides, illustrated in Scheme 5 (8). Additional specific examples of drug degradation in the presence of polyethylene oxide containing solvents are discussed later in this commentary.

While this paper will primarily focus on drug chemical stability issues related to the addition of drugs to lipid,



Scheme 3 Degradation pathway for O^6-benzylguanine (**4**) in the presence of polyoxyethylene 400 (PEG 400) due to the presence of formaldehyde in aged PEG samples (3) and due to the presence of benzaldehyde from hydrolysis of **4** to benzyl alcohol which was presumably oxidized to benzaldehyde (unpublished results).

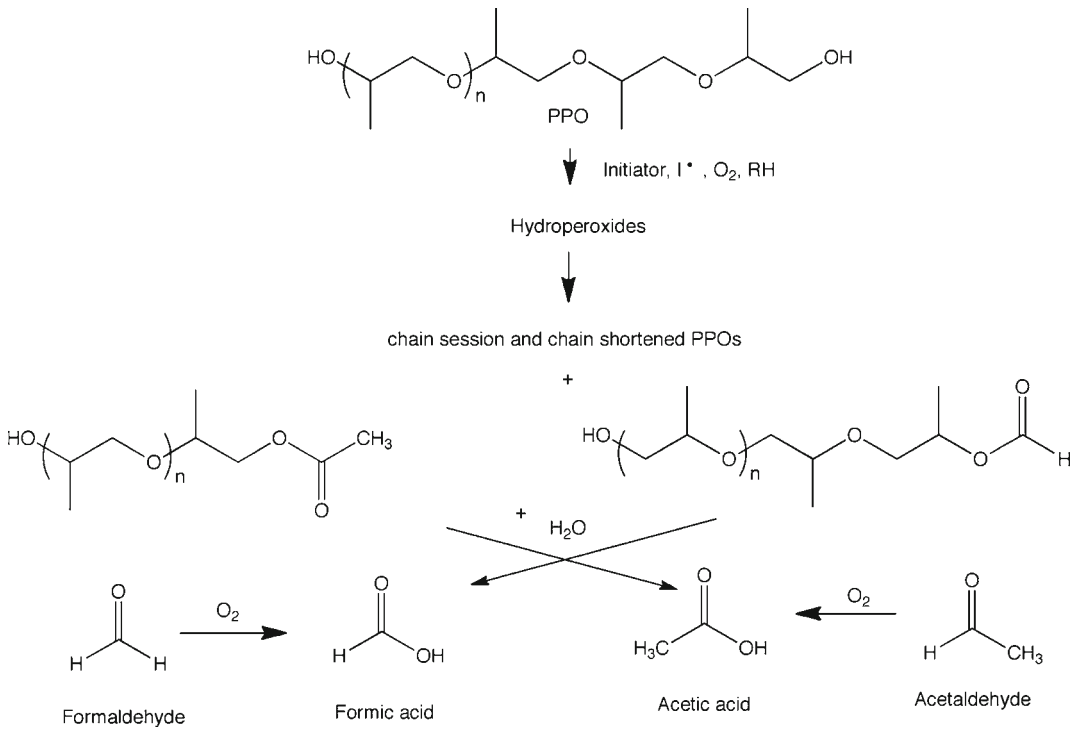


Scheme 4 Degradation pathways and products for polyethylene oxide (PEO) (8). This is similar to that proposed later by Hemenway *et al.* (24).

modified lipids, polyethylene oxide (PEO), including polyethylene glycols (PEG), and surfactant based oral liquid or semi-solid capsule formulations, some relevant examples also come from the parenteral formulation literature. Also, many of the reactions discussed here are relevant to the formulation of injectable drugs.

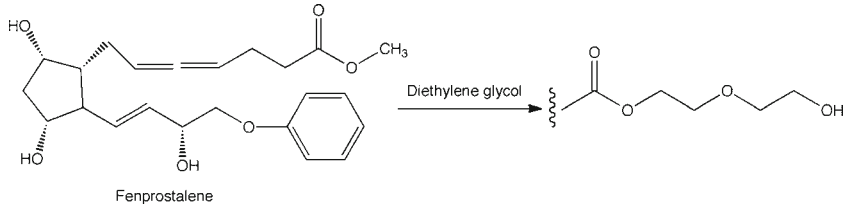
ACYLATION, TRANSACYLATION, AND TRANSESTERIFICATION REACTIONS

One can speculate that the presence of fatty acids, various glycerol esters and modified lipid and those surfactants with ester groups present in their structure could lead to ester,



Scheme 5 Degradation pathways and products for polypropylene oxide (PPO) (8).

Scheme 6 Transesterification of fenprostalene in diethylene glycol (9).



thioester and amide formation with drugs containing nucleophilic groups such as a primary or secondary alcohol, an amine and/or a thiol. Similarly, drugs with an ester group can undergo a transesterification reaction in solvents that have, for example, an alcohol function.

Although chemists have extensively studied acylation and transacylation reactions, there are not a lot of practical example references in the pharmaceutical literature related to formulations. Our earlier referenced work on the stability of WR 30090 was one example (1).

Johnson and Taylor studied the stability of fenprostalene, a methyl ester of a prostaglandin derivative with significant unsaturation in its structure, in both PEG 400 and diethylene glycol and noted not only significant degradation in the PEG 400 solution due to oxidation but a slow transesterification reaction with diethylene glycol (9). The reaction is illustrated in Scheme 6.

Ballard *et al.* studied the stability of vitamin D_3, with a free secondary alcohol group, in medium chain triglycerides (Captex 300 EP) composed of C6, C8, C10 and C12 esters and found on storage the presence of both the octanoate and decanoate esters (10). This reaction is illustrated in Scheme 7.

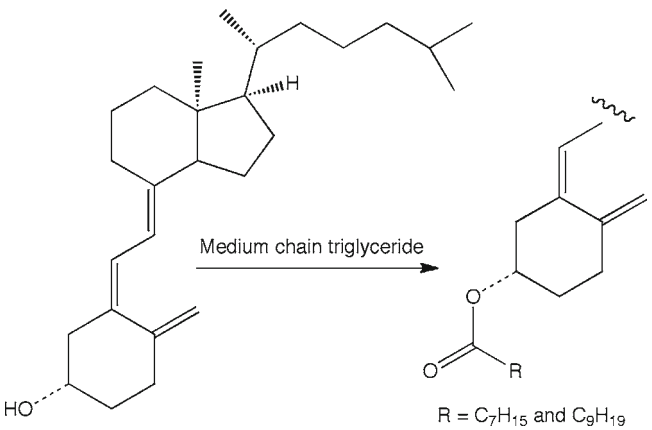
Grove *et al.* studied the bioavailability of seocalcitol, a polyunsaturated drug with two secondary and one tertiary alcohol functional groups, in various lipid formulations including a medium chain triglyceride, a long-chain triglyceride (sesame oil), a medium chain triglyceride SMEDDS vehicle that included Viscoleo (a medium chain triglyceride), Alcoline MCM (mono- di- and triglyceride mixture composed of octanoic and decanoic acids) and Cremophor RH40, and a long-chain triglyceride SMEDDS vehicle that included Peceol (the monooleate of glycerol) and Cremophor RH40 (11). The degradation of seocalcitol over three months at various temperatures is shown in Table II. Significantly greater decomposition was seen in the SMEDDS formulations (to be discussed later) but not insignificant degradation was also seen in the relatively inert medium chain triglyceride and sesame oil formulations. The degradation products in the triglycerides were not identified by Grove *et al.* but most probably could have been esterified seocalcitol as was seen with vitamin D_3 in a medium chain triglyceride.

While most degradation of drugs in PEO based vehicles seems related to oxidative breakdown or reaction with impurities in the PEO solvents, PEO also has terminal hydroxyl groups capable of reacting with esters, carbonates, carbamates, and ureas, or esterifying with carboxylic acids, especially under acidic conditions. Kochling *et al.* studied the stability of an experimental, urea functional group containing drug, VX-497 in PEG 400 in soft gelatin capsules and found evidence of multiple degradation peaks on HPLC-MS analysis consistent with various PEG ester conjugates (12). The proposed products are illustrated in Scheme 8. Kochling also saw products related to PEG 400 reacting with a process impurity complicating the stability analysis.

Gursoy *et al.* (13) also noted the instability of paclitaxel in SEDDS vehicle consisting of α-tocopheryl polyethylene glycol 1,000 succinate (TPGS), tyloxapol (Triton WR-1339) and sodium deoxycholate. Paclitaxel has multiple ester functional groups in its structure and is also subject to a facile isomerization reaction under basic aqueous and non-aqueous conditions (14,15).

The instability of paclitaxel in its injectable concentrate consisting of a 50:50 Cremophor/ethanol solvent has been the subject of a number of patents. Both Craver *et al.* (16) and Agharkar and Gogate (17), solved the instability by acidification of the vehicle or the removal of basic impurities, respectively. These patents illustrate that reactions may not always be related to the vehicles themselves but processing impurities found in the vehicle.

Illustrative of reactions related to the topic at hand can be seen in the work of Yu *et al.* who showed that the carboxylic acid drug, cetirizine, reacted with various polyols to form esters (18). Ma showed that methylparaben, an ester and a



Scheme 7 Transacylation of Vitamin D3 in medium chain triglycerides (Captex 300 EP) composed of C6, C8, C10 and C12 esters (10).

Table II Seocalcitol Stability (% Degradation) at Various Temperatures Over Three Months in Medium and Long Chain Triglyceride and Medium and Long Chain-SMEDDS Formulations (11)

Various storage conditions	Formulations (% degradation)			
	Medium chain triglyceride (MCT, Viscoleo)	Long chain triglyceride (LCT)	Medium chain - SMEDDS[a]	Long chain - SMEDDS[b]
5°C	0.2	0.2	0.8	5.9
25°C, 60% RH	0.1	0.4	5.8	8.4
40°C, 75% RH	1.6	2.6	10.4	11.3

[a] Contains a medium chain triglyceride (Viscoleo), Cremophor RH, a surfactant, and Akoline MCM (mono- di- and triglyceride mixture composed of octanoic and decanoic acids), a co-surfactant

[b] Contains sesame oil, Cremophor RH, a surfactant, and Peceol (the monooleate of glycerol), a co-surfactant

common preservative used in various pharmaceutical formulations could undergo a transesterification reaction with various polyols, including propylene glycol (19).

While citric acid is often considered fairly inert, Larsen *et al.* showed that carvedilol reacts with citric acid to form various esters and amides with the secondary alcohol and amine groups of carvedilol (20). Not well known is the fact that citric acid and other polycarboxylic acids form intramolecular anhydrides capable of acylating alcohol and amines (21). While not a lipid *per se*, citric acid and other di- or polycarboxylic acids are occasionally added to various vehicles either as an acidifying agent or potentially as a chelating agent.

OXIDATION REACTIONS – UNSATURATED FATTY ACIDS AND PEO – FREE RADICALS AND PEROXIDES AND THEIR BYPRODUCTS

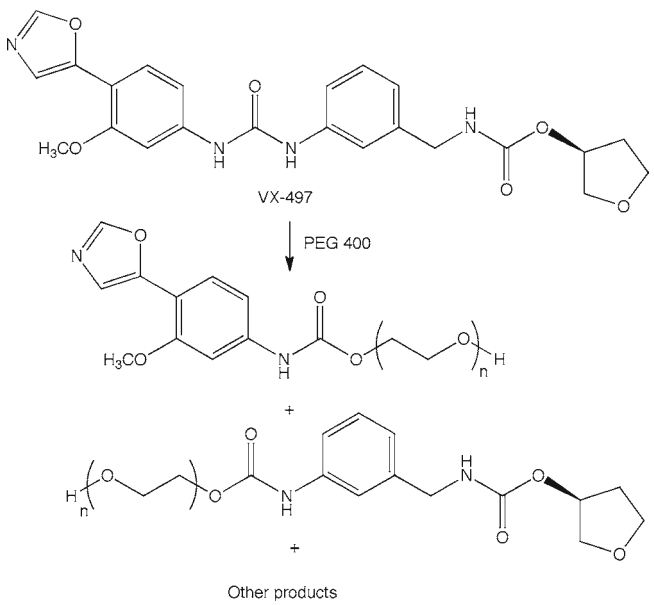
The presence of hydroperoxides and radical species in polyethylene oxide based vehicles and the formation of formaldehyde, formic acid and formic acid esters has been well documented (5–8). The high interest in PEO based solvents and co-solvents in SEDDS/SMEDDS/etc., as well as in hot-melt extrusion matrix tablets, has triggered renewed interest in the stability of the PEO based vehicles themselves, and on the stability of various drug molecules incorporated into these vehicles (22–26).

Dronabinol or Δ^9-tetrahydrocannabinol is formulated in sesame oil but must be stored from 8-15°C and must be protected from freezing (27). Munjal *et al.* (28) reported on the thermo-oxidation of Δ^9-tetrahydrocannabinol to form cannabinol in TPGS, PEG, Capmul PG-12 and PEO (Scheme 9). In TPGS there was 48% degradation after one month at 40°C, 9.6% degradation in Capmul PG-12, and 3.2% degradation in both PEG and PEO were reported. Degradation also significantly increased in all vehicles with an additional month of storage.

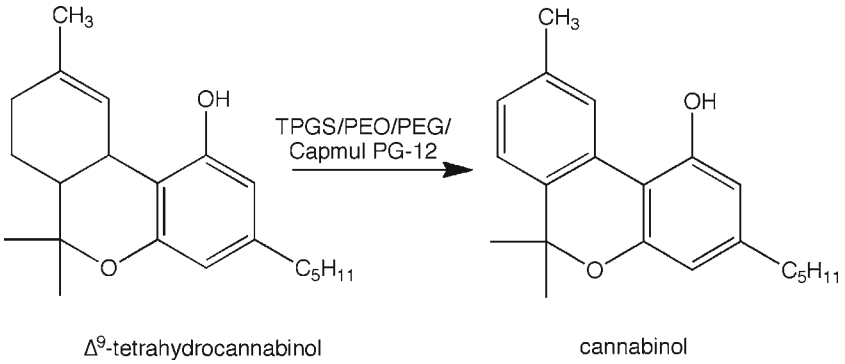
While many studies have focused on PEO solvents and semisolids, commonly used surfactants such as polysorbate 80 and 20, TPGS, Cremophor, Tyloxapol, and Solutol and a number of other non-ionic surfactants also contain PEO chains and are subject to degradation (29,30).

Horvorka and Schöneich have elegantly discussed the oxidative degradation mechanisms of small drug molecules and proteins (31). The role played by metal ions and peroxide as initiators and reactants in the degradation of drug molecules is fully acknowledged. The peroxide content of many pharmaceutical excipients has been the basis for a number of publications (3,24,32,36).

To quote Wasylaschuk *et al.* (32), "The HPO [hydroperoxide] data…clearly show that PS80 [polysorbate 80] and PEG 400 have much higher HPO levels than MCG [medium chain triglycerides] and poloxamer. Liquid formulations using PS80 and PEG 400 represent a highly "oxidizing"



Scheme 8 Reaction of the urea functional group containing drug, VX-497, with the terminal alcohol groups of PEG 400 (12).



Scheme 9 The oxidative conversion of Δ^9-tetrahydrocannabinol to cannabinol in TPGS, PEO, PEG, and Capmul PG-12 (28).

environment that can be conducive to radical chain degradation reactions as well as the two-electron nucleophilic reactions."

The incompatibility of easily oxidized drugs has been recognized for some time (33). For example, earlier we discussed the work of Grove *et al.* (11) who reported on the stability of seocalcitol (see Table II). While seocalcitol was modestly stable in the MCT and LCT vehicles, seocalcitol was significantly unstable in the two SMEDDS formulations containing Cremophor, a PEO side-chain containing surfactant. Specific oxidative degradation pathways for seocalcitol were not identified in the Grove paper but the presence of a polyunsaturated site makes this site the most likely affected by the hydroperoxides and radicals from the PEO chain of Cremophor and oxygen exposure.

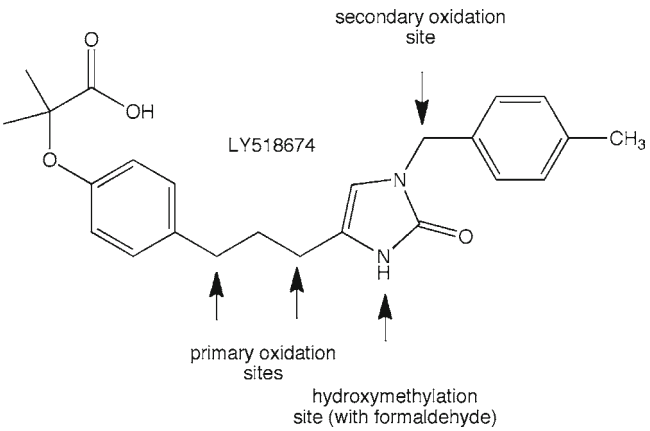
When Johnson and Taylor studied the stability of fenprostalene in PEG 400 they noted significant degradation in the PEG 400 solution due to oxidation (9). A transacylation reaction with diethylene glycol was noted earlier. Like seocalcitol, fenprostalene has two cumulated double bonds and a second isolated double bond. These are the likely oxidatively vulnerable sites of degradation.

Nishikawa and Fujii studied the stability of the antifungal agent, miconazole from hydrogenated castor oil with a PEO side chain (HCO-60) (34). Also studied were polysorbate 20, PEG 400 and laureth 9 (hydroxypolyethoxydodecane, LAR-9). The authors noted the mM growth hydroperoxides with time at two temperatures for the HCO-60. An interesting observation but not surprising, was that miconazole degraded much more rapidly in previous degraded HCO-60 compared to freshly prepared samples.

Kiehl *et al.* (35) studied the stability of LY518674 in the presence of PEG and formaldehyde. Multiple sites of hydroperoxide formation, disproportionation and one site of hydroxymethylation were identified. These sites of LY518674 are illustrated in Scheme 10.

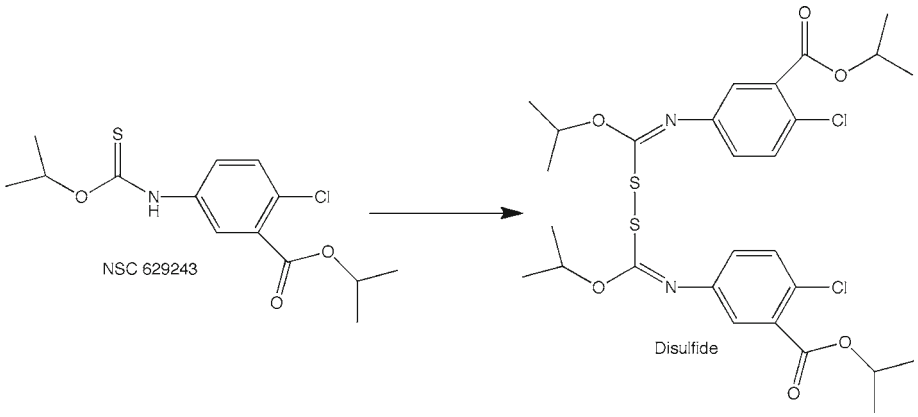
Also, well appreciated is the presence of hydroperoxide and aldehyde species formed during the oxidation of unsaturated fatty acids and fatty acid esters including mono-, di- and triglycerides. Quite a bit is known about the oxidation of oleic, linoleic and linolenic acids as they are found in many cooking oils and their oxidation leads to loss of freshness. Oxidative instability of drugs in unsaturated and polyunsaturated oils is usually compromised compared to stability in saturated medium chain triglycerides. Note the greater instability of seocalcitol in a long-chain triglyceride compared to a medium chain triglyceride seen in Table II. Strickley and Anderson (36) studied the stability of NSC 629243 in various oily vehicles (sesame, safflower, soybean, cottonseed, peanut, triacetin) and PEG 400 at both −5°C and 25°C. The oxidation reaction is shown in Scheme 11 and the stability data summarized in Table III. To quote Strickley and Anderson, "A qualitative correlation was found between the initial rate of oxidation and the peroxide concentration in the oil."

As with many such autoxidations, the pathways are complex and the reaction initiated by the presence of reactive radical, metal ions or the disproportionation of peroxide impurities. While these reactions can be slowed or even stopped by the use of judicial use antioxidants, one must remember that most antioxidants are simply molecules that are more easily oxidized than the drugs they are trying to protect and form end products due to oxidation that are



Scheme 10 Multiple sites of oxidation, and one site of hydroxymethylation of LY518674 in various drug excipients rich in peroxides and formaldehyde (35).

Scheme 11 Major oxidation degradation pathway for NSC 629243 in various oil with varying levels of peroxide (36).



relatively inert. However, if your drug is more oxidatively reactive than the antioxidant, your drug will be oxidized and the antioxidant protected. Also, while some antioxidants form inert end products, other can catalyze further reaction with drug molecules by forming hydrogen peroxide or electrophilic molecules capable of undergoing attack by nucleophiles. For example, the antioxidants BHT and BHA can form quinone methide species capable of reaction with alcohols, amines, thiols and other nucleophilic groups.

FORMALDEHYDE AND FORMIC IMPURITIES

While the ^{6}O-benzylguanine example discussed earlier (3) was an example of where formaldehyde from PEG 400 oxidation lead to dimerization of a primary amine drug, formaldehyde and formic acid in PEO solutions have been implicated in the degradation of many other drugs.

A novel finding by Waterman *et al.* (37) was the N-methylation and N-formylation of the secondary amine drug, varenicline, in osmotic tablets, the coating of which contained PEG. The same products where seen in a PEG solution. Waterman evoked the Eschweiler-Clarke reaction to account for the N-methylation product (see Scheme 12) while direct reaction with formic acid was implicated for the N-formylation product. An interesting reference cited by Waterman was that of Gannett *et al.* who saw similar N-methylation reactions of amine drugs as a result of embalming fluids (38).

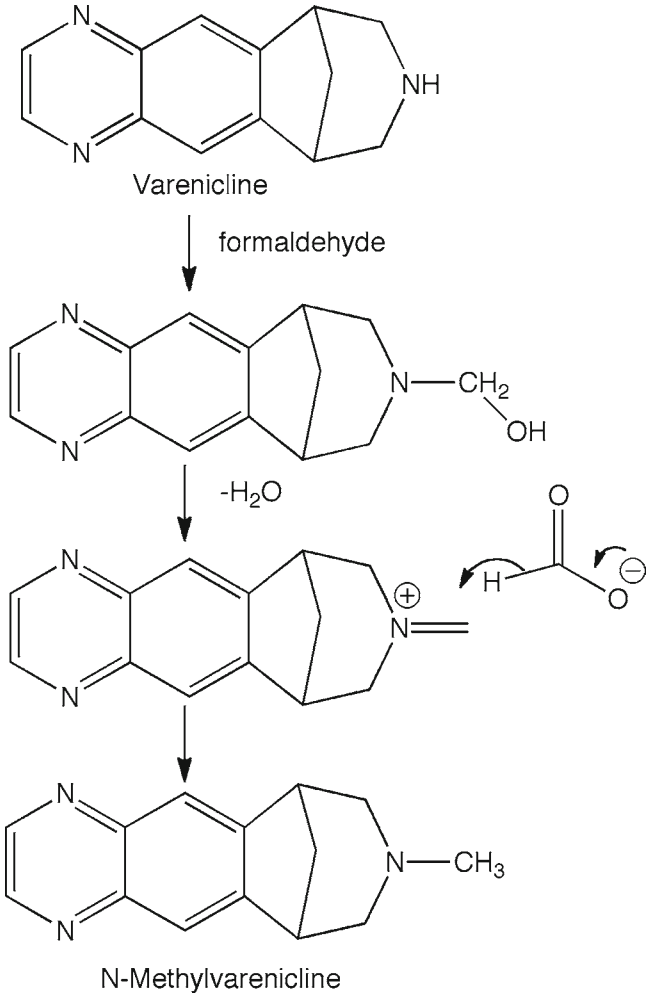
The formaldehyde impurity in polysorbate 80 and PEG 300 was also responsible for the degradation of BMS-204352 as reported by Nassar *et al.* (39). Not only were the N-hydroxymethyl degradation product of BMS-204352 identified but the formaldehyde content of various batches of PEG 300 and polysorbate 80 were also determined. The authors noted a correlation between the formaldehyde content of various lots and the amount of N-hydroxymethyl degradation product formed. Fujita *et al.* (40) showed that formaldehyde could be trapped and removed using meglumine to form a cyclic product.

Formic acid in a PEG 400/glycerol vehicle used to deliver FK480, a cholecystokinin antagonist, from soft gelatin capsules was implicated in the isomerization of FK480 at its C-3 position (41).

Table III Relative Stability as Indicated by Estimated Shelf-Lives of NSC 629243 in Various Vehicles[a] at −5°C and 25°C (36)

Vehicle	Condition[a]	Shelf-life in days		Peroxide content (mM)
		−5°C	25°C	
Sesame oil	USP	35	30	1.6
Sesame oil		10	2	3.9
Sesame oil	aged	3	2	6.1
Sesame oil	fresh	–	>100	1.2
Safflower oil		<1	<1	2.6
Soybean oil		<1	<1	4.2
Soybean oil	USP	>100	>100	1.0
Cottonseed oil	USP	>100	>100	0.63
Peanut oil	USP	>100	>100	0.32
Triacetin		>210	>210	0.03
PEG 400	USP	>240	>240	0.03

[a]This study was performed in the 1990s and may not reflect the purity of similar current vehicles from the sources used. The brands or source of the various vehicles was identified in the reference 36



Scheme 12 N- methylation and N- formylation of the secondary amine drug, varenicline, caused by formaldehyde and formic acid impurities in PEGs (37).

GELATIN CAPSULES AND AMMONIA

One tends to think of soft (and hard) gelatin capsules as being fairly inert yet loss of plasticizer and migration of drugs into gelatin as well as water into the formulation is at least appreciated. As noted earlier, formaldehyde is a byproduct of PEO and PPO oxidation. Formaldehyde and other aldehydes are known to crosslink gelatin and affect *in vitro* release of drugs (42,43).

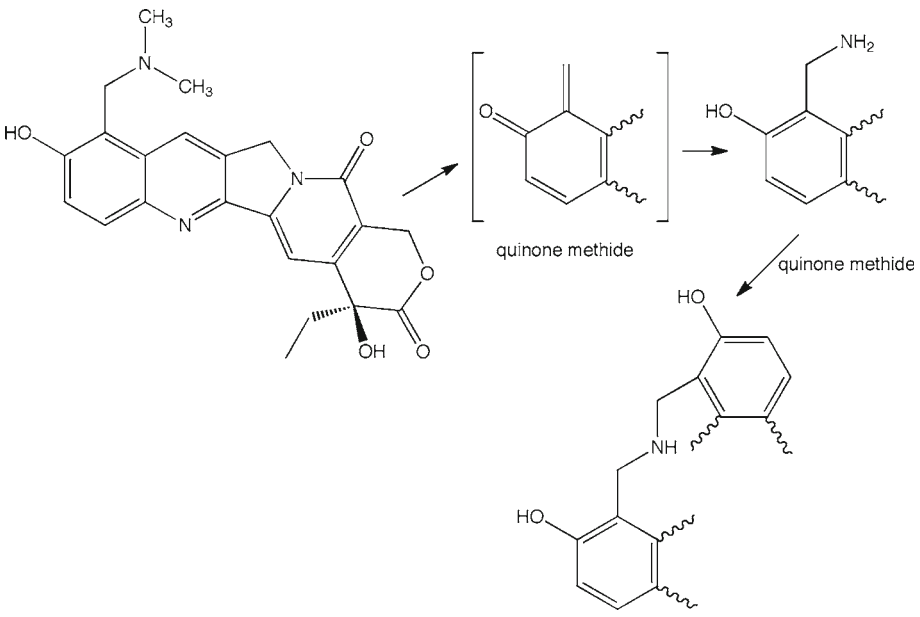
Patel *et al.* (44) also showed gelatin can be a source of the nucleophile, ammonia. When studying the stability of topotecan in an oil-based suspension formulation of topotecan in a vehicle of 5% glyceryl mono-oleate in fractioned coconut oil, they observed the formation of various degradation products consistent with breakdown of topotecan through a quinone methide reactive intermediate with ammonia from gelatin (See Scheme 13). They estimated the ammonia content as 0.25 μmoles of ammonia per capsule.

CONCLUSION

The chemical stability of drugs in liquid and semi-solid formulations in the presence of lipids, modified lipids, surfactants and polyoxyethylene oxide based solvents is complex and can lead to a plethora of degradation pathways often not seen when the same drugs are formulation in solid dosage forms. The use of gelatin capsules can also contribute to the complexity.

Yet, the advantage of improved delivery from such vehicles is inviting and has given us the ability to formulate problematic, poorly water-soluble drugs.

Scheme 13 Some novel degradation products of topotecan arising from ammonia migration from gelatin capsules into an oil-based formulation (44).



Drugs that tend to show chemical stability challenges in such vehicles are ones that have functional groups in their structure that are capable of acting as nucleophiles (reactive amine, alcohol and thiol groups), have reactive electrophilic centers (activated esters groups and polarized unsaturated double bonds) and drugs suspect to oxidative breakdown (non-aromatic double bonds, benzylic carbons, ether linkages and sulfur atoms). While the solvents themselves are often quite inert, impurities and these solvents often contribute significantly to the degradation.

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