

(4) I understand that the claim directed to: [a]n ophthalmic composition comprising, in an ophthalmically acceptable medium: a solid complex comprising dexamethasone and γ -cyclodextrin, wherein the composition comprises less than 1.0% by weight of dexamethasone enol aldehyde based on the weight of the dexamethasone.

(5) I have also been advised that the claims have been rejected as allegedly being anticipated by and/or obvious over *Tanito et al.* (Topical Dexamethasone-Cyclodextrin Microparticle Eye Drops for Diabetic Macular Edema, *Invest. Ophthalmol. Visual Sci.*, 52 (11): 7944-7948 (2011); hereafter "*Tanito*").

(6) I am a co-author of the study described in *Tanito*.

(7) This application describes how we were able to surprisingly invent a ophthalmic composition with a reduced concentration of certain undesirable degradation products, such as dexamethasone enol aldehydes. I respectfully disagree that we could do this merely by avoiding excess heating of aqueous eye drop formulations. For example, we discovered that at high temperature cyclodextrin catalyzes dexamethasone degradation. Furthermore, the degradation products formed in aqueous cyclodextrin formulations during autoclaving (e.g., dexamethasone enol aldehydes) are not normally observed in aqueous dexamethasone drug formulations. (See e.g., specification at [000149].) In fact, until this invention, I was not aware of the existence of such degradation products. It was only upon extensive examination and study that we discovered that we could produce an ophthalmic composition with decreased concentration of these degradation products by autoclaving the active pharmaceutical ingredient and cyclodextrin separately and then mixing the two aqueous media at a lower temperature to produce the claimed ophthalmic composition. (See, specification at

[00026].)

(8) As described in Table 2 of the specification (reproduced below), the claimed ophthalmic composition provides several material and significant advantages that are not achieved by the composition disclosed in the cited art. Some of the significant advantages include: (i) a substantial decrease in the concentration of degradation product of dexamethasone from 1.45% to 0.20% or less; and (ii) a method of controlling the particle size of the ophthalmic composition. Some of these significant advantages are discussed in further detail below.

TABLE 2

	Formulation								
	F1	F2	F3	F4	F5	F6	F12	F13	F14
Autoclaving at 121°C for 20 min with dexamethasone	X					X	X	X	X
Heating to 90°C for 15 min with dexamethasone		X	X	X	X	X			
Comprises -cyclodextrin	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
pH	4.5	5.1	5.0	5.0	4.7	4.8			
Fraction of dexamethasone in solution (%)	12.4	29.2	31.9	27.0	12.9	16.1	1.17	4.16	5.73
Fraction degraded 16,17-unsaturated dexamethasone and enol aldehydes (%)	1.45	0.16	0.11	0.11	0.08	0.20	0.18	1.34	0.13

(9) **First, the claimed ophthalmic composition has the advantage of achieving less than 1% degradation product in the final ophthalmic composition.**

According to the USP43-NF38 (Monograph 1086: Impurities in drug substances and drug products) all drug products are subject to control of organic impurities such as drug degradation products. A threshold-based approach that is described in the FDA's Guidance for Industry, Q3B(R2) (Impurities in New Drug Products, U.S. Department of Health and Human Services, Food and Drug Administration,

Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), July 2006) is used for the control of degradation products generated during the manufacturing process or storage. The thresholds are listed in Appendix B to the guidelines.

(10) Any degradation product at a level greater than (>) the reporting threshold (see Appendix B) has to be identified and reported with the analytical procedures indicated. If the qualification thresholds given in Appendix B are exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data may be appropriate (see Appendix C).

(11) The maximum daily dose of ophthalmic drugs that are administered as eye drops is generally below 10 mg. Thus, for eye drops, the reporting threshold is 0.1%, the identification thresholds are 0.5% and 1.0% (depending on dose), and the qualification threshold is 1.0%. If a given degradation product exceeds a given qualification threshold, then either: a) extensive toxicological and safety studies have to be performed at substantial time and cost; or b) the level of the degradation product has to be reduced below the qualification threshold (see Appendix C).

(12) Second, at the time of the '954 and '040 Patents and *Tanito*, the dexamethasone enol aldehyde degradation product was unknown to me. At the time of filing the '954 and '040 Patents, I was not aware of the degradation of dexamethasone during the autoclaving process, which produces the dexamethasone enol aldehyde. Such degradation products are not normally observed in aqueous dexamethasone formulations. The '954 and '040 Patents describe academic studies where drug degradation was followed by monitoring the disappearance of the active drug -- dexamethasone. Neither the '954 Patent nor the '040 Patent identifies, or otherwise studies, these degradation products. Furthermore, as described in the '954 and '040 Patents, the active drug and cyclodextrin were mixed together and then heated to generate a high amount (above 1%) of the dexamethasone enol aldehyde by-product. In particular, as described at column 25 of the '040 Patent:

Formulation of the eye drops: a) Cold solution: Aqueous 0.5 and 1.5% (w/v) dexamethasone eye drop solution was prepared by **dissolving 250 or 750 mg of dexamethasone in 45 ml of aqueous solution containing benzalkonium chloride (10 mg), EDTA (50 mg), HPMC (50 mg), NaCl (0 or 360 mg) and RM β CD (2.65 or 9.0 g)** and then filled up to 50 ml. The solution was **heated in an autoclave (Midmark M7 SpeedClave) in sealed containers to 121° C. for 20 min.** The solution was allowed to cool to room temperature (22-23° C.) and equilibrate for 7 days. To prevent drug precipitation during storage 10% excess RM β CD was included in the aqueous eye drop formulation. (Emphasis added.)

(13) This process described in the '040 Patent is similar to Formulation F1 of Example 1 of the subject application. As shown in Table 1 of the subject application, the concentration of 16,17-unsaturated dexamethasone enol aldehyde in Formulation F1 is 1.45%. In comparison, when the process includes separate steps of heating the pharmaceutical excipients to a temperature of 121°C, cooling the resulting mixture, and then adding the dexamethasone (formulations F4 to F6), a significantly lower concentration of less than 1 wt%, and even less than 0.5 wt%, of the dexamethasone enol aldehyde degradation product is produced. The '954 Patent describes a similar autoclaving step after the pharmaceutical excipients are mixed with the dexamethasone. (See *e.g.*, col. 3, ll. 28-52.)

(14) *Tanito* also describes a process where the dexamethasone was mixed with the γ -cyclodextrin *prior to* autoclaving. Table A below includes comparative data for a composition prepared by autoclaving a mixture of γ -cyclodextrin and dexamethasone and a composition prepared using the process described in the subject application, which includes separately autoclaving the γ -cyclodextrin and dexamethasone and mixing these ingredients only after cooling each individual autoclaved component to a temperature below 100°C. As shown in Table A, the concentration of dexamethasone enol aldehyde in the composition described in *Tanito* is 2.8%, which is *seven times higher* than the amount of dexamethasone enol aldehyde in the composition of the subject application, and significantly higher than the presently-claimed amount of less than 1.0% by weight of dexamethasone enol aldehyde based on the weight of the dexamethasone.

TABLE A

Study:		Tanito study	Subject Application
Manufacturing site:		Site 1	Site 2
Dexamethasone	1.50 g	v	v
γ-Cyclodextrin	14.00 g	v	v
Benzalkonium chloride	0.02 g	v	Not included
Disodium edetate	0.10 g	v	v
Poloxamer 407	2.50 g	v	v
Sodium Chloride	0.57 g	v	v
Sodium thiosulfate, 5H ₂ O	0.471 g	Not included	v
Water for injection ad	100 ml	v	V
Container		Glass, multidose	LDPE, single dose
Process		1 pot, 2x15 min at 121°C	2 pots, 1x15 min at 121°C
Dexamethasone enol aldehyde		2.8%	≤ 0.5%
Viscosity		3.0 cP	5-25 cP
Osmolality		253 mOsm/kg	~300
Mean particle diameter		2 and 5 μm	15 μm

(15) This application claims benefit of U.S. Provisional Application No. 62/427,737, which clearly shows that 16,17-unsaturated dexamethasone and the dexamethasone enol aldehydes are only formed when dexamethasone and γ-cyclodextrin are suspended together in aqueous media and then sterilized by heating in an autoclave (for example, heated to 121°C for 20 minutes). (Emphasis added.) In Example 5 and Table 4, the shelf-life of the dexamethasone eye drops is estimated to be over 80 years at 25°C. (See, specification at [000225]-[000226].) Furthermore, it is shown that in the eye drops at 25°C, it takes 4.0 years for dexamethasone to degrade from 100% to 99.5%. Based on Example 5, it can be

calculated that much less than 0.1% degradation product will be observed during storage for 7 months at 22-23°C.

(16) In paragraph [000227], the effect of temperature on the rate of formation of 16,17-unsaturated dexamethasone and the enol aldehydes is explained and it is concluded that “In general, values of E_a [the energy of activation] range from about 50 to 85 kJ/mol and values greater than 100 kJ/mol are very uncommon. The apparent value of E_a for dehydration of dexamethasone in aqueous γ -cyclodextrin solution to form 16,17-unsaturated dexamethasone and the dexamethasone enol aldehydes is 134.5 kJ/mol and, thus, 16,17-unsaturated dexamethasone and the dexamethasone enol aldehydes are only formed in aqueous γ -cyclodextrin solutions at exceptionally high temperatures.” In other words, and as indicated above, 16,17-unsaturated dexamethasone and the dexamethasone enol aldehydes are only formed when dexamethasone and γ -cyclodextrin are suspended together in aqueous media and then sterilized by heating in an autoclave (i.e., heated to 121°C for 20 minutes). (Emphasis added.)

(17) As noted above, these degradation products were certainly not known to me at the time of *Tanito* and the '954 and '040 Patents. Additionally, the degradation products formed under these specific conditions, that is the dexamethasone enol aldehydes were not universally known at the time, and are, therefore, not listed in USP43-NF38 (Dexamethasone Ophthalmic Suspension), and European Pharmacopoeia 10.0 (e.g., 0388E Dexamethasone). That is, I was not aware of these degradation products until this invention, and the dexamethasone enol aldehydes also cannot be considered as either disclosed or described in any of *Tanito* and the '954 and '040 Patents, for arriving at an ophthalmic composition, as claimed, wherein the weight of dexamethasone enol aldehyde based on the weight of the dexamethasone is advantageously reduced to an amount of less than 1% by weight.

(18) For at least the above reasons, it is my expert opinion that the claimed ophthalmic composition comprising, *inter alia*, “less than 1% by weight of dexamethasone enol aldehyde based on the weight of the dexamethasone” is nonobvious over *Tanito* and the '954 and '040 Patents. As discussed above, the specific by-products and degradation product (of this application) resulting from sterilization of the ophthalmic composition was totally unknown to me at the time of *Tanito* and the '954 and '040 Patents. Therefore, the instant-claims are distinguished and patentable over *Tanito* and the '954 and '040 Patents, because none of these references identify these degradation products or any ophthalmic composition wherein their concentration is reduced to less than 1% by weight.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.