USP Excipient Stakeholder Forum, September 29th 2016

Chinese Manufacturer's Perspective on Excipient Monograph Specifications for Polysorbate 80 used for Injection

Design of the polysorbate 80 for injection

南京威尔化工有限公司

Nanjing Well Chemical Co.,Ltd

Ya Wang

About Well Chemical

01

Specialized manufacturer of pharmaceutical excipients in China.

02

All the excipients of Well Chemical have been approved by CFDA.

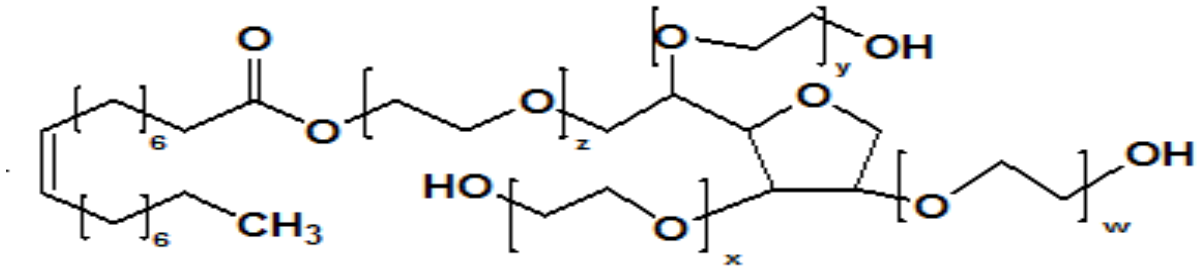
03

For polysorbate 80, we have pharma grade and for injection grade.

Introduction of Polysorbate 80

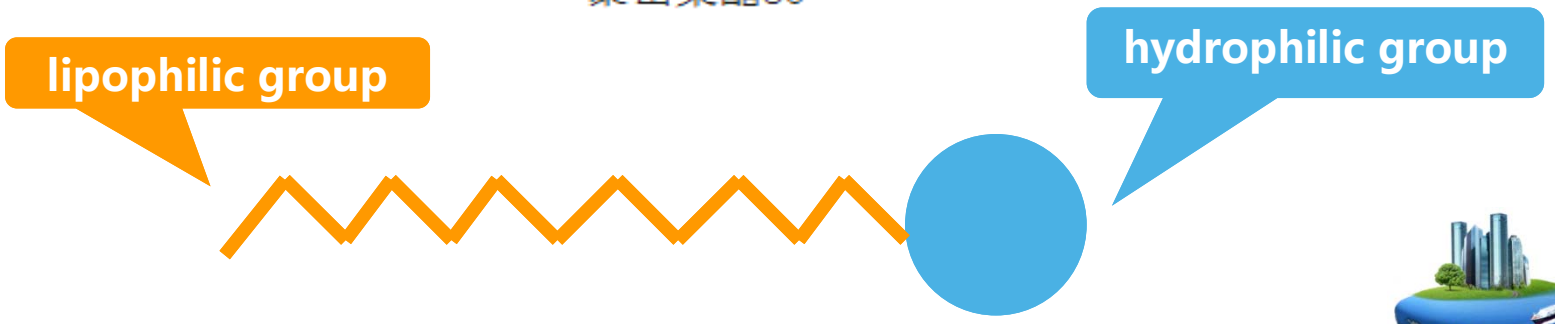
Definition：Polysorbate 80 is a mixture of partial esters of fatty acids,mainly oleic acid, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.（USP-39, NF34）

Structure:



W+X+Y+Z=20

聚山梨酯80



Introduction of Polysorbate 80

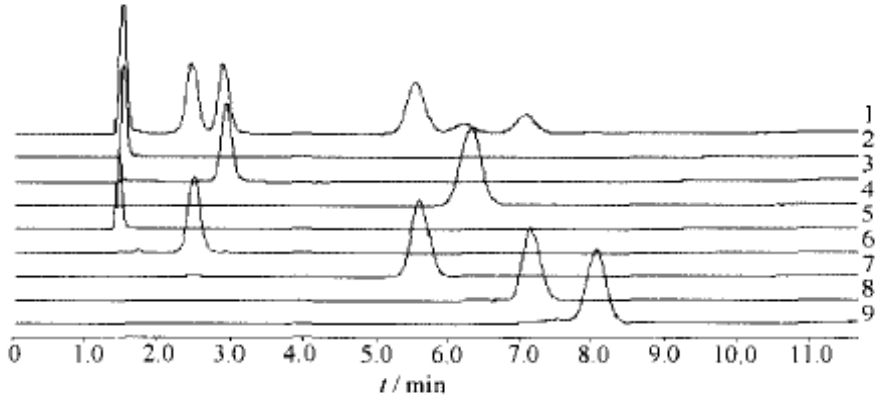


图 1 聚山梨酯 80 8 类化学组分的高效液相色谱图

1 – 聚山梨酯 80 样品(Well 20080412);2 – 聚氧乙烯(12)异山梨醇;3 – 聚氧乙烯(12)异山梨醇一油酸酯;4 – 聚氧乙烯(12)异山梨醇二油酸酯;5 – 聚氧乙烯(24)山梨醇酐;6 – 聚氧乙烯(24)山梨醇酐一油酸酯;7 – 聚氧乙烯(24)山梨醇酐二油酸酯; 8 – 聚氧乙烯(24)山梨醇酐三油酸酯;9 – 聚氧乙烯(24)山梨醇酐四油酸酯

Fig. 1 HPLC Chromatograms of eight chemical compositions of polysorbate 80

1 – polysorbate 80 sample(Well 20080412); 2 – polyoxyethylene (12) isosorbide (PI); 3 – polyoxyethylene (12) isosorbide monooleate(PIM); 4 – polyoxyethylene (12) isosorbide dioleate (PID); 5 – polyoxyethylene (24) sorbitan (PS); 6 – polyoxyethylene (24) sorbitan monooleate(PSM); 7 – polyoxyethylene (24) sorbitan dioleate (PSD); 8 – polyoxyethylene (24) sorbitan trioleate (PSTri); 9 – polyoxyethylene (24) sorbitan tetraoleate(PSTetra)

Actual composition:

polysorbate 80
polyoxyethylene(12)isosorbide
polyoxyethylene(12)isosorbide monooleate
polyoxyethylene(12)isosorbide dioleate
polyoxyethylene(24)sorbitan
polyoxyethylene(24)sorbitan monooleate
polyoxyethylene(24) sorbitan dioleate
polyoxyethylene(24)sorbitan trioleate
polyoxyethylene(24)sorbitan tetraoleate
and so on……

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Chin Pharm J, 2013 May, Vol. 48 No. 9

Introduction of Polysorbate 80

Widely used in many formulations;

Solubilizer-injection, oral solution, topical lotions

Emulsifier-ointment, cream, gel

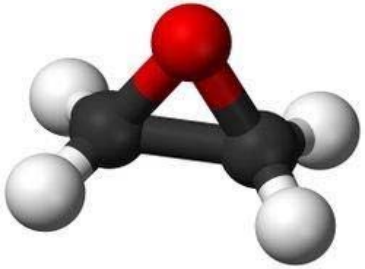
Dispersing agent-biological product

Introduction of Polysorbate 80

Polysorbate 80 is added as solubilizer in dozens of injections and the proportion ranges from 0.1% to 50%;

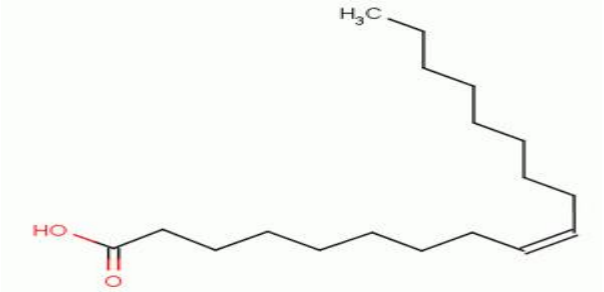
Typical formulation		
EPO injection	Vitamin k1 injection	Docetaxel injection
Vitamin supplements	Monoclonal antibody	Isosorbide Dinitrate for injection
Triamcinolone acetonide injection	Amiodarone hydrochloride injection	Traditional Chinese injections

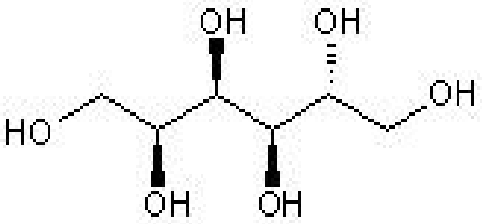
The raw materials of polysorbate 80



Ethylene Oxide (EO)

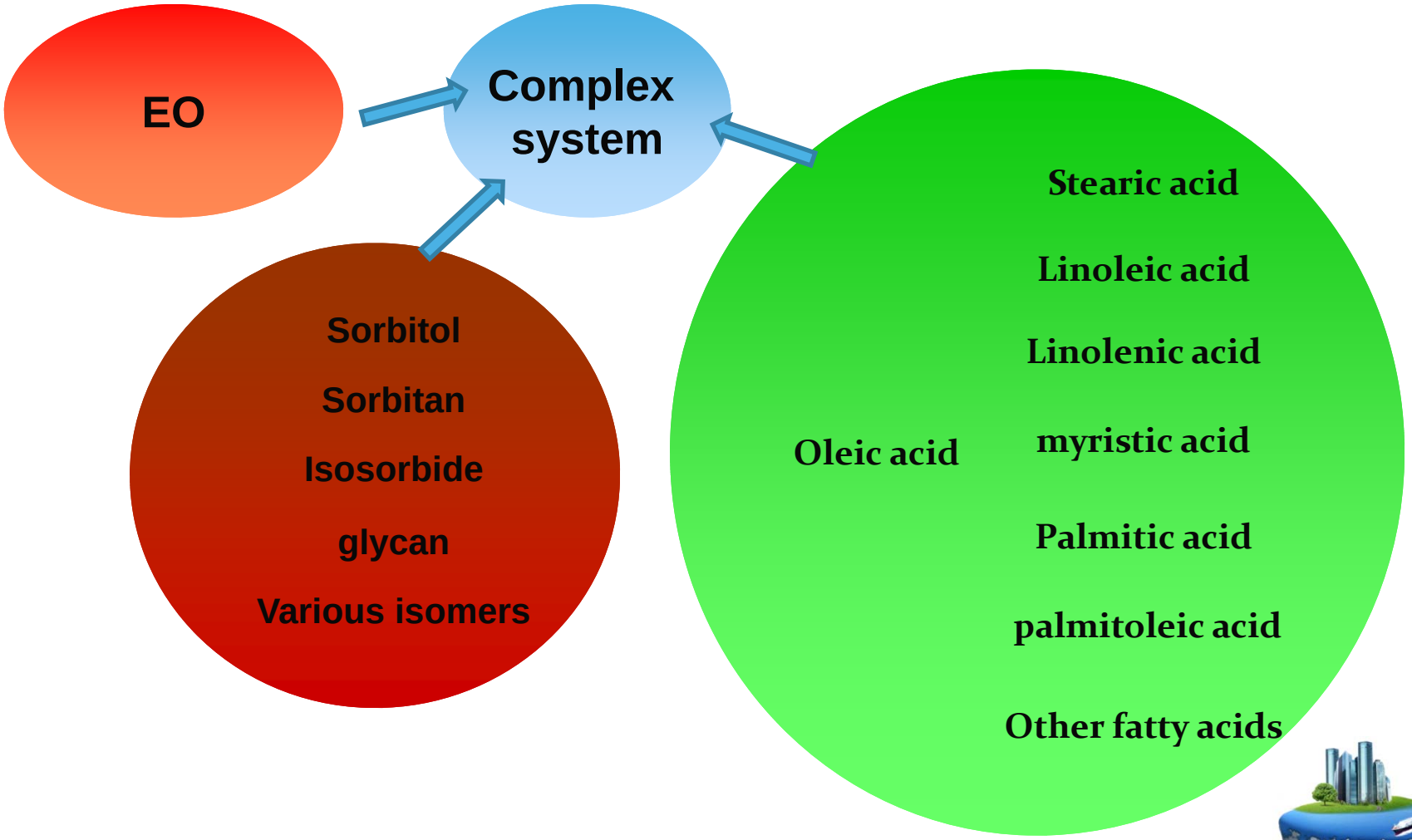
Oleic Acid



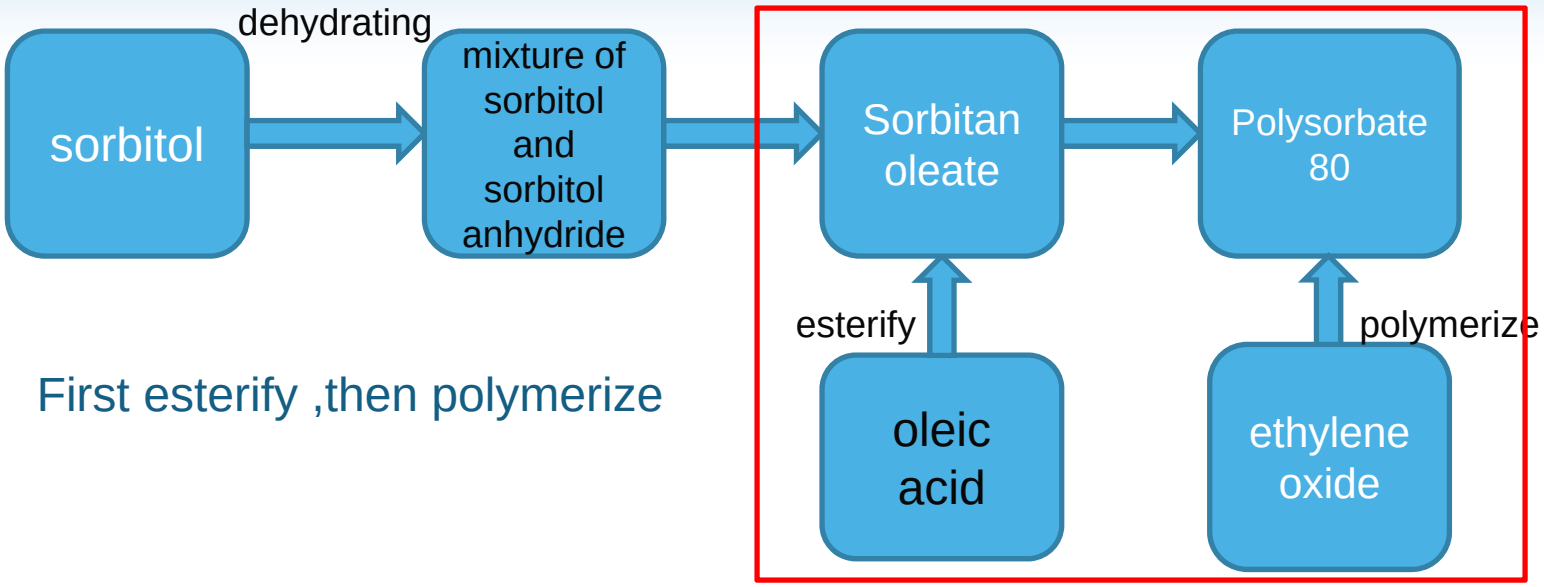


Sorbitol

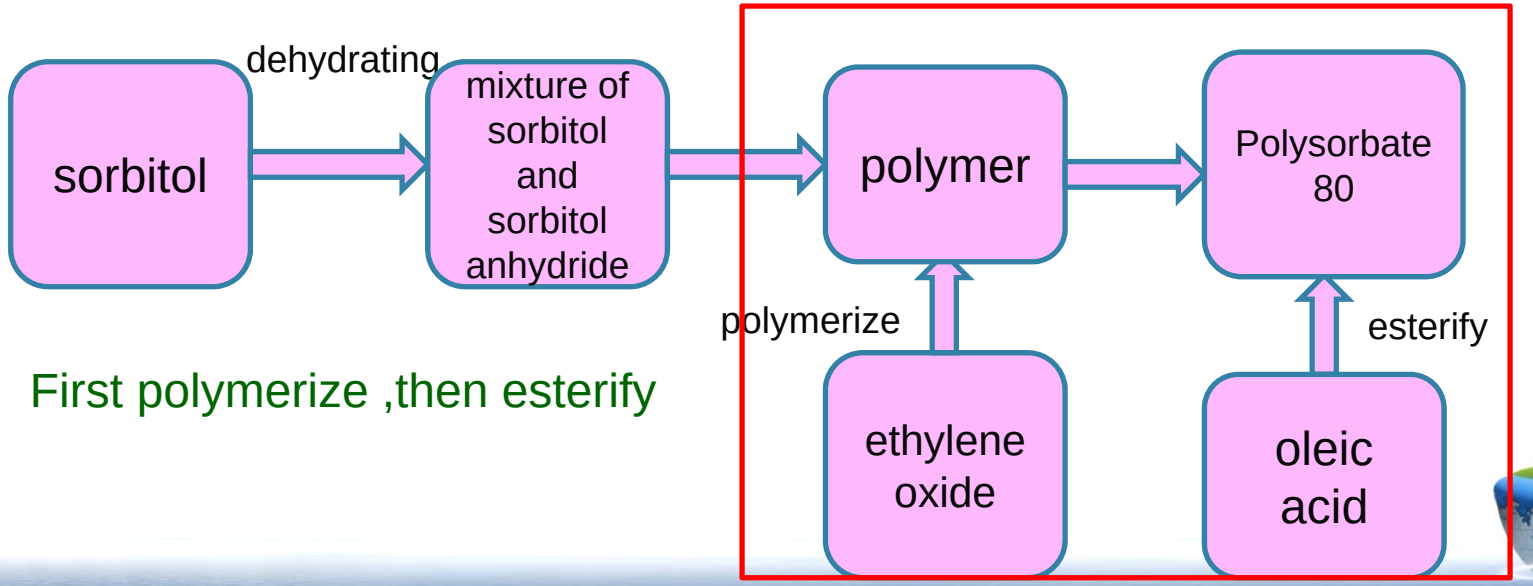
The composition of polysorbate 80:



Two synthetic routes



First esterify ,then polymerize



First polymerize ,then esterify

Two synthetic routes

1:First esterify ,then polymerize

(1) After dehydrating partly, sorbitol becomes the mixture of sorbitol and sorbitol anhydride, then esterify with oleic acid to produce sorbitan oleate(span80).

(2) Sorbitan oleate polymerize with about 20 mol ethylene oxide and produce Polysorbate 80 .

Current problems:

(1)The source and purity of oleic acid have not been controlled.The purity of oleic acid is about 70% generally, the source has still not been determined.

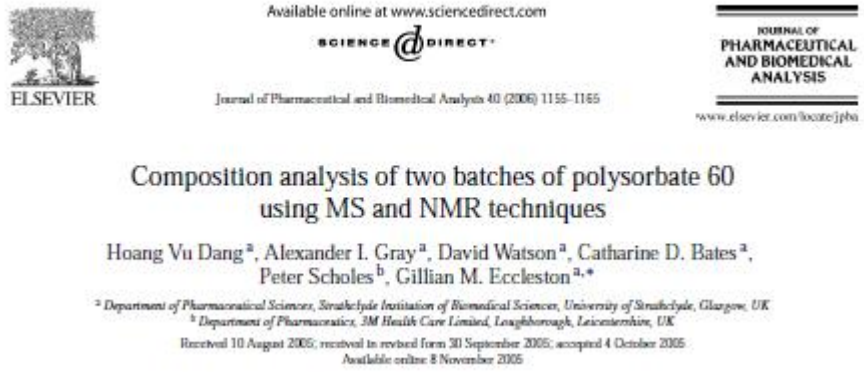
(2) Sorbitan oleate keeps dehydrating incessantly in the stage of polymerization , which results in uncontrollable manufactruring procedure, many by-products and poor Inter batch stability.

Two synthetic routes

2:First polymerize ,then esterify

Ethylene oxide react prior with sorbitol and sorbitol anhydride and occupy hydroxyl group site, which aviod the uncontrollable incessant dehydration in the stage of polymerization between sorbitol and sorbitol anhydride in the former route.

Reference



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JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS

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Composition analysis of two batches of polysorbate 60 using MS and NMR techniques

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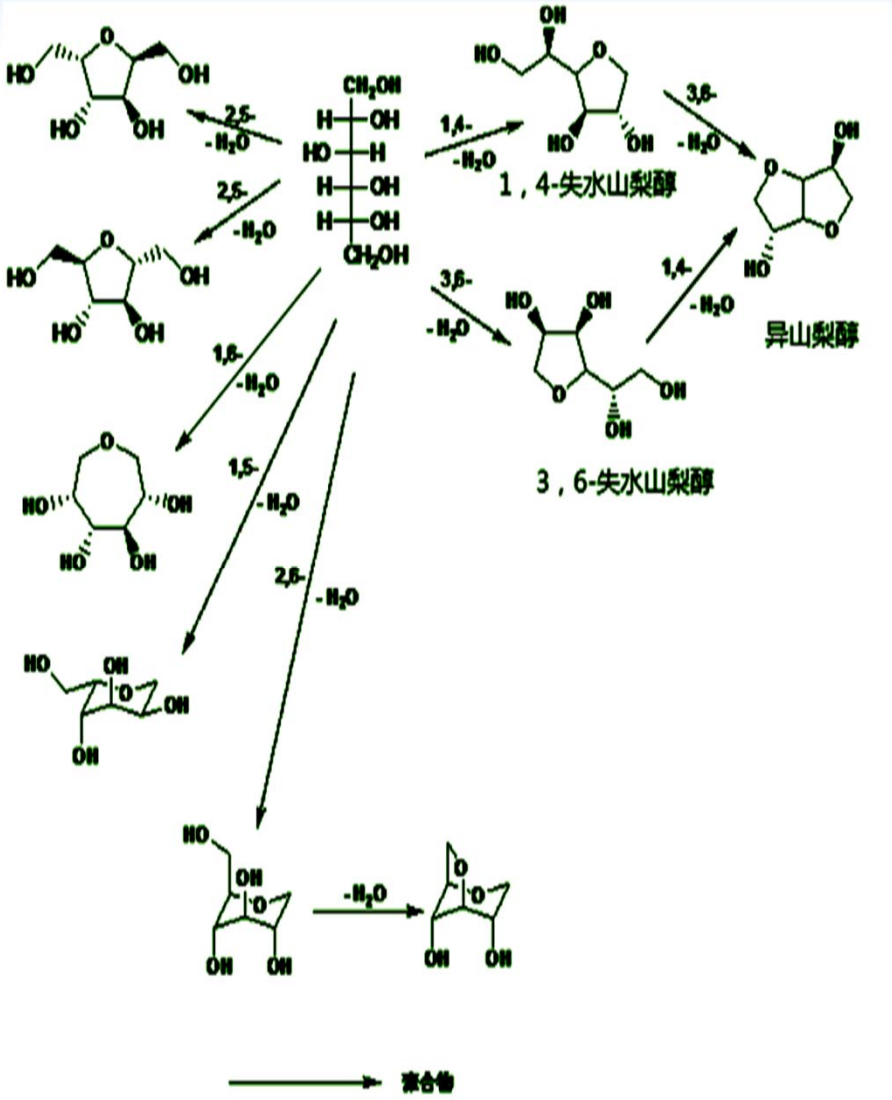
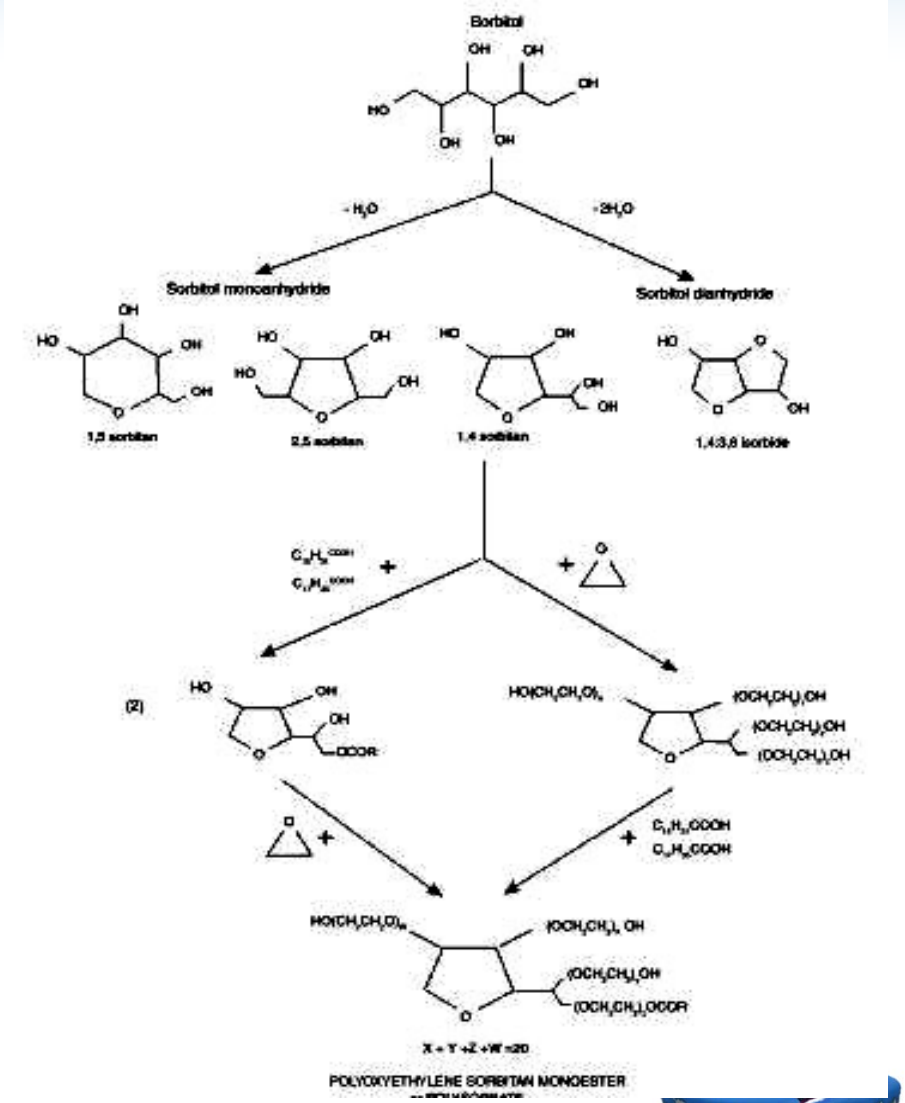
Received 10 August 2005; received in revised form 30 September 2005; accepted 4 October 2005
Available online 8 November 2005

Dehydration reaction of sorbitol



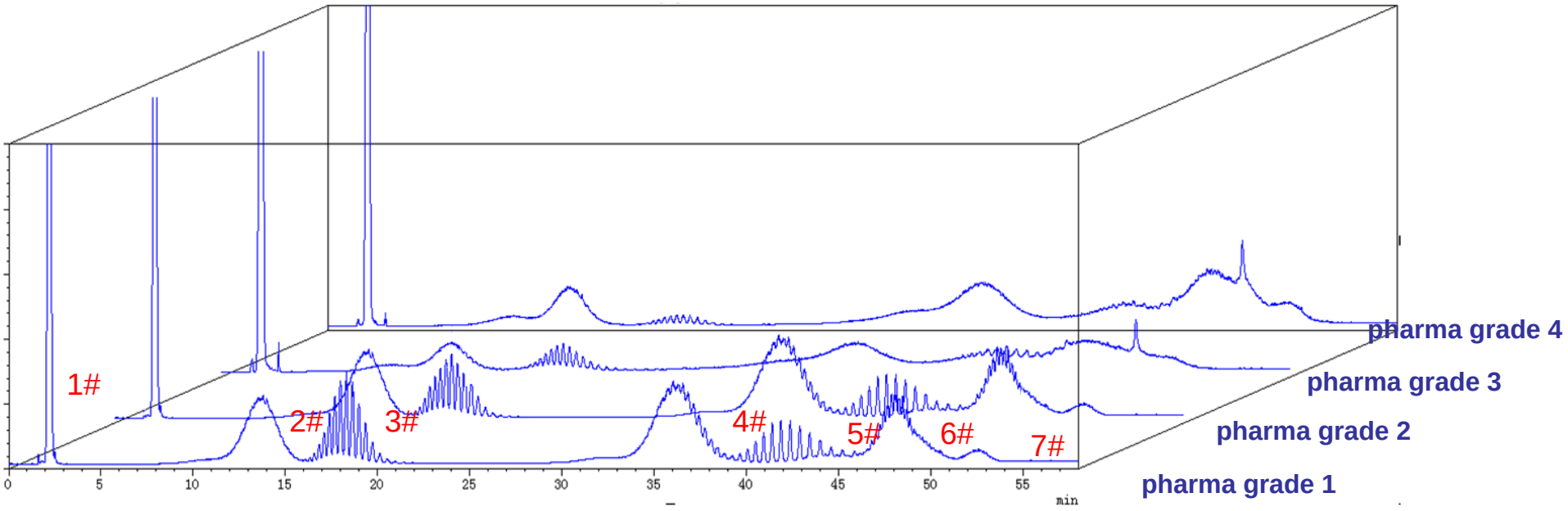
Two synthetic routes



Current status of Polysorbate 80

We carried out the test using HPLC-ELSD to analysis the internal composition of polysorbate 80 and found products from different manufacturers are various.

HPLC-ELSD



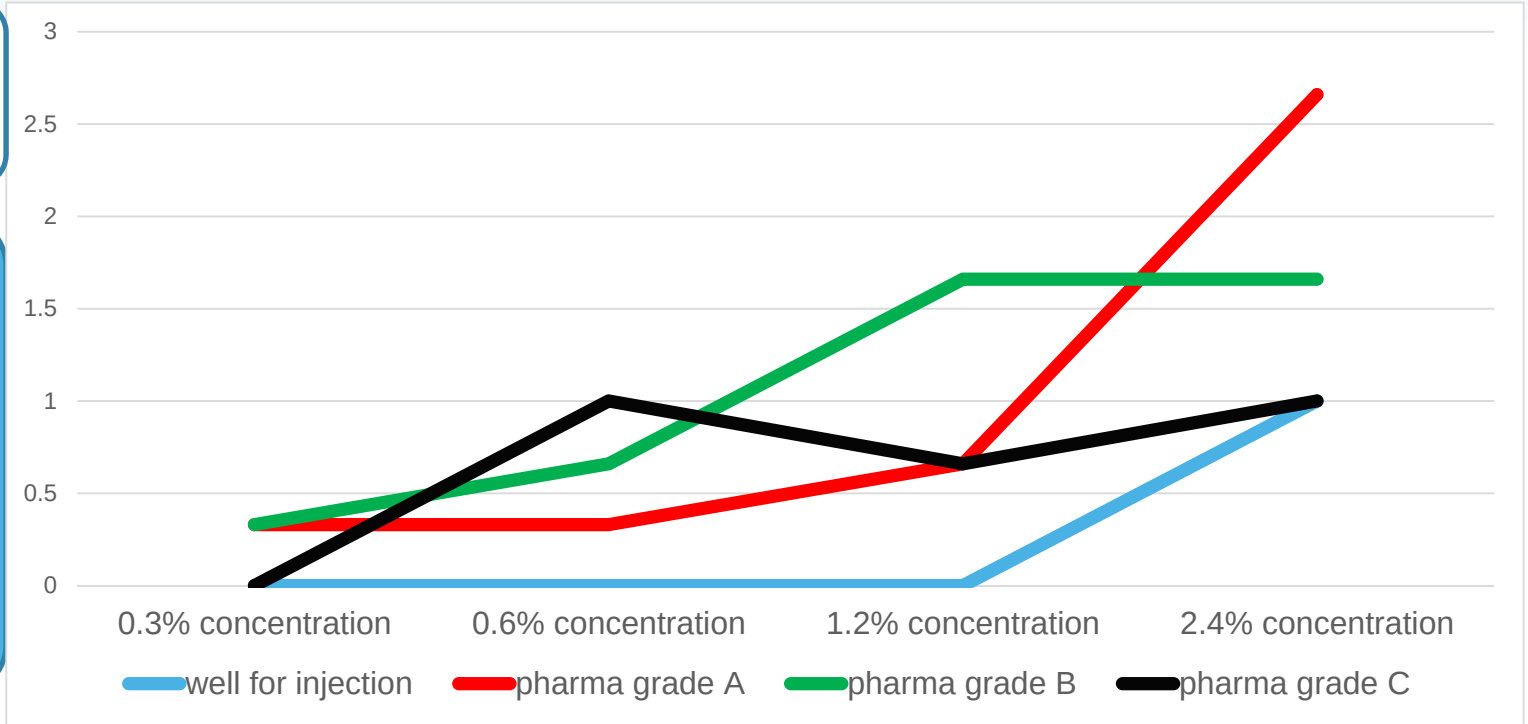
Result of four manufacturers

Safty comparison of polysorbate 80 from different sources

scale

The degree of allergic reactions

test animal: guinea pig



scale	phenomenon
0	No obvious reaction
1	catching nose slightly，trembling or pilo-erection
2	cough ,nose-catching frequently,trembling or pilo-erection,ear vasodilation,etc.
3	high-frequency or continuous cough, complicated by difficulty in breathing or spasms, convulsions
4	spasm, tic,gatism,shock and death

Current status of Polysorbate 80

The differences in compositions and safety of Polysorbate 80 from different sources induce the diparaties in the application.

According to the reference, Docetaxel injection’s abnormal phenomenon was induced by the quality of polysorbate 80, whose fatty acid composition and solidifying point are the crucial standards.

聚山梨酯80致多西紫杉醇注射液异常现象的初步分析

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【摘要】**目的**:确定引起多西紫杉醇注射液异常现象的原因,并给予建议。**方法**:综合分析原辅料、生产工艺、储藏等因素,找出主要影响因素,并通过实验明确关键指标以及其限度。**结果**:与聚山梨酯80质量及凝点密切相关的脂肪酸是油酸和棕榈油酸,油酸含量越高、棕榈油酸含量越低,聚山梨酯80的质量越好,凝点越低。**结论**:多西紫杉醇注射液异常现象为辅料聚山梨酯80质量所致,关键指标为聚山梨酯80的脂肪酸组成及凝点,建议限度分别为油酸含量≥80%,棕榈油酸含量≤0.1%,凝点≤-5℃

The concept of our design:

- The intrinsic composition of polysorbate 80 is complex. It consists of many substances of the same character.
- We can not separate them by purification reaction after synthetic process.
- We start from the preprocessing of raw materials and try our best to reduce the content of impurities.
- It is our aim that to acquire higher stability and safety.

Features of manufacture procedure of polysorbate 80 for injection

(1) Purification of the raw materials

Purify the Oleic acid and make the content of Oleic acid not less than 98%;
The Oleic acid must be plant source;
Purify the Sorbitol & Sorbitan and fix their reaction proportion;

(2) Process route (First polymerize ,then esterify)

Ethylene oxide react prior with sorbitol and sorbitol anhydride and occupy hydroxyl group site, which aviod the uncontrollable incessant dehydration in the stage of polymerization between sorbitol and sorbitol anhydride in the former manufacturing procedure.

(3) Production control

High efficient esterification technology and narrow molecular distribution technology of ethoxylation.

Comparison of specifications of polysorbate 80

Test item	USP 39, NF 34	JP 16	EP 8.0	Well spec & CHP 2015 polysorbate 80 for injection
peroxide value	max 10	max 10	max 10	max 2
UV absorption	-	-	-	≦1.0（225nm）≦0.1（267nm）
viscosity	300 - 500 cSt	345 - 445 mm^2/s	about 400 mPa·s	350 - 450 mm^2/s
Water content	≦3.0%	≦3.0%	≦3.0%	≦0.5%
acid value	≦2.0%	≦2.0%	≦2.0%	≦1.0%
colour	-	-	-	lighter than yellow #2
ethylene glycol diethylene glycol Triethylene glycol	-	-	-	max 100ppm max 100ppm max 100ppm
Fatty Acid Composition	oleic acid≧58%	oleic acid≧58%	oleic acid≧58%	oleic acid≧98% other acid ≦0.5%
Bacterial endotoxin	-	-	-	≦12EU/g
sterile	-	-	-	common test method in CHP 2015

Purpose on setting up or modifying these tests

Peroxide value: no more than 2

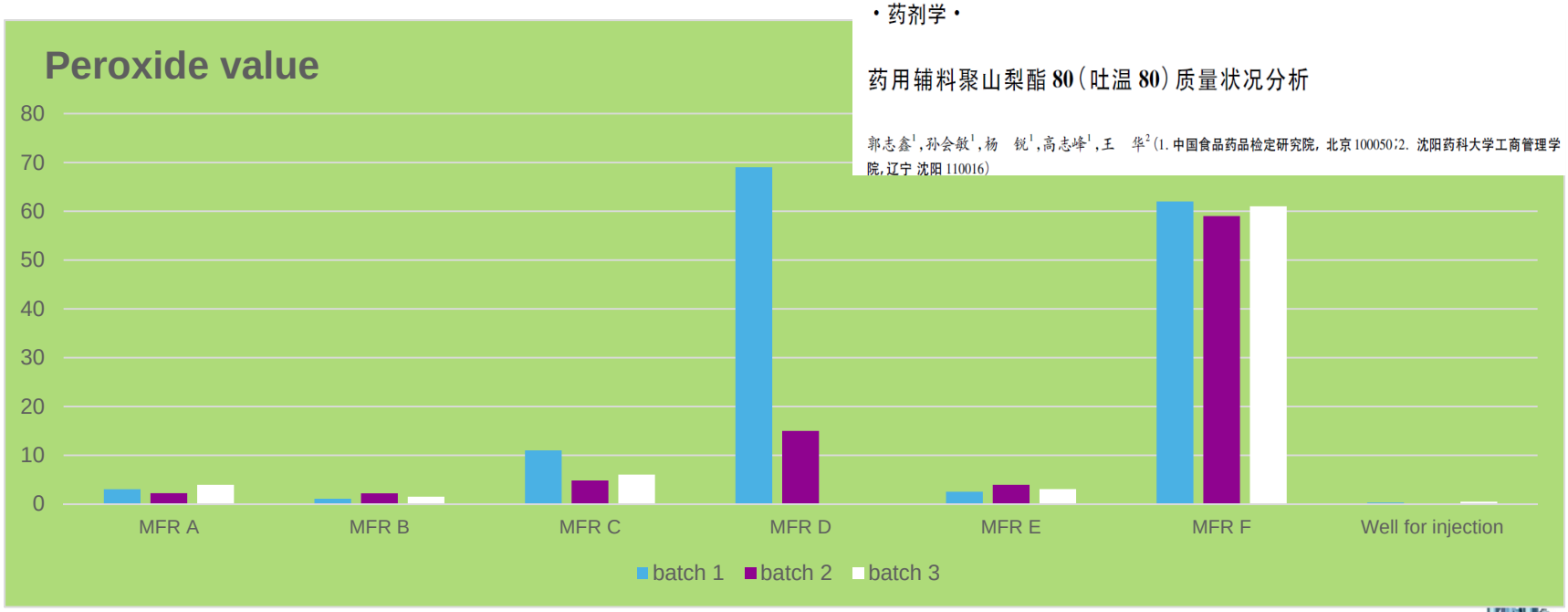
The peroxide value has a negative correlation with the stability of the formulations. High peroxide value will lead to the decrease of stability and the raise of related substances during the storage, especially some protein-drugs. It should be lowered as much as possible.

药学实践杂志 2012 年 11 月 25 日第 30 卷第 6 期
Journal of Pharmaceutical Practice, Vol. 30, No. 6, November 25, 2012 459

·药剂学·

药用辅料聚山梨酯 80（吐温 80）质量状况分析

郭志鑫[1]，孙会敏[1]，杨 锐[1]，高志峰[1]，王 华[2]（1. 中国食品药品检定研究院，北京 100050；2. 沈阳药科大学工商管理学院，辽宁 沈阳 110016）



All the test result were provided by National institutes food and drug control center of China.

Purpose on setting up or modifying these tests

Central South Pharmacy. October 2014, Vol. 12 No.10 中南药学 2014 年 10 月 第 12 卷 第 10 期

聚山梨酯 **80** 对尼莫地平注射剂安全性的影响

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表 **4** 尼莫地平在不同来源聚山梨酯 **80** 中的光照试验

Tab 4 Light test of nimodipine in different sources of polysorbate 80

聚山梨酯 80 生产企业（source of polysorbate 80）	过氧化值（peroxidation value）	12 h 光照杂质 Ⅰ 含量（amount of impurity Ⅰ over 12 h light test）/%
TA	9.51	9.13
TB	2.15	4.16
TC	1.69	4.11
TD	1.22	3.05
空白对照	0.00	1.87

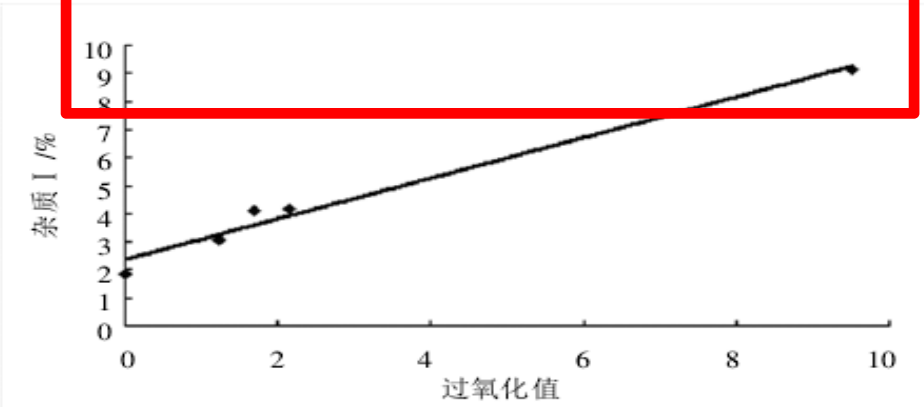


图 5 过氧化值与杂质 Ⅰ 线性关系

Fig 5 Linearity between the peroxidation value and impurity Ⅰ

High peroxide value will lead to the increase of impurity I in nimodipine injection.

Purpose on setting up or modifying these tests

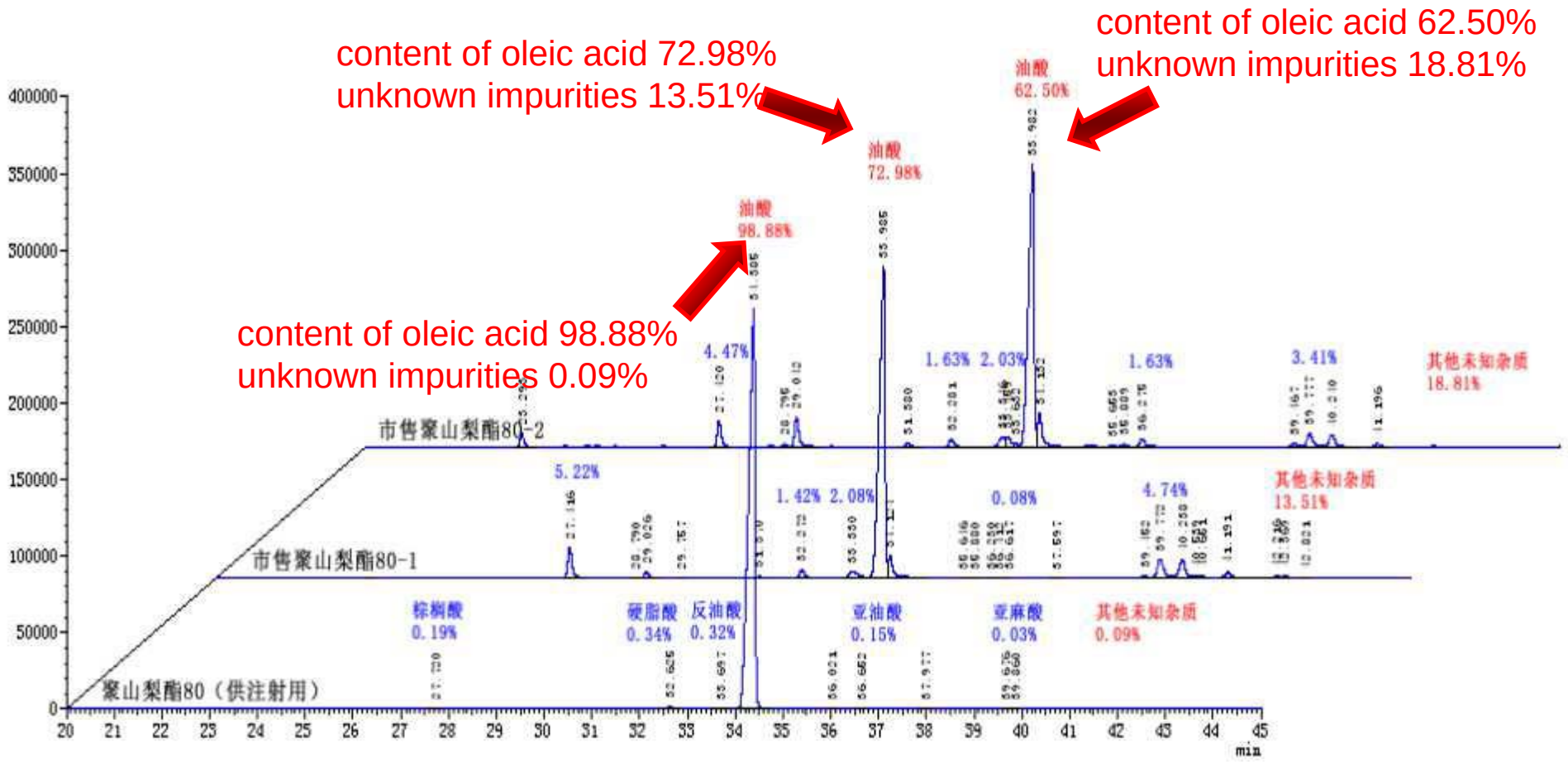
Composition of fatty acid : oleic acid ≧98%, other individual fatty acid ≦0.5%

Ensure product reproducibility and decrease other fatty acid and unknown impurities to the minimum.

Strict restriction on the fatty acid of high freezing point (stearic acid and palmitic acid) , which is not suitable for injection

The composition of fatty acid has influences on the other attributions: colour, viscosity, freezing test, peroxide value and solubility

Purpose on setting up or modifying these tests



The higher the purity of oleic acid is, the less the unknown impurities exist.

Purpose on setting up or modifying these tests

Absorbance: ≦1.0（225nm）≦0.1（267nm）

To control the content of the “C=C” and “C=O” in peroxy radical, organic peroxide acid and other fatty acid.

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JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS

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Polysorbate 80 UV/vis spectral and chromatographic characteristics – defining boundary conditions for use of the surfactant in dissolution analysis

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Received 22 September 2005; received in revised form 4 January 2006; accepted 10 January 2006
Available online 6 March 2006

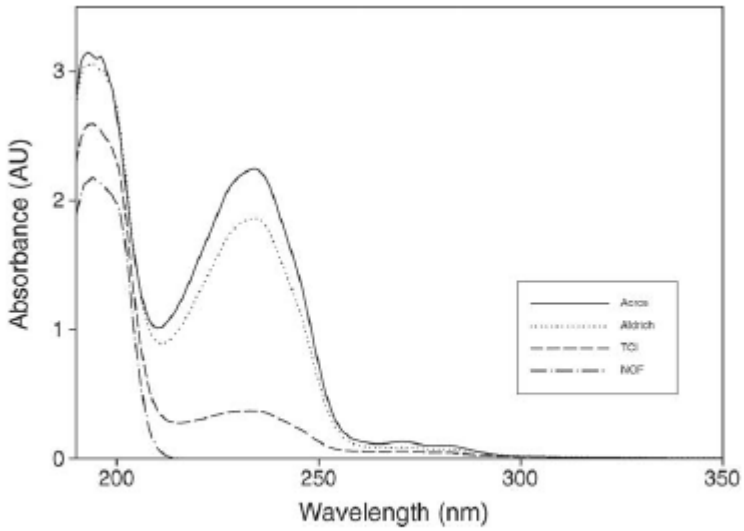


Fig. 4. UV/vis spectra of four commercially available Polysorbate 80 brands (0.1%, w/w solution).

Purpose on setting up or modifying these tests

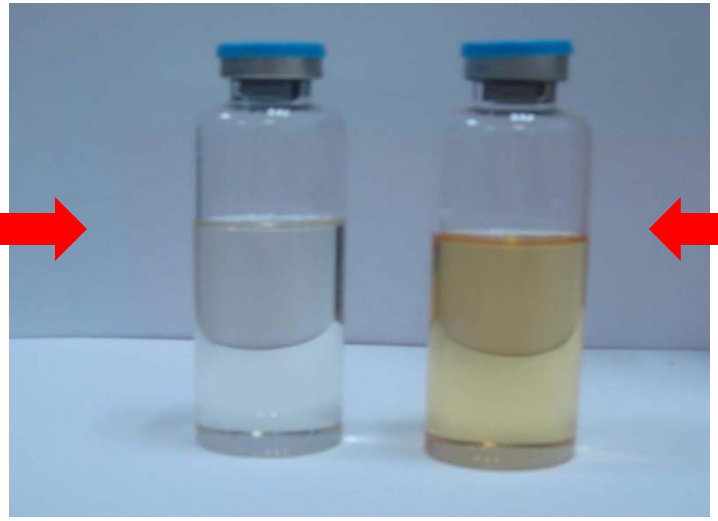
Colour: lighter than yellow #2 (common test method in CHP 2015)

Polyosrbate 80 is colourless come from raw materials with high purity.

Conjugated double bond and unsaturated carbonyl-compound are impurities,which come out in the extremely high temperature and will make product darker.

The product will become darker when there are too much glycan, for glycan will be carbonized in the esterification.

polysorbate 80
for injection



polysorbate 80
pharma grade

Purpose on setting up or modifying these tests

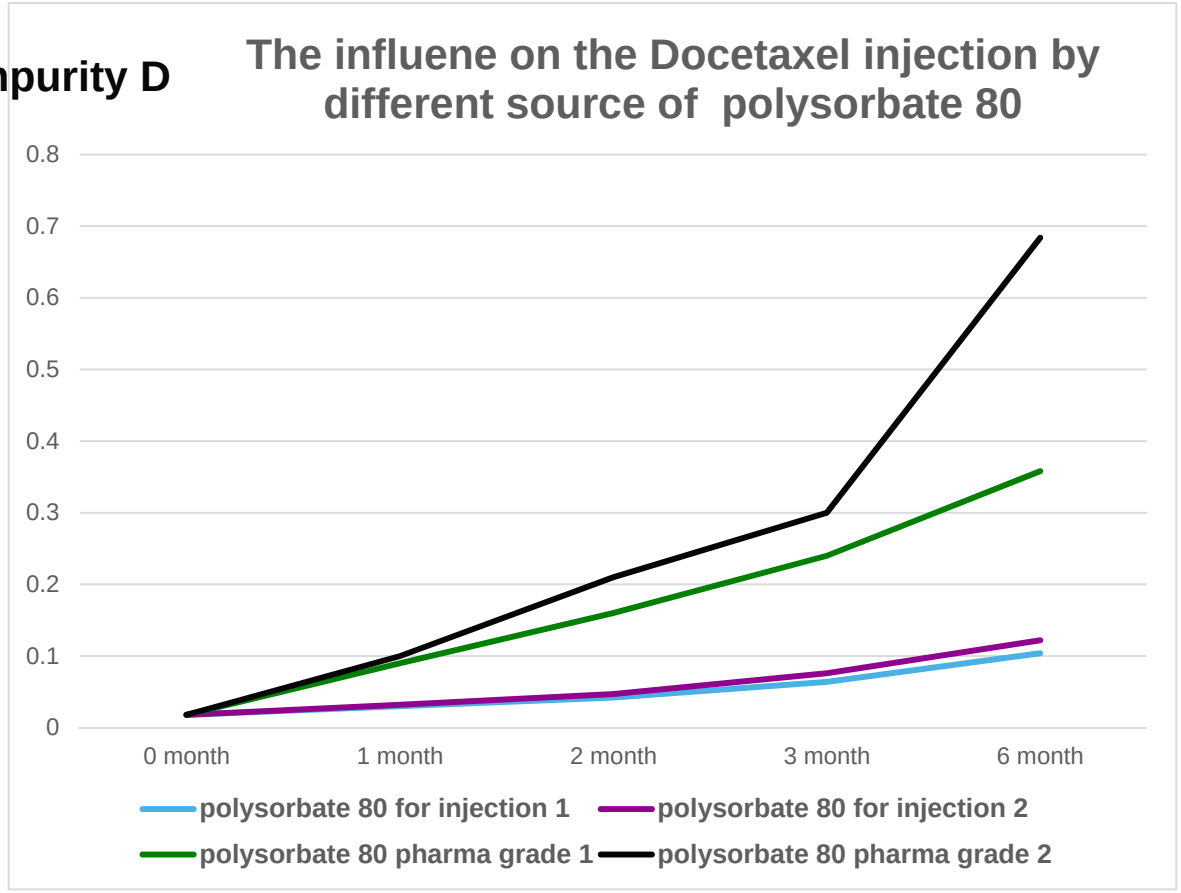
Acid value ≦1.0%	**Improve the stability and application performance**	**Ethylene glycol** ≦100 ppm	**Ensure the safety**
		Diglycol ≦100 ppm	
Water content ≦0.5%		**Triethylene glycol** ≦100 ppm	
		Ehylene oxide ≦1ppm	
Freezing test		**Dioxane** ≦5ppm	
		Bacterial endotoxin 〈12EU/g	
		Sterility	

Features of polysorbate 80 for injection

- Extremely low peroxide value
- Ultra-high purity(>98%)
- Improve the stability of drug formulation
- Hypoallergenic
- Excellent producibility between batches

The influene on the preparation by different source of polysorbate 80

1. Docetaxel injection

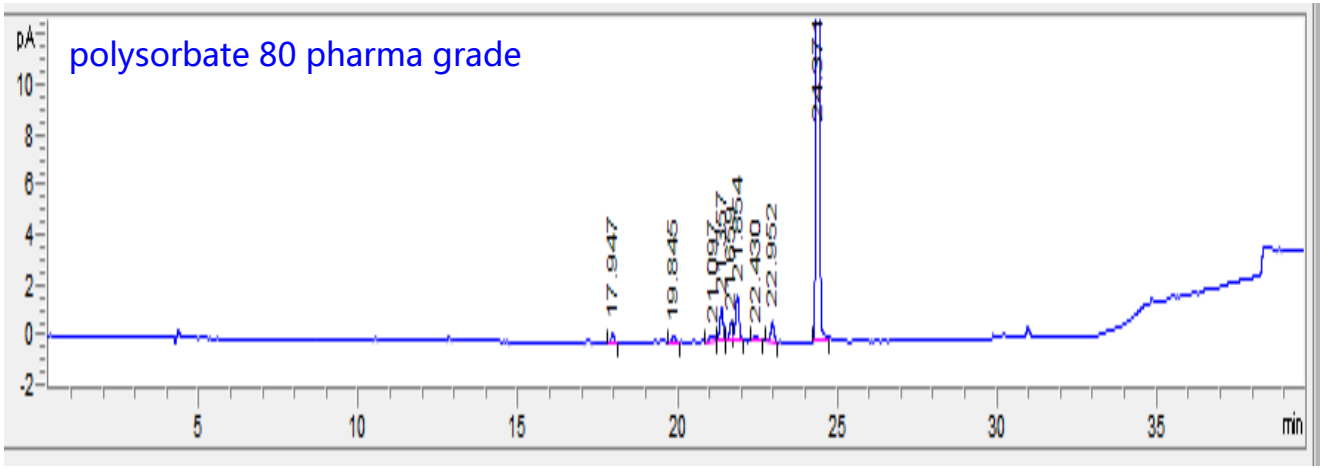


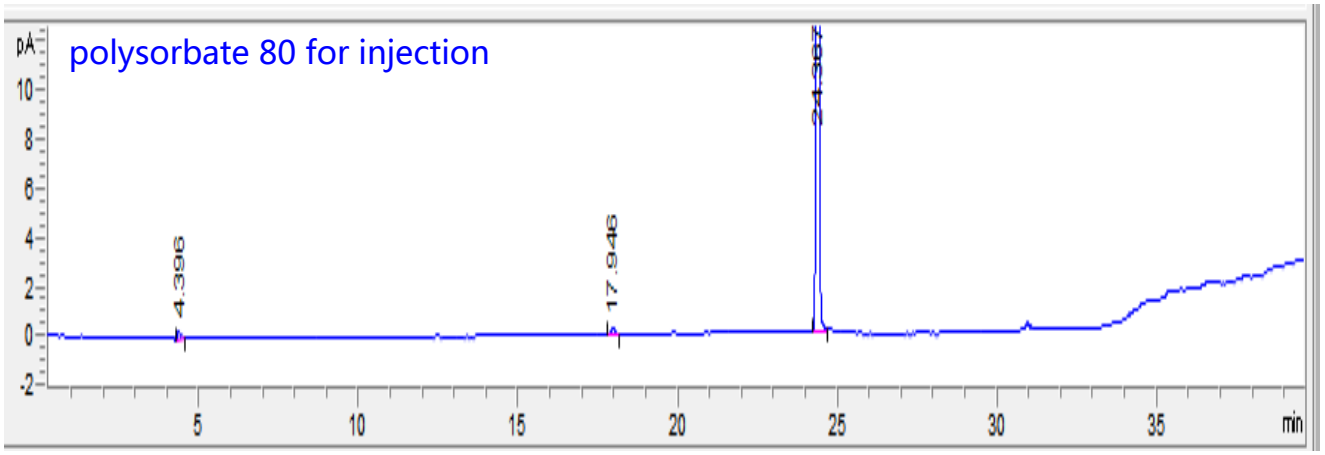
According to stability test, Polysorbate 80 may increase the impurity D in accelerated testing , nevertheless , Polysorbate 80 for injection could reduce the impurity D apparently.

（accelerated testing）

The influene on the preparation by different source of polysorbate 80

2.Vitamin k1 injection





The comparison of volatile constituents in Vitamin k1 injections made of different Polysorbate 80s shows that the polysorbate 80 for injection decrease volatile constiuents remarkably.

Conclusion and Suggestion

01 **Injections are very important to the treament of the patients.**

02 **The criteria compiling of the phamocopoeia should pay more attention for the essential attributes of the product as much as possible.**

03 **The specific items of injections should be added on the basis of the general pharmacopoeia as criteria of excipients of injections.**

THANK YOU !