

POSITION PAPER ON CELOX SAFETY

Purpose:

To contrast the safety data of a chitosan based hemostatic product (CELOX) with clay based hemostatic products.

CELOX: A hemostatic product composed of chitosan flakes (a polysaccharide derivative).

Clay based hemostatic products: Aluminum Silicate (smectite¹ or kaolin nanoparticles²).

Summary:

The safety of CELOX has been repeatedly demonstrated. Unlike some clay based hemostatic products:

- CELOX does not initiate thrombogenesis at a distance from the product.
- CELOX has a long history of safe human use.
- CELOX demonstrates natural degradation pathways in the human body.
- CELOX is not a clay nanoparticle.
- CELOX has undergone rigorous Class III regulatory scrutiny.

1) Thrombogenic activity – CELOX

a. Pseudo-Clot:

Cationic chitosan interacts directly with negatively charged thrombocytes (platelets) and erythrocytes (red blood cells), and rapidly absorbs fluids.³⁻⁴ This dual mechanism forms a cross-linked pseudo-thrombus (pseudo-clot), which adheres to tissue and plugs the bleeding site.

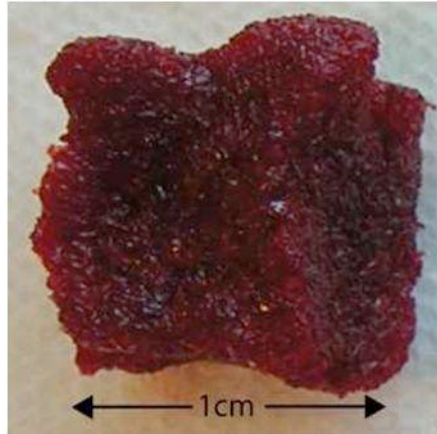


Figure 1: CELOX flakes gelled with fresh rabbit blood.

b. No Distal Clot Formation:

CELOX does not initiate the normal clotting cascade. Therefore, CELOX does NOT initiate a thrombogenic response which would result in clots being formed at a distance to the product.

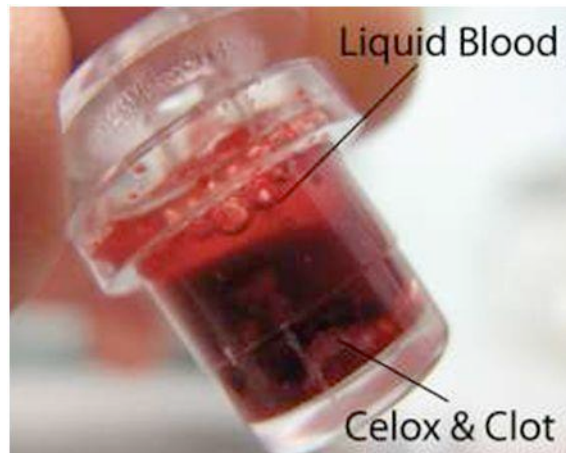


Figure 2: Non-coagulated blood surrounding CELOX/Blood pseudo-clot.

2) Thrombogenic activity – Clay based hemostatic products

a. Clot activator:

Clay is known as an activator of the contact (intrinsic) coagulation activation pathway. Clays initiate the clotting cascade through activation of Factor XII.⁵

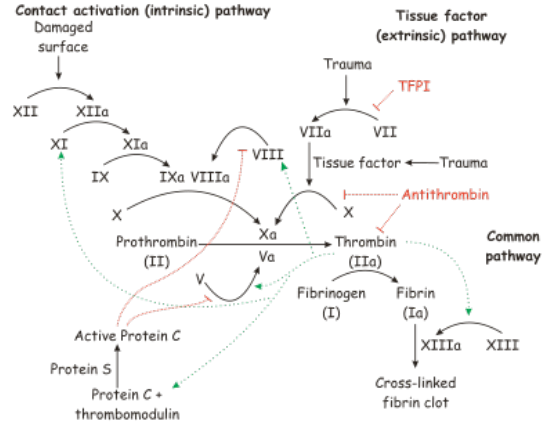


Figure 3: Intrinsic and Extrinsic coagulation pathways.

b. Distal Clot Formation:

Thromboelastograph (TEG) studies reveal that a very small amount of clay based product (<.5%) placed in blood dramatically accelerates thrombogenesis.¹ This demonstrates the propensity of clay based hemostatic products to form a clot at a distance to the product. In contrast, CELOX did not accelerate thrombogenesis (same clotting time as untreated blood).

TEG analysis of blood mixed with agents

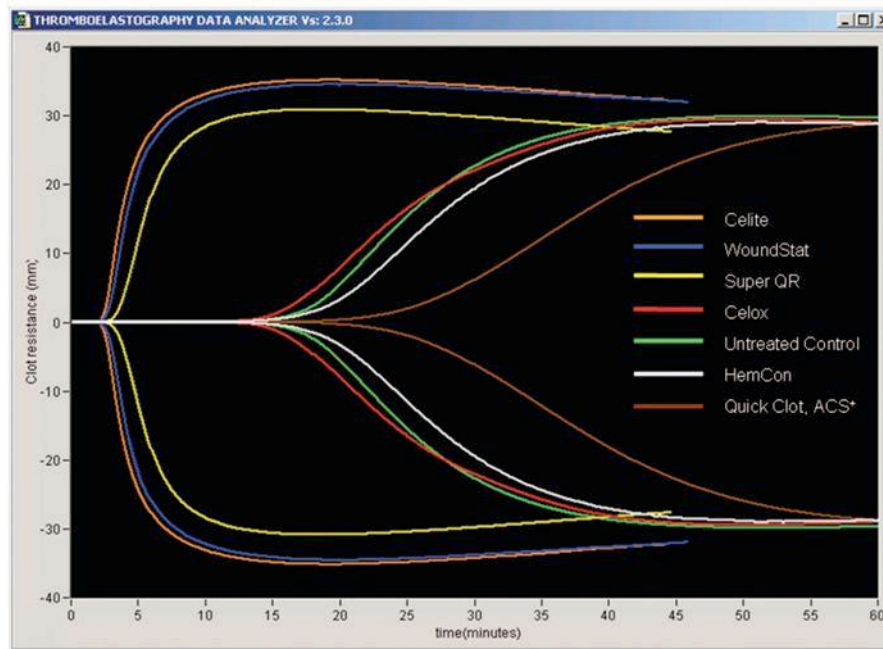


Figure 4: Average thrombograms of pig blood after treatment with different hemostatic agents.

3) Human Use History – CELOX

a. Trauma Use:

CELOX has a 3 year history (since 2006) of use in emergency, military, and retail first aid with no reported problems.

b. Surgical use:

CELOX has a history of successful use in human cardiac surgery with no reported adverse events. Surgical use of CELOX has been documented in peer reviewed and published case study reports.⁶

c. Human allergy trials:

The chitosan in CELOX has been tested on 221 human subjects with suspected hypersensitivity. None of the subjects showed any skin reaction to the chitosan. Eleven of the subjects gave a positive reaction in a standard fish/shrimp prick test but did not react to chitosan.

d. Ingredient use:

Polysaccharides have a substantial history of internal use in the human body to stop bleeding. This includes materials such as chitosan, oxidized regenerated cellulose (ORC), Surgicel from Johnson and Johnson, alginate, and potato starch.

Polysaccharide granules such as potato starch (Arista) and ORC granules have an ample history of use as hemostatics in surgery.

4) Human Use History – Clay based hemostatic products:

Kaolin and other clays have a long history of use in oral (anti-diarrheal) and topical (emollient, protectant) applications. However, there is a limited history of use in applications involving contact with the circulatory system.

5) Degradation in the Body – CELOX

MedTrade commissioned an external review of the safety of Celox's ingredients in the body by the safety and toxicology company Covance Laboratories Ltd (North Yorkshire, UK). Through a review of degradation mechanism and clearance pathway, Covance concluded that Celox was safe to use internally in surgery and that residual quantities presented no risk.

a. Degradation mechanism:

Celox is made with chitosan. Chitosan is broken down and digested in the body. The human enzyme lysozyme converts chitosan to the sugars glucosamine and n-acetyl glucosamine. This enzyme commonly exists in various human body fluids and tissues with concentrations from 4-13 mg/L in serum.⁷

b. Clearance pathway:

Excretion: Glucosamine and N-acetylglucosamine undergo rapid clearance by the liver and kidney and excretion in the urine.

Utilization: Glucosamine is a natural substance produced in the body and is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue.⁸⁻⁹ Glucosamine is incorporated into skeletal muscle and articular cartilage, tendons and ligaments, while N-acetylglucosamine is distributed into connective tissue and cartilage.

6) Degradation in the Body – Clay based hemostatic products:

Clay minerals have no known metabolic pathway in the body¹⁰. Without a metabolic pathway, any material left in the body will remain for an indefinite time.

7) Size – CELOX

a. Not a nanoparticle:

CELOX is presented as high surface area flakes (smaller than 20 mesh or .841 mm). It is not a nanoparticle.



Figure 5: CELOX flakes (magnified)

b. Not dispersible:

CELOX flakes do not disperse readily in fluid. They swell, gel, and agglomerate when in contact with any fluid (including blood).

8) Size – Clay based hemostatic products

a. Nanoparticles:

Kaolin and other clays can be classified as nanoparticles². A nanoparticle is a substance that displays sub-micron diameters (< 0.00004 inches).

b. Dispersible:

Clays disperse readily in fluid to give a fine dispersion.

9) Regulatory Approvals – CELOX

a. Device Class:

Celox is regulated as a Class 3 medical device in Europe. A Class 3 medical device receives a very high level of scrutiny. Approval involves the presentation of a dossier, over 1000 pages in length, for external agency review.

The review process is rigorous, lasting at least one month in duration. The safety and efficacy of Celox has therefore undergone a very substantial external review.

b. Biocompatibility testing:

As part of a thorough regulatory approval process, a battery of ISO 10993 studies with CELOX confirmed its biocompatibility:

- Cytotoxicity: negative
- Hemolytic potential: negative
- Skin irritation: negative
- Skin sensitization: negative
- Systemic toxicity: negative

10) Regulatory Approvals – Clay based hemostatic products

a. Device Class:

Clay based hemostatic products are regulated either as Class 1 or Class 2 devices. Class 1 and Class 2 devices are reviewed by audit only.

FDA assessment of emergency hemostatic products requires a relatively limited dossier and exam in comparison with Class 3 CE mark approval.

References:

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