Z-Medica Corporation is proud to be the global leader in the rapidly growing area of products that stop severe brisk bleeding. First to market with the original QuikClot® brand hemostatic agent, the company continues to develop new products, technologies and delivery mechanisms to provide these products that make a difference wherever bleeding presents a problem. Our products make a difference around the world: from the battlefields of Iraq and Afghanistan, to the tactical law enforcement officer in Los Angeles, to the mass casualty preparedness teams in New York, to a mother in Illinois whose son's life was saved by QuikClot® 1st Response™ brand. Our technology has come a long way since its introduction in 2002, and along the way it has saved many lives.

HOW QUIKCLOT® BRAND PRODUCTS WORK TO STOP BLEEDING

Z-Medica provides products based on two separate platform technologies. While the two technologies are similar and overlap in their mechanisms of action, it makes sense to discuss each separately. This paper will address the **Zeolite Based Products.**

The original QuikClot® brand products derive their primary hemostatic properties from zeolite, a naturally occurring mineral material with fascinating properties that have applications in many areas. One of the amazing properties of zeolite is the tremendous surface area found in a small volume of material. One teaspoon of zeolite provides a surface equal to that of a football field. Zeolite has many uses, some highly technical and some very commonplace. These use include: detergents, where they are used as water softeners; insulated glazed windows, where they act to prevent condensation; packaging at the supermarkets to preserve food freshness; oil refineries, as molecular sieves that separate complex mixtures of hydrocarbon based on size and other attributes; and zeolite can even be found in some toothpastes. In addition to the naturally occurring zeolite, approximately 1.5 million tons of various forms of engineered zeolite are manufactured every year.

Z-Medica's zeolite based products include:

- The original QuikClot® brand hemostatic agent
- QuikClot® 1st Response™ brand
- QuikClot® ACS+™ brand
- QuikClot® Sport™ brand
- QuikClot® Sport™ Silver brand

Nature provides us with wonderfully redundant systems when it deems a system important to our survival. Certainly, keeping our blood inside our body where it belongs is one of those things important to our survival. Our bodies have multiple complex systems to help make sure this happens. The two main systems are platelet activation and the coagulation cascade. QuikClot® brand zeolite based products work in both these systems.

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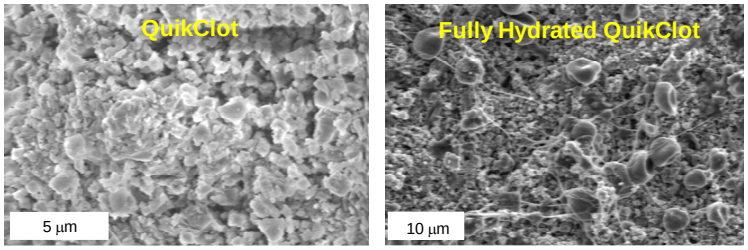
In collaboration with Professor Galen Stucky at the University of California at Santa Barbara, we have shown that the above agents activate platelets. Activated platelets help stop bleeding because they form a plug. This occurs in conjunction with the body's own mechanisms of platelet activation, which occur whenever there is an injury to a blood vessel.

QuikClot® products also work in the coagulation cascade. The specific engineered zeolite used contains a cation (Ca^{++}) that is a cofactor in many steps of the coagulation cascade. Also, there is evidence from Professor Stucky's group that QuikClot® facilitates a phenomenon widely known as the "glass effect". It has been known since the 1800's that blood clotted faster than otherwise when it came in contact with glass. Since then, it has been shown that this is due to the negative surface charge found on glass. Further research tells us that the negative surface potential activates a protein at the very beginning of the contact pathway, one of the two chains in the coagulation cascade. Ostomel and Baker[1] have clearly demonstrated in thromboelastography (TEG) that the surface charge and isoelectric point of inorganic oxides such as zeolite promote rapid onset of clotting and strong clot formation as a result of protein activation in the coagulation cascade.

Furthermore, QuikClot® products adsorb water from the blood. Water is trapped in the zeolite and held there by the charge within the zeolite pores, zeolite framework and hydrogen bond formation. This locally concentrates the cellular and large protein components of the blood further catalyzing clot formation.

SEM of Porcine Blood with QuikClot

Fibrin formation and red blood cell adhesion even on fully hydrated QuikClot.



AM Sawvel, SE Baker and GD Stucky. *Manuscript in Preparation*, **2007.**

[1] "Metal Oxide Surface Charge Mediated Hemostasis", Ostomel, T; Qihui, S., Stoimenov, P.K., Stucky, D.; *Langmuir* **2007,** *23*, 11233-11238.

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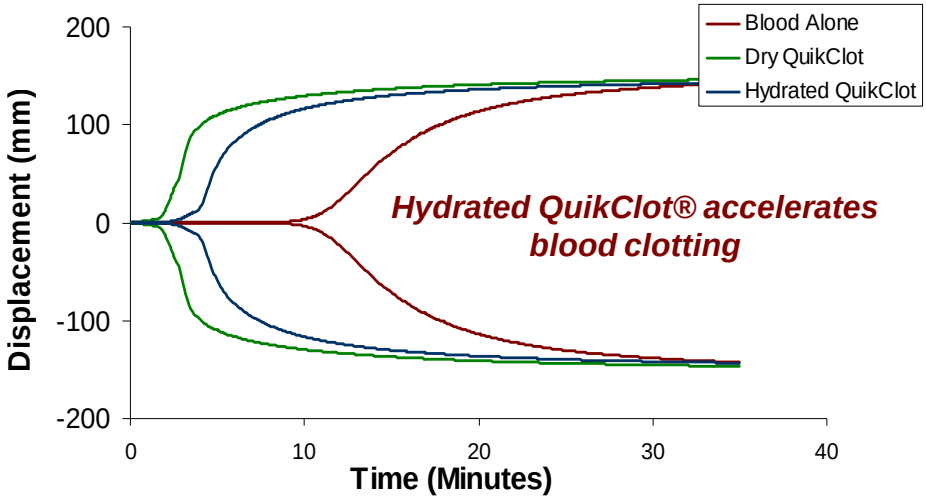
Delivery mechanisms can also enhance the powerful blood clotting properties of zeolite. The original QuikClot® brand hemostatic agent is a granular powder that is simply poured into the wound. While it is very effective, a powder is a primitive delivery system and has several drawbacks. First, in a pumping arterial wound some of the material may be washed away by the powerful flow of the blood itself. Secondly, powders cannot be poured in an upward direction, against gravity, so a wound must be beneath the person applying the powder. Z-Medica's second generation QuikClot® brand products address this shortcoming. These products contain 3 mm diameter zeolite beads packaged in a very porous surgical mesh. This delivery system is available in several different sizes. It allows the hemostatic agent to be applied in any direction, up, down or sideways; it also allows the application of the material against a wound producing very high blood flow. And it allows the caregiver to apply pressure.

One last point to note regards the heat generation found only in the original granular product, but not found in the newer products. When water is adsorbed by the zeolite and trapped by hydrogen bond formation heat is generated. When used incorrectly, very high temperatures could be reached, posing a risk of burn to the patient. The company has addressed that problem by selectively preloading the zeolite with some water minimizing any heat generation to very acceptable and safe levels.

Sheep Blood

Sample	R (minutes)	α (degrees)	MA (mm Displacement)
Blood Alone	10.0	53.4	72.7
Dry QuikClot	1.4	74.0	71.4
Hydrated QuikClot	2.8	65.4	70.3



Working with Stucky and the team at UCSB, we have optimized the level of prehydration while maintaining the clotting efficacy found in the original granular product. Using TEGs, we have shown that even with a partially hydrated zeolite, clotting is accelerated and the clot strength is high. Coupled with the improved delivery

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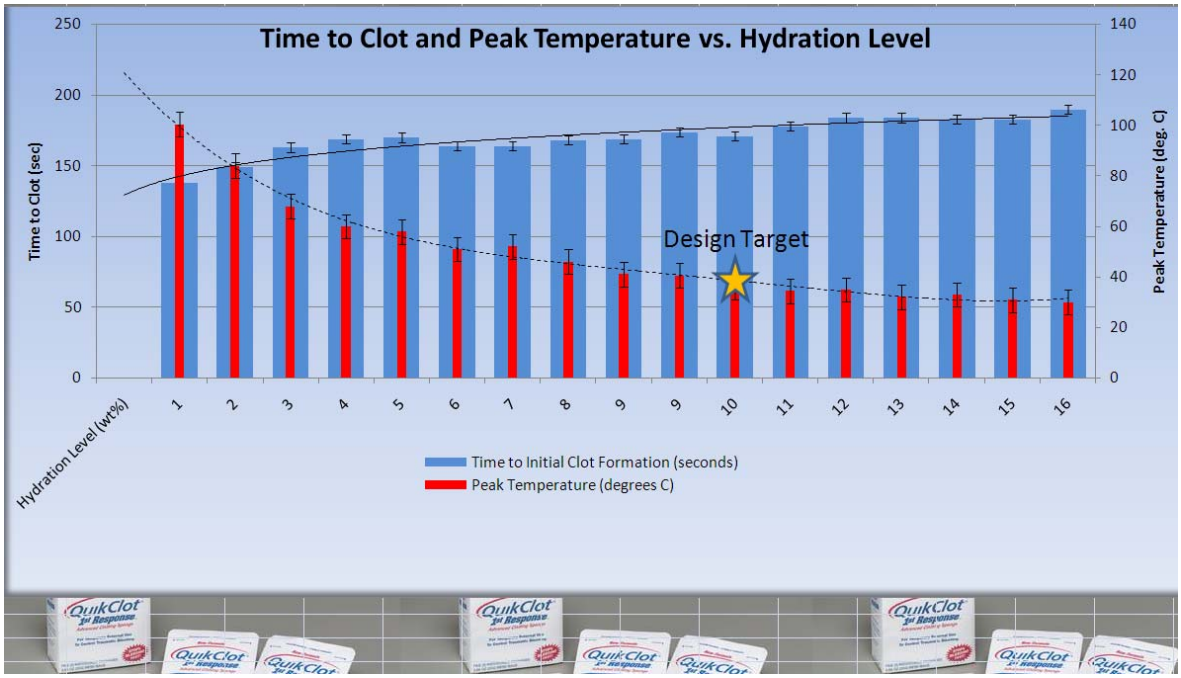
mechanism, the partially hydrated material provides the required life saving technology in the most commonly occurring applications.



The design challenge in reducing the exothermic reaction was to maintain clotting efficacy and safety. Prehydration of the material presented an approach that would guarantee safety. The remaining challenge would be to demonstrate efficacy. One measurement of efficacy was the time to clot, which presented a classic engineering tradeoff problem. It turned out the clotting efficacy as measured by time to clot was not compromised by the target peak temperature as can be seen in the figure.

In summary, Z-Medica's zeolite based QuikClot® brand products provide an extremely effective toolkit to stop bleeding of any kind, brisk or oozing. Mechanisms of action include:

- Adsorption of water thereby accelerating fibrin formation Platelet activation
- Activation of the coagulation cascade due to the "glass effect"
- Supplying a resource for Ca^{++}, a cofactor in the coagulation cascade
- A large zeolite pore surface area facilitating fibrin formation

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