



## The Potential for Improving Medical Textiles with Cyclodextrin Inclusion Compounds

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### ABSTRACT

*Cyclodextrins (CDs), 1,4 - $\alpha$ -linked cyclic starches containing 6 ( $\alpha$ -CD), 7 ( $\beta$ -CD), and 8 ( $\gamma$ -CD) glucose units, are water soluble molecular bracelets, with hydrophobic interiors and hydrophilic exteriors. They are widely known for their ability to serve as hosts in the formation of both soluble and solid crystalline inclusion complexes (ICs) with a large variety of non-covalently included guest molecules. Recently we have demonstrated that a wide range of high molecular weight polymers, as well as small-molecule guests may be included in the host CD channels and cavities of their CD-ICs. These CD-IC crystals melt at high temperatures ( $\sim 300^\circ$  C) and effectively screen their included guests from environmental influences. For example, crystalline CD-ICs may even be formed with polymer and small-molecule guests that are liquids in their pure bulk states. In polymer-CD-ICs the CD bracelets pack to form parallel stacks with narrow continuous channels ( $\sim 0.5$ - $1.0$  nm in diameter), where the included polymer guests reside in highly extended conformations and are segregated from neighboring included polymer chains. Coalescence of guest polymers from their CD-ICs, which can be accomplished with a solvent for CD that is a non-solvent for the guest polymer or by treatment with an amylase enzyme, results in their consolidation into bulk samples with morphologies that are uniquely different from those normally obtained by consolidation from their disorder-ed solutions and melts. As a consequence, we have found their crystallinities, miscibilities with other polymers and small-molecules, and the phase separation of their block copolymers can be controlled by coalescence from their CD-IC crystals. Here we offer an assessment of the potential for using polymer materials processed with CD-ICs as a means to improve medical textiles, including applications such as the controlled delivery of drugs and genes and for fabricating anti-bacterial sutures, wound dressings, and implants.*

*Keywords: anti-bacterial sutures, wound dressings, implants*

*+ Many students and colleagues (see references) have contributed to and the National Textile Center (US Dept. of Commerce) and NC-State University have financially supported the research described here.*

## Introduction

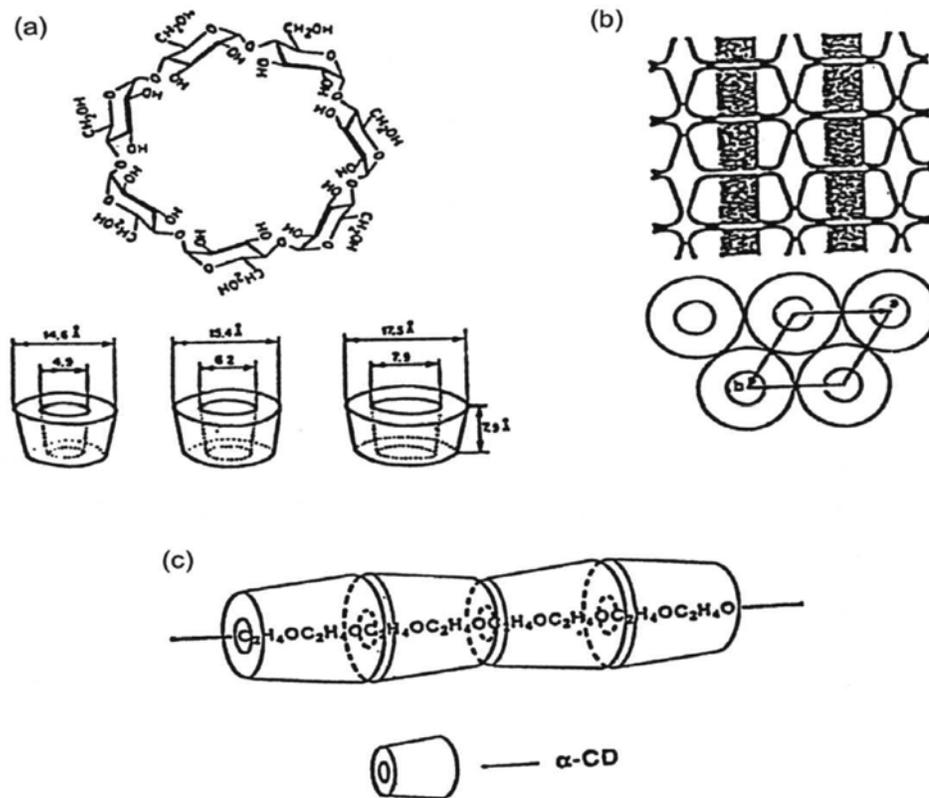
During the past decade it has been demonstrated that crystalline inclusion compounds (ICs) may be formed between host cyclodextrins (CDs) and a wide variety of guest polymers<sup>1-13</sup>. In Figure 1(a) the structures and dimensions of the host  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CDs are presented along with the channel crystal structure of CD-ICs (b) and a single  $\alpha$ -CD stack of the  $\alpha$ -CD-IC channel structure crystal containing a guest polymer (c). Two important features of polymer-CD-IC crystals are (i.) the segregation of polymer chains occupying different CD-IC channels, and (ii.) the highly extended conformations required of the included, guest polymers by the narrow cross-sections (5-10Å) of the CD-IC channels. As a consequence of the unique environment provided by CD-ICs for their guest polymers, it might be expected that consolidation of guest polymers from their CD-ICs could yield bulk polymer samples with structures and morphologies that are significantly altered from those normally achieved from their disordered solutions and melts. When guest polymers are coalesced from their CD-IC crystals by disruption of the IC and removal of CD with a solvent that is good for the CD host, but which is a non-solvent for the polymer, or by the selective degradation of the host CD with an amylase enzyme or an acid, the resultant consolidated guest polymer chains may retain some degree of their extended, unentangled natures. As is apparent from Figure 1 (b), polymer guests in neighboring CD-IC channels are necessarily proximal, because of their separation by the walls created by the CD bracelets in adjacent IC stacks. Consequently, if two or more polymers are dissolved in a common solvent and this mixed polymer solution is used to form a CD-IC containing both or more

polymers, then the subsequent coalescence of polymer guests from the common CD-IC could possibly result in their intimate blending.

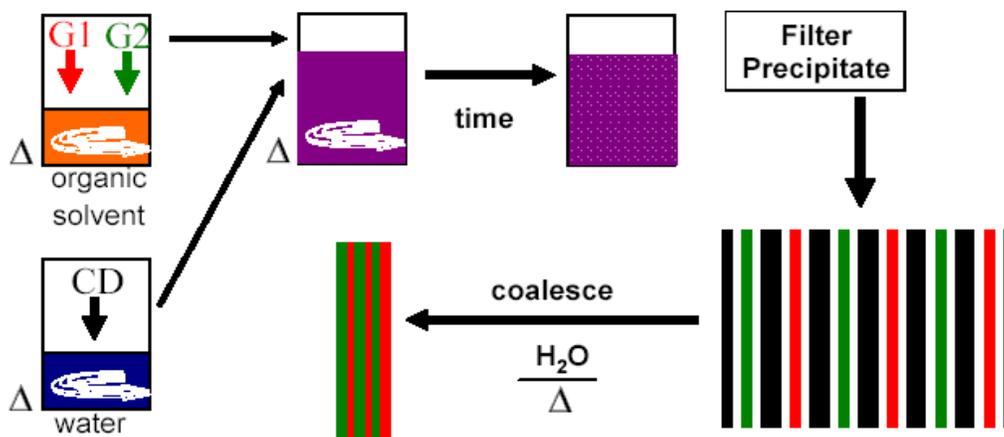
The effects produced by coalescing polymers from their CD-IC crystals may be generally summarized<sup>5,7-10,12,14-20</sup> in the following ways: (i.) crystallizable homopolymers can evidence increased levels of crystallinity and higher melting and decomposition temperatures than samples consolidated from their disordered solutions and melts; (ii.) molecularly mixed, intimate blends of two or more polymers that are normally believed to be immiscible can be achieved by coalescence from their common CD-IC crystals, as illustrated in Figure 2, (iii.) the phase segregation of incompatible blocks can be greatly suppressed when block copolymers are coalesced from their CD-IC crystals, and (iv.) the thermal and temporal stabilities of the well-mixed homopolymer blends and block copolymers obtained by coalescence from their CD-ICs appear to be substantial, thereby suggesting retention of their as-coalesced structures and morphologies under normal thermal processing conditions.

In addition, additives may be delivered to polymers and textiles using CDs by two methods: i.) by forming an intimate additive (G1)/polymer(G2) blend as indicated above in Figure 2, and ii) by first forming a crystalline additive-CD-IC, followed by melt-processing the additive- CD-IC crystals into polymer fibers and films. The latter approach is made feasible by the high melting temperatures (~300° C) of additive-CD-IC crystals. Here we offer an assessment of the potential for using polymer materials processed with CD-ICs as a means to improve medical textiles, including applications such as the controlled delivery of drugs and anti-bacterial sutures and implants.

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**Figure 1. Cyclodextrins (CDs)** (a) Chemical structure of  $\beta$ -CD and the dimensions of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CD bracelets. (b) Channel or tubular crystal structure of CD-ICs, where the host CD bracelets are stacked to form nanotubes and wherein reside the included guest polymers. (c) A single CD-nanotube threaded by a polymer chain.



**Figure 2. Blending via complexation and subsequent coalescence.**

## Experimental

Details concerning the formation of polymer- and additive-CD-ICs, their characterization, their coalescence into homo- and block copolymer and polymer1/polymer2 and additive/polymer blends, and their characterization can be found in the appropriate references cited during the following discussion of results.

## Results and Discussion

### Homopolymers Coalesced from Their CD-ICs

In general when homopolymers are coalesced from their CD-IC crystals the resulting bulk samples have structures, morphologies, and even chain conformations which differ markedly from those produced by normal consolidation from their disordered solutions and melts, where their chains are randomly coiling and usually entangled. Crystallizable polymers are observed<sup>8,12,17</sup> to have enhanced crystallinities, usually with elevated melting temperatures ( $T_m$ ), and even distinct crystalline poly-morphs<sup>12</sup> when coalesced from their CD-ICs. For example, when poly(ethylene tere-phthalate) (PET) is coalesced from its  $\gamma$ -CD-IC crystals<sup>8</sup>, its level of crystallinity is  $\sim$  three times that of as-received PET, although its  $T_m$  is only marginally elevated from that of typical bulk or solution crystallized samples. However, after melting the  $\gamma$ -CD-IC-coalesced PET crystals, it is difficult to quench the resultant PET melt into the usual amorphous PET glass, characterized by a  $T_g \sim 80^\circ$  C. Instead, the coalesced PET melt rapidly crystallizes (See Figure 3) during the attempted quench, and so upon reheating, it displays neither a  $T_g$  nor a crystallization exotherm, which are normally observed in melt-quenched PETs, but simply remelts at the as-coalesced  $T_m$ . This behavior is unaffected by holding the coalesced sample above  $T_m$  for 2 hr, indicating that the extended, unentangled nature of the PET chains in the non-crystalline regions of the coalesced sample are not easily converted into the usual

completely disordered, randomly coiled, entangled PET melt.

Analysis of the FTIR spectrum of the  $\gamma$ -CD-IC-coalesced PET sample has revealed<sup>8</sup> that extended kink conformations, with gauche  $\pm$ , trans, gauche  $\mp$  ethylene glycol bonds, necessary<sup>21</sup> for inclusion in the narrow channels of the  $\gamma$ -CD-IC crystals, are largely retained upon coalescence. It is not surprising that these kink conformations can be readily converted to the all trans crystalline conformation, *via* counter rotations about the  $-\text{O}-\text{CH}_2-$  and  $-\text{CH}_2-\text{O}-$  ethylene glycol bonds from their gauche  $\pm$  and gauche  $\square$  conformations, leading to rapid crystallization of the coalesced PET chains. In contrast, the completely disordered amorphous PET chains normally found in PET melts and glasses possess a high concentration<sup>22</sup> ( $>80\%$ ) of ethylene glycol residues with energetically favorable gauche  $\pm$   $-\text{CH}_2-\text{CH}_2-$  bonds, which retards their crystallization into the all trans conformation. However, what remains surprising is the observation that the kink conformers in the non-crystalline regions of the coalesced PET sample are not readily converted to the usual disordered, randomly coiling, entangled melt above  $T_m$ .

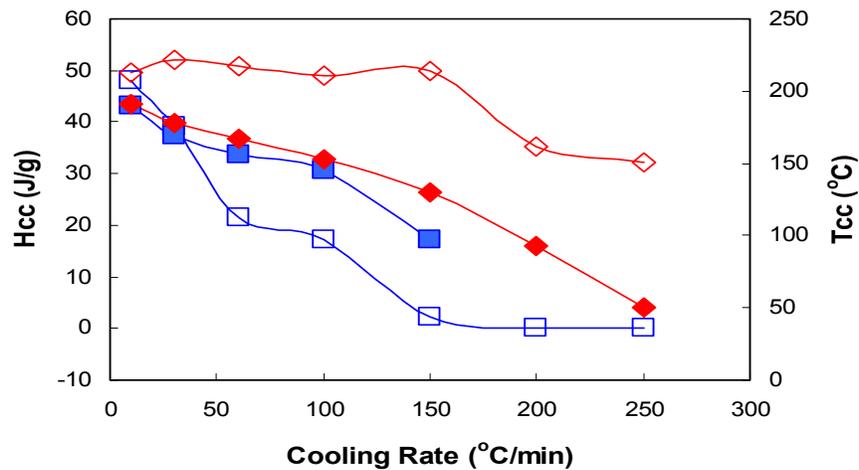
In any event, inclusion in and coalescence from its  $\gamma$ -CD-IC renders PET repeatedly and rapidly crystallizable. This implies that melt spun and melt-blown fibers with high levels of crystallinity should be achievable from coalesced PET<sup>23</sup> without drawing or using a second polymer component that is rapidly crystallizable, to produce strong fibers, yarns, fabrics, and non-woven webs. When these are incorporated into textile structures appropriate for medical applications, their performance will likely be superior to those manufactured from normally produced PETs.

### Block Copolymers Coalesced from Their CD-ICs

When the biodegradable/bioabsorbable diblock copolymer poly( $\epsilon$ -caprolactone)-b-

Poly(L-lactic acid) (PCL-b-PLLA) is coalesced from its  $\alpha$ -CD-IC<sup>18</sup> the phase segregation of immiscible PCL and PLLA is greatly suppressed, as observed<sup>16</sup> by 50-60% and 54-79% reductions in the crystallinities of PCL and PLLA blocks, respectively, from those observed in the as-synthesized sample. In addition, the rates of crystallization of PCL and PLLA blocks are much faster in the coalesced PCL-b-PLLA<sup>19</sup>.

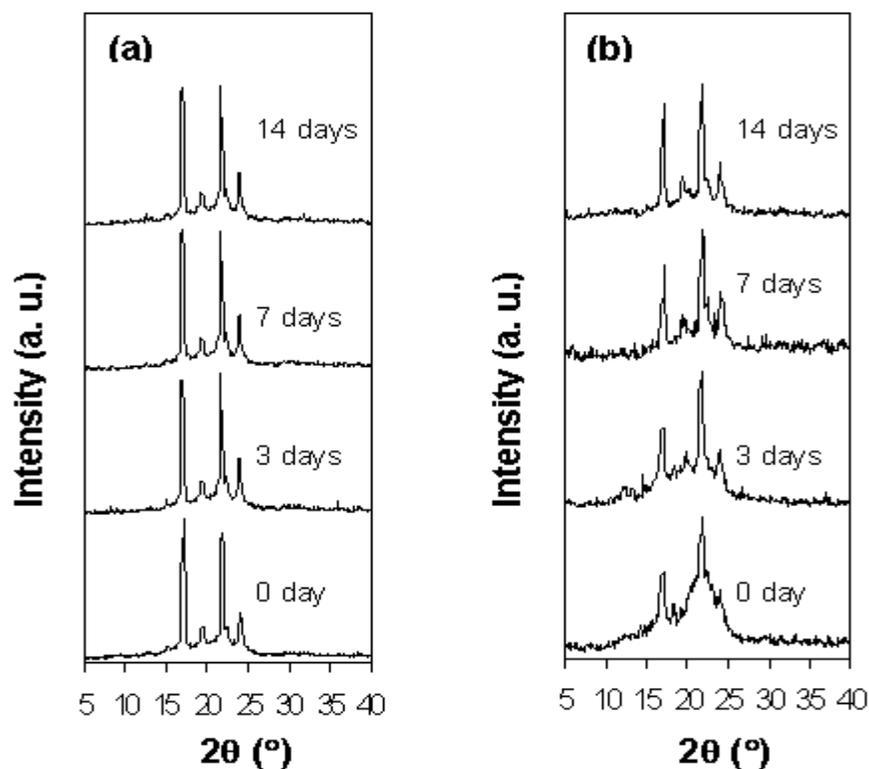
The biodegradation of as-received and coalesced PCL-b-PLLA samples using the lipase from *Rhizopus arrhizus* were compared<sup>18</sup>. The coalesced diblock copolymer was observed to undergo much more rapid biodegradation as demonstrated in Figure 4. The increased rate of biodegradation of the coalesced PCL-b-PLLA is apparently attributable to the suppressed phase segregation of PCL and PLLA blocks in the coalesced sample,



**Figure 3.** Cooling crystallization enthalpies (Hcc) and temperatures (Tcc) (solid markers) observed at different DSC cooling rates for as-received (squares) and coalesced (diamonds) PET samples.

which led to reduced PCL and PLLA crystallinities. The wide angle X-ray diffraction patterns of as-synthesized (a) and coalesced (b) PCL-b-PLLA films observed after various enzymatic degradation times shows that the level of crystallinity clearly increases with the enzymatic degradation of the coalesced PCL-b-PLLA. This is a consequence of the preference of the lipase enzyme for the amorphous sample regions,

which are initially more plentiful compared with the as-synthesized sample. It is apparent that the biodegradation of the PCL-b-PLLA block copolymer can be controlled by coalescence from its  $\alpha$ -CD-IC, and this can have important implications for its use in drug delivery and controlled release applications, as well as in other medical textile applications.



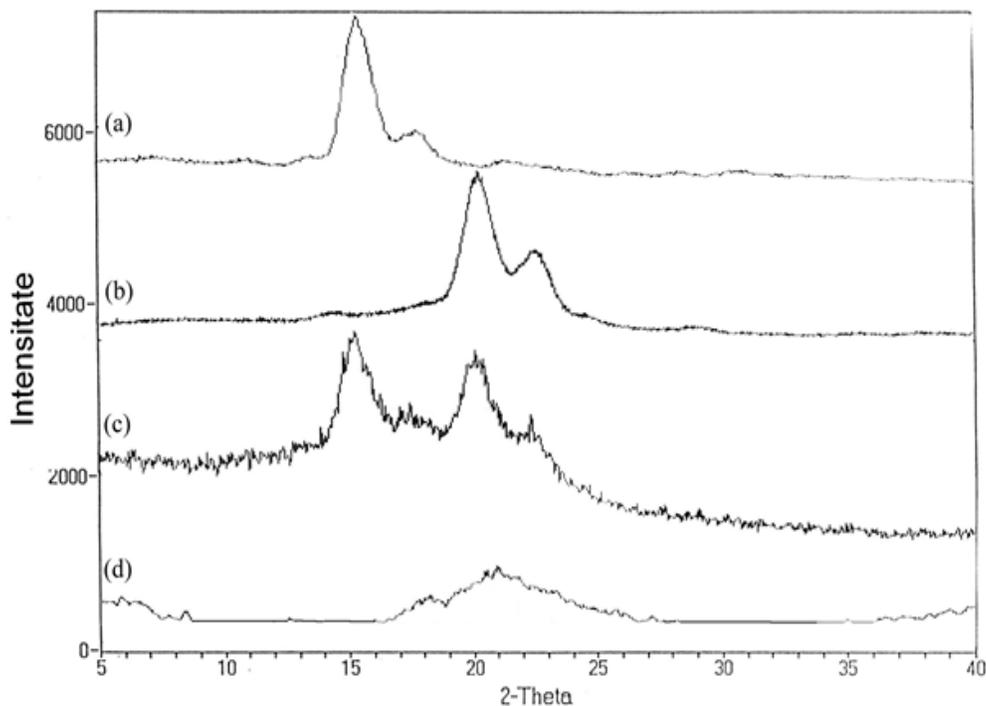
**Figure 4.** X-ray diffraction patterns of as-synthesized (a) and coalesced (b) PCL-b-PLLA films observed following various enzymatic degradation times.

### Homopolymer Blends

When PCL and PLLA chains are dissolved in dioxane at 50° C and added to a saturated aqueous solution of  $\alpha$ -CD also maintained at 50° C with stirring, common  $\alpha$ -CD-IC crystals containing both polymers (PCL/PLLA- $\alpha$ -CD-IC) result<sup>5</sup>. Coalescence of PCL and PLLA chains from their common  $\alpha$ -CD-IC crystals appears to yield a well-mixed predominantly amorphous blend, as is evidenced by the comparison of x-ray diffractograms presented in Figure 5, where the degrees of crystallinity of both PCL and PLLA are dramatically reduced following the coalescence from their common  $\alpha$ -CD-IC. DSC observations in fact do not detect a melting endotherm for PCL and only a very small endotherm for PLLA, which indicate that 0 and 5% of their chains, respectively have crystallized, which may be

compared to ~50% PCL and PLLA crystallinities in the pure homopolymers and their solution-cast blend.

Surprisingly, when the coalesced PCL/PLLA blend is heated at 200° C for up to 12 hrs, which exceeds the  $T_m$ s for both components, the DSC thermogram recorded after annealing did not change from that of the original coalesced sample. Apparently the initially well-mixed, almost entirely amorphous PCL/PLLA blend achieved by coalescence is thermally stable and has not phase-segregated following high temperature annealing. Based on our experience with the biodegradation of the PCL-b-PLLA block copolymer, it would appear that the well-mixed PCL/PLLA homopolymer blend obtained by coalescence from its common  $\alpha$ -CD-IC would make an excellent material for non-removable sutures for example.



**Figure 5.** X-ray diffractograms of pure PCL (a) and PLLA (b) and PCL/PLLA blends obtained by casting from dioxane solution (c) and hot water coalescence from PCL/PLLA- $\alpha$ -CD-IC (d)<sup>5</sup>.

#### Delivery of Polymer Additives with CD-Ics

CD-ICs are high-melting crystalline materials which may be readily delivered to polymer fibers and films by melt-processing techniques. Additives that are normally liquids may be delivered by this means, because in their CD-ICs they are encapsulated by the host CD crystalline lattice (See Figure 1), and so their retention by polymer solids is improved. In addition, for additives like flame retardants (FRs) and anti-bacterials discussed below, their efficacy may be improved by confinement inside the crystals of their CD-ICs.

For example, the commercial FR, Anti-Blaze RD-1, shown in Table 1 is normally padded on to cotton-polyester fabric from a bath followed by heating the FR treated fabric in an oven to improve retention of the FR. If instead the FR is first incorporated into an IC formed with  $\beta$ -CD and this is melt-processed into PET films we find<sup>25</sup> that

a superior level of protection may be imparted to the PET film, as demonstrated by the results presented in Table 1. Note that only the PET film embedded with FR-CD-IC, and not the normally treated film (PET-FR) survived the burning test. In addition, because the FR is encapsulated by the host CD crystalline lattice, it would not come into direct contact with human skin if PET-FR-CD-IC were used to make a fabric. Thus, much more aggressive, even potentially carcinogenic, agents could be considered as FRs if they were delivered in the form of their CD-ICs.

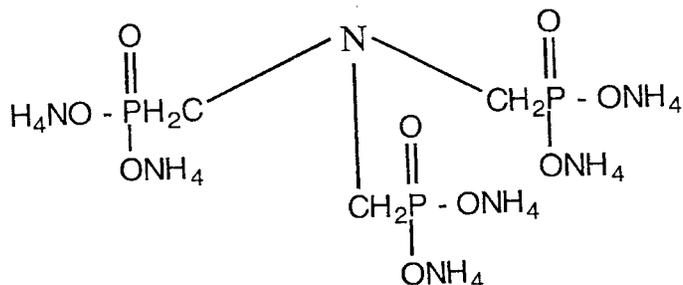
In Figure 6 the chemical structures of two anti-bacterial agents neomycin and Trichlosan are presented, because these were used<sup>26,27</sup> in the form of their  $\beta$ -CD-ICs to make antibacterial films, fibers and fabrics. When these anti-bacterial  $\beta$ -CD-ICs were melt-processed into biodegradable/bioabsorbable PCL and PLLA films and fibers they were observed to prevent the

growth of *E. coli* bacteria. For example, in Figure 7 the results observed for cotton fabric laminated with low-melting PCL films containing Trichlosan- $\beta$ -CD-IC<sup>27</sup> prevented the growth of *E. coli* (zone of

inhibition) as efficiently as pure Trichlosan, even though the concentration of Trichlosan in the Trichlosan-IC PCL film is only ~10% of that in the Trichlosan film.

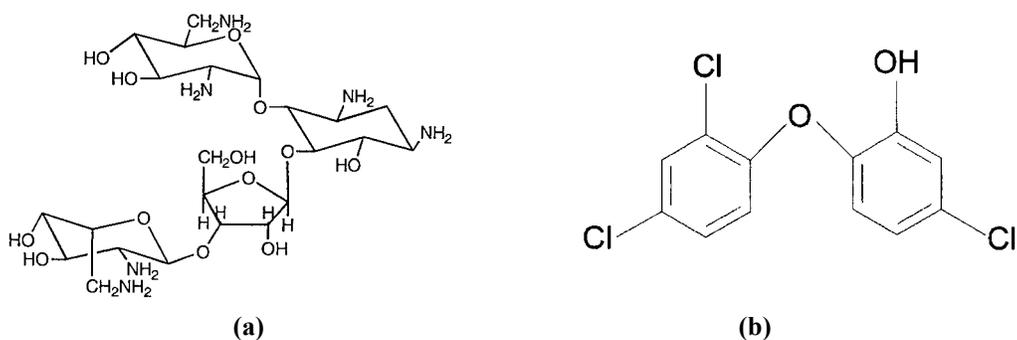
**Table 1. Flame Resistance\* of PET Films Treated with Antiblaze RD-1**

Antiblaze RD-1



Sample	Char length	cm	Burn Time	Sec.
Trial	1	2	3	3
B. PET	BEL	BEL	BEL	26
A. PET /FR	5.3	BEL	BEL	14
PET/ $\beta$ -CD	BEL	BEL	BEL	15
PET/FR- $\beta$ -CD-IC	1.0	0.8	1.0	6

- Modified AATCC Test Method 34

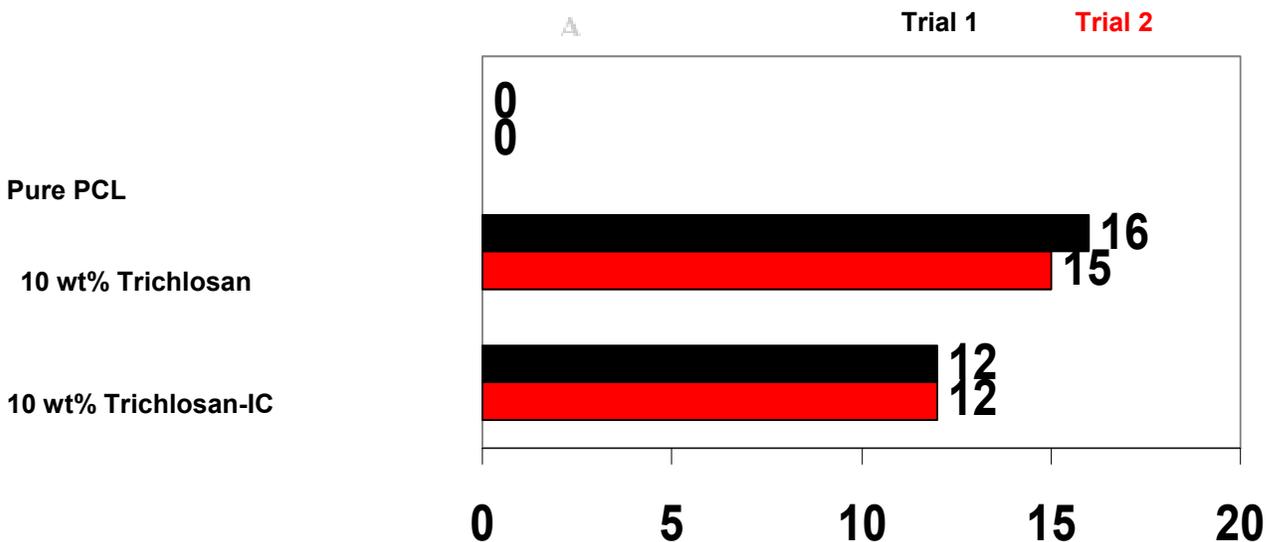


**Figure 6.** (a) Neomycin and (b) Trichlosan anti-bacterials.

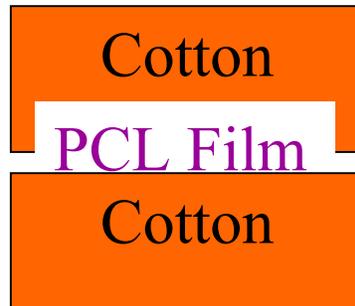
When PLLA fibers were melt spun from a PLLA powder containing a small amount of neomycin- $\beta$ -CD-IC<sup>26</sup>, it was observed that small bundles of the resulting fibers resisted the growth of *E. coli* bacteria when placed in an Agar medium after the bacteria were introduced. This shows the potential for producing non-removable sutures that are anti-bacterial, as well as biodegradable and bioabsorbable.

Finally by the method illustrated schematically in Figure 8, we may obtain<sup>19</sup> a well-mixed blend of a polymer and an additive, which in this case is a drug. This can serve as an alternative to embedding additive-CD-ICs into polymer films and fibers, and has the added potential benefit of direct use in the form of the

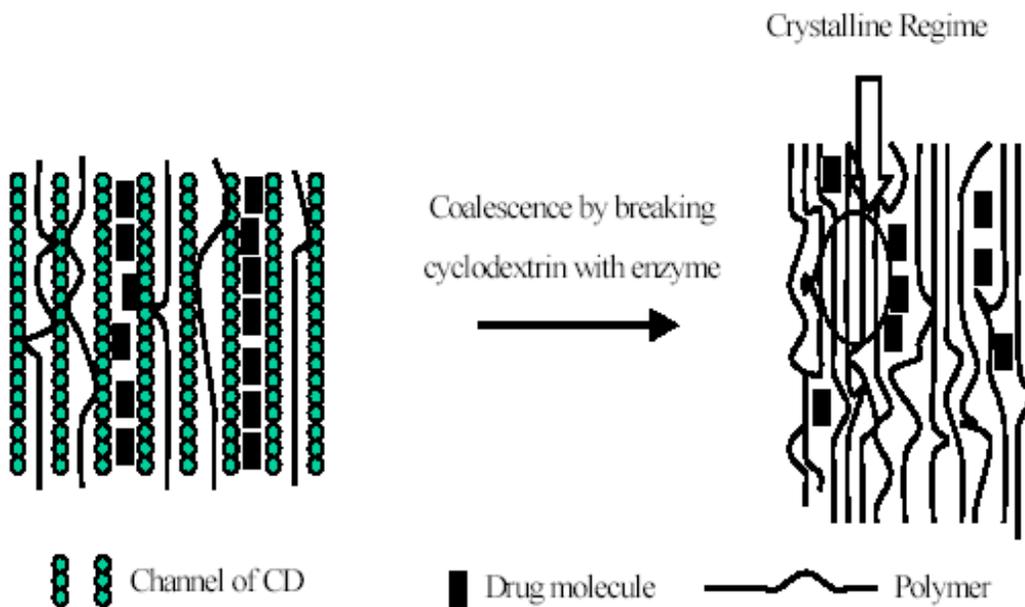
polymer/additive-CD-IC. For example, when exposed to certain enzymes in the body that digest amylases, CD from the polymer/additive-CD-IC will be digested resulting in the coalescence of the guest polymer and additive into a well-mixed blend. If a biodegradable/bioabsorbable polymer is chosen for this application, then we may achieve a controlled delivery of the additive, which may be a drug. Because the additive is protected first by inclusion in the host CDs and then by encapsulation in its well-mixed blend with the biodegradable/bio-absorbable polymer, this means of delivery might be useful for additives/drugs whose exposure to certain *in vivo* environments might lead to their degradation.



Zone of Inhibition – Diameter (mm)



**Figure 7.** Anti-bacterial behavior of cotton fabric laminates with PCL / Triclosan films.



**Figure 8.** Scheme of a polymeric drug delivery system formed by the simultaneous coalescence of matrix polymer and drug molecules from their common inclusion complex.

It is hoped by way of the several examples discussed above, that the potential for using CD-ICS formed with polymers and/or additives to construct medical textiles with improved properties and possibly new capabilities has been demonstrated.

#### Acknowledgements

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