含侧氨基可降解 PLA-(*L*-Asp-*alt*-Diol)$_x$-PLA 多元共聚物：体外降解性能研究

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关键词：PLA-(*L*-Asp-*alt*-Diol)$_x$-PLA 体外降解 降解机理

聚乳酸（PLA）、聚乙醇酸（PGA）及共聚物（PLGA）是目前组织工程和药物缓释中研究和应用最多的一类材料[1]。这类材料的物理形态、机械性能和降解性能可通过改变单体的立体化学结构及化学组成进行一定的调控，不足之处是亲水性不够并缺乏对细胞特异性的黏附。为改善这类聚酯材料的亲水性，本文作者报道了[2]系列含侧氨基的聚丙/乙交酯-(天冬氨酸-*alt*-二醇)$_x$-聚丙/乙交酯[PLGA-(*L*-Asp-*alt*-Diol)$_x$-PLGA]多元共聚物的合成与结构研究，由于该共聚物中分别含有亲水性的醚链段（乙二醇或聚乙二醇）和侧氨基功能基团，可以通过调节醚链段的长短实现调控侧氨基密度的目的，这对于固定不同密度的生物活性因子有重要价值。这种结构上的变化对共聚物降解性能也有一定影响，而研究共聚物的组成和结构对于其降解性能的影响对于指导这种多嵌段共聚物在组织工程和药物缓释中的应用也有重要作用。

共聚物的合成参照作者以前的报道[2]。简述如下：首先合成两端含羟基的聚（*L*-天冬氨酸-*alt*-二醇）交替预聚物 [poly(*L*-Asp-*alt*-Diol)]（Diol：乙二醇 EG、二缩乙二醇 TEG、三缩乙二醇 BEG、聚乙二醇 PEG400、PEG600）。以上述预聚物为大分子引发剂，辛酸亚锡 [Sn(Oct)$_2$]为催化剂引发丙交酯（*D,L*-LA）开环聚合得到多元共聚物。在 40℃采用热压方式成膜，尺寸为直径Φ1cm, 厚度约 0.2cm。将预先称重（m_0）的样品膜（3×8 片）浸泡在 pH=7.4，温度为 37±1℃的磷酸盐缓冲溶液中，缓冲介质每周更新一次。分别在 0d，2d，4d，7d，14d，21d，28d，42d 取样，真空干燥至恒重（m_t)。以乌式粘度计测定共聚物降解前后的特性粘度（$[\eta]_0$、$[\eta]_t$），温度 25±0.1℃。并通过 ^{1}H NMR 和 GPC 考察共聚物翟体外降解中组成、结构以及分子量的变化。

共聚物的降解速率主要与聚合物链结构单元中易于水解断裂的酯键数目以及聚合物的亲/疏性有关。在所研究的组成范围内，共聚物表现为本体水解的特征；共聚物中 PLA 链段分子量越大，易于水解的酯键数目增多，表现为初始粘度下降速率加快；共聚物中 Diol 链段越长，预聚物含量越高，共聚物的亲水性越好，表现为质量损失速率加快。从共聚物降解过程中组成的变化可以判断其降解机理如 Scheme 1 所示，降解首先发生Ⅲ形式的断裂，后期发生Ⅰ和Ⅱ形式的断裂。

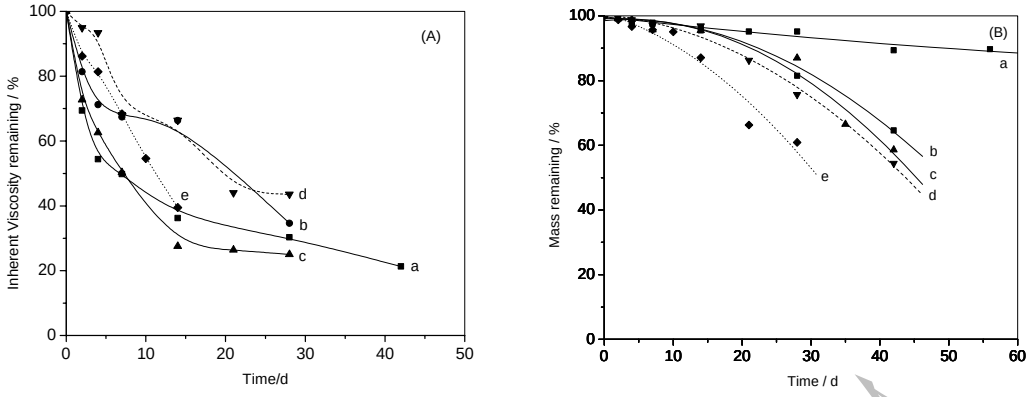


Figure 1 Normalized inherent viscosity(A) and mass(B) remaining of PLA-(N-Cbz-*L*-Asp-*alt*-Diol)$_x$-PLA incorporated into 10% of prepolymers as the function of the degradation time *in vitro* (pH=7.4) at 37 °C.(a. PLA-(N-Cbz-*L*-Asp-*alt*-EG)$_x$-PLA; b. PLA-(N-Cbz-*L*-Asp-*alt*-TEG)$_x$-PLA; c. PLA-(N-Cbz-*L*-Asp-*alt*-BEG)$_x$-PLA; d. PLA-(N-Cbz-*L*-Asp-*alt*-PEG400)$_x$-PLA; e. PLA-(N-Cbz-*L*-Asp-*alt*-PEG600)$_x$-PLA)

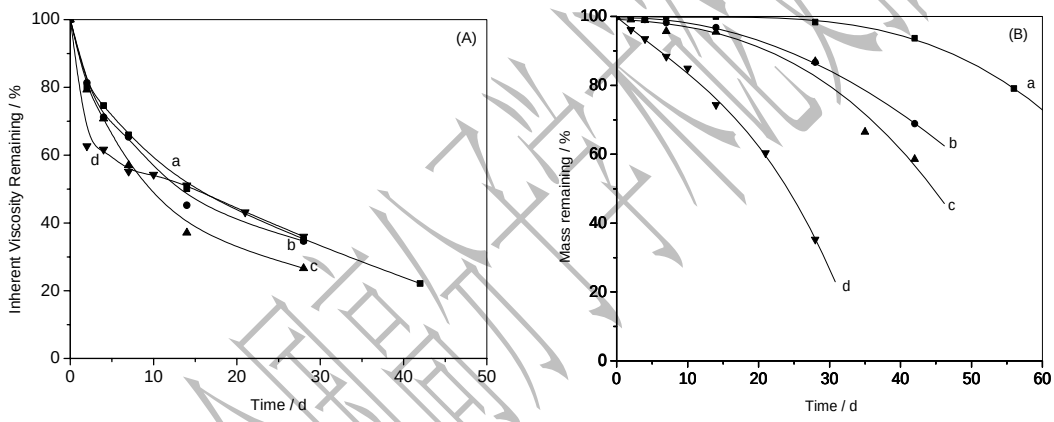
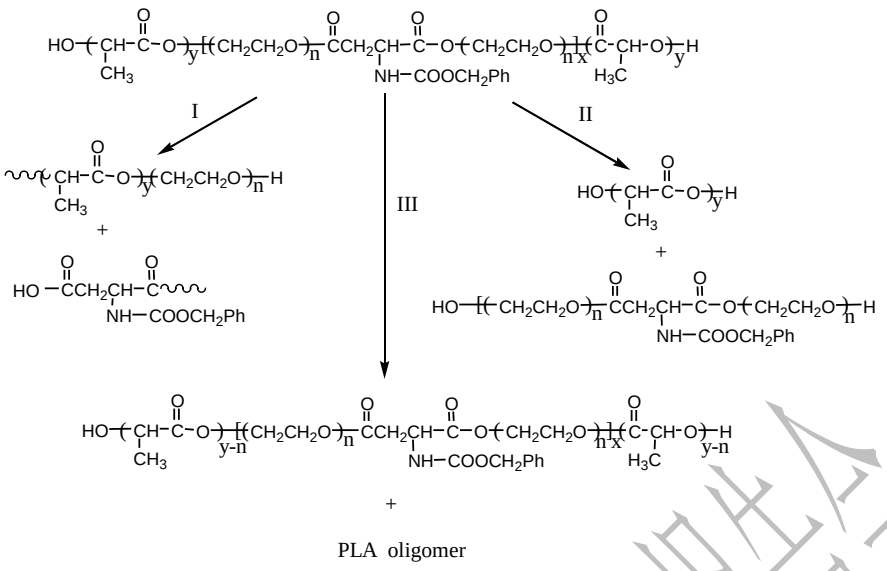


Figure 2 Normalized inherent viscosity(A) and mass(B) remaining of PLA-(N-Cbz-*L*-Asp-*alt*-BEG)$_x$-PLA incorporated into different contents of prepolymers as the function of the degradation time *in vitro* (pH=7.4) at 37 °C.($m_{prepoly.}$ /$m_{copoly.}$= 5%(a), 10%(b), 15%(c), 20%(d))

Table1 Changes of the compositions for PLA-(N-Cbz-*L*-Asp-*alt*-BEG)$_x$-PLA copolymer with different degradation times *in vitro* (pH=7.4) at 37 °C

Degradation time/day	LA/EG (I_j/I_c)	EG/Asp (I_c/I_f)
0	22.0	2.9
2	14.9	2.8
7	15.2	2.9
14	14.4	2.8
21	13.9	2.8
28	8.7	4.7



Scheme 1 The degradation of PLA-(N-Cbz-*L*-Asp-*alt*-Diol)$_x$-PLA copolymers

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PLA-(*L*-Asp-*alt*-diol)x-PLAs with Different Contents of Pendant Amino Groups: Degradation *in Vitro*

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Abstract: PLA-(*L*-Asp-*alt*-Diol)$_x$-PLA copolymers with different contents of pendant amino groups were cultured in pH=7.4 phosphate buffer at 37℃. Their degradation behaviors were monitored by means of weighing, inherent viscosity determination, GPC and ^{1}H NMR. The results showed that the molecular weight loss rate was slower than that of the weight loss. With the increase of the molecular weight and content of diol incorporated into the copolymers, the degradation rate increased. ^{1}H NMR

spectra confirmed the formations of PLA oligomer and lactates in the degraded products due to the random cleavages of the PLA blocks in the copolymer chains at the initial degradation period. It was found that some EG-LA and EG-Asp junctions remained after degradation for 4 weeks and the LA/EG ratio decreased with the degradation time because of the release of PLA oligomer and lactates. Compared with LA-LA linkage, the EG-LA and EG-Asp junctions are more stable.

Key words: PLA-(*L*-Asp-*alt*-Diol)$_x$-PLA Degradation *in vitro* Degradation mechanism