·实验研究 Experimental research·

Kinetics of Iododeoxyuridine release from sodium alginate hydrogel in vitro

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【Abstract】 **Objective** To investigate the kinetics of Iododeoxyuridine (IUdR)release from sodium alginate hydrogel cross-linked with varying amounts of calcium chloride, and to optimize sustained release for further periadventitial I^{125}-labeled IUdR delivery to suppress intimal hyperplasia following angioplasty in vivo. **Methods** Four hydrogels, composed of 0.16 mEq sodium alginate and 200 g IUdR, were cross-linked with calcium chloride to yield ion equivalence (IE) ratios (Calcium: alginate) of 3:1, 4:1, 5:1, or 6:1. 2 ml of normal saline was placed on top of each hydrogel and allowed to remain in contact at 37℃ for up to 30 days. At set time intervals, the concentration and amount of IUdR in the eluate were assayed by high performance liquid chromatography using UV detection and Water symmetry C18 column. The data for accumulated release rate and concentration in the eluate were calculated based on the calibration curve of peak area versus IUdR concentration. The hydrogel morphologic degradations were also observed. **Results** The hydrogels entrapped 92.9%, 98.6%, 98.4% and 98.6% of the IUdR with 3:1, 4:1, 5:1 and 6:1 IE ratios, respectively. IUdR concentration in eluates from 3:1 IE ratio hydrogel decreased faster than that from other hydrogels over time ($P < 0.01$). The 4:1, 5:1 and 6:1 IE ratio hydrogels produced more than 10 μm IUdR concentrations in eluates for the first 8 days, while the 3:1 IE ratio hydrogel for 4 days. IUdR release rates of the 4:1, 5:1 and 6:1 IE ratio hydrogels were very close, however they were lower than that of the 3:1 IE hydrogel in the first 48 hours ($P < 0.05$). At day 30, the 3:1 and 4:1 IE ratio hydrogels had 100% and 88% degradation, but no significant degradation was observed in the other hydrogels. **Conclusion** The sodium alginate hydrogel with 4:1 IE ratio exhibited an optimal IUdR sustained release and almost complete degradation in 30 days. (J Intervent Radiol, 2006, 15: 293-298)

【Key words】 Drug delivery, Kinetics; Hydrogel, Alginate; Iododeoxyuridine

Introduction

Vascular smooth muscle cell (SMC) proliferation plays an important role in intimal hyperplasia that mainly causes restenosis following angioplasty [1, 2]. Despite considerable effort to develop a therapeutic pharmacologic strategy to efficiently suppress SMC proliferation, there has not been a clinically effective drug to prevent restenosis following angioplasty [3]. Iododeoxyuridine (IUdR), which can be incorporated into the DNA of dividing cells, has been used as a carrier to deliver I-125 for intracellular molecular radiation of cancer therapy [4-8]. Such radiolabeled IUdR could be used to suppress the intimal hyperplasia by targeting proliferating SMC and avoiding surrounding normal tissue damage. However, its clinical application is limited because of the rapid clearance from blood, significant toxicity (usually marrow suppression) and low incorpoation rationrate

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at the targeted tissues after systemic administration[6-8]. Therefore, local drug delivery should be a preferred way of ensuring that adequate IUdR is delivered to the pathological site without the risks of side effects. Furthermore, IUdR competes with thymidine to incorporate into DNA during S-phase of cell cycle. It is imperative to keep a high enough concentration of IUdR for contact with targeting cells at the interval[9].

Polymer conjugated with therapeutic agent has been used for local drug delivery[10]. In this system, a drug is attached to the polymer through a biodegradable spacer enabling drug release at a relatively controlled rate and keeping its concentration higher for a relatively longer time at the local site. Sodium alginate cross-linked calcium gluconate is a biodegradable multiblock polymer, which has been studied as a drug delivery system in vitro [11]. A periadventitial delivery of drugs with a sustained release system following angioplasty can provide theoretically high concentration of drugs at the target site for a prolonged period and avoid blood flow clearance. Therefore, alginate hydrogel may provide a potential and powerful drug delivery system facilitating I^{125}-IUdR delivery for inhibiting the proliferation of SMCs. However, there has been no information on the profile of IUdR release from alginate gel. In the present study, IUdR was entrapped in alginate hydrogel to obtain a system for prolonging IUdR release with the optimization of kinetics, and the characterization of the alginate hydrogel were investigated as well.

Materials and Methods

5-iodo-2′-deoxyuridine (IUdR)(stock solution 10 mg/ml; Sigma, USA) was diluted in distilled water to concentrations of 5, 10, 20, 40, and 80 u mol/L. 20 ul samples of IUdR at each concentration were analyzed by a water 1 high-performance liquid chromatography (HPLC) with an allethenic C18 5 μm (4.6 mm × 150 mm) column without a guard column, at a flow rate of 1.0 ml/min with mobile phase of 100 umol/L acetic acid with 4% (v/v) acetonitrile (Sigma, St. Louise, MS), pH = 5.45. Total run time was 20 minutes. Absorbance was measured with use of a water UV detector set at 276 nm. Absorbance area of IUdR peak was recorded, and a calibration curve of peak area versus IUdR concentration was generated.

Hydrogels were created in glass vials (23 mm diameter, 85 mm high, 20 ml) with use of 1.6 ml (0.16 mEq) of 2% (W/V) aqueous solution of sodium alginate (LVG ultrapure, Pronova biopolymer, Gaustadalleen, Oslo, Norway) (0.1 mEq/ml), 0.2 ml of IUdR (200 μg) and 0.2 ml of 0.48, 0.64, 0.80 and 0.96 mEq of calcium chloride (Fisher Scientific, Hampton NH). Three hydrogels were created with each concentration of calcium chloride for total 12 hydrogels (Table 1).

All hydrogels lost their flow ability and mobility within 2 minutes (Figure 1). Two additional hydrogels were created with use of Ca: Alginate ratio 1:1 and 2:1, but these two hydrogels were only partially gelled at 24 hours. The vials were covered and placed in a plastic box within a 37℃ incubator.

Table 1　Components of hydrogels formed

Hydrogel	IE Ratio 3 : 1(1,2,3)	IE Ratio 4 : 1(1,2,3)	IE Ratio 5 : 1(1,2,3)	IE Ratio 6 : 1(1,2,3)
Alginate(0.1 mEq/ml)	0.16 mEq	0.16 mEq	0.16 mEq	0.16 mEq
IUdR(1000 μg/mL)	200 μg	200 μg	200 μg	200 μg
Calcium(6.4 mEq/ml)	0.48 mEq	0.64 mEq	0.8 mEq	0.96 mEq
Ca:Alg Ratio	3 : 1	4 : 1	5 : 1	6 : 1

After gelling for 24 hours, 2 ml of 0.9% sodium chloride was placed gently on the top of the formed hydrogel. The eluate was removed and filtered, and 20 μl was injected into the HPLC for analysis. The remaining eluate was stored in a vial. 2 ml of fresh 0.9% sodium chloride were then replaced on the surface of the gel and allowed to remain in contact with the hydrogel for 1 hour prior to analysis with HPLC. This process was repeated at 2, 4, 8, 12, 24 and 48 hours, and then every other day up to 30 days. HPLC was performed on 20 μl samples of the eluates from each gel at each time point, as described previously[11].

The amount and concentration of IUdR in the eluates at each time point were calculated based on the calibration curve of peak area versus IUdR

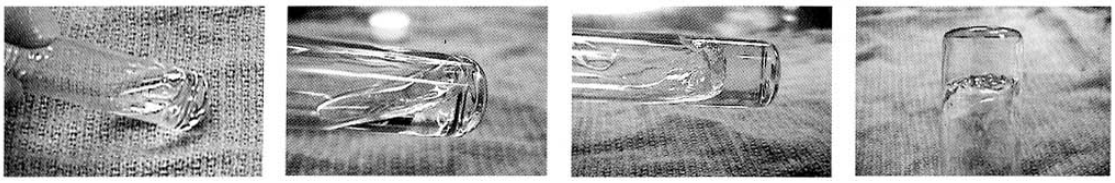

Fig.1 Flowability and mobility.**(a)**Alginate started as a liquid. When the calcium was added, the liquid alginate started to become solid. **(b)**With increased cross-linked, the liquid became thicker but continued to flow with the consistency of molasses. **(c)**When flowability is lost, the alginate no longer changed shape as the vial was turned. The gel would still move in the vial but it moved as a unit. **(d)**When mobility was lost, the vial could be turned upside down without seeing motion of the gel.

concentration. The amount of IUdR in the eluates at time 0 was considered as the amount of IUdR excluded from hydrogel. This was recorded and subtracted from the amount of IUdR used to create the hydrogel for determining the amount of IUdR immobilized in the hydrogel. The amount of IUdR in the eluate at subsequent time point was recorded and divided by the amount of loaded IUdR to determine the percentage of release from the gel at each time point. The cumulative release percentages were plotted versus time point. Morphologic changes of gels were observed daily and their degradations were calculated based on the original gels.

Statistics: The cumulative release rate and concentration comparison were analyzed with use of log-rank tests and log-linear models. Piece-wise linear regression was performed on the percent release data from 0 to 48 hours, 4 to 16 days, and 18 to 30 days. The slopes of these regressions were compared using a nonpaired Student t test to assess the differences in the rate of IUdR release during these three time periods. These time periods were chosen because the data approached linearity in every period. The statistics significance is defined as $P < 0.05$.

Results

Calibration curves of peak area versus concentration had excellent linear correlation (R^2 = 0.9999). IUdR concentrations in eluates based on the calibration curve are shown in Figure 2. IUdR concentration in eluates from 3: 1 IE ratio hydrogel decreased faster than those from other hydrogels over time ($P < 0.01$). The 4:1, 5:1 and 6:1 IE ratio hydrogels produced more than 10 mol/L IUdR concentrations in eluates for the first 8 days, while the 3:1 IE ratio hydrogel for 4 days. The hydrogel entrapped 92.94%, 98.6%, 98.4% and 98.6% of the IUdR with 3:1, 4:1, 5:1 and 6:1 IE ratios, respectively. The cumulative percentages of the IUdR released are illustrated in Table 2 and analyzed in Figure 3 with use of piece-wise linear regression. The IUdR released from gels showed a biphasic profile: a burst phase and a sustained release phase. The early rates of release (burst phase) were high for all loadings of IUdR in the first 48 hours. After 48 hours, the profile showed a decrease in the amount of IUdR released over time and obtained an approximately zero-order release until day 20 for 3:1 IE ratio gel and until at least day 26 for 4:1, 5:1and 6:1 IE ratio gels. Typically the release rate decreased as the drug was depleted from hydrogel. IUdR release rates of the 4: 1, 5:1 and 6:1 IE ratio hydrogels were very close, however they were lower than that of the 3:1 IE ratio hydrogel in the burst phase($P < 0.05$).

Because of water penetration into the polymer matrix, the volume of all gels gradually increased. Among them, 5:1 and 6:1 IE ratio gels had more than

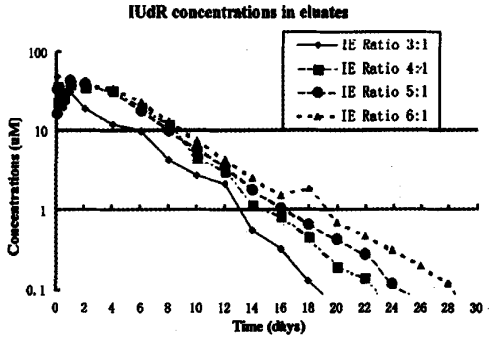

Fig.2 Concentration of IUdR release in eluates in vitro as a function of time. IUdR concentration in the elutes of 3:1 IE ratio hydrogel decreased significantly faster than those of 4:1,5:1,6:1 IE ratio hydrogels overtime ($P < 0.01$).

Table 2　IUdR　cumulated release rate over time(%)

Time	IE Ratio 3 : 1	SD	IE Ratio 4 : 1	SD	IE Ratio 5 : 1	SD	IE Ratio 6 : 1	SD
Average percent release of IUdR from calcium alginate gels								
0	7	2.81	1.39	0.52	1.56	0.97	1.44	0.32
1 h	25.28	3.98	13.74	1.62	13.79	0.6	13.38	0.46
2 h	36.33	5.36	21.25	0.8	19.64	0.42	19.35	0.49
4 h	46.4	6.08	29.31	1.46	27.39	0.91	27.1	1.97
8 h	62.68	7.8	39.31	1.98	37.07	1.19	35.74	1.7
12 h	69.98	8.02	48.12	2.18	45.7	1.61	43.75	2.03
1 d	81.35	7.05	61	2.59	60.84	1.78	57.87	2.38
2 d	88.76	3.15	72.49	2.29	74.67	1.21	70.9	2.08
4 d	92.89	0.72	83.2	1.46	86.06	0.84	82.79	0.52
6 d	96.38	0.79	89.79	1.39	92.36	0.26	90.23	0.67
8 d	97.9	0.6	93.75	1.56	95.8	0.23	94.56	0.16
10 d	98.85	0.53	96.25	0.94	97.71	0.03	96.6	0.54
12 d	99.59	0.17	97.66	0.47	98.6	0.14	97.84	0.35
14 d	99.79	0.1	98.61	0.16	99.17	0.16	98.33	0.26
16 d	99.91	0.05	99.11	0.08	99.47	0.12	99.32	0.17
18 d	99.97	0.02	99.54	0.04	99.68	0.08	99.58	0.16
20 d	99.99	0.00	99.74	0.04	99.81	0.04	99.75	0.13
22 d	100.00	0	99.92	0.04	99.92	0.03	99.86	0.07
24 d	100.00	0	99.98	0.01	99.97	0.01	99.86	0.03
26 d	100.00	0	100.00	0	100.00	0	99.94	0.02
28 d	100.00	0	100.00	0	100.00	0	99.98	0.01
30 d	100.00	0	100.00	0	100.00	0	100.00	0

* Cumulative in vitro release of IUdR from four hydrogels. Release eluate was removed at 1h, 2h, 4h, 8h, 12h, 1d and 2d, followed by every other day up to 30 days and quantified by HPLC.

2 times of the original gels. After reaching maximal volume, the volume deceased as the gels degraded. 3:1 IE ratio gels all broke and disappeared at day 18. The 4:1, 5:1 and 6:1 IE ratio gels had 18%, 130% and 180% volume of the original volume at day 30 (Fig. 4).

Discussion

For IUdR to substitute thymidine and be incorporated into DNA of proliferating SMC in vivo, the controlled and protracted administration of IUdR is particularly important. Polymers have been considered as the carrier for local drug delivery. Alginates are a family of natural block copolymers comprised of beta-D-mannuronic acid (M) and alpha-L-guluronic acid (G). Ca^{2+}, divalent cation, bind to the G locks of the polymer, thereby forming linkages or cross-links between adjacent polymer stands [12]. It belongs to phase-change polymer, which can undergo reversible sol-gel phase transitions. This polymer would entrap the drug in sol-to-gel phase and trigger drug release in the gel-to-sol phase. On its percutaneous delivery with calcium chloride, the loaded copolymer formed a gel that can act as a sustained-release matrix for drug. The rate of drug release from this matrix can be varied by changing the concentration of calcium to vary the hydrogel crosslink density and it had been reported that sodium alginate could be cross-linked with calcium gluconate for heparin entrapment [11]. However, comparing with heparin, IUdR is a small molecular compound with molecular weight of 354.2. The optimal ratio of calcium to alginate should be determined for prolonging IUdR release from the hydrogel.

The release rate of IUdR was assayed with use of HPLC, which is a reliable modality for IUdR

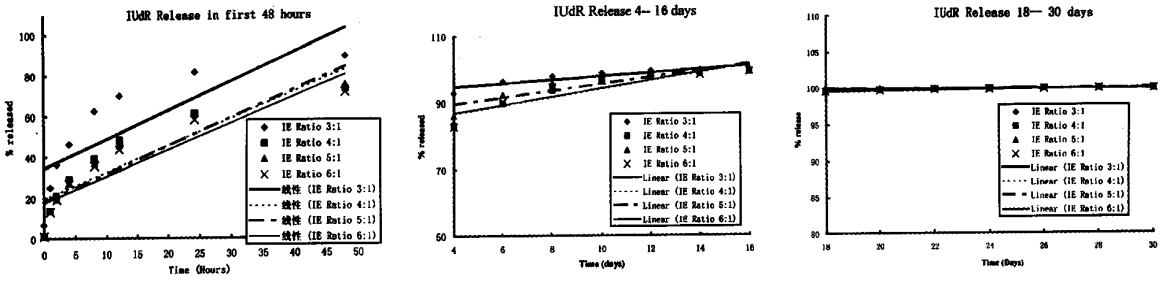

Figure 3. Percent of heparin release over time. Piece-wise linear regression. **(a)**In the first 48 hours, the release rate of 3:1 IE ratio hydrogel was higher than that of other 3 hydrogels ($P < 0.05$). **(b)** From 4-18 days, the process of diffusion predominately decreased. Here the release rate of 3:1 IE ratio was still higher at this earlier period and then gradually close to those of the other 3 hydrogels. **(c)**From 18-30 days, the IUdR release rates of all gels were approximately the same at zero-order release. In this period, hydrogel started shrinkage and/or dissolution, and the amounts of IUdR in the gels were almost all depleted.

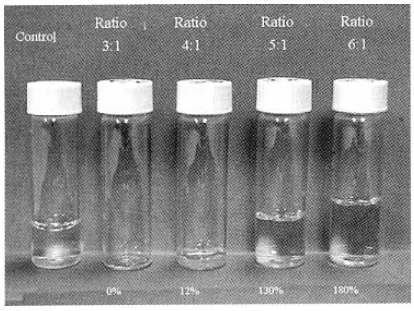

Figure4 3:1 IE ratio gel all dissolved at day 18. The 4:1,5:1 and 6:1 IE ratio gels had 18%,130% and 180% volume of the original volume, respectively, at day 30.

measurement [13]. HPLC with a size exclusion column can easily separate IUdR from alginate because of the big difference between their molecular weights.

The gel formation characteristics for these four hydrogels were very similar. They became hydrogel within 2 minutes. The gel formation in such a short time would prevent diffusion of IUdR into surrounding tissues for aqueous IUdR-laden alginate administration. We found that only 3:1 IE ratio hydrogel did not have complete gel formation, which resulted in 92.9% IUdR entrapment.

IUdR incorporation into intracellular DNA is based on its extracellular concentration [14] and the time of exposure to experience multiple cellular divisions. The duration of IUdR release with a relatively high concentration is critical for the potential IUdR incorporation rate of proliferating cells. This in vitro experiment showed that the initial IUdR diffused fast and the release rates from 3:1 IE hydroge were higher than those from the 4: 1, 5:1 and 6:1 IE ratio hydrogels in the first 48 hours. This burst release is known to depend on the rapid water penetration into the polymer matrix[12]. After the initial rate, the eventual rate of release of IUdR was slower and protracted over duration of approximately 8 days in all gels except IE ratio 3:1 gel, which had slow release only for 4 days. During this period, the concentrations of IUdR in the eluates maintained more than 10 μm, which was within the optimal range for proliferating SMC to uptake IUdR[15]. Lawrence[16] reported the incorporation of halogenated pyrimidines plateaued for 4 days of exposure to IUdR. For in vivo application, however, comparatively more protracted exposure may be necessary to achieve the maximal replacement of thymidine, because maximal proliferating activity may occur after 3 days following angioplasty[17]. Because the 4:1, 5:1 or 6:1 IE ratio hydrogels released 10 μm up to 8 days, the cell exposed to these gel would have ample time for thymidine replacement.

Because of its hydrophilic characteristics and high water content, the volume of hydrogel expanded as it sucked water during eluting. The expanding volume increased with higher IE ratio. The reason is probably high concentration of calcium chloride in the gel resulting in the increase of entry of water into the polymer. The volumes of 5:1 and 6:1 IE ratio hydrogels could reach over two times the volume of the original gels. It may not be beneficial for adventitial delivery since the expanded gel may press

the wall of the vessel.

For the hydrogel administrated around the vessels, its degradation is very important for the solubilization of the system. This experiment showed 5:1 and 6:1 IE ratio hydrogels did not significantly degrade after 30 day eluting, and at that time point no IUdR was left in the gels. Theoretically, the higher IE ratio could produce more cross-linked of polymer, resulting in the decrease rate of entry of water into the gel, which eventually would decrease release rate. Actually, 4:1 IE ratio hydrogel had almost the same release rate of IUdR as 5:1 or 6:1 IE ratio hydrogel. IUdR entrapped in the polymer matrix would be released at first by diffusion, and later by the combination of both diffusion and degradation mechanism. It seems that the diffusion actually played a major role for drug release, even if the degradation may also influence the release kinetics.

This in vitro study confirmed and quantified the controlled release of IUdR from sodium alginate hydrogel and provided the basis for the further quantification of the delivery of IUdR in the in vivo experiment. The results showed that the sodium alginate hydrogel with 4:1 IE ratio gel exhibited IUdR release of more than 10 μm concentration for 8 days without significant gel swelling over the 30 day time period studied. Thus, 4:1 IE ratio hydrogel can be an appropriate gel to exhibit relatively longer IUdR sustained release.

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