CONSORTIUM

Editorial

CALIBRATING HYDROGELS FOR DELIVERY OF BIOLOGICS

Kamla Pathak

Professor, Pharmacy College Saifai, Uttar Pradesh University of Medical Sciences, Etawah 206130, Uttar Pradesh, India.

Abstract

In the past decade, depot systems for tissue engineering, cell therapy, biomedical research, and therapeutic proteins, have been extensively investigated. Hydrogels offer an interesting platform for sustained delivery of biologicals as these can be readily formulated with limited impact on their integrity and stability. Their high-water content and porous structures make them especially suitable for loading with therapeutic proteins However, relatively rapid release of the hydrophilic compounds (period of hours to days) and limited drug loading capacity (<10%) present major challenges. Cleavable cross-linker or hydrogels that respond to an external trigger such as ultrasound have been suggested as suitable alternatives. However, scale-up and cost-effective manufacturing using safe and established excipients remains a challenge and hydrogels for biologicals are at present scarcely developed beyond the clinical evaluation phases. While some commercial products are available the future of hydrogels for biologicals depends on the medical needs, the general benefit/risk balance, and overall costs.

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Corresponding author:
Kamla Pathak. Professor, Pharmacy College Saifai, Uttar Pradesh University of Medical Sciences, Etawah 206130, Uttar Pradesh, India.
E.: kamlapathak5@gmail.com

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Hydrogels as depot systems for sustained release of low molecular weight therapeutic proteins are attractive options for pharmaceutical industry. These are of particular industrial interest because many hydrogels can be produced solely by mixing aqueous solutions. Thus, the relatively “delicate” proteins (e.g. immunoglobulins) can be formulated without compromising their integrity and stability[1]. Besides full-sized immunoglobulins, the amenable architecture of antibodies has made it possible to develop more than 60 alternative antibody formats[2]. More than thirteen have proceeded into clinical development[3]. The antibody formats with molecular weights less than 50 kDa are of interest to the formulators for development as depot systems because of their relative short circulation half-life that requires frequent subcutaneous or intravenous dosing. The most commonly used depot systems are inserts, coatings, microparticles, based on natural products or synthetic polymers; and hydrogels[4]. Currently an increasing number of antibody formulations are developed as high concentrated liquid formulations (50 to 150 mg/ml) that can be self administered[5]. However, the advantage is contrasted by the manufacturing complexities that require special equipment and novel excipients.

From a manufacturer’s point of view, hydrogels appear to be an attractive format as

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compared to other depot systems since hydrogels are typically produced by a simple mixing procedure of biocompatible materials in aqueous solutions at ambient temperature. Hydrogels are elastic, hydrophilic, cross-linked, 3-dimensional networks, composed of natural or synthetic polymeric, water insoluble materials that can bind a high amount of water[6]. Their high-water content and their mechanical properties of soft matter and porous structures make them especially suitable for loading with therapeutic proteins[7]. However, hydrogels suffer from limited loading capacity; short time period (hours to days) in which hydrogels release their hydrophilic cargo and the relative high plasma concentrations needed to achieve a therapeutic effect. This may limit the use of hydrogels for antibodies but the same is not true for several alternative antibody formats namely Fab, Fab2, Fab3, scFv, triabodies, diabodies, minibodies, nanobodies, Bi-specific T-cell engagers (BiTE), dual-affinity re-targeting antibodies (DARTs) and single-domain antibodies which often possess plasma half-lives of less than one day and can be highly potent[8].

In order to develop advanced and cost-effective depot formulations, the properties of hydrogels need to be optimized. Apart from pharmaceutical criteria (formulator/ manufacturer point of view) safety issues are equally important. From the drug developer's point of view, hydrogel building blocks should be FDA approved and the cargo molecule should be stable and not interact with the hydrogel during the manufacturing process and during the entire release period at body temperature[9]. The manufacturing process should be simple without the use of heat or organic solvents leading to a formulation that can be sterile-filtered and injected within seconds through a 27G or 30G needle. The hydrogel depot formulations should represent a platform technology, which could serve for a variety of drugs or drug categories. Loading capacities should be ideally at least 10% and drug product shelf-life at 2-8°C should be at minimum two years[10]. The reality is, however, quite different. Many delivery systems currently developed by research groups in academic institutions aim at increasing complexity rather than simplicity. Academic researchers tend to work on innovative and rather complicated delivery systems, whereas industrial research is focused on ease of production, cost of goods and manufacturing, process scalability, process robustness, and on reducing the number of excipients to the bare minimum. Collaborations between academia and industry need to be fostered to keep exchanging ideas, acknowledging all aspects needed for the development of a depot formulation, such as drug metabolism and pharmacokinetics, pharmacology, and toxicology.

A significant challenge of hydrogel formulations is their hydrophilicity and high-water content, which typically results in relatively rapid drug release of hydrophilic molecules (hours or days). The concepts to prolong the release duration to weeks/months include accentuating the interactions between the drug and the hydrogel matrix, or incorporation of a diffusion barrier to retard the drug release. These strategies have been successfully implemented for hydrophobic drugs in InGell gamma by InGell Labs (Groningen, The Netherlands) wherein the depot system based on the gamma technology releases its hydrophobic cargo over a period of days to weeks[11]. For hydrophilic drugs, such as

antibodies and other immunoglobulins, the challenges are far greater. In addition to short release period, challenges concerning use of hyaluronidase to widen the injection space and their loading capacities (1-5% by weight) are significantly important. Typical antibody dose ranges between 2 to 6 mg/kg, which translates into a plasma concentration of 50-150 µg/ml[12]. Depending on the plasma half-life, this concentration will, however, only be a fraction of that when released over the course of a week or even a month. A depot formulation for therapeutic proteins is therefore especially useful for highly potent drugs. An alternative solution to increase the loading capacity by use of highly concentrated crystalline/ solid amorphous protein solutions and to pre-administer an IV bolus dose followed by subcutaneous depot maintenance dose to achieve clinically relevant steady state concentrations.

Despite enormous academic research on hydrogel-based drug delivery systems, the number of hydrogels approved by the FDA or those in clinical development is limited. One of the few marketed hydrogels used for subcutaneous drug delivery is “Supprelina LA” by Endo Pharmaceuticals Solutions Inc., Dublin, Ireland, for sustained delivery formulation for histrelin acetate[13]. Another is Eligard™ 7.5 mg, (Novelon therapeutics, US) a polymeric matrix formulation for controlled delivery of leuprolide acetate, for over a month[14]. A platform technology from Foresee Pharmaceuticals Co., Ltd., Taipei, Taiwan, is a stabilized injectable formulation, for controlled-release formulations of small molecules, peptides, and proteins. Amongst the various successful research products, Foresee's FP-001(LHRH agonist), is in clinical phase III study for advanced prostate carcinoma therapeutics and FP02C-14-001 (MMP-12 inhibitor) is in phase I study[15]. Another platform sustained release technology BEPO® developed by MedinCell (Jacou, France) claimed as a game changer by the company is a simple yet flexible technology. BEPO® on subcutaneous injection forms a fully bioresorbable depot that can provide controlled release of therapeutic molecules for days, weeks or months and therefore can be used for treatment of chronic and short term illnesses[16].

For proteins that require intravitreal injections, a hydrogel formulation is particularly attractive to improve patient convenience and compliance. For example, the anti-VEGF Fab-fragment ranibizumab (LucentisR) and the anti-VEGF monoclonal antibody bevacizumab (AvastinR) are clinically used to for age-related macular degeneration and proliferative diabetic retinopathy. Both treatments need to be administered via intravitreal injection every four to six weeks[17]. Many academic groups have developed intravitreal depot formulations for ranibizumab and bevacizumab so as to extend the duration to months instead of weeks. Considering the extreme uncomforting injection procedure, any reduction in the injection frequency would be an instant marketing advantage. Besides ophthalmological applications, hydrogels have been researched for anti-cancer mAbs such as a trastuzumab (HerceptinR) hydrogel for breast cancer therapy[18].

Though the progress in hydrogel technologies is evident, the commercialization of hydrogel formulations remains challenging. Scale up and cost-effective manufacturing using safe and

established excipients need special mention. Hydrogels for biologicals are at present scarcely developed beyond the clinical evaluation phases. The future of “next generation” hydrogels for biologicals will thus depend on the success of suitable molecule formats especially those that are highly potent or exhibit short plasma half-lives in addition to the medical needs, the general benefit/risk balance, and overall costs.

References

1. Vermonden T, Censi R, Hennink WE, Hydrogels for protein delivery, Chem Rev, 2012, 112, 2853-2888.
2. Hollinger P, Hudson PJ, Engineered antibody fragments and the rise of single domains, Nat.
3. Biotechnol, 2005, 23(9), 1126-1136.
4. Spiess C, Zhai Q, Carter PJ, Alternative molecular formats and therapeutic applications for
5. bispecific antibodies, Mol Immunol, 2015, 67(2), 95-106.
6. 4. Vaishya R, Khurana V, Patel S, Mitra AK, Long-term delivery of protein therapeutics, Expert Opin Drug Deliv, 2015, 12(3), 415-440.
7. 5. Garidel P, Kuhn AB, Schafer LV, Karow-Zwick AR, Blech M, High-concentration protein formulations: How high is high? Eur J Pharm Biopharm, 2017;119: 353-360.
8. 6. Ahmed EM, Hydrogel: Preparation, characterization, and applications: A review, J Adv Res, 2015, 6(2), 105-121.
9. 7. Schweizer D, Serno T, Goepferich A, Controlled release of therapeutic antibody formats, Eur J Pharm Biopharm, 2014, 88(2), 291-309.
10. 8. Seliktar D, Designing cell-compatible hydrogels for biomedical applications, Science, 2012, 336, 1124-1128.
11. 9. Baldrick P, Pharmaceutical excipient development: The need for preclinical guidance, Regul.
12. Toxicol Pharmacol, 2000, 32, 210-218.
13. 10. Alexander C, Shakesheff KM, Responsive polymers at the biology/materials science
14. Interface, Adv Mater, 2006, 18(24), 3321-3328.
15. 11. http://ingellpharma.com/products/ingell-gamma/, accessed 20 Mar 2018.
16. 12. Newsome BW, Ernstoff MS, The clinical pharmacology of therapeutic monoclonal antibodies in the treatment of malignancy; Have the magic bullets arrived? Br J Clin
17. Pharmacol, 2008, 66(1), 6-19.
18. 13. http://www.endo.com, accessed 21Mar 2018.
19. 14. Kumar TR, Novel delivery technologies for protein and peptide therapeutics, Curr Pharm

20. Biotechnol, 2006, 7(4), 261-276.
21. 15. http://www.foreseepharma.com, accessed 20 Mar 2018.
22. 16. https://www.medincell.com/technology/, accessed on 16 April 2018.
23. 17. Keane PA, Sadda SA, Development of anti-VEGF therapies for intraocular use: A Guide for clinicians, J Ophthalmol. 2012; 2012: 483034.
24. 18. Lee ALZ, Ng VWL, Gao S, Hedrick JL, Yang YY, Injectable hydrogels from triblock copolymers of vitamin E functionalized polycarbonate and poly (ethylene glycol) for subcutaneous delivery of antibodies for cancer therapy, Adv Funct Mater, 2014, 24, 1538-1550.