Research Article

Formulation and Evaluation of Metronidazole Nanogel

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ABSTRACT

This study involves the development and testing of metronidazole-loaded nanogels for topical use. Six formulations (F1–F6) were developed and evaluated according to organoleptic characteristics, grittiness, pH, drug content uniformity, in-vitro diffusion, particle size, zeta potential, polydispersity index, conductivity, and antimicrobial activity. All the formulations had clear, homogenous nanogels with pale yellow color and less odorous, as they were fit for dermal application. pH values were 5.0 to 6.0, all within the skin-compatibility range. Drug content was between 94.70% and 99.94%, reflecting effective drug entrapment and even distribution. Biphasic release was indicated from *in-vitro* diffusion studies with formulation F6 exhibiting highest cumulative release (97.03%) in 8 hours. Particle size analysis identified F3 (7.119 nm) and F6 (143.4 nm) as the smallest with highest diffusion potential. Zeta potential measurements indicated favorable colloidal stability for all but F2 and F5 formulations. Antimicrobial assessment revealed that only F3 and F6 produced notable activity against *Staphylococcus aureus*, of which F6 presented the greatest and most consistent sizes of inhibition zones. Activity was not detected against Escherichia coli. Out of all formulations, F6 presented the best overall performance and therefore is a potential nanogel candidate for the topical delivery of metronidazole.

Keywords: Metronidazole, Nanogel, Topical drug delivery, *In-vitro* drug release, Antimicrobial activity.

INTRODUCTION

The advent of nanotechnology has greatly impacted on the environment of pharmaceutical sciences, and new drug delivery systems have been created to improve bioavailability, minimize side effects, and amplify therapeutic effects[1-3]. Of these systems, nanogels nanoscale hydrogel particles are unique in that they present high water content, soft and yielding structure, adjustable size, high drug carrying capacity, and responsive nature to bodily stimuli. Because of their capacity to merge the benefits of hydrogels and nanoparticles, nanogels are increasingly being investigated for site-specific, controlled drug delivery, especially in dermal and topical applications[4-6].

Metronidazole is a synthetic derivative of nitroimidazole and is a recognized antimicrobial and antiprotozoal drug employed in treating anaerobic bacterial and protozoal infections. It is widely used in dermatological treatments such as rosacea, acne vulgaris, pressure ulcers, and surgical wounds owing to its strong antimicrobial and anti-inflammatory activity. Nonetheless, conventional topical preparations like creams, lotions, or ointments are usually connected with drawbacks such as poor skin permeability, short retention time on the skin surface, and regular reapplication due to low residence time. These demerits can diminish treatment efficiency as well as patient compliance[7-10].

Nanogel-based drug delivery systems have been attracting significant attention for topical use over the past few years because of their increased permeability across the stratum corneum, sustained release of the drug, increased retention at the site of action, and biocompatibility[11]. The nanogels' high surface area and small particle size allow for greater interaction with the skin, resulting in deeper penetration and prolonged effects. Moreover, nanogels also provide potential labile drug protection against environmental degradation such as that of Metronidazole and enable controlled release kinetics[12-15].

This study aims at the design and systematic assessment of Metronidazole-loaded nanogels to improve its topical delivery. A set of batches of nanogels (F1–F6) are formulated with appropriate gelling and stabilizing agents, and the effect of formulation parameters is examined by a thorough evaluation protocol. The major formulation factors examined are particle size analysis, zeta potential measurement, polydispersity index (PDI), conductivity, organoleptic evaluation, and drug content uniformity. The in-vitro release behavior of the developed nanogels is assessed. Also, antimicrobial evaluation is carried out against chosen microbial strains to check the biological effectiveness of the nanogel formulations[16-19].

This research postulates that an appropriately formulated Metronidazole nanogel has the potential to drastically enhance therapeutic efficacy through sustained release of drugs, increased antimicrobial efficacy, and enhanced patient compliance. The findings of this research could be a useful basis for future clinical translation of topical nanogel delivery systems and add to the development of intelligent drug delivery systems in dermatology and infection control.

MATERIALS AND METHODS

Materials

Metronidazole was obtained as a gift sample from Aarti Drugs Pvt. Ltd. Hydroxypropyl methylcellulose (HPMC, E5 LV PREMIUM) was procured from Research-Lab Fine Chem Industries (CAS No: 9004-65-3). Carbopol 940 was supplied

by Sisco Research Laboratories Pvt. Ltd. (CAS No: 9003-01-4). Propylene glycol (CAS No: 57-55-6) and triethanolamine were purchased from Loba Chemicals Pvt. Ltd. and Sisco Research Laboratories Pvt. Ltd., respectively. Glycerol and sodium benzoate were obtained from Nice Chemicals Pvt. Ltd. Isopropyl alcohol (CAS No: 67-63-0) was procured from Finar Ltd., and ethanol was supplied by Changshu Hongsheng Fine Chemical Co. Ltd. All chemicals used were of analytical grade and used without further purification.

Preparation Using Solvent Evaporation Method

At First water taken in a beaker then placed to magnetic stair then add slowly HPMC E 5 LV Premium (For F1, F2, F3) and Carbopol 940 (For F4, F5, F6) polymer was mix well. Then Glycerol added as a humectant. Take Sodium Benzoate as a preservatives mixed in slight q.s. water and mixed in the solution.

Isopropyl alcohol q.s. and Ethanol as a solvent was added in the mixture (For F1, F2, F3). Metronidazole API mixed in slight q.s. water and mixed the solution. Next Propylene Glycol as a solvent added in the solution and Triethanolamine as a pH adjuster added then the gel is formed (For F4, F5, F6). Then mixed well for 1 hr in Homogenizer at 8000 rpm in this time solvents are evaporated and Nanogel was formed.

Table 1: Formulation Table

Ingredient	Batch					
	F1	F2	F3	F4	F5	F6
Metronidazole (g/ml)	0.02 gm	0.02 gm	0.02 gm	0.02 gm	0.02 gm	0.02 gm
Hydroxy propyl methyl cellulose (g/ml)	0.042 gm	0.042 gm	0.042 gm	-	-	-
Carbopol 940 (g/ml)	-	-	-	0.02 gm	0.02 gm	0.02 gm
Glycerol (g/ml)	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml
Iso-propyl alcohol (g/ml)	q.s.	q.s.	q.s.	-	-	-
Propylene Glycol (g/ml)	-	-	-	0.30 ml	0.30 ml	0.30 ml
Sodium Benzoate (g/ml)	0.002 gm	0.002 gm	0.002 gm	0.002 gm	0.002 gm	0.002 gm
Triethanolamine (g/ml)	-	-	-	0.01 ml	0.01 ml	0.01 ml
Ethanol (g/ml)	0.2 gm	0.2 gm	0.2 gm	-	-	-
Distilled water (g/ml)	0.7 ml	0.7 ml	0.7 ml	0.6 ml	0.6 ml	0.6 ml

Characterization of Metronidazole Nanogel

Organoleptic Analysis

Nanogels were transferred to transparent beakers and assessed visually for color, homogeneity, and odor. The formulations were also checked for appearance and the occurrence of any aggregates to assess uniformity and aesthetic acceptability[20].

Grittinesss

The formulations were examined under an optical microscope to identify any particulate matter or coarse aggregates. Lack of grittiness is crucial to provide smooth application on the skin[21].

pH Determination

pH of metronidazole nanogels was measured by a calibrated digital pH meter and universal pH paper. Standard buffer solutions of pH 4, 7, and 9.2 were used to calibrate it. The electrode was placed in the gel for 10 minutes prior to reading the value. Triplicate readings were taken, and the mean was recorded[22].

Drug Content Uniformity

To provide even distribution of metronidazole within the nanogels, 1 g of the gel was filled into a 10 mL volumetric flask, dissolved in phosphate buffer (pH 6.8), and shaken for 1 hour. The solution was filtered and characterized by UV-Vis spectrophotometry in the range of 200–400 nm. Drug content was determined from a standard calibration curve[23].

***In-vitro* Diffusion Study**

In-vitro release studies of drugs were done with Franz diffusion cells. Phosphate-buffered saline (PBS, pH 6.8) was filled in the receptor compartment and kept at 37 °C ± 0.5 °C by a circulating water jacket. The medium was kept continuously stirred during the course of the experiment to provide sink conditions and perfect distribution[24].

Particle Size Determination, Zeta Potential, Polydispersity Index, and Conductivity Determination

Particle size, zeta potential, polydispersity index (PDI), and conductivity of the optimized metronidazole nanogel were determined by dynamic light scattering (DLS) method using Malvern Zetasizer (Version 7.11) and Anton Paar Litesizer 500. The dispersion of nanogel was suitably diluted with purified water before measurement[24].

Microbial Study

Antimicrobial activity was determined by agar well diffusion method. Nutrient agar plates were set and seeded with Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria. Sterilized paper discs were imbibed with the test samples and were put over the agar surface. Plates were incubated at 37 °C for 24 hours in a BOD

incubator. Zone of Inhibition was determined in millimeters to assess antibacterial activity. Minimum Inhibitory Concentration (MIC) and killing time were also determined[25].

RESULT AND DISCUSSION

Organoleptic Analysis

The appearance of the prepared formulations of Metronidazole Nanogels were evaluated by visual inspection, while homogeneity was assessed by taking little amounts of hydrogel formulations between the thumb and index finger and looking for any coarse particles. In a similar way, the back hand was given a tiny application of nanogel formulations and massaged independently. This procedure was repeated simultaneously for 3 times. All six formulations (F1–F6) were visually examined and noted to be clear, having a homogeneous appearance and being free of lumps or coarse particulates. The color of all nanogels was uniform, having a pale yellow (straw-like) coloration, and the odor was characterized as less intense, which is desirable for topical use since strong odors can impair patient compliance. These features as a whole are indicative of the aesthetic and user-friendly nature of the formulations.

Grittiness

No presence of aggregates and lumps was seen in the formulations under optical microscope. There was shows only air lumps in the formulations.

Microscopic analysis showed no evidence of particulate matter, aggregates, or formulation-induced lumps, proving a smooth and fine nanogel texture. The only inclusions seen were air bubbles, which are inevitable while formulating the gel and do not affect drug delivery. This lack of grittiness increases spreadability and is more comfortable for the patient during application.

pH Determination

The pH of the formulations were determined using digital pH meter and Universal pH tester. The pH range was 5 to 6. The pH of the formulations was between 5.0 and 6.0, which is within the acceptable range for dermal application (4.5–6.5). This means that the nanogels are not expected to induce irritation or discomfort on dermal application. F1, F2, F3, and F6 had a pH of 6.0, while F4 and F5 had a slightly acidic pH of 5.0 but were still within the safe dermal application range.

Drug Content Uniformity

The drug content was found to be in the range 94.70% - 99.94%, which is an acceptable range. The drug content in all six formulations was 94.70% to 99.94% of acceptable pharmacopeial range, which will be consistent with dosage across applications. F6 had the highest drug content (99.94%), followed by F3 (99.22%) and F1 (98.81%), pointing towards effective entrapment of drug during the process of gel preparation. The lowest value (94.70%) was observed in F4 but still was within acceptable limits, pointing towards overall uniformity distribution and stability of metronidazole in the nanogel matrix.

In-vitro Diffusion Study

The results of the evaluation *in-vitro* diffusion study of metronidazole nanogels are tabulated in table 3.

Table 2: Results of evaluation parameter of metronidazole nanogels

TESTS	F1	F2	F3	F4	F5	F6
Homogeneity	Clear	Clear	Clear	Clear	Clear	Clear
Colour	Pale Yellow (Straw)	Pale Yellow (Straw)	Pale Yellow (Straw)	Pale Yellow (Straw)	Pale Yellow (Straw)	Pale Yellow (Straw)
Odour	Less	Less	Less	Less	Less	Less
pH	6.0	6.0	6.0	5.0	5.0	6.0
Drug Content Uniformity (%)	98.81	97.99	99.22	94.70	98.63	99.94

Table 3: Evaluation of *In-vitro* Drug Release

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	15.87	10.37	12.06	10.88	13.06	12.22
2	26.3	28.4	24.3	26.54	23.67	25.49
3	34.73	33.96	36.61	35.96	32.38	36.75
4	43.53	52.08	49.11	52.23	45.36	49.1
5	63.55	66.5	61.73	64.35	57.65	61.77
6	75.09	78.76	74.45	79.47	65.86	74.44
7	88.21	85.23	87.17	89.63	81.58	87.16
8	91.07	93.36	95.32	95.57	92.54	97.03

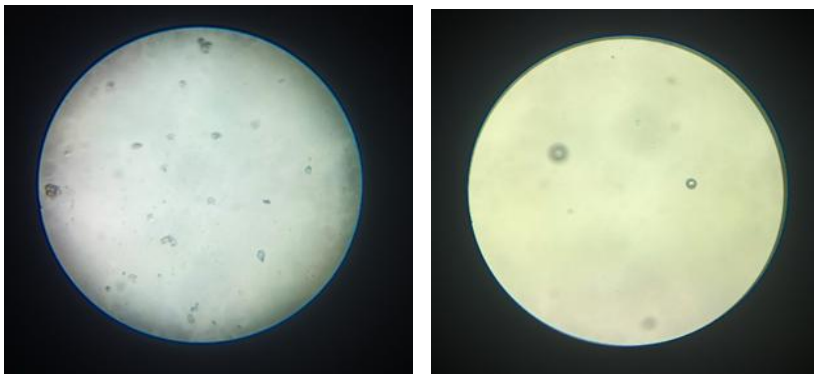

Figure 1: Formulations under optical Microscope

Drug release profiles of Metronidazole nanogel formulations (F1–F6) were compared for 8 hours by the in-vitro diffusion method. All the formulations followed a biphasic type of release pattern having an initial burst release during the initial 2–3 hours, with a sustained release thereafter. At 1 hour, release of drug varied between 10.37% (F2) and 15.87% (F1), possibly because of the release of loosely adsorbed drug at or close to the surface of the nanogel. This burst effect is useful in topical applications where instant therapeutic activity is required. Then, steady and sustained release was seen from all formulations. At 8 hours: F6 had the most cumulative release (97.03%), while F4 (95.57%), F3 (95.32%), and F2 (93.36%) came almost next. F5 (92.54%) and F1 (91.07%) also showed good sustained release, albeit slightly lower. The increased release in formulations like F6 and F3 may be due to their smaller particle size, better surface area for diffusion, and better drug distribution within the gel matrix.

Particle Size Determination, Zeta Potential, Polydispersity Index, and Conductivity Determination

Zeta potential measurements reflect the surface charge of the nanogels and are important in forecasting the stability of the formulation. Fifty-three batches showed moderate values of zeta potential from -11.0 mV to -13.6 mV (F1, F3, F4, and F6), implying adequate physical stability as a result of adequate repulsive forces between particles. F2 and F5, however, showed comparatively low zeta potential values (-0.1 mV), implying inadequate electrostatic repulsion, leading to a possibility of aggregation or a smaller shelf life. This difference is an indication of the effect of excipient interactions and polymer interaction on the colloidal stability of the gels.

Conductivity analysis gives information on the ionic character and dispersion stability of the nanogels in general. The majority of batches exhibited low conductivity levels between 0.029 mS/cm and 0.043 mS/cm, indicative of non-electrolytic or weak electrolyte behavior appropriate for topical applications. F3 and particularly F6, however, exhibited significantly higher values of conductivity at 0.190 mS/cm and 6.97 mS/cm, respectively. The elevated conductivity of F6 could be due to the existence of stronger ionic strength ingredients or phase separation, which would influence its overall stability. These results also align with F6's high PDI score, which denotes less stable formulation traits.

The particle size of the prepared Metronidazole nanogels differed considerably throughout the batches. F1, F2, and F4 had particle sizes ranging from 440.1 to 484.3 nm, reflecting comparatively larger nanogel particles. On the other hand, F3, F5, and F6 presented significantly smaller particle sizes, with F3 having an extremely low particle size of 7.119 nm and F6 having the lowest at 143.4 nm. A smaller particle size is preferred in nanogel formulations because it enhances penetration of the drug and topical bioavailability. The considerable variability of F3's particle size indicates formulation-dependent control, probably because of the polymer type and homogenization effectiveness during production.

The polydispersity index is an indication of the uniformity of particle size distribution. Optimal nanogels should possess a PDI value less than 0.5, representing a monodisperse system. Out of the six formulations, F1, F2, and F4 presented PDI values ranging about 30–31%, reflecting acceptable uniformity. F3 and F5 possessed PDI values of 0.557 and 0.357, respectively, within a favorable range for nanogels but slightly suggest moderate heterogeneity. Batch F6 had an elevated PDI value of 1.000, indicative of a polydisperse system with a broad particle size range, which could impact drug release and absorption consistency.

Table 4: Particle Size, Zeta Potential value, Polydispersity Index and Conductivity values

Batch	Particle Size	Zeta Potential	Polydispersity Index	Conductivity
F1	482.8 nm	-13.6mV	30.0%	0.033 mS/cm
F2	440.1 nm	-0.1mV	29.5%	0.041mS/cm
F3	7.119 nm	-11.0mV	0.557	0.190 mS/cm
F4	484.3 nm	-11.0mV	31.2%	0.029 mS/cm
F5	323.5 nm	-0.1mV	35.7%	0.043 mS/cm
F6	143.4 nm	-12.3mV	1.000	6.97 mS/cm

Microbial Study

Anti-Microbial activity shows only F3 and F6 formulation on Gram positive bacteria (*Staphylococcus aureus*) the zones were shows for F3 2mm, 3mm, 2.25 mm here standard drug was not showing anti-microbial activity. For F6 shows 7mm, 9.5mm, 5.25mm, 7mm here standard drug was show zone. Gram negative bacteria (*Escherichia coli*) and F1, F2, F4, F5 were not show zone of inhibition. Antimicrobial activity of the obtained metronidazole nanogel formulations (F1–F6) was assessed by the zone of inhibition technique against some selected microbial pathogens: Gram-positive bacteria (Staphylococcus aureus) and Gram-negative bacteria (Escherichia coli).

Activity Against *Staphylococcus aureus* (Gram-positive)

Among all the formulations that were tested, only F3 and F6 had measurable antimicrobial activity against *Staphylococcus aureus*: F3 had zones of inhibition of 2.0 mm, 3.0 mm, and 2.25 mm in repeated tests. F6 had much larger zones of inhibition of 7.0 mm, 9.5 mm, 5.25 mm, and 7.0 mm, which implies better antimicrobial activity. Interestingly, the control metronidazole drug itself exhibited no zone of inhibition in the F3 tests, suggesting better antimicrobial activity when administered through the nanogel formulation. However, the control drug was inhibitory in the F6 experiment, which might indicate better synergy or release pattern of the F6 nanogel. This enhanced antimicrobial activity of F6 might be due to: Smaller particle size (143.4 nm) and Highest swelling index (33%), both of which enhance drug release and diffusion.

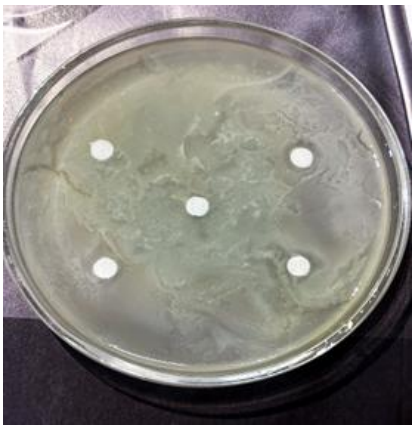

Figure 2: F3 Formulation

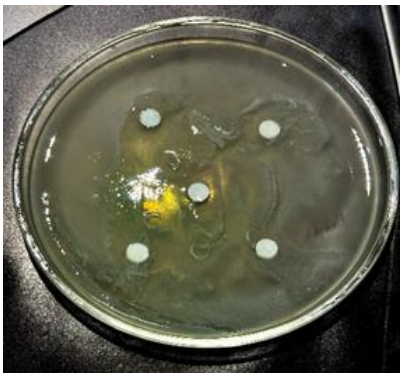

Figure 3: F6 Formulation

Activity Against *Escherichia coli* (Gram-negative)

No zone of inhibition for any of the formulations, F1, F2, F3, F4, F5, or F6, was measurable against *Escherichia coli*. This indicates that metronidazole and the formulations of its nanogel are ineffective against Gram-negative bacteria under these conditions, as might be expected from the known antimicrobial spectrum of metronidazole, which targets mainly anaerobic and some Gram-positive bacteria.

The antimicrobial activity results confirm that F3 and F6 formulations have encouraging activity against Staphylococcus aureus, with F6 exhibiting the strongest and most reproducible inhibition zones. This indicates that nanogel formulation, especially F6, can improve the therapeutic effect of metronidazole by enhancing its release and potentially facilitating drug penetration into bacterial cells. The failure to show activity against Escherichia coli confirms the established antibacterial spectrum of metronidazole.

CONCLUSION

This current study was able to successfully develop and test Metronidazole-loaded nanogels for local delivery. All six formulations (F1–F6) were esthetically acceptable with organoleptic properties being uniform, not gritty, and pH in the ideal dermal range (5.0–6.0), denoting their feasibility for skin application. Drug content was between 94.70% and 99.94%, implying very high entrapment efficiency and homogeneity.

The in-vitro diffusion test indicated a biphasic release pattern with a burst effect followed by prolonged release, and F6 exhibited the greatest cumulative drug release (97.03%) within 8 hours. Particle size measurement indicated that F6 (143.4 nm) and F3 (7.119 nm) possessed the lowest particle sizes, which will ensure better drug penetration and bioavailability. Yet, F6 exhibited a greater polydispersity index (1.000), representing some degree of heterogeneity in particle distribution.

Zeta potential analysis indicated good colloidal stability for the majority of formulations, particularly F1, F3, F4, and F6, and F2 and F5 had lesser stability. F6 had maximum conductivity (6.97 mS/cm), which could be caused by ionic interactions and might impact long-term stability.

Antimicrobial analysis proved that F3 and F6 alone produced zones of inhibition against Staphylococcus aureus, with F6 having the better antibacterial activity. No formulation inhibited Escherichia coli, consistent with metronidazole's established antimicrobial range.

In total, formulation F6 was found to be the best candidate for topical treatment, exhibiting ideal physicochemical properties, improved drug release, and better antimicrobial activity against Gram-positive bacteria. The formulation has great potential for further clinical development as a topical therapeutic in the form of a nanogel for skin infections.

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REFERENCES

1. He, Q., Liu, J., Liang, J., Liu, X., Li, W., Liu, Z. Towards improvements for penetrating the blood–brain barrier—recent progress from a material and pharmaceutical perspective. *Cells*, 2018;7(4): 24-9.
2. Cui, W., Li, J., Decher, G. Self-assembled smart nanocarriers for targeted drug delivery. *Advanced Materials*, 2016;28: 1302–1311.
3. Torchilin, V.P. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nature Reviews Drug Discovery*, 2014;13:813–827.
4. Jensen, L.B., Griger, J., Naeye, B., Varkouhi, A.K., Raemdonck, K., Schiffelers, R. Comparison of polymeric siRNA nanocarriers in a murine LPS-activated macrophage cell line: gene silencing, toxicity and off-target gene expression. *Pharmaceutical Research*, 2012;29(3): 669–682.
5. Jiang, Y., Chen, J., Deng, C., Suuronen, E.J., Zhong, Z. Click hydrogels, microgels and nanogels: Emerging platforms for drug delivery and tissue engineering. *Biomaterials*, 2014;35: 4969–4985.
6. Soni, K.S., Desale, S.S., Bronich, T.K. Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. *Journal of Controlled Release*, 2016;240: 109–126.
7. Li, Y., Maciel, D., Rodrigues, J., Shi, X., Tomás, H. Biodegradable polymer nanogels for drug/nucleic acid delivery. *Chemical Reviews*, 2015;115: 8564–8608.
8. Raemdonck, K., Demeester, J., De Smedt, S. Advanced nanogel engineering for drug delivery. *Soft Matter*, 2009;5: 707–715.
9. Sahiner, N., Godbey, W.T., McPherson, G., John, V. Microgel, nanogel and hydrogel-hydrogel semi-IPN composites for biomedical applications: Synthesis and characterization. *Colloid and Polymer Science*, 2006;284: 1121–1129.
10. Vinogradov, S.V., Bronich, T.K., Kabanov, A.V. Nanosized cationic hydrogels for drug delivery: Preparation, properties and interactions with cells. *Advanced Drug Delivery Reviews*, 2002;54: 135–147.
11. Maya, S., Bruno, S., Amrita, N., Rejinold, N.S., Shantikumar, V.N., Jayakumar, R. Smart stimuli sensitive nanogels in cancer drug delivery and imaging: A review. *Current Pharmaceutical Design*, 2013;19: 7203–7218.
12. Kabanov, A.V., Vinogradov, S.V. Nanogels as pharmaceutical carriers: Finite networks of infinite capabilities. *Angewandte Chemie International Edition*, 2009;48: 5418–5429.
13. Szilágyi, B.Á., Némethy, Á., Magyar, A., Szabó, I., Bősze, S., Gyarmati, B., Szilágyi, A. Amino acid based polymer hydrogel with enzymatically degradable cross-links. *Reactive and Functional Polymers*, 2018;133: 21–28.
14. Wang, H., Chen, Q., Zhou, S. Carbon-based hybrid nanogels: A synergistic nanoplatform for combined biosensing, bioimaging, and responsive drug delivery. *Chemical Society Reviews*, 2018;47:4198–4232.
15. Cortez-Lemus, N.A., Licea-Claverie, A. Poly(N-vinylcaprolactam), a comprehensive review on a thermoresponsive polymer becoming popular. *Progress in Polymer Science*, 2016;53: 1–51.
16. Buwalda, S.J., Vermonden, T., Hennink, W.E. Hydrogels for therapeutic delivery: Current developments and future directions. *Biomacromolecules*, 2017;18: 316–330.
17. Wang, J., Wang, X., Yan, G., Fu, S., Tang, R. pH-sensitive nanogels with ortho ester linkages prepared via thiol-ene click chemistry for efficient intracellular drug release. *Journal of Colloid and Interface Science*, 2017;508: 282–290.
18. Dispenza, C., Spadaro, G., Jonsson, M. Radiation engineering of multifunctional nanogels. *Topics in Current Chemistry*, 2016;374: 69.
19. He, J., Tong, X., Zhao, Y. Photoresponsive nanogels based on photocontrollable cross-links. *Macromolecules*, 2009;42: 4845–4852.
20. Lee, H., Fonge, H., Hoang, B., Reilly, R.M., Allen, C. The effects of particle size and molecular targeting on the intratumoral and subcellular distribution of polymeric nanoparticles. *Molecular Pharmaceutics*, 2010;7:1195–1208.
21. Liu, R., Hu, C., Yang, Y., Zhang, J., Gao, H. Theranostic nanoparticles with tumor-specific enzyme-triggered size reduction and drug release to perform photothermal therapy for breast cancer treatment. *Acta Pharmaceutica Sinica B*, 2019;9: 410–420.
22. Liu, R., Xiao, W., Hu, C., Xie, R., Gao, H. Theranostic size-reducible and no donor conjugated gold nanocluster fabricated hyaluronic acid nanoparticle with optimal size for combinational treatment of breast cancer and lung metastasis. *Journal of Controlled Release*, 2018;278:127–139.
23. Wang, D., Huang, H., Zhou, M., Lu, H., Chen, J., Chang, Y.T., Gao, J., Chai, Z., Hu, Y. A thermoresponsive nanocarrier for mitochondria-targeted drug delivery. *Chemical Communications*, 2019;55:4051–4054.
24. Tokuyama, H., Kato, Y. Preparation of poly(N-isopropylacrylamide) emulsion gels and their drug release behaviors. *Colloids and Surfaces B: Biointerfaces*, 2008;67: 92–98.
25. Chen, Y., Ballard, N., Bon, S. Moldable high internal phase emulsion hydrogel objects from non-covalently crosslinked poly(N-isopropylacrylamide) nanogel dispersions. *Chemical Communications*, 2013;49:1524–1526.