Mini Review

IT Medical Team
https://www.itmedicalteam.pl/

International Journal of Drug Development and Research
0975-9344

2023
Vol. 15 No. 3: 999

Development of Nonionic Bisphosphonate-Modified Drug-Loaded Nanoparticles Binding to Hydroxyapatite

Mohammad Oves*

Department of Biotechnology, High Institute of Biotechnology of Sidi Thabet, University of Manouba, BP-66, 2020 Ariana, Tunis, Tunisia

Corresponding author:
Mohammad Oves

smohammad.oves@gmail.com

Department of Biotechnology, High Institute of Biotechnology of Sidi Thabet, University of Manouba, BP-66, 2020 Ariana, Tunis, Tunisia

Citation: Oves M (2023) Development of Nonionic Bisphosphonate-Modified Drug-Loaded Nanoparticles Binding to Hydroxyapatite. Int J Drug Dev Res J, Vol. 15 No. 3: 999.

Abstract

Developing drug-loaded nanoparticles that bind to hydroxyapatite (HA) and can be used to make bone graft substitutes that release medications or growth hormones was the aim of this research. To do this, the non-ionic surfactant Brij 78 (polyoxyethylene (20) steady ether) was first modified using pamidronate (Pa). Pa-Brij 78 was used as a surfactant and an affinity ligand to HA to construct three different types of Pa surface functionalized nanoparticles: solid lipid nanoparticles (Pa-SNPs), nanoemulsions (Pa-NEMs), and PLGA nanoparticles (Pa-PNPs). The model drug curcumin was successfully encapsulated using the three nanoparticles. Pa-NEM, Pa-PNP, and Pa-SNP all had widths of about 150 nm and polydispersity indices (PDIs) less than 0.20. The drug encapsulation efficiency rates of the three nanoparticles were all greater than 85%. Additionally, this order was determined by the nanoparticles' affinity for attaching to HA. Although the three nanoparticles' affinities for binding to HA were roughly equal to those of newly made nanoparticles, their diameters were increased by 0.5-2.0 fold following lyophilization. A Pa-modified Brij 78 was synthesised and used in the production of many drug-loaded nanoparticles in order to develop drug-eluting HA-based bone graft substitutes.

Keywords: Drug development; Drug discovery; Drug designing; Nanoparticle; Nonionic surfactant

Received: 27-Feb-2023, Manuscript No. ijddr-23-13430; **Editor assigned:** 13-Mar-2023, Pre-QC No. ijddr-23-13430(PQ); **Reviewed:** 16-Mar-2023; QC No. ijddr-23-13430; **Revised:** 23-Mar-2023; Manuscript No. ijddr-23-13430(R); **Published:** 30-Mar-2023, **DOI:** 10.36648-0975-9344.23.15.3-999

Introduction

Hydroxyapatite (HA), a mineral form of calcium apatite with the chemical formula Ca5 (PO4)3, is the main inorganic component of mammalian bone and teeth (OH). Because the crystalline phase of natural bone is comparable to that of HA, HA ceramics have frequently been used as a substitute for natural bone in bone grafts. The HA's 100–200 m diameter porosity allows for the migration, adhesion, proliferation, and differentiation of Mesenchymal cells into osteoblasts. The osteoconductive characteristics of the HA are also supported by this structure. Because of the unique physical properties of HA, osteogenic precursor cells can invade bone during the formation of new bone tissue. An osteoconductive graft material can only operate as a scaffold for bone development and cannot transmit inductive simulative impulses; hence an ideal graft substitute would contain exogenous bioactive small molecules or growth factors. In addition, for the specific surgical or defect sites in musculoskeletal diseases and disorders, pharmaceutical therapy is frequently required. In addition to conventional drugs like antibiotics, anticancer drugs, and anti-inflammatory drugs, biological substances such as proteins and nucleic acids that produce exogenous osteoinductive signals could also be employed as pharmaceuticals in bone tissue engineering and treatment. Therefore, it is vitally necessary to create medications and/or HA that releases growth factors for bone transplants and healing [1].

There are several ways to include drugs or growth hormones into HA. For instance, growth factors can be chemically changed to have the binding affinity to HA, and the surface of calcium phosphate-based biomaterials can physically absorb small molecule drugs. These techniques rely on the restricted and fixed surface of HA. Since the incorporation of pharmaceuticals into HA necessitates

© Under License of Creative Commons Attribution 3.0 License |

knowledge of the unique chemical or physical properties of the drugs, a universal method for producing drug-loaded and drug-releasing HA is also not feasible. It is also difficult to include drugs that are particularly hydrophobic into HA crystal [2].

Nanoparticle (NP)-based drug delivery systems can release medicines or growth factors from bone graft replacements in a controlled and sustained manner. In order to develop drug-eluting HA while keeping the advantages of both NPs and HA, drug-loaded NPs and HA can be combined. Because the binding affinity between NPs and HA is mostly dictated by their surface qualities rather than the chemical or physical properties of pharmaceuticals inside of NP, the complex (NP-HA) generated by NPs and HA can theoretically contain drugs with a wide variety of physical and chemical properties. Second, the NP system virtually overcome the limitation of the HA surface to enhance HA's drug loading capabilities. Thirdly, by carefully selecting the elements of the NPs matrix, which serves as a diffusion barrier for the release of drugs and growth factors, researchers may regulate the rate of release [3].

Bisphosphonates (BP) is hypothesised to have a strong affinity for bone and HA because of the two phosphatase groups that share a carbon atom in their structure (P-C-P). For bone targeting, BP was applied to the micelle, liposome, and NP surfaces in the literature. For example, bone-specific liposomes and micelles have been developed utilising BP-modified cholesterol, DSPE-PEG2000, and BPA. De Miguel et al. also made PBLG-b-PEG-BP and succeeded in making bone-targeted NPs. PLGA NPs were made, and coating BP on their surface resulted in efficient bone targeting effects. Theoretically, such BP-decorated bone-targeted NPs might be used to make HA bone graft substitutes that release drugs. It is desirable to build a universal surfactant chemical for the synthesis of different types of NPs in order to suit the needs of bone tissue engineering and treatment [4].

Material and Methods

Creation of Pa-Brij 78

Brij 78 (1.15 g, 1 mmol) was first dissolved in 15 mL dichloromethane (DCM) and heated at 0°C before adding the 4-methyl-benzenesulfonyl chloride (380 mg, 2 mmol) and triethylamine (303 mg, 3 mmol) premixed in 5 mL DCM. Afterwards, the precipitate was dissolved in 65 mL of ethanol that had been acidified with 250 L of 1 M HCl after the mixture had been stirred for 18 hours at room temperature. To produce a precipitate, the solution was centrifuged at 5000 g at 10°C after being kept at 20°C overnight. The solid Ts-Brij 78 was maintained at 20°C [5].

Calculation of Pa-Brij 78's Critical Micelle Concentration (CMC)

Ts-Brij 78 (1.3 g, 1 mmol), pamidronate disodium (370 mg, 1 mmol), and sodium bicarbonate were dissolved in 20 mL of water (420 mg, 5 mmol). The mixture was evaporated under decreased pressure after 24 hours of refluxing, and the precipitate was then dissolved in 30 mL of ethanol. The precipitate was created by filtering the solution, removing the leftovers, rotating evaporating the filtrate under decreasing pressure, washing it three times in petroleum ether, and finally drying it under vacuum. For storage, the Pa-Brij 78 solid was left at room temperature. The electrical conductivity method, which is often employed to assess the degree of ionisation of ionic micelles, was utilised to compute the CMC of an ionic surfactant. At 25°C, the molar conductivities of various Pa-Brij 78 aqueous solution concentrations (0.1-3.9 mM) were evaluated using the software of a particle size analyzer. This enabled scientists to determine the compound's CMC (Zetasizer Nano-ZS, Malvern Instruments Ltd, Malvern, UK). The axis of a graph of molar conductivities vs concentrations is the CMC of Pa-Brij 78 [6].

A little amount of modification was made to the method utilised to make the E-wax-based solid lipid NPs. In a nutshell, 200 L of 65°C distilled water was added after a glass vial containing 4 mg of E-wax, 7 mg of Pa-Brij 78, or a mixture of Brij 78 and Pa-Brij 78, and 0.4 mg of the model drug curcumin was heated at 65°C. After 10 minutes of swirling at 65°C, a slurry-like substance was produced. The vial was next filled with 1.8 mL of distilled water heated to 65 °C, and the mixture was agitated for 40 minutes at that temperature to produce a warm, clear oil-in-water micro emulsion [7].

The preparation method was slightly altered from previous research. To summarise, the following components were added: 200 litres of distilled water at 55 degrees Celsius, 2 mg of glycerol trioctanoate as the oil phase, 3.5 mg of Pa-Brij 78 or, in some experiments, a combination of Brij 78 and Pa-Brij 78 as surfactants, 1.2 mg of TPGS as a surfactant, and 0.6 mg of curcumin as a model drug are the ingredients used in this experiment. When the mixture was thoroughly stirred for 10 min at 55°C, a slurry-like mixture was produced. A warm, clear oil-in-water micro emulsion was then created in the vial by adding 1.8 mL of distilled water heated to 55°C and stirring the mixture for at least 40 minutes [8].

The preparation method was slightly altered from previous research. In a nutshell, 20 mg of PLGA and 2 mg of curcumin were dissolved in 1 mL of DCM. Then, 4 mL of a 0.3% Pa-Brij 78 aqueous solution was mixed with the organic solution. In order to form a microemulsion, the solution was vigorously stirred for five minutes before being repeatedly put through a high pressure homogenizer (JN-02C by Junbio, Guangzhou, China) with a pressure of 1500 bars and a temperature of 4°C. By eliminating the DCM from the microemulsion while using reduced pressure, the curcumin-loaded PLGA NPs were produced. The size and PDI of the NPs were measured using a particle size analyzer [9].

Discussion

Because Brij 78 contains a hydrophilic PEG chain, TsCl first activated the PEG's hydroxyl end group to produce Ts-Brij 78. The amine group of Pa then successfully conjugated the Ts-Brij 78 by reacting with it, and sodium bicarbonate was added to the process to keep it in a basic form. It was possible to get about 80% of the total output. The structural stability of Pa-Brij 78 was confirmed by 1H-NMR (the solvent was D2O). This molecule had a -NH-CH2-CH2, as evidenced by the signals (7.73-7.39, m, 1H), 2.43, s, and 1.61, s, 2H. Using the molar conductivity method, it

was shown that Pa-Brij 78's CMC ranged between 1.9 and 2.1 mM at 25°C [10].

After being kept at 4°C for seven days, the colloidal suspensions of Pa-NPs retained their original appearance without precipitation or cloudiness. Pa-NPs' PDIs and particle sizes were tracked for a period of 7 days, and the results revealed that only a minuscule (20%) size increase occurred during that time. Additionally, all of the Pa-NPs' PDIs were lower than 0.25 over the length of the 7-day storage, suggesting that the particles were monodisperse. The hydrophilic PEG shielding and the Pa-NPs' negatively charged surface were probably what gave them their exceptional stability, Lipid-based SNPs and NEMs were frequently used to improve the solubility and bioavailability of hydrophobic medicines. Protein- or peptide-based growth factors as well as hydrophilic medicines may be delivered using biodegradable PLGA-based PNPs. Therefore, Pa-Brij 78 has the capacity to generate a variety of Pa-NPs that may incorporate medicinal substances with different chemical or physical properties [11].

We then continued looking into the requirements for building the drug-loaded HA/Pa-NPs complex. The binding study started with a predetermined number of Pa-SNPs, and when HA levels climbed, so did the HA binding ratio. A maximum HA binding ratio of roughly 45% for the Pa-SNPs was achieved. Pa is essential to the binding process, as evidenced by the little interaction that SNPs without Pa change demonstrated with HA under the identical circumstances. Similar to this, the HA binding ratio of Pa-maximal NEM was about 55%. The non-specific interaction between PNPs lacking surface Pa and HA that resulted in a feeble binding between PNPs and HA is interesting to notice. The maximum HA binding ratio of Pa-PNPs was only about 70%, though. The results revealed that whereas Pa on the surfaces of the NPs was essential for the binding of HA to NPs, the NPs themselves might also affect binding affinity [12].

Conclusions

Using the newly synthesised compound Pa-Brij 78 as both a target ligand and a surfactant, a variety of drug-loaded Pa-NPs that could interact with HA were produced. The HA/Pa-NP mixture has the potential to develop an alternative to HA-based bone grafts that release growth factors or medications.

Conflict of Interest

None

Acknowledgment

None

© Under License of Creative Commons Attribution 3.0 License

References

1 Bayraktar S, Gluck S (2013) molecularly targeted therapies for metastatic triple-negative breast cancer. Breast Cancer Research and Treatment 138:21-35.

2 Stearns ME, Wang M, Hu Y, Garcia FU (2003) Interleukin-10 activation of the interleukin-10E1 pathway and tissue inhibitor of metalloproteinase-1 expression is enhanced by proteasome inhibitors in primary prostate tumor lines. Molecular Cancer Research 1:631-642.

3 Neve RM, Chin K, Fridlyand J (2006) a collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. Cancer Cell 10:515-527.

4 Beausoleil SA, Villén J, Gerber SA, Rush J, Gygi SP (2006) A probability-based approach for high-throughput protein phosphorylation analysis and site localization. Nature Biotechnology 24:1285-1292.

5 Caraux G, Pinloche S (2005) PermutMatrix: a graphical environment to arrange gene expression profiles in optimal linear order. Bioinformatics 21:1280-1281.

6 Watanabe N, Osada H (2012) Phosphorylation-dependent protein-protein interaction modules as potential molecular targets for cancer therapy. Current Drug Targets 13:1654-1658.

7 Mehta R, Katta H, Alimirah F (2013) Deguelin action involves c-Met and EGFR signaling pathways in triple negative breast cancer cells. PLoS ONE 8:65-113.

8 Zhang L, Gu FX, Chan JM , Wang AJ, Langer RS et al (2008) Nanoparticles in medicine: therapeutic applications and developments. Clinical Pharmacology and Therapeutics 83:761-769.

9 Mouridsen HT (1992) Systemic therapy of advanced breast cancer. Drugs 44:17-28.

10 Azzariti S, Porcelli L, Simone GM (2010) Tyrosine kinase inhibitors and multidrug resistance proteins: interactions and biological consequences. Cancer Chemotherapy and Pharmacology 65:335-346.

11 Emerich DF, Thanos CG (2007) Targeted nanoparticle-based drug delivery and diagnosis. Journal of Drug Targeting 15:163-183.

12 Woodle MC (1998) Controlling liposome blood clearance by surface-grafted polymers. Advanced Drug Delivery Reviews 32:139-152.