Review Article

Intranasal Drug Conveyance Frameworks in the Treatment of Postmenopausal Osteoporosis

Sai Gayathri. V*, Srinivasa Reddy.K
Department of Pharmaceutics, Jawaharlal Nehru Technological University, Kakinada, 533003, Andhra Pradesh, India.
***Corresponding author's E-mail:** gayisweety.33@gmail.com

Received: 01-08-2022; **Revised:** 24-10-2022; **Accepted:** 02-11-2022; **Published on:** 15-11-2022.

ABSTRACT

Osteoporosis is a disease common to postmenopausal women that leads to an increased risk of fractures, pain, and fewer quality of life. One bone for every three seconds will break due to osteoporosis. It can be detected by resorption of bone exceeding bone formation, and by measuring bone mineral density (BMD) using non-invasive dual-energy x-ray absorptivity. Many of the marketed drugs include anabolic agents and anti-resorptive agents such as estrogen and its analogues, calcitonin, bisphosphates, and parathyroid hormone along with newer antibiotics administered through oral route, but this route results in more complications such as short half-life, first-pass metabolism also as patient non-compliance. To avoid this, an intranasal delivery system is used as an alternate approach for the systematic delivery of medicine through nasal cavity bypassing hepatic metabolism. Intranasal drug delivery system has more potential to improve absorption, enhance the bioavailability of the drug, increase patient compliance, and possibility of self-administration. The introduction of this new delivery system increases patient convenience and various pharmacokinetic profiles diminish the side effects. An example of this drug delivery system is the in situ thermosensitive nanoemulgels of raloxifene hydrochloride, an intranasal drug delivery system for risedronate sodium nanoparticles. In-vivo pharmacodynamic studies have shown that by using these systems, bone density was enhanced by 162% in comparison to per-oral marketed products. This review mainly focuses on pathophysiology, Etiology, diagnosis, and various nasal approaches for delivering therapeutically active agents to revive homeostasis of bone.

Keywords: Postmenopausal osteoporosis, Bone mineral density (BMD), resorption, nasal delivery, non-pharmacological therapy.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2022.v77i01.032

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v77i01.032

INTRODUCTION

Osteoporosis is a disease of a skeletal system associated with decreased bone mineral density (BMD) and the microstructural deterioration of bone tissue, usually resulting in fractures with minimal trauma, mostly in the hip, spine and forearm which affects women following menopause and elderly men. Most of the women were not aware of the risk after menopause and fail to take preventive measures.it is estimated that about 200 million people are suffering from this problem. The drugs which are used for the treatment of osteoporosis are limited in terms of scope, anti-fracture efficacy, tolerability. Many efforts have been made to develop newer drugs. Some of the USFDA drugs used for the treatment of osteoporosis are estrogen, raloxifene, Bisphosphates (BPs), salmon calcitonin, Teriparatide, Denosumab, etc[1]. Among all these drugs, Bisphosphates (BPs) are the standard drugs used in the treatment of osteoporosis (OP). These drugs are available as both oral and intravenous (IV) formulations. These nitrogen-containing BPs are used to treat postmenopausal osteoporosis, glucocorticoid osteoporosis, osteoporosis in men, and Paget's disease. The main problem associated with these drugs is that they injure upper GIT. To overcome this problem, tablets should be taken with some water and don't allow patients to laid down for about 30 min before drug administration[2]. Currently, Intranasal DDS are anabolic therapy that is designed to overcome these issues for osteoporosis by promoting the bone deposition by increasing bone density and reducing bone loss through bone deposition. These nasal formulations are used as a strategy for enhancing patient compliance and reducing economic burdens associated with manufacturing. However, due to the larger absorption site, more blood supply and porous and thin endothelial basement membrane of the nasal cavity, the nasal delivery system is the major approach for the systemic delivery of drugs by bypassing first-pass metabolism. It involves exposure to nasal mucosa followed by systemic delivery. Nasal dosage forms allow faster onset of action, easy and painless administration of drugs and are convenient for self-administer. The major problem associated with this route is large molecular weight compounds such as proteins and peptides cannot penetrate through the nasal membrane. For this reason, the dosage forms must include permeation enhancers to attain desired bioavailability[3].nano-drug delivery systems are developed with a droplet size of 50-2oo nm such as nanoemulgels, polymeric nanoparticles. A Nanoemulgels is a nanosized isotropic thermodynamically stable colloidal dispersion of an oily and aqueous phase stabilized by non-ionic surfactants[4] whereas polymeric

nanoparticles (NPs) are nanoparticles with sizes between 1 to 1000 nm, which are loaded with active compounds entrapped within or surface adsorbed onto the polymeric core.

Pathophysiology of bone:

Bone remodelling involves four stages

i. Activation phase: In this phase, osteoclasts laid on to the surface of the bone

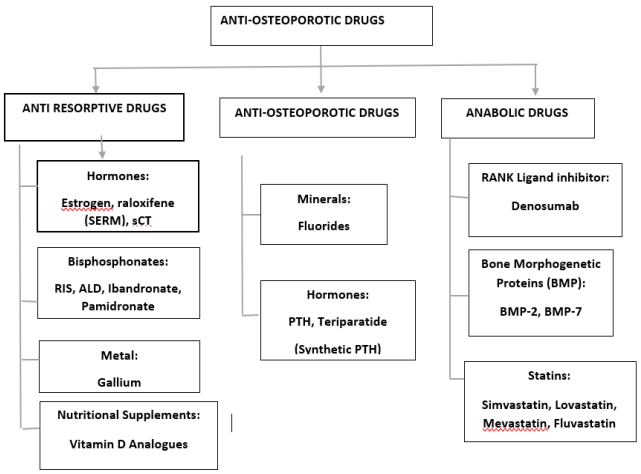
ii. Resorption: occurs when osteoclasts dissolve the mineral content of the bone by creating an acidic environment.

iii. Reversal phase: osteoclasts encounter apoptosis and osteoblasts are recruited to the bone surface

iv. Formation phase: finally, osteoblasts deposit collagen which is mineralized to form bone.

Dysregulation of modulators that are responsible for remodelling behaviours such as macrophage colony-stimulating factor(M-CSF), osteoprotegerin (OPG), sclerotin results in an imbalance between osteoblast and osteoclast activity leads to primary osteoporosis in post-menopausal women. The average rate of bone loss per annum is about 2% in the beginning 1 to 3 years before menopause and lasting for 5 to 10 years resulting in an average loss of 10 to 12%. Rates of bone loss vary based on body weight. This results in decreased bone density of about 0.5% per year. Other factors such as bone mineralization, microstructure as well as age related factors such as accumulation of advanced glycation end products decrease the strength of bone tissue and increase the risk of postmenopausal osteoporosis

Table 1: Classification of Anti-osteoporotic Drugs[4]



Risk factors for post-menopausal osteoporosis[5]:

- Poor diet:

A proper diet with vitamin D and calcium is necessary to prevent the risk of osteoporosis.

- Family history of osteoporosis:

Because of inherited factors that affect bone development, osteoporosis occurred in families. if your family member suffered from fractured bone due to osteoporosis, then there is a greater risk for you too

- Excessive alcohol and caffeine consumption:

Drinking alcohol reduces the ability of new bone formation and increases the risk of bone breaking.

- Disease conditions:

Many diseases such as rheumatoid arthritis, obesity greatly affect bone and cause malabsorption leading to osteoporosis

- Other risk factors include:
- Hyperparathyroidism
- Low calcium and vitamin D consumption
- People with chronic diseases such as rheumatoid arthritis and chronic hepatitis
- Heparin therapy
- Low body weight
- Post transplantation
- Chronic renal failure

Etiology:

Bones are metabolically active organs that continuously undergo remodelling processes throughout their life. This process involves the removal of mineralised bone by osteoclasts followed by the formation of new bone by osteoblasts. The actions of both osteoclasts and osteoblasts are generally balanced and regulated by hormones such as parathyroid hormone (PTH), calcitriol, growth hormone, sex hormones, etc. Osteoporosis is observed when there is an imbalance between osteoclasts and osteoblasts and results in bone resorption and bone loss.

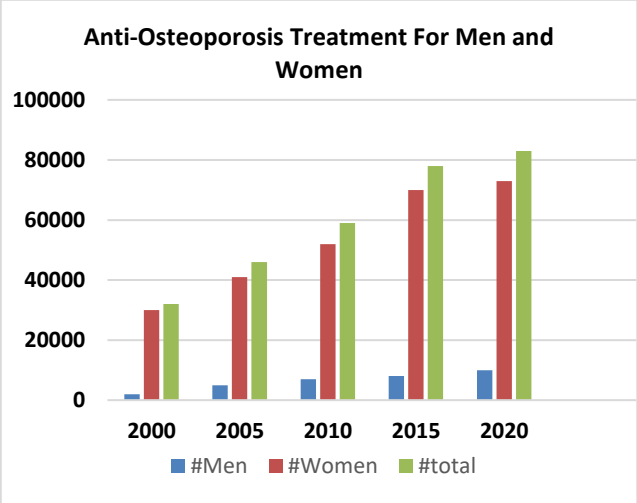


Figure 1: bar graph illustrating the annual anti-osteoporosis medication rates for men and women from 2000 to 2020[6]

Primary osteoporosis:

Primary osteoporosis is of two types

i. Post-menopausal osteoporosis (generally occurs between 50-70 years of age)

ii. Age related osteoporosis (occurs after 70 years)

Post-menopausal osteoporosis is due to the continuous deterioration of trabeculae in bone. And increased estrogen levels in post-menopausal women also result in the breakdown of bone. Whereas age related osteoporosis involves thinning of both trabecular and hard cortical bone results in pelvic fractures, femoral neck, proximal humerus, etc. In men, sex-hormone-binding globulin inactivates testosterone and estrogen as aging occurs, which may contribute to the decrease in BMD with time[6].

Secondary osteoporosis:

Secondary osteoporosis often results in neurologic diseases. These diseases are mainly caused due to deficiency of calcium, vitamin D, and sex hormones. Common causes for secondary osteoporosis are hypogonadism (men), malabsorption, chronic glucocorticoid therapy etc[7].

Table 2: National academy of sciences dietary references intakes of calcium and vit-D[8]

Age	Elemental calcium (mg/day)	Vitamin D (IU/day)
Birth to 6 months	400	400
6-12 months	600	400
1-4 years	600	400
5-8 years	800	400
9-14 years	1300	400
15-18 years	1300	400
19-30 years	1500	400-800
31-50 years	1000	400-800
50-70 years	1500	800-1000
>70 years	1200	1000
Pregnancy		
≤18 years	1300	400-800
20-50 years	1000	400-800
Lactation		
≤18 years	1300	400-800
20-50 years	1000	400-800

Diagnosis:

Osteoporosis is diagnosed by measuring bone mass density (BMD) with dual energy x-ray absorptiometry (DXA) device or occurrence of nontraumatic hip or vertebral fractures. T-scores that are obtained from the results are used to interpret BMD and to determine fracture risk. this testing is used for estrogen-deficient women who are at increased risk for osteoporosis, individuals with vertebral abnormalities, patients with hyperparathyroidism etc. Testing may be performed once every 2 years, although more frequent testing is permitted if a physician considers it medically necessary[8].

- IF T-score ranges from +2.5 to -1.0 then it indicates the individual is in normal condition
- If T-score ranges between -1.0 to -2.5, it indicates osteopenia
- If a T-score is -2.5 or below, it indicates osteoporosis.
- The presence of fragility fracture doesn't depend on T-score.

Nonpharmacological therapy for postmenopausal osteoporosis:

The goal of nonpharmacological therapy is to prevent or reduce the risk of postmenopausal osteoporosis. It is associated with modifying risk factors like weight-bearing exercise, alcohol cessation, balanced diet etc. malnutrition is frequently observed in the old age population ranging from 15- 40%. Protein supplementation in those patients with hip fractures decreases the duration of hospitalization and occurrence rate of osteoporosis. Protein supplementation increases the muscle strength reduces the bone resorption process and increases levels of somatomedin c. Adequate intake of foods containing calcium and vitamin D reduces hip and vertebral fractures by increasing bone mineral density[9].

1. Calcium:

Calcium is the essential element for the proper growth of skeletal muscle in the childhood and adolescence stages. Calcium is rich in milk, bony fish and dairy products Calcium in supplements when taken in a dose of less than 500 mg then it is effectively absorbed. In fasted state calcium is more absorbed from calcium citrate when compared to calcium carbonate whereas in fed state calcium is better absorbed from carbonate[10]. Also, 500 mg calcium as citrate is equivalent to 1000 mg of calcium as carbonate in bone remodelling. Patients with malabsorption require higher doses of calcium. Most of the calcium supplements require an acidic environment to optimize the absorption process (except calcium citrate) doses higher than 600 mg cannot absorbed from the stomach. So, calcium supplements should be taken in the form of divided doses[11]

2. Vitamin-D:

Patients with vitamin-D deficiency are treated with bisphosphonates to induce symptomatic hypocalcaemia. However, it has been proved that vitamin D with or without calcium increase bone density and decrease the incidence of fractures[12]. Age-related vitamin-D deficiency is more common due to lesser exposure to ultraviolet light leads to decreased renal response to PTH hormone. It is not supposed to increase the duration of skin exposure to ultraviolet light because of the risk of skin cancer. following oral administration of vitamin-D, blood levels begin to rise at 4 hours showing peak concentration at 12 hours and reaches baseline by 72 hours this pharmacokinetic profile

is used as a clinical test for predicting adequate dose of Vit-D[13].

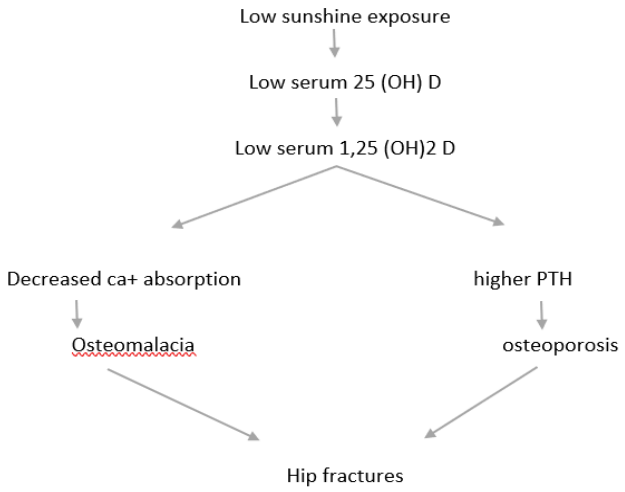


Figure 2: Vitamin-D deficiency[13]:

Various pharmacological therapies for postmenopausal osteoporosis via nasal route:

Nasal administration commonly known as snorting is a route of administration in which drugs are directed through nostrils has been used as an alternative for the systematic delivery of drugs. Nasal delivery is used in various conditions such as headache, migraine, estrogen replacement therapy, alcohol cessation etc. Nasal mucosa offers a large surface area with a substantial blood supply which makes it a suitable target for DDS. Recent developments in intranasal drug delivery systems are prodigious. When the dosage form is instilled into the nostrils, immediately escaped through the nasal cavity, and undergoes systemic absorption to provide rapid therapeutic action. Several approaches have been developed to increase the residence time of drugs in the nasal cavity[14].However, the uptake of high molecular weight drugs such as PTH, CT is limited. The major obstacle for the systemic delivery of CT is limited paracellular transport across the epithelial membrane because of tight junctions and rapid mucociliary clearance of administered drugs from the nasal cavity. Further, when compared to oral delivery, enzymatic degradation has no impact on nasal delivery[15].

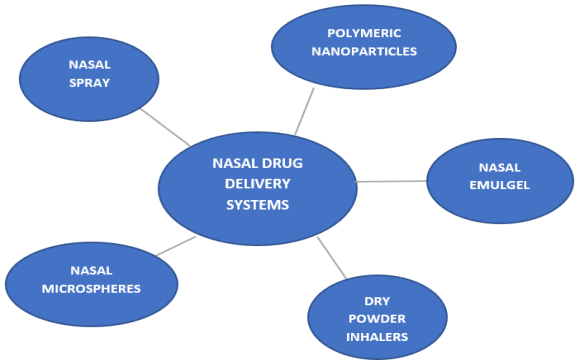


Figure 3: Various intranasal drug delivery systems for postmenopausal osteoporosis:

1. Nasal sprays:

In the last decades, nasal sprays are used to deliver small molecular weight compounds to attain faster onset of action. Nasal spray delivery systems facilitate easy, painless administration of the drug and allow the patients to self-administer. The main drawback of this delivery system is it doesn't allow the penetration of large hydrophilic polymers like proteins through the nasal membrane. For this reason, it must include a penetration enhancer to achieve therapeutic activity[15]. However, these systems also create a challenge because most of the penetration enhancers are not tolerated by the nasal membrane. Permissive technologies have been developed in the form of nasal delivery devices and nasal mucosal penetration enhancers are being developed to deliver proteins and peptides [16] This is preferred only if the patient cannot tolerate other therapies. The therapeutic efficacy of these nasal sprays depends on the pharmacokinetics of drugs. A nasal spray containing salmon calcitonin (Miacalcic) at a dose of 200 IU was developed to decrease the risk associated with vertebral fractures that occurred during postmenopausal osteoporosis. Calcitonin treatment constitutes the best choice to control osteoporosis but produces some side effects such as diarrhoea, abdominal pain when given parenterally. Patients who are treated with calcitonin result in increased BMD enhanced intestinal absorption of calcium[17].Recent studies show that the severity of side effects is dose dependent. For this reason, Sal calcitonin nasal spray was developed to increase patient compliance and reduce side effects. Several studies reveal that the use of this nasal spray can stabilize or increase bone mineral density and decreases bone resorption which allows it to use in the prevention of osteoporosis. Intolerance due to nasal spray was not observed among the individuals[18].

2. Intranasal Polymeric nanoparticles:

Polymeric nanoparticles are solid colloidal particles within the size range from 1 to 1000 nm and can be loaded with active chemical compounds entrapped within or surface-adsorbed onto the polymeric core[19]. These particles are widely used as an organic nanomaterial for the delivery of drugs because of their release kinetics and tuneable biodegradability These are more stable in GI tract when compared to other carriers such as liposomes and provide protection to the encapsulated drugs. This type of nanoparticles requires the incorporation of various types of polymeric materials to alter Physico-chemical properties (e.g.: crystal structure, hydrophobicity), pharmacokinetic properties (e.g.: extended, prolonged) and biological behaviour (e.g.: targeting, bio adhesion)[20]. Ultimately the surface of the particles can be modified by adsorption or chemical grafting of certain molecules such as polyethylene glycol (PEG), poloxamers' etc. Accordingly, it has been shown that nanoencapsulation of proteins and peptides protects them from the adverse environment of GIT. A biodegradable intranasal nanoparticulate drug delivery system of risedronate sodium was developed for

the treatment of osteoporosis to reduce peripheral toxic effects. These nanoparticles are prepared using polymer PLGA using the nanoprecipitation method. There are various types of polymeric nanoparticles for the oral delivery of drugs including chitosan NPs, calcitonin NPs, PLGA NPs, etc.

i. Chitosan NPs:

Chitosan is an important derivative of chitin produced by eliminating acetate moiety from chitin. Chemically chitosan is a copolymer of β-(1-4) linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose[21].In this type of polymeric nanoparticles, chitosan is used as a carrier for the delivery of drugs. These nanoparticles have positive surface charge and mucoadhesive properties which permits sustained release of drugs to the systemic circulation. Raloxifene-loaded chitosan nanoparticles are prepared that are delivered intranasally for the treatment of osteoporosis. These NPs are formed by the ionic gelation method to enhance plasma drug concentration[22]

ii. Calcitonin NPs:

Calcitonin is a hormonal inhibitor of bone resorption used in the treatment of osteoporosis. It is available as nasal sprays or subcutaneous injections. It plays an important role in calcium and bone homeostasis. In this type of nanoparticles, sCT is incorporated into nanoparticles through encapsulation with efficiency ranging from 70-80%. Intranasal salmon calcitonin was prepared which is 50 times more potent than human calcitonin involved in bone homeostasis. The analgesic activity of salmon calcitonin is due to increased plasma β-endorphin level or modification of intracellular calcium levels in CNS. This salmon calcium should be used along with calcium supplements because there is a high risk of secondary hyperparathyroidism[23]

iii. PLGA nanoparticles:

Poly-Lacto-co-glycolic acid (PLGA) nanoparticles are the most widely used synthetic polymers used in drug delivery systems to attain sustained or controlled release of the drug. In these NPs the drug may be either encapsulated inside the core of the nano capsule or adsorbed onto the surface of the matrix nanosphere. PLGA nanoparticles are mostly preferred because of their biodegradability and biocompatibility, protects drugs from degradation, possibility to target specific tissue or organ. The method used for the preparation of PLGA nanoparticles is the emulsification-solvent evaporation technique. This method involves encapsulation of hydrophobic drug that dissolves in polymer and the compound in organic solvent[24]. An intranasal nanoparticulate drug delivery system of risedronate sodium was developed using PLGA nanoparticles for the treatment of postmenopausal osteoporosis. In this DDS, PLGA nanoparticles were prepared by modified nanoprecipitation by dissolving PLGA in the organic phase (chloroform) and the drug was dissolved in an aqueous phase because RIS is a water-soluble drug. By using these nanoparticles, intranasal delivery of RIS showed good results for the treatment of osteoporosis[1]

3. Nasal emulgels:

Nasal emulgels have the advantage of both gels and nanoemulsions and provide controlled release of a drug. Nano emulsions may be defined as nanosized isotropic thermodynamically stable colloidal dispersions of oily and water phases stabilized by non-ionic surfactants. This oil in water nano emulsion facilitates solubilization of drug in a hydrophilic component. When nanoemulsions are instilled into nostrils, there may be a possibility of nasal drainage which leads to wastage of drug. so, they can be formulated as *Insitu* gel to enhance drug residence time. These formulations are used to reduce the dose of drug with less side effects and provide increased bioavailability through bypassing first pass metabolism. These in-situ gels should have a pH range of 4.5-6.5. To enhance the muco-adhesion properties of these gels, they must incorporate PEG-based polymers to their surfaces as they can penetrate by forming hydrogen bonds[25]. *In situ* nano emulgel of raloxifene hydrochloride was developed for the treatment of postmenopausal osteoporosis. Thermosensitive gels were prepared using P407 and C934 to prolong the nasal residency of RH[26].

4. Dry powder inhalers:

Dry powder inhalers are preferred because of their high loading capacity, increased patient convenience and ease of administration. But there is a risk of particle aggregation that leads to decreased inhalation efficiency. DPI's can be prepared by various methods like wet milling, micro fluidization process, spray freeze-drying. These methods produce unstable particles with variable size distribution. Hence, nanosized particles are used as dry powder inhalers which are generated by supercritical fluidization techniques like rapid expansion of supercritical solution (RESS), supercritical antisolvent (SAS) etc [27]. A nanosized alendronate sodium inhaler was prepared by an anti-solvent precipitation technique to treat osteoporosis. For the particles having a similar charge, particles deposited on surface due to electrostatic interaction and decreased surface density. Interactions between the particles can be controlled by coating the powder with stabilizer. It shows that stabilizer plays an important role in controlling the size of nanoparticles and surface morphology to produce inhaler with desired characteristics[28].

5. Nasal microspheres:

Most of the microspheres used for the nasal delivery are water insoluble but absorb water into matrix resulting in swelling of spheres and forming a gel. The advantage of using microspheres is that low molecular weight compounds such as metoclopramide can be delivered, and increased residence time was observed[29] Nasal delivery of gelatin microspheres was developed for the delivery of salmon calcitonin. Both the positive and negative gelatin microspheres are prepared using acidic and basic gelatin[30]. These are prepared by pouring aqueous gelatin solutions

in olive oil followed by glutaraldehyde cross-linking without using surfactant. The activity of gelatin microspheres was determined by administering microsphere suspension in PBS of pH 7 and assessing the hypocalcaemic activity in plasma samples. Mucoadhesion of positively charged gelatin microspheres was more when compared to negatively charged particles. Hypocalcaemic effect of sCT in positively charged particles is not influenced by variation in particle size for intranasal administration and does not shows sustain release of drug.[31]

CONCLUSION

This review mainly focuses on pervasiveness of osteoporosis and various nasal drug delivery systems developed for the treatment of osteoporosis. In the early stage of osteoporosis, non-pharmacological therapy should follow regularly to overcome the severity. Also, vitamin-D should include in diet about 800-900 IU per day especially in winter. Various nasal drug delivery systems were prepared using different techniques for the treatment of postmenopausal osteoporosis. Nasal delivery is mostly preferred over oral and parenteral route for the prolonged duration of therapy because of reduced cost of manufacturing, avoiding first pass metabolism and increased patient compliance. Further studies are needed to confirm the efficacy of these nasal systems in treating osteoporosis. For those people who are not tolerable to estrogen replacement therapy, intranasal drug delivery systems are the best-suited alternative in curing postmenopausal osteoporosis. However, for the marketing approval of these nasal dosage forms, regulatory deliberation and guidelines should be required.

REFERENCES

1. Fazil M, Hassan MQ, Baboota S, Ali J. Biodegradable intranasal nanoparticulate drug delivery system of risedronate sodium for osteoporosis. Drug delivery. 2016 Sep 1;23(7):2428-38.,https://doi.org/10.3109/10717544.2014.1002947

2. Li WW, Kendler DL. Pharmaceutical care and community pharmacists' understanding of bisphosphonate dosing information 1. Journal of clinical pharmacy and therapeutics. 2004 Dec;29(6):531-6.https://doi.org/10.1111/j.1365-2710.2004.00597.x

3. Pearson RG, Masud T, Blackshaw E, Naylor A, Hinchcliffe M, Jeffery K, Jordan F, Shabir-Ahmed A, King G, Lewis AL, Illum L. Nasal administration and plasma pharmacokinetics of parathyroid hormone peptide PTH 1-34 for the treatment of osteoporosis. Pharmaceutics. 2019 Jun 7;11(6):265.https://doi.org/10.3390/pharmaceutics11060265

4. Zhang Y, Shang Z, Gao C, Du M, Xu S, Song H, Liu T. Nanoemulsion for solubilization, stabilization, and in vitro release of pterostilbene for oral delivery. Aaps Pharmscitech. 2014 Aug;15(4):1000-8.https://doi.org/10.1208/s12249-014-0129-4

5. Pouresmaeili F, Kamalidehghan B, Kamarehei M, Goh YM. A comprehensive overview on osteoporosis and its risk factors. Therapeutics and clinical risk management. 2018;14:2029.https://doi.org/10.2147%2FTCRM.S138000

6. Jeremiah MP, Unwin BK, Greenawald MH, Casiano VE. Diagnosis and management of osteoporosis. American family physician. 2015 Aug 15;92(4):261-8.https://pubmed.ncbi.nlm.nih.gov/26280231

7. Kamel HK. Postmenopausal Osteoporosis. Journal of Managed Care Pharmacy. 2006 Jul;12(6 Supp A):S4-9.https://www.jmcp.org/doi/pdf/10.18553/jmcp.2006.12.S6-A.S4

8. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. American journal of obstetrics and gynecology. 2006 Feb 1;194(2):S3-11.https://doi.org/10.1016/j.ajog.2005.08.047

9. Blake J, Cosman FA, Lewiecki EM, McClung MR, Pinkerton J, Shapiro M. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. MENOPAUSE-THE JOURNAL OF THE NORTH AMERICAN MENOPAUSE SOCIETY. 2021 Sep 1;28(9):973-97.*DOI: 10.1097/GME.0000000000001831*

10. Sunyecz JA. The use of calcium and vitamin D in the management of osteoporosis. Therapeutics and clinical risk management. 2008 Aug;4(4):827.*doi: 10.2147/tcrm.s3552*

11. Chiodini I, Bolland MJ. Calcium supplementation in osteoporosis: useful or harmful?. European journal of endocrinology. 2018 Apr 1;178(4):D13-25. *DOI: 10.1530/EJE-18-0113*

12. Lips P, Van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best practice & research Clinical endocrinology & metabolism. 2011 Aug 1;25(4):585-91.*DOI: 10.1016/j.beem.2011.05.002*

13. Hill TR, Aspray TJ. The role of vitamin D in maintaining bone health in older people. Therapeutic advances in musculoskeletal disease. 2017 Apr;9(4):89-95.*https://doi.org/10.1177/1759720X17692502*

14. Türker S, Onur E, Ózer Y. Nasal route and drug delivery systems. Pharmacy world and Science. 2004 Jun;26(3):137-42.*doi: 10.1023/b:phar.0000026823.82950.ff.*

15. Hoyer H, Perera G, Bernkop-Schnürch A. Noninvasive delivery systems for peptides and proteins in osteoporosis therapy: a retroperspective. Drug Development and Industrial Pharmacy. 2010 Jan 1;36(1):31-44.DOI: 10.3109/03639040903059342

16. Pearson RG, Masud T, Blackshaw E, Naylor A, Hinchcliffe M, Jeffery K, Jordan F, Shabir-Ahmed A, King G, Lewis AL, Illum L. Nasal administration and plasma pharmacokinetics of parathyroid hormone peptide PTH 1-34 for the treatment of osteoporosis. Pharmaceutics. 2019 Jun 7;11(6):265.DOI: 10.3390/pharmaceutics11060265

17. Downs Jr RW, Bell NH, Ettinger MP, Walsh BW, Favus MJ, Mako B, Wang L, Smith ME, Gormley GJ, Melton ME. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. The Journal of Clinical Endocrinology & Metabolism. 2000 May 1;85(5):1783-8.*DOI: 10.1007/s00198-014-2655-z*

18. Chesnut III CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. The American journal of medicine. 2000 Sep 1;109(4):267-76. *DOI: 10.1016/s0002-9343(00)00490-3*

19. Zielińska A, Carreiró F, Oliveira AM, Neves A, Pires B, Venkatesh DN, Durazzo A, Lucarini M, Eder P, Silva AM, Santini A. Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology. Molecules. 2020 Aug 15;25(16):3731. *DOI:10.3390/molecules25163731*

20. Fazil M, Ali A, Baboota S, Sahni JK, Ali J. Exploring drug delivery systems for treating osteoporosis. Expert opinion on drug delivery. 2013 Aug 1;10(8):1123-36.DOI: 10.1517/17425247.2013.785518

21. Mohammed MA, Syeda JT, Wasan KM, Wasan EK. An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics. 2017 Nov 20;9(4):53. *DOI: 10.3390/pharmaceutics9040053*

22. Saini D, Fazil M, Ali MM, Baboota S, Ameeduzzafar, Ali J. Formulation, development and optimization of raloxifene-loaded chitosan nanoparticles for treatment of osteoporosis. Drug delivery. 2015 Aug 18;22(6):823-36.DOI: 10.3109/10717544.2013.870259

23. Plosker GL, McTavish D. Intranasal salcatonin (salmon calcitonin). Drugs & aging. 1996 May;8(5):378-400.https://doi.org/10.2165/00002512-199608050-00006

24. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. Journal of controlled release. 2012 Jul 20;161(2):505-22.*DOI: 10.1016/j.jconrel.2012.01.043*

25. Soliman ME, Elmowafy E, Casettari L, Alexander C. Star-shaped poly (oligoethylene glycol) copolymer-based gels: Thermo-responsive behaviour and bio applicability for risedronate intranasal delivery. International Journal of Pharmaceutics. 2018 May 30;543(1-2):224-33.*DOI: 10.1016/j.ijpharm.2018.03.053*

26. Zakir F, Ahmad A, Farooq U, Mirza MA, Tripathi A, Singh D, Shakeel F, Mohapatra S, Ahmad FJ, Kohli K. Design and development of a commercially viable in situ nanoemulgel for the treatment of postmenopausal osteoporosis. Nanomedicine. 2020 May;15(12):1167-87.*DOI: 10.2217/nnm-2020-0079*

27. Ezzati Nazhad Dolatabadi J, Hamishehkar H, Valizadeh H. Development of dry powder inhaler formulation loaded with alendronate solid lipid nanoparticles: solid-state characterization and aerosol dispersion performance. Drug Development and Industrial Pharmacy. 2015 Sep 2;41(9):1431-7. *doi: 10.3109/03639045.2014.956111*

28. Sultana S, Talegaonkar S, Ali R, Mittal G, Ahmad FJ, Bhatnagar A. Inhalation of alendronate nanoparticles as dry powder inhaler for the treatment of osteoporosis. Journal of microencapsulation. 2012 Aug 1;29(5):445-54. *https://doi.org/10.3109/02652048.2012.655428*

29. Pereswetoff-Morath L. Microspheres as nasal drug delivery systems. Advanced Drug Delivery Reviews. 1998 Jan 5;29(1-2):185-94.*DOI: 10.1016/s0169-409x(97)00069-0*

30. Gedam SH, Jadhav P, Talele S, Jadhav AN. Effect of crosslinking agent on development of gastroretentive mucoadhesive microspheres of risedronate sodium. Int. J. Appl. Pharm. 2018;10:133-40.DOI: http://dx.doi.org/10.22159/ijap.2018v10i4.26071

31. Morimoto K, Katsumata H, Yabuta T, Iwanaga K, Kakemi M, Tabata Y, Ikada Y. Evaluation of gelatin microspheres for nasal and intramuscular administrations of salmon calcitonin. European Journal of Pharmaceutical Sciences. 2001 May 1;13(2):179-85.. *DOI: 10.1016/s0928-0987(01)00094-x*

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.