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## RECENT DEVELOPMENT IN ORAL DELIVERY OF BISPHOSPHONATES - AN OVERVIEW.

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### ABSTRACT

Osteoporosis is major problem in women and geriatric patients where antiresorptive agents are normally recommended. Bisphosphonates (BPs), which have proven efficacy in terms of bone resorption reduction, increase of bone in mineral density, and reduction in fracture risk. Although the oral bioavailability of Bisphosphonates is low, their clinical efficacy favors oral administration. Currently marketed oral bisphosphonates preparations suffer from the drawback of discontinuation of therapy due to side effects. This paper provides a comprehensive review of literature on various approaches and technologies attempted to improve the bioavailability and reduce gastric intolerance of oral bisphosphonates. Simultaneously future opportunities for oral delivery of bisphosphonates are also examined.

**Key words:** Bisphosphonates, side effects, poor oral bioavailability, approaches, patented technology, future opportunities.

### INTRODUCTION

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhanced bone fragility. This increases the susceptibility to fracture. Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs. It is a cause of substantial morbidity, reduction in quality of life, and increased mortality.<sup>1, 2</sup> universal public health measures (calcium/vitamin/ exercise) are recommended in all patients regardless of

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bone mineral density (BMD), as they are efficacious, safe and cost-effective. Pharmacological interventions are expensive and should therefore be targeted to those at high risk of fractures. If vitamin D deficiency is a major contributor to the low bone density very striking rises in bone density can be observed with calcium/ vitamin D supplementation<sup>3,4</sup>. Supplementations are having minimal effects, more medication is needed. Pharmacological agents are classified into anticatabolic (bisphosphonates, raloxifene, estrogen, calcitonin) and anabolic agents (teriparatide) depending on their effects on bone remodeling and with respect to the mechanisms of fracture reduction. If the goal is to decrease risk of vertebral fractures, then the choices would include raloxifene or bisphosphonates in mild cases. Bisphosphonates (alendronate, risedronate or ibandronate) are clearly the drugs of choice in the usual moderate to severe cases, but for those with severe osteoporosis especially with preexisting fracture, teriparatide would be the preferred option. The role of calcitonin has gradually declined with the availability of newer agents, while strontium still needs further evaluation. In this review besides elaborating on bisphosphonates as to their structure activity relationship, clinical pharmacology, mechanism of action, marketed formulations, much focus has been given on approaches attempted for enhancement of oral bioavailability and reduction of gastro intestinal intolerance. Various absorption enhancement strategies which may be more efficacious are also mentioned.

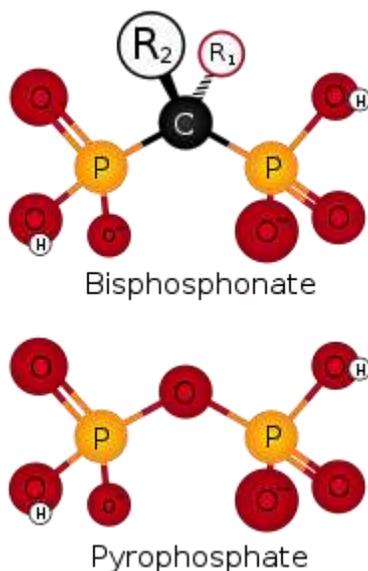
## BISPHOSPHONATES

Bisphosphonates are used in the management of disorders of calcium and bone metabolism.<sup>5</sup> They are BCS class III drugs analogs of inorganic pyrophosphate.<sup>6,7</sup> They contain carbon atom substituted for oxygen in pyrophosphate, which allows a great number of possible variations<sup>8</sup>, Pyrophosphate can prevent calcification by binding to hydroxyapatite (bone mineral) crystals<sup>6,7</sup>. Orally used pyrophosphate is inactivated in the gastrointestinal tract by mucosal brush border phosphatases.<sup>9</sup> Bisphosphonates bind strongly to hydroxyapatite crystals<sup>10</sup> and are resistant to enzymatic hydrolysis due to the carbon atom in their structure as shown in figure 1.<sup>5</sup>

The first therapeutically used bisphosphonate is etidronate.<sup>12</sup> Bisphosphonates prevent the osteoclast-mediated bone resorption.<sup>13, 14</sup>

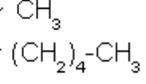
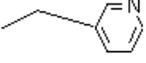
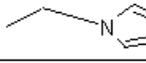
### Structure Activity Relationship

The activity of bisphosphonates differs from one to another due to the length and substitution of the aliphatic carbon atom<sup>11</sup>. The potency of inhibiting bone resorption varies between different bisphosphonates by up to 5000-fold to 1. The antiresorptive activity increases in order, as etidronate < tiludronate < clodronate < pamidronate < alendronate < risedronate<sup>12</sup>. The biological



**Figure 1: Chemical structure of Bisphosphonates**

activity of the bisphosphonates can be modified by altering the structure of the two side chains on the carbon atom. The binding to bone mineral depends upon the P–C–P structure and is enhanced by including a hydroxyl group at R1. The structure and three-dimensional configuration of the R2 side chain determines the cellular effects of bisphosphonates, and their relative efficacies as inhibitors of bone resorption. Each bisphosphonate has its own profile of activity, determined by its unique side chain in Figure 2 Bisphosphonates side chains.

Agent	R <sub>1</sub> side chain	R <sub>2</sub> side chain
Etidronate	-OH	-CH <sub>3</sub>
Clodronate	-Cl	-Cl
Tiludronate	-H	-S- 
Pamidronate	-OH	-CH <sub>2</sub> -CH <sub>2</sub> -NH <sub>2</sub>
Neridronate	-OH	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>
Olpadronate	-OH	-(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>
Alendronate	-OH	-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>
Ibandronate	-OH	-CH <sub>2</sub> -CH <sub>2</sub> N 
Risedronate	-OH	
Zoledronate	-OH	

**Figure 2: Bisphosphonates side chains**

After the promise shown in the early clinical use of etidronate and clodronate, newer bisphosphonates were synthesized, containing a primary nitrogen atom in an alkyl chain (pamidronate, alendronate). This increased the antiresorptive potency by up to one hundred times. Later modifications of the R2 side chain to produce compounds containing tertiary nitrogen groups, such as ibandronate and olpadronate, further increased potency. The most potent bisphosphonates to date, risedronate and zoledronate, contain a nitrogen atom within a heterocyclic ring. They are up to 10 000 times more potent than etidronate in some experimental systems. Although the structure of the R2 side chain is the major determinant of antiresorptive potency, both phosphonate groups are required for the drugs to be pharmacologically active.

### **Pharmacodynamic Parameters**

Intestinal absorption is low and variable (1–10%). It takes place by passive diffusion through paracellular route in the stomach and upper small intestine, and is reduced if the drug is given with calcium or iron. Bisphosphonates are therefore never given at meal times or with dairy products. However, the clinical efficiency shown by the bisphosphonates is sufficient to justify the use of the oral route. Bisphosphonates absorption would be benefited from increased residence in gastric or small intestine region.<sup>19</sup> Bisphosphonates are characterized by poor intestinal absorption but highly selective localization and prolonged storage in bone. Due to their stability the bisphosphonates are absorbed, stored and excreted unchanged.

With 20–80% of absorbed bisphosphonates rapidly taken up by bone and the remainder rapidly excreted in the urine, the half-life of bisphosphonates in the circulation is short (0.5–2 hours). Deposition in bone takes place at sites of bone formation and resorption.

## **MECHANISMS OF ACTION**

### **Ectopic calcification**

Pyrophosphate inhibits ectopic calcification *in vivo*, and this was one of the earliest observed actions of bisphosphonates<sup>15</sup>. The concentrations of etidronate required to inhibit bone resorption are similar to those which prevent calcification. This has the disadvantage that significant undermineralisation of bone can occur if etidronate is not administered with care in limited dosage. As new bisphosphonate analogues came along, the alterations to the carbon side chains had the effect of progressively increasing their potency as inhibitors of bone resorption, so that they have essentially no effect on calcification.

### **Remodelling**

When bisphosphonates are given to growing rats, remodeling at the ends of long bones is reduced and an abnormal shape results. This effect is currently used as a model to estimate the potency of new compounds.

### **Resorption**

Bisphosphonates are very effective inhibitors of bone resorption *in vivo* and *in vitro*<sup>16</sup>. They act rapidly, and the maximum effect and its duration are related to the dose. In organ cultures of bone, whatever treatment is used to enhance bone resorption, it can be inhibited by bisphosphonates. The structure-activity relationships seen *in vitro* preserved in *in vivo* studies in the rat. The resorption of isolated osteoclasts on bone or dentine slices too is inhibited by bisphosphonates. They appear to be taken up by osteoclasts active upon bone, and to inhibit crucial intracellular processes.

### **Osteoclastic and osteoblastic activity**

Bisphosphonates may not act solely through direct actions on osteoclasts. They can inhibit the activity and proliferation of osteoblasts *in vitro*. Osteoblasts are important stimulators of osteoclast formation. The bisphosphonates stimulate the osteoblast to produce inhibitor(s) of osteoclasts formation and therefore of bone resorption<sup>17</sup>.

### **Therapeutic Use of Bisphosphonates<sup>18</sup>:**

- Treatment and prevention of postmenopausal osteoporosis
- Treatment to increase bone mass in men with osteoporosis
- Treatment and prevention of glucocorticoid induced osteoporosis
- Treatment of Paget's disease
- Prevention of Skeletal Relevant Events (bone fractures)
- Treatment of the hypercalcemia of malignancy
- Bone loss caused by cancer treatment
- Bone loss and bone pain caused by bone cancer and metastases

### **Major Unwanted effects:**

Bisphosphonates cause a complication known as "Dead Jaw Syndrome" or Osteonecrosis of the Jaw. They cause gastric irritation and ulceration.

The clinical efficiency shown by the 2.5 mg daily or 70 mg weekly or 150 mg monthly dose of bisphosphonates is sufficient to justify the use of the oral route.<sup>18</sup> If increased absorption could be attained, oral administration would be a viable route of administration even in situation of

tumor osteolysis where higher doses are required. Improved bioavailability would lead to decrease in dose giving improvement in osteoporosis therapy significantly<sup>21</sup>.

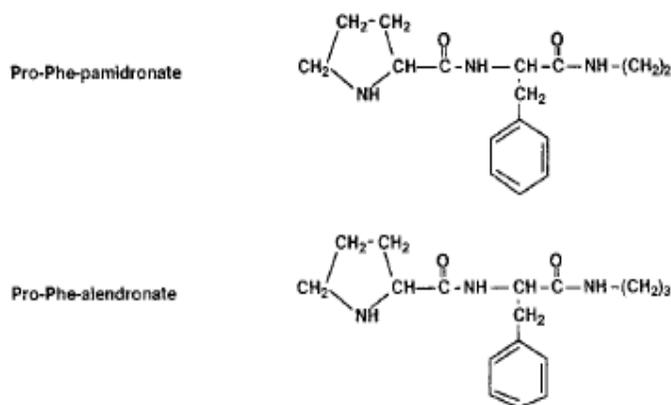
## RECENT APPROACHES ATTEMPTED FOR ORAL BIOAVAILABILITY ENHANCEMENT OF BISPHOSPHONATES

For the development of an effective oral delivery system the following approaches have been attempted:

- (i) Addition of a novel functionality (e.g. receptor recognition or cell permeability)
- (ii) Modification of the physicochemical properties of the drug molecule (e.g. lipophilicity and enzyme susceptibility)
- (iii) The use of carrier system
- (iv) Modification of Physiological Barrier by Various Agents<sup>29</sup>.

### Prodrug-Carrier-mediated transport

A relatively novel method to increase membrane permeability is by utilizing the carrier systems of the brush-border membrane of intestinal mucosa which are active transporter for di- and tripeptides (hPEPT1)<sup>22</sup>. Gershon Golomb *et al.*, (2000) coupled <sup>14</sup>C-Labeled pamidronate and alendronate with dipeptide, proline-phenylalanine to produce peptidylbisphosphonates, Pro-[<sup>3</sup>H]Phe-[<sup>14</sup>C]pamidronate, and Pro-[<sup>3</sup>H]Phe-[<sup>14</sup>C]alendronate known to be actively transported by the peptide carrier (Figure 3). Prodrug transport in the Caco-2 cell line was significantly better than that of the parent drugs, and the prodrugs exhibited high affinity to the intestinal tissue. Oral administration of the dipeptidyl prodrugs resulted in a three-fold increase in drug absorption following oral administration in rats, and the bioavailability of Pro-Phe-alendronate was higher than that of the parent drug<sup>23</sup>.

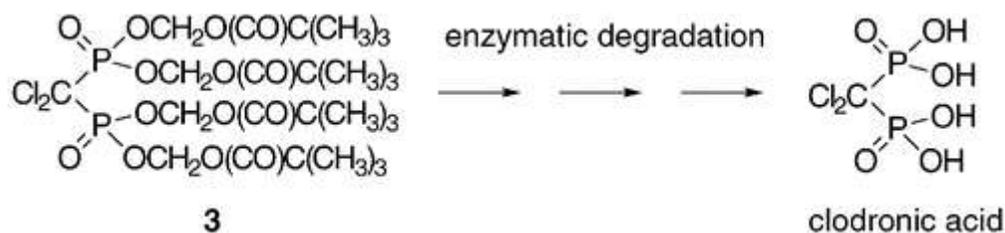


**Figure 3:** Pro-Phepamidronate, and Pro-Phe-alendronate.

## Prodrug

Using the prodrug approach, oral absorption can be increased by masking one or more ionizable groups in clodronate, etidronate etc. Erez *et al.*, (2008) used a self-immolative linker to attach tryptophan to a bisphosphonate component through a carbonate-labile linker, 4-hydroxy-3, 5-dimethoxybenzyl alcohol, which was further attached through a stable carbamate linkage to the amine group of tryptophan. The carbonate linkage hydrolyzed with a half-life of 90 h, but it can be modulated through the nature of the substituent on the aromatic ring of the self-immolative linker. Prodrug showed more lipophilicity causing passive transport across intestinal membrane with more oral absorption than the parent polar, hydrophilic bisphosphonates. Prodrug was stable in gastric fluid. Prodrugs were having significant binding capability to hydroxyapatite, the major component of bone, and were hydrolytically activated under physiological conditions.<sup>24</sup>

Niemi *et al.* (1999) synthesized Prodrug of clodronic acid which was tetra-, tri-, and  $P,P'$ -dipivaloyloxymethyl esters of clodronic acid as shown in figure 4 and evaluated in vitro. All pivaloyloxymethyl esters were significantly more lipophilic ( $\log P_{app}$  ranged from  $-2.1$  to  $7.4$ ) than clodronate ( $\log P_{app} \leq -5.4$ ), which suggests that it may be possible to change the intestinal absorption mechanism of clodronate from a paracellular to a transcellular pathway by a prodrug approach. Intermediate degradation products were further degraded, and clodronic acid was released in quantitative amounts mostly due to the chemical hydrolysis.<sup>34</sup>



**Figure 4: Enzymatic degradation of Dipivaloyloxymethyl esters of clodronic acid**

Marko *et al.* (1999), in a study synthesized  $P,P'$ -Diacetyl,  $P,P'$ -dibutyryl,  $P,P'$ -dipivaloyl, and  $P,P'$ -dibenzoyl (dichloromethylene)bisphosphonic acid dianhydride disodium salts as novel bioreversible prodrugs of clodronate. The dianhydrides alone were more lipophilic than the parent clodronate, as determined by drug partitioning between 1-octanol and phosphate buffer at pH 7.4. The aqueous solubility of clodronate decreased considerably in the presence of  $\text{Ca}^{2+}$  ions. This is most probably due to formation of poorly water-soluble chelates, which may also hinder the oral absorption of clodronate. However,  $\text{Ca}^{2+}$  ions did not have an effect on the aqueous solubility of clodronic acid dianhydrides, and therefore, these prodrugs may improve oral absorption of the parent drug. In conclusion, these novel dianhydride derivatives may be

potentially useful prodrugs of clodronate which, due to their lipophilicity and lack of  $\text{Ca}^{2+}$  chelating, increase its bioavailability after oral administration<sup>35</sup>.

### **Co-crystal**

Josef *et al.* (2010), manufactured various mixtures of ibandronate and excipients (more hydrophobic adducts) in different ratios and under various conditions. Various pharmaceutically acceptable agents were evaluated as potential counter ions:  $\alpha$ -D-glucose,  $\alpha$ -D-mannose,  $\alpha$ -D-galactose, methyl- $\alpha$ -D-glucopyranoside, methyl- $\beta$ -D-galactopyranoside, methyl- $\alpha$ -D-mannopyranoside, phenyl- $\beta$ -D-glucopyranoside, phenyl- $\beta$ -D-galactopyranoside. Out of the evaluated co-crystals of ibandronate, phenyl- $\beta$ -D-galactopyranoside showed similar or relatively low absorption related to permeability of ibandronate API<sup>25</sup>.

### **Micro emulsion**

Fulya and Nevin *et al.*, (2008) in their study formulated water in oil micro emulsion of alendronate with Captex 200®, lecithin, propylene glycol and bi distilled water. Rheological behavior, phase stability and type of the microemulsion formulation were investigated by Brookfield viscometer, centrifugation test and dye method, consequently. Phase behavior of the formulation was found to be Newtonian. No precipitation was observed in the stressed conditions and formulation was W/O. The physical characterization of the formulation (physical appearance, viscosity, refractive index, conductivity, density and turbidity) was investigated at 4°C and 25°C during 6 months while droplet size was investigated for three months<sup>26</sup>.

Meng *et al.* (2011) and his coworkers prepared positively charged micro emulsion of alendronate for bioavailability improvement. The bioavailability of alendronate from the microemulsion was compared with the commercially available tablet (Fosmax) for beagle dogs. The permeability enhancement was parallel to the reduction in transendothelial electrical resistance, which indicated the micro emulsion modulated the tight junctions and widened the paracellular pathway<sup>33</sup>.

### **Micro particulate delivery**

Cruza *et al.* (2010), encapsulated alendronate sodium in blended micro particles composed of Eudragit® S100 and Methocel® K15M with an objective to prepare gastro protective drug delivery and sustained release system. In vivo experiments carried out in ovariectomized rats showed bone mineral density significantly higher for the sodium alendronate-loaded micro particles than for the negative control groups. Furthermore, the microencapsulation of the drug showed a significant reduction in the ulcerative lesion index. The blended micro particles were

excellent oral carriers for sodium alendronate since they were able to maintain the drug antiresorptive effect and to reduce the gastrointestinal drug toxicity.<sup>42</sup>

### **Particulate adducts**

Dissetea *et al.*, (2010) prepared particulate adducts of sodium risedronate and titanium dioxide for the oral bioavailability enhancement. Nanocrystalline and colloidal TiO<sub>2</sub>, was used to obtain the adducts In vivo studies indicate that after oral administration to male Wistar rats, the micro particles of adduct Were able to prolong the presence of risedronate in the bloodstream during an 8 h period, resulting in a relative bioavailability almost doubled with respect to the free drug. This behavior allows envisioning an improvement of the risedronate therapeutic effects and/or a reduction of its frequency of administration with consequent reduction of gastro-oesophageal injuries typically induced by oral administration of bisphosphonates.<sup>43</sup>

### **Floating Matrices**

Chauhan *et al.*, (2004) prepared floating matrices of Risedronate sodium with an objective to avoid gastric irritancy by formulating it in lipidic material and achieve sustained release . The matrix systems were prepared by melting Gelucire® 39/01 derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids and Caprol PGE 860 at 10 °C above the melting point of Gelucire®39/01. Results confirmed the use of Gelucire® 39/01 as sustained release carrier in gastro retentive drug delivery system.<sup>27</sup>

### **Hydrophilic Matrix Tablet**

Ochiuz *et al.*, (2008) formulated a controlled release tablet of alendronate with various grades of hydrophilic Carbapol polymer and other excipients. The tablets were intended to release the alendronate in gastric region since absorption is favored in this region. Controlled release of alendronate over long period caused enhancement in bioavailability. Three grades of carbopol 974 P NF, Carbopol 971 P NF, carbopol 71 G NF mixed in various ratios and the tablets were pressed. Some blends displayed the best swelling and erosion characteristics, being recommended for the preparation of the extended release alendronate tablets.<sup>28</sup>

### **Penetration enhancers**

Penetration enhancers are chemical substances which alter the membrane function reversibly and increase the permeation of low permeable drugs. They act generally by disrupting the lipid structure of the membrane, open the tight junctions or extract lipid from the membrane. Raiman *et al.*, (2003) in their study assessed the effects of four different absorption enhancers—palmitoyl carnitine chloride (PCC), *N*-trimethyl chitosan chloride (TMC), sodium caprate (C10), and

ethylene glycol-bis( $\beta$ -aminoethyl ether)- *N,N,N',N'*- tetraacetic acid (EGTA)—on the transport of clodronate using Caco-2 cell culture model. According to the results, the permeation of clodronate through Caco-2 cells could be significantly promoted by the absorption enhancers, which cause widening of the tight junctions and, thus, increase the permeability of the paracellular route.<sup>29</sup>

## PATENTED TECHNOLOGIES FOR BISPHOSPHONATES TABLETS

### **GIPET® (Merrion Pharmaceuticals, Dublin, Ireland)**

Gastrointestinal Permeation Enhancement Technology (GIPET®) formulations (Merrion Pharmaceuticals, Dublin, Ireland) are a group of oral solid dosage forms designed to promote absorption of poorly permeable drugs. GIPET is based primarily on promoting drug absorption through the use of medium-chain fatty acids, medium-chain fatty acid derivatives and micro emulsion systems based on medium-chain fatty acid glycerides formulated in enteric-coated tablets or capsules. The typical GIPET®-I preparation contains a poorly-absorbed drug with Sodium caprate C10 as the promoter in an enteric-coated tablet. In a Phase I study, GIPET® also improved the oral F of the bisphosphonate, alendronate, 12-fold compared to alendronate sodium tablets (Fosamax®, Merck), to yield an oral F of 7.2 % based on urinary excretion data of the unchanged molecule<sup>30,31</sup>.

### **VitB<sub>6</sub>-conjugate technology (MBC Pharma, Inc)**

MBC Pharma has patented a drug discovery technology based on the concept of chemically attaching established pharmacophores to bisphosphonates through specifically designed labile bonds. To improve the oral absorption of aminobisphosphonates, they chemically attach a vitamin B<sub>6</sub> molecule known to be actively absorbed in the GI tract to the bisphosphonate. Active absorption will enable lower doses and improved patient tolerance, which could be a critical improvement in bisphosphonate therapy.

Once inside the cell, the bisphosphonates will be released by a specific enzyme (pyridoxine/pyridoxamine phosphate oxidase). Thus, the bisphosphonate will be both absorbed and delivered inside cells using vitamin B<sub>6</sub> metabolic pathways.<sup>36</sup>

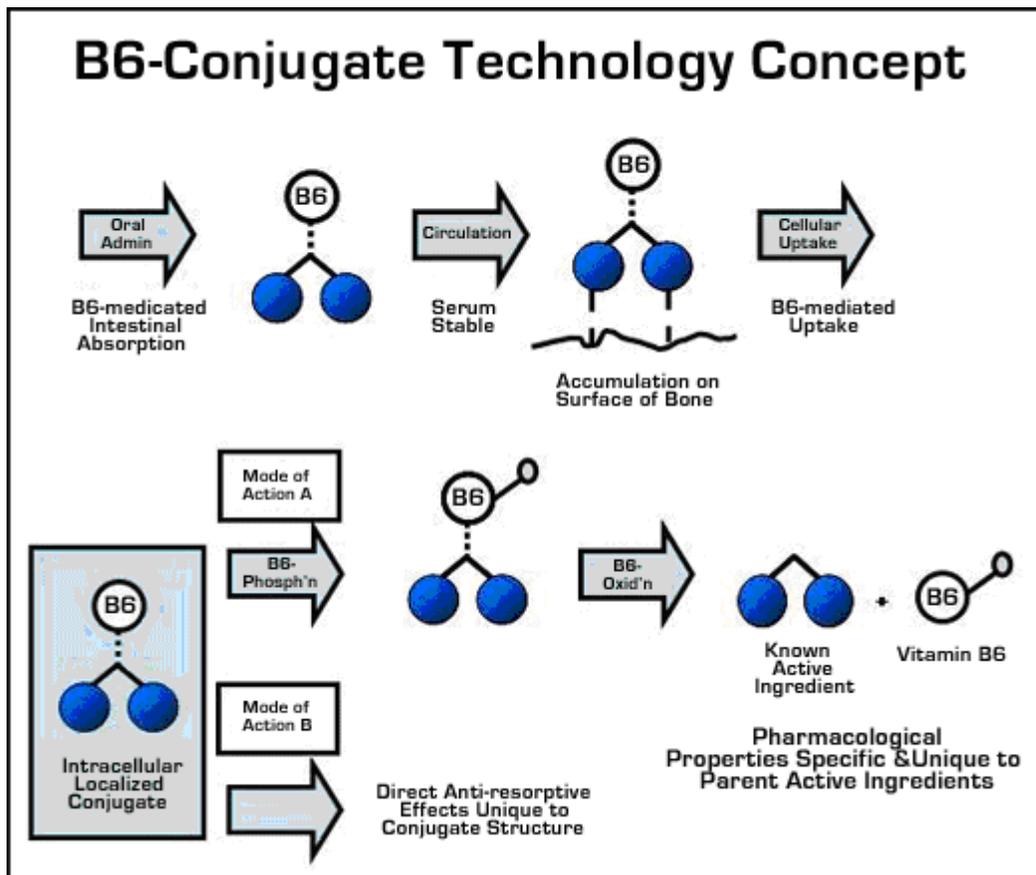


Figure 5: Vit. B<sub>6</sub> – Conjugate technology

**EX101 Proprietary Buffered Effervescent Dosage (Eff Rx Pharmaceuticals SA)**

EX101 is a proprietary buffered effervescent dosage form of alendronate sodium administered once weekly for treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. The EX101 formulation is the first and only effervescent bisphosphonate alternative to tablets. EX101 has a pleasant taste of strawberry and is quickly and completely dissolved.<sup>37</sup>

Tomaz *et al.*, (2004) patented pharmaceutical technology where a pharmaceutical composition for oral administration of alendronic acid, pharmaceutically acceptable salts or esters thereof, which reduces the potential for irritation and erosion of the mucosal tissue and pain in the upper gastrointestinal tract and provides relatively good absorption of the active substance in the gastrointestinal tract.<sup>38</sup>

Boyd *et al* (2007) received an US patent on Compositions for delivering bisphosphonates and methods of preparation, administration and treatment are provided as well. The present disclosure related to compositions comprising at least one of the delivery agent compounds depicted as carboxylic acids may be in the form of the carboxylic acid or salts thereof, amines

may be in the form of the free amine or salts thereof and at least one bisphosphonate. These compositions facilitate the delivery of the bisphosphonate to selected biological systems and increase or improve the bioavailability of bisphosphonate compared to administration without the delivery agent compound. The administration compositions can be in the form of a liquid. The solution medium may be water. Dosing solutions may be prepared by mixing a solution of the delivery agent compound with a solution of the bisphosphonate, just prior to administration. Alternately, a solution of the delivery agent compound (or bisphosphonate) may be mixed with the solid form of the bisphosphonate (or delivery agent compound). The delivery agent compound and the bisphosphonate can also be mixed as dry powders. The administration compositions can alternately be in the form of a solid, such as a tablet, capsule or particle, such as a powder or sachet. Solid dosage forms may be prepared by mixing the solid form of the compound with the solid form of the bisphosphonate. Alternately, a solid can be obtained from a solution of delivery agent compound and bisphosphonate by methods known in the art, such as freeze-drying (lyophilization), precipitation, crystallization and solid dispersion. The administration compositions of the present invention can also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or epiactinonin and derivatives thereof. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.<sup>39</sup>

Lulla *et al.* (2004) received an US patent for an enteric coated formulation for bisphosphonic acids and salts thereof. The pharmaceutical composition comprises an inert core surrounded by an active coating containing one or more bisphosphonic acids or salts thereof, a seal coating surrounding the active coating and an enteric coating surrounding the seal coating. Alendronic acid and alendronate sodium trihydrate are the preferred active ingredients. The composition can be provided in the form of pellets in a capsule or Peltabs. The composition includes one of the bisphosphonic acids and salts thereof, typical enteric coatings for use include one or more of hydroxypropyl methylcellulose phthalate, hydroxypropyl cellulose acetyl succinate, cellulose acetate phthalate, polyvinyl acetate phthalate, and methacrylic acid-methyl methacrylate copolymers. The compositions are preferentially released in the lower gastrointestinal tract upon ingestion and thus avoid oesophageal discomfort and ulceritis for the prior art.<sup>40</sup>

Khandelwal *et al.*, (2004) received an US for Pharmaceutical preparations containing alendronate sodium. An oral composition in tablet form containing therapeutic amounts of alendronate sodium for release of the alendronate sodium in the stomach and by passing the

esophagus, comprising a compacted granulated core with the alendronate sodium embedded in an inert fiber matrix, lined with a moisture barrier film and enclosed in a sugar based inert fiber matrix shell. The drug is released directly into the stomach (the site of absorption) and the swallowing of the tablets is made much simpler and no postural restrictions are required any longer. The formulation is modified to release the drug at the site of absorption. The hydrophilic matrix and the sugar inert fiber shell used impart the above characteristics.<sup>41</sup>

**Table 1: Patents on bisphosphonates oral delivery**

Patent Number	Title	Owner	Issue Date
<a href="#">5431920</a>	Enteric coated oral compositions containing bisphosphonic acid antihypercalcemic agents	Bechard	7/11/1995
<a href="#">5462932</a>	Oral liquid alendronate formulations	Brenner, et al.	10/31/1995
<a href="#">5622721</a>	Dosage forms of risedronate	Dansereau, et al.	4/22/1997
<a href="#">5853759</a>	Effervescent alendronate formulation	Katdare, et al.	12/29/1998
<a href="#">6143326</a>	Oral pharmaceutical preparation containing ibandronat	Mockel, et al.	11/7/2000
<a href="#">6432932</a>	Method for inhibiting bone resorption	Daifotis, et al.	8/13/2002
<a href="#">6676965</a>	Enteric coated formulation for bisphosphonic acids and salts thereof	Lulla, et al.	1/13/2004
<a href="#">6677320</a>	Parenteral bisphosphonates composition with improved local tolerance	Diederich, et al.	1/13/2004
<a href="#">7309698</a>	Compositions for delivering bisphosphonates	Boyd, et al.	12/18/2007

#### FUTURE OPPORTUNITIES:

Moreover all the forgoing studies are aimed to increase the intestinal permeability of the bisphosphonates and protecting gastric side effects. Some of the tried approaches are potential and showed good results. Following approaches can become promising for improvement oral bioavailability of such drugs.

**1. Ion-pair complex**-An analogous strategy to a covalent Prodrug approach is an ion-pairing approach, wherein a highly charged, polar molecule with poor membrane permeability is coupled with a lipophilic counter ion of equal and opposite charge to form an ion-pair in solution that is able to passively permeate cell membranes. Cationic counter ions may be employed to make ion pair complex with anionic bisphosphonates. Increased lipophilic nature of ion pair complex makes their transcellular absorption.<sup>44</sup>

**2.MPCcombination**-Synergist effects can be achieved by utilization of Mucolytic agent to remove mucus from small intestinal surface, chelating agent to remove calcium ions present in food and fluid otherwise forms insoluble bisphosphonates calcium salt. Penetration enhancer alters the intestinal barrier to absorption finally leading to improvement in bioavailability.<sup>45</sup>

**3.w/o/w Nanosize Multiple emulsion-**A Balanced Nanosize Multiple emulsions are complex polydispersed systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized by lipophilic and hydrophilic surfactants respectively. Hydrophilic drugs can be dissolved in internal aqueous phase and outer oily phase provides lipophilic vesicle which would serve as carrier for lymphatic transport of hydrophilic drugs .Palatability is improved by emulsifying water in oil emulsion in aqueous phase to give water in oil in water multiple emulsion.<sup>46,47</sup>

**4. Enteric pellets-**Enteric pharmaceutical formulations are manufactured in such a way that the product passes unchanged through the stomach of the patient, and dissolves and releases the active ingredient quickly when it leaves the stomach and enters the small intestine. Pellets of bisphosphonates along with suitable filler, chelating agent and penetration enhancers can be formed which can be enclosed in a hard gelatin capsule and applied the "enteric coating", which is insoluble in acid environments, such as the stomach, but is soluble in near-neutral environments such as the small intestine. Pellets can be prepared by extrusion and spheronization. Enteric coated capsule, enclosing bisphosphonates can be delivered orally to release in small intestinal region where by avoiding gastric irritancy of drug and food interaction.<sup>48</sup>

**5. Mucoadhesive Tablet-** Mucoadhesive polymers interact with mucus layer of stomach and adhere for longer time. Due to an increased residence time it enhances absorption of active ingredient and hence the therapeutic efficacy of the drug. Hence it may be useful to administer bisphosphonates in Mucoadhesive system to offer continuous drug release at preferred absorption window, thus ensuring optimal bioavailability.<sup>49</sup>

### **6. Gas Empowered Drug Delivery System**

A novel Gas Empowered Drug Delivery (GEDD) system can be designed for CO<sub>2</sub> forced transport of hydrophilic drugs like bisphosphonates together with mucoadhesive polymers to the surface of the small intestine. The GEDD effect of the core tablet can be achieved using CO<sub>2</sub> gas to push bisphosphonates together with the mucoadhesive excipients eg. Poly ethylene oxide (PEO) and the permeation enhancer eg. Trimethyl chitosan (TMC) to the surface of the small intestine. This bioactive polymer may be used to deliver bisphosphonates drugs to the mucous membrane by attaching to the gut wall. The bisphosphonates permeation can be achieved by the GEDD system may be primarily due to the enhancing effect of TMC and the mucoadhesive properties of PEO both of which synergistically increase the bioavailability.<sup>50</sup>

## 7. Tight junction modifiers

More recently, alternative tight junction modifiers have been proposed. These compounds enhance macromolecules delivery through different mechanisms. The most promising candidate among these is zonula occludens toxin (ZOT), which is proven not to be cytotoxic to GI cells. ZOT interacts with specific receptors mainly in the small intestine and is thought to modify tight junctions through protein kinase C (PKC)-induced effects on the cell cytoskeleton. More specifically, ZOT induces a dose- and time-dependent PKC- $\alpha$ -related polymerization of actin filaments. This process occurs at a very low level and is a prerequisite to the tight junctions opening. The toxin exerts its effect by interacting with a specific surface receptor that is present in the small intestine, but not in the colon.<sup>51</sup>

## CONCLUSION:

Bisphosphonates are effective in the treatment of various osteopathies and are administered preferably through oral route. Since their poor oral bioavailability and GIT adverse effects limit their therapeutic compliance. To establish the technology that improves oral absorption of poorly absorptive drugs with low membrane permeability and elimination of GIT drawbacks associated with oral administration of bisphosphonates has been tested through Prodrug-Carrier-mediated transport, prodrug delivery, micro emulsion, Micro particulate delivery, Particulate adducts, Floating Matrices, Hydrophilic Matrix Tablet and use of Penetration enhancers and promising results are obtained. Several companies have received patented technology on bisphosphonates oral formulations. Ion-pair complex, MPC combination, w/o/w Nanosize Multiple emulsion, Mucoadhesive Tablet, Gas Empowered Drug Delivery System and Tight junction modifiers can become potential tool to improve oral absorption of bisphosphonates.

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