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Review

Skeletal drug delivery systems☆

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Abstract

Selective drug delivery to any organ becomes very important in certain diseases and clinical manifestations, especially when the drug affects other exposed tissues adversely. The importance of selective drug action is still further increased when the affected part is poorly perfused. Although a network of blood vessels is present throughout skeletal tissue (or bone), it is not sufficient for immediate delivery of drugs to the desired site of action in the tissue and in sufficient amounts over appropriate time periods. Hence, selective drug delivery to the skeletal system has remained a great challenge to pharmaceutical scientists over the years. However, in the recent past, attention has been focused on the importance of skeletal drug delivery and the first Skeletal Drug Delivery System (SDDS) was introduced by Bucholz and Engelbrecht in 1970 for the delivery of drugs to skeletal tissues at a high concentration to achieve desirable therapeutic effects. SDDS is used to deliver the drug directly to skeletal tissue through self-setting cement, which also acts as a bone filler, thereby improving the therapeutic effectiveness of drugs in bone diseases. The present review highlights the applicability of various materials as bone fillers for the purpose of skeletal drug delivery.

Keywords: Skeletal drug delivery; Bone filler; Self-setting calcium phosphate cement

1. Introduction

Although bone seems lifeless, it is made up of a very alive, porous framework that is constantly rebuilding itself. Bone is a composite material of organic and inorganic components. The mineral phase of bone comprises approximately 60–70% of the total dry bone weight while the remainder is comprised of organic material such as collagen. Bone mineral is an apatite calcium phosphate containing carbonate and small amounts of sodium, magnesium and other trace components (Glimcher et al., 1981). This carbonate apatite termed dahllite contains 4–6% carbonate by weight and is also a constituent of teeth and of some invertebrate skeletons (Lowenstam and Weiner, 1989).

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Bone tissue replaces itself through the action of osteoclasts that produce acids to dissolve (resorb) hydroxyapatite and enzymes to break down collagen. The resulting release of calcium and protein prompts other cells osteoblasts to lay down a new matrix that mineralizes forming hydroxyapatite and collagen. In normal conditions bone density is maintained due to the dynamic equilibrium between the functions of osteoclasts and osteoblasts. Any change in this equilibria by uncoupling between bone resorption by osteoclasts and bone formation by osteoblasts causes an absolute reduction in the amount of bone in osteoporosis. Some growth factors such as bone morphogenic proteins are manufactured by bone cells themselves to either increase or decrease bone remodeling.

Serious open bone fractures are common in our society because of our predilection for high-speed transportation and high risk sports. The association of bacterial or fungal bone infections (osteomyelitis) with such fractures is reported to be 10–15% and treatment is very difficult. Conventional treatment of osteomyelitis involves repeated surgical removal of dead bone tissue, coupled with repeated irrigation of the wound, and prolonged systemic administration of antibiotics. Treatment of fracture requires not only plaster cast but also screws, pins and metal plates to provide the support to fractured bone. Major surgery is required to install the metal plates in the body that results in hospitalization for 10–15 days and still more surgery is required later to remove the hardware. Always these procedures are associated with pain and risk (there is a chance of infection and the screws can further damage the bone) and they are also expensive. Osteoporotic type fractures are observed more commonly among post-menopausal women because level of steroidal hormones with oestrogenic activity is reduced (Eriksen and Mosekilde, 1990) thereby bone mineral density (Lee et al., 1981) and bone mechanical strength is decreased. Surgical procedures are required to restore normal bone function in fractures due to accident and, in skeletal deficiencies from trauma, tumors and bone diseases or abnormal development. Although most of these surgical treatments are successful, these are associated with postoperative problems, i.e. infection of bone and associated tissue pain and possibility of metastasis (in bone cancer).

The routine use of systemic antibiotics and anti-inflammatory drugs for prophylaxis in postoperative complications are not adequate to alleviate these ailments due to poor perfusion of diseased 'bone site' and are also responsible for drug toxicity to other sites. Thus, to reduce the toxicity and increase the effectiveness of therapy, the local delivery of drugs to bones is a basic requirement to treat the postoperative complications and this to a large extent can be fulfilled/or achieved by localized delivery, which will reduce systemic body burden of drug (Dhanikula and Panchagnula, 1999).

In addition to bone infection and inflammation, poor mechanical integrity (due to the void remaining in the bone after surgery) is another complication. Bone strength can be increased by bolting enough screws, pins and metal plates to bones, bone grafting and use of synthetic polymeric material as bone filler. The latter option is becoming increasingly more viable as new synthetic materials are being found to be used as bone fillers. Synthetic materials have the advantage of eliminating the need for surgery to claim bone for graft procedure and also excluding the chance of rejection or transmission of infectious disease, e.g. AIDS, Hepatitis B. The biggest advantage of bone fillers to pharmaceutical scientists is that they can be used as a vehicle to administer drug directly to the site of requirement. Synthetic bone cement or bone filler with a drug has been termed 'Skeletal Drug Delivery System (SDDS)'. Drugs that can be used in a SDDS include NSAIDs like indomethacin to reduce post-operative pain (Otsuka et al., 1994e), aspirin (Otsuka et al., 1994b), 6-mercaptopurine (6-MP) in bone cancer (Otsuka et al., 1995), oestradiol (and oestrone) for regulation of bone resorption and bone formation (Eriksen and Mosekilde 1990), insulin for diabetic osteopenia (Levy et al., 1986), and antibiotics, e.g. cephalexin, norfloxacin for treating bone infection (Otsuka et al., 1990).

There is, in the literature, a dearth of articles, which attempt to review current knowledge re-

garding SDDS in terms of rationale, material of construction, formulation, and characterization with different drugs.

2. Materials used as bone filler

An ideal bone filler should have the following characteristic (Aoki, 1991; Ritter, 1997):

1. it should be biocompatible and biodegradable;
2. it should have optimum porosity to facilitate the vasculature regeneration along with bone regrowth;
3. it should have enough mechanical strength to bear the load; and
4. it should be resorbed by natural process and assist in the bone formation by osteoblasts.

As of today, only two type of materials are used as bone fillers:

1. synthetic polymers: polymethyl methacrylate (non-biodegradable), poly(lactic acid) or poly(glycolic acid) (biodegradable); and
2. minerals (or inorganic material): hydroxyapatite from different sources.

2.1. Polymethyl methacrylate (PMMA)

PMMA can be used as bone filler either in the form of cement or beads. PMMA along with antibiotics as a bone filler (cement) was described for the first time by Bucholz and Engelbrecht (1970). Bone cement consists of two components viz. PMMA powder with drug and monomer methyl methacrylate, that upon mixing, undergo an exothermic polymerization reaction causing a local thermal necrosis in the bone tissues immediately adjacent to the cement. In fact theoretically, a suitable antibiotic for use in an acrylic bone cement should be water soluble, and be able to resist degradation by extreme temperature (up to 100°C) produced during the exothermic reaction (Goodell et al., 1986).

Several research groups (Bucholz and Engelbrecht, 1970; Marks et al., 1976; Josefsson et al., 1981; Marr and Alozozzine, 1983; Desto and Hart, 1984) have reported negligible serum concentrations after use of aminoglycoside-impregnated bone cement, which implies that a lesser potential risk for toxicity than systemic therapy. This property of aminoglycoside-impregnated bone cement (i.e. its lower toxicity and thereby better efficacy) makes it very useful to be used as an effective alternative to systemic therapy in deep bone infections after total hip arthroplasty. Vorrhoeve and Stohr (1973) exemplified the inherent drawback associated with the antibiotic impregnated beads approach by reporting that in the treatment of osteomyelitis, the cement prevented drainage of secretions from the debridement area and was nearly impossible to remove if further debridement was necessary. To overcome these problems Klemm (1976) developed acrylic beads made from the same materials to aid in the treatment of osteomyelitis. However the toxicity of PMMA makes its application undesirable (Petty and Florida, 1978). Even at a low concentration, the polymer can seriously suppress the phagocytic and antibacterial activity of human polymorphonuclear leukocytes. Because of its stability in vivo, it is responsible for many tissue incompatibility reactions like bacterial growth and inflammatory responses. In addition to these unwanted biological reactions, PMMA also hinders drug release from SDDS, e.g. sometimes as much as 90% of load retention of drug in PMMA beads was reported by Levin (1975) and Goodell et al. (1986). Yu et al. (1992) reported that the tendency of PMMA to shrink during setting leaves the defect in polymeric cement with marginal mechanical support and in addition it must be removed before sound bone can regrow in the defect. At present, use of PMMA in regular clinical practice is restricted because of all aforementioned disadvantages.

2.2. Hydroxyapatite (HAP)

Self-setting apatite (Brown and Chow, 1986b) is transformed into hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HAP), which has a high compatibility with natural hard tissue and sets within half an hour in-situ, and it is also easy to use in a clinical setting (Takezawa et al., 1989). HAP has the following advantages:

1. same elementary chemical composition as natural bone and teeth;
2. it has a high affinity for hard tissue (Aoki, 1991); and
3. it would therefore be a viable candidate for long term use (Otsuka et al., 1995).

These properties of HAP have prompted intensive efforts by various pharmaceutical research groups to investigate SDDS for delivery of drugs, which contribute very important therapeutic category in skeletal disorder treatment such as antibiotics (Otsuka et al., 1990), anti-inflammatory drugs (Otsuka et al., 1994b), growth hormone (Guicheux et al., 1997) and polypeptide drugs (Otsuka et al., 1994a).

However brittleness and poor strength of HAP has limited its use as an implant in loaded situations. Hence, HAP coated metal implant with sufficient mechanical strength has been proposed as an alternative (Jansen et al., 1991). Although the load wearing capacity of HAP is low, however in a recent report (Solberg et al., 1999), the authors showed that the gentamycin impregnated HAP cement to be very efficacious to treat bone infection (e.g. osteomyelitis) in rats.

2.2.1. HAP from calcium phosphate

Brown and Chow (1986a) and Constantz et al. (1995) reported that biocompatible self setting calcium phosphate cement (CPC), which is a mixture of a basic calcium phosphate, tetracalcium phosphate (TECP), with an acidic calcium phosphate and dicalcium phosphate anhydrous, can be used as a bone filler since it gets transformed into hydroxyapatite in the body. The setting reaction is:

$$Ca_4(PO_4)_2O + CaHPO_4 \xrightarrow{H_2O} Ca_5(PO_4)_3OH$$

The conversion of calcium phosphate into HAP is very different from the formulation of HAP ceramic, which is created by sintering, where HAP powder formed by precipitation is heated to 800–1200°C. The CPC has an advantage over HAP ceramic for its contour adaptability, while both are highly compatible with tissues (Gruninger et al., 1984; Chohayeb et al., 1987; Sugawara et al., 1990; Costantino et al., 1992).

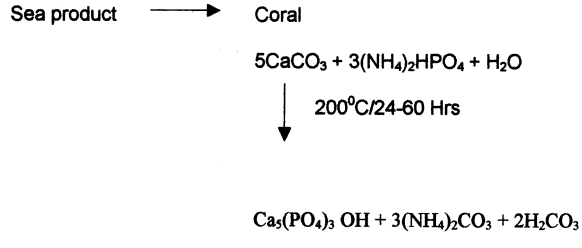
Constantz et al. (1995) reported a new skeletal repair system (SRS) known as Norian SRS, a paste that comprises of different calcium salts. The paste can be injected to the bones where drug and bone filler is required, 5 min after formulation. Norian SRS maintains the physiological temperature and pH during the setting process. This solid support allows the orthopedic physician to use much less hardware to increase the mechanical strength of fractured sites, and sometimes none at all. In the long term, SRS offers an advantage due to its similarity in structure to bone. Hence, the body treats it as endogenous material, leading to gradual resorption and replacing it with new bone growth, which is, in turn responsible for formation of natural bone at the break site. Natural bone is preferable to implants because the body constantly reworks bone to adopt to stresses.

2.2.2. HAP from CaO-SiO_2-P_2O_5

Kokubo et al. (1991) and Yoshihara et al. (1992) developed a novel self-setting bioactive bone glass cement based on CaO-SiO_2-P_2O_5, which has the capability to transform into HAP. The bioactive bone cement hardens within 5 min in the body, with suitable strength and high bioactivity (Nishimura et al., 1991), thereby considerably reducing the time required for self-setting than that required for other self-setting cements (Doi et al., 1987). Since the bioactive bone glass cement has sufficient mechanical strength and quick setting characteristics, it is suitable as the basis of a drug delivery system for skeletal tissue (Otsuka et al., 1994f)

2.2.3. HAP from coral

Ritter (1997) reported a thermochemical process to produce HAP from coral as given in the following sequence.



Currently, it is the only synthetic product in the market that has a porous infrastructure similar to natural bone. The interconnected structure of the coral remains intact throughout processing providing a matrix through which blood vessels and new bone tissue can grow. This product is marketed by Interpore International of Irvine, California under the name of Pro Osteon®. It is the only FDA approved company for manufacturing synthetic bone void filler.

2.3. Poly(lactic acid) (PLA) or poly(glycolic acid) (PLG)

Meyer et al. (1998) reported efficient delivery of ionic aminoglycosides (e.g. gentamycin) for over 4 months from PLA beads. The main advantage associated with PLA or PLG or co-polymers is their biodegradability, which ensures complete removal of polymer from the body. But this type of system cannot be used to give strength to fractured bone because it gradually disappears from the site of application due to degradation.

The interactions between implant (bone cement/or bone substitute) and natural bone is very weak. This causes graft rejection, low mechanical stability, infections and inflammation. Now, these problems can be overcome by coating the bone cement with integrin-specific and cell selective molecules to bind and activate the integrin-expressing cells, the osteoblasts (Kantlehner et al., 1999).

3. Formulation

Self-setting cement based skeletal drug delivery systems are classified into two groups, as follows:

1. homogeneous drug loaded cement; and
2. heterogeneous drug loaded cement.

In the heterogeneous drug loaded cement both the drug and self-setting cement are separated. The drug release rate through heterogeneous cement is dependent on the diffusion through various inorganic matrix materials used for cement formation. Drug release rate is controlled by factors similar to those which control drug release from common polymer coated formulations viz. tortuosity, porosity and thickness of diffusion layer.

4. Characterization of the skeletal drug delivery system

4.1. X-ray diffraction

X-ray diffraction has been used to characterize the transformation of metastable calcium phosphate to HAP and crystallinity of HAP. The typical diffraction pattern of HAP, which occurs between diffraction angle 2θ, 26–32°, indicates that metastable calcium phosphate is transformed into HAP. The fresh fixed cement containing 5% indomethacin shows a typical diffraction pattern of HAP without the diffraction peaks due to crystalline indomethacin, indicating that the metastable calcium phosphate transformed into HAP and indomethacin crystal is transformed into the amorphous form (Otsuka et al., 1994e) and Fig. 1 shows the diffraction pattern of cement with and without drug. The diffraction peaks of hardened cements were broader than those of the synthetic HAP, indicating an apatite with low crystallinity, which is reported to have a higher affinity for hard tissue than the high crystallinity apatite. Crystallinity of the intact cement is different from the drug loaded cement as it depends upon the nature of the drug, e.g. crystallinity follows the order:

$$\text{Intact cement} > 1.0\% \text{ bovine albumin} > 0.5\% \text{ bovine insulin}$$

The crystallinity of drug loaded HAP cement increases after drug release due to recrystallization of HAP as seen with 0.5% insulin and 1.0% bovine albumin.

4.2. Mechanical strength

Surface mechanical strength of the fixed cement with drug or without drug is measured in terms of Vickers Hardness, (kg/cm^2; Otsuka et al., 1994a). The Vickers Hardness of the fresh drug loaded cement is less than the cement without the drug,

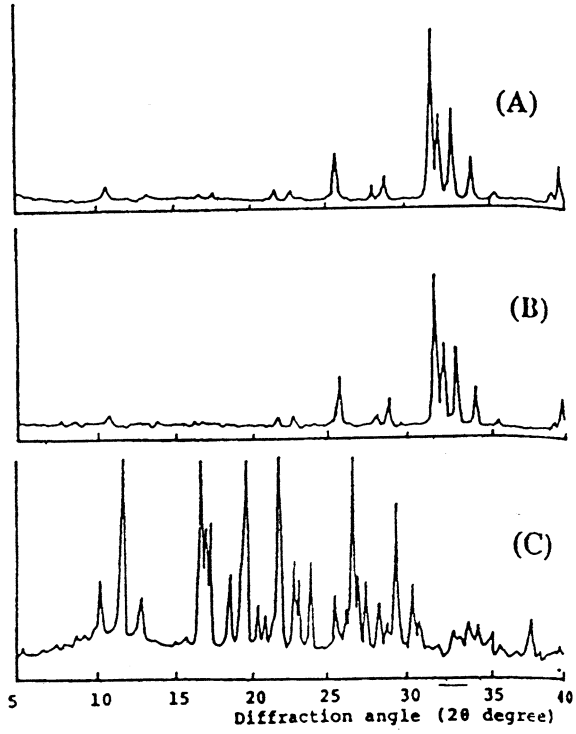


Fig. 1. X-ray diffraction profiles of indomethacin-loaded calcium phosphate cement: (A) calcium phosphate cement; (B) 5% indomethacin-loaded cement; (C) indomethacin (γ form). Reproduced from Otsuka et al. (1994e).

e.g. indomethacin in Table 1 (Otsuka et al., 1994e). This index of hardness of drug loaded cement changes during the dissolution of drug. The changes depend upon the interaction of drug with the surface of HAP, e.g. after the dissolution test the Vickers Hardness of cement containing 5% of indomethacin increased significantly as can be seen from values summarized in Table 1 (Otsuka et al., 1994e). The hardness of drug loaded cement increases after the dissolution due to the recrystallization of HAP to fill voids left by dissolving drug.

Table 1
Vicker's Hardness of cement

Cement	Vicker's Hardness (kg/cm^2)
Without drug	291.40 ± 24.2
Containing 5% drug	263.00 ± 23.0
Containing 5% drug (after a 30-day dissolution test)	427.00 ± 28.0

4.3. Fourier transform-infrared spectroscopy (FT-IR)

FT-IR is used to confirm the conversion of calcium salts into HAP and to ensure that the drug is not interfering in conversion reaction. The IR spectrum of synthetic HAP showed the absorption peaks (LeGeros et al., 1971) at 3400–3100 cm^{-1} and at 1040 and 520–450 cm^{-1}, attributable to OH and PO_4 groups, respectively. Otsuka et al. (1994f) reported absorption peaks in FT-IR (Fig. 2) of fresh fixed cement at 1640 and 1420 cm^{-1}, and at 1710 cm^{-1} due to carbonate group and indomethacin, which can be attributed to transformed HAP from bioactive glass cement containing carbonate ions and indomethacin, which is not interfering in conversion reaction.

4.4. Differential scanning calorimetry (DSC)

DSC endotherms of the fixed cement containing 5% indomethacin are shown in Fig. 3. The DSC endotherm of the crystalline form of indomethacin showed an endothermic peak at 160°C due to melting, and that of the amorphous form showed endo- and exothermic peaks at 80–105°C due to the glass transition point and crystallization, respectively. Because the X-ray diffraction profiles of the drug loaded cement did not show any diffraction peaks of indomethacin and the DSC endotherm showed an exothermic peak at 80–105°C due to crystallization, it was concluded that the drug has been apparently transformed into its amorphous form in the pores of the cement matrix (Otsuka et al., 1994e).

4.5. Drug release

The drug release rate from the cement depends on the percentage of the drug loading, e.g. the amount of released albumin from 0.2, 0.5 and 1.0% albumin containing cements were about 5, 10 and 15%, respectively, after 950 h (Otsuka et al., 1994a). Drug release from homogeneous and

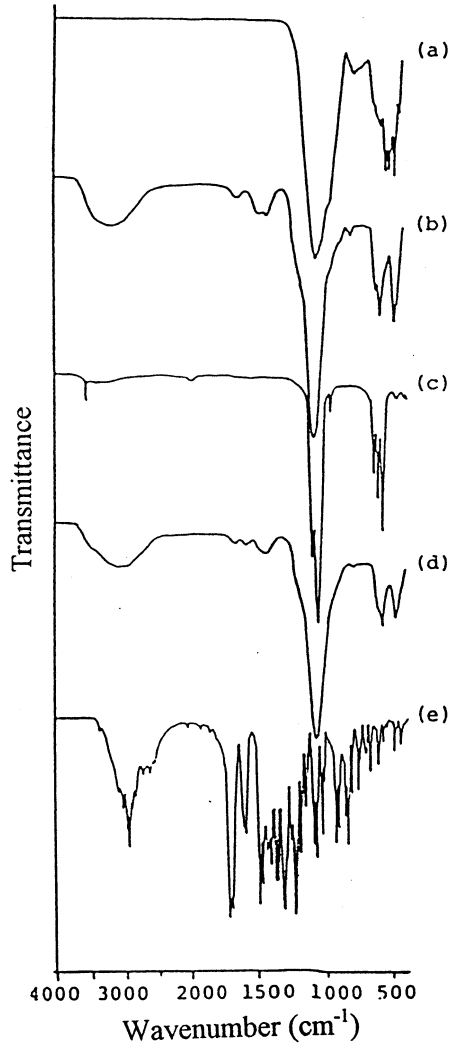


Fig. 2. FT-IR spectra of bioactive cement containing drug. (a) The bulk cement powder; (b) freshly fixed cement without drug; (c) synthetic hydroxyapatite; (d) fresh cement containing 5% indomethacin; (e) indomethacin. Reproduced from Otsuka et al. (1994f).

heterogeneous cement is a function of time, e.g. from the 5% 6-mercaptopurine loaded homogeneous cement, the amounts of drug released were about 7 and 17 mg after 50 and 570 h, respectively. The initial release rate was rapid, but after 100 h the release rate became very slow and continued for prolonged time. On the other hand, the drug release profile of the heterogeneous drug loaded cement showed lag times before drug release, e.g. heterogeneous cement loaded with 5% 6-MP had about a 70-h lag time and the release rate after this was about the same as the release from the homogenous cement after 70 h (Otsuka et al., 1994c).

4.5.1. Drug release kinetics from homogenous drug loaded self setting cement

The drug release from the homogeneous drug loaded cement follows Higuchi kinetics similar to homogenous matrix based drug loaded tablets (Higuchi, 1963).

$$M_t = A\, M_o \sqrt{[C_s(D_i\, \varepsilon/\tau)(2C_d - C_s\, \varepsilon)t]}$$

where, M_t is the amount of drug released from the cement at time t; M_o is the initial amount of drug; D_i is the diffusivity of the drug; A is the surface area of tablet; C_s is the solubility of drug; C_d is the concentration of drug in calcium phosphate buffer; τ is the tortuosity; and ε is the porosity.

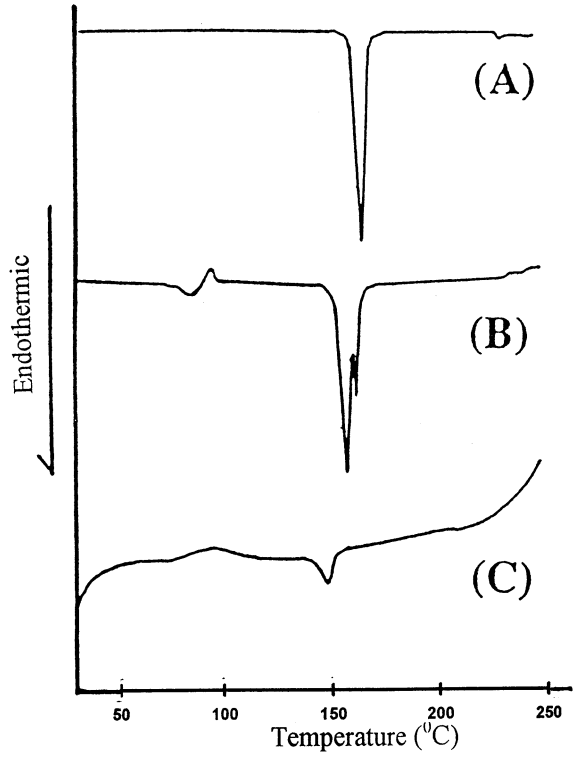


Fig. 3. DSC endotherms of indomethacin-loaded HAP cement: (A) indomethacin (γ form), (B) indomethacin (amorphous form), (C) 5% drug-loaded calcium phosphate cement. Reproduced from Otsuka et al. (1994e).

Table 2
Relationship between diffusivity and molecular weight of peptides

Peptide	Molecular weight (Da)	Diffusivity (cm^2/s)
Cephalexin	3.47×10^2	8.0×10^{-6}
Insulin	3.6×10^4	7.5×10^{-7}
Albumin	6.6×10^4	5.9×10^{-7}

In the homogenous drug loaded cement, in the initial stage of cement setting process, free ammonium ions are released from the cement and pH increases from 7.25 to 8.0, which facilitate the solubilization of drug with carboxylic acid group by formation of ammonium salt (Otsuka et al., 1994f). In the initial stages the release rate from homogeneous drug loaded cement is high for some time, then it declines and remains constant for a long time period. This initial burst of drug may be occurring due to the shrinkage of cement volume, as seen with indomethacin (5% drug) loaded cement which, before the drug release test, had a volume of 0.3456 ± 0.0032 cm^3, but after 14 days, 0.3364 ± 0.0022 cm^3 (Otsuka et al., 1994f).

It has been shown that the release profile of bovine insulin and bovine albumin loaded cements are linear with an induction period on the Higuchi plots, indicating that the release rate depends on the diffusion of drug in the pores of the cement matrix (Otsuka et al., 1994a). Diffusivity of drug is indirectly proportional to its molecular weight, e.g. diffusivity of peptides in decreasing order as a function of molecular weight, as depicted in Table 2. Otsuka et al. (1998) reported that the release rate from the cement increased with decreasing geometrical diameter of cement, reflecting the surface area of cement.

4.5.1.1. Effect of mixing solution volume. Otsuka et al. (1995) reported the linear relationship between drug release rate and volume of mixing solution required to knead the inorganic salts in the formulation stage, indicating that it is possible to control the drug release by varying the mixing solution volume.

4.5.2. Drug release from heterogeneous system

The drug release rate from the heterogeneous drug loaded cement system follows the modified Fick's Law (Baker, 1987),

$$J = \frac{DK\Delta C\varepsilon}{l\tau}$$

where, J is the permeate flux; D is the diffusion coefficient; C is the difference in the concentration; K is the permeate diffusion coefficient; τ is the tortuosity; ε is the porosity; and l is the thickness of the membrane.

In microporous membranes, K is the distribution coefficient between surrounding fluid and that in the membrane pores. When both fluids surrounding as well as in pores of the membrane are the same, K is 1 and C is the solubility in sink condition.

Otsuka et al. (1994c) reported that the drug release profiles from the heterogeneous systems were dependent on the thickness of the cement, indicating that the rate of drug release could be controlled by the formulation of the cement. They also showed that the drug release rate through the heterogeneous system was not controlled by porosity of cement, but tortuosity was playing an important role in drug release.

4.5.2.1. Drug release and liquid/powder ratio (L/P). Otsuka et al. (1994b) observed that the minimum volume of mixing solution required to knead the cement increased as the amount of HAP (as seed crystal) increased. This finding contributed to the dissolution behavior of the raw powders, because tetracalcium phosphate (TTCP) and dicalcium phosphate dihydrate (DCPD) dissolved rapidly in the mixing solution, whereas HAP seed crystals did not dissolve as rapidly. The relationship between porosity and liquid/powder ratio is linear (Fig. 4) indicating that the cement porosity depend on the volume added for mixing of solutions but not on the amount of seed crystal, e.g. two cements with 10 and 20% seed crystal had almost the same porosity. Drug release rate increases with increase in volume of mixing solution or L/P. The relationship between the drug release rate and the liquid/powder ratio of various formulations of the cement is shown in Fig. 5.

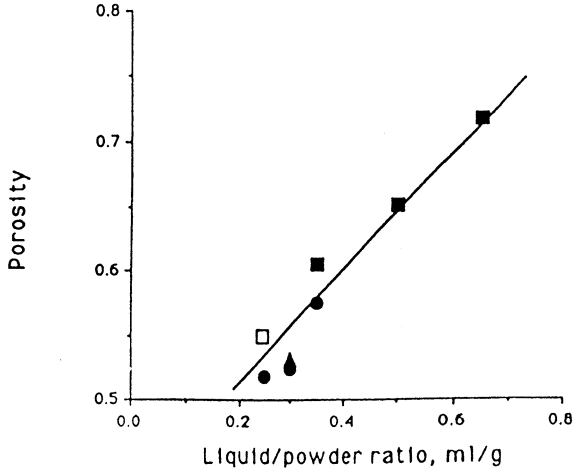


Fig. 4. Effect of the mixing solution volume on the porosity of self-setting calcium phosphate cement: □, 3% seed cement; ●, 10% seed cement; ▲, 20% seed content; ■, 40% seed cement. Reproduced from Otsuka et al. (1994b).

The drug release rate of all cements increased with an increase in the mixing solution volume but in contrast to homogeneous cement (Otsuka et al., 1995), it was not linear. The results suggested that the drug release rate from the cement did not simply depend on the volume of mixing solution;

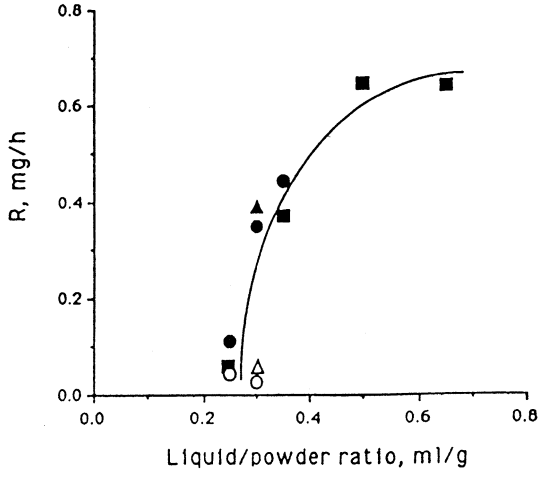


Fig. 5. Effect of the mixing solution volume on the drug-release rate of self-setting calcium phosphate cement: △, 3% seed cement; ●, 10% seed cement; ▲, 20% seed cement; ■, 40% seed cement; ○ 10% seed cement from the latter part of drug release profile; △, 20% seed cement from the latter part of drug release profile. Reproduced from Otsuka et al. (1994b).

however it is possible to control the drug release rate by changing the mixing solution volume.

The tortuosity of cement pores also affects the drug release, as increase in tortuosity of pores, leads to a decrease in the percentage of porosity of drug loaded cement, which in turn decreases the drug release, e.g. aspirin (Otsuka et al., 1994g).

4.6. Effect of polymer coating on drug release

Since the dissolution of the bulk powder in the pores of cement matrix affected the drug release from the cement device, various co-precipitate products were tried in cement system, e.g. polyvinyl pyrrolidone (PVP) PVP K-30, PVP K-90 and Eudragit®.

The drug release from the PVP K-30 and PVP K-90 was slightly higher than those from the system without polymer. It has been shown that the transformation of HAP from amorphous calcium phosphate was dramatically retarded in the presence of polyvinyl alcohol (PVA) which facilitate the drug release from the cement (Otsuka et al., 1994c), whereas the amount released from the Eudragit® system was slightly lower than from the polymer-free system.

4.7. Effect of calcium ion concentration on drug release

Calcium ion concentration in dissolution media affects the drug release by altering solubility of the drug and the pore diameter in hardened cement. The amount of drug released in simulated body fluid (SBF; containing 2.5 mM of Ca^{2+}) was much lower than that in 0.1 M phosphate buffer (Otsuka et al., 1994d). The calcium ion concentration not only affects the drug release rate in vitro testing, but it also affects the drug release rate from the cement in vivo. Otsuka et al. (1997, 1999) concluded that apatite cement is an intelligent material with the ability to change the rate of drug release appropriately in response to changes in plasma calcium concentration. The drug release rate decreased in presence of calcium ion due to the precipitation of calcium salt on the surface of all materials. This precipitate was iden-

tified as HAP by thin film X-ray diffraction analysis (Tanahashi et al., 1992). The release of indomethacin was also reduced at the later stages of release test by depression of drug diffusion in micropores caused by HAP precipitation (Otsuka et al., 1997).

4.8. Effect of cement loaded site on drug release

The drug release rates from the cements on the defective bone was higher than those from the medullary cavity. The drug release from the sealed cement was negligible. This suggests that the porosity of bone was quite low (Otsuka et al., 1994d).

5. Conclusion

The work that has been done in the field of skeletal drug delivery system is not exhaustive specially when compared to other new drug delivery systems such as liposomes, transdermal and iontophoresis drug delivery systems. But on the basis of the research work so far, self-setting cement skeletal drug delivery system may be an effective way to treat localized bone diseases such as bone cancer, infection, and fracture with high therapeutic effectiveness and minimum systemic side effects/or toxicity.

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