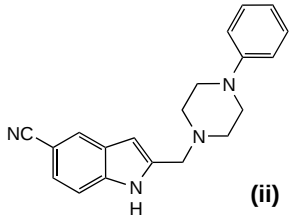
A small library of 13 compounds was synthesized on solid phase. One of the most potent compounds isolated was **(ii)**, which possessed a K_i value of 0.52 nM for human D_4 affinity, and 25000-, 6000-, 550- and 3300-fold selectivity over the bovine D_1, human D_{2long}, human D_{2short} and human D_3 receptors, respectively. This library has been successful in generating highly potent and selective D_4 receptor-binding compounds, which could serve as an interesting tool for the treatment of various neuropsychiatric disorders.



(ii)

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Paul Edwards
Lead Discovery Technologies
Pfizer Global Research and Development
Sandwich
Kent, UK
fax: +44 (0)1304 643555
e-mail: paul_edwards@sandwich.pfizer.com

Drug delivery

A drug delivery system for the treatment of periodontitis

Gum disease is a common medical problem, affecting up to 75% of adults over the age of 35. Periodontitis is one of the more severe forms of gum disease and is characterized by the formation of periodontal pockets. These pockets are lesions between the teeth and junctional epithelium resulting from a localized pathogenic bacterial infection below the gum line. Periodontal pockets are easily accessed through the mouth and are a convenient site for using a localized drug delivery system (LDDS). Currently, the commercially available subgingival LDDSs are designed to deliver a single antibacterial agent into the gingival crevicular fluid (GCF), for up to seven days. The effectiveness of subgingival LDDSs could be increased if they: (1) were capable of delivering a range of antibacterial agents; (2) exhibited controlled release over an extended period of time; (3) had limited swelling in GCF and; (4) possessed adhesive properties that prolonged the retention time on the surface of the tooth.

Recently, Bromberg and colleagues have reported an *in vitro* investigation of an LDDS that possesses all of the above characteristics[1]. This LDDS is composed of a composite wafer with an adhesive surface layer and a bulk layer, which consists of antibacterial agents, biodegradable polymers and matrix polymers. *In vitro* investigations of drug release from the wafer into human serum, scanning electron microscope (SEM) studies and measurements of the adhesive properties on calf's teeth, indicate that this wafer composition is promising as an LDDS for the treatment of periodontitis.

Periodontal LDDS wafers were prepared from polylactic-co-glycolic acid (PLGA), ethyl cellulose and an active ingredient mixture (chosen from silver nitrate, benzylpenicillin and tetracycline) using a compression-molding technique. Subsequently, the sheets were cut into ~4 × 4 × 0.5 mm wafers. Previous periodontal LDDSs, composed entirely of biodegradable and water-soluble components, have a tendency to swell considerably in GCF, leading to possible reduced residence time in the periodontal pocket[2]. Ethyl cellulose was found to decrease the swelling of the wafer, and the maximum swelling decreased with an increased content of ethyl cellulose. LDDS wafers with a 9–12% ethyl cellulose content swelled to a maximum of ~250%, whereas wafers with a 15% cellulose content swelled to a maximum of ~200%, a range that is comparable to some commercially available periodontal LDDS wafers. Wafers with 0–3% ethyl cellulose swelled the most, with a maximum swelling of >600%. The amount of silver nitrate in the wafer (12–24%) had little effect on the swelling characteristics of the LDDS.

LDDS wafers composed of 67% PLGA, 9% ethyl cellulose and 24% of an antibacterial agent (chosen from silver nitrate, benzylpenicillin and tetracycline) were prepared and their drug-release characteristics studied (in water). All formulations exhibited zero-order release of antibacterial agent, in water, over 30 days. The LDDS wafer that contained 24% silver nitrate was further studied for its drug-release characteristics in human serum (readily available and similar to GCF): the release of silver nitrate was measured for total silver by inductively coupled plasma atomic emission spectroscopy (ICP), and for bactericidal silver by an *E. coli* bioassay[2]. Again, zero-order release was observed over ~30 days. The measurement of total silver by ICP showed a cumulative release of ~80% of the silver nitrate from the matrix over 30 days. The cumulative release of bactericidal silver, as measured by the bioassay, only reached ~20%. The overall lower cumulative release of bactericidal silver, compared with total silver, is thought to be caused by the binding and/or redox reactions with serum proteins.

Another goal was to design an LDDS that would not require manual removal after a 30-day treatment. As a test for disintegration, wafers were kept in serum for 28 days and their degradation characteristics followed by SEM. The initially smooth surface of the wafers degraded to an irregular surface after 14 days as the PLGA in the matrix degraded and eroded. After 28 days in human serum, the wafers consisted of particles of ethyl cellulose ~1–10 μm in size, small enough for the residual wafer particles

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to be flushed from the pocket by the flow of GCF.

Having developed a suitable bulk wafer composition, experiments were performed to improve the adhesion of the wafers to the tooth. Because the wafer is inserted between the tooth and the gum tissues, adhesion to the tooth could increase the residence time of the LDDS in the periodontal pocket. The strategy to engineer such a wafer involved immobilization of an adhesive formulation on the PLGA surface by adsorption. Wafers were coated with solid layers of starch, sodium carboxymethyl cellulose or polyacrylic acid (each blended with silver nitrate). The resulting wafers were tested for their adhesive characteristics using polished calf teeth pre-wetted with serum before measurement. The wafers were applied to the surface of the tooth with a pressure of 200 g for 10 seconds and the maximum detachment load (peel force) was measured. LDDS wafers coated with adhesive compositions possessed up to 35-fold higher maximum detachment force compared with identical uncoated wafers. Among the adhesive compositions tested, starch–silver nitrate-coated wafers exhibited maximum adhesion to the teeth. It is interesting to note that the other two polymers tested, polyacrylic acid and carboxymethyl cellulose, have been previously reported to be most adhesive toward mucosal membranes[3], because of polymer-mucin hydrogen bonding. By contrast, adhesion of polymers to tooth enamel depends on the interaction of polymer with collagen fibers on the surface of the tooth.

Studies of the adhesive-coated LDDS wafers by SEM, showed a 2–5 μm thick layer of starch–silver nitrate on both surfaces of the wafer. These SEM studies clearly showed the composite nature of the adhesive-coated wafers. The wafers were also studied for the release of silver, based on bioactivity assays. Using uncoated LDDS wafers as the control, more bioactive silver was detected with the adhesive-coated wafers caused by the release of silver nitrate from the outer layer, which caused an initial burst and could be regulated by varying the silver nitrate concentration. After this initial burst, a linear release of bioactive silver was observed over the course of 30 days, which compares to results obtained with the uncoated LDDS wafer.

These initial *in vitro* experiments show promise for the eventual development of an LDDS wafer that is capable of delivering a variety of antibacterial agents to the periodontal pocket. The LDDS wafer, composed of PLGA as a biodegradable component and ethyl cellulose as a binder, shows zero-order release kinetics of antibacterial agents *in vitro* over a four-week period. The swelling of the wafers is minimal and they can be made of a composite structure that includes an adhesive outer layer. These properties should maximize their retention in the periodontal pocket and could lead to an improved treatment for periodontal disease.

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John Weidner
Scientist, Parallel Synthesis
Medicinal Chemistry
Emisphere Technologies
765 Old Saw Mill River Rd
Tarrytown, NY 10591 USA
tel: +1 914 785 4792
fax: +1 914 593 8250
e-mail: Jweidner@emisphere.com