Asthma

In America, more than 80 billion aspirin tablets are consumed each year. Aspirin is a trade name for acetyl salicyclic acid and is effective as an analgesic, antipyretic, and anti-inflammatory drug.

History

Aspirin's predecessors, derivatives of salicylic acids, have been used to treat a variety of conditions for more than 2,500 years.
The Greek physician, Hippocrates (400BC), recommended the use of willow bark (a natural source of salicylates) to ease pain during childbirth. This use of salicylates was also advocated by Galen, a second century Roman physician, and mentioned in medical texts of the Middle Ages and Renaissance.
In 1757, Reverend Edward Stone conducted the first scientific study of natural sources of salicylates and wrote about the success of willow bark in the cure of fevers and aches.
Leroux showed in 1829, that salicin is the active agent in willow and was first extracted by Fontana and Brugnatelli. Salicin was concerted into Salicylic acid by the Italian chemist Piria in 1839. It was synthesised by a process discovered by Kolbe and Lautemann in 1860 which led to the introduction of Salicylic acid and sodium salicylate (forerunners of aspirin) for treatment of fever and arthiritis. However, these compounds were toxic to the stomach and caused diarrhoea and vomiting.
German chemist Felix Hoffmann was set the task by Arthur Eichengrun of Friedrich Bayer & Co in 1893, to find a less toxic alternative. Hoffmann returned with a related compound. Putting salicin through a series of chemical reactions, acetylsalicylic acid was created.
Acetylsalicylic acid passed chemical trials and was introduced to the market in 1899 with the trade name, Aspirin.

How does aspirin work?

Prostaglandins (PGs) are chemical messengers of the immune system responsible for pain and inflammation. For example, PGE2 acts on nerve endings, causing the sensation of pain.
In the 1970's John Vane speculated that aspirin might affect Prostaglandin synthesis (associated with tissue injury) thereby reducing pain and inflammation. Knowing that prostaglandins are made from arachidonic acid (produced by fatty acids of phospholipids in cell membranes) Vane incubated cell extracts from damaged tissues with arachidonic acid and different aspirin concentrations. Dependant on the dose, Vane found that aspirin did inhibit prostaglandin production.
Further experimentation established that aspirin inhibits the enzyme cyclooxygenase which converts arachidonic acid into the peroxy radical intermediate and then to compound 6, preventing PGE2 production.
It was proposed that aspirin ethanoylates the serine residue on the cyclooxygenase enzyme by attacking its hydroxl group. In the process, an ethanoyl group is transferred from aspirin to serine, and aspirin in converted to salicylic acid.

To confirm this theory the serine residue was replaced by alanine (which does not have an OH group). The cyclooxygenase activity of the modified enzyme was unaffected by aspirin.
When serine was replaced by asparagines, however, the modified enzyme did not show cyclooxygenase activity. This suggests that ethanoylation of the enzyme's active site prevents binding of arachidonic acid to its surface so that the enzyme cannot convert arachidonic acid into a prostaglandin.

Super Aspirins

In 1992, chemists discovered that cyclooxygenase (COX) had two forms COX1 and COX2. COX1 converts arachidonic acid to PGl2 which protects the stomach lining whereas COX2 converts arachidonic acid into PGE2 which causes pain. Aspirin inhibits both forms of cyclooxygenase, relieving pai n whilst enabling acidic digestive juice to irritate the stomach.
X-ray crystallography has allowed a greater understanding of the structure of cyclooxygenase and the ways aspirin works, leading to the development of COX2 inhibiting drugs such as Meloxicam. These 'super aspirins' selectively inhibit COX2 without blocking COX1, therefore reducing pain and inflammation with little damage to the gastrointestinal system.

Asthma

Asthma is a chronic lung disease making the airways sensitive, swollen and inflamed. In order to relieve an asthma attack bronchodilators are used, which interact with body cells relaxing smooth muscle tissue widening airways.
Glaxo launched the bronchodilator salbutamol, in 1969 after its development by chemists, biochemists and biologists.
The starting point for Salbutamol's discovery was adrenaline (our natural bronchodilator). After identifying the chemical compound in nature, chemists had to determine its chemical structure and modify it to produce a drug with only desirable effects.
As well as dilating airways, adrenaline also leads to brain stimulation, high heart rate and increased blood pressure. Chemists had to modify its structure through organic synthesis preventing these unwanted side effects. Organic synthesis involves the construction of required compounds from cheap, commercially available chemicals. In a multi-stage synthesis, the products of each stage are purified and examined using spectroscopic techniques such as n.m.r. spectroscopy. Higher percentage yields are obtained from synthetic routes involving few steps.
Adrenaline has many structural sites available for modification by either removing groups, changing sizes of groups, altering electronic properties or adding/removing hydrogen bonding groups such as -OH.
With knowledge of the biological mode of action of adrenaline, chemists suggested that changing the methyl group on the nitrogen could improve properties, leading to isoprenaline being prepared and tested. This maintained beneficial bronchodilator effects whilst preventing increased blood pressure. However, enzymes in the body, interacting with one of the phenol groups, metabolised the drug so its effects were not long lasting.
Adrenaline diol was produced aimed at solving this problem by having one phenol group. However, it was not an effective broncholdilator because the methyl ester group could not participate in hydrogen bonding.
Adrenaline triol was synthesised with an OH group replacing the methyl ester. However, this OH group was not bonded directly to the be nzene ring and so not metabolised by the body. Adrenaline triol was an effective, long lasting bronchodilator but still increased heart rate.

Chemists made one further change replacing the 2-propyl group on the nitrogen with a 2-methylpropyl group creating the compound, Salbutamol.
In the development of Salbutamol chemists produced and tested over 100 compounds through organic synthesis. This meant the modification process alone, took two years.
Salbutamol is effective for 4 hours but chemists at Glaxo later produced Salmeterol (a bronchodilator effective for 12 hours) through an even more drastic change to the group on the nitrogen in Salbutamol. Both Salbutamol and Salmeterol are effective asthma treatments.