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(54) Micelles containing a non-steroidal antiinflammatory compound.

(57) Non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam and sulindac are administered in micelles to alleviate their adverse effects on the gastrointestinal tract. The drugs are formulated with surfactants such as polyethoxylated nonionics to give micelle-forming compositions.

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Pharmaceutical Delivery Systems

This invention relates to pharmaceutical compositions for use in the treatment of inflammatory arthropathy.

Inflammatory arthropathy is the general name for a collection of debilitating and painful diseases which are extremely common in many countries of the world. Their classification is somewhat difficult, but inflammatory arthropathy or rheumatic disease seem to be the most common generic terms. In this specification, the term "inflammatory arthropathy" is used as the preferred generic term, but is to be understood to include forms of the disease known to some practitioners as rheumatic disease.

Of the various forms of inflammatory arthropathy, osteoarthrosis (or osteoarthritis) on the one hand and rheumatoid arthritis on the other hand are the commonest. Some workers in the field prefer the term osteoarthrosis to the term osteoarthritis, although it has been suggested that there is a place for both words. It is has been suggested that osteoarthrosis is the most sensible way of labelling the presence of simple degenerative joint disease but osteoarthritis separates the acute episodes of an inflammatory nature which occur in degenerative joint disease.

Osteoarthrosis usually has an insidious onset of pain, stiffness and a reduced range of movement. It commonly effects one or only a small number of joints. Intermittent swelling due to an effusion or an inflammatory episode in the affected joint may appear and, later in the disease, a permanent increase in size or change of shape may result from bony enlargement. Joint laxity develops with locking and grating.

It is often the joints which have been used the most or previously effected by trauma or inflammatory processes that suffer greatest damage. Thus, the weight-bearing joints of the hips and knees, the lumbar spine and the thumb bases (first capometacarpal joints) are common victims of the disease. The latter are particularly effected in those who have been manual workers or even keen knitters.

The essential features of rheumatoid arthritis are pain and swelling of several joints with morning stiffness continuing for at least a few weeks. Rheumatoid arthritis tends to affect the peripheral small joints symmetrically. Whereas the joints in osteoarthrosis may be described as dry, in rheumatoid arthritis they are "juicy", often swollen, hot, tender and red. There may also be accompanying systemic symptoms of a general malaise, weight loss, anorexia, mild fever and, on investigation, the finding of a normochromic (or hypochromic) normocytic anaemia.

Other common causes of inflammatory arthropathy include viral arthritis, ankylosing spondylitis, psoriatic arthropathy, Reiter's disease, gouty arthritis, septic arthritis (suppurative arthritis), erythema nodosum and Henoch-Schoenlein purpura. The most important in the present context are ankylosing spondylitis and gouty arthritis.

Ankylosing spondylitis is characterised by the gradual onset of low-back pain (sometimes bilateral buttock pain) with morning stiffness. Peripheral joints may become effected. There is a reduced range of spinal movement and chest expansion. Rigidity of the spine follows, often in a cranial direction (first lumbar, then dorsal then cervical) with a characteristic clinical picture of high dorsal kyphosis, obliteration of lumbar lordosis and flattening of the chest.

Gouty arthritis is due to the deposition of monosodium urate monohydrate crystals in the joint. Gouty arthritis is a very common disease: it is estimated that there are over 300,000 suffers in the United Kingdom alone. The popularly held belief that gout is largely due to an over indulgence of port and pheasant is mainly fallacious, although provocative factors may often be related to its onset. Examples include trauma, surgery, unusual physical exercise, severe illness, dietary excess, alcohol and drugs. Any joint may be affected, and the onset may be polyarticular. Affected joints are painful, red, hot, swollen and exquisitely tender.

The treatment of inflammatory arthropathy has naturally received a fairly large amount of attention from pharmacologists and pharmaceutical manufacturers. A first class of drugs that have been used in the treatment of inflammatory arthropathy are steroids. Cortisol and its synthetic analogues have the capacity to prevent or suppress the development of the local heat, redness, swelling and tenderness by which inflammation is recognised. At the microscopic level they inhibit not only the early phenomena of the inflammatory process (oedema, fibrin deposition, capillary dilation, migration of leukocytes into the inflamed areas and phagocytic activity) but also the later manifestations (capillary proliferation, fibroblast proliferation, deposition of collagen and, still later, cicatrization).

In clinical terms, the administration of such corticosteroids for their anti-inflammatory effects is palliative therapy. The underlying cause of the disease remains; the inflammatory manifestations are merely suppressed. Nevertheless, they are effective in affording symptomatic relief, but prolonged administration of corticosteroids may be a very high price to pay for such relief: the adrenal cortex may become atrophied,

thereby limiting the body's own ability to survive and adapt in a constantly changing environment. The adrenal cortex is the organ of homeostasis: in the absence of the adrenal cortex, survival is possible, but only under the most rigidly prescribed conditions. In more general terms, it has long been recognised that corticosteroids are powerful drugs with slow cumulative toxic effects on many tissues, which may not be apparent until made manifest by a catastrophe.

In the treatment of inflammatory arthropathy, the focus of attention shifted from steroids to a structurally unrelated group of compounds known as slow acting anti-rheumatic drugs (SAARDs). SAARDs have empirically been categorised into three groups. Group I, including drugs of proven value which are widely used, encompasses azathioprine, chloroquine, D-penicillamine and gold salts. Group II relating to clinically active drugs under continuing investigation, includes cyclophosphamide, dapsone, levamisole, methotrexate, sulphasalazine, thiols and thymopoietin. The group III SAARDs are those of less practical or unproven treatment; this group includes methylprednisolone pulsing.

The range of SAARDs is considerable, as has been seen above, and despite much experimental work their modes of action are largely unknown. Logistical and toxicity factors prevent the use of SAARDs in all patients.

A third category of drugs for use in the treatment of inflammatory arthropathy consists of the non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is the prototype NSAID, and for this reason this group of drugs is also known as the "aspirin-like" drugs. This secondary nomenclature gives a key to a functional similarity of NSAIDs in the absence of any overall chemical similarity: they all appear to owe their anti-inflammatory action, at least in part, to the inhibition of prostaglandin synthesis. According to Goodman and Gilman in "The Pharmacological Basis of Therapeutics" MacMillan 7th Edition 1985, it has been established in recent years that:

1. All mammalian cell types studied (with the exception of the erythrocyte) have microsomal enzymes for the synthesis of prostaglandins;

2. Prostaglandins are always released when cells are damaged and have been detected in increased concentrations in inflammatory exudates - all available evidence indicates that cells do not store prostaglandins, and their release thus depends on biosynthesis de novo;

3. All aspirin-like drugs inhibit the biosynthesis and release of prostaglandins in all cells tested; and

4. With the exception of the anti-inflammatory glycocorticoids, other classes of drugs generally do not affect the biosynthesis of prostaglandins.

NSAIDs (or aspirin-like drugs - the two terms are used interchangeably in this specification) can be categorised conveniently into six structural groups. First, there are the salicylic acids and esters including aspirin, benorylate, aloxiprin, salsalate and choline magnesium trisalicylate.

Secondly, there are the propionic acid derivatives, including ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, benoxaprofen and suprofen.

Thirdly, there is the class of oxicams, including piroxicam.

Fourthly, acetic acid derivatives can be split into two subclasses. Phenylacetic acids include diclofenac and fenclofenac; carbo-and heterocyclic acetic acids include indoles such as indomethacin and sulindac and pyrroles such as tolmetin.

Fifthly, there are the pyrazolones which include oxyphenbutazone, phenylbutazone, feprazone and azapropazone.

Sixthly, the fenamic acid derivatives include flufenamic acid and mefenamic acid.

NSAIDs have emerged as the drugs of choice in the treatment of inflammatory arthropathy. This is possibly more due to the disadvantages associated with other classes of drugs than in anything else. As indicated previously, the inflammatory diseases of the joints cause an extremely high level of discomfort and in many instances the results are crippling. The requirement for treatment is unquestioned and the treatment is in many cases chronic, that is to say it is continuous as the diseases are generally incurable. Unfortunately, the common element in the therapeutic properties of the NSAIDs is also the principle cause of side effects. As has been mentioned, the salicylates and other NSAIDs are thought to be effective in inflammatory joint disease, and their effectiveness is thought to be partly mediated through prostaglandin inhibition. Prostaglandins have been shown to have a protective effect on the gastrointestinal mucosa and, therefore, drugs which inhibit their activity are likely to cause gastrointestinal intolerance. Drugs with a potent inhibitory action on prostaglandin synthetase are marketed as having a potent anti-inflammatory action but have been shown to cause more faecal blood loss than those with weak anti-prostaglandin activity. Aspirin, for example, causes as much as an 8-to 10-fold increase in faecal blood loss and indomethacin a nearly 3-fold loss, compared with controls. However, when oral prostaglandin E2 (PGE2) at doses of 1mg three or four times daily is given with indomethacin or aspirin, the blood loss is reduced to control levels without reducing the effectiveness of the drugs.

Protection of the stomach from the drug has in some circumstances been shown to be effectively achieved by the use of enteric coating, as demonstrated by enteric coated aspirin preparations. However, the use of conventional enteric coating means that the drug is released in the neutral or slightly alkaline environment of the small or large intestine, which consequently experiences a considerably heightened local concentration from direct contact by the drug. Intestinal ulceration can occur with chronic administration of NSAIDs.

There is therefore a need for an improved and safer form of administration of NSAIDs to give protection both in the stomach and in the intestine. In addition, it would be advantageous to be able to provide a means of enhancing the absorption of the NSAIDs, which tend to be poorly water soluble, as well as providing an improved concentration of the drug at the cellular level at the site of its action. It is known that drugs with a low water solubility have a slow and variable dissolution pattern which can lead to reduced and erratic bioavailabilty. In short, what has been needed for some time is a delivery system for NSAIDs which protects the gastrointestinal tract from the drug, and which provides a means of alleviating the difficulties associated with very poor water solubility.

The present invention is based on the discovery that the use of micelles enables a particularly appropriate form of administration of NSAIDs to be achieved.

According to a first aspect of the present invention, there are provided micelles containing a non-steroidal anti-inflammatory drug.

Although NSAIDs themselves tend not to form micelles, amphipathic compounds, known more familiarly as surfactants, can form micelles. Surfactants have two distinct regions in their chemical structure, termed hydrophilic (water-liking) and hydrophobic (water-hating) regions. Micelles are aggregates in which the surfactant molecules are generally arranged in a spheroidal structure with the hydrophobic region at the core shielded, in a aqueous solution, from the water by a mantle of outer hydrophilic regions. According to a second aspect of the invention, therefore, there is provided a pharmaceutical composition comprising a non-steroidal anti-inflammatory drug and a surfactant, the composition being capable of forming micelles containing the non-steroidal anti-inflammatory drug when administered orally. It will generally be the case that the drug will be dissolved in the surfactant. In its simplest form, the pharmaceutical composition can be a solution of the drug in a surfactant, although other components may be present in the system if desired or necessary.

In a third aspect, the invention provides a process for the preparation of an anti-inflammatory composition capable of forming non-steroidal anti-inflammatory drug-containing micelles on oral administration to a human or non-human animal, the process comprising admixing a non-steroidal anti-inflammatory drug with a surfactant. The process may involve dissolving the drug in the surfactant.

According to a fourth aspect, the invention provides the use of a non-steroidal anti-inflammatory drug and a surfactant in the preparation of a composition for administering the drug in micellar form. Insofar as the law allows, the invention also relates to a method for the treatment or prophylaxis of inflammatory arthropathy, the method comprising the administration of micelles containing a non-steroidal anti-inflammatory drug.

Micelles are to be contrasted in terms of their structure with vesicles and with liposomes. Vesicles are aggregates of amphipathic molecules arranged in a bilayer. Typically, a vesicle will have a hydrophilic interior and a hydrophilic exterior: hydrophilic regions of an internal layer of the molecules will be directed inwardly, and hydrophilic regions of an outer layer of the molecule will be directed outwardly. Hydrophobic regions of the two layers will be directed towards one another within the molecular wall of the vesicle.

Liposomes are nothing more than multilamellar vesicles, as is revealed by the fact that liposomes disintegrate to vesicles upon ultrasonication.

Surfactants can be variously classified, and often by reference to the nature of the hydrophilic region, which can be anionic, cationic, zwitterionic or non-ionic. In the present invention, nonionic surfactants are preferred. A particularly preferred subcategory of nonionic surfactants are polyoxyethylated surfactants, including polyoxyethylated glycol monoethers, polyoxyethylated fatty acids, polyoxyethylated sorbitan fatty esters, and polyoxyethylated castor oils. However, other nonionic surfactants are also particularly appropriate, including sorbitan fatty acid esters, poloxamers, polyethylene glycol fatty acid esters and polyethoxylated glyceryl fatty acid esters.

Whatever the precise chemical structure of the surfactant or surfactants used, it is generally preferred to use one or more of those that have been already cleared for human ingestion. Therefore, surfactants with a low toxicity are preferred. For example, surfactants having an LD_{50} exceeding 10 g/kg and preferably 15 g/kg, are generally suitable. The absence of other side effects is of course also appropriate. Although surfactants which have already been approved for human ingestion are naturally preferred, the use of other

surfactants is not ruled out, not least because they may in time come to be approved for human ingestion.

The availability of nonionic surfactants is not perceived to be a cause of difficulty. For example, the following surfactants are known to be available.

Polyoxyethylene Alkylphenols POE(n) octylphenol n = 1-70
Triton X series (Rohm & Haas) Igepal CA series (GAF, USA) Antarox CA series (GAF, UK)
POE(n) nonylphenol n = 1.5-100
Triton N series (Rhom & Haas) Igepal CO series (GAF, USA) Antarox CO series (GAF, UK)

None of the polyoxyethylene alkylphenols are as yet approved for human ingestion.

Polyoxyethylated Glycol Monoethers POE(n) lauryl ether n = 4,23
Volpo L series (Croda)
Brij 30 series (Atlas ICI Specialties, UK)
POE(n) cetyl ether n = 2,10,20
Brij 50 series(Atlas ICI)
POE(n) stearyl ether n = 2,10,20
Brij 70 and 700 series (Atlas ICI)
POE(n) oleyl ether n = 2-20
Volpo N series (Croda)
Brij 90 series (Atlas ICI)
POE(n) ceto stearyl ether n = 3-20
Volpo CS series (Croda)

None of these have been approved for internal use, although Cetomacrogol 1000 (Brij 58, Volpo CS20) has been extensively used in topical applications.

Polyoxyethylated Glyceryl Fatty Acid Esters

POE(n) glyceryl monolaurate n = 15,40 Glycerox L series (Croda)
These products have not been cleared for internal ingestion.

Polyoxyethylated Fatty Acids POE(n) monolaurate n = 4-100
Crodet L series (Croda)
POE(n) monooleate n = 4-100
Crodet O series (Croda)
POE(n) monostearate n = 4-100
Crodet S series (Croda)
Myrj series (Atlas/ICI)

POE(8) monostearate and POE(40) monostearate appear to be approved for internal ingestion in the UK and EEC, and the latter is also approved by the FDA in the US. The other POE(n) monostearates appear valid contenders for approval, with the POE(n) monooleates and monolaurates also being likely candidates.

Sorbitan Fatty Acid Esters Sorbitan monolaurate
Crill 1 (Croda)
Span 20 (Atlas ICI)
Sorbitan monopalmitate
Crill 2 (Croda)
Span 40 (Atlas ICI)

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