CHAPTER 2
LITERATURE REVIEW

2.1 Aceclofenac sustained release dosage forms

Sustained release dosage forms are becoming increasingly important, either to achieve the desired level of therapeutic activity required for a new drug entity or to extend life cycle of an existing drug through improved performance or patient compliance. The long period of treatment with conventional drug delivery systems and adverse effects of some drug often lead to discontinuation of treatment by a substantial proportion of patients as soon as they begin to feel better. The polymers that are more widely used for design of sustained release of a drug include hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC). The major challenge in the development of new sustained release systems is to achieve optimal drug concentration at the site of action. To achieve optimal concentration at the site of action, release drug from the system must be sustained as accurately as possible. The drug candidate selected under the present study is aceclofenac, a synthetic NSAID, used in treatment of rheumatoid arthritis\(^7\), osteoarthritis\(^8\) and ankylosing spondylitis. It is almost rapidly and completely absorbed from the gastrointestinal tract after oral administration. It is reported to have plasma half life 4 h, time of peak plasma concentration occurs about 1.25 to 3 h after an oral dose. It is reported to have considerable first pass metabolism. Aceclofenac is usually administered as conventional tablet, containing 100 mg, two times daily. These bio pharmaceutical and physiochemical properties reveal that aceclofenac is an ideal candidate to develop the oral sustained drug delivery system.
So, we selected this drug to prepare a sustained release matrix tablets. The objective of this study is to develop a formulation, which releases the drug in a sustained manner over a period of 12 h.

Aceclofenac belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDS). It works by blocking the action of a substance in the body called cyclooxygenase. Cyclooxygenase is involved in the production of various chemicals in the body. Some of which are known as prostaglandins. Prostaglandins are produced in response to injury or certain diseases and would otherwise go on to cause pain, swelling and inflammation. Arthritic condition is one example of this.

Aceclofenac is used to relieve pain and inflammation in arthritic conditions. All the medicines in this group reduce inflammation caused by the body’s own immune system and are effective pain killers.

Aceclofenac is an orally administered phenylacetic acid derivative with effects on a variety of inflammatory mediators. Through its analgesic and anti-inflammatory properties, aceclofenac provides symptomatic relief in a variety of painful conditions. In patients with osteoarthritis of the knee the drug decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam and naproxen. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to ketoprofen, diclofenac, indomethacin and tenoxicam in these patients. The
duration of morning stiffness and pain intensity are reduced, and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis, with improvements being similar to those observed with indomethacin, naproxen or tenoxicam. Aceclofenac is also effective in other painful conditions (eg:- dental and gynaecological). In contrast to some other NSAIDS, aceclofenac has shown stimulatory effects on cartilage matrix synthesis. Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Although the incidence of GI adverse events with aceclofenac was similar to those of comparator NSAIDS in individual clinical trials, withdrawal rates due to these events were significantly lower with aceclofenac than with ketoprofen and tenoxicam. Superior overall and/or gastrointestinal tolerability of the drug relative to other NSAIDS has been indicated by a nonrandomized comparison with sustained release diclofenac in 10,142 patients, a meta-analysis of 13 comparisons with diclofenac, naproxen, piroxicam, indomethacin, tenoxicam or ketoprofen in 3574 patients, and preliminary details of a comparison with 10 other NSAIDS in 142,776 patients. Further analysis of the above meta-analytical data has indicated that costs incurred as a result of adverse events management are lower with aceclofenac than with a range of comparator NSAIDS.

Conclusions: Trials of 2 to 6 months duration have shown aceclofenac to be an effective agent in the management of pain and rheumatic disease. Data from in vitro studies indicate properties of particular interest with respect to cartilage matrix effects and selectivity for cyclooxygenase-2. Aceclofenac is well tolerated, with encouraging
reports of improved general and gastrointestinal tolerability relative to other NSAIDS from a meta-analysis of double blind trials from large nonblind studies.

**Preparation and evaluation of aceclofenac microemulsion for transdermal delivery system**

To develop novel transdermal formulation for aceclofenac, microemulsion was prepared for increasing its skin permeability. Selection of oil and surfactant ratio were based on solubility and phase studies. Microemulsion was spontaneously prepared by mixing ingredients and the physicochemical properties such was investigated. The mean diameters of microemulsions were approximately 90 nm and the system was physically stable at room temperature at least for 3 months. In addition, the in vitro and in vivo performance of microemulsion formulation was evaluated. Aceclofenac was released from microemulsion in acidic aqueous medium, and the dissolved amount of aceclofenac was approximately 30% after 240 min. Skin permeation of aceclofenac from microemulsion formulation was higher than that of cream. Following transdermal application of aceclofenac preparation of delayed onset muscle soreness, serum creatine phosphokinase and lactate dehydrogenase activity were significantly reduced by aceclofenac. Aceclofenac in microemulsion was more potent than cream in the alleviation of muscle pain. Therefore, the microemulsion formulation of aceclofenac appears to be a reasonable transdermal delivery system of the drug with enhanced skin permeability and efficacy for the treatment of muscle damage.
Hydrolytic activity is essential for aceclofenac to inhibit cyclooxygenase in rheumatoid synovial cells\textsuperscript{12}

To investigate the mechanism of action underlying the anti-inflammatory effects of the nonsteroidal anti-inflammatory drug aceclofenac in humans, Yamazaki et al. studied the metabolism of aceclofenac in detail in primary cultured synovial cells of 10 patients with rheumatoid arthritis. Aceclofenac and 4-hydroxy aceclofenac are the major compounds in human blood after the administration of aceclofenac, but they had no inhibitory effects on cyclooxygenase (COX) activity or COX expression in rheumatoid synovial cells. In contrast, aceclofenac and 4-hydroxy aceclofenac reduced prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) production by the rheumatoid synovial cells. We also observed that aceclofenac and 4- hydroxy aceclofenac were hydrolyzed into the COX inhibitors diclofenac and 4- hydroxy diclofenac respectively, by the rheumatoid synovial cells. However, the hydrolytic activity differed markedly among the cell preparations. Because the suppressive potency of aceclofenac and 4-hydroxy aceclofenac against the PGE\textsubscript{2} production was proportionally correlated with the hydrolytic activity in rheumatoid synovial cell preparations, we suggest that the suppressive effects of aceclofenac and 4- hydroxy aceclofenac on PGE\textsubscript{2} production are facilitated by the hydrolytic activity in rheumatoid synovial cells.

Aceclofenac, a new nonsteroidal anti-inflammatory drug, decreases the expression and function of some adhesion molecules on human neutrophils\textsuperscript{13}

To study the effect of aceclofenac, a new nonsteroidal anti-inflammatory drug (NSAID), on the expression and function of adhesion molecules in human neutrophils.
Methods: Gonzalez et al. used flow cytometry analysis to determine peripheral blood neutrophil expression of L-selectin, CD11a, CD11b, CD31, CD43, CD44 and intercellular adhesion molecule 2 (ICAM-3) surface adhesion molecules after treatment with aceclofenac, diclofenac or dexamethasone. Granular enzyme activity was quantitated in extracellular medium of neutrophils treated with different NSAIDs. In vitro adhesion assays were developed to examine the effects of aceclofenac on both neutrophil adhesion to tumour necrosis factor alpha stimulated human umbilical vein endothelial cells under nonstatic conditions, and homotypic neutrophil aggregation induced by anti-ICAM-3 and anti-CD18 monoclonal antibodies.

Results: Aceclofenac induced a dramatic decrease of L-selectin expression, whereas a moderate and slight decrement of CD43 and ICAM-3 expression was also observed. In contrast, the expression of other adhesion molecules by neutrophils was unaffected (CD11a, CD31, CD44) or slightly increased (CD11b). Cell adhesion assays, performed under nonstatic conditions, revealed that aceclofenac significantly diminished the L-selection dependent neutrophil adhesion to endothelial cells. Neutrophil aggregation was induced with anti-CD43. Monoclonal antibodies were also significantly inhibited by aceclofenac.

Conclusion: Aceclofenac had a faster and more potent effect than the other NSAID studies, mainly on the expression of cell adhesion molecules. This new NSAID efficiently interferes with neutrophil adhesion to endothelium and this effect may represent an additional relevant mechanism in its anti-inflammatory activity.
Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac

Aceclofenac (2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic acid; is a new orally effective non-steroidal anti-inflammatory agent of the phenylacetic acid group which showed remarkable anti-inflammatory, analgesic and antipyretic properties. Hence, aceclofenac possesses a potent inhibitory activity in several models of acute and chronic inflammation in rodents and resembles indomethacin and diclofenac in its pharmacodynamic profile, being superior to naproxen and phenylbutazone. In addition, aceclofenac was found to be highly active against sodium urate induced synovitis in dogs and adjuvant induced polyarthritis in rats, both prophylactically and therapeutically. The analgesic effect of aceclofenac on the pain elicited by chemical and mechanical stimuli was nearly equal to or slightly better than that of indomethacin and diclofenac. Fever induced by brewer’s yeast injection in rats was also markedly suppressed by aceclofenac. In contrast, the acute gastric ulcerogenic activity of aceclofenac was about 2,4 and 7-fold lesser than that of naproxen, diclofenac or indomethacin respectively. As a consequence of its high anti-inflammatory activity and lower potential for gastric damage aceclofenac exhibited the most favourable therapeutic ratio in comparison with indomethacin, diclofenac, naproxen and phenylbutazone. These data indicate that aceclofenac could be a potent anti-inflammatory and analgesic agent with a wide margin of safety in clinical practice.
**Anti-inflammatory mechanism of NSAIDS**

John R. Vane elucidated the mechanism of non-steroidal anti-inflammatory drug in 1971 and shared the nobel prize in physiology and medicine with Sune Bergstrom, Bengt Samuelson in 1982 (Versteeg et al. 1999). Although the mechanism was not known until the 1970s, the usage of NSAIDS dated back to the discovery of aspirin at the end of the last century (Diaz-Gonzalez and Sanchez Madrid 1998). Since then, the most common uses of NSAIDS are to reduce pain, inflammation and fever (Vander et al. 1998). Besides the common uses, other functions of NSAIDS are still being investigated; such as Alzheimer, breast cancer prevention effects (Versteeg et al. 1999; Sawdy et al. 1997). The broad functions of NSAIDS are due to the prostaglandin and thromboxanes pathways, which act on numerous biological and physiological processes, including inflammation (Versteeg et al. 1999; Dewitt and Smith 1995).

The synthesis of prostaglandin begins with the release of the precursor lipid, arachidonic acid, from the plasma membrane phospholipids by either phospholipase A or phospholipase C. The enzyme cyclooxygenase also known as PGH synthase, converts it to prostaglandin G and subsequently peroxidized to prostaglandin H by the same enzyme. Here COX activity serves as an important rate limiting and commitment step in the prostaglandin synthesis pathway. Prostaglandin H is then converted to various types of prostanoids in cells by specific synthases (Versteeg et al. 1999).

Since the increase of prostaglandins attributes to the inflammatory response, NSAIDS reduce inflammation and pain by inhibiting the cyclooxygenase activities. There are two isoforms of the cyclooxygenase, COX-1 and COX-2 which share 60% amino acid homology (Verteeg 1999). COX-1 is a constitutively active enzyme that
produces prostaglandins on the endoplasmic reticulum, which is then excreted and used for signaling purpose. COX-1 is expressed in various tissues at a constant level. In tissue where COX-1 serves specialized functions, the concentration is increased. Prostaglandins have specialized functions in the kidney, stomach and vascular epithelium for the regulation of renal H_2O and Na^+ reabsorption, gastroprotection by the affecting mucus and bicarbonate secretion and vascular homeostasis respectively. (Riendeau et al. 1997; Dewitt and Smith 1995)

The second isoform, COX-2 is normally absent in cells and is induced by growth factors, tumour promoters or cytokines. In some tissue such as the brain and macula densa of the kidney, COX-2 serves specialized functions and is expressed regardless of stimulation. It is expressed in high concentration at the site of inflammation and in monocytes and macrophages. Unlike COX-1, COX-2 synthesizes prostaglandin in the nuclear envelope, which suggests that COX-2 prostaglandin pathway participates in the regulation of gene transcription. (Dewitt and Smith 1995)

The 3-D structure of COX-1 and COX-2 obtained from X-ray crystallography revealed that the two enzymes consist of a narrow channel with a hairpin bend at the end. Arachidonic acid released from plasma membrane is pulled into the hydrophobic channel of the enzyme and twisted around the heparin. The insertion of two oxygens and removal of a free radical produce the characteristic five carbon ring of prostaglandins. (Hawkey 1999)

X-ray crystallography was also used to explore the specific action of NSAIDS. The data proposed that NSAIDS inhibit the COX-1 activity by blocking the channel midway. The drug hydrogen bonds to polar arginine at position 120. COX-2 also has an
arginine at position 120, but the difference between the two enzymes actually appears on position 523. Isoleucine occupies this position on COX-1 and valine on COX-2. Due to the smaller size of valine, it does not provide sufficient coverage of the side-pocket. Thus, specific COX-2 inhibitors, such as celecoxib and rofecoxib, take advantage of this gap to access their binding site in the side-pocket. Isoleucine, on the other hand, completely blocks access to the side-pocket. Point mutation performed on COX-1, changing the isoleucine to valine completely change the enzymes so that it is now inhibited by COX-2 selective inhibitors. (Hawkey 1999)

Because of the different binding mechanisms, both enzymes have different kinetics properties. COX-1 inhibitor is based on hydrogen bonding and so the process is instantaneous and reversible. COX-2 inhibition on the other hand has a more complicated binding mechanism which involves covalent binding and secondary conformational changes in the channel. (This mechanism is not yet clear at the moment). Thus COX-2 selective inhibitors have delayed response and the inhibition is irreversible. (Hawkey 1999)

X-ray crystallography revealed many interesting facts about the two isoforms. But in-order to fully understand the effects of NSAIDS, the functions of the cyclooxygenase must be examined and explored. The following summary of a transgenic mice experiment attempts to analyse the complex and intricate properties of COX-1 and COX-2.

Study using COX-1 gene knockout mice provides four key roles of COX-1. The COX-1 knockout mice had few phenotypic abnormalities. The only significant impairment was the inability for homozygote mice to produce offsprings when bred.
Offsprings produced by mating homozygote males and females with heterozygote males and females suggested that COX-1 expression is needed in parturition, and not ovulation or spermatogenesis. Secondly, on a molecular level, COX-1 mediates the aggregation of platelets. Mice without COX-1 were unresponsive to platelet aggregation even with the addition of precursor arachidonic acid. Since these cells do not have nuclei, COX-2 expression cannot be induced to counterbalance the lack of COX-1. The results validated COX-1 as the main player in thromboxane A₂ production and explained the medical uses of “baby” aspirin for the prevention of cardiovascular disease. Thirdly and surprisingly, the study showed the lack of stomach ulcers in COX-1 knockout mice. Since the inhibition of COX-1 by NSAIDS normally produces ulcers, knockout mice were expected to develop ulcers too because they do not have the enzyme. The mice only showed slight increased sensitivities to ulcers compared to a wild-type mice. One of the serious side effects of NSAIDS is the developments of ulcers with long term use. Thus this result might suggest other the involvement of other factors that affect gastrotoxicity. At the moment there is no explanation for this result. One hypothesis suggests that NSAIDS only inhibit the cyclooxygenase activities of COX-1 and COX-2 but not their peroxidase activities to development of ulcers. Lastly, results also showed that COX-1 partake in the early response phase (<2 hours) of inflammation, which involves the edema formation and recruitment of inflammatory cells. Inflammatory cells, including monocytes, will induce the expression of COX-2. Thus the maintenance of inflammation is thought to be the result of COX-2 only. (Langenbach et al 1995 Morham et al 1995)
The COX-2 knockout mice experiment was not very successful. The homozygote COX-2 deficient mice started to die at 8 months and only a few survived to 16 months. The mice were examined and showed no signs of severe physiological abnormalities except for dysfunctional kidneys. Nephropathy is the cause of death for all the mice. The kidneys are premature with undeveloped nephrons, small tubules and immature glomeruli. Even though both COXs are expressed in the kidney, they both have different unique roles. COX-1 expression in the kidneys produces prostaglandins, which serves to regulate vasopressin and ultimately ions and H$_2$O reabsorption. COX-2, on the other hand, might be required for the vascular perfusion or the production of growth factors during renal development. The other important information retrieved from the experiment concerns the inflammatory mechanism of COX-2. All of the mice that survived past 8 weeks had a condition called suppurative peritonitis, which is a full blown classical inflammation of the peritoneum and the surrounding organs. These findings indicated that COX-2 is not important in inflammatory reaction, conversely COX-2 might be an essential factor for the prevention of serious and life threatening infection that results from inflammation. COX-2 might also be a significant agent that will help repair damaged tissue after inflammation. From the findings of this experiment nothing is certain at the moment. (Langenbach et al 1995, Morham et al 1995)

Cyclooxygenase inhibition is believed to be the main mechanism for the action of NSAIDS, but Diaz-Gonzalez and Sanchez-Madrid proposed an alternative mechanism. In order to understand the new mechanism proposed some detail of inflammation on must be explained. Inflammatory response begins with the activation of the epithelium cells
(ECS) and the increased concentration of leukocytes in the area. Leukocytes then attach to the ECS in a multi-step process called adhesive cascade.

The first step of the cascade begins when cellular damage activates the ECS by changing their adhesive properties. Leukocytes attach to ECS by a family of proteins called selectins. Leukocytes constitutively express L-selectin while activated ECS express E-selectin and P-selectin. The second step involves leukocyte interaction with chemokines, which are locally produced by ECS. This causes the shedding of L-selectin and activation of integrin adhesion receptors on the leukocytes. In step 3, integrin association with vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) is the key event for firm adhesion of leukocytes to ECS. In the fourth step, leukocytes move towards the enflamed tissue by squeezing between ECS.

Diaz-Gonzalez and Sanchez-Madrid suggested that NSAIDS mediate the inflammatory response by inhibiting the attachment of leukocytes on ECS. In vitro study showed that several NSAIDS, i.e., indomethacin diclofenac, ketoprofen, aspirin, aceclofenac, mefenamic acid and flufenamic acid inhibited neutrophil EC attachment. This inhibition was due to the reduction of L-selectins on the leukocytes. NSAIDS caused rapid cleavage and shedding of L-selectins. In vitro study showed a decrease in L-selectin expression in volunteers 24 hours after a standard dose of indomethacin. But NSAIDS do not directly affect L-selectin expression, because specific inhibitors of metalloproteinase (cleaves L-selectin) can prevent the process. Another surprising finding is that other NSAIDS, i.e., piroxicam and meloxicam, do not reduce L-selectin expression or inhibit the neutrophil EC attachment. This suggests that different classes of NSAIDS affect
different steps of leukocytes immigration process and have different anti-inflammatory mechanisms.

With numerous ongoing researches like the ones described above, scientists are now able to understand better the underlining details needed to design new drugs that relieve specific conditions without unnecessary side-effects. The classical NSAIDS, e.g. aspirin, ibuprofen, naproxen and flosulide do not discriminate between the two isoforms. Thus, while NSAIDS reduce inflammation, pain and fever, they also cause troublesome side effects, the most severe is stomach ulcer. The race to find a new, so-called “safe aspirin” is very important to the pharmaceutical companies because NSAIDS are the most commonly prescribed drugs on the market and will be worth billions of dollars. In the past NSAIDS were known to have little to no selectivity between the two COXs. New medications are specific COX-2 inhibitors, for example celebrex, which appear to reduce some of the side effects of classical NSAIDS, mainly gastrotoxicity (Hawkey 1999).

Although the exact effects of cyclooxygenase inhibition are not known at the moment, clinical studies provided clues towards the mechanism the two isoforms. Studies compared the effects of COX-1 and COX-2 on gastrotoxicity suggest that COX-2 inhibitors are better relieving conditions such as inflammation and pain with the gastric erosion. Single dose of celecoxib 100 mg or 400 mg proved to be as effective as to aspirin and better than placebo after dental extraction. Celecoxib 100 mg and 200 mg were also better at providing relief with lower level of gastric erosion than naproxen 500 mg and placebo (Hawkey 1999)
The FDA (Food and Drugs Administration) approved celecoxib for rheumatoid arthritis and osteoarthritis, but not for analgesia, on December 31, 1998. The cost per pill is $2.42 for 200 mg. The drug has a 375 fold selectivity for COX-2. Although there are some inhibition of COX-1 also; major side-effects such as stomach ulcers only appear at higher doses. New drugs, such as rofecoxib, with high selectivity of the COX-2 will be approved within 1999 and marketed for prescription (Hawkey 1999)

**Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach**

In this study the significant effect of chitosan on improving the dissolution rate and bioavailability of aceclofenac has been demonstrated by simple solvent change method. Chitosan was precipitated on aceclofenac crystals using sodium citrate as the salting out agent. The pure drug and the prepared co- crystals with different concentrations of chitosan (0.05-0.6 %) were characterized in terms of solubility, drug content, particle size, thermal behaviour (differential scanning calorimetry, DSC), X-ray diffraction, morphology (scanning electron microscopy), in vitro drug release and stability studies. The in vivo performance was assessed by preclinical pharmacodynamic (analgesic and anti-inflammatory activity) and pharmacokinetic studies. The particle size of prepared co- crystals was drastically reduced during the formulation process. The DSC showed a decrease in the melting enthalpy indicating disorder in the crystalline content. The XRD also revealed a characteristic decrease in crystallinity. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with pure drug. The
considerable improvement in dissolution rate of aceclofenac from optimized crystal formulation was attributed to the wetting effect of chitosan, decreased drug crystallinity, altered surface morphology and micronization. The optimized co-crystals exhibited excellent stability on storage at accelerated conditions. The in vivo studies revealed that the optimized crystal formulation provided a rapid pharmacological response in mice and rats besides exhibiting improved pharmacokinetic parameters in rats. (Int J Pharm. 2008)

**Aceclofenac has greater COX-2 specificity when compared to diclofenac sodium.** (Hifenac, Intas Pharmaceuticals)

Recent studies have shown aceclofenac to have the highest COX-1 : COX-2 IC\textsubscript{50} ratio. Data given below is from proceedings of the European League Against Rheumatism (EULAR); 2001 Jun 13-16; Prague.

<table>
<thead>
<tr>
<th></th>
<th>Aceclofenac</th>
<th>Diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox-1 IC\textsubscript{50}</td>
<td>100 micro M</td>
<td>0.6 micro M</td>
</tr>
<tr>
<td>Cox-2 IC\textsubscript{50}</td>
<td>0.77 micro M</td>
<td>0.04 micro M</td>
</tr>
<tr>
<td>Ratio</td>
<td>129</td>
<td>2.77</td>
</tr>
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</table>

COX specificity ratio for aceclofenac and diclofenac from the above data suggest that aceclofenac has greater COX-2 specificity than diclofenac.
Bioequivalence study- Hifenac Vs Preservex

Bioequivalence of two aceclofenac tablet formulations after a single oral dose to healthy adult male Indian volunteers. (Aceclofenac of Intas Pharmaceuticals Vs the innovator aceclofenac brand of UCB).

A bioequivalence study of aceclofenac tablets from Intas Pharmaceuticals Ltd, India (Hifenac) with innovator brand available internationally (Preservex of UCB) was conducted in 12 healthy adult male Indian volunteers who received each medicine at a dose of 100 mg in a 2x2 crossover study. There was a two-week washout period between the doses. Plasma concentrations of aceclofenac were monitored by high performance liquid chromatography over a period of 24 hours after the administration. AUCinf (the area under the plasma concentration-time curve from time zero to time infinity) was calculated by the linear-log trapezoidal method. $C_{\text{max}}$ (maximum plasma drug concentration) and $T_{\text{max}}$ (time to reach $C_{\text{max}}$) were complied from the plasma concentration-time data. Analysis of variance was carried out using logarithmically transformed AUCinf and $C_{\text{max}}$, and non-transformed $T_{\text{max}}$. There were no significant differences between the medications in AUC and $C_{\text{max}}$. The point estimates and 90% confidence intervals for AUCinf (parametric) and $C_{\text{max}}$ (parametric) were 91.17%-105.88% and 85.10% - 109.09%, respectively, satisfying the bioequivalence criteria of the European Committee for proprietary medicinal products and the US Food and Drug Administration Guidelines. Moreover, the modified Pitman-Morgan’s adjusted F-test indicated that the bioavailabilities of aceclofenac in the two medications were
comparable regarding intra-and interindividual variability. Therefore, these results indicate that the two medications of aceclofenac can be used interchangeably.

Pharmacokinetic parameters of bioequivalence study

<table>
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<tr>
<th>Parameters</th>
<th>Preservex</th>
<th>Hifenac</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>14.14 ± 0.93</td>
<td>13.64 ± 0.98</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.42 ± 0.10</td>
<td>1.96 ± 0.25</td>
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<tr>
<td>$AUC_{(0-1)}$ (µg/mL *h )</td>
<td>35.24 ± 2.54</td>
<td>34.10 ± 1.71</td>
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<tr>
<td>$AUC_{(0-\infty)}$ (µg/mL *h )</td>
<td>35.94 ± 2.61</td>
<td>34.70 ± 1.74</td>
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</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ratio % Hifenac/Preservex</th>
<th>90% Confidence interval</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>96.35</td>
<td>85.10 – 109.09</td>
</tr>
<tr>
<td>$AUC_{(0-1)}$ (µg/mL *h )</td>
<td>98.43</td>
<td>91.32 – 106.09</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$ (µg/mL *h )</td>
<td>98.25</td>
<td>91.17 – 105.88</td>
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Large observational SAMM (Safety Assessment of Marketed Medicines) study in general practice to compare the incidence of adverse events of aceclofenac with diclofenac in patients with rheumatic disease.

Tolerability – aceclofenac Vs diclofenac.

This study was conducted to compare the incidence of adverse events of aceclofenac with diclofenac in patients with rheumatic disease. An open-label, non-blinded observational study was conducted comparing the safety of aceclofenac with diclofenac. The study was conducted under the SAMM guidelines issued by a working party, which included representation from the Medicines Control Agent (MCA), the committee on the safety of medicines, the British Medical Association, the Association of the British Pharmaceutical Industry and the Royal College of General Practitioners.
Highlights

A total of 10142 patients were enrolled for the study. The study was conducted for patients with rheumatic diseases like osteoarthritis, rheumatoid arthritis & ankylosing spondylitis. Patients were prescribed aceclofenac 100 mg bid or diclofenac (sustained release) 75 mg bid prior to study entry at the discretion of their GP.

Adverse events

Both study drugs were well tolerated with most adverse events being mild to moderate in nature. Fewer patients receiving aceclofenac (22.4%) reported adverse events compared with patients receiving diclofenac (27.1%; P<0.001). The most frequent adverse events recorded in both groups involved the digestive system (11.5%), the body as a whole (6.8%) and nervous system (2.7%). Furthermore, the incidence of adverse events affecting the gastrointestinal system was also significantly lower for aceclofenac than diclofenac with 10.6% of aceclofenac recipients reporting adverse events compared with 15.2% for diclofenac (P<0.001).

The number of adverse events occurring in > 1%, of patients is presented in the Table. The reported frequency of dyspepsia, nausea, abdominal pain and diarrhoea were significantly more common among the diclofenac treated patients. The incidence of these events was 1.3, 1.5, 1.8 and 2.5 fold higher, respectively for diclofenac compared with aceclofenac.
<table>
<thead>
<tr>
<th>Nature of adverse event</th>
<th>Aceclofenac (n=7890)</th>
<th>Diclofenac (n=2252)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>5.4</td>
<td>6.7</td>
<td>0.017</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.5</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.5</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
<td>2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1</td>
<td>0.7</td>
<td>0.073</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0</td>
<td>0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion

The large prospective community based study very clearly concluded that aceclofenac is significantly better tolerated than diclofenac.

**Aceclofenac drug profile**

Aceclofenac is [(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid.

- Molecular formula: C_{16}H_{13}Cl_{2}NO_{4}
- Molecular weight: 354.2
Appearance - White crystal powder

Purity - 99.0 – 101.0 %

Melting point - 149-153°C

Relative substance - 0.5 % max

Loss on drying - 0.5 % max

Heavy metal - 10 ppm max

Ash of sulphuric acid - 0.1 % max

**Mechanism of action**

Aceclofenac has been shown to exert effects on a variety of mediators of inflammation.

The drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1β and tumour necrosis factor, and inhibits prostaglandin E2 (PGE2) production.

In contrast to some other NSAIDs, aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1β activity. Aceclofenac and the metabolites also inhibit IL-6 production by human chondrocytes. This leads to inhibition of increase of inflammatory cells in synovial tissue, inhibition of IL-1 amplification, inhibition of increased MMP synthesis and thus increasing proteoglycan production.
Aceclofenac inhibits neutrophil adhesion and accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of neutrophils.

In addition, aceclofenac inhibits COX-2 more potently than COX-1 whereas diclofenac shows equal inhibition of COX-1 and COX-2. This indicates that aceclofenac is less likely to cause GI adverse effects than diclofenac.

**Therapeutic indication**

Symptomatic treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

**Posology and method of administration**

**Adults**

The maximum recommended dose, is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening.

**Children**

The safety efficacy in children and adolescents has not been established.

**Hepatic insufficiency**

The dose of aceclofenac should be reduced in patients with mild to moderate hepatic impairment. The recommended initial dose is 100 mg daily.
Renal insufficiency

There is no evidence that the dose of aceclofenac needs to be modified in patients with mild renal impairment, but caution is advised.

Contraindications

Aceclofenac is contraindicated in the following situation:

- Patients previously sensitive to aceclofenac or to any of the excipients of the product.

- Patients in whom substances with a similar action, (e.g. aspirin, or other NSAIDs), precipitate attacks of asthma, bronchospasm, acute rhinitis or urticaria or patients hypersensitive to these drugs.

- Patients with active or suspected peptic or duodenal ulcer or history of recurrent peptic or who have gastrointestinal bleeding or other active bleedings or bleeding disorders.

- Patients with severe heart failure or severely impaired hepatic or renal organ function.

- During the last three months of pregnancy.
**Special warnings and special precautions for use**

Aceclofenac should be administered with caution and under close medical surveillance to patients suffering from gastrointestinal disease and to those with the history of peptic ulceration, cerebro-vascular bleeding, ulcerative colitis, Crohn’s disease, porphyria, hematopoietic or coagulation disorders.

Caution should be exercised in patients with mild to moderate impairment of hepatic, renal or cardiac function as well as in patients with other conditions predisposing to fluid retention. In these patients, the use of NSAIDs may result in deterioration of renal function and fluid retention. Caution is also required in patients with diuretic treatment or otherwise at risk of hypovolemia.

Caution should be exercised in the treatment of elderly patients, who are generally more prone to adverse reactions. The consequences, e.g. gastro-intestinal bleeding and/or perforation, are often more serious and may occur without warning symptoms or previous history, at any time during treatment. Elderly patients are more likely to be suffering from impaired renal, cardiovascular or hepatic function.

All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts).
**Interaction with other medicinal products and other forms of interaction**

No pharmacokinetic interaction studies have been performed, except with warfarin. Aceclofenac is metabolized through cytochrome P450 2C9 and a risk of pharmacokinetic interaction is therefore possible with phenytoin, digoxin, cimetidine, tolbutamide, phenylbutazone, amiodarone, miconazole and sulphaphenazole. As with other products within the NSAID- group, there also exists a risk of pharmacokinetic interactions with other drugs eliminated by active renal secretion, such as methotrexate and lithium. Aceclofenac is bound practically completely to plasma albumin and consequently the possibility of displacement interactions with other highly protein bound drugs must be borne in mind.

Due to the lack of pharmacokinetic interaction studies the following is based upon knowledge from other NSAIDs:

**The following combinations should be avoided**

NSAIDs inhibit the tubular secretion of methotrexate and a slight metabolic interaction may also occur, resulting in decreased clearance of methotrexate. Therefore, during treatment with high dose methotrexate prescription of NSAID drugs should always be avoided.

Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of lithium. The combination should be avoided unless frequent monitoring of lithium levels can be performed.
NSAID drugs inhibit the platelet aggregation and damage the mucous membrane in the gastrointestinal tract which may enhance the activity of anticoagulants and increase the risk of gastrointestinal bleedings in patients using anticoagulant drugs. The combination of aeclofenac with oral anticoagulants of the coumarin group, ticlopidine, thrombolytics and heparin should be avoided unless careful monitoring is exercised.

**The following combinations may require dose adjustments and precautions**

The possible interaction between NSAIDs and methotrexate should be borne in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are administered within a 24-hour period, since the methotrexate levels may increase and result in increased toxicity.

Administration of NSAID drugs together with cyclosporine or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacycline in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

Concomitant therapy with aspirin and other non-steroidal anti-inflammatory drugs may increase the frequency of side effects and therefore caution is required.
Antiphlogistics of NSAID type may counteract the diuretic effect of furosemide and bumetanide, respectively, possibly due to inhibition of the synthesis of prostaglandin. They may also counteract the antihypertensive effect of thiazides. Concomitant treatment with potassium sparing diuretics may be associated with increased potassium levels. Hence, serum potassium should be monitored. The combination of NSAIDs and ACE inhibitors is associated with a risk of acute renal failure in dehydrated patients.

Aceclofenac was not found to affect blood pressure control when it was co-administered with bendrofluazide, although an interaction with other antihypertensive drugs, such as beta-blockers, cannot be ruled out.

**Other possible interactions**

There have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus for aceclofenac, consideration should be given to adjustment of the dosage of agents, that might produce hypoglycaemia.

**Use during pregnancy and lactation**

Several fetal effects, probably resulting from the inhibitory effects of antiphlogistics on prostaglandin synthesis, have been described.

Antiphlogistics may block uterine contractions and delay delivery. They may induce intrauterine constriction or closure of the ductus arteriosus leading to neonatal pulmonary hypertension and respiratory insufficiency. Antiphlogistics may
depress fetal platelet function and inhibit fetal renal function, resulting in oligohydramnios and neonatal anuria.

Treatment with antiphlogistics is contraindicated during the last three months of pregnancy.

It is not known whether aceclofenac is excreted in human milk. Therefore, aceclofenac should not be given during lactation unless considered essential by the physician.

**Effects on ability to drive and use machines**

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

**Undesirable effects**

The majority of side effects are gastrointestinal (dyspepsia, abdominal pain, nausea and diarrhoea). More frequent are dyspepsia (7, 5%) and abdominal pain (6, 2%).

**Common: (> 1/100)**

Gastrointestinal system disorders: Dyspepsia, abdominal pain, nausea, diarrhoea.

Liver and biliary: Increased hepatic enzymes.

**Uncommon: (1/100-1/1000)**

General: Dizziness.

Gastrointestinal system disorders: Flatulence, gastritis, constipation, vomiting, ulcerative stomatitis. Skin and appendages: pruritus, rash, dermatitis.

Metabolic and nutritional: Urea increased, serum creatinine increased.
Rare: (<1/1000)

General: Headache, fatigue, face oedema, allergic reactions, anaphylactic shock, weight increase.

Blood: Anaemia, granulocytopenia, thrombocytopenia, neutropenia.

Cardiovascular: Oedema, palpitation, cramps in legs, flushing, purpura.

Central and peripheral nervous system: Paraesthesia, tremor.

Gastrointestinal system disorders: Gastrointestinal bleeding and gastrointestinal ulceration, haemorrhagic diarrhoea, pancreatitis, melaena, stomatitis.

Urinary system disorders: Interstitial nephritis nephritic syndrome.

Skin and appendages: Eczema.

Metabolic and nutritional: Alkaline phosphatase increased, hyperkalaemia.

Psychiatric: Depression, abnormal dreaming, somnolence, insomnia.

Eye: Abnormal vision.

Others: Taste perversion, vasculitis.

As with other NSAIDs, severe mucocutaneous skin reactions may occur.

Overdose

There are no human data available on the consequences of aceclofenac overdosage.

The symptoms could be: Nausea, vomiting, stomach pain, dizziness, somnolence and headache.
Treatment: If required, gastric lavage, charcoal in repeated doses. Antacids when necessary and other symptomatic treatment.

**Pharmacological properties**

**Pharmacodynamic properties**

Therapeutic classification

Aceclofenac is a non-steroidal substance with anti-inflammatory and analgesic effects. Its mechanism of action is thought to be due to inhibition of prostaglandin synthesis.

**Pharmacokinetic properties**

**Absorption**

After oral administration, aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak plasma concentrations are reached approximately 1, 25 to 3 hours following ingestion. $T_{\text{max}}$ is delayed with concomitant food intake whereas the degree of absorption is not influenced.

**Distribution**

Aceclofenac is highly protein bound (>99, 7%). Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 60% of those in plasma. The volume of distribution is approximately 30L.

**Elimination**

The mean plasma elimination half-life is 4-4.3 hours. Clearance is estimated to 5 litres per hour. Approximately two-thirds of the administered dose is
excreted via the urine, mainly as conjugated hydroxymetabolites, only 1% of an oral single dose is excreted unchanged.

Aceclofenac is probably metabolized via CYP2C9 to the main metabolite. 4-OH- aceclofenac whose contribution to the clinical activity probably is negligible. Diclofenac and 4- OH- diclofenac have been detected amongst many metabolites.

**Characteristics in patients**

No change in the pharmacokinetics of aceclofenac has been detected in the elderly.

A slower rate of elimination of aceclofenac has been detected in patients with decreased liver function after a single dose of aceclofenac. In a multiple dose study using 100 mg once daily, there was no difference in the pharmacokinetic parameters between subjects with mild to moderate liver cirrhosis and normal subjects.

In patients with mild to moderate renal impairment no clinically significant differences in the pharmacokinetics were observed after a single dose.

**Preclinical safety date**

Similar to other NSAIDs, aceclofenac is poorly tolerated by experimental animals. Additionally, pharmacokinetic differences between animals and man make it difficult to evaluate the potential toxicity of aceclofenac. However, toxicity studies employing maximally tolerated dosages in the rat, a species which metabolizes
aceclofenac to diclofenac, and in the monkey (some exposure to unchanged aceclofenac) showed no toxic effects other than those commonly seen with NSAIDs.

Carcinogenicity studies in the mouse (systemic exposure to aceclofenac unknown) and in the rat (metabolism to diclofenac) did not show any carcinogenic effect and aceclofenac was negative in genotoxicity tests.

Special precautions for storage

Store below 25°C.

Nature and content of container

Blister package (aluminium/ aluminium) containing [10, 20] 30 [50, 60] 100 and [600(30x20)] tablets. Each strip contains 10 tablets.
2.2 Literature review on polymers and excipients

Hydroxypropyl methylcellulose

**Nonproprietary names**\(^{22,23}\)

BP: Hypromellose

JP: Hydroxypropyl methylcellulose

PhEur: hypromellosum

USP: Hypromellose

**Synonyms**

Benecel MHPC; cellulose, hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose;

HPMC; methocel; methylcellulose propylene glycol ether; methyl hydroxypropyl cellulose; metolose; pharmacoat; spectracel 6; spectracel 15; tylopur.

**Chemical name**

Cellulose, 2-hydroxypropyl methyl ether

**Empirical formula and Molecular weight**

Hypermellose is a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of apparent viscosity, in mPas, of a 2% w/w aqueous solution at 20°C. Hypermellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary
name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxyl group (OCH$_3$). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH$_2$CH(OH)CH$_3$), calculated on a dried basis. Molecular weight is approximately 10,000-150,000.

**Structural formula**

![Structural formula of hypromellose]

**Functional category**

Coatings agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

**Application in pharmaceutical formulation or technology**

Hypromellose is widely used in oral and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder, in film coating, and as an extended-release tablet matrix. Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes. High-viscosity grades may
be used to retard the release of drugs from matrix at levels of 10-80 % w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2-20 % w/w are used for film forming solutions to film coat tablets. Lower viscosity grades are used in aqueous film coating solutions, while higher viscosity grades are used with organic solvents.

Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations in the range 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used as an emulsifier in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**Description**

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.
Typical properties

Acidity/alkalinity: pH = 5.5-8.0 for a 1% w/w aqueous solution.

Ash: 1.5-3.0%, depending upon the grade.

Autoignition temperature: 360ºC

Density (bulk): 0.341 g/cm$^3$

Density (tapped): 0.557 g/cm$^3$

Density (true): 1.326 g/cm$^3$

Melting point: browns at 190-200ºC: chars at 225-230ºC. Glass transition temperature is 170-180ºC.

Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Ethyl cellulose

Nonproprietary names$^{23}$

BP: Ethyl cellulose

PhEur: Ethyl cellulosum

USPNF: Ethyl cellulose

Synonyms

Aqacoat ECD; aqualon; E462; ethocel; Surelease.

Chemical name

Cellulose ethyl ether
**Empirical formula**          **Molecular weight**

Ethyl cellulose with complete ethoxyl substitution is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where $n$ can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of $\beta$-anhydroglucose units joined together by acetal linkages.

**Structural formula**

![Structural formula of ethyl cellulose]

**Functional category**

Coating agent; flavouring fixative; tablet binder; tablet filler; viscosity-increasing agent.

**Applications in pharmaceutical formulation or technology**

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations.

The main use of ethyl cellulose in oral formulations is as a hydrophobic agent for tablets and granules. Ethyl cellulose coatings are use to modify the release of drug to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former.
Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can to be used on its own to produce water insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films. They may be modified to alter their solubility, by the addition of hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethyl cellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethyl cellulose films without the need for organic solvents. Drug release through ethyl cellulose coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g., pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

High-viscosity grades of ethyl cellulose are used in drug microencapsulation.

Release of drug from microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations, ethyl cellulose may additionally be employed as a binder, the ethyl cellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethyl cellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g., dental) applicants.
In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethyl cellulose is additionally used in cosmetics and food products.

**Description**

Ethyl cellulose is a tasteless, free-flowing, white to light tan-coloured powder.

**Typical properties**

Density (bulk): 0.4g/cm\(^3\)

Glass transition temperature: 129-133°C

Moisture content: ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility: Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%), ethyl acetate, methanol, and toluene.

Specific gravity: 1.12-1.15 g/cm\(^3\)

Viscosity: the viscosity of ethyl cellulose is measured typically at 25°C using 5% w/v ethyl cellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). Grade of ethyl cellulose with various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging 7-100 cP range.
**Stability and storage**

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230-340 nm range.

Ethyl cellulose should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

**Incompatibilities**

Incompatible with paraffin wax and microcrystalline wax.

**Lactose**

**Nonproprietary names**

BP: Lactose
JP: Lactose
PhEur: Lactosum monohydricum
USPNF: Lactose monohydrate
Synonyms
Lactochem; Lactohale; Lactopress; Microfine; Microtose; Milk sugar; Pharmatose; Prisma Lac; Respitone; Saccharum lactis.

Chemical name
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate

Empirical formula  Molecular weight
C₁₂H₂₂O₁₁  342.30 (anhydrous)
C₁₂H₂₂O₁₁.H₂O  360.31 (monohydrate)

Structural formula

Functional category
Diluent for dry-powder inhalers; tablet and capsule diluent.
Applications in pharmaceutical formulation or technology

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant feed formulas. Lactose is also used as a diluent in dry-powder inhalations.

Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application. For example, the particle size range selected for capsules is often dependent upon the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use as a carrier/diluent for inhalation products and in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

The method for obtaining lactose from milk was patented in 1937. The process for making spray-dried lactose for use as direct-compression excipient was patented in 1958. Since that time, lactose has been used as the standard comparison for all modern direct-compression excipients. Today, many other lactose grades are commercially available, including anhydrous α-lactose, α-lactose monohydrate, and, to a lesser extent, anhydrous -lactose.
Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactoses that contain specially prepared pure α-lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of lactose. Other specially produced direct-compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas that impart improved compressibility. Direct-compression grades of lactose may also be combined with microcrystalline cellulose or starch, and usually require a tablet lubricant such as 0.5% w/w magnesium stearate. The use of direct-compression grades of lactose results in tablets of higher breaking strength than does use of standard lactose. Concentrations of lactose generally used in these formulations are from 65% to 85%. Lower amounts of spray-dried lactose can be used if additional direct-compression material such as pregelatinized starch is substituted.

Description

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while α-lactose is sweeter than the β-form.

Several different forms of lactose are commercially available: anhydrous α-lactose, β-lactose monohydrate, and to a lesser extent, anhydrous β-lactose, which typically contains 70% anhydrous lactose and 30% anhydrous α-lactose, although grades
containing a greater proportion of anhydrous β-lactose are also available, e.g., Pharmatose DCL 21 (DMV Pharma). α–Lactose may also contain a small quantity of the β-form.

**Microcrystalline cellulose**

**Nonproprietary names**

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcrystallinum
USPNF: Microcrystalline cellulose

**Synonyms**

Avicel PH; Celex; Cellulose gel; Celphere; Ceolus KG; Crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

**Chemical name**

Cellulose

**Empirical formula**

\[(C_6H_{10}O_5)n\]

**Molecular weight**

36000

where \(n = 220\)
Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrating properties that makes it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products.

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades with different properties and applications.
Uses of microcrystalline cellulose.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>Adsorbent</td>
<td>20-90</td>
</tr>
<tr>
<td>Antiadherent</td>
<td>5-20</td>
</tr>
<tr>
<td>Capsule binder/diluent</td>
<td>20-90</td>
</tr>
<tr>
<td>Tablet disintegrant</td>
<td>5-15</td>
</tr>
<tr>
<td>Tablet binder/diluent</td>
<td>20-90</td>
</tr>
</tbody>
</table>

**Typical properties**

Density (true): 1.512-1.668 g/cm³

Melting point: 260-270º C.

Moisture content: typically less than 5% w/w.

**Polyvinyl pyrrolidone**

**Nonproprietary names**

BP : Povidone

JP : Povidone

PhEur : Povidonum

USP : Povidone

**Synonyms**

Chemical name

1 – Ethenyl – 2 – pyrrolidinone homopolymer

Functional category

Disintegrant
Dissolution aid
Suspending agent
Tablet binder

Application in pharmaceutical formulation or technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid – dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid – dosage forms. Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing or viscosity – increasing agent in a number of topical and oral suspension and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.
Special grades of pyrogen – free povidone are available and have been used in parenteral formulations.

Description

Povidone occurs as a fine, white to creamy – white coloured, odourless or almost odourless, hygroscopic powder. Povidone with K – values equal to or lower than 30 are manufactured by spray – drying and present as spheres. Povidone K – 90 and higher K – values povidone are manufactured by drum drying and present as plates.

Solubility

Freely soluble in acids, chloroform, ethanol, ketones, methanol and water; practically insoluble in ether, hydrocarbons and mineral oil.

Stability and storage conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110 - 130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation without undergoing decomposition or degradation.
However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

**Incompatibilities**

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin and other compounds.

**Propylparaben sodium**

**Synonyms**

Propylparaben sodium (USAN); Sodium propylparaben; Soluble propyl hydroxybenzoate. Sodium salt of propyl 4-hydroxybenzoate.

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁₀H₁₁NaO₃</td>
<td>202.2</td>
</tr>
</tbody>
</table>

**Structural formula**

![Propylparaben Sodium Structural Formula](attachment:image.png)
Description

A white, odourless or almost odourless, hygroscopic, crystalline powder.

Solubility

One in one of water, one in fifty of alcohol, and one in two of alcohol (50%); practically insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 - 10.5

Adverse effects and precautions

Hypersensitivity reactions occur with the hydroxyl benzoates. Generally these are of the delayed type, appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely. The activity of the hydroxybenzoates can be diminished by a number of mechanisms.

The activity of hydroxybenzoates can be adversely affected by the presence of other excipients or active ingredients. There may be adsorption onto substances like magnesium trisilicate, aluminium magnesium silicate, talc, polysorbate 80, or plastics. Nonionic surfactants can reduce hydroxybenzoate activity, as may essential oils. Other incompatibilities that have been reported include atropine, iron, sorbitol, weak alkalis, and strong acids. Syrup preserved with hydroxybenzoates is incompatible with a range of compounds. Increasing heat or pH can reduce stability and activity; freeze-drying may also lead to loss of activity.

Hypersensitivity

Immediate hypersensitivity reactions have been reported following the injection of preparations containing hydroxybenzoates. Delayed contact dermatitis occurs
more frequently, usually after topical application but also occurs after oral administration of an ester or of p-hydroxybenzoic acid. The North American Contact Dermatitis Group 6 provided an incidence of 3% while another review of a large number of patients gave an incidence of 2.2%. However, subjects with healthy skin exposed to hydroxybenzoates, for example in cosmetics, are considered to have a much lower incidence of reactions. Unusually, patients who have reacted to a hydroxybenzoate with a contact dermatitis appear to be able to apply that preservative to another unaffected site and yet not suffer a reaction; this has been termed the paraben paradox.

Hypersensitivity reactions have occurred in patients given local anaesthetics containing hydroxybenzoates and cross-sensitivity between the two groups of drugs has been proposed.

**Pregnancy and the neonate**

An in vitro study on serum from neonates with hyperbilirubinaemia indicated that methyl hydroxybenzoate at a concentration of 200 µg per mL of serum increased the concentration of free conjugated bilirubin and interfered with the binding of bilirubin to serum proteins. Methyl hydroxybenzoate was present in an injection of gentamicin sulphate at a concentration of 1.3 to 1.8 mg per mL. Neither gentamicin nor propyl hydroxybenzoate had a significant effect on bilirubin. Measurement of urinary excretion of methyl hydroxybenzoate in 6 pre-term infants given multiple intramuscular doses of a gentamicin formulation preserved with hydroxybenzoates, produced variable results. Whether there was accumulation of the preservative in some infants and whether the albumin binding capacity for bilirubin was affected remained to be determined.
Use and administration

The hydroxybenzoate preservatives (parabens) are alkyl esters of p-hydroxybenzoic acid with antibacterial and antifungal properties. They are active over a broad pH range (4 to 8), though are generally more active in acidic solutions. Activity increases with increasing alkyl chain length but aqueous solubility decreases, although this may be overcome by employing the more soluble sodium salt as long as the pH of the preparation is not increased. Activity may also be increased by combining two hydroxybenzoate with short alkyl chains. Another way of increasing activity is to use hydroxybenzoate with propylene glycol.

They are used as preservative in oral or topical pharmaceutical preparations in concentrations of up to 0.25%. Methyl hydroxybenzoate and propyl hydroxybenzoate are used together in some injectable preparations. There are reports of the hydroxybenzoate not being satisfactory as preservatives for ophthalmic preparations because of their relative lack of efficacy against some gram-negative bacteria, particularly pseudomonas aeruginosa.

The hydroxybenzoate preservatives are widely used in cosmetics and are also used in food preservation.

Isopropyl alcohol

Nonproprietary names

BP : Isopropyl alcohol
JP : Isopropanol
PhEur : Alcohol isopropylicus
USP : Isopropyl alcohol
Synonyms

Dimethyl carbinol; IPA, isopropanol, petrohol, 2 – propanol.

Chemical name

Propan – 2 – ol

Empirical formula

C₃H₈O

Molecular weight

60.1

Structural formula

Functional category

Disinfectant, solvent

Application in pharmaceutical formulation ( or ) technology

Isopropyl alcohol ( propan – 2 – ol ) is used in cosmetics & pharmaceutical formulations primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity.

Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl
alcohol is also used as a solvent both for tablet film – coating & for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation.

Isopropyl alcohol has some antimicrobial activity and a 70 % v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of post operative nausea (or) vomiting.

**Description**

Isopropyl alcohol is a clear, colourless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol & acetone, it has a slightly bitter taste.

**Solubility**

Miscible with benzene, chloroform, ethanol, ether, glycerin & water. Soluble in acetone, insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.37° C).

**Stability and storage conditions**

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

**Incompatibilities**

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which are salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate and other salts, or by the addition of sodium hydroxide.
Method of manufacture

Isopropyl alcohol may be prepared from propylene; by the catalytic reduction of acetone, or by fermentation of certain carbohydrates.

Talc

Nonproprietary names

BP : Purified talc
JP : Talc
Ph Eur : Talcum
USP : Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate, hydrous magnesium silicate; luzenac; luzenac pharma; magnesium hydrogen metasilicate; magsil star; powdered talc; purified French chalk; purtalc; soapstone.

Chemical name

Talc

Empirical formula

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg₆[SiO₅]₄[OH]₄. It may contain small, variable amounts of aluminum silicate and iron.
Description

Talc is a very fine, white to grayish – white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Solubility

Practically insoluble in dilute acid and alkalis, organic solvents and water.

Functional category

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Application in pharmaceutical formulation or technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled – release products.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
Magnesium stearate

Nonproprietary names

BP: Magnesium stearate
JP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical name

Octadecanoic acid magnesium salt

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>Molecular weight</th>
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<tbody>
<tr>
<td>C_{36}H_{70}MgO_{4}</td>
<td>591.34</td>
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The USPNF 20 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C_{32}H_{62}MgO_{4}). The PhEur 2002 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.
**Structural formula**

\[ \text{CH}_3(\text{CH}_2)_{16}\text{COO}]_2\text{Mg} \]

**Functional category**

Tablet and capsule lubricant.

**Applications in pharmaceutical formulation or technology**

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

**Description**

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

**Typical properties**

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate and an anhydrate.

- Density (bulk): 0.159 g/cm³
- Density (tapped): 0.286 g/cm³
- Flash point: 250°C
- Flowability: Poorly flowing, cohesive powder.
- Melting range:
117-150°C (commercial samples)

126-130°C (high purity magnesium stearate)

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%)

Specific surface area: 1.6-14.8 m²/g

**Stability and storage conditions**

Magnesium stearate is stable and should be stored in well-closed container in a cool, dry place.

**Incompatibilities**

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamin, and most alkaloidal salts.