

Comparison of different ibuprofen dosage forms



Both ibuprofen gel and ibuprofen tablet produced similar efficacy in terms of pain relief in their respective groups. However, lower dose was administered in gel dosage form and fewer side effects were observed, in comparison to ibuprofen tablet.

Patients consuming ibuprofen oral suspension reached the therapeutic effect at a quicker rate and were in that period for a longer duration compared to the other dosage forms. This suggested that it caused faster pain relief for a longer duration compared to ibuprofen tablets and ibuprofen chewable tablets.

Introduction

Ibuprofen (Figure 1) is chemically known as iso-butyl-propanoic-phenolic acid. It is a well known drug that belongs to a class of therapeutic agents known as non-steroidal anti inflammatory drug (NSAID). It possesses antipyretic (fever reducing) and anti-inflammatory (reduces inflammation) properties among others (i. e. anti-platelet effect). It is used in the treatment of pain and inflammation in rheumatic disease and other musculoskeletal disorders including minor aches and discomfort 7&8. A recent report showed ibuprofen had analgesic (pain-relieving) properties. This was shown by testing analgesic properties of ibuprofen on a mouse writhing and an inflamed rat foot. It showed there was similarity of analgesic activity in both species. However, ibuprofen failed to show analgesic activity in the normal foot of the rat or in the mouse hotplate test. Therefore it was established that ibuprofen is not a central, but a peripheral analgesic 13.

Ibuprofen has fewer side effects than any other NSAID; however its anti-inflammatory properties are weaker than others. Doses of 1.6-2.4g are required daily for rheumatoid arthritis. It is unsuitable for conditions where inflammation is prominent such as acute group 8.

Ibuprofen was discovered by Dr. Stewart Adams and his team (Figure 2) 3 in the 1950's, at Boots Company. The drug was patented in the 1960's and was initially marketed under the name Brufen. Initially the drug was tested on hangover, but the drug was launched for the treatment of rheumatoid arthritis in UK (1969) and USA (1974) 3.

The mechanism of action of ibuprofen is not completely understood. However, ibuprofen is known to be a non-selective inhibitor of cyclooxygenase-1 and 2 (COX-1 and COX-2). COX is an enzyme that is involved in the production prostaglandins 8. Prostaglandins have an important role in the production of pain, inflammation and fever 13.

Following administration of ibuprofen, it is rapidly absorbed and distributed throughout the whole body. The drug is eliminated through the kidneys 14.

Ibuprofen is a derivative of phenylpropionic acid (Figure 3) 4. It contains a chiral centre (Carbon), therefore is non-superposable on its mirror image 2. This gives rise to enantiomers, resulting in two possible structures of ibuprofen. The importance of enantiomers is that all amino acids (apart from glycine) have a chiral centre. Amino acids are the fundamental blocks of enzymes and proteins in all forms of life including humans.

Thus suggesting the human body is controlled by chiral molecules and effectively is a chiral environment. This results in different enantiomers having different effect on the body, including metabolism, toxicity to name a few 1. These enantiomers exist as (S) and (R)-enantiomers (Figure 4) 4. It was found that (S)-ibuprofen was the active form in, in vitro and in vivo 2.

Ibuprofen began to be marketed as a single enantiomer ((S)-isomer) so the selectivity and potency of ibuprofen could be improved.

However, further in vivo testing led to the inactive (R)-ibuprofen to rapidly convert to active (S)-ibuprofen. Therefore the single enantiomer was scrapped and ibuprofen was to be marketed as a racemic mixture (50% of each enantiomers) 2, even now it is the same. Another reason was the likeliness of producing pure (S)-ibuprofen was too expensive on a large scale.

The difference between both the enantiomers is the way the atoms are arranged and connected to the chiral centre. In the (S)-isomer the CH₃ group is in the back, whereas in the (R)-isomer it is at the front.

Since being launched it is widely available all over the world as over the counter (OTC), prescription only medicine (POM) and general sale list (GSL) products.

In all countries over the world they are available under different names, formulations, strengths etc. In North America (Canada), ibuprofen is known as Motrin and Advil. In South America (Brazil) it is known as Alivium and Advil 5. Different countries have different guidelines and policies regarding selling and prescribing of ibuprofen. People are not just restricted to pharmacies but they can be obtained in supermarkets, general retailers etc. In many parts of <https://assignbuster.com/comparison-of-different-ibuprofen-dosage-forms/>

the world including Australia and New Zealand, ibuprofen lysine is licensed for the same treatment as ibuprofen. Ibuprofen lysine is the salt form of ibuprofen and is the cationic form. As ibuprofen lysine has a net positive charge, it is more soluble than ibuprofen allowing the drug to be administered intravenously. This makes ibuprofen lysine to have a greater onset time of action than ibuprofen 15.

Since 1977, World Health Organisation (WHO) has been producing a model list of essential medicines. This list is updated every 2 years and is known as 'List of WHO Essential Medicines'. Ibuprofen is the only NSAID present in the list among other classes (opoids, antimetabolites etc) 6. It is classed as a 'core medicine', which means it is an essential drug for basic healthcare. The drugs listed are the most effective, safe and cost effective medicines for conditions that are a priority. This priority conditions are on the basis of present and future public health relevance. The drugs present on the list are recognised throughout the world. Ibuprofen tablets (200mg and 400mg) are present for the treatment of gout and rheumatoid arthritis. Also present is ibuprofen solution, which is used as an injection (5mg/ml). It is used in neonatal care for the treatment of mild to moderate pain 6&8.

Discussion

The most important role of a drug delivery system is to get the drug 'delivered' to the site of action in sufficient amount and at the appropriate rate. This can be achieved by a predictable therapeutic response of the drug 11. However it must meet essential requirements, which include physical & chemical stability, ability to be economically mass produced in a manner

that assures the proper amount of active pharmaceutical ingredient (API) is present in each dosage and patient acceptability 9.

It can be seen from Table 1 11, different dosage forms have different time of onset of action.

Table 1: Shows the variation in time of onset of action for different dosage forms. It can be seen that intravenous injection is the most superior dosage form in terms of time of onset of action, as it takes seconds to produce an effect. Depot injections and implants take days to produce an effect.

Tablets are one of the most popular ways of delivering a drug through the oral route. Tablets are solid preparations each containing a single and accurate dose of active pharmaceutical ingredient(s) (API). They are completed by compressing or compacting uniform volume of particles to a solid dose 10.

There are different types of tablets available; they include effervescent/soluble, modified release etc. The aim of the modified release tablet is it enables the biopharmaceutical behaviour of the drug to be controlled. Many tablets are available that have coatings; these include film or sugar coating. All these tablets exist and are formed by the incorporation of different types of excipients 11. They vary in shape, colour, size, design etc 10.

Tablets are popular for several reasons including the oral route to be the most safest and convenient route of administration. Compared to other dosage forms such as liquid, they are far superior in terms of chemical and

physical stability. The procedure enables accurate and precise dosing of the API 11. These are a few among a large list. Drawbacks include elderly having difficulty swallowing, irritation and harm to the GIT, possibly leading to liver and kidney damage.

Examples of ibuprofen tablets include Anadin, Ibuprofen tablets etc.

Effervescent formulation is a type of immediate release tablet, as the tablet is dissolved and administered as a solution. This is the most common type of tablet 11. They are used to obtain rapid drug action.

Effervescent tablets are placed into a glass of water, where carbon dioxide is liberated. The carbon dioxide is produced by a reaction in the water between a carbonate or bicarbonate and a weak acid. Once liberated, this helps tablet disintegration and drug dissolution. Then the water with the drug is administered. Effervescent formulations of ibuprofen commonly use a carbonate to assist in the liberation of carbon dioxide, such as Anadin LiquiFast 200mg Effervescent Tablets 16. Effervescent formulations can be prepared in two ways: direct compaction or compaction through granulation 11. They are produced in the same manner as conventional tablets; however production must occur in low humidity areas 17.

Examples of ibuprofen effervescent tablets include Advil, Ibuprofen losan effervescent tablet etc.

Gel is a semi-solid, topical formulation. It is formed by aggregation of particles and interpenetrated by a liquid. The particles are linked together forming a network thus imparting rigidity to the structure. The continuous

phase is held together by meshes 11. Gels tend to be epicutaneous, it is directly applied to the skin, and works by diffusing through the skin. There is a liquid phase that may be retained within a three dimensional polymer matrix. Drugs can be suspended in the matrix or dissolved in the liquid phase. They tend to be aqueous gels that is applied to the body surfaces such as skin or used as lubricant. A few advantages of gels include it avoids drug absorption in the gastrointestinal, therefore reducing side effects. It avoids first pass metabolism suggesting more drug is present in the systematic circulation. They are cheap to manufacture and have a localised effect, hence greater pain relief 12.

Examples of ibuprofen gels include Ibuleve, Ibugel etc.

A suspension is a coarse dispersion of sparingly soluble or insoluble drugs dispersed in a liquid medium; oily or aqueous vehicle. The aqueous solution is a beneficial formulation as it provides administration of poorly soluble or insoluble drug. As the drug is dispersed, it provides a large surface area which ensures high bioavailability for dissolution thus absorption 11.

Aqueous suspensions can be used for oral, topical, ophthalmic and parenteral administration of drugs.

The rheological properties are affected by the degree of flocculation. This is because the quantity of free continuous phase is decreased as it is entrapped in the diffused follicles 11.

From Figure 5 9, the process involved in the formation of suspensions can be seen. The flocculated state (C) can be reached directly or indirectly. The direct method includes wetting and dispersing of hydrophobic particles (A) <https://assignbuster.com/comparison-of-different-ibuprofen-dosage-forms/>

with a surfactant. The indirect approach includes first wetting and dispersing to form a peptized particle (B) with a surfactant, and then flocculating with a hydrophilic colloid. Flocculated suspensions (C) are considered stable, compared to peptized particles, and they can be re-suspended through agitation. Over-flocculation can be caused through high amount of flocculating agent, which tends to cause agglomeration (E). If the protective colloid agent is not present, the process of crystal growth is indicated by the arrow connecting (A) to (D) 9.

Examples of ibuprofen suspensions include Nurofen, Calprofen etc.

Chewable tablets, as the name suggests is placed in the mouth and chewed. Thus the tablet is mechanically disintegrated in the mouth. However, the drug is dissolved in the stomach or intestine once swallowed and not in the mouth. This formulation is intended so the drug is immediately released, just like effervescent tablets 11. They also have similar composition to conventional tablets, apart from disintegrant is not present.

This formulation can be useful as many patients (e. g. elderly) have difficulties swallowing tablets, therefore this can be an alternative dosage form. It can also be administered without the aid of water. It also complies with patient compliance.

Examples of ibuprofen chewable tablets include Motrin, Advil etc.

Comparison of conventional tablet and effervescent formulation

In a report comparing the antinociceptive effect of both conventional and effervescent tablets, it was discovered that the mean plasma concentration

of ibuprofen effervescent formulation was far greater than the conventional tablet 60 minutes after intake. This showed that more API (ibuprofen) is present in the blood, thus more drug is being absorbed by the body in the effervescent formulation than in the conventional tablet. This showed that the effervescent formulation produced a faster pain relief as it had a faster onset of action. The effervescent dosage form also appears to have a more consistent effect on intensity estimates of painful stimuli than tablets 18.

The 'chemo-somatosensory event related potentials' were also investigated and it was concluded that after 60 minutes of administration of the ibuprofen tablet, there was a decrease of 20-25% in bioavailability. As there was a large drop (a quarter of the bioavailability), it shows there is 20-25% less ibuprofen present in the blood thus less API is being absorbed. This means a higher dose of ibuprofen tablet (20-25%) is required to have the same effect as initially thought 18. The effervescent formulation is far more effective in terms of chemo-somatosensory. This is because greater amount of carbonate is present; therefore after dissolution a buffered solution is attained. This increases the pH of the stomach resulting in the emptying of the stomach at a rapid rate and the residence time of ibuprofen in the stomach is short. This ensures that ibuprofen-induced gastric irritation and other side effects can be avoided 11.

Ibuprofen effervescent tablet is readily absorbed in the small intestine; ensuring fast drug bioavailability 11.

In another report, Lange and Schettler showed that effervescent formulations of ibuprofen produced a higher maximum plasma concentration

(Cmax) than the conventional tablet in a shorter duration. The same as the previous report 19.

In respect to antinociceptive and chemo-somatosensory activity, the effervescent formulation is superior to the conventional tablet.

To consume the ibuprofen tablet you require water to administer it. While with the ibuprofen effervescent formulation it requires water so the tablet can disintegrate.

Effervescent formulations also have to be manufactured at a low humidity area compared to the conventional tablets. This is to avoid moisture content, light and oxygen and this procedure is more costly than the conventional tablet. Effervescent tablets also have to be packaged in waterproof containers which have aluminium foil present which ensures protection, otherwise in ambient conditions it would degrade and reduce the shelf-life 11. If the shelf-life is reduced this would increase the cost, as more effervescent tablets would have to be manufactured over the same duration. An example of an effervescent tablet is Anadin LiquiFast 200mg Effervescent Tablets (Figure 6) 20 and a conventional tablet is Nurofen Tablets (Figure 7) 21.

Figure 6: Shows Anadin Effervescent Tablets Figure 7: Shows Nurofen Tablets

Comparison of conventional tablet and a topical gel

There was a report comparing the oral (tablet) and topical (gel) ibuprofen for chronic knee pain. Ibuprofen tablets were taken 3 times daily (2400mg total)

and the ibuprofen gel 4% was applied 4 times daily (320mg total) over a duration of 2 weeks 22.

The aim was to compare the efficacy of both formulations in chronic knee pain.

Both the treatment groups were comparable in terms of baseline pain severity and demographic composition, this ensured a fair test.

When the patients took their respective ibuprofen medications, they reported side effects. With the administration of the tablets, 7 patients (out of 10) reported side effects which included headache, stomach-ache and constipation. For the application of the gel, 2 patients (out of 9) suffered a side effect which included an acute skin rash and dizziness. This implies that over two-thirds of the patients taking the oral formulation reported a side effect, and for the topical formulation less than third reported a side effect. As a result there were fewer side effects associated with the topical formulation compared to the oral formulation 22.

In both treatments, the patients experienced consistent relief and improvements in terms of pain and stiffness. There was no distinguishable difference between both groups in term of improvements. Both the treatment groups were similar and no group was better than the other. However, the oral group ranked their treatment more convenient as it met patient adherence.

Comparing the physical function and relief of pain and stiffness, it shows the oral ibuprofen treatment saw notable improvements. In the topical ibuprofen

treatment there were significant improvements over the two week duration. However for the oral treatment there was a decline in the improvement of the drug in the second week. Also in the topical treatment, the patients encountered within-group improvements which led to the assumption that it was due to the potential benefits of massaging.

The topical ibuprofen was applied to the skin therefore there was less amount of drug was present in the blood compared to ibuprofen tablets. This avoided both the systemic side effects and adverse drug interactions (e. g. aspirin), unlike the oral ibuprofen 22.

The total daily dose of the topical ibuprofen was 320mg, which is a small fraction compared to the oral ibuprofen (2400mg). However, similar clinical outcomes were produced using both treatments.

Another report concluded a study where the patients were receiving equivalent doses of oral and topical formulations. During the topical application greater concentrations of ibuprofen were found in the subcutaneous tissue, which led to the assumption as more ibuprofen is present in the tissue; it is able to provide greater pain relief 23.

In terms of physical function, pain and stiffness relief, the topical formulation is superior to the oral formulation.

An advantage of topical ibuprofen over ibuprofen tablets is first pass metabolism is bypassed therefore it avoids risks and unwanted effects.

Topical ibuprofen is a transdermal delivery system, which is more efficient than the oral delivery due to having an effect at a localised level.

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Comparison of conventional tablet, chewable tablet and suspension

There was a report comparing the pharmacokinetic parameters of ibuprofen tablets, ibuprofen chewable tablets (Motrin chewable tablets) and ibuprofen suspension (Motrin suspension) on patients with cystic fibrosis. This study is limited as the number of patients taking each formulation is different; suspension (n= 22), chewable tablets (n= 4) and tablet (n= 12). , nor is the strength or concentration given for any of the formulations. However patients took a dose of approximately 20mg/kg.

The time to reach the peak concentration (T_{max}) was compared for all formulations and it was concluded that the ibuprofen suspension had a shorter T_{max} than the ibuprofen tablet, which was expected when liquid forms are compared with solid dosage forms. But with the ibuprofen chewable tablet there was no statistical difference from either the tablet or suspension. This was not expected as it was predicted the chewable tablet would have a greater T_{max} to suspension but less than that of tablets. This is because chewing the chewable tablet produces small particles hence larger surface area, which should increase the dissolution of the drug 24. As the T_{max} for suspension was shorter than the tablet it can be concluded more drug was present in the body at a quicker rate, hence more drug would be absorbed thus causing faster pain relief.

From Figure 8 24 and Table 2 24, it can be concluded that 15 of the patients taking the suspension formulation were present in the desired range of peak concentration (therapeutic range), and this was achieved at a quicker rate of ~0.5 hours compared to the other formulations. For the chewable tablet it can be seen that 2 of the patients consuming it were in the therapeutic

range, however it took patients to reach this level between ~1.0-2.0 hours. For the patients who consumed the tablet, 8 patients were in the therapeutic range. However it took between ~0.75-2.0 hours to reach to this level.

There was also one anomaly present

In the suspension group 5 patients, and 2 patients from the tablet groups exceeded the therapeutic range ($> 100\text{mg L}^{-1}$), therefore they are more prone to experience side effects. None of the patients who consumed chewable tablets exceeded the therapeutic range.

For all formulations, 2 patients were below the therapeutic range ($< 50\text{mg L}^{-1}$). Therefore the drug would have no effect 24.

It can be concluded statistically tablets were superior in terms of achieving the desired range of peak concentration compared to other formulations. But statistically suspensions were superior in terms of the time taken to reach the therapeutic range compared to both formulations.

Figure 8: Shows the relationship between C_{max} versus T_{max} for suspension, chewable tablet and tablet groups. The plotted points represent blood sampling times when peak ibuprofen concentrations occurred. The horizontal dashed lines show the therapeutic range.

Table 2: Shows the comparison of C_{max} among suspension, chewable tablets and tablet groups.

From Figure 9 24, it can be seen patients taking the suspension reached max plasma concentration and at a quicker duration compared to other formulations. It took 0.5 hours to reach a plasma concentration of 70mg L^{-1} , <https://assignbuster.com/comparison-of-different-ibuprofen-dosage-forms/>

while tablets took 1.0 hour to reach a plasma concentration of 60 mg L⁻¹. The chewable tablet took 1 hour to reach 50mg L⁻¹ (C_{min}). Also for the suspension, between 0.5-1.0 hours it remained in the therapeutic range. For the tablet, the period between 0.75-1.0 hours it remained in the therapeutic range. It took the chewable tablets 1 hour before it reached the therapeutic range, before and after this period it had little effect.

As the time reaches 6 hours, the suspension had the lowest plasma concentration, while the tablet had the highest concentration. However it was below the therapeutic range therefore at this point all formulations have no effect 24.

It can be concluded ibuprofen suspension is the superior formulation in terms of pain relieving as it reached the highest plasma concentration at a quicker duration, and was in the therapeutic range for the longest period. It is closer to C_{max} at 70 mg L⁻¹, while the other formulations were below this. Due to these factors it can be seen that the suspension has greater amount of ibuprofen present in the blood, hence more drug is going to be absorbed in the body.

Figure 9: Shows the plasma concentration-time curve (mean' SEM) for children with cystic fibrosis who received a dose of 20mg/kg ibuprofen suspension (n= 22), chewable tablets (n= 4) or tablets (n= 12). The SEM bars are not included for chewable tablet group.

Conclusion

Ibuprofen is a derivative of phenylpropionic acid, and is chemically known as iso-butyl-propanoic-phenolic acid. It is a non-steroidal anti inflammatory drug

(NSAID), possessing properties such as analgesic, antipyretic and anti-inflammatory. It is commonly used in the treatment of pain and rheumatoid arthritis among others. It is the only drug from its therapeutic class present on the 'List of World Health Organisation Essential Medicines'. This 'list' represents the minimum medicine required for a basic healthcare system. It includes drugs that are efficacious, safe and cost effective for conditions that are a priority. These conditions are selected on the foundation of current and future public health relevance.

In terms of pain relief, antinociceptive and chemo-somatosensory effect, ibuprofen effervescent tablets are far superior to ibuprofen tablets. They caused faster pain relief at a quicker rate.

Both ibuprofen gel and ibuprofen tablet produced similar efficacy in terms of pain relief in their respective groups. However, the dose administered in the gel dosage form was four times less than that of the ibuprofen tablet. Fewer side effects were observed as it avoided gastric irritation, in comparison to ibuprofen tablet. Ibuprofen tablet caused gastric irritation, which can possibly lead to liver and kidney damage.

Patients consuming ibuprofen suspension reached the therapeutic effect at a quicker rate and were in that period for a longer duration compared to the other dosage forms. This suggested that it caused faster pain relief for a longer duration compared to ibuprofen tablets and ibuprofen chewable tablets. Ibuprofen chewable tablets reached a maximum concentration of 50mgL^{-1} , so it just reached the base of the therapeutic effect, which suggests it has poor efficacy.