Introduction: suffering from fever or mild to

Introduction: Acetaminoph

en (N-acetyl-p-aminophenol, APAP, alsoknown as paracetamol, PARA. The European pharmacopoeia statesthat the specification limit of 4-Ap in paracetamol is 50 ppm 4-AP/PARA.

(DejaegherB, 2017). The molecular formula of paracetamol is C8H9NO2 andits molecular weight is ? 151. 165 g/mol. (Pubchem. ncbi. nlm. nih.

gov, 2017) It is commonly used as it contains anaesthetic andsoothing properties. It can be bought over the counter for both adults andchildren. The synthesis of acetaminophen occurs through a reaction of theprodrug phenacetin. The prodrug phenacetin was removed from many stores as aresult of the carcinogens it produced. A dose of 4 grams per day is recommendedfor adults and 50 to 75 milligrams per day for children suffering from fever ormild to moderate pain.

If more than 7 grams of the drug is taken by an adultand more than 150 milligrams is taken by a child, it can become toxic to theliver and kidneys because of the metabolite N-acetyl-p-benzoquinone imine whichis a highly active metabolite. (PharmGKB, 2018)Metabolism: The major organs involved in the metabolism ofacetaminophen are the liver, the kidney and the intestine to a lesser extent. When consumed APAP is converted to an inactive glucuronide (APAP-gluc, 52 to 57% of the urinary metabolites and sulphate APAP 30 to 44 %.

A small percentageis then oxidized to NAPQI which is about 5 to 10% and less than 5% of APAPremains unaffected and is therefore removed. NAPQI is very sensitive and istherefore mainly responsible for acetaminophen induced

hepatotoxicity. Theabrupt withdrawal of NAPQI occurs when it binds to the sulfhydryl groupglutathione (GSH) which produces APAP-GSH, this is passed in the urine ascysteine ad mercapturic acid conjugates. The majority of the glucuronide andsulphate metabolites which come from the liver are transported into the kidneysvia the bloodstream, but some APAP-gluc which remains in the bile can betransferred into the intestine. The kidney is the fundamental location of thedisposition of APAP sulphate. Acetaminophentoxicity: When APAP is consumed at a high dose, glucuronidation becomessaturated and large volumes of the drug is excreted unchanged and oxidised toNAPQI. Remaining NAPQI minimizes GSH stores and begins to form protein adducts. NAPQI targets mitochondrial proteins as well as ion channels and this resultsin the loss of energy production and cell death.

N-acetyl cysteine (NAC) is avery useful remedy for acetaminophen overdose in humans. If (NAC) is given topatients 8 to 10 hours after an acute overdose, it reduces the risk of hepatotoxicityto as less than 5% which prevents liver damage, renal failure and death. (PharmGKB, 2018) The misuse of paracetamols has led to 1/5 peopleoverdosing, and has resulted in acute liver failure in over 7 Europeancountries.

This was outlined by the British Journal of clinical pharmacology. This has led to the rise in liver transplants. Various attempts have been madein order to reduce the overdose such as “ changing the amount per preparation orper box, restricting dispensing, and packaging such as blister packaging hasbeen shown to reduce the number of intentional overdoses and referrals forliver transplantation”. (Medscape, 2017)Drug– drug interactions: Many drugs have

been reportedly combined with acetaminophenleading to its toxicity. Numerous case reports have revealed that epilepticpatients that are on long term therapy displayed a heightened acetaminopheninduced hepatotoxicity. When a large amount of alcohol is combined with amoderated dosage of acetaminophen it can often lead to liver damage and evendeath. (PharmGKB, 2018)The university of Oxford, centre for suicide researchconducted an investigation on the legislation which was passed in September1998. It was put in place to limit the number of suicides and non-fatalself-poisoning.

The legislation reduced the number of tablets per packet ofparacetamols sold. Before the legislation, 100 tablets could be purchased frompharmacies and 24 tablets could be purchased in supermarkets. No limit was putin place on the number of packs that could be purchased at one time. Thisresulted in an increased number of deaths and liver transplants due to overdose. After the legislation only 32 tablets could be purchased from a pharmacy and 16from a supermarket.

Three to four years after the legislation was passedsuicide deaths from paracetamol fell by 22% and liver transplants forparacetamol induced liver damage were reduced to 30%. (Cebmh. warne. ox. ac. uk, 2018)” F. D. A.

is taking this action to make prescriptioncombination pain medications containing acetaminophen safer for patients touse,” as said by Dr. Sandra Kweder, deputy director of the agency’s new drugoffice. The food and drug administration banned pills such asPercocet and Vicodin. Manufactures who mixed narcotics with acetaminophen weregiven three years to change the

formula of the drugs or they would be forced tostop producing more products. The new limit stated that pills should notcontain no more than 325 milligrams of acetaminophen. The F. D. A also requiresthat warning labels about the danger of overdosing with acetaminophen should beincluded in all packaging.

(Harris, 2018) Degradation can be divided into three groups theseinclude: Physical degradation: This involves the physical change of a drug such as its appearance, propertiesand size. Factors that would affect physical degradation would bedisintegration time, dissolution profile, hardness and colour changes. Theseproblems could affect the drug release. Physical changes can arise due toabrasion, temperature changes such as thawing, shearing and freezing, impactand vibrations. (Japsonline.

com, 2018) Chemical degradation: chemical degradation involves the change in the chemical and the separation ofits compounds into smaller much simpler compounds. The types of chemicaldegradation include hydrolysis and oxidation. Oxidation: oxidation occurs through the removal of electrons from a molecule or throughthe addition of oxygen; a reaction is produced by light, heat and trace metals. In order to reduce Oxidative degradation it is important to apply the correctstorage such as storing drugs in dark environments where light and oxygen isabsent.

The addition of antioxidants in the formula can also reduce oxidationdegradation. Hydrolysis: hydrolysis occurs when a molecule reacts with water and this leads to thecleavage of a chemical bond in the molecule. Esters and amides are the mostcommon functional groups found in drugs

prone to hydrolysis. Oxygen attractselectrons towards itself more than carbon, this results in the double bond ofthe ester becoming polarised and therefore resulting in a slightly positivelycharged carbon.

Because of polarisation, electrons present on the waters oxygenatom, move towards the positively charged carbon atom. Opposite charges, attract each other leading to hydrolysis. In terms of preventing hydrolysis, itis often harder to overcome hydrolysis in vivo metabolism. By modifying thestructure of the active compound chemically, this leads to the reduction ofhydrolysis in the early stages of drug development. In terms of unstable drugs, alterations of the dosage may be done in numerous ways. Liquid dosage formsrely on water being present. Drugs that are more sensitive to hydrolysis atroom temperature should be stored in a cool dry place. Pharmacists shouldprovide correct labelling on packaging and should have a good knowledge of drugstability in order to produce safe products for consumers.

(Pharmaceutical-journal. com, 2018) Microbial degradation: Microbial degradation can arise due to incorrect storage conditions and if thecontainers are made of cheap materials. Microbial changes such as growth ofmicroorganisms in non-sterile products and changes in preservation can have amajor effect on the stability of a pharmaceutical product.

Packaging materialssuch as plastic or glass are of often used as they protect the drugs againstexposure to moisture / heat, as the humidity can weaken the effect of the drug.(Japsonline. com, 2018) FTIR(Fourier Transform Infrared Spectroscopy)FTIR Identifies chemical compounds in product,

coatingand pharmaceuticals as well as other products. In terms of inorganic andorganic samples, FTIR provides quantitative as well as qualitative analysis fororganic and inorganic samples. It can be used with other spectroscopytechniques. The function of FTIR is to observe a molecules molecular structurewhen used with other techniques such as UV/VIS spectroscopy. (Intertek. com, 2017)Radiation is absorbed by the sample and some of itpasses through when IR radiation is passed through the sample being analysed.

The result signal at the detector is spectrum representing a molecule of thesample. Infrared spectroscopy is very efficient as many molecules/chemicalstructures produce various spectral fingerprints. The detector output isconverted to an interpretable spectrum by the Fourier transform. Spectra andpatterns are created by the FTIR and they provide structural insights.

The FTIR uses interferometry, which recordsinformation about a substance or a compound that is placed in the IR beam. TheFourier converts results in spectra that analysts can use to distinguish /assess the material. Each technique has its own strengths and weaknesses, whichpredetermines their use for specific samples.

Either FTIR can be a simple toolused for one specific function or it can be a highly flexible instrument usedfor research. The spectrometer presents a range of information suchas; identification of an unidentified molecule, quantitative information andkinetic information as well as complex information when used alongside otherdevices such as GC and TGA. Infrared

is an effective tool for the identificationof functional groups as they have identical absorption frequencies for groupsin different molecules. The environment affects frequency therefore thereference chart demonstrates wide bands instead of specific frequencies.

Thereare four important sampling techniques in FTIR are Transmission, AttenuatedTotal Reflection (ATR), Specular Reflection and Diffuse Reflectance. (Thermofisher. com, 2018). Stabilitytesting: It is vital to carry out stability studies in order toensure that the product is of good quality and most importantly, it is safe.

Studies regularly carried out by following guidelines published by ICH alongwith other agencies. Stability testing of pharmaceutical products is oftenexpensive and time consuming but it ensures quality, efficacy and safety indrug production. In order to guarantee commercial and scientific success of aproduct, understanding of the processes that go into the development of thedrug is very important.

Development stages include stability studies, pharmaceutical analysis in order to ensure that the ingredients are pure andpotent and can be easily identifiable. Stability is the length of time in whicha drug can remain within the limits specified. Stability testing examines theway in which environmental factors affect the quality of the drug and itpredicts the shelf life and determines suitable conditions and labellinginstructions. Data gathered from a stability test is vital for regulatoryapproval. Because of the various factors involved that influencethe stability of a drug product, stability testing can often be a complicatedprocess.

These factors include the container and closure system, themanufacturing process followed, interaction that occurs between the activeingredients used, light, heat and moisture conditions that is met duringshipment, handling and storage, degradation such as hydrolysis and oxidationcan alter the stability that can have a negative effect on the stability of thepharmaceutical product. The materials used during manufacturing and theduration of time between the usages of the product and manufacturing. Importanceof stability testing: Stability testing is important as it is concerned onthe well-being of the patient suffering from the disease for which the productsis designed. Because of this concern, it is a requirement to have collecteddata for various types of stability test for regulatory agencies before a newproduct is approved. The reputation of the manufacturer is maintained byensuring the product functions as described. Stabilitytesting methods: In the early stages of drug development, stabilitytesting at high or humid temperatures is used to identify the type ofdegradation products that can be found after long-term storage. Productsrecommended for long-term shelf storage are tested under less harsh conditions.

A products shelf life and expiration date is determined by raising thetemperature slightly. (Japsonline. com, 2018) References: PharmGKB. (2018). PharmGKB. online Available at: https://www.

pharmgkb. org/pathway/PA165986279Accessed 10 Jan. 2018.

Medscape. (2017). Acetaminophen-Linked Liver FailureVaries Widely in Europe. online Available at: https://www. medscape. com/viewarticle/845501 Accessed 13 Oct.

2017. Cebmh. warne. ox.

ac. uk. (2018). Paracetamol – Universityof Oxford Centre for Suicide Research.

online Available at: http://cebmh. warne. ox.

ac. uk/csr/resparacet. html Accessed 10 Jan. 2018. Harris, G. (2018).

F. D. A. Plans New Limits onPrescription Painkillers. online Nytimes. com. Available at: http://www. nytimes.

com/2011/01/14/health/policy/14fda. html Accessed 10 Jan. 2018. Thermofisher. com.

(2018). FTIR Basics | Thermo FisherScientific. online Available at: https://www. thermofisher.

com/us/en/home/industrial/spectroscopy-elemental-isotope-analysis/spectroscopy-elemental-isotope-analysis-learning-center/molecular-spectroscopy-information/ftir-information/ftir-basics. htmlAccessed 10 Jan. 2018. Pharmaceutical-journal. com.

(2018). online Availableat: https://www. pharmaceutical-journal. com/download? ac= 1065775 Accessed 10Jan. 2018. Japsonline. com.

(2018). online Available at: http://japsonline.

com/admin/php/uploads/409_pdf.

pdf Accessed 11 Jan. 2018. Pubchem. ncbi. nlm. nih. gov. (2017).

acetaminophen. online Available at: https://pubchem. ncbi. nlm. nih.

gov/compound/acetaminophen#section= Spectral-PropertiesAccessed 13 Oct.

2017. Dejaegher B, e. (2017). Validation of a fluorimetricassay for 4-aminophenol in paracetamol formulations. – PubMed – NCBI.

onlineNcbi. nlm. nih.

gov. Available at: https://www. ncbi.

nlm. nih. gov/pubmed/18371877Accessed 12 Oct. 2017