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ORIGINAL STUDY

Comparative Quality Control Study of Widely Used Brands of Paracetamol Tablets in Iraq

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Abstract

Based on the World Health Organization definitions, the term quality control refers to the sum of all steps and procedures undertaken by a drug manufacturer to ensure the identity, safety, efficacy and purity of a particular pharmaceutical product. Quality control is an essential operation within the field of pharmaceutical industry and it is a vital part of current Good Manufacture Practice. It ensures that the pharmacokinetic and the pharmacodynamics properties are predictable and reproducible for the same active pharmaceutical ingredient when manufactured by different companies. The quality assurance of oral solid dosage form especially tablets is a priority for drug manufacturing companies. In addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, thickness, hardness, disintegration, and dissolution. In addition the content uniformity was investigated by HPLC technique. Thus, in this project, paracetamol tablets from five different companies which are widely used by Iraqi population were subjected to different quality control tests to indicate whether these products are fit to the standard criteria of the United States Pharmacopeia or not. The data indicated that all tested brands succeeded to pass most tests and failed in others.

Keywords: Tablets, Paracetamol, Quality control

1. Introduction

Acetaminophen (trade name, Paracetamol) belongs to the non-steroidal anti-inflammatory drugs. Paracetamol is commonly used as analgesic for mild to moderate pain management and antipyretic in the treatment of fever [1,2]. It is widely used and well known by Iraqi population for headache and fever relief. Locally, paracetamol is available as over the counter drug (OTC) and it is available in different dosage forms and different strengths in local pharmacies.

Pharmacologically, it exerts its action by inhibiting cyclooxygenase (COX) especially COX1, COX2. It also inhibits N-methyl-D-aspartate (NMDA) receptor, substrate P, and peroxisome proliferator-activated receptor gamma. It leads to reduce pain perception or the transduction of neuropathic pain [3].

Paracetamol has weak anti-inflammatory effects and usually not used for such purpose [4].

Generally, paracetamol can be used to treat several conditions such as headache, muscle ache, fever and cold, arthritis, backache, and toothache. Paracetamol combined with opioids is also used for severe pain such as cancer pain and pain after surgery [5,6].

The bioavailability of paracetamol following oral administration is about 63–89% and its protein binding is 10–25%. It is widely metabolised in the liver, the major resulting metabolites are glucuronide and sulphate conjugates. A minor fraction (less than 10%) of the drug is converted to a highly reactive alkylating metabolite which is normally inactivated *in vivo* with reduced glutathione and excreted via the kidneys as highly water-soluble cysteine and mercapturic acid conjugates. It distributes rapidly and evenly after absorption throughout most tissues and fluids and has a volume of distribution of approximately 0.9 L/kg. Ten to twenty percent of the drug is bound to red blood cells. Its urinary excretion is about 85–90% after administration [7].

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The usual side effects of the drug are nausea, vomiting, dark urine, yellowish skin, loss of appetite and stomach pain. Paracetamol toxicity may cause liver damage and skin reactions [8]. The commercially available dosage form of paracetamol includes tablets, caplets, capsules, effervescent tablets, suppositories, suspensions, injections, chewable tablets, oral drops, syrups, elixirs and extended release tablets. In addition, the drug is formulated in combination with other active ingredients. Recommended doses of paracetamol are: For adults and children aged 16 years and older: 500 mg-1 g every 4–6 h up to a maximum of 4 g daily. For children aged 12–15 years: 480–750 mg every 4–6 h up to a maximum of four doses daily. For children aged 10–11 years: 480–500 mg every 4–6 h up to a maximum of four doses daily. For children aged 8–9 years: 360–375 mg every 4–6 h up to a maximum of four doses daily. For children aged 6–7 years: 240–250 mg every 4–6 h up to a maximum of four doses daily. For children aged 4–5 years: 240 mg every 4–6 h up to a maximum of four doses daily. For children aged 2–3 years: 180 mg every 4–6 h up to a maximum of four doses daily. For children aged 6 months-1 year: 120 mg every 4–6 h up to a maximum of four doses daily. For children aged 3–5 months: 60 mg every 4–6 h up to a maximum of four doses daily [9].

Pharmaceutical characteristics of paracetamol tablet are the following: solid dosage form (tablets and caplets) of paracetamol is the most widely used pharmaceutical form of the drug worldwide. The tablets are usually uncoated, uncolored, round or caplet shape and compressed using different punch strengths. The purpose of the research is to focus on the effective and efficacious aspects of the tablet in the type of pharmaceutical dosage form. The pharmaceutical components of the tablet include the active pharmaceutical ingredient (API) and different excipients, which ensures efficient tableting, such as disintegrants, binders, diluent, lubricants, etc. [10]. The amount, nature and type of such excipients may dramatically affects the therapeutic effects of the API mainly by interfering with its absorption from the GIT following oral administration and thereby affecting its bioavailability (rate and extent of absorption).

Thus, the excipients of the tablet play an essential role in the tablet formulation. In addition, other physical characteristics of the API and the excipients such as particle size, crystal shape and uniformity also play a crucial role in tablets manufacturing [11].

The study tested certain features like friability, disintegration, hardness, weight variation and contents uniformity in order to ensure that the tablet is

within the standards of the United States Pharmacopoeia (USP). In this project paracetamol tablets from five different brand companies, which are widely used in the private pharmacies in Hilla city were subjected to different quality control. The study is quite important, not to prove that one drug brand is better than the others, but to provide the basis to use these methods for quality assessment of other APIs formulated as tablets by different companies available on a commercial scale through QC testing.

1.1. Quality control testing

The term “Quality Control” refers to “*the production of a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in production*” [12]. In pharmaceutical industry, QC testing ensures the safety of the drug, its efficacy as well as its effectiveness. It involves specific instruments to ensure the quality of drug testing as per set guidelines provided by the USP [13].

Although the assuring of product quality is principally within the responsibility of quality assurance department, it involves many other departments and disciplined lines within a pharmaceutical company. To be effective, it must be supported by a team effort [14].

Premium quality must be built into a drug product during both production and process design, and it is an essential aspect of good manufacture practice (GMP). It is influenced by many factors in addition to the production process such as the physical plant design, space, ventilation, cleanliness, and sanitation during routine production [14].

1.1.1. Quality assurance

The assurance of product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. Prime responsibility of maintaining product quality during production rests with the manufacturing department. Quality assurance personnel must establish control or checkpoints to monitor the quality of the product as it is processed and upon completion of manufacture. These begin with raw materials and components testing and include in process, packaging, labeling, and finished product testing as well as batch auditing and stability monitoring [12].

1.1.2. Sources of quality variation

Because of the increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms, complex ethical,

legal and economic responsibilities have been placed on those factors is the responsibility of all those involved in the development, manufacture, control and marketing of quality products. A systematic effective quality assurance program takes into consideration potential raw materials, manufacturing process, packaging material, labeling and finished product variables [11].

2. Materials and methods

2.1. Materials

Paracetamol tablets sheets (500 mg per tablet) from five different companies were obtained from a local drug store in Hilla city. The randomly selected types included Safacetol®, (SAFA Co., Private manufacturer based in Iraq), Omol (NP Pharma Co., Private manufacturer based in Iraq), Paracetol (SDI Co., Government manufacturer based in Iraq), Apmol (AJANTA Co., Private manufacturer based in India) and Supofen (BASI Co., Private manufacturer based in Indiana, USA). Solvents and NaOH were provided by Pharmaceutics Depart./College of Pharmacy/University of Babylon.

2.2. Methods

2.2.1. Physical examination

Ten tablets were removed from the plastic blisters and carefully examined by naked eye to detect its physical properties (appearance, color, break line, any cracked edges or any deformations). The process was repeatedly performed for each type of paracetamol from different companies.

2.2.2. Weight variation test

Ten tablets were removed from the sheet of each type separately and the weight of each tablet was measured individually by H-digital sensitive balance (DENVER Instrument/China). The mean and standard deviation were calculated and the accepted values of variation of $\pm 5\%$ were measured and compared with the standard deviation [11].

2.2.3. Size variation test

Ten tablets were removed from the sheet and each tablet was placed in digital caliper (WEILIANG Co./China) to measure its height. The steps were repeated for the rest of the tablets and then mean and standard deviation were calculated and compared with the accepted $\pm 5\%$ value [11].

2.2.4. Friability test

Friability of tablets may be defined as “the tendency of tablet to powder, chip or fragment” and this can affect the elegance, appearance and the consumer acceptance of the tablet. Friability tester machine (GUOMING CS-2/China) was used to measure friability of the different brand of paracetamol tablet [11].

The process was performed based on the guidelines of the USP as follow. The weight of 20 tablets of each brand of paracetamol were measured and the tablets were loaded in the friability tester. The apparatus exposed tablets to rolling and repeated shocks as they fall 15 cm in each turn within apparatus. After 4 min of 100 cycles, the tablets were removed from the device, brushed to remove any powders and weighed again. The percentage of weight loss (Friability %) was calculated according to the following equation:

$$\text{Friability \%} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100\%$$

where W_{initial} is the initial weight and W_f is final weight.

A maximum loss of weight from a single test not greater than 1% is acceptable for most tablets based on the USP criteria [11].

2.2.5. Disintegration test

Disintegration is a process by which tablets are fragmented into granules or small particles. It is defined as “the time required for a group of tablets to fragment into particles under a given set of conditions which is measured by disintegration tester”. This test is basic for tablets intended for administration by mouth except those intended to be chewed before being swallowed or those that should dissolve slowly in the mouth. Moreover, disintegration test is usually does not apply to similar types of sustained-release tablets [11].

Before each run, the apparatus (Disintegration tester \ GUOMING CS-2/China), was cleaned from any residue of the previous test. The tank of the device was filled with distilled water and left to reach the desired temperature (37 °C). Six tablets of paracetamol were used by putting one tablet in each basket of the 6 tubes and fixed by the specified disk. The device was operated to start continuous immersing and lifting of the tubes in the tank. The tablets in each tube were carefully monitored until disintegrated completely and the time was recorded. The mean and standard deviation of the disintegration time were

calculated and compared between different paracetamol brands. Values less than 10 min (600 s) were considered as accepted values [11].

2.2.6. Hardness test

Hardness (crushing strength) is the load required to crushing the tablet when placed on its edge. Hardness is the force required to break the tablet by diametric compression tester. Usually, tablet hardness tester is a portable semi-automatic electronic tablet hardness tester designed to accept tablet up to 30 mm in diameter. Unfortunately, in this project, such device was not available within the facility, and an alternative manual hardness tester (Campbel HN \ China) was used to perform this test.

The hardness for ten tablets of each brand was measured by placing 1 tablet each time in the hardness tester and the force required to break or crack the tablet was recorded. The mean and standard deviation of the hardness were calculated and compared between different paracetamol brands. Based on the USP, conventional tablet hardness should range between 4 and 8 kg/cm² [11]. Values outside this range were considered unaccepted results.

2.2.7. Content uniformity test

Uniformity of content is a pharmaceutical analysis parameter for the quality control of capsules or tablets. The test is performed by randomly selecting multiple tablets and a suitable analytical method is applied to assay the individual content of the API in each tablet. In this project, High performance liquid chromatography (HPLC) were chosen to perform quantitative analysis of API in different paracetamol tablets brands under investigation.

The HPLC analysis was performed using a shimadzu HPLC system. The column is a symmetry C18 (250 mm × 4.6 mm, 5 μm particle size) maintained at 40 °C and UV detection was performed at 230 nm. The mobile phase consisted of acetonitrile and water (25:75) % at a flow rate of 1 ml/min and the injection volume was 20 μL [15].

2.2.8. Preparation of standard and reference solutions

To prepare paracetamol standard solution, 20 mg of paracetamol reference standard (Schering, UK) was weighed and transferred to 500 ml flask. One ml of 0.5 N NaOH was added to ensure complete solubility and the solution was diluted to 500 ml mark with DW to give a stock solution of 40 μg ml⁻¹. A series of dilutions were made with water to give the concentrations of 2, 4, 8, 16, and 32 μg ml⁻¹ of paracetamol which were analyzed by HPLC to

determine the corresponding area under the curve (AUC) (Fig. 1).

To measure the paracetamol content in the tested tablets, 1 tablet was finely powdered using mortar and pestle and then transferred to 500 mL flask, 0.5 N NaOH (1 ml) was added for solubility and the solution was then diluted to mark with DW. One ml of the resulted solution was further diluted by DW in a ratio of 1:100. The solution was filtered with 0.45 μm membrane filter paper prior to analysis by HPLC to determine the AUC. The AUCs were converted to the corresponding concentration using the standard curve generated by standard paracetamol solutions [15].

The percentage stated content of sample paracetamol tablet can be calculated by using the formula:

$$\text{Percentage of stated content} = \frac{\text{Calculated weight in tablet}}{\text{Expected weight in tablet}} \times 100\%$$

3. Results and discussion

According to World Health Organization (WHO), the term QC refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical [15]. QC is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. It does not only protects the manufacturer against compensation claims, but also guarantees the patient a safe and effective product [16].

Thus, in addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production (in-process controls) and verified after the production of each batch to ensure that established product quality standards are met [14].

3.1. Physical examination

The various types of paracetamol tablet brands were subjected to physical examination using naked eye. The shape, engravings, color, sharpness of edges and extent of powder loss were investigated and the results are listed in Table 1.

3.2. Weight variation

The average weights of ten paracetamol tablets of each brand were measured as well as the standard

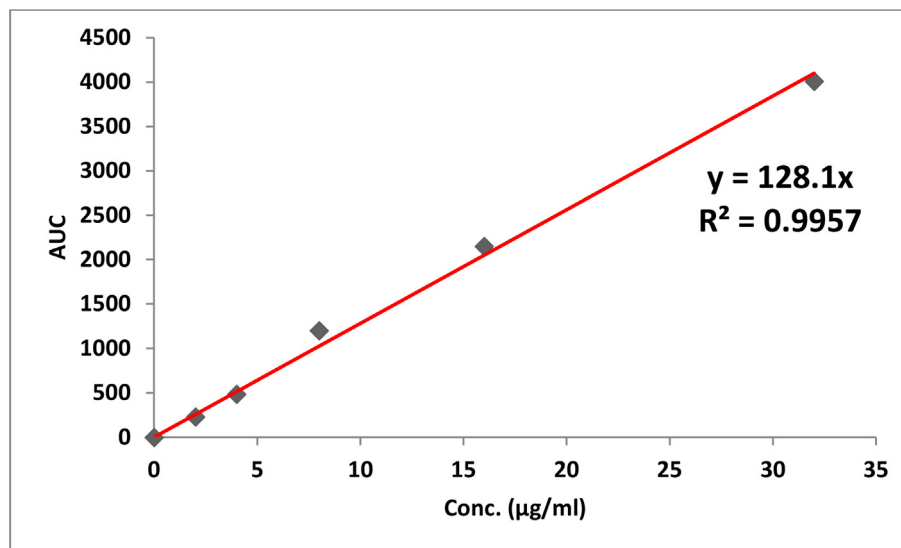


Fig. 1. Calibration curve of standard paracetamol powder.

deviation and the accepted values based on the $\pm 5\%$. The results are listed in Table 2.

The variation in weight in tablets dosage form may be caused by several factors such as flow properties of powders, size and shape of particles and the amount and type of excipients [14]. The lowest weight variation was detected in the Omol brand. The data indicated that all types of paracetamol tablets were within the accepted range except the Apmol brand.

3.3. Size variation

The average size of ten paracetamol tablets of each brand were calculated as well as the standard deviation and the accepted values based on the $\pm 5\%$. The results are shown in Table 3.

Two types of paracetamol (Safacetol and Sapofen) did not pass the size variation test while the rest of the types were within the accepted range. The Paracetol and Apmol brands showed the best values with minimum size variation.

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compression. Many of these factors are affected by the flow properties of powders, size and shape of particles and the amount and type of excipients (glidants). To produce tablets of uniform thickness during and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure [14].

3.4. Friability test

Friability is the phenomenon where the surface of the tablet is damaged or shown a site of damage due to mechanical shock. The purpose of the test is to evaluate the ability of the tablets to withstand the breakage during the packaging, transportation and handling. The average percentages of weight loss of paracetamol tablets of each brand were calculated

Table 1. Physical examination of different paracetamol brands.

Product	Description
Paracetol	Round, white tablets with excessive presence of powders and irregular edges. The tablets contain break-line with engraved with "500" sign.
Safacetol	Round, white tablets with loss of powders and irregular edges. The tablets contain a break-line with no engravings.
Sapofen	Round, white tablets with moderate loss of powders and irregular edges also. The tablets do not contain break-line or any engravings.
Apmol	Round, white tablets with excessive loss of powders and regular edges. The tablets contain break-line and engraved with "500" sign.
Omol	Round, white tablets with excessive powder loss and few tablets with irregular edges. The tablets contain a break-line with no engravings.

Table 2. Weight variation of different paracetamol brands.

Product	Weight (mg)	SD	Acceptable value	Verdict
Paracetol	616.07	9.19	30.80	Approved
Safacetol	605.73	6.31	30.28	Approved
Sapofen	681.64	10.72	34.08	Approved
Apmol	581.41	51.98	29.07	Rejected
Omol	555.93	7.11	27.79	Approved

Table 3. Size variation of different paracetamol brands.

Product	Size (mm) \pm SD	Acceptable value	Verdict
Paracetol	4.303 \pm 0.095	0.215	Approved
Safacetol	4.369 \pm 0.286	0.218	Rejected
Sapofen	4.273 \pm 0.255	0.233	Rejected
Apmol	4.273 \pm 0.096	0.213	Approved
Omol	4.137 \pm 0.124	0.206	Approved

Table 4. Percentage of weight loss of different paracetamol brands.

Product	% Wt. loss	Verdict
Paracetol	7.71	Rejected
Safacetol	6.53	Rejected
Sapofen	7.29	Rejected
Apmol	0.2	Approved
Omol	0.24	Approved

and the accepted values based on the $\pm 5\%$. The results are shown in Table 4.

The results revealed that only two brands of paracetamol (Apmol and Omol) succeeded to pass the test. However, other brands (Paracetol, Safacetol and Sapofen) were out of the accepted range. The friability is affected by the type and amount of binder, method of preparation and the force of compression [14].

3.5. Disintegration test

For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet disintegration also is important for tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract. In these instances, tablet disintegration provides drug particles with an increased surface area for activity within the gastrointestinal tract. All USP tablets must pass a test for disintegration, which is conducted *in vitro* using a disintegrator testing apparatus. The average disintegration time of different paracetamol brands were determined and the results are shown in Table 5.

Table 5. Disintegration time of different paracetamol brands.

Product	Disintegration time \pm SD (sec)	Verdict
Paracetol	109 \pm 11	Approved
Safacetol	378 \pm 68	Approved
Sapofen	161 \pm 21	Approved
Apmol	34 \pm 5	Approved
Omol	141 \pm 21	Approved

The disintegration of all types of paracetamol tablets were accepted and below the 10 min threshold. However, the fastest time was shown by Apmol brand (34 s). The faster disintegration time will improve rate of dissolution rate of absorption, bioavailability, rapid onset of action and faster response [17]. The longest disintegration time was related to Safacetol brand which reached almost 7 min.

3.6. Hardness test

Generally, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. Certain tablets, such as lozenges and buccal tablets, are intended to dissolve slowly and are intentionally made hard; other tablets, such as those for immediate drug release, are made soft [16]. In general, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet [11]. Multifunctional automated equipment can determine weight, hardness, thickness, and diameter of the tablet. The average hardness of different paracetamol brands were determined and the results are shown in Table 6.

3.7. Contents uniformity test

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. The term “uniformity of dosage unit” is defined as the degree of uniformity in the amount of the drug

Table 6. Hardness of different paracetamol brands.

Product	Hardness \pm SD (Kg)	Verdict
Paracetol	109 \pm 11	Approved
Safacetol	378 \pm 68	Approved
Sapofen	161 \pm 21	Approved
Apmol	34 \pm 5	Approved
Omol	141 \pm 21	Approved

Table 7. Average API contents & percentages of stated contents of different paracetamol brands.

Product	Average API content \pm SD (mg)	Percentage of stated content	Verdict
Paracetol	539 \pm 28	107.8%	Approved
Safacetol	528 \pm 44	105.6%	Approved
Sapofen	533 \pm 37	106.6%	Approved
Apmol	504 \pm 10	100.8%	Approved
Omol	525 \pm 16	105%	Approved

substance among dosage units. The test for Content Uniformity of preparations presented in dosage units is based on the quantitative assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The Content Uniformity method may be applied in all cases [11].

To perform this test, tablets from each brands were subjected to quantitative analysis of the API using HPLC. The API produced a distinctive peak in monograph which eluted at minute 6 of the run time.

The AUCs for each run were recorded and the corresponding percentage of contents were calculated for each brand which are listed in Table 7.

The results indicated that all tablet brands under investigation contained higher contents of the API (paracetamol) than the stated content (500 mg). This may be attributed to the fact that the raw material of the API is commercially cheap in addition to the wide therapeutic window of the drug (minimum chance of drug toxicity in even in higher concentrations). For such reasons many manufacturer may turn a blind eye for such higher API contents.

In general, it is essential for drug manufacturers to maintain the quality of their products by performing various QC testing to make sure that it is safe and at the same time, it maintains the efficiency and quality of the overall product. QC testing also makes sure that the drug adheres to the details as per the description and data listed on the drug label. This may include checking the purities and impurities in a drug, API content, drug absorption by the body, etc. The *in vitro* testing performed in these tests determines the quality, efficacy, and effectiveness of paracetamol drug as required by the standards of the USP.

4. Conclusion

Different brands of paracetamol tablets which are widely available in Iraqi market were subjected to different QC test to indicate whether it will meet the criteria of USP for tablets manufacturing. It should be kept in mind that, the aim of this study was not to

favour a certain brand or company on the others, nor to prove that a certain manufacturer or the more expensive product is better than other manufacturers or the lower cost product. Such comparative studies are usually performed by drug companies as a part of their marketing and advertising propaganda to try to demonstrate to health care professional and consumers that their products is better than other drug providers. Such claims should not be taken for granted by scientific researchers and instead researchers must be unbiased and not affected by such propaganda. Official QC tests may be applied to prove whether these claims are right or wrong.

In conclusion, the five different brands of the tested drug showed variable results, which is quite expected not only for different manufacturers but also for different batches of the same company. Only the brand type, Omol, passed all tests included in this study based on the QC standards of the USP. The four other brands did not pass all tests and based on the USP such batches may not be approved. However, it should be kept in mind, that these results may be affected by many factors such as shipment method, storage conditions and production date and such factors were not taken in consideration in this study.

Finally, this research can be expanded to be used to prove or refute manufacturers claims not only for paracetamol, but for other active pharmaceutical ingredients.

Conflicts of interest

The authors certify that there is no conflict of interest.

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References

- [1] Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, Wells GA. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006;(1). <https://doi.org/10.1002/14651858.CD004257.pub2>.
- [2] McKay GA, Reid JL, Walters MR. *Lecture notes: clinical pharmacology and therapeutics*. John Wiley & Sons; 2010.
- [3] Milani DAQ, Davis DD. *Pain management medications*. StatPearls Publishing; 2022. StatPearls [Internet].
- [4] Bannwarth B, Pehourcq F. Pharmacological rationale for the clinical use of paracetamol: pharmacokinetic and pharmacodynamic issues. *Drugs* 2003;63:5–13. PMID: 14758786.
- [5] Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain Physician* 2009;12(1):269–80. PMID: 19165309.
- [6] Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the a merican H eadache S ociety evidence assessment of migraine pharmacotherapies. *Headache J Head Face Pain* 2015;55(1):3–20. <https://doi.org/10.1111/head.12499>.

- [7] Kulo A, Peeters MY, Allegaert K, Smits A, de Hoon J, Verbesselt R, et al. Pharmacokinetics of paracetamol and its metabolites in women at delivery and post-partum. *Br J Clin Pharmacol* 2013;75(3):850–60. <https://doi.org/10.1111/j.1365-2125.2012.04402.x>.
- [8] Wang X, Wu Q, Liu A, Anadón A, Rodríguez J-L, Martínez-Larrañaga M-R, et al. Paracetamol: overdose-induced oxidative stress toxicity, metabolism, and protective effects of various compounds in vivo and in vitro. *Drug Metab Rev* 2017; 49(4):395–437. <https://doi.org/10.1080/03602532.2017.1354014>.
- [9] Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384(9954):1586–96. [https://doi.org/10.1016/S0140-6736\(14\)60805-9](https://doi.org/10.1016/S0140-6736(14)60805-9). Epub 2014 Jul 23.
- [10] Su S-F, Chou C-H, Kung C-F, Huang J-d. In vitro and in vivo comparison of two diclofenac sodium sustained release oral formulations. *Int J Pharm* 2003;260(1):39–46. [https://doi.org/10.1016/s0378-5173\(03\)00237-0](https://doi.org/10.1016/s0378-5173(03)00237-0).
- [11] Pharmacopeia US. USP 37–NF 32. USP-NF Standard Updates 2013;37 (second supplement).
- [12] Allen L, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins; 2013.
- [13] Gupta MM, Gupta M. In-vitro pharmaceutical quality control testing: a comparative study of different brands of metformin tablets available in the Trinidad & Tobago, West Indies. *J Pharmaceut Sci Res* 2016;8(4):238.
- [14] Lachman L, Lieberman H, Khar R, Vyas S, Farhan A, Jain J. The theory and practice of industrial pharmacy. 4th ed., vol. 245. New Delhi: CBS Publishers & Distributors Pvt Ltd; 2013. p. 450–8.
- [15] Franeta J, Agbaba D, Eric S, Pavkov S, Aleksic M, Vladimirov S. HPLC assay of acetylsalicylic acid, paracetamol, caffeine and phenobarbital in tablets. *Il Farmaco* 2002;57(9): 709–13. [https://doi.org/10.1016/s0014-827x\(02\)01265-x](https://doi.org/10.1016/s0014-827x(02)01265-x).
- [16] Organisation WH. Supplementary guidelines on good manufacturing practices: validation. (2006). Appendix 4 on Analytical method validation vol. 937. WHO Tech Rep Ser; 2006 (Annex 4).
- [17] Shargel L, Wu-Pong S. Andrew yu applied biopharmaceutics and pharmacokinetics. McGraw-Hill Education; 2015.