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Research Article

Formulation of a newly effervescent paracetamol tablets

Ahmed M.A. Masaad[1], Ibrahim A. Maghrabi[2]

[1] Department of Pharmaceutics and Pharmaceutical technology
[2] Department of Clinical Pharmacy
College of Pharmacy, Taif University, Kingdom of Saudi Arabia

Address for Correspondence:
Ahmed M. A. Masaad
Email: a.msaad@tu.edu.sa

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ABSTRACT

This research is a formulation of the drug paracetamol as an effervescent tablet by two methods (direct compression and wet granulation). The bitter taste was masked by saccharine as sweeting agent with guargum and Tragacanthgum, furthermore the effervescent effect of citric acid, tartaric acid and sodium bicarbonate lead to improve the taste of the drug beside increase the effect of formula. Also the Guargum with Tragacanth gum and PVP were used as binder agent lead to hide the taste. The strawberry with banana which was used as flavoring agent also enhances the palatability. The formulated tablets were passed all the fundamental testes in the monograph. This study was found that formulating the paracetamol as effervescent tablet by wet granulation method and die cavity twenty is the suitable one and that might be lead to increase the drug efficacy, therapeutic effect as well as increase patient acceptability as effervescent tablet.

Key words: *Tablets; Paracetamol; Newly Formula; effervescent; patient acceptability; Taste*

INTRODUCTION

Tablet formulations may be rendered effervescent for several reasons, including improvement of their disintegration characteristics, increase dissolution rate and thus enhance liberating the ciprofloxacin HCl beside together with sweetener, flavor and guar to mask the taste.[1] Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agent for ciprofloxacin HCl (in ratio 1:2:3.4).[2] It comprise effervescent base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition by other non-active material such as sweeteners, flavoring agent, guar gum and filers. Thus all that contributes in success theformula.[1-3-4] Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever. It is typically used for mild to moderate pain.[5] There is poor evidence for fever relief in children.[6] It is often sold in combination with other ingredients such as in many cold medications.[5] In combination with opioid pain medication, paracetamol is used for more severe pain such as cancer pain and after surgery. It is typically used either by mouth or rectally but is also available intravenously. Effects last between two and four hours.[5-7] Paracetamol is generally safe at recommended doses. Serious skin rashes may rarely occur, and too high a dose can result in liver failure. It appears to be safe during pregnancy and when breastfeeding.[5] In those with liver disease, it may still be used, but lower doses should be taken. Paracetamol is classified as a mild analgesic. It does not have significant anti-inflammatory activity and how it works is not entirely clear.[7] Paracetamol was discovered in 1877. It is the most commonly used medication for pain and fever in both the United States and Europe.[8]It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Paracetamol is available as a generic medication with trade names including Tylenol and Panadol among others. The wholesale price in the developing world is less than 0.01 USD per dose. In the United States it costs about 0.04 USD per dose.[9]

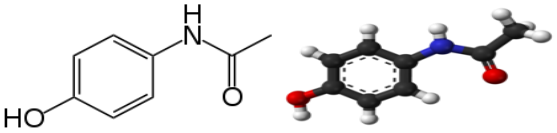

Figure 1: Chemical Structure of Paracetamol N-(4-hydroxyphenyl) Ethan Amide Synthesis

ORIGINAL (BOOTS) METHOD

The original method for production involves the nitration of phenol with sodium nitrate gives a mixture of two isomers, from which 4-nitrophenol (b.p 279°C) can easily be separated by steam distillation (Fig. 2). In this electrophilic aromatic substitution reaction, phenol's oxygen is strongly activating, thus the reaction requires only mild conditions as compared to nitration of benzene itself. The nitro group is then reduced to an amine, giving 4-aminophenol. Finally, the amine is acetylated with acetic anhydride. Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves.[10-11]

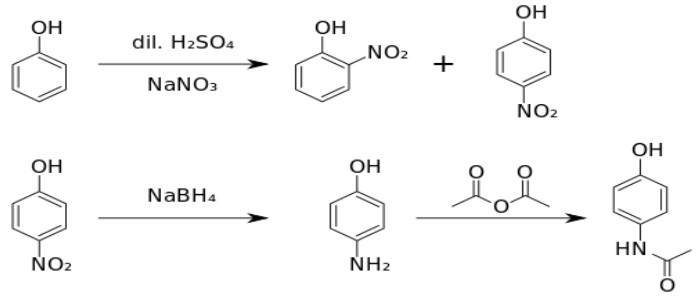

Figure 2: Synthesis of paracetamol from phenol.

GREEN(ER) SYNTHESIS

An alternative industrial synthesis developed by Hoechst–Celanese involves direct acylation of phenol with acetic anhydride catalyzed by HF, conversion of the ketone to a ketoxime with hydroxylamine, followed by the acid-catalyzed Beckmann rearrangement to give the amide (Fig. 3).[12-13]

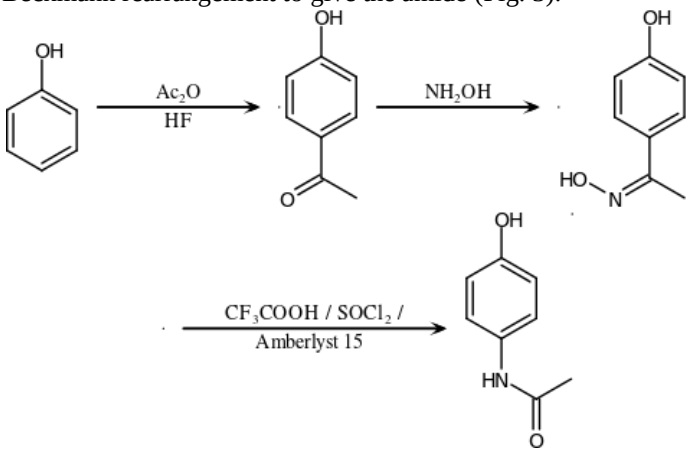

Figure 3: Celanese synthesis of paracetamol.

DIRECT SYNTHESIS

More recently (2014) a "one-pot" synthesis from hydroquinone has been described before the Royal Society of Chemistry.[13] The process may be summarized as follows:

Hydroquinone, ammonium acetate, and acetic acid were mixed in an argon atmosphere and heated slowly to 230°C. The mixture was stirred at this temperature for 15 hours. After cooling the acetic acid was evaporated and the precipitate was filtered, washed with water and dried to give paracetamol as a white solid.

The authors go on to claim an 88% yield and 99% purity.

REACTIONS

4-Aminophenol may be obtained by the amide hydrolysis of paracetamol. 4-Aminophenol prepared this way, and related to the commercially available Metol, has been used as a developer in photography by hobbyists. This reaction is also used to determine paracetamol in urine samples: After hydrolysis with hydrochloric acid, 4-aminophenol reacts in ammonia solution with a phenol derivate, e.g. salicylic acid, to form an indophenol dye under oxidization by air.[15]

MECHANISM OF ACTION

To date, the mechanism of action of paracetamol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2. Because of its selectivity for COX-2, it does not significantly inhibit the production of the pro-clottingthromboxanes. While it has analgesic and antipyretic properties comparable to those of aspirin or other NSAIDs, its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of peroxides present in inflammatory lesions.[16]

MEDICAL USES

Fever: Paracetamol is used for reducing fever in people of all ages.[23] The World Health Organization (WHO) recommends that paracetamol be used to treat fever in children only if their temperature is greater than 38.5°C (101.3°F).[24] The efficacy of paracetamol by itself in children with fevers has been questioned and a meta-analysis showed that it is less effective than ibuprofen.[17]

Pain: Paracetamol is used for the relief of mild to moderate pain. The use of the intravenous form for pain of sudden onset in people in the emergency department is supported by limited evidence.[18]

Osteoarthritis: The American College of Rheumatology recommends paracetamol as one of several treatment options for people with arthritis pain of the hip, hand, or knee that does not improve with exercise and weight loss. A 2015 review, however, found it provided only a small benefit in osteoarthritis. Paracetamol has relatively little anti-inflammatory activity, unlike other common analgesics such as the NSAIDs aspirin and ibuprofen, but ibuprofen and paracetamol have similar effects in the treatment of headache. Paracetamol can relieve pain in mild arthritis, but has no effect on the underlying inflammation, redness, and swelling of the joint. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin due to concerns about bleeding with aspirin.[19]

Low back pain: Based on a systematic review, paracetamol is recommended by the American College of Physicians and the American Pain Society as a first-line treatment for low back

pain. However, other systematic reviews concluded that evidence for its efficacy is lacking.[19]

Headaches: A joint statement of the German, Austrian, and Swiss headache societies and the German Society of Neurology recommends the use of paracetamol in combination with caffeine as one of several first line therapies for treatment of tension or migraine headache. In the treatment of acute migraine, it is superior to placebo, with 39% of people experiencing pain relief at one hour compared with 20% in the control group.[20]

Postoperative Pain: Paracetamol combined with NSAIDs may be more effective for treating postoperative pain than either paracetamol alone or NSAIDs alone.[21]

Dental Use: NSAIDs such as ibuprofen, naproxen, diclofenac are more effective than paracetamol for controlling dental pain or pain arising from dental procedures; combinations of NSAIDs and paracetamol are more effective than either alone.[37] Paracetamol is particularly useful when NSAIDs are contraindicated due to hypersensitivity or history of gastrointestinal ulceration or bleeding. It can also be used in combination with NSAIDs when these are ineffective in controlling dental pain alone. The Cochrane review of preoperative analgesics for additional pain relief in children and adolescents shows no evidence of benefit in taking paracetamol before dental treatment to help reduce pain after treatment for procedures under local anaesthetic, however the quality of evidence is low.[21]

Other: The efficacy of paracetamol when used in combination with weak opioids (such as codeine) improved for approximately 50% of people but with increases in the number experiencing side effects.[22] Combination drugs of paracetamol and strong opioids like morphine improve analgesic effect. The combination of paracetamol with caffeine is superior to paracetamol alone for the treatment of common pain conditions including dental pain, postpartum pain, and headache.[23]

METHOD

Formulation of Tablets: Tablets were prepared by two methods. In the two Methods: The ratios of the effervescent ingredients were taken as (1:2:3.4) respectively for citric acid: tartaric acid: sodium bicarbonate according to the following equation.[2-24-25]

Citric acid:

$$3NaHCO_3 + C_6H_8O_7 \cdot H_2O \rightarrow 4H_2O_+ 3CO_{2+} Na_3C_6H_5O_7 (1)$$

$$3\times84 \qquad 210$$

Tartaric acid:

$$2NaHCO_3 + C_4H_6O_6 \rightarrow 2H_2O + 2CO_2 + Na_2C_4H_4O_6 (2)$$

$$2\times84 \qquad 150$$

From the above equations the ratio of effervescent ingredients used was (1:2:3.4) for the citric acid tartaric acid: sodium bicarbonate.[2-24]

Wet Granulation: The most widely used and most general method of tablet preparation is the Wet Granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluents, and disintegrant are mixed or blended well.[2]

Specific amount of paracetamol and saccharin were weighed and were divided into two pestles in equal amount and well mixed to each one of pestles effervescent base was added Citric and Tartaric acid in one and sodium bicarbonate in another one to avoid reaction then the binder combination (Guargum and Poly vinyl pyrollodine) was added slowly after dissolving in a very small amount of water and then the mixture was blended continuously to make the paste, granulated using mesh,[10] and then put in oven for drying for twenty hours. The mixture was passed through mesh[14] after drying using mesh.[14] The micro crystalline cellulose when added before granulation used as disintegrant and after granulation as glident. Talc powder and magnesium stearate were added as lubricant and glident. Granules were compressed into two types one tablet 250 mg (0.25 gm active ingredient) by 20mm die and 125 mg (0.125 gm ingredient) by 13mm die as divided dose.[2-25]

CALCULATIONS

Formula (1) (high binder concentration):

Guar: 1% & PVP: 4% (w/w)

Formula (2) (low binder concentration):

Guar: 0.05% & PVP: 2% (w/w)

- Guar with poly Vinyl pyrrolidone as a binder indifferent ratios for the two formulae.
- Saccharin was used from three to five time of active ingredient and the best one it was used in ratio five times to active ingredient.
- Saccharine can be used as a binder.
- Tablet weight in these two formulae 1600 mg and 2000 mg can be used in two tablets to be easy to carry, handle, stand packaging and transportation.
- Micro crystalline cellouse (Avicil) 5% is used as disintegrating agent and glidant and lubricant.
- Mg stearate and Talc powder combinations as lubricant and glidant.
- Vanillin was used as flavoring agent.

Direct Compression: As its name implies, Direct Compression consists of compression of tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as the method of tablet

manufacture was reserved for small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet.[2-28] Paracetamol is mixed with lactose to improve compression characteristic then $NaHCO_3$ and saccharine sodium four times (active ingredient) were added to active ingredient and mixed well and named (A). In another mortar, specified amount of tartaric acid and citric acid were weighed accurately and named (B). Then (A) and (B) were mixed in third mortar and specified amount of banana and vanillin flavor was added and then the whole mixture was passed through a sieve for more mixing. One percent of guar is used in dry form for all formula, vanillin and strawberry were added as flavor agents. The powder was put in an oven for drying and then tableting machine.[2-28]

Determination of uniformity of weight: 20 tablets from effervescent tablet were weighed individually with an analytical weighing balance. The average weights for each effervescent tablet and the percentage deviation from the mean value wereobtained.[25]

Hardness Test: The crushing strength was determined with a tablet hardness tester (Monsant, U.K). Four tablets were randomly selected from effervescent tablet and then the pressure at which each tablet crushed was recorded and the hardness value obtained.[26]

Friability Test: Ten tablets of effervescent ciprofloxacin HCl were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev-min for four minutes. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.[26]

Content Uniformity: Test for uniformity of content is based on the assay of the individual contents of active ingredient of a number of single dose units. Test to weight variation is also used to show the uniformity of active ingredient (AI) and the excipients. According to BP the weight for tablet weighing greater than 325mg there should not be more than two tablets deviating from the average by no more than 5 percent and none deviated by more twice of 5 percent (10 percent). Tablets out of this specification are not uniform enough in terms API or excipient or both.[26]

Assay: Assay is a single test carried out for the purpose of estimating the potency of material preparation or pooled result of two or more such tests which pharmacopoeia depend. So in this research assay was performed in compliance to BP to assess percentage content of paracetamol. BP specifies the content of Paracetamol to be between 95 to 105% of the stated amount.[26]

Dissolution Test: The tablets were dissolved in sink condition and the time of dissolution of effervescent tablet was recorded by stop watch.[27]

pH Adjustment: The effervescent tablets were dissolved and then filtered and the pH of resultant solution was read by pH meter.[26]

Figure 4: newly formulated effervescent paracetamol granules and tablets

RESULTS AND DISCUSSION

Table 1: Summary of the Quality Control Tests Undertaken on the two types of the Ibuprofen Effervescent Tablets

Effervescent Tablet	Friability	Hardness (Kg/cm^2)	Deviation%	pH	Assay %	Mean of Dissolution Time (min)
Direct Compression	1.4	6.0	1.05	6.12	98	2.42
Wet Granulation 13mm tablet	1.1	6.70	1.12	6.10	97	4.09
Wet Granulation 20mm tablet	1.2	6.50	0.94	6.00	96	2.8

In wet granulation method we can omit the binder when we use saccharin in any formula when it use with a very low quantity of water. The problem of bitterness of soluble drug (paracetamol) can be overcome by using saccharin from four to six time's active ingredient in effervescent formula. The resultant effervescent tablet figure 4 formula can be used to enhance solubility and might increase the palatability and mask taste and bioavailability and activity that agree with Ahmed *et al*.[25] Flavoring agent (vanillin) might mask taste beside good odor. Wet granulation is very good for production of effervescent tablet rather than dry compression method. Guar 1% is very strong binder when it was used in combination with PVP 4% in

formula. All tablets passed the requirement of monograph this agree with Ahmed *et al.* [25-24] Ten times dilution were needed for binder (0.1 guar gum and 0.4 PVP) with saccharin to avoid very hardness value in compression in previous method in which we use guar 1% dry lactose PVP 1% we find weight granulation method give good compressibility rather than direct compression table (1) this result agree with Nicole *et al*[2] and Ahmed *et al.*[24] The use of MCC is work as lubricant which intended to reduce the friction during tablet rejection between the wall of tablet and the wall die cavity in which the tablet was formed furthermore has glidant effect and disintegrating action. This agree with Nicole *et al*[2] and Ahmed *et al.*[25]

CONCLUSION

1. The study managed to improve the palatability of the paracetamol solution, via the utilization of saccharin sodium and vanillin flavor and using effervescent formula. Formulation into effervescent tablet is suitable for larger dose size which has difficulty in production of a convention tablet due to the difficulty in swallowing, besides enhancing solubility, which masking the taste and may lead to higher bioavailability and compression.
2. Formulating tablet as wet granulation method (when it is possible and applicable) is better than in direct compression method because of good distribution active ingredient.
3. The effervescent formula is needed and sometimes it is a must to enhance palatability of certain drugs.[24]
4. The correlation can be made between dissolution rate of effervescent paracetaml tablets as an indication for its effectiveness without in vivo studies and effervescent base can be used to relief precipitation of any residual to drugs.
5. Wet granulation method (when it is applicable) is better than the direct compression method; this might be good distribution of active ingredient.
6. The effervescent tablets which prepared by wet granulation method (punch13) two tablets must be used to give 250 mg active ingredient (paracetamol) or four tablets to give 500 mg.

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