Research Article

Formulation of a Newly Effervescent Diclofenac K Tablets

Ahmed. M. A. Masaad*
Department of Pharmaceutics and pharmaceutical technology, College of Pharmacy, Taif University, Kingdom of Saudi Arabia.
***Corresponding author's E-mail:** ahmad.mosaad@hotmail.com

Received: 21-11-2017; **Revised:** 26-12-2017; **Accepted:** 13-01-2018.

ABSTRACT

This research is a formulation of the drug diclofenac potassium as an effervescent tablet by two methods (direct compression and wet granulation). The bitter taste was masked by saccharine as sweetening 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, PVP and Avicil 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 diclofenac potassium as effervescent tablet by wet granulation method, die cavity twenty is the suitable one, and that might be lead to increase the drug efficacy. Thus it was concluded that the effervescent diclofenac potassium containing sustained release properties was found improve bioavailability, patient compliance, minimize side effects via clearance the residual of drug by effervescent effect.

Keywords: Tablets, Diclofenac potassium, Newly Formula, effervescent, patient acceptability, increase effect.

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 the formula. [1-3-4.]

Diclo" redirects here. For the organic solvent sometimes called Di-clo, see Dichloromethane[5].

Medical uses:

Pain

Inflammatory disorders may include musculoskeletal complaints, especially arthritis, rheumatoid arthritis, polymyositis, dermatomyositis, osteoarthritis, dental pain, temporomandibular joint (TMJ) pain, spondylarthritis, ankylosing spondylitis, gout attacks[5] and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines[6]. Diclofenac is used commonly to treat mild to moderate postoperative or post-traumatic pain, in particular when inflammation is also present, [5] and is effective against menstrual pain and endometriosis.

Diclofenac is also available in topical forms and has been found to be useful for osteoarthritis but not other types of long-term musculoskeletal pain.[7]

It may also help with actinic keratosis, and acute pain caused by minor strains, sprains, and contusions (bruises).[7]

In many countries,[8] eye drops are sold to treat acute and chronic nonbacterial inflammation of the anterior part of the eyes (e.g., postoperative states). Diclofenac eye drops have also been used to manage pain for traumatic corneal abrasion.[8]

Diclofenac is often used to treat chronic pain associated with cancer, in particular if inflammation is also present (Step I of the World Health Organization (WHO) scheme for treatment of chronic pain). Diclofenac can be combined with opioids if needed such as a fixed combination of diclofenac and codeine.[8]

Other

Diclofenac has been found to increase the blood pressure in patients with Shy–Drager syndrome and diabetes mellitus. Currently, this use is highly investigative and cannot be recommended as routine treatment.

Mechanism of Action

The primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis[9]

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive

to corrosion by gastric acid. This is also the main side effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have, therefore, a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin. The action of one single dose is much longer (6 to 8 hr) than the very short half-life of the drug indicates. This could be partly because it persists for over 11 hours in synovial fluids.[30] Diclofenac may also be a unique member of the NSAIDs. Some evidence indicates it inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). It also may inhibit phospholipase A_2 as part of its mechanism of action. These additional actions may explain its high potency - it is the most potent NSAID on a broad basis.[10]

Marked differences exist among NSAIDs in their selective inhibition of the two subtypes of cyclooxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side effects of NSAIDs such as aspirin. In practice, use of some COX-2 inhibitors with their adverse effects has led to massive numbers of patient family lawsuits alleging wrongful death by heart attack, yet other significantly COX-selective NSAIDs, such as diclofenac, have been well tolerated by most of the population. Besides the COX-inhibition, a number of other molecular targets of diclofenac possibly contributing to its pain-relieving actions have recently been identified. These include Blockage of voltage-dependent sodium channels (after activation of the channel, diclofenac inhibits its reactivation also known as phase inhibition), Blockage of acid-sensing ion channels (ASICs) and Positive allosteric modulation of KCNQ- and BK-potassium channels (diclofenac opens these channels, leading to hyper polarization of the cell membrane) [10].

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.

Citric acid:

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

3×84 210

Tartaric acid:

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

2×84 150

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

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. [2-15]

Specific amount of diclofenac K 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 (Guar 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. [15-16-17]

Calculations

Formula (1) (high binder concentration):

Guar: 1% & PVP: 5% (w/w)

Formula (2) (low binder concentration):

Guar: 0.06% & PVP: 6% (w/w)

- Guar with poly Vinyl pyrrolidone as a binder in different 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 it 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 stearte 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. [2-15-17] Ciprofloxacin 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 was added as flavor agent. The powder was put in an oven for drying and then tableting machine.[2-6-9]

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 were obtained[18].

Hardness Test

The crushing strength was determined with a tablet hardness tester (Monsanto, 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.[18]

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.[18]

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.[18]

Assay

A series of diclofenac potassium solutions were prepared ranging from 200 ppm to 12.5 ppm. After preparation of a standard stock solution of 200 ppm in 100 ml of water, different dilutions were made (100ppm, 50ppm, 25ppm and 12.5ppm). At the wavelength 242nm, the absorbance of the standard preparation and dilutions was measured using the UV spectrophotometer. The quantity in mg, of diclofenac potassium was determined.

Dissolution Test

The dissolution test was undertaken using (USP apparatus1) (basket method) in six replicates (six tablets for each brand). The dissolution medium was 900ml 0.1NHCl which was maintained at 37 ± 0.5 C^{o}. In all the experiments, 5ml of dissolution sample was withdrawn at 45 min and replaced with equal volume to maintain sink condition.

Samples were filtered and assayed by ultraviolet spectrophotometer at 277λ (nm) and compared to standard. The concentration of each sample was determined from a calibration curve obtained from pure samples of ciprofloxacin according to the monograph. [18]

Medical uses

Inflammatory disorders may include musculoskeletal complaints, especially arthritis, rheumatoid arthritis, polymyositis, dermatomyositispain, spondylarthritis, ankylosingspondylitis, gout attacks, and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate postoperative or post-traumatic pain, in particular when inflammation is also present, and is effective against menstrual pain and endometriosis.

Diclofenac is also available in topical forms and has been found to be useful for osteoarthritis but not other types of long-term musculoskeletal pain. It may also help with actinic keratosis, and acute pain caused by minor strains, sprains, and contusions (bruises).

In many countries, eye drops are sold to treat acute and chronic nonbacterial inflammation of the anterior part of the eyes (e.g., postoperative states). Diclofenac eye drops have also been used to manage pain for traumatic corneal abrasion[2-3].

Effervescent tablet are convenient, easy to use, pre-measured dosage forms that are already in solution when ingested [38]. Effervescent mixtures have been moderately popular over the years since along with medicinal value of the particular preparation, they offered the public ionic dosage form that was interesting to prepare.

RESULTS AND DISCUSSION

Table 1: Summary of the Quality Control Tests on the two types of the diclofenac K formula

Effervescent Tablet	Friability	Hardness (Kg/cm^2)	Deviation %	pH	Assay %	Mean of Dissolution Time (min)
Direct Compression	4.5	5.5	1.45	6. 2	97	1.53
Wet Granulation 13mm tablet	2.9	7.9	1.02	6.25	98	3.00
Wet Granulation 20mm tablet	3.6	6.2	0.9	6.19	96	2.7

Figure 1: Formulated effervescent diclofenac K tablets.

In addition, they provided a pleasant taste due to carbonation which masks the taste of objectionable materials [13]. The tablets were formulated by two methods wet granulation method and direct compression method (table 1).

On comparing tablets formulated as effervescent ones (wet granulation and direct compression) (Fig1) (table1) their dissolution rate were found higher than the marketed brands. This due to more distribution of the active ingredient by mixing and the addition of masking agents by techniques was done on a new formula not affected the active ingredient [(13)].

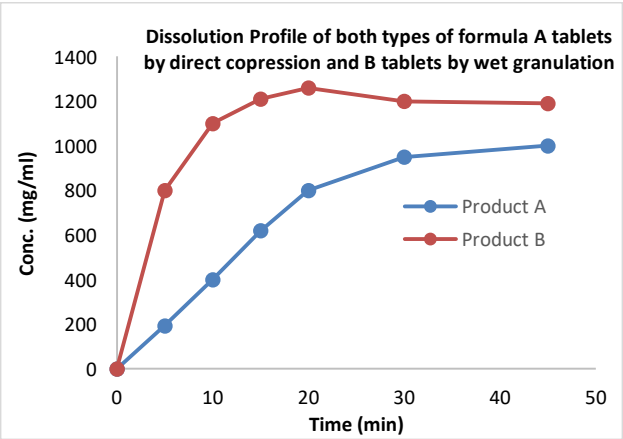

Figure 2: dissolution profile of two types of effervescent diclofenac K formula

The dissolution time of effervescent tablet (direct compression) (173sec) and the dissolution time of effervescent tablet (wet granulation) 180 Figure (2) second the two types of effervescent tablets complied with the pharmacopeia specifications for the effervescent tablets, which is up to 300 seconds (5min) (European pharmacopeia, 2002) [17] table (1), so this indicates the good effect of effervescent base as enhancer solubility beside the masking effect. Also all physicochemical properties complying with monograph this indicates the masking agent not affect the physicochemical properties of the tablets and this agree with studied done by Ahmed et al [4].

CONCLUSION

After concerting all these factors in formulating diclofenac K (as an effervescent tablet) it is concluded that an ideal taste masking formulation should have following properties:

1. Involve least number of equipments and processing steps.
2. Require minimum number of excipients for an optimum formulation (ciprofloxacin HCl).
3. No adverse effects on drug bioavailability require excipients that are economical and easily available.
4. Least manufacturing cost.
5. Can be carried out at room temperature.
6. Require excipients that have high margin of safety.
7. Rapid and easy to prepare.

Acknowledgement: Great thanks for the University of Department of Pharmaceutics faculty of Pharmacy University of Khartoum. The thanks expanded to department of Pharmaceutics and pharmaceutical technology, college pharmacy, Taif University for the great help to complete this research and to graduate college especially prof Alrasheed Altahir Ismaeel who the dean of the graduate college Aleelain University.

REFERENCES

1. Nichols, W. K. (2000) Oral Solid Dosage Form. In: Remington: The Science and Practice of Pharmacy. 20th ed. Alfonso, R.G. Philadelphia College of Pharmacy and Science. Pp. 1507-89.
2. Food and Drug Administration (FDA). (2003) Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. General Considerations, Center for Drug Evaluation and Research (CDER), Rockville, MD, USA. 1-21.
3. Rang, H. P.; Dale, M. M.; Ritter, J. M. and Moore, P. K. (2003). Drugs Used In the Treatment of Infections and Cancer Pharmacology, 5th ed. Churchill Livingston.

4. Ahmed M. Masaad, Ibrahim M Maghrabi, Majed M. Al Robaian, Badraddin M. Al-Hadiya, Mohammed E. Shayoub. (2016) Enhancement of Taste Masking by a Newly Formulated Effervescent Ciprofloxacin Tablets. International Journal of Research in Pharmacy and Science 7(3).

5. Drugs.com Diclofenac international availability.

6. "RUFENAL". Birzeit Pharmaceutical Company. Archived from the original on 2011-05-26.

7. Dutta, NK; Mazumdar, K; Dastidar, SG; Park, JH (October 2007). "Activity of diclofenac used alone and in combination with streptomycin against Mycobacterium tuberculosis in mice." International journal of antimicrobial agents. 30 (4), 336–
40. PMID 17644321. doi:10.1016/j.ijantimicag.2007.04.016.

8. Wakai A, Lawrenson JG, Lawrenson AL, Wang Y, Brown MD, Quirke M, Ghandour O, McCormick R, Walsh CD, Amayem A, Lang E, Harrison N (2017). "Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions". Cochrane Database Syst Rev. 5: CD009781. PMID 28516471. doi:10.1002/14651858.CD009781.pub2.

9. Dastidar SG, Ganguly K, Chaudhuri K, Chakrabarty AN (2000). "The anti-bacterial action of diclofenac shown by inhibition of DNA synthesis". Int. J. Antimicrob. Agents. 14 (3), 249–51. PMID 10773497. doi:10.1016/S0924-8579(99)00159-4

10. Voilley N, de Weille J, Mamet J, Lazdunski M: Nonsteroid anti-inflammatory drugs inhibit both the activity and the inflammation-induced expression of acid-sensing ion channels in nociceptors. J Neurosci. 21(20), 2001 Oct 15, 8026-33.

11. Polli JE, Rekhi SG, Augsburger LL, Shah VP (1997). Methods to compare Dissolution Profile and A Rationale for Wide Dissolution Specification for Metoprolol Tartrate Tablets. J. Pharm. Sci. 86 (6), 690-700.

12. Hamam.S.Badri, Ahmed. M.A. Massad, Mohammed. E.A. Shayob formulation of Effervescent Ciprofloxacin. World Journal of Pharmacy and Pharmaceutical Sciences. Vol (4) Issue (15), 24-35.

13. Ahmed M. A. Masaad, Ibrahim M Maghrabi, (2016) Bioequivalence Study of A newly Formulated Effervescent Ciprofloxacin Tablets With reference Tablets in Rabbits. International Journal of Current Research In Chemistry And Pharmaceutical Sciences Vol(3) Issue(5), Pp:11-20.

14. Ahmed. M.a. masaad, Mohammed. E.A. Shayoub, Ali.M. Shayub formulation of Effervescent Ciprofloxacin HClKhartoum Pharmacy Journal, 2012, Pp: 6-12.

15. Ahmed M. A. Masaad; Ibrahim A. Maghrabi; Mohammed E. A. Shayoub; Naglaa (2016). In Vitro-In Vivo Correlation Study of A newly Formulated Effervescent Ciprofloxacin Tablets With reference Tablets. International Journal of Current Research In Chemistry and Pharmaceutical Sciences Vol(3) Issue(6) Pp:1-15. 24.

16. Ahmed M. Masaad, Ibrahim M Maghrabi, Majed M. AlRobaian, Mohammed E. Shayoub. (2016) Improvement in the Characters of a newly formulated Effervescent Ciprofloxacin Tablets by Enhancement in the Excipient Properties of the Formula. International Journal of Current Research In Chemistry and Pharmaceutical Sciences Vol(3) Issue(10), Pp:58-64.

17. European Pharmacopoeia, 4th Edition. (2002), Published by: Directorate for the Quality of Medicine of the Council of Europe, (EDQM), 2002; Pp. 199, 201, 562.

18. British Pharmacopeia (2008), Vol. I and II. The Stationery Office, London.

19. Safila Naveed, Rehman H, Qamar F, Zainab S. (2015). Development of a spectrophotometric method for the assay of Diclofenac potassium JIPBS, Vol 2 (1), Pp. 7-11.

Source of Support: Nil, **Conflict of Interest:** None.