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Original Research Article

Assessment of *In-vitro* dissolution, disintegration time, and acid-neutralizing capacity of Butaproxyvon capsules (Paracetamol 325mg and diclofenac potassium 50mg)

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ABSTRACT

Background: This study was carried out to assess the in vitro dissolution of Butaproxyvon Capsule (Paracetamol 325mg and Diclofenac 50mg) by calculating the percentage mean drug dissolved and disintegration time, as well as acid neutralizing time.
Methods: The capsules were tested using three different types of dissolution medium, including pH6.8 phosphate buffer, pH7.5 phosphate buffer, and pH4.5 acetate buffer. The disintegration apparatus was used to calculate the disintegration time, and the acid neutralizing capacity was determined by titrating the capsule content mix with hydrochloric acid with 0.5N sodium hydroxide.
Results: Acid neutralizing capacity was found 12.33 mEq/g. Disintegration time was found in the range of 4.40 to 10.00 minutes. % Mean Paracetamol release was found to be almost similar after 60 minutes in all media. % Mean Diclofenac Potassium release was to be found almost similar after 60 minutes by using pH 6.8 and pH 7.5 phosphate media.
Conclusion: % Mean drug released for Diclofenac Potassium was found 13% in 4.5 Acetate media, and the released pattern was not uniform. This may be attributed to the low solubility of Diclofenac potassium in 4.5 Acetate media.

1. Introduction

Paracetamol and Diclofenac potassium combination are the most commonly used combination because of their antipyretic and analgesic properties.[1] Paracetamol is widely available for purchase by the public, alone or in combination. Prescription pain relievers also contain the drug in combination with opioids.[2] Diclofenac with paracetamol is used to treat a variety of conditions due to its analgesic, anti-inflammatory, and antipyretic properties. The primary motivations for developing combination analgesics are to improve efficacy and reduce toxicity.[3]

Paracetamol is the most commonly prescribed analgesic and antipyretic agent to treat fever, headaches, and other minor aches and pains. 4-hydroxy acetanilide is the chemical formula acetaminophen. In general, at recommended doses, (for adults and children 12 years and over are 500 mg to 1000 mg every four to six hours, and the maximum dose of 4000 mg in any 24 hours) paracetamol is safe for human consumption.[4] Paracetamol's analgesic action is due to its inhibition of the cyclooxygenase (COX-2) pathway in the central nervous system, which reduces the production of pain-mediating prostaglandins.[5]

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Diclofenac is the sodium salt of phenylacetic acid. Diclofenac may be unique among NSAIDs in its pharmacological effect on the arachidonic acid cascade due to three potential mechanisms of action. First, Diclofenac inhibits the cyclooxygenase (COX-2) pathway, resulting in a decrease in prostaglandin and thromboxane production. Second, Diclofenac reduces leukotriene production, implying an inhibitory effect on the lipoxygenase pathway. Third, arachidonic acid availability is reduced by inhibiting its release and stimulating its reuptake. In terms of cyclooxygenase inhibition, diclofenac is 3-1000 times more potent than other NSAIDs on a molar basis.[6]

The Biopharmaceutics Classification Scheme (BCS) uses the link between solubility, permeability, and human dosage to assess the potential impact on human absorption. For instance, molecules in class I are thought to be extremely soluble and permeable. Class II molecules are permeable yet have a limited ability to dissolve. Class III molecules have good solubility but poor permeability, while Class IV molecules have both poor permeability and solubility. However, BCS can be helpful early in development as a tool to predict drug features as an assist to drive drug discovery. Careful BCS determination is often done later in drug development for compounds that have been chosen to advance into Phase 1 clinical testing. Paracetamol has a high solubility in water and low permeability therefore classified as a BCS class III drug. Diclofenac potassium has low solubility and high permeability, therefore, classified as a BCS class II drug.[7]

The safety and efficacy of a pharmaceutical dosage form can be defined when its quality is reliable.[8] The efficacy of pharmaceutical dosage forms generally depends on their formulation properties and manufacturing methods.[9] These formulating properties involve particle size, disintegration time, solubility, and drug dissolution.

When it comes to pharmaceutical formulations, drug solubility, disintegrating and dissolution are the key elements that affect how well-soluble drugs are absorbed orally.[10]

The therapeutic efficacy of the drug is directly impacted by the disintegration performance, which must be evaluated and preferably, measured using specially created disintegration assays. For most solid dosage forms, the disintegration process is a crucial step in ensuring and even enhancing the bioavailability of the API.[11]

Dissolution is a process that allows a solid substance to enter the solution. The words "rate of the solution" (dissolution) and "amount that can be dissolved" are not interchangeable since "solubility" refers to the level of dissolution that takes place when a specific set of conditions are met. The Noyes-Whitney equation states that a drug's solubility has a direct impact on its rate of dissolution, which in turn has an impact on how rapidly it is absorbed and made accessible to the body.[12]

Dissolution test is one of the in vitro tests performed to assess the quality of oral pharmaceutical solid dosage forms such as tablets and capsules. In vitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor formulation quality from batch to batch, predict the in vivo performances, and serve as a surrogate for bioavailability and bioequivalence.[13]

The quantity of acid that can be neutralized by an antacid is known as the acid-neutralizing capacity (ANC). The ANC test is described as a back-titration method by the United States Pharmacopoeia (USP) that uses sodium hydroxide (0.5N solution) to a predetermined endpoint of pH 3.5 to ascertain how many milliequivalents of acid (hydrochloric acid 1N solution) are neutralized by the minimal labeled dosage (MLD) of an antacid.[14]

Although the majority of paracetamol is still absorbed in the stomach, it tends to break down and enter the bloodstream more quickly in the less acidic environment of the intestines when taken orally. Acetaminophen is also easily dissolved in water, making it possible to conduct experiments using water as a versatile media. The use of pH buffers in antacids, which neutralize the stomach's produced acid to treat ailments like heartburn, is a form of the drug. A tablet antacid would have less of an effect than a liquid antacid, similar to how most other medications work because a tablet has a far less surface area than a liquid. Some antacids can create a substance that shields the esophagus from stomach acid secretions in circumstances like acid reflux when mixed with alginates according to the International Foundation for Gastrointestinal Disorders [IFFGD], 2019.[15]. The neutralization of stomach acids has been reported to increase the absorption of some medications in studies on antacids. This would be clinically significant in that it would hasten the onset of pain relief with painkillers like paracetamol.

Additionally, quality control parameters and tablet physical characteristics are helpful tools for preserving consistency in batch-to-batch manufacturing and ought to be used for every medication product. According to Awofisayo et al. (2010)[16] and Jain et al. (2012)[1], all these characteristics are intimately related to one another and affect drug absorption, bioavailability, etc. Because consistent quality parameters are crucial for producing better-quality drugs[17] the study's goal was to evaluate the parameters such as in vitro dissolution, disintegration time, and acid neutralizing capacity of the Butaproxyon (Paracetamol 325mg and Diclofenac potassium 50 mg) capsules.

2. Materials and Methods

The methodology was intended for the Acid-Neutralizing capacity test, Disintegration test, and In-Vitro Dissolution test study of Butaproxyvon Capsules (Paracetamol and Diclofenac potassium 325mg and 50mg) manufactured by

Dr. Reddy's Laboratories Limited.

2.1. In-vitro dissolution test

Dissolution was carried out using Apparatus II of USP (Paddle) with Japanese Sinkers

Dissolution of the capsules was carried out in 12 vessels, each containing 900 ml of dissolution media at 75 rpm maintained at 37°C ± 0.5°C. The dissolution study was performed separately for all the different dissolution media i.e. Acetate buffer (pH 4.5) and phosphate buffer (6.8 and 7.5). After a specified interval, 10 ml of the aliquots were withdrawn from each vessel and filtered through a 0.45μm nylon filter.

In the case of the Diclofenac estimate, the filtrate was used as same, but for Paracetamol the filtrate of 4ml was diluted up to 50 ml. The concentration and quantity of the active pharmaceutical ingredients in each sample were determined using liquid chromatography.

3. Test Procedure for Chromatographic Estimation

3.1. Preparation of buffer pH 7.0

Dissolved 2.72 g potassium dihydrogen phosphate in 1000 mL water, adjusted to pH 7.0 ±0.05 with triethylamine and mixed. Filter the solution with a 0.45 membrane filter to the solution.

3.1.1. Preparation of mobile phase

Prepare a mixture of buffer pH 7.0 and acetonitrile in the ratio of 70:30 v/v and Degas.

Recorded the chromatograms after injecting dissolving media as a blank (one injection), standard solution (five injections), and sample solution (one injection). Analyte peak area counts were measured.

3.1.2. Chromatographic condition

1. *Column:* Hypersil BDS, C8, 250 x 4.6 mm, 5μ or Equivalent
2. *Flow Rate:* 1.0 mL/min (Flow gradient)
3. *Wavelength:* 280nm for Diclofenac potassium: 246nm for Paracetamol Column
4. *Temperature:* 30°C.
5. *Injection Volume:* 20μL.
6. *Run Time*: 15 minutes

The column efficiency for the Paracetamol and Diclofenac potassium peaks derived from standard solution should be at least 3000 theoretical plates. The tailing factor for each analyte peak should be between 0.8 and 2.0 from the standard solution. The relative standard deviation for the Paracetamol and Diclofenac potassium peaks in Standard Solution should not exceed 2.0. The % dissolution of Paracetamol and Diclofenac potassium was calculated.

3.2. Disintegration time

Six Butaproxyvon capsules (Paracetamol 325mg and Diclofenac 50mg) were chosen to determine the disintegration time. Each capsule of Butaproxyvon was inserted in six tubes of disintegration apparatus, the disc was added, and the assembly was suspended in water at 37°C ±0.2°C. The test was repeated until all the residues were removed from the mesh, and the time was recorded.

3.2.1. Acid Neutralizing capacity study

The method's reference was obtained from USP Chapter 301 –acid-neutralizing capability. The equipment and reagents used during the test are as follows

1. *Reagents:* Sodium Hydroxide pellets, AR grade Hydrochloric Acid, HPLC grade Water, Milli-Q
2. *Equipment:* Magnetic stirrer Calibrated pH Meter Motor and Pestle Burette

3.2.2. Preparation of 0.5 N sodium hydroxide solution

In a 500 mL volumetric flask, add 300 mL of water, and 10 g of sodium hydroxide pellets, sonicate to dissolve, then make up with Milli Q water and mix.

3.2.3. Preparation of 1.0 N hydrochloric acid solution

In a 500 mL volumetric flask, add 300 mL of water, and 42.5 mL of concentrated HCl, sonicate to dissolve, then make c up with Milli Q water and stir.

3.2.4. Determination of acid neutralizing capacity

Weigh not less than 20 Butaproxyvon capsules (Paracetamol 325mg and Diclofenac 50mg). Remove the capsule contents entirely, using a cotton swab if necessary. Weigh the empty capsules precisely and calculate the average weight of the contents of each capsule. To get a homogeneous mixture, combine the capsule contents. Fill a 250 mL beaker with a properly weighed amount of it, equal to the minimum specified dosage. Mix for 1 minute on the magnetic stirrer with 70 mL of water. While continuing to swirl the magnetic stirrer, pipette 30 mL of 1.0 N hydrochloric acid volumetric solutions into the test preparation (250 mL beaker). After adding the acid, stir for 15 minutes and begin titrating immediately and at a time. Excess hydrochloric acid was titrated with 0.5 N sodium hydroxide volumetric solutions for 10 to 15 seconds to achieve a stable (for 10 to 15 seconds) pH of 3.5 then determine the amount of acid consumed in mEq.

4. Results

4.1. Dissolution time study

The process by which a medicine dissolves into a solution is known as dissolution. The dissolution test determines the extent and rate of solution production from a dosage form

such as a tablet, capsule, ointment, and so on. A drug's dissolution is critical for its bioavailability and therapeutic effectiveness.

Observation

1. *Paracetamol:* In 60 minutes, the mean drug release for Paracetamol was determined to be 96.2%. The maximum amount of drug released in pH 7.5 phosphate buffer was found in 30 minutes.
2. *Diclofenac potassium:* In 60 minutes, 99.6% of the Diclofenac potassium was released. The greatest amount of drug released was discovered in 10 minutes in pH 7.5 phosphate buffer.

Observation

1. *Paracetamol:* In 60 minutes, the mean drug release for Paracetamol was determined to be 96.1%. The maximum amount of drug released in pH 6.8 phosphate buffer was found to be in 30 minutes.
2. *Diclofenac potassium:* In 60 minutes, the mean drug release for Diclofenac potassium was found to be 98.4%. The maximum amount of drug released was found to be in 10 minutes in pH 6.8 phosphate buffer.

Observation

1. *Paracetamol:* In 60 minutes, the mean drug release for Paracetamol was determined to be 97.6%. The maximum drug release in time was found to be 30 minutes.
2. *Diclofenac potassium:* In 60 minutes, 13.0% of the Diclofenac was released in pH 4.5 acetate buffer. Diclofenac's release was not consistent. This could be related to Diclofenac potassium's limited solubility in the media.
3. *Paracetamol:* After 60 minutes, the % Mean drug released was found to be nearly identical in all three different media for paracetamol.
4. *Diclofenac potassium:* After 60 minutes, the mean drug release for Diclofenac potassium was identical in two phosphate media, pH 6.8 and pH 7.5. The mean drug released for Diclofenac Potassium was 13% in pH 4.5 Acetate media, and the released pattern was not uniform, which could be attributable to Diclofenac potassium's poor solubility in pH 4.5 Acetate media.Tables 1 and 2

4.2. Disintegration time (DT)

The Disintegration Time (DT) determines if tablets, capsules, granules, or pills disintegrate within the specified period when placed in a liquid medium under experimental conditions. Six Butaproxyvon capsules were used in the disintegration investigation. The results are shown in the table below.Table 3

Table 1: Mean dissolution of paracetamol in different pH media

Time/Media	Mean Drug Release- Paracetamol		
	pH 7.5	pH 6.8	pH 4.5
10 minutes	92.7	91.4	93.7
20 minutes	96.6	94.2	98.1
30 minutes	97.3	96.2	97.2
60 minutes	96.2	96.1	97.6

Table 2: Mean dissolution of diclofenac in different pH media

Time/Media	Mean Drug Release- Diclofenac		
	pH 7.5	pH 6.8	pH 4.5
10 minutes	99.3	97.9	32.1
20 minutes	100.1	99.3	15.7
30 minutes	100.1	98.5	13.2
60 minutes	99.6	98.4	13

Table 3: Result of disintegrating time of Butaproxyvon

No. of Capsule	Disintegration Time (Minutes)
1	4.40
2	4.50
3	8.45
4	5.00
5	9.20
6	10.00
Range	**4.40 to 10.00**

According to the results, the disintegration time was found to be between 4.40 and 10.00 minutes

4.3. Acid neutralizing capacity

Acid Neutralizing power is a measure of a solution's overall buffering power against acidification. It is measured in milliequivalents of acid consumed per gram of material (mEq/g)Table 4

Table 4: Results of acid neutralizing capacity of Butaproxyvon

mEq Results per gram (g)				
Result 1	Result 2	Result 3	Mean	%RSD
12.12	12.53	12.33	12.33	1.66

According to the findings, the Mean Acid Neutralizing Capacity of Butaproxyvon Capsules was 12.33

5. Discussion

Capsules are typically powder compacts that include the API and a variety of excipients inside a gelatin capsule shell that can be either hard or soft.[18] Excipients are included in a formulation to help it process more easily, obtain the appropriate fill weight for a dosage form, or modify how medicine will behave after it is released into the body1. When capsules interact with bodily fluids, they proceed through many methods.[19] The disintegration and dissolving behavior of the powder compact have a significant impact on a drug's efficacy.

Considering the results of disintegration time was found to be between 4.40 and 10.00 minutes. In the case of the disintegration time of capsules, there are no official limits specified ideally unless not specified in the monograph it should disintegrate in 20 minutes but should not exceed more than 25 minutes. From the above specifications, the Butaproxyvon capsule's disintegration time was found to be within the given limits.

Following the disintegrations, the capsules were put through a dissolution test in three different dissolution media (phosphate buffer pH 6.8 and pH 7.5 and acetate buffer pH 4.5); according to the results, the release of paracetamol was highest in pH 4.5 and the least for diclofenac because of its solubility restriction. While pH 7.5 and pH 6.8 were both above 95% of those cases.

A study conducted by Michael u. Uhumwangho et al stated that the capsules disintegrated rapidly within 2 to 3 minutes. And the capsules displayed a faster dissolution compared with the tablets. Similarly, the Butaproxyvon capsules disintegration time was found to be 4 minutes and then, the % mean drug release for paracetamol was found to be nearly the same in all the dissolution mediums but in the case of Diclofenac, it was found, same for pH 7.5 and pH 6.8 phosphate buffer. In pH 4.5 acetate buffer the % mean drug release was 13% due to the low solubility of Diclofenac in the acetate buffer**.**

An acid neutralizing capacity test was performed on the content of the capsules and mixing it with the 0.1N hydrochloric acid solution and titrating against 0.5N sodium hydroxide and calculating the milliequivalents (mEq), and it was found to be 12.33 milliequivalents.

6. Conclusion

The present studies of the in vitro drug release profile demonstrated significance for Paracetamol in all three-dissolution mediums (phosphate buffer pH 7.5 and pH 6.8, acetate buffer pH 4.5), but the release was less for Diclofenac potassium due to its low solubility in the acetate buffer. Therefore, this formulation of Butaproxyvon was determined to be promising and a prospective alternative to the standard dosage form based on the values of acid neutralizing, disintegration time, and% mean dissolution.

7. Source of Funding

None.

8. Conflict of Interest

None.

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