



COMPARATIVE IN VITRO DISSOLUTION STUDY OF A NOVEL ACECLOFENAC AND PARACETAMOL FIXED DOSE COMBINATION WITH MARKETED FORMULATION IN INDIA

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ABSTRACT:

Introduction: Aceclofenac has low aqueous solubility leading to poor dissolution and insufficient oral bioavailability. The improvement of its dissolution is an important issue for enhancing its onset of action and therapeutic efficacy.

Aim: To compare in vitro dissolution of a novel aceclofenac and paracetamol fixed dose combination with reference product available in India.

Methods: The new formulation consists of paracetamol and aceclofenac (Ace-Proxyvon) as the active ingredients blended in a readily dispersible matrix with a combination of Effer-soda[®] and novel combination of buffer salts. This new formulation was compared with the reference brand available in Indian market. A comparative dissolution study was performed in pH 4.5 acetate buffer. Peak area of Ace-Proxyvon and reference product were measured and recorded on High Performance Liquid Chromatography system.

Results: The invitro release data (cumulative percent drug release) have been plotted against time to get a graphical presentation of the data. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. Around 64% of aceclofenac and 88% of paracetamol were released within 15 min from Ace-Proxyvon as compared to 32% of aceclofenac and 79% of paracetamol from reference product in 500 ml, pH 4.5 acetate buffer.

Conclusion: In this study, aceclofenac showed faster dissolution as compared to reference product in 500 ml, pH 4.5 acetate buffer. The addition of novel excipients like Effer-soda[®] and combination of buffer salts can lead to faster onset and better therapeutic efficacy of Ace-Proxyvon as compared to reference product.

KEYWORDS: Solid dosage form, Aceclofenac, Paracetamol, invitro dissolution, onset of action

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INTRODUCTION:

Drug dissolution testing is an analytical technique used to assess release profiles of drugs from pharmaceutical products, generally solid oral products such as tablets and capsules¹. If a drug from its dosage form has to produce its effect, it must be released from the product and should generally be dissolved in the fluids of the gastrointestinal tract. The main purpose of solid dosage form is to make a drug available to the human body at a certain rate and define amount through the GIT so that the drug can produce pharmacological effects. But studies on bioavailability of drugs from a given dosage form revealed that, in many situations, solid dosage forms did not give the same therapeutic effects. This is mainly due to the insufficient dissolution and subsequent absorption of the drug from the GIT. So, dissolution analysis of pharmaceutical solid dosage forms is a very important test of product quality².

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenyl acetoxyacetic acid) is a non-steroidal anti-inflammatory drug (NSAID) of phenyl acetic acid group, which possesses remarkable anti-inflammatory, analgesic and anti-pyretic properties^{3,4}. It is widely used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The dose is 100 mg twice daily. Aceclofenac shows comparatively higher anti-inflammatory action than conventional NSAIDs^{5,6,7}. The drug works by blocking the action of cyclooxygenase that is involved in the production of prostaglandins causing pain, swelling and inflammation. Aceclofenac appears to be well tolerated among NSAIDs with a lower incidence of gastrointestinal adverse effects⁸. Unfortunately aceclofenac suffers from low aqueous solubility (0.058 µg/ml), leading to poor dissolution and insufficient oral bioavailability. The biopharmaceutical classification system (BCS) divides all drug candidates into four different groups, according to their solubility and permeability⁹. Aceclofenac is an example of BCS class II compound (highly permeable & low soluble)^{10, 11}; its oral bioavailability is determined by dissolution rate in the gastrointestinal tract^{12,13}. Therefore the improvement of Aceclofenac dissolution is an important issue for enhancing its onset of action and therapeutic efficacy.

Aceclofenac is soluble in the alkaline environment (pH 7-7.5) and it is practically insoluble in gastric pH of 1-1.5¹⁴. Since the drug dissolution in the physiological environment of the GI tract is the primary step in the oral absorption process, only dissolved drug can permeate the mucosa at the absorptive sites in the GI tract¹⁵. Therefore for Aceclofenac, relief from pain would be unlikely until the drug traverses the intestinal part (pH 6 and above) which takes about 1-2 hours. To provide faster pain relief the dissolution of Aceclofenac in the gastric fluid is of prime importance. With this rationale a new fast disintegrating and rapidly soluble tablet was developed at Wockhardt Research and Development Centre. The formulation consists of paracetamol and aceclofenac as the active ingredients blended in a readily dispersible matrix with a combination of Effer-soda[®] and superdisintegrants (sodium starch glycolate) and a novel combination of buffer salts to provide a pH micro-environment suitable enough to increase the solubility of aceclofenac.

To assess the standard of a product, in vitro dissolution test is widely used because, for any solid dosage forms, gastrointestinal absorption first requires dissolution of the tablet or capsule that liberates the drug into solution¹⁶. The dissolution characteristic of a drug from the dosage form depends on many factors including its formulation and manufacturing process¹⁷. This study deals with the assessment of comparative dissolution profile of aceclofenac and paracetamol fixed dose combination (FDC) Tablets of M/s Wockhardt (Ace-Proxyvon) & reference marketed formulation.

MATERIALS AND METHODS:

Drug: Aceclofenac WS (Amoli Organics Pvt. Ltd., India), Paracetamol WS (Bharat Chemicals)

Solvents and reagents: Sodium acetate trihydrate (AR Grade) (Merck, India), Acetonitrile (HPLC Grade) (Merck, India), Methanol (HPLC Grade) (Merck, India), Triethylamine (GR Grade) (Merck, India), Acetic acid (GR Grade) (Merck, India), Potassium dihydrogen phosphate (GR Grade) (Merck, India), Sodium hydroxide (GR Grade) (Merck, India), Sodium Acetate Trihydrate (GR Grade) (Merck, India), Acetic Acid (GR Grade) (Merck, India), Water (Milli-Q / HPLC Grade).

Equipments: HPLC system (Waters Alliance), Digital pH meter (Orion Star A211), Tablet dissolution tester (Electro lab, India), Electronic balance (Metler Toledo)

Dosage forms

Ace-Proxyvon tablets, manufactured by – Wockhardt Limited was compared against reference aceclofenac and paracetamol fixed dose combination formulation available in the market.

These samples were properly checked for their batch number, manufacturing and expiry dates before the study. The labelled active ingredients were Aceclofenac 100 mg and Paracetamol 325.

In discriminatory and biorelevant dissolution medium

A discriminatory and biorelevant dissolution system able to simulate the conditions of the human GI tract in terms of dosing conditions and therapeutic objective was selected. Since NSAIDs are recommended to be administered after meals and typical pH values measured soon after food intake ranges from 4-4.5, a 4.5 acetate buffer medium which reflects the GI conditions that is relevant to drug release from this formulation was selected. Further with respect to the volume of the medium, gastric juice secretion is usually low in fasted state with the result that the volume of fluid available to dissolve the dose is much lower than the standard dissolution test volume of 900 ml or 1000 ml. Taking into account the co-ingested fluid and food a more reasonable volume is in the order of 400-500 ml. In this study, dissolution parameter was: Dissolution Medium- 500 ml, pH 4.5 Acetate Buffer, Dissolution Apparatus- USP apparatus II (Paddle) RPM: 50, Temp of dissolution medium: $37\pm 0.5^{\circ}\text{C}$.

Preparation of dissolution medium: (pH 4.5 Acetate buffer):

2.9 g sodium acetate trihydrate was dissolved in 900 ml water. 14 ml of 2N acetic acid was added and diluted to mark 1000 ml with water. If necessary, pH was adjusted to 4.5 ± 0.05 with dilute acetic acid or 2N sodium hydroxide.

Preparation of Standard Solution:

Accurately weighed 28 mg Aceclofenac and 90 mg Paracetamol working standard were transferred to 50 ml volumetric flask. 5 ml methanol was added to it and sonicated to dissolve and was diluted to the mark

with dissolution media and mixed. 5 ml of this primary stock solution was taken in 25 ml volumetric flask and diluted to mark with dissolution media and mixed.

Performance of Dissolution study:

500 ml, pH 4.5 Acetate Buffer

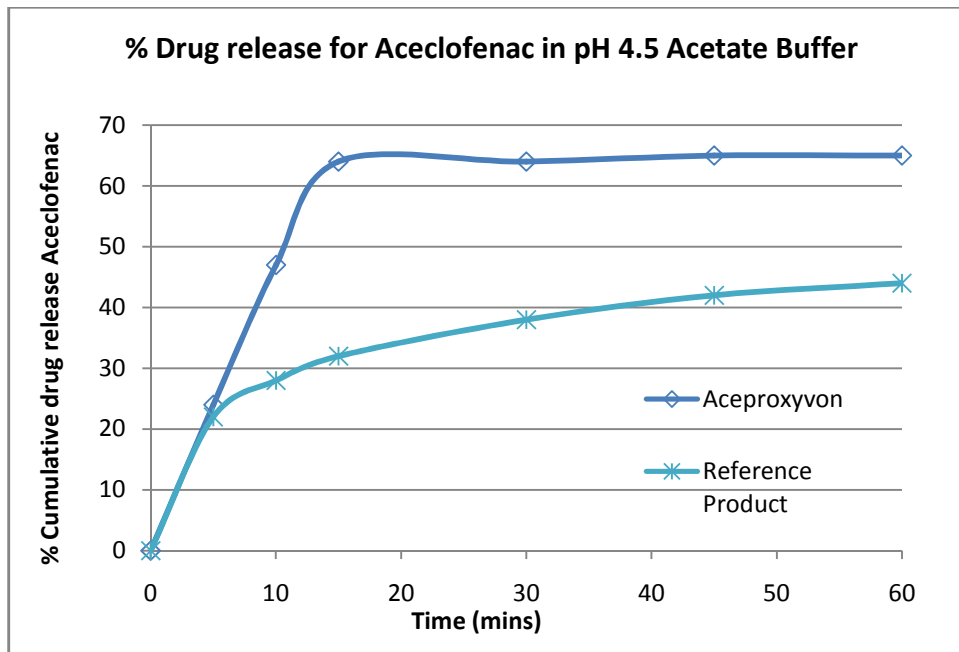
500 ml medium was added to each vessel and waited till media temperature was not achieved to $37\pm 0.5^{\circ}\text{C}$ for each vessel. The apparatus II (paddle) was then assembled and rotation set to 50 rpm and then system was allowed to equilibrate for 15 minutes. Six tablets of each manufacturer were dropped in each vessel and apparatus was immediately operated for 60 minutes for each set of sample. Six time points were selected for dissolution profile at 5, 10, 15, 30, 45, 60 min. 10ml of aliquot was withdrawn from each timepoint and filtered through 0.45μ nylon filter. Dissolution medium as injected in HPLC as blank, standard solution (five injections) and sample solution (one injection). Peak area of standard and samples were measured and recorded on HPLC system.

RESULTS

Drug dissolution profiles may be distinct due to differences in formulations and manufacturing processes, but the differences must not compromise product bioequivalence. The in-vitro release data (cumulative percent drug release) have been plotted against time to get a graphical presentation of the data. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. The release profiles of different brands of aceclofenac and paracetamol FDC tablets are shown in Fig. 1 & 2 and Table 1 (500 ml, pH 4.5 Acetate Buffer). During first 10 mins 47 % of aceclofenac was released from Ace-Proxyvon as compared to 28% from reference brand. Around 64% of aceclofenac and 88% of paracetamol were released within 15 min from Ace-Proxyvon as compared to 32% of aceclofenac and 79% of paracetamol from reference product in 500 ml, pH 4.5 acetate Buffer. At 1 hr around 65% of aceclofenac and 90% of paracetamol were released from Ace-Proxyvon as compared to 44 % of aceclofenac and 84% of paracetamol from reference product.

Table 1: Comparative Dissolution Study

	Dissolution for Aceclofenac		Dissolution for Paracetamol	
Medium	pH 4.5, Acetate Buffer		pH 4.5, Acetate Buffer	
Apparatus	Paddle		Paddle	
Volume	500 ml		500 ml	
RPM	50		50	
Time point	Ace-Proxyvon	Reference brand	Ace-Proxyvon	Reference brand
5	24	22	64	66
10	47	28	85	76
15	64	32	88	79
30	64	38	88	82
45	65	42	88	83
60	65	44	90	84

Results in 500 ml, pH 4.5 Acetate Buffer**Figure 1: % Drug release for aceclofenac in pH 4.5 acetate buffer**

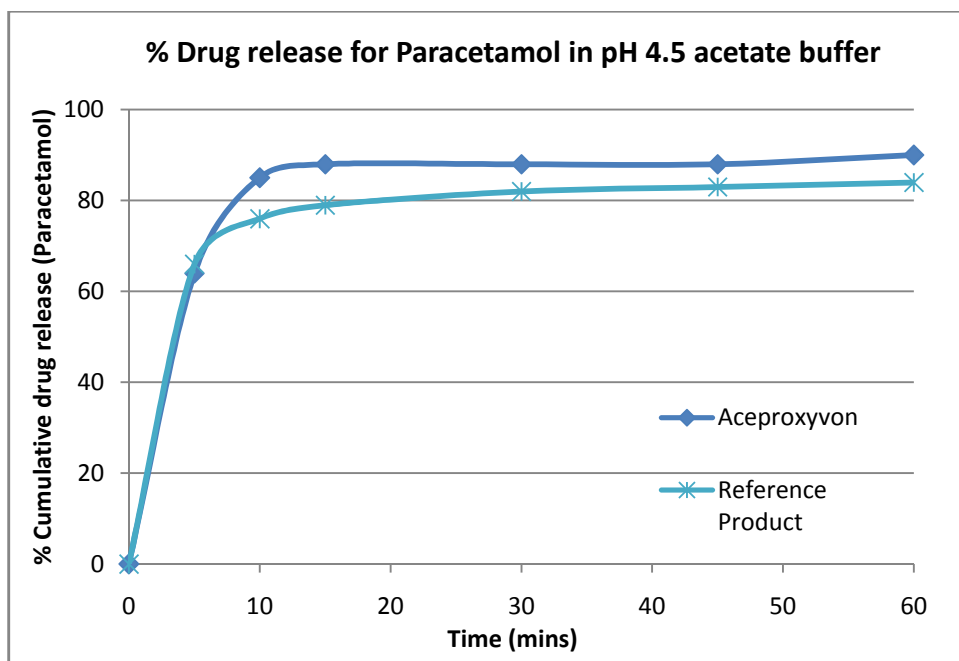


Figure 2: % Drug release for paracetamol in pH 4.5 acetate buffer

DISCUSSION:

Drug dissolution testing is a quantitative analytical technique for assessing drug release from pharmaceutical products, in particular solid oral dosage forms such as tablets and capsules¹⁸. The reason for conducting the test is that generally for a drug to be absorbed, usually from the gastrointestinal tract, the drug should be in solution form. Thus evaluation of dissolution becomes useful and necessary^{19,20,21}. Faster dissolution of aceclofenac seen in this study may have been due to the presence of superdisintegrants and some special alkalizing agents in the formulation which increase the pH of the dissolution media and facilitate drug release. Superdisintegrants like sodium starch glycolate is used as a pharmaceutical grade dissolution excipient for tablets and capsules. Sodium starch glycolate absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets. C. Mallikarjuna Setty et al. also demonstrated that fast-dispersible aceclofenac tablets could be prepared by direct compression using superdisintegrants²².

Effer-Soda[®] is a highly stable, surface modified sodium bicarbonate powder developed for use in

pharmaceutical and nutraceutical applications²³. Effer-Soda[®], is a novel excipient comprising of coated sodium bicarbonate which provides stability to the formulation against moisture and helps in creating an alkaline micro-environment for the dissolution enhancement of drugs having solubility in alkaline environment. Aceclofenac is soluble in the alkaline environment (pH 7-7.5) and it is practically insoluble in gastric pH of 1-1.5. Therefore by creating alkaline microenvironment, the increased dissolution of aceclofenac was seen in the pH 4.5, which also mimics the pH of stomach in fed conditions. Similar results were also reported by Srivastav et al. (2011) in case of gliclazide, a poorly water soluble drug²⁴.

CONCLUSION:

The present study demonstrates that novel aceclofenac and paracetamol fixed dose combination developed by Wockhardt Research Centre shows faster dissolution as compared to reference product. Unique excipient combination of buffer salts, surface modified sodium bicarbonate and superdisintegrants have resulted in increased solubility & faster dissolution of aceclofenac. This enhancement in dissolution rate may further result in rapid onset of action and better therapeutic efficacy.

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