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# Comparative study of marketed tablets of analgesic and antipyretic drugs

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**ABSTRACT**

**DOLO tablets are popular OTC products among patients marketed by a lot of suppliers around the world, being extensively used as antipyretic and general analgesic. The purpose of this research work was to compare and evaluate quality standards in the various brands of DOLO tablets marketed in Maharashtra state. Six different brands of DOLO 500mg manufactured by multinational companies and local companies were randomly sampled from different Pharmacy shops. The study was exclusively experimental that used BP, USP and other official books to assess the in vitro quality of DOLO tablet using different analytical techniques and procedures. Evaluations of parameters were performed through the determination of weight variation, hardness, friability, drug content, and disintegration time and dissolution profile. All brands showed acceptable weight variation and friability except one which was more fragile. Percentage content for analyzed samples by UV method ranges from 92.32-102.2% indicating none of the brand contains less than 92% of the active principle. The physical and chemical tests like in-vitro dissolution, disintegration, hardness etc. were found to be varying but within the specified limits. It can be concluded that DOLO brands of local companies are safe enough and could be used to achieve desired therapeutic effects.**

**Keywords: DOLO, Quality Control Parameters, Evaluation, Local brands, Multinational brands.**

## INTRODUCTION

DOLO is one of the most popular and widely used drugs for the treatment of pain andfever1. It has a very similar structure of aspirin and because of this they are recognized by the same enzyme2. The enzyme is responsible for biosynthesis of prostaglandins which are involved in the dilation of blood vessels that cause the pain experienced in a headache. Reduction of the amount of prostaglandin, therefore helps prevent headache and other pain like migraine headache, muscular aches, neuralgia, backache, joint pain, rheumatic pain, general pain, toothache, period pain and also used for the reduction of fever of bacterial or viral origin. It is suitable for most people, including elderly and young children, because it has very few side effects3. DOLO is chemically N-(4-hydroxyphenol) acetamide.

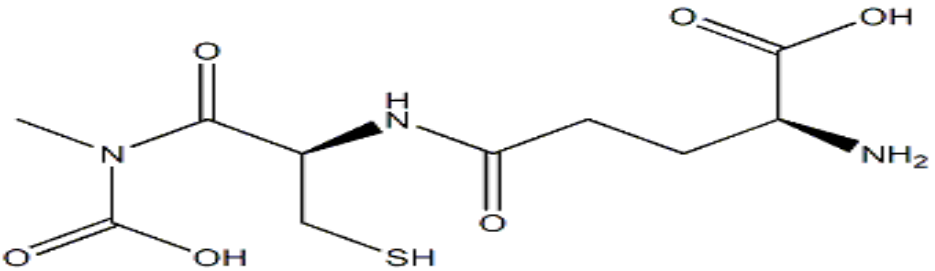


**Figure 1: Structure of DOLO**

DOLO is classified as biopharmaceutics classification system (BCS) class I drug.4 It is weak acid with a pKa of 9.0.5 DOLO, like many other analgesics, has a short half-life around 2-3 hours which necessitates frequent dosing.6 In UK the recommended regimen is500-1000 mg every 4-6 hour. DOLO is well absorbed from the proximal small bowel and is not subject to significant first pass metabolism in the liver, with oral bioavailability estimated at between 63-89% in adults7,8.

DOLO is not significantly bound to plasma, proteins, and has a volume of distribution of 0.7-1 L/Kg. Maximal analgesic and antipyretic activity occur 1-2 hour after peak plasma levels7,9, and the time to achieve this varies with the route of administration. Metabolism of DOLO occurs primarily in the liver, whale estimation occurs a most entirely through the kindly following absorption of therapeutic doses, approximately 90% is metabolized by glucuronidation and sulphonation to form nontoxic metabolites, which are exerted in the urine. Quality control procedures, which are useful tools for batch-to-batch consistency in manufacturing, should be performed for every drug product. Drugs having more than three generic products require analysis for their biopharmaceutical and chemical equivalency. These methods ensure that any of the generic products can be used interchangeably. This observation is that most of the generics have much raises the issue of the likelihood of unequal product performance. Pharmaceutical test used in assessing the equivalence includes weight uniformity, crushing strength, friability test, disintegration time, dissolution rate and chemical assay. The aim of the work as a surveillance study is to assess the product quality of different generics of DOLO tablets, sourced from different pharmaceutical manufacturer's representatives in India by evaluating their pharmaceutical and chemical equivalence in order to determine the appropriateness of their interchangeability.

DOLO (DOLO) is a non- steroidal anti-inflammatory drug (NSAID) and is prescribed most frequently. It is widely used over- the-counter analgesic and antipyretic drug. Generally, it is used to treat headache, other minor aches, pain and as in cold and flu remedies. It could also be used in the management of more severe pain in cancer in combination with other drugs. Generally, DOLO is safe for human use at recommended doses. It is used for the relief of pain associated with many parts of the body. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin in patients whom excessive gastric acidsecretion or prolongation of bleeding time may be a concern. Available without a prescription, it has in recent years increasingly become a common household drug. In addition, safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable. Generally, the efficacy of pharmaceutical dosage forms depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary. Dissolution test is one of the in vitro tests usually employed to assess the quality of oral pharmaceutical solid dosage forms such as tablets and capsules. Invitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor formulation quality from batch to batch and also serve as a surrogate for bioavailability and bioequivalence.

Drug products that are chemically and pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and should be in the same dosage form, for the same route of administration. Any substantial variations in the dissolution rate among same generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution testing of drug products plays an important role as a quality control tool to monitor batch to batch consistency of drug release and also for prediction of in-vivo bioavailability in most oral preparations. To this extent, manufacturing methods, coupled with excipients used in the production processes, could contribute to the overall quality and release proficiency of medicament. Therefore, in order to ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing. and at various intervals during the shelf life of the product. As such the need to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized and the necessity to select oneproduct from several generic drug products of the same active ingredients during the course of therapy is always a cause for concern to healthcare practitioners [7, 8]. The present study was conducted to evaluate the pharmaceutically and chemical equivalency of different DOLO brands marketed in the Middle East. The difference between the dissolution profiles was determined to identify the critical manufacturing variables and to predict the in vivo performances. Additionally, the stability of the tested brands by storage at temperatures 4ºC, 25ºC and 40ºC at 75% relative humidity over a period of two months was performed. Then the tablets were evaluated for their physical properties and their release kinetics. Statistical data analysis and study of the release kinetic were achieved by fitting the data to the release models; Zero order, order, Hixon–crewel, Higuchi and Kores Meyer-Peppas. The order and the mechanism of drug release were investigating

## RESEARCH ENVISAGED & PLAN OF WORK

The long-term administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is often limited by the emergence of gastrointestinal or cardiovascular complications. It has been estimated that over two-thirds of regular NSAID users develop gastrointestinal complications. The gastro toxic effects of NSAIDs are caused by the inhibition of protective prostaglandin biosynthesis in the stomach and the direct contact between acidic drugs and mucosal cells. Interestingly, some NSAIDs have been shown to be able to reduced ulcer genic effects, which is attributed to the masking of the carboxylic acid moiety present in these drugs. Therefore, anti-inflammatory and analgesic compounds with a NAH subunit is less likely to induce ulcers than NSAIDs without this subunit.

Several clinical studies investigating the cardiovascular toxicity of NSAIDs have shown that COX-2 and COX-1 inhibitors increase the risk of cardiovascular events, including myocardial infarction. In fact, patients treated with high doses of diclofenac or ibuprofen have a high riskof vascular events, similar to patients treated with coxibs.

These deleterious effects of NSAIDs seem to be associated with the inhibition of prostacyclin synthesis, increased blood pressure, and oxidative stress-induced endothelial dysfunction.

The objectives of this study were to synthesize prodrug that consist of naproxen separately esterified with DOLO.
The synthesized prodrug esters were identified, and their physicochemical properties were determined using various techniques. Anti- inflammatory and anticoagulant bioactivities of the synthesized prodrugs were also performed.

**Plan Of Work:**

- Literature survey
- Selection, Collection and Authentication of materialFormulation and Optimization
- Evaluation of optimized formula ofStability studies
- The selected research work has to be performed on the basis of following outlines

**1. Preformulation Study**

- The following pre formulation studies will be carried out for drug and polymers;Determination of melting point of drug
- Drug–excipient compatibility studies

**2. MICROMETRICS PROPERTIES**

- Angle of repose
- Bulk density and Tap density
- Carr's consolidation index

## EXPERIMENTAL WORK

**1.MATERIALS AND METHODS**

**Chemicals and Reagents**

The reagents used were ferric chloride, Hydrochloric acid, potassium dichromate, Sodium Hydroxide (Loba Chemise Pvt Co., India) all analytical grade reagent and freshly deionized distilled water used throughout the work.

**Apparatus and Equipment's**

Double beam UV-Visible Spectrophotometer (Jasco 630), Analytical balance (Shimadzu AUW220D), Hardness Tester (Monsanto, Mht-20), Tablet Friability Tester (Roche, FTV-2), Disintegration apparatus (Electro Lab ED-2L), Dissolution apparatus (Electro Lab, EDT-08LX) Drying oven (Meta Lab.) and Ultrasonicate (Toshcon, SW 4).

**Sample Collection**

To perform the study DOLO tablets of six different brands of multinational and local companies were purchased from the pharmacy shops within Marathwada region and coded as A, B, C, D, E and F respectively. All DOLO brands were labeled to contain

500 mg of DOLO per tablet. The commercial brands selected were of different manufacturers. The labeled shelf life of all of the tablets was three years from the date of manufacturing and was taken for the evaluation before two years of the labeled expiry date (Table 1).

**Study Design**

Comparative *in-vitro* quality control parameters between commercially available local pharmaceutical brands with that of multinational pharmaceutical brands were studied through the evaluation of weight variation, hardness, friability, disintegration time, dissolution profile and drug content.

## METHODOLOGY

Various analytical methods and tests are important for the development and manufacture of pharmaceutical formulations. The evaluation was done according to USP and BP standards.

**Identification Test of DOLO**
Two identification tests were conducted in the compliance to the British pharmacopeias.

**Weight Variation**
Tablets of each brand were weighed individually using a digital analytical balance Shimadzu. The percentage deviation of the individual tablets from the mean was determined according to USP.

**Hardness Test**
A tablet was placed vertically on the Monsanto Hardness tester. The load was then applied along the radial axis of the tablet. The weight or load required for breaking the tablet was noted down. Similarly, it was done for 10 tablets.

**Friability**
It was performed using Roche Friabilator, 10 tablets were weighed and placed in apparatus. The apparatus was rotated at a speed of 25 rpm. The apparatus was made to rotate for 4 min. The tablets were then weighed and the weights were compared with the initial weights. The % friability was calculated using the formula. % F = [1 - (W/Wo)] x 100 Where, % F = Friability in %, Wo = Initial weight of tablets, W = Weight of the tablets after revolution.

**Tablet Disintegration**
It was performed using Electro Lab disintegration apparatus, 6 tablets were placed in disintegration test apparatus. It was maintained at 37 ± 0.2$^{o}$C containing simulated gastric fluid (0.1N HCl). Noted down the time taken for tablets to disintegrate.

## RESULTS AND DISCUSSION

The results of the present study conducted on six different brands of DOLO tablets, met the USP and BP requirements of quality control tests within specified limits.

**Weight Variation**
According to official books, the specified limit on weight variation for tablets more than 324 mg is ± 5 %. It was found that all the tablets passed the USP specifications for weight variation as none of the brands deviated by up to ±5% from the mean value. Weight variation gives a rough idea of content uniformity, but not a confirmatory test.

**Friability**
Friability is another important parameter that is related to hardness, disintegration and dissolution. According to the USP. [12] the allowed limit of friability is not more than 1.0 % of weight Loss. The friability was carried out for all the brands. It was less than 1% for all the brands except F tablets that were more fragile (2.0%), which may be due to the nature of the binders and additives used in the manufacturing procedures.

**Hardness**
In the pharmaceutical industry, hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. However, if the hardness exceeds a certain limit, it increases the disintegration time, which ultimately affects the bioavailability. Hardness is not an official test so there is no such a compendial limit for hardness but a crushing strength of between 4 kg/cm$^2$ to 10 kg/cm$^2$ is considered minimum requirement for a satisfactory tablet. The average hardness of the local and multinational brands was within the limits.

**Disintegration Time**
Disintegration could be related to dissolution and similarly availability of drug to body (absorption) and finally the therapeutic efficacy of product. The result showed that disintegration time of all the selected tablets was found to be within specified limits of USP and BP. According to BP [14] (Figure 2), which specifies 15 minutes as disintegration time whereas uncoated USP tablets have disintegration time standards as low as 5 minutes. Total of the results of above evaluated physicochemical parameters were presented.

**Dissolution**
Dissolution of the all the selected brands of DOLO tablets was found to be within the specified limits of not less than 80 % in 30 min (USP) and not less than 70% (BP). Excellent results were obtained for all brands of tablets (Table 4). Depending upon the above facts & cost effectiveness it can be clearly stated that the commercially available local brands are of same quality and clinical effectiveness as the multinational brands available (Figure 4). So, the trends about the local brands

should be changed. Since the analgesic and antipyretic medications containing DOLO are used by patients to relief pain within short time to give the onset of action which depends mainly on the release of the drug.

**Assay**

Test for percentage of content is based on the assay of the individual content of active ingredient of a number of single dose units. All the DOLO tablets i.e., multinational and local brands, contained the DOLO within 100 ±10 % of the labeled claim. The USP and BP specifications for assay are that the DOLO contents should not be less than 90 % and not more then 110 (Table 3). Therefore, the assay results ascertain the presence and compendial quality of the drug in all products.

**Table 1: DOLO brands used in the study**

| Code | Brand name | Batch no. | Date of manufacture | Expiry date | Labeled strength | Manufacturer |
|---|---|---|---|---|---|---|
| A (F1) | Paracip | GS1406 | 06/2011 | 05/2014 | 500 mg | HSN international (Haridwar) |
| B (F2) | Crocin | R1118 | 03/2011 | 02/2014 | 500mg | Remidex Pharma Pvt Ltd. (Bangalore) |
| C (F3) | Calpol | RF461 | 04/2011 | 03/2014 | 500mg | GlaxoSmithKline Pharmaceuticals Limited (Mumbai) |
| D(F4) | Pyrigesic | 0021 | 05/2010 | 04/2013 | 500mg | East India pharmaceutical works limited. |

**Table 2: Comparative evaluation of different quality control parameters of DOLO tablets**

| Tablet Code | Weight Variation % | Friability % | Hardness ($kg/cm^2$) | Disintegration Time (Min.) |
|---|---|---|---|---|
| A | 0.6 | 0.45 | 4.3 | 2 |
| B | 0.9 | 0.34 | 5.3 | 3.2 |
| C | 0.65 | 0.43 | 4.6 | 2.5 |
| D | 0.7 | 0.36 | 5.1 | 3 |
| E | 1.0 | 0.55 | 4.4 | 2.43 |
| F | 1.2 | 2.0 | 4.0 | 2.12 |

**Table 3: Showing result obtained for percent content of DOLO tablets by UV method**

| Tablet Code | Concentration (mg/ml) | Absorbance | % Content | Content (mg) |
|---|---|---|---|---|
| A | 0.000731 | 0.523 | 102.23 | 511.15 |
| B | 0.000700 | 0.501 | 97.0 | 485 |
| C | 0.000696 | 0.498 | 97.34 | 486.7 |
| D | 0.000718 | 0.514 | 100.41 | 502.05 |
| E | 0.000685 | 0.490 | 95.80 | 479.05 |
| F | 0.000660 | 0.472 | 92.32 | 461.6 |

**Table 4: Comparative Evaluation of dissolution profile of DOLO tablets**

| Time interval (Minutes) | % Release of DOLO content | | | | | |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | F |
| 10 | 71 | 77 | 74 | 70 | 67 | 63 |
| 20 | 81 | 87 | 90 | 84 | 82 | 80 |
| 30 | 93 | 94 | 93 | 94 | 91 | 90 |
| 40 | 97 | 96.5 | 97 | 95 | 94.5 | 92 |
| 50 | 99.5 | 91 | 90 | 99 | 89 | 88 |
| 60 | 97 | 89 | 88.5 | 94 | 87 | 86 |

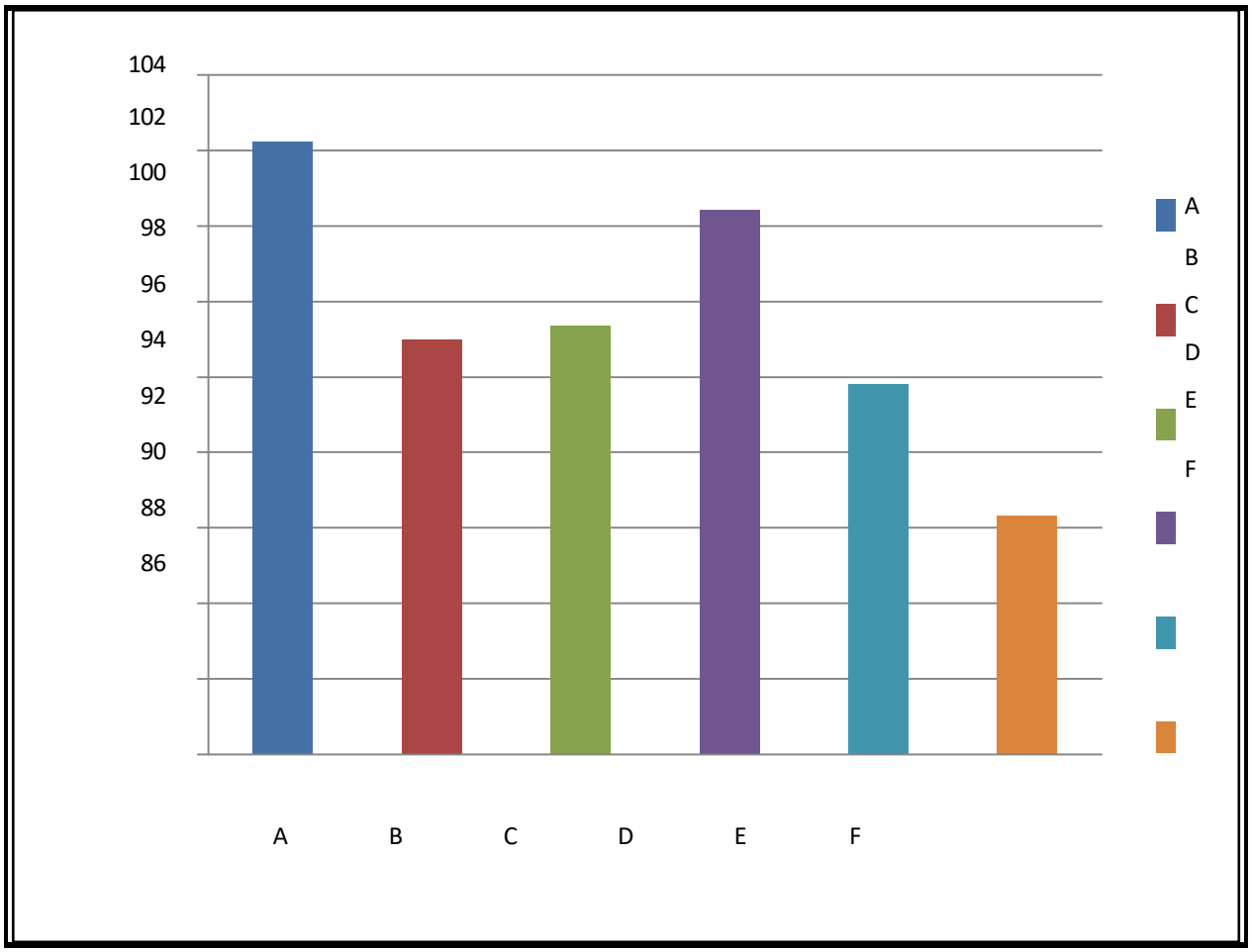


**Fig 2: Assay of different brands DOLO tablets**

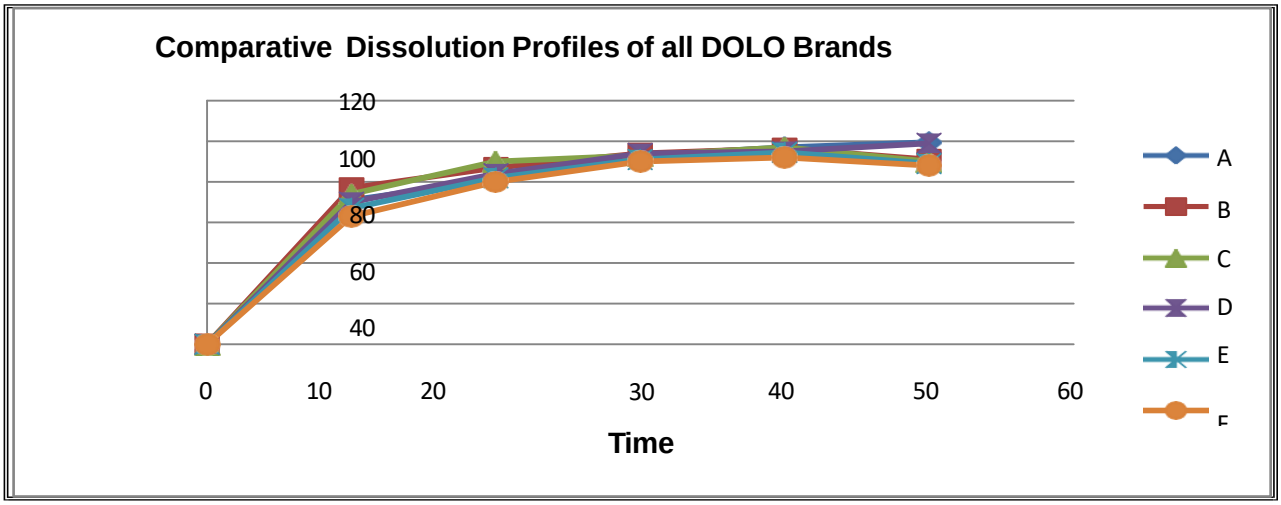


**Fig 4: Dissolution profile of different brands of Dolo tablets**

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## CONCLUSION

The present quality control method is useful in monitoring the production consistency of batch-to-batch product release of each brand of DOLO and in comparing the quality characteristics of different brands marketed. The study attempted to assess the quality of DOLO tablet and the physicochemical equivalence of the four brands. Drug content, hardness, friability, disintegration time and dissolution profile of all products used in the study were within specified limits. Hence the safety, quality, and efficacy of essential drugs in the region should be continuously monitored through post marketing surveillance practices.

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