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Study on Release Pattern and Potency Status of Ketoprofen Solid Dosage Forms Available in the Pharma-Market of Bangladesh

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Abstract: Ketoprofen, a widely used analgesic drug is available in two solid dosage forms in the pharma-market of Bangladesh: enteric-coated tablet and capsule of sustained-release pattern. Seven brands of ketoprofen enteric-coated tablets and four brands of ketoprofen sustained release capsules were studied for their *in vitro* release behavior as well as potency status. From the seven samples of tablets, two brands (KT-03 and KT-07) were found noncompliant in respect of disintegration test in acid stage, whereas all the brands complied with BP (British Pharmacopoeia) specification in buffer stage at pH 6.8. The dissolution study of ketoprofen tablets were carried out in both acid and buffer stages and all the samples satisfied with USP specification in both stages. All of the brands of ketoprofen capsule also complied with the USP specification. Potency was determined by UV spectroscopic method according to BP. Two brands (KT-03 and KT-07) of tablets were found non-compliant, whereas all the brands of capsules exerted compliance in respect of potency.

Key words: Enteric-coated tablet, sustained-release capsule, disintegration test, dissolution test, potency estimation

INTRODUCTION

Ketoprofen is an analgesic drug used widely in the treatment of patients with rheumatic diseases. It acts by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activities and thereby inhibiting the synthesis of prostaglandin (Hardman and Limbird, 1996). The prevalence of rheumatic diseases is increasing day by day in our country, especially among elderly and that creates a demand of quality analgesic drugs. Most conventional drug products, such as tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. In recent years, various modified drug products have been developed to release the active drug at a controlled rate. A variety of controlled release drug products designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug (Shargel and Andrew, 1941). The valid reasons for coating tablets to control the site of release of drug which is best illustrated in terms of enteric coating and to provide a controlled, continuous drug release rate. The release pattern of a coated tablet can be revealed by disintegration and dissolution tests (Chambliss *et al.*, 1984). Dissolution analysis of pharmaceutical dosage forms has now emerged as a very important test for product quality. The rate of drug dissolution may be directly proportional

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to the efficiency of the product. *In vitro* testing procedures, dissolution test is the only test that can more or less indirectly correlate the *in vivo* bioavailability (Tripathi, 2000).

Sustained release dosage form of a drug contributes some advantages. Since, the frequency of drug administration is reduced, patient compliance is improved and drug administration can be made more convenient as well. Blood level fluctuation characteristic of multiple dosing of convenient dosage form is reduced because a more even blood level is achieved through sustained release dosage form (Lachman and Liberman, 1991).

The evaluation of *in vitro* release of actives from semisolid preparations has received much attention in recent years. Release is a function of several physicochemical characteristics within the semisolid, so that constancy of release from one batch to another implies that the manufacturing process is the same (Fares and Zatz, 1995). A bioavailability study of a topical formulation begins with the *in vitro* investigation of the drug release from the formulation under evaluation (Csoka *et al.*, 2005). Historically, although *in vitro* release rate testing from semisolids could potentially provide valuable information about product performance, it is not an industry wide quality control test requirement as compared to the utility of *in vitro* dissolution testing of oral dosage forms (Liebenberg *et al.*, 2004). To change this situation the extension of *in vitro* dissolution methodology to semisolid dosage forms has been the subject of substantial effort and debate. Similar to the dissolution testing of oral dosage forms, a simple, reliable and reproducible release rate method can guide formulation development, help to monitor batch-to-batch quality and stability and control the manufacturing process. It is particularly useful for detecting the effect of product changes including drug substance, excipients and manufacturing processes (Liebenberg *et al.*, 2004; Shah *et al.*, 1999; Zatz, 1995; Shah, 1993).

A large number of studies have been conducted previously on the dissolution and disintegration pattern of ketoprofen dosage forms. All these extensive studies were conducted to evaluate mainly the in-vivo bioavailability pattern of ketoprofen formulations.

The aim of the study is to investigate the release pattern and potency status of different preparations of ketoprofen solid dosage forms available in the local market of Bangladesh, so that quality brand (s) could be identified.

MATERIALS AND METHODS

Sample

Seven brands of ketoprofen enteric-coated tablet and 4 brands of ketoprofen capsule were purchased from the different regions of Bangladesh. The areas include different wholesale and retail medicine shops of Khulna City including Heraj Market (Khulna), Moilapota and Gollamari (Khulna), Savar and Mitford of Dhaka City in Bangladesh. The samples were collected in such a way that some samples were immediately after manufacturing, some were just before their expiry dates and others were intermediate of two kinds to know about the stability status of the drug products during their shelf-life. The labels of ketoprofen tablets and ketoprofen capsules claimed to contain 50 mg of ketoprofen per tablet and 100 mg of ketoprofen per capsule, respectively.

Chemicals

Standard sample of ketoprofen sustained-release pellets and that of ketoprofen powder were collected from Beximco Pharmaceuticals Ltd. and Eskayef Bangladesh Ltd., respectively to use as reference standard. Disodium hydrogen phosphate, potassium dihydrogen phosphate and trisodium phosphate dehydrate were purchased from E. MERK (India) Ltd.

Disintegration Studies

Disintegration test was carried out by Thermonic Tablet Disintegration Test Unit, Campbell Electronics, Mumbai, India. The BP specification for disintegration time test: no tablet should

show the sign of cracks that would allow the escape of content in acid stage and all tablets must be disintegrated within 1 h in buffer stage.

Dissolution Studies

In vitro drug release studies were conducted using type 2 dissolution apparatus at $37 \pm 0.5^\circ\text{C}$ in two stages. For calculating the amount of drug dissolved, the calibration curves for both acid and buffer stages were prepared from standard solutions of different concentrations of the respective drug. According to USP specification for dissolution study, drug must be dissolved $<10\%$ of the labeled amount after 2 h in acid stage and drug must be dissolved $>80\%$ of the labeled amount after 1 h in the buffer stage.

Potency Studies

A UV spectrophotometer (Camspec, UK) was used to determine the amount of ketoprofen present in the samples at 258 nm and was compared with the standard sample of that drug. The BP specification for potency study: $100 \pm 5\%$ for tablet preparations and $100 \pm 10\%$ for capsule dosage forms.

The experiments were conducted in the Bio-pharmaceutics laboratory of Pharmacy Discipline, Khulna University, Khulna-9208, Bangladesh. The study was carried out from February 2008 to July 2008.

RESULTS

Disintegration Test

The results of disintegration test of 7 samples of ketoprofen tablets were shown in Table 1 and Fig. 1 for acid stage and buffer stage, respectively.

Table 1: Disintegration test of ketoprofen tablets in acid stage

Sample code	No. of tablets	Status of tablets after 2 h (in 0.1M HCl media)	Observations
KT-01	6	Intact, no cracking	Compliance
KT-02	6	Intact, no cracking	Compliance
KT-03	6	Small crack found, ingredient may leak.	Non compliance
KT-04	6	Intact, no cracking	Compliance
KT-05	6	Intact, no cracking	Compliance
KT-06	6	Intact, no cracking	Compliance
KT-07	6	Small crack found, ingredient may leak.	Non compliance

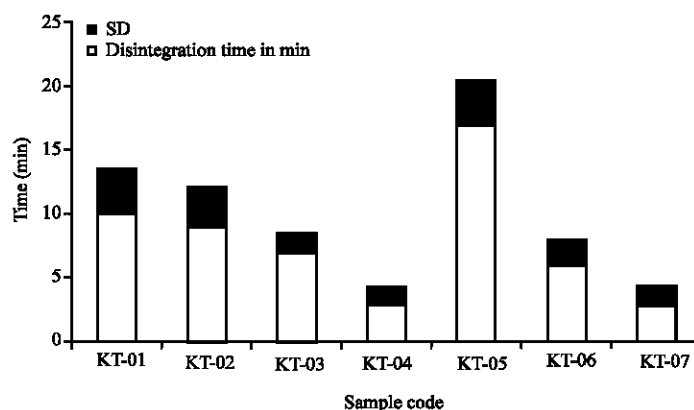


Fig. 1: Disintegration pattern of ketoprofen tablet brands, in buffer stage

Dissolution Study

The dissolution study of ketoprofen tablet was carried out in both acid and buffer stages. All the brands satisfied with USP specification in both stages. Result found in the dissolution study of ketoprofen tablet in acid stage was presented in Table 2.

Also, in the buffer stage of dissolution study all Ketoprofen tablet brands were found to be complied with USP specification (Fig. 2).

Dissolution study of four ketoprofen capsule brands was carried out only in buffer stage. The result was shown in Fig. 3.

Table 2: Dissolution study of Ketoprofen tablet, KT-01 to KT-07, in acid stage

Sample code	No. of tablets	Percent drug dissolved after 2 h in acid stage	Observations
KT-01	6	6.44	Compliance
KT-02	6	2.09	Compliance
KT-03	6	1.73	Compliance
KT-04	6	5.40	Compliance
KT-05	6	4.38	Compliance
KT-06	6	6.84	Compliance
KT-07	6	2.15	Compliance

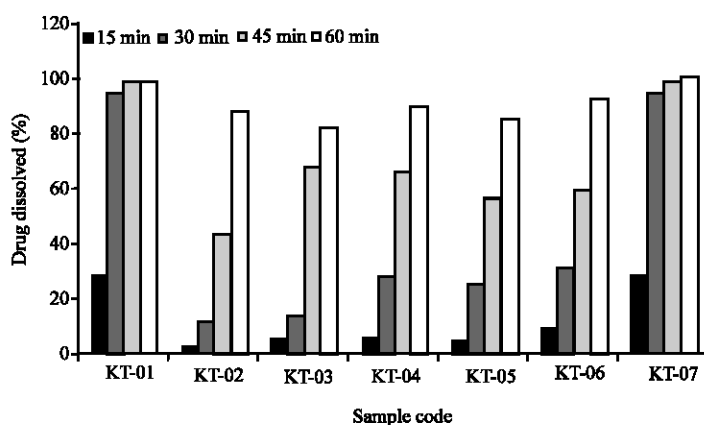


Fig. 2: Dissolution pattern of ketoprofen tablets in buffer stage (KT-01 to KT-07)

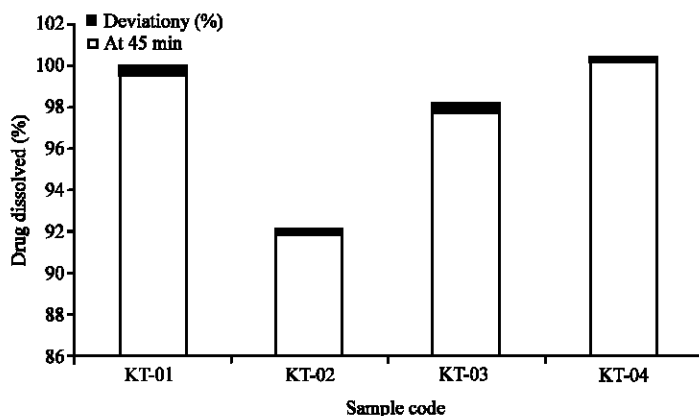


Fig. 3: Dissolution pattern of ketoprofen capsules in buffer stage (KC-01 to KC-04)

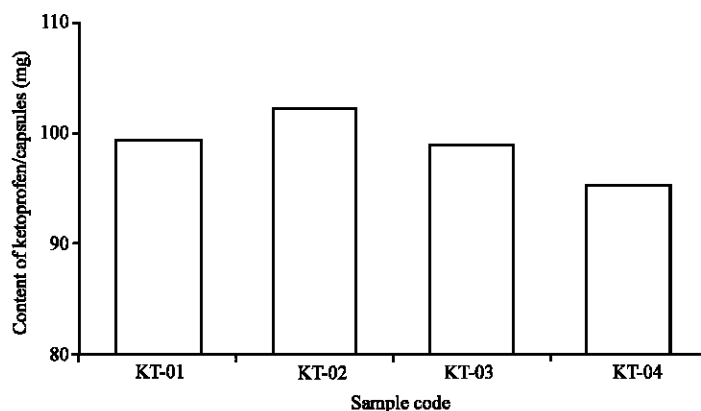


Fig. 4: Potency of different brands of ketoprofen capsules (KC-1 to KC-4)

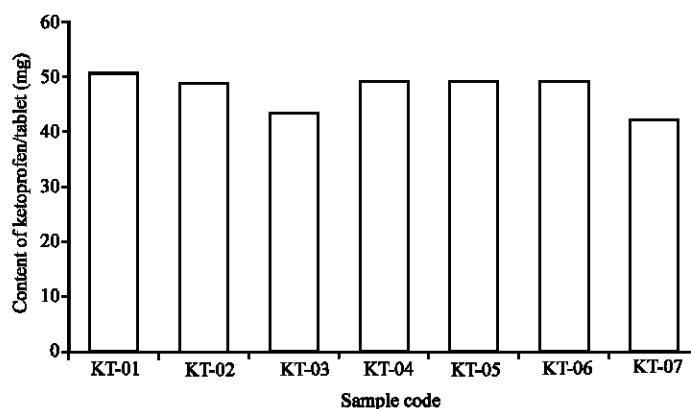


Fig. 5: Potency of different brands of ketoprofen tablets (KT-01 to KT-07)

Potency Determination

The potency of ketoprofen tablet and capsule brands was determined by UV spectroscopic method and the amount of ketoprofen present in the sampled 7 tablet brands was shown in Fig. 4. The potency of 4 brands of ketoprofen capsule was also determined by UV spectroscopic method and all brands complied with BP specification (Fig. 5).

DISCUSSION

Ketoprofen (3-benzoyl- α -methylbenzeneacetic acid, KP) is a widely used nonsteroidal anti inflammatory drug (NSAID) that causes both phototoxicity and photoallergy (He *et al.*, 2003). Disintegration time of tablets was related to the effect of the formation of solid bridges between lactose particles. Porosity, hydrophilicity (solubility if the tablet constituents are water-soluble), swelling ability of the particles and interparticle force are important factors for tablet disintegration (Bi *et al.*, 1999, 1996).

From Table 1, it was observed that 2 brands (KT-03 and KT-07) did not comply with BP specification in acid stage and small crack was observed in these brands. But finally at the buffer stage all brands were found to comply with BP specification as illustrated in Fig. 1.

Finally, it can safely be concluded that the disintegration pattern of all the marketed ketoprofen tablet brands taken in the study were found to demonstrate satisfactory pattern of disintegration, in respect of official compendia. So, huge possibility was there to get a satisfactory release pattern of these brands in the disintegration study.

The dissolution of the prepared ketoprofen Sustained Release (SR) Pellets was studied by Erweka (Heusenstamm, Germany) dissolution tester USP (XXVIII) using USP apparatus I (Basket method). The individual effect of pH and surfactants on the solubility and dissolution of drugs has been studied previously. Olander (1960) proposed both the film theory and the surface renewal theory of simple mass transfer in conjunction with various equilibrium reactions (Olander, 1960). Elworthy and Lipscomb (1968) analyzed the effect of four different non-ionic surfactants on the dissolution of poorly soluble drug, griseofulvin. During the late 1970s and early 1980s, research on the effects of pH (Carlson *et al.*, 1983; Sakr *et al.*, 1980) and surfactant (Schott *et al.*, 1982; Samaligy and Szantmiklosi, 1978) on drug solubilization and dissolution focuses on disintegration and dissolution of traditional tablets.

Dissolution is the prime factor for proper absorption of the drug particles by the intestine and ultimately bioavailability of the drugs (Miyagawa *et al.*, 1996). The most effective solid dispersion is the 10-80-10 w/w drug-PEG-SDS ternary coevaporate, which allowed dissolution of 50% drug after only 6 min (in comparison with >2 h for drug alone and 17 min for the binary coevaporate) and dissolution of about 100% drug after 30 min (in comparison with >2 h for the binary coevaporate) (Mura *et al.*, 2005).

The particle surface, therefore, shows hydrophobic properties, which influence the dissolution process by reducing the effective surface (Lippold and Ohm, 1986).

Dissolution study of four ketoprofen capsule brands was showed excellent dissolution rate and were found to be dissolved >80% of the labeled amount after 45 min which satisfied USP specification (Fig. 3). Finally, it can be concluded that the dissolution of all the available reputed ketoprofen enteric-coated tablet and capsule brands were found to be complied with official compendia and in terms of release pattern, all these brands were satisfactory in nature, as per our expectation from disintegration study. So, it is obviously expected to get desired efficacy from these brands. Further *in vivo* study is required to conclude about the bioavailability pattern of the test brands.

Ketoprofen is an anionic nonsteroidal anti-inflammatory drug (NSAID) with approximately 160 times the anti-inflammatory potency of aspirin on a per weight basis (Insel, 1996; Bethesda, 1996).

In respect of potency, it can be concluded that except 2 tablet brands all other ketoprofen tablet and capsule brands showed excellent result and are potent enough to meet official recommended compendia. The lower potency of 2 tablet brands may be due to the degradation of active ingredient at the time of manufacturing or shelf-life.

We found that among tablet preparations only 2 brands (KT-3 and KT-7) were found to be noncompliant with BP specification. These two brands contained less active ingredient and may not be able to produce the effect that is naturally expected after administration of a standard drug.

The study covered only some selected brands of ketoprofen solid dosage products subject to the availability in local market. These are insufficient to show the overall quality of this family of drugs. Besides, *in-vivo* bioavailability studies are of utmost importance to draw conclusion regarding quality status of the samples.

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