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In vitro Evaluation of Food Effect on The Bioavailability of Nimesulide and Paracetamol from Fixed Dose Combination of Nimesulide and Paracetamol

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ABSTRACT

The present study was undertaken to evaluate the *in vitro* food effect on the bioavailability of Nimesulide and paracetamol from fixed dose combination. *In vitro*, effect of food on the bioavailability was studied by simulating *in vivo* conditions in dissolution fluid. In this study, we assessed the effect of hydrodynamic stress in presence of food and meal composition on Nimesulide containing fixed dose combination formulations by carrying out dissolution at different agitation rates (simulation of fasted and fed state) as well as in the presence of different percentage of oil (fatty food). It was concluded that agitation intensity as well as presence of oil indicates that the food can play an important role on the release of Nimesulide and paracetamol. Nimesulide and paracetamol show delayed release behavior as percentage of oil increased. This formulation had shown delayed release characteristics at all the conditions studied, showed agitation rate dependent release and also release was affected in presence of oil. Further, effect of food on the Nimesulide and paracetamol release was a function of dosage form characteristics such as disintegration time and dissolution rate, which will subsequently affect the release behavior of a formulation in presence of food.

Keywords: Nimesulide; Paracetamol; Bioavailability; Food effect; Dissolution rate.

INTRODUCTION

Fixed Dose Combination (FDC) products are those, which have two or more drugs present in a fixed ratio, where one of the drugs either potentiates or synergises the effect of the other, or the symptomatic relief provided by the two of them differs in nature in the same disorder. The rationality of a FDCs is the most controversial and debated issue in today's clinical practice. Therefore, the risk-benefit assessment is essential before choosing a combination for therapy. The FDCs are valuable only when they have been developed according to rationale pharmacokinetic and pharmacodynamic criteria, and when claims for their benefits have been supported by evidence-based data and well-designed clinical studies. Research into this area has been negligible, and there are limited reports to describe *in vitro* food effect on the bioavailability of Nimesulide and paracetamol from fixed dose combination of Nimesulide and Paracetamol.

In vitro effect of food on the bioavailability can be studied by simulating *in vivo* conditions in dissolution fluid hence, to understand the variable effect of food on Nimesulide and paracetamol release, dissolution studies were done by simulating *in vivo* conditions after meal intake. [1] In this study, we assessed the effect of hydrodynamic stress in presence of food and meal composition on Nimesulide and paracetamol containing fixed dose combination formulations by carrying out dissolution at different agitation rates (simulation of fasted and fed state) as well as in the presence of different percentage of oil (fatty food).

Dissolution test is the most important test employed for *in vitro* evaluation of solid dosage forms. In order to predict the *in vivo* performance of drug products, dissolution tests should be designed so as to simulate the *in vivo* conditions. [2-3] One of the important factors affecting bioavailability of the drug is the effect of food that induces changes in the physiology of the gastrointestinal tract resulting in delayed gastric emptying, changes in pH or stimulation of bile flow. Effect of food on bioavailability and bioequivalence depend on physicochemical (solubility) and pharmacokinetic (site, rate, and extent of absorption, first pass metabolism) properties of the drug and on the dissolution of the drug substance from the drug product. The physiological changes induced by food can be studied *in vitro* by simulating these conditions e.g. reduced agitation intensity as an indication of low hydrodynamic flow around the dosage form in the human GI tract in presence of food and addition of co-administered fluid/food components to dissolution medium to reflect the conditions in the stomach soon after meal intake. [4]

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MATERIALS AND METHODS

The influence of food on Nimesulide and paracetamol from FDC formulation of Nimesulide (100 mg) and paracetamol (500 mg) were studied by taking into consideration factors such as agitation rate and presence of oil.

Dissolution study at different agitation rates

Effect of agitation intensity on the Nimesulide release as a function of hydrodynamic stress around the dosage form was studied by *in vitro* dissolution at different agitation rates (50, 75 and 100 rpm, using USP Type II apparatus, (paddle). The 10 ml samples were withdrawn at 15, 30, 45 and 60 min with replacement by fresh dissolution medium. Dissolution test, were carried out in triplicate in order to avoid biases and compared with reference containing pure drug equivalent to amount present in the formulation. [1, 5]

The dissolution parameters and methodology were kept constant in all the experiments except agitation rate. The samples collected at different time intervals were diluted with dissolution medium, analyzed immediately by spectrophotometer at 395 and 244 nm and % release of Nimesulide and Paracetamol was calculated with respect to the reference. [6]

Effect of oil

Effect of oil on the release profiles of Nimesulide and Paracetamol from the formulation was studied by adding different percentage of oil (20 %, 30 %) to the dissolution medium. This study was carried out in a similar manner at 75 rpm. In order to further study the effect of oil at higher agitation rate, the dissolution was also carried out at 100 rpm with 20 % oil (equivalent to the amount of fats present in the normal Indian fatty meal). [1] The samples were centrifuged at 5000 rpm for 10 min and bottom aqueous layer was analyzed for nimesulide and paracetamol at 395 and 244 nm. Percentage release of nimesulide and paracetamol were calculated with respect to the absorbance of reference vessel. [7]

RESULT AND DISCUSSION

Effect of agitation rate

Normally food delays the gastric emptying as motility is affected and to simulate this condition state [8, 9], the dissolution studies were carried out at different agitation rates (50, 75 and 100 rpm). Low agitation intensity is an indication of reduced hydrodynamic flow around the dosage form in fed state and high agitation intensity is simulates fasted. As evident from Fig.1, Nimesulide did not show 100 % release even after 45 min in fed state. In addition, according to USFDA guideline [10] when both test and reference products dissolve 85 % or more of the label amount of the drug in 15 min, dissolution profiles may be accepted as similar without further mathematical evaluation. Hence, based on this, dissolution profiles of Nimesulide showed agitation dependant release at lower rpm i.e. dissolution rate of Nimesulide decreased with decrease in agitation rate. Despite of this difference in the dissolution profiles at different agitation rates, all the dissolution tests passed the USP dissolution criteria of not less than 75 % release in 45 min at all the agitation rates. Figure 1 shows comparative dissolution profile of Nimesulide at different agitation intensities.

Among the many factors that the FDA examines to ensure that drug products are safe and effective is the effect of food on the bioavailability of the active drug from the drug product. Thus, the FDA asks applicants seeking marketing approval of new or generic drug products to conduct human pharmacokinetic studies examining the effects of food on drug absorption and bioavailability. [11]

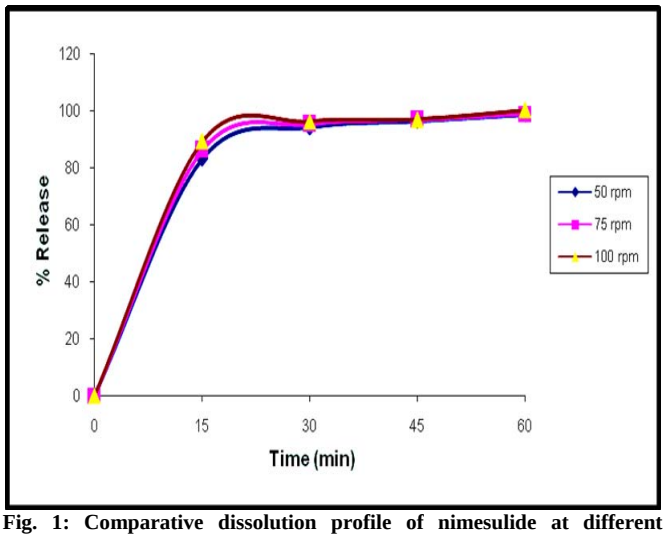

Fig. 1: Comparative dissolution profile of nimesulide at different agitation intensities

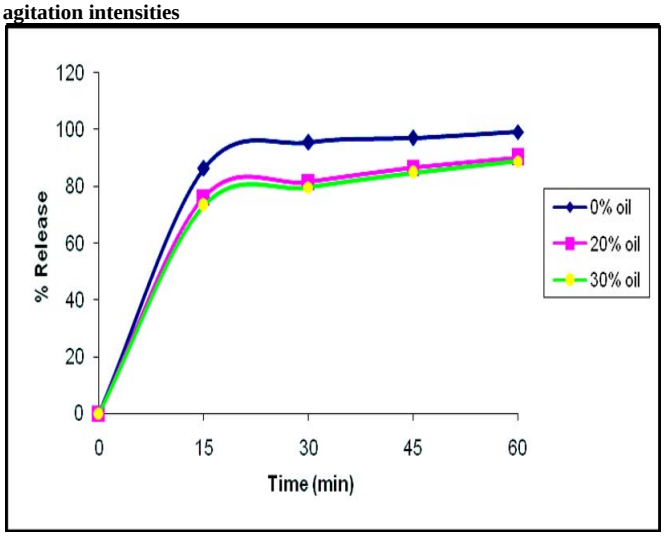

Fig. 2: Comparative dissolution profile of nimesulide at 75 rpm using different percentage of oil in dissolution media

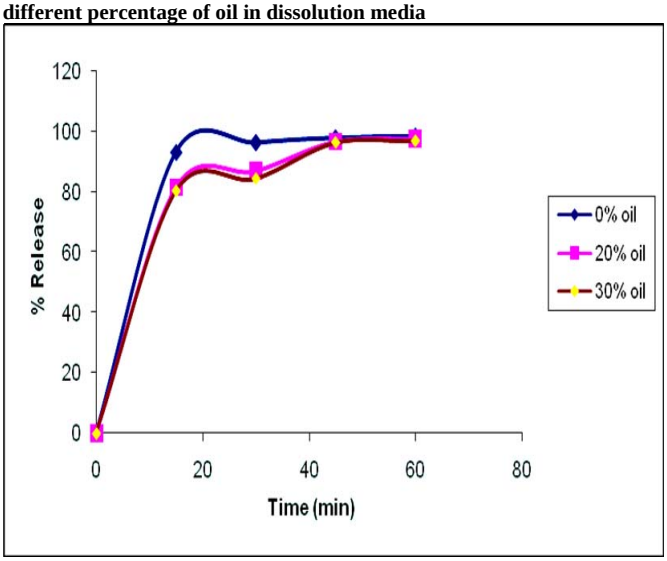

Fig. 3: Comparative dissolution profile of paracetamol at 75 rpm using different percentage of oil in dissolution media

Effect of oil

In the fed state, the luminal composition of the stomach is highly dependent on the composition of the meal ingested. In

order to simulate the *in vivo* conditions in the presence of fatty meal, a volume of oil reflecting the fat content of the meal can be added to dissolution medium and hence dissolution were done in the presence of different percentage of oil added to dissolution medium. Fig. 2, 3 shows the effect of presence of oil on the release of the Nimesulide and paracetamol from FDC.

Thus, agitation rate and percentage of oil have effect on Nimesulide and paracetamol release from FDC. Nimesulide and paracetamol, the dissolution rate was decreased with the decrease in the agitation rate. This decrease in dissolution at lower rpm simulating the fed state may be due to increased disintegration time of the formulation as hydrodynamic stress experienced by the formulation is considered to be low.

This study indicates that the food can play an important role on the release of Nimesulide and Paracetamol. Nimesulide and paracetamol show delayed release behavior as percentage of oil increased.

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