CHAPTER 1

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Lithium salts have been used for years in the therapy of manic patients. Lithium carbonate is widely accepted for the treatment of mania and also for the prophylaxis of manic–depressive disorders.

Lithium Carbonate comes under the category of narrow therapeutic index drugs under section 320.33 (c) of Code of Federal Register 21 USA. The US FDA defines a product as having narrow therapeutic ratio as follows (CDER):

➤ There is less than a 2 fold difference in median lethal dose and median effective dose values, or
➤ There is less than 2 fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
➤ Safe and effective use of the drug requires careful titration and patient monitoring.

An updated definition stated in the 2000 guidance, which defined narrow therapeutic range drug products as those “containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation” (AMA Annual Report, 2002).

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. There are a host of factors that influence this. These factors are classified as drug factors and host factors (Brahmankar and Jaiswal, 1995). The drug factors include physicochemical properties of drug substance and dosage form characteristics. The host factors include age, blood flow to gastrointestinal tract (GIT), presence of food or other contents in GIT, GIT pH, gastric emptying, disease state and presystemic metabolism by enzymes in the gut wall or in the liver. Changes in the bioavailability are invariably reflected in the
concentration of the drug in circulation and thereby at the site of action (Chow and Liu, 2000).

Prescribing generic drug products may be actually beneficial as there is no significant change in the quality of the patient care and it may be actually better as they may lead to significant cost saving (Marriott JF, 1999). However, it is critical that these savings are not accrued at the expense of the quality of health care (Spino et al, 2000). Thus, a system must be in place to ensure that generics will have the same level of safety and efficacy as the brand products, which they replace. Therefore, it has become an important clinical issue to check the bioequivalence of drugs in human subjects, which appear equivalent chemically.

The important objectives of drug formulation with regard to influencing drug absorption are to reduce dosing frequency, attain better patient compliance, reduce the fluctuations in plasma drug concentrations, maintenance of drug effects over an extended period of time and to reduce the inter-subject variability (Ritschel, 1989). Sustained release (SR) preparations are capable of and are useful in increasing the required dosage interval and achieving the above goals of therapy. But SR dosage forms also suffer from many limitations such as loss of efficacy due to missing a dose, loss of effect due to failure of the system, local irritation or damage of epithelial lining (lodging of dosage forms).

The antimanic action of lithium carbonate has generally been associated with serum levels in the range of 0.6-1.25 mEq/l. Though the onset of toxicity is usually seen above 1.8 mEq/l, the adverse effects are not uncommon in patients whose serum levels are maintained within the therapeutic range (Johnson, 1980; Foster et al, 1980; Caldwell et al, 1981; Frost & Messiha, 1983). Because of low therapeutic index for lithium carbonate (as low as 2 or 3); concentrations in plasma or serum are periodically determined to assure safe use of the drug.

Adverse effects are commonly associated with high lithium serum concentrations. To avoid wide blood level fluctuations, controlled release lithium preparations were
developed (Amdisen and Sjogren, 1968; Caldwell et al, 1971; Otto et al, 1972; Ventouras and Bury, 1976). These preparations are designed to release the drug more slowly and hence the rate of absorption is decreased, without a concomitant decrease in the extent of absorption. They intend to avoid the high peak serum level, achieved rapidly after the administration of the conventional rapid release dosage forms. In addition, controlled release preparations which can be administered twice a day instead of the three times daily administration of conventional tablets, may improve the compliance of the patients with the dosage regimen (Caldwell et al, 1981; Amdisen, 1980).

The British National Formulary (BNF) includes a special precaution attached to the entry for a number of drugs like Carbamazepine, Phenytoin, Lithium, Sodium Valproate, Theophylline modified release, Aminophylline modified release, Diltiazem long acting, Nifedipine modified release, Cyclosporin (Marriott JF, 1999). These warnings indicate generally that brand substitution after dose stabilization might produce undesirable effects of some kind and should therefore be avoided.

Borgherini G (2003) in his review summarized available data comparing the bioequivalence and therapeutic efficacy of brand-name psychoactive drugs with those of the corresponding generic products. These studies, however, few in number revealed differences in the efficacy and tolerability of brand-name and generic psychoactive drugs that had not been noted in the original bioequivalence studies. Specifically, in a study, the plasma levels of phenytoin were 31% lower after a switch from a brand name to a generic product. Several controlled studies of carbamazepine showed a recurrence of convulsions after the shift to a generic formulation (Welty TE et al, 1992; Pedersen SA and Dam M, 1985; Meyer MC et al, 1992).

In India, where large number of small scale pharmaceutical industries (over 20,000, the largest number in the world) is engaged in generic manufacturing have inadequate facility and little concern to follow GMP guidelines. In addition, lithium
has a low therapeutic index and side effects are not uncommonly seen in patients whose serum lithium levels are maintained within the therapeutic range.

The present study was, therefore, planned in accordance with DCGI guidelines to compare bioequivalence and steady-state lithium blood level fluctuations of three-marketed brands of lithium carbonate ER (extended release) preparations, available in the Indian market.