1.0 INTRODUCTION

Extended release (ER) mode of drug administration has certain features that have an important impact on the magnitude of the pharmacologic response: (a) it minimizes fluctuation in blood drug concentrations (i.e. between peak and trough). (b) it produces a slow input rate which tends to minimize the body's counteraction to the drug's intervening effect on regulated physiological processes; and (c) it provides a continuous mode of drug administration. For many drugs with non-concentration-dependent pharmacodynamics, the exposure time, rather than the area under the curve (AUC), is the relevant parameter and it can therefore be optimized by ER preparations (1).

Modified release (MR) formulations provide higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate release (IR), twice-daily formulations. Additionally, therapeutic drug levels with ER formulations achieved rapidly and maintained over the course of 24 hrs, allowing once-daily dosing. The studies have also confirmed good tolerability and safety of ER formulations similar to the IR formulations (2).

The ER formulations drew attention in search for the improved patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, an ER formulation maintains therapeutic blood level of a drug for a specific period of time. Oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects (2, 3).

Side effects for ER formulations are often more favorable because controlled-release formulations exhibit lower peak plasma drug concentrations when compared with IR
formulations. Venlafaxine sustained-release (XR), bupropion sustained-release, and paroxetine controlled-release are 3 commonly utilized controlled-release antidepressants that have demonstrated improvement over their immediate-release predecessors in reducing certain adverse effects (4, 5).

ER formulation of a short-acting drug lead to better disease control than a corresponding immediate-release (IR) formulation at the equivalent total daily dosage (6, 7). Another undoubted advantage of ER formulation is improved patient compliance. Compliance improves dramatically as prescribed dose frequency decreases (8-11). However, ER 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) and release of active ingredient in unexpected manner (dose dumping) (12). Even different mechanisms of drug release can affect the rate and extent of absorption of the drug into systemic circulation.

The therapeutic effectiveness of a drug depends upon its bioavailability to elicit the desired pharmacological response. There are many drug related (physicochemical properties) and host factors (physiological factors like age, blood flow to gastrointestinal tract (GIT), pH, gastric emptying etc.) that influence the rate and absorption of the drugs (13). Bioavailability becomes a matter of crucial importance for the drugs which has typical characteristics such as poor solubility in water, toxic drugs, narrow therapeutic drugs (i.e., the difference between therapeutic and toxic concentrations is small), non-linear kinetics, modified release products or drugs used for chronic diseases like diabetes, cancer, epilepsy etc.

Allergic rhinoconjunctivitis and chronic urticaria, as well as eczema and bronchial asthma,
are associated with a hypersensitive response of the immune system. These type 1 hypersensitivities are characterized by the large quantities of IgE antibodies and begin with an acute IgE mediated reaction. This occurs following the interaction of allergen with a specific antibody that has been adsorbed onto the surface of mast cells and basophils located in the tissue and blood, respectively. To a lesser extent, IgE also binds to eosinophils and macrophages. When an allergen binds with several antibodies attached to a mast cell or basophil, the cell degranulates and releases mediators of allergic inflammation. Following mast cell and basophil degranulation, released chemical mediators cause vasodilation and attraction of neutrophils, eosinophils, lymphocytes and monocytes to the active site and damage to local tissues. Other effects include increased vascular permeability that results in loss of fluid in the surrounding tissues and edema, increased glandular secretion, contraction of smooth muscle and stimulation of sensory nerve endings. Allergic rhinitis and conjunctivitis, which are the most common forms of atopic disease, are characterized by sneezing, rhinorrhea, nasal obstruction and itching of the nose and eyes. Allergic skin conditions are also extremely common and often manifest as urticaria. This reaction involves the lower layer of the surface of the skin and becomes present as localized swelling and as the development of wheals and flares, which are associated with severe pruritis. There are many antiallergic and antihistaminic drugs for the treatment of rhinoconjunctivitis, urticaria, eczema and bronchial asthma as follows: ketotifen fumarate, azelastine hydrochloride, oxatomide, emedastine fumarate, epinastine hydrochloride, terfenadine, astemizole, ebastine, cetirizine hydrochloride, fexofenadine hydrochloride, bepotastine besilate, loratadine, ramatroban, pranlukast hydrate, diphenhydramine hydrochloride, chlorpheniramine maleate and clemastine maleate. However, the incidence of these allergic diseases in general has been
increasing. As the prevalence of these allergic diseases rises, efforts at the discovery of novel and effective medications for prevention and treatment of these conditions also rise (14).

Olopatadine hydrochloride is a novel antiallergic/histamine H1-receptor antagonist. It is a tricyclic compound with multiple mechanisms of action against multiple allergic conditions. It is a potent histamine H1-receptor antagonist and a specific mast cell stabilizer, with additional anti-inflammatory properties (15). Olopatadine hydrochloride principally acts as a selective histamine H1 receptor antagonist. This drug also inhibits the production and release of chemical mediators (leukotriene, thromboxane, PAF, etc.) and the release of the neurotransmitter tachykinin. Olopatadine is indicated for allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, prurigo, pruritus cutaneous, psoriasis vulgaris, multiform exudative erythema) (16).

Olopatadine is approved as an ophthalmic solution in Europe, Japan, and the United States. In the United States, olopatadine as Patanol (Alcon Laboratories, Inc., Fort Worth, TX) is approved at a b.i.d. dose for the treatment of allergic conjunctivitis. A q.i.d. formulation, Pataday (Alcon Laboratories, Inc.), is also available to treat itching associated with allergic conjunctivitis. Additionally, a nasal spray, Patanase (Alcon Laboratories, Inc.), is available in the United States for relief of the symptoms of seasonal allergic rhinitis (SAR); and in Japan the molecule is available as an oral formulation (Allelock®; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) for treatment of allergic conditions (15).

Allelock® conventional tablets are currently administered twice daily, in the morning and before going to bed. Hence, it is advantageous to formulate once daily dosage regimen for olopatadine hydrochloride as it will exhibit better patient compliance in outpatient therapy.
So considering aforementioned points, the present study was designed to evaluate bioavailability of single dose of olopatadine hydrochloride 10 mg extended release tablet (two formulations) of Ranbaxy laboratories limited in comparison with two doses of Allelock® 5 mg tablets of Kyowa Hakko Kogyo Co. Ltd., in healthy, adult, human male subjects under fed condition.