3 Need and objective of study

3.1 Need of study

Certain pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. This can be done by a regimen in which the patient follows a prescribed time schedule, but because of patient noncompliance, scrupulous adherence to a schedule often requires the assistance of a medical professional. Even those therapies that involve only two dosages, such as an immediate but rapidly declining high-level dosage combined with a prolonged low-level or moderate level dosage, either of the same drugs or of two different drugs, can be a nuisance to the individual or troublesome to maintain if the individual is required to take separate unitary dosage forms. Certain pharmaceutical formulations have therefore been developed that combine both functions into a single dosage form.

3.2 Objective of study of salbutamol sulphate and theophylline combination for asthma

Asthma is an inflammatory disorder of the airways, which causes attacks of wheezing, shortness of breath, chest tightness, and coughing. The airways are the tubes that carry air in and out of your lungs. Over 300 million people around the world suffer from this non-communicable respiratory disease. Asthma affects 3.5 per cent to over 20 per cent of the population in any country. Asthma cause more deaths in India than in any other country. About 60% of patients develop this allergy in childhood itself.

Salbutamol is a moderately selective beta (2)-receptor agonist similar in structure to terbutaline, and widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. Theophylline is a xanthine derivative chemically similar to caffeine and theobromine, is used to treat asthma and bronchospasm. Theophylline has two distinct actions in the airways of patients with reversible (asthmatic) obstruction; smooth muscle relaxation (i.e., bronchodilation) and suppression of the response of the airways to stimuli.

The concept of dual retard multicomponent therapy is beneficial when the selected agents posses differing mechanism of action that provide additive or synergistic efficacy, reducing the required doses of individual agents as compared with monotherapy and potentially limiting side effects. Multicomponent therapy may seem costlier than monotherapies in the short term; but causes significant savings, lower treatment failure rate, lower case fatality ratios, reduction in development of
resistance and consequently less money needed for the development of new products in long-term therapy.

Conventional tablets containing a fixed dose of salbutamol sulphate and theophylline are widely available in the market. An alternative approach for effective control of asthma is to manufacture oral dosage forms delivering both immediate release and sustained release antiasthmatic drugs from single-dosage form i.e dual retard mechanism.

Salbutamol sulphate was chosen as immediate release part because it contained low dose and suitable to deliver immediately. It has also half life of only 1.2 h and absorption window is stomach. So after dissolving the drug in g.i. tract, it was supposed to give quick action. Theophylline was used in sustained release part because it has the major side effect of dose dumping. It requires different dose to different sex, different age, effect of food, taking with alcohol etc. The effective drug conc range is 5-15 µg/mL and it becomes toxic at 20 µg/mL. Also salbutamol gives additive effective in presence of theophylline.

The aim of the present research work is to be developed and optimized a immediate release part containing salbutamol sulphate which release more than 90% of drug within 1 h and theophylline as SR which start release up to 12 hr in sustained pattern. Immediate action of salbutamol sulphate will be helpful to control asthma, which will be maintained by theophylline action later on. Thus, the developed single dual retard tablet will be sufficient instead of three to four tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy.

3.3 Objective of study of amlodipine besylate and atenolol combination for hypertension

Hypertension, commonly referred to as high blood pressure, is a medical condition where the pressure is chronically elevated is one of the commonly found diseases, affecting most of the populations in the world. For treating hypertension, commonly used drugs include ACE inhibitors, alpha blockers, beta blockers, angiotensin receptor blockers, calcium channel blocker, diuretics and combination of any of these categories.

Combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each.
The rational for combination therapy is to encourage the use of lower doses of drug to reduce the patient’s blood pressure to goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized.

The current invention provides a control release formulation of amlodipine besylate and atenolol for a once a day oral administration that is effective immediately upon administration, as well as through a period of time of at least 12 hr after administration.

Amlodipine is a prototype second generation dihydropyridine calcium channel blocker (CCB). They have a longer duration of action and can be given once daily. Amlodipine is used in the treatment of mild to moderate hypertension, chronic stable angina pectoris or vasospastic angina (prinzmetal’s or variant). In these conditions it may be employed as monotherapy or in combination with other antihypertensives or antianginals. Amlodipine can be safely combined with β blockers, ACE inhibitors, thiazides and nitrates. It has a half life of 40 hr and the initial effects are cumulative over many days.

Atenolol is a cardio selective beta-1 adrenoceptor blocker devoid of intrinsic sympathomimetic and membrane stabilizing activity. Atenolol is mainly absorbed in the stomach than in the lower gastrointestinal tract and the oral bioavailability has been reported to be 50%. It is ideally suited for the gastroretentive floating tablets. The human jejunal permeability to atenolol and the extent of absorption is low. Thus, it seems that an increase in gastric retention time may increase the extent of absorption and bioavailability of the drug.

Atenolol has short half life therefore to reduce the frequency of administration and to improve patient compliance; a sustained-release formulation of atenolol is desirable. A combination of CCB and β-blocker that mutually interfere with compensatory responses was considered more likely to increase blood pressure control and even prevent untoward side effects.

Formulation of dual retard floating tablet of amlodipine besylate and atenolol is beneficial as increase in patient compliance, increase in stability, dual action in single formulation and increase the absorption of atenolol by retaining it into stomach. A patient whose blood pressure is not adequately controlled with atenolol extended-release or amlodipine mono-therapy may be switched to the combination therapy.
Chapter 3

Aim of present work

The aim of the present research work is to be developed and optimized an immediate release part containing amlodipine besylate which release more than 90% of drug within 1 h and atenolol as sustained action which start release up to 12 hr in sustained pattern. Immediate action of amlodipine besylate will be helpful to control hypertension, which will be maintained by atenolol action later on.

3.4 Aim of study

1. To check compatibility of drug with polymers and super disintegrating agents.
2. To formulate immediate release layer of salbutamol sulphate and sustained release layer of theophylline.
3. To optimize immediate release layer and sustained release layer of respective drugs.
4. To evaluate immediate release layer and sustained release layer of respective drugs.
5. To formulate and evaluate dual retard tablets of salbutamol sulphate and theophylline.
6. To formulate immediate release layer of amlodipine besylate and sustained release layer of Atenolol.
7. To optimize immediate release layer of amlodipine besylate and sustained release layer of atenolol.
8. To evaluate immediate release layer of amlodipine besylate and sustained release layer of atenolol.
9. To formulate and evaluate dual retard tablets of amlodipine besylate and atenolol.
10. To apply factorial design for optimization of dual retard tablet of amlodipine besylate and atenolol.
11. To study effect of concentration of super disintegrating agents and polymers desired drug release profile.
12. To achieve sustained action of the drug for 12 hr.
13. To achieve immediate release of more than 90% of drug in 1 h time.
14. To represent dissolution profiles in charts, contour plots and response surface plots.
15. To determine mechanism of drug release by fitting dissolution data to various kinetic equations.