CHAPTER II

OBJECTIVE AND SCOPE
OF WORK
Successful drug therapy depends not only on the choice of an appropriate drug but also on the choice of a suitable formulation. The task of the research and development scientists involved in the formulation of a new product is to develop a dosage form which is optimum from both technical and biopharmaceutical point. The majority of drugs are formulated into dosage forms which deliver the drug to the general circulation at a rate which is controlled by the physiological process in the body and not controlled by the dosage form themselves. However, for optimal administration of a number of drugs it may be necessary to deliver the drugs from their dosage form in required amount at a controlled rate to the target organ over desired period of time.

Although continuous intravenous infusion has been recognized as a superior mode of drug administration to main a constant and prolonged drug level in the body, such mode of administration entails certain risks and, hence, requires hospitalization of the patients and close medical supervision. This is a long time to spend over an intravenous therapy in a busy department especially in areas with inadequate provision of medical personal. Parenteral administration also precipitates psychological pain and also induces injury to the site of administration. Pain, a local reaction to injection, causes most concerns in humans, especially in children. The adventitial inflammation may occur due to irritation in the lining of the vessel. Prolonged irritation and severe intimal injury may lead to granulation of tissues. Moreover, severe intimal injury may lead to thrombus formation.

With the conventional drug delivery systems, the delivery of the required amount of drugs to the target organ for desired period of time to produce pharmacological effects is a goal often approximated but rarely satisfactorily achieved. Most of the drugs that are administered by oral route are absorbed rapidly through the gastrointestinal mucosa. The drugs are finally transferred into the blood stream where they are widely distributed throughout the organs of the body. A typical plasma-concentration time profile following a single dose of administration of an oral dosage form of drug produces a curve that reaches its peak gradually after administration and then begins to decay in systemic elimination. If it is necessary to maintain a constant therapeutic blood level of drug between the medication intervals then a greater dose has to be administered. The greater dose of the drug may, however, produce inordinately high and often toxic levels for
significant periods. In order to reduce toxic manifestations due to unduly high levels of
drug, the dose of the drug may be reduced. This may, on the other hand, produce blood
levels of drug which for much of the period of treatment will remain below the threshold
of efficacy. In either case, the fraction of the administered dose is utilized by the patient
is depressingly small amount. Maximum availability of a drug from conventional drug
delivery systems utilizing minimum amount of the drug can be achieved by repeated
administration of small increments of the total dose. However, continuous
administrations of drugs by conventional drug delivery systems are either impossible or
impractical.

A drug should be present in blood at a certain level to elicit the desired
therapeutic response in patients. This serum level of drug is known as “minimum
effective level”. Conventional drug delivery systems like tablet, capsules are usually
administered 3 to 4 times a day in order to produce and maintain the desired therapeutic
response. Initially each dose will produce a maximum drug concentration which is much
above the minimum effective dose. As the drug is eliminated and inactivated the drug
concentration falls below the minimum effective dose level, a level known as
subtherapeutic level at which inadequate therapeutic response is exerted until the next
dose is administered. Thus multidose are wasteful and inadequate. Patient compliance is
one of the major disadvantages of conventional drug delivery system. It has been found
that the compliance is the poorer, the more dosage the patient has to take per day. Non-
compliance is a well recognized problem with patients, particularly suffering from
chronic illness and requiring long-term maintenance therapy. Some studies have shown
that the rate of non-compliance may be as high as 50% or more. Many factors may be
responsible to patient non-compliance including the number of medication, frequency of
administration, and unpleasant side effects.

The findings that rate of adsorption of drugs into the body can be controlled by
controlling the rate of release of drugs from the dosage forms, have led to development of
more practical and highly promising methods which can provide the desired blood level
of drugs over the desired period of time. One such method is known as controlled drug
delivery system. A controlled release formulation is often administered to the total
systemic biological environment by a conventional method, although the formulations
deliver the drug to the system at a predetermined rate. If a drug is administered in a sustained release dosage form, a more sustained and less variable plasma concentration of the drug may be obtained and may also lead to more economical utilization of drugs without waste. Sustained release dosage form of a drug may produce reduced side effects than when administered in conventional dosage form. Drug induced gastrointestinal disturbances are reduced when they are administered in sustained release dosage form probably because the gastrointestinal mucosa are not exposed to the same concentration of drugs as it would be with immediately available products. In addition to maintaining the blood level of drug within the therapeutic range without much fluctuation and minimizing the toxic manifestations, sustained release also offers other advantages like patient compliance and relieves the burden of excessive dosing.

A great majority of sustained release products are formulated in the form of tablet. However, during dosing of such products due attention should be paid to the physiological characteristics of the gastrointestinal tract. There are wide physiological and environmental varieties in the gastrointestinal tract with respect to surface area of absorption, pH, fluidity, and rate of transit time. In addition, many factors, including food constituents and many drugs, influence the rate of gastric emptying. Thus if a sustained release product is formulated in the form of tablet which keeps its integrity throughout the gastrointestinal tract, then the location of the tablet will vary under different circumstances. This will lead to the variation in the rate of drug delivery to the systemic circulation.

In order to overcome the vagaries of gastric emptying, different transit rates through the gastrointestinal tract and different degrees of fluidity, sustained release dosage form should be formulated in multi-unit dosage forms like microcapsules and microspheres, rather than in single unit dosage form like tablet. It has been found that multi-unit preparations pass through the pyloric sphincter almost as if a solution and then become scattered throughout the gastrointestinal tract and also they move up and down during their slow passage down the gastrointestinal tract.

It has been reported that drugs like KCl produces gastrointestinal side effects, even when administered in single-unit sustained release tablet. When the same drug was
administered in multi-unit sustained release dosage form, there was no damage to the mucous membrane.

Therefore, there will be a great difference in conditions when a sustained release form is administered as multi-unit package which become scattered in gastrointestinal tract than when administered in single unit package from which drug becomes available at any one time to a small region of the tract.

Oil in oil emulsion solvent evaporation method for the preparation of microcapsules and microspheres has gained popularity because of its simplicity, reproducibility and amenability to tailoring process parameters. Although the drug loading efficiency achieved by the method is considerably high, it suffers from a major disadvantage which is the use of large volume of organic solvents. To avoid the toxicity to the working personal, explosion hazards and environmental pollution, a modified oil in water emulsion solvent evaporation method has been developed. Although the method requires considerably less amount of organic solvent, it is not suitable for entrapping water soluble drugs. In addition, considerable research efforts have been concentrating in recent years to develop microcapsule or microsphere dosage form of drugs using natural polymers to avoid the use of organic solvent completely and to use ecofriendly conditions for formulation. Sodium alginate has drawn considerable attention in this regard as it forms water insoluble calcium alginate beads through ionotropic gelation of alginate by Ca\(^{+2}\) ions. However, this method too suffer from disadvantages like low drug entrapment efficiency of water soluble drugs and rapid release especially in simulated intestinal fluid.

The objective of this investigation was to develop microsphere or microcapsule dosage form of water soluble drugs using both synthetic polymer like polystyrene utilizing oil in water emulsion solvent evaporation method, and natural polymer like sodium alginate utilizing ionotropic gelation method in a completely aqueous environment. In addition, this investigation involved optimization of the process parameters to achieve reasonably high drug loading and prolonged release in simulated gastrointestinal fluid. The basic principle of this investigation was based on the preparation of drug-resin complexes followed by coating with polystyrene or sodium alginate. Diltiazem hydrochloride and propranolol hydrochloride were selected as two
water soluble drugs in this study as better therapeutic effects can be achieved when these drugs are administered in the form of sustained release preparation.