CHAPTER VI

SUMMARY

A major approach in current pharmaceutical research is directed towards the development of newer and better drug delivery systems of known drugs rather than the development of new drugs. Such development work should be mostly based on, although not restricted to, optimum utilization of indigenously available resources and technology with an objective of making available most effective as well as economical drug delivery systems. This is of particular relevance in national context in a developing country like India. The designing of controlled drug delivery systems specifying the rate and duration of delivery rather than the drug content, with particular emphasis on safety, efficacy and patient convenience has been one such major path of technological innovation to better utilize the already known drugs, over the past decade. In view of the present trend and need an attempt has been made in this study to employ the indigenously available laser technology in designing a NEW controlled drug delivery system for oral administration by refining the indigenously manufactured, readily available hard gelatin capsules without involving much of sophistication.

Over the years there has been available a variety of dosage forms with which an attempt has been made to control

the time course and specificity of drug action in the body; these have been indentified by various names such as "controlled release", "sustained release", "prolonged release", "timed release", "long acting" and "slow release". In each of these drug delivery systems, there has beer some degree of "control" over the temporal pattern of drug placement in target tissue. In some situations the term control might mean that the drug be delivered more promptly for short period of the time and in other cases it would mean prolongatic̈n of drug levels. Actually controlled drug delivery is the desired effect of all such systems fabricated.

Chapter I (A) gives a brief account of several approaches that can be used to control drug release in designing oral control drug delivery systems with particular emphasis on the system design. Schematic representation of these systems and their theory are discussed in detail with a view to better understand their working and differentiate them from the NEW controlled drug delivery system proposed and studied in the present investigation. One such system proposed to control the drug delivery, which is relevant to the present study is the system designed based on the principle of an elementary osmotic pump and this system operate in the following manner : a semipermeable membrane placed around a tablet particle or drug solution allows the transport of water into the tablet, with eventual pumping of drug solution out of the tablet through a small

delivery hole in the tablet coating. An important aspect to the success of this type of delivery system is the size of the delivery hole. Hence a high degree of accuracy and precision over the size of the orifice is essential in designing such a controlled drug delivery system. Theeuwes et al. recently reported the use of automated laser drilling in making accurate and precise exit pore for indomethacin in designing an elementary osmotic pump. The unique properties of lasers (Light Amplification by Stimulated Emission of Radiation) like monochromatic and coherent nature of the beam, possibility of focusing the beam to a small spot using an appropriate lens, accurate and precise control over the drilled micropores and large scale production possibilities; have made it the tool of choice in designing a controlled drug delivery system involving the drilling of accurate and precise micropores. An account of the lasing process, type and application of laser, etc. has been presented in Chapter I (B).

The literature survey reveals that the potential use of laser in the field of communication, industry, medicine etc. has been well established by now, however its use in pharmacy has not been explored to any significant extent. The attempts to use laser in pharmacy apart from the report of Theeuwes et al. mentioned above is limited to fields like aerosol valve drilling and surface sterilization.

An attempt has been made in this study to employ indigenously available laser technology and materials in designing a new controlled release drug delivery system, based on the combined principle of dissolution and diffusion. The new drug delivery system design proposed consists of a GIT resistant capsule with minute laser drilled pores made on the walls of the capsules. The capsules are band sealed using a suitable GIT resistant material after encapsulating the contents. On oral administration, the release of the drug can take place only through minute laser drilled pores (unlike conventional capsules) and the release rate would be proportional to the total surface area available for diffusion i.e. size and number of laser drilled pores. Also the dosage form design does not involve any treatment to the drug which probably might reduce the bioavailability, but in this case the drug release is retarded by treating the system encapsulating the drug. Hence the objectives of the present investigation were to :

I. design a new controlled drug delivery system using laser and standardize the system with respect to preparation of GIT resistant capsules and laser drilling technique using an appropriate model drug;

II. use the new drug delivery system in designing slow release capsules;

III. use of suitably modified form of the new drug delivery system in designing sustained release capsules, and

IV. prepare a commercial and economical feasibility report on use of laser in designing controlled release drug delivery system as envisaged herein, in a Pharmaceutical Industry.

I. Designing a New controlled Drug Delivery System, Employing Laser

A systematic approach to the controlled release system design using laser drilling involves the following steps (as discussed in Chapter II) :

i) Preparation of GIT resistant capsules by formalin vapour treatment of conventional hard gelatin capsules and confirming their GIT resistance by *in vitro* and *in vivo* GIT resistance test.

ii) Standardization of the system designed with respect to the laser drilling technique to make minute pores of accurate and precise diameter on hardened wall of the capsules.

iii) Optimization of parameters which are likely to influence the preparation of GIT resistant laser drilled capsules and the factors likely to influence the release of the drug from the capsule by *in vitro* dissolution tests using tetracycline hydrochloride as the model drug.

Preparation of GIT Resistant Capsules - The GIT resistant capsules were prepared by giving formalin vapour treatment to conventional hard gelatin capsules under standardized conditions. The residual formalin content, formalin vapour contact time, drying time temp. etc. were standardized to get the GIT resistant capsules of required quality. The GIT resistance of the capsule was confirmed by *in vitro* test in simulated gastric and intestinal fluids containing enzymes and by *in vivo* X-ray studies in human volunteers.

In Vitro Performance Test - The influence of variation in diameter of laser drilled pores and the pattern of drilling on the release rate of the drug from the capsule was studied, by *in vitro* dissolution studies in an USP XX dissolution apparatus using a basket stirrer assembly.

The variation in number and diameter of drills considerably affected the release rate of the encapsulated drug, unlike the variation in pattern of drilling which did not show significant influence on release rate of drug, indicating that it is possible to control the release rate of the drug from the system by varying the number and diameter of laser drilled pores and thereby varying the total surface area available for the release of the drug from the capsule. The capsules with drilled pores in the size range of 50-125 μm were found to be satisfactory for encapsulating the drug, since the loss

of the content from these capsules was less than 0.8%, when subjected to friability test. The common capsule formulation additives like lactose, microcrystalline cellulose, magnesium stearate did not significantly affect the rate of release of the drug from the capsules. The presence of wetting agent like dioctyl sodium sulfosuccinate significantly affected the release rate, unlike polysorbate 80, which though enhanced the release was not statistically significant. Physical property of the encapsulated drug like particle size and size distribution, considerably affected the release rate of the drug from the capsules. These experimental findings (ChapterII) indicated that laser drilling technique could be successfully employed in designing the proposed NEW controlled release drug delivery system.

II. Use of NEW Laser Drilled Controlled Drug Delivery System in Designing Slow Release Capsules

Two commonly used drugs, aspirin (a slightly soluble drug) and tetracycline hydrochloride (freely soluble drug) were selected for the study with following objectives.

i) Use of the NEW drug delivery system in preparing slow release capsule of slightly soluble drug.

ii) Prepare slow release capsule of a soluble drug employing the NEW drug delivery system.

iii) Make a comparative evaluation of <u>in vitro</u> and <u>in vivo</u>

performance of the above capsules and their stability with conventional dosage form of these drugs, prepared using conventional hard gelatin capsules.

Slow Release Aspirin Capsules - Slow release aspirin capsules were prepared by encapsulating aspirin 250.0 mg coated with 0.5% (w/w) dioctyl sodium sulfosuccinate; in laser drilled GIT resistant capsules having 50 minute laser drilled pores of about 100 um average diameter made on the body wall of the capsule, using lactose as the diluent. The capsules were band sealed with a suitable GIT resistant material.

Slow Release Tetracycline Capsules - Slow release tetracycline capsules were prepared by;(a) encapsulating tetracycline hydrochloride 250.0 mg coated with 0.5% (w/w) dioctyl sodium sulfosuccinate in GIT resistant laser drilled capsules with 50 minute pores of 100 um average diameter on the body, using lactose as the diluent and (b) encapsulating tetracycline hydrochloride 250.0 mg coated with 0.5% (w/w) dioctyl sodium sulfosuccinate in GIT resistant laser drilled capsules with 100 minute pores of about 100 um average diameter using 50.0 mg sucrose with lactose as the diluent. The capsules were band sealed with a suitable GIT resistant material.

In Vitro Performance Test : In vitro performance test was carried out in an USP XX dissolution apparatus, using a

basket stirrer assembly under standardized conditions in appropriate dissolution media.

In vivo Performance Test - A crossover study was carried out with one week wash out period in between on four healthy human volunteers, as the subjects.

Experimental findings indicate that the NEW drug delivery system may not be suitable for slow release capsule preparation of a slightly soluble drug. This finding also supported the proposed mechanism of drug release from the system i.e. the first step of drug release from the system is dissolution. A drug having pH dependent solubility characteristics does not follow zero-order release pattern, when encapsulated in laser drilled capsules. Laser drilled slow release tetracycline capsules with 50 laser drilled pores on the body, prepared using lactose as the diluent released only 21.8% of the drug in 8.0 hr when subjected to in vitro dissolution studies, however, it failed to release the drug in vivo, when administered orally to human volunteers may be because the surrounding gastric fluid failed to make an entry into the capsule and dissolve the drug initially because of the poor attraction force offered by the capsule core to the surrounding fluid. Hence the formulation needed modification.

Use of 50.0 mg sucrose as the channeling agent in combination with lactose as the diluent increased the amount of the drug released in vitro from 21.8% to 67.6%. Further increase in number of drilled pores from 50 to 100 increases the amount of drug released in vitro from 67.6% to 74.4%.

The conventional capsules released 100.0% of tetracycline hydrochloride in less than 10 min in comparison to slow release capsule which releases only 74.4% of the drug in 8.0 hr, when subjected to in vitro dissolution studies. The slow release capsules performed well when subjected to in vivo studies giving low C_{max} and high t_{max} with significantly similar $t_{0.5}$ and K_e values as compared to conventional capsules. Hence it is inferred that the use of sucrose as a channeling agent improved the performance of the capsule possibly by increasing the attractive force of the core material and facilitating imbibition of surrounding gastric fluid into the capsule. The possible advantage of such laser drilled slow release capsule may be :

i) the potential hazard associated with encapsulation of highly soluble drug in conventional hard gelatin capsule due to sudden release of such compounds resulting in localized irritating concentrations of the drug, could be overcome.

ii) The drug with narrow therapeutic range could be administered by oral route safely because of relatively low C_{max} value.

iii) The therapeutic efficacy of the drug may be increased and the frequency of administration may be reduced since slow release capsules maintain blood levels of the drug for a longer duration of time, thus allowing better and longer interaction of the drug at the active sites.

The minute pores made on the wall of the capsules did not considerably affect the stability of the encapsulated drug under the storage conditions as compared to conventional capsules. Considerable reduction in the residual formalin content at 35°C-65% RH and 50°C affecting the *in vitro* and *in vivo* GIT resistance indicated that slow release capsule should be advised to be stored under refrigerated conditions, as storage under refrigerated conditions did not affect the residual formalin content.

III. Use of Laser Drilled Capsules in Designing Sustained Release Capsules - Propranolol hydrochloride with good water solubility, independent of pH was selected for the study with the following objectives :

i) Design a sustained release capsule dosage form capable of delivering loading dose immediately and then the maintenance dose at a controlled rate, using laser drilled capsules.

ii) Use the above dosage form to prepare propranolol sustained release capsule (Laser Drilled SR capsule) for maintaining the blood level of the drug for 12.0 hr.

iii) Make a comparative evaluation of <u>in vitro</u> and <u>in vivo</u> performance of Laser Drilled SR capsules with that of Inderal® LA and Inderal® conventional tablets.

Laser Drilled SR Capsules, System Design - The Laser Drilled SR capsule consisted of an outer Mother capsule with loading dose and an inner Baby capsule encapsulating the maintenance dose. The amount of propranolol hydrochloride to be taken as loading dose and the maintenance dose was calculated, based on the reported pharmacokinetic parameters, considering the average weight of an individual as 70.0 kg, with a view to maintain an average therapeutic blood level concentration of about 52.5 ng/ml of the plasma, for 12.0 hr.

<u>In Vitro</u> Dissolution Assessment - The dissolution studies were carried out in an USP XX dissolution apparatus, using a basket stirrer assembly at a stirrer speed of 100 rpm and

the dissolution medium temperature held at 37±0.5°C. 300.0 ml each of 1.2, 2.5, 4.5, 7.0 and 7.5 pH dissolution media were prepared and changed at different interval of time as per the method recommended in NF - under Timed Release Tablets and Capsules In Vitro Test Procedure.

In Vivo Study - A crossover study was carried out with one week washout period in between on six mongrel dogs weighing 6-10 kg as the subjects. The blood samples were analysed by spectrofluorimetric method.

The results of these experimental findings (Chapter IV) indicate that;

i) laser drilling technique can be successfully used in designing a system for making a sustained release dosage form that is capable of releasing the loading dose immediately and the maintenance dose slowly at a controlled rate for 8.0 hr, and maintain the blood level for 12.0 hr like a commercial product, Inderal® LA capsules;

ii) the pH independent, zero-order in vitro and in vivo release pattern of propranolol hydrochloride from the Laser Drilled SR capsule indicates that the drugs with pH independent solubility characteristics may be released following zero-order kinetics from the NEW laser drilled controlled drug delivery system

designed, irrespective of the pH of the GIT fluid surrounding the capsule; and

iii) Laser Drilled SR capsules of propranolol hydrochloride could be used therapeutically as a product for twice daily administration after confirming the findings in human volunteers.

IV. Commercial and Economic Feasibility Report - A commercial and economic feasibility report on establishing facilities for the manufacture of NEW controlled drug delivery system employing laser drilling technique in a pharmaceutical industry was worked out. A continous manufacturing process for the manufacture of laser drilled GIT resistant capsule was proposed based on the processes involved in commercial scale manufacture of conventional hard gelatin capsule and the laboratory scale method developed in this study to prepare GIT resistant laser drilled capsules. The proposed continous manufacturing process of laser drilled GIT resistant capsule increases the fixed cost by 50.0%, variable cost by 100.0%, with 66.0% decrease in production as compared to the cost of a conventional capsule. As a result the cost of the laser drilled GIT resistant empty capsule increases by approximately 4 times as compared to conventional empty hard gelatin capsules. However, this increase in cost of empty capsules would be very nominal as compared to the cost of

the dosage form and the overall increase in the price of the dosage form may be only 10%. But the preparation of sustained release product by other methods like bead formulation would involve an increase of not less than 25 to 30% in the cost of dosage form as compared to the conventional dosage form. Hence it was concluded that use of laser in designing controlled release drug delivery system is commercially and economically feasible and it provides simple improved, more effective and convenient dosage form at a very reasonable cost. Thus the findings of this investigation clearly establish that one of the promising applications of laser in pharmacy could be in the field of designing controlled drug delivery systems.

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