C H A P T E R I

INTRODUCTION

A. Controlled Drug Delivery Systems

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. This is of particular interest in national context in a developing country like India. Such developmental 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. 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 the 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 have 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 identified by various names such as "controlled release", "sustained release", "prolonged release", "slow release" and "timed release". In each of these drug delivery systems, there has been some degree of control over the temporal pattern of drug placement in target tissue. However, a maximization of therapy has generally not been achieved. To maximize drug utilization, it is necessary to deliver the drug to the target tissue in correct amount at proper time to elicit the desired response. Moreover, drug delivery must be continued at a rate such that the condition in question is cured or controlled in a minimum time with fewest side effects. J.R. Robinson defined controlled drug release as the phasing of the drug administration to the needs of the condition at hand, so that an optimal amount is used to cure or control the condition in a minimum time. In some situations this might mean that the drug be delivered more promptly for short period of time and in other cases it would mean prolongation of drug levels. In the latter category we employ the terms "sustained release" and "prolonged release", interchangeably. This designates only one aspect of controlled release namely, to produce protracted levels of drug in the body. Actually, controlled drug delivery is the desired effect of all the drug delivery

systems, and all presently fabricated sustained, prolonged and slow release drug delivery systems, provide some degree of control, albeit incomplete. Thus according to Robinson none of the commercially available systems presently in the market is in truth a controlled drug delivery system, some are just better than the others.

A.1 Routes of Administration

The development of controlled drug delivery system has been investigated through a wide range of routes of administration. The major routes of drug entry into the body involving controlled release dosage forms may be roughly classified as : oral, percutaneous or transdermal, local drug application to a particular tissue organ and parenteral. The data on clinical trials involving various types of controlled drug delivery systems conducted in the past 16 years has been compiled by Robinson (1). The oral route of administration though has its own limitations, still enjoys preference over the other routes of administration, because of several advantages. Drug absorption from gastric and intestinal regions have been extensively reviewed (2-12).

In general, gastrointestinal tract (GIT) is a hostile environment which must be contended with, in product design. Frequently changing environment is the most important factor

to be considered in designing oral sustained release products. The changes occur as one traverses the GIT, and there is also patient to patient variation in the GIT content, stomach emptying time and peristaltic activity. These physiological properties can introduce considerable variations in dosage form performance and resulting blood concentrations. With some drugs and drug delivery systems these variations can be more severe than with others. However, oral route is also a safe route of administration of controlled drug delivery system with minimum constraints of sterility and potential damage at the site of administration in comparison to the parenteral route. Thus, although the constraints of the oral route are numerous and at times severe, there is still more flexibility in dosage form design than that exists for other routes of administration.

A.2 Mechanism of Drug Delivery

Several controlled release dosage forms have been designed for oral administration in which prolonged action tablets and capsules predominate, with one or two liquid type products available. Several approaches that can be used to retard drug release are discussed in the following sections, 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.

a) Methods Based on Diffusion - The principles of diffusion controlled release of drug have been extensively discussed in the literature. A particularly comprehensive article in this regard is the review by Flynn et al. (13), in which the various conditions for diffusion release of drug are presented together with appropriate equations for data treatment.

Basically diffusion involves the moment of drug molecules from a region of higher concentrations to one at a lower concentration. The parameters which need to be considered by the formulator in designing controlled release drug delivery system can be explained by Fick's first law, Eq. (1)

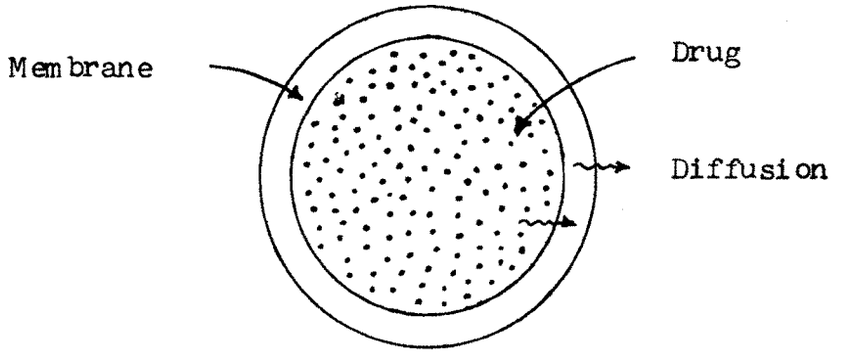
$$J = -D \frac{dc}{dx} \qquad \ldots \text{ Eq. (1)}$$

where, J (in amount/area-time) is the flux of the drug across the membrane in the direction of decreasing concentration, D is the diffusion coefficient (in area/time) and $\frac{dc}{dx}$ is the change in concentration, c with distance, x.
The release rate from the system is given by the Eq. (2).

$$\frac{dM}{dt} = \frac{A\ D\ K\ \Delta C}{l} \qquad \ldots \text{ Eq. (2)}$$

where A is the area, D is the diffusion coefficient, K is the partition coefficient of the drug between the membrane and the drug core, l is the diffusional path length, and C is the concentration difference across the membrane. In order to have a constant rate of release of the drug from such a system, it is necessary to maintain constant area, diffusional path length, concentration difference and diffusion coefficient.

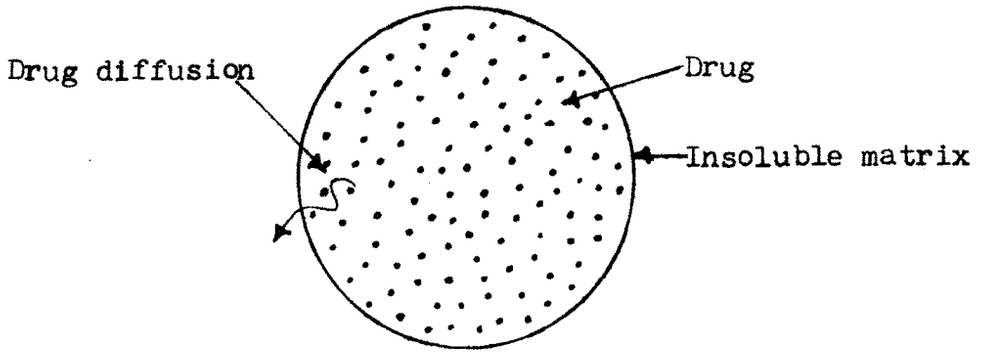
Scheme 1 as shown below represents the basic diffusion



Scheme : 1. Diffusion control of drug release by a water insoluble polymer.

controlled system. In this system a water insoluble polymeric material encloses a core of the drug. The drug will partition to the membrane and exchange with the fluid surrounding the particle. Additional drug will enter the polymer, diffuse to periphery and exchange with the surrounding media.

An alternate type of diffusion controlled system is shown in Scheme 2. Here a solid drug is dissolved in an insoluble matrix and the rate of release of the drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. An appropriate equation



Scheme : 2. Diffusion control of drug release by solid drug dispersed in insoluble matrix.

describing drug release from this system has been derived by T. Higuchi, Eq. (3).

$$Q = \frac{DE}{T} (2A - E C_s) C_s t^{1/2} \qquad \text{... Eq. (3)}$$

Where, Q = weight in grams of the drug released per unit area of the surface at time, t,

D = diffusion coefficient of the drug in the release medium,

E = porosity of the matrix,

C_s = is the solubility of the drug in the release medium,

T = tortuosity of the matrix;

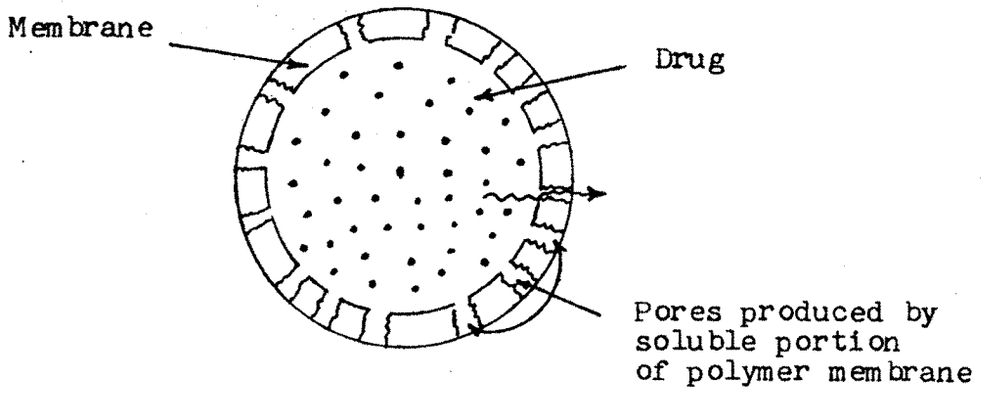
and A = concentration of the drug in the tablet expressed as gm/ml

For the purpose of data treatment Eq. (3) is reduced to Eq. (4).

$$Q = kt^{1/2} \qquad \ldots \text{ Eq. (4)}$$

where k is a constant, so that a plot of amount of drug released versus the square root of the time should be linear if zero-order release is occurring.

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of the membrane allows for diffusion of the enclosed drug through the pores in the polymer coat.



Scheme : 3. Diffusion control of drug release by partially water soluble polymer.

Scheme 3 shows an illustration of this approach. The release of the drug from such a system is explained by Eq. (5).

$$\text{Release Rate} = \frac{AD}{l}(C_1 - C_2) \qquad \ldots \text{Eq. (5)}$$

where, C_1 is the drug concentration in the core, C_2 is the drug concentration in the surrounding media and the other terms are as previously defined. The fraction of the soluble polymer in the coat is the dominant factor in controlling drug release rates.

The diffusion controlled drug delivery systems are generally based on two approaches : (i) placement of drug in an insoluble matrix, and (ii) enclosing the drug particle with a polymer coat. In both the cases a constant area for diffusion together with a constant diffusional path length and constant concentration of the drug are essential to achieve a constant drug release rate.

(i) Placement of Drug in an Insoluble Matrix : One of the earlier reports on core tablets that release drug by diffusion is the study by Sjogren and Fryklof (14). In this case the core is produced by direct compression of a granulate of drug with an insoluble plastic material, so that a porous skeleton of the matrix material forms around

the drug. Release rate and absorption of various drugs incorporated in a plastic matrix-type tablet have been extensively studied by Sjogren and associates (15-16).

The release rates of creatinine, lobeline hydrochloride, nitroglycerin, potassium penicillin G and ammonium bromide have been studied (14) and a good correlation between *in vitro* and *in vivo* results was found. Asker *et al.* (17-19) and El-Egakey *et al.* (20) have also examined the *in vitro* release of drugs from polymeric matrices and granulations.

Water soluble drugs dispersed in hydrophillic matrices were studied by Lapidus and Lordi (21). The results using chlorpheneramine maleate dispersed in methylcellulose, showed that the release rate was controlled mostly by drug diffusion, rather than polymeric dissolution. Thus even when drugs are placed in a water soluble matrix which will be subjected to erosion, the rate limiting step is diffusion of drug out of matrix. Huber *et al.* (22) employed hydrophillic gum as the matrix material and showed that drug diffusion from a gel barrier, at the periphery of the tablet was rate limiting. The type of plastic matrix investigated most extensively is that of a drug dispersed in an insoluble, plastic, inert matrix (23-26). The kinetics of release of drugs dispersed in a methyl-acrylate-methyl methacrylate

matrix have been reported by Farhadich and co-workers (27-28). They found that exposing such tablets to acetone vapour, thus causing fusion of the plastic material and hence decreased porosity, resulted in a significant decrease in release rate of the drug from the matrix. Sjuib et al.(29-30) extended the work of Higuchi (31). The original model described by Higuchi was tested for binary mixtures of acidic and amphoteric drugs. The data showed that precipitation of drug in the matrix during release into alkaline media, such as one might encounter in intestinal fluids has to be considered.

The matrix diffusion control systems which showed good potential of use by in vitro studies were subjected to clinical trials to study their performance in vivo. Levy and Hollister (32) described the effects of gastric emptying time and intestinal peristaltic activity on absorption of aspirin from a sustained release tablet containing coated particles in a hydrophillic gel-type matrix. The lag times in the absorption profiles were attributed to the time required for transfer of dosage form from the stomach to the intestine.

Theophylline aminoisobutanol, administered in a tablet containing sustained release core having a matrix of hydrophillic gums, a delayed barrier coat on the core, and an

outer coat containing drug for immediate release, was investigated by Kaplan (33). The *in vitro* and *in vivo* data correlated well. The *in vivo* absorption and excretion of pentylene tetrazole was studied by Ebert *et al.* (34). Human volunteers were given either a single dose of sustained release insoluble matrix tablets, or divided doses of conventional tablets. It was shown that sustained release product gave absorption and excretion pattern similar to those obtained by non-sustained tablet. Clinical trials have been conducted on a sustained release form of triethenolamine trinitrate (35) for use in angina pectoris. The drug was provided in a plastic matrix from which it was leached out every 7-8 hr. Patients experienced no side effects and the severity of angina diminished in 80% of the patients tested.

Cass and Frederik (36) clinically evaluated pentobarbital sodium administered via conventional capsules and Abbott's Gradumat plastic matrix sustained release form. The results indicated that the Gradumat form was free of side effects and did provide daytime tranquilization. Ferrous sulphate administered in the Gradumat matrix form has also been evaluated (36). On the basis of hematocrit and hemoglobin response it was found to be equally effective as its nonsustained counterpart. However, the incidence of

side effects was diminished with the sustained release form. In contrast Crosland-Taylor and Keeling (37) have found that hematocrit and hemoglobin responses were insensitive means of assessing matrix sustained release ferrous sulphate. They further indicated considerable absorption variation in the sustained release form and found no advantage to the sustained release product.

Wiseman and Federici (38) have developed a sustained release aspirin tablet employing the matrix principle. By comparing the in vivo data to the in vitro data they were able to formulate a good sustained release product. Clinical studies (39) showed that the product gave highly reproducible blood levels that exhibited less fluctuations than the conventional tablets. Harris and Regalado (40), however, compared conventional and sustained release aspirin for relief of arthritis. They reported no difference between the sustained and conventional dosage forms although the patient preferred the sustained release form.

(ii) Encapsulated Diffusion Control : Controlled drug delivery systems of this type have the drug particles contained in the coating film as well as in the core of the microcapsule. Drug release from this system involves a combination of diffusion and dissolution with dissolution

being the overriding process. If the encapsulating material is selected properly, diffusion control will predominate.

Several studies have been reported wherein cast films containing drugs were tested for their release pattern (41-43). Borodkin and Tucker (42-43), examined the release of methapyrilene, pentobarbital and salicylic acid from cast films of hydroxypropylcellulose. These drugs were released from the film by a diffusion-controlled process. Modification of the film by laminating a second film without drug to the releasing side of the film containing drug gave good in vitro zero-order release characteristics. The non-drug layer functioned as a rate controlling membrane and the drug containing film functioned as a reservoir.

An interesting related study is the work with Sinsule sustained release dosage form (44). In this product the film applied to the drug granule is reported to function as a microdialysis membrane. Thus environment conditions of GIT such as pH, enzyme concentration and general GIT content should have limited influence on the release rate. Fluid from the GIT penetrates through the dialysis membrane into the granule and dissolves the drug. The drug then diffuses through the intact membrane at a rate proportional to the permeability of the membrane, concentration of the drug within the hydrated microdialysis cell, and mobility of

the drug molecule. The product performed very well in clinical trials.

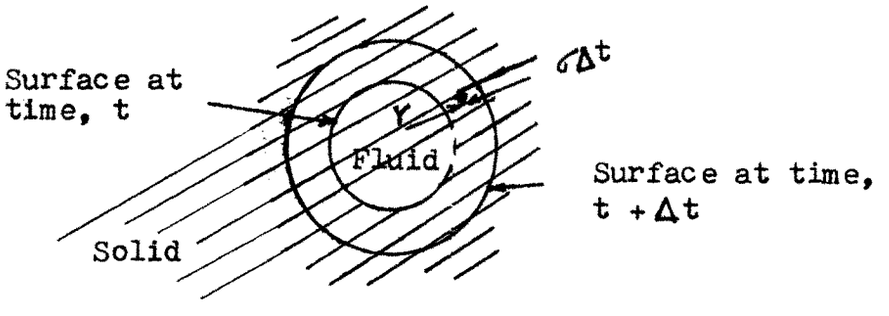
Coletta and Rubin (45) and Wood and Syarto (46) reported on the use of methylcellulose and ethylcellulose films to coat aspirin particles using Wurster air-suspension coating technique. In this case, the methyl-cellulose dissolves out of the film leaving small channels in the film through which drug can diffuse. The ethylcellulose barrier left on the particle serves as a restraining barrier to maintain constant diffusional area and constant diffusional pathlength.

A.3 Methods Based on Dissolution

Sustained oral products employing dissolution as the rate limiting step are in principle the simplest to prepare. A drug with a slow dissolution rate is inherently sustained and for those drugs with high water-solubility one can decrease solubility through appropriate salt or derivative formation. Even if a drug has rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has slow rate of dissolution. Simply leaving out the disintegrating agent will often suffice to delay the dissolution of the drug and thus prolong drug release. Dissolution of particle, pellet or tablet, without

maintaining constant dissolution area will lead to a change in rate of dissolution as the particle or tablet becomes smaller. This will cause variations from the desired constant rate of drug release, but will still lead to prolongation of drug levels. A more appropriate approach is to try to control the area of dissolution as well as the concentration and diffusional pathlength to obtain a constant release rate in the case of diffusion.

Cleave (47) suggested geometrical modification of tablets, to compensate for the decrease in dissolution rate because of decrease in surface area available for dissolution as indicated in Scheme 4.

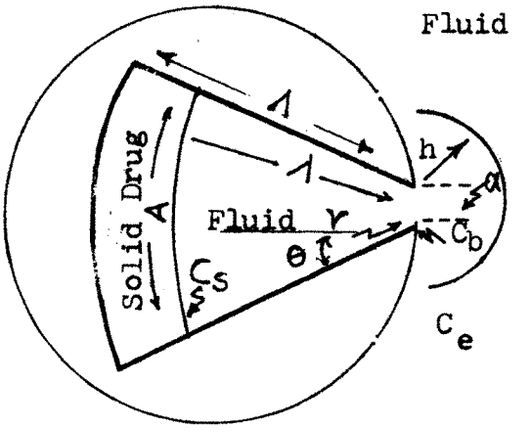


Scheme : 4. Geometrically modified Tablet, with a central hole.

Scheme shows a tablet with a centrally made hole. If the radius of the hole is r, at time t, then the radius will increase to r + $\sigma\Delta t$ at time $t + \Delta t$. Hence as the

tablet dissolution proceeds the surface area of the outer periphery of the tablet decreases gradually, while the surface area of the hole will increase maintaining the total available surface area constant. Hence a zero-order release pattern was obtained by such geometrical modification of tablets. Possibility of having more than one hole in a tablet was also considered in this study.

Brooke and Washkuhn (48) proposed an alternative method of geometric modification of a controlled drug delivery system as shown in Scheme 5, tc control the area of dissolution as well as the concentration and dissolution pathlength to obtain a zero-order release of the drug.



Scheme : 5. Cross section of a zero-order drug delivery system containing solid drug.

The drug delivery system designed is a cavity of length L having uniform cross section with geometric properties like

those depicted in Scheme 5. Here the bold lines describe the cross section of a cavity that might be found within a rigid cylinder having a base of radius r. The cavity communicates with the fluid in which the device is placed, only through a narrow opening of width, a, which runs along the length of the device, this width being indicated by a pair of dashed lines. The cavity must be considered as a portion of a right circular cylinder of radius Λ and altitude L. Thus in the ideal construction, the wall opposite the opening will be arcuate. The device in Scheme 5 had been charged with a solid pellet of drug, which dissolves isotropically. It is assumed that diffusion of drug out of device and into the surrounding fluid is the rate-controlling process. In this case, about 60% of the initial charge has been released and fluid has diffused into the cavity. As drug continues to dissolve and diffuse from the curved surface through a distance, λ to the opening, length A of the curve grows. It is clear from the inspection that $A = 2\theta\lambda$ (for θ in radians). The fact that relationship between the area of the dissolving drug, AL and the diffusion pathlength λ is a constant is a key to the zero-order performance of the device.

The rate equation describing the release of the drug into the surrounding fluid can be derived by assuming that

the rate of transport of the drug to the opening of the device is equal to the rate of transport into the surrounding fluids. The concentration of drug at the dissolving surface is the solubility of the drug, C_s in the fluid. The concentration of the drug at the opening is taken as C_b, and the concentration of the drug at some distance, h into the fluid is taken as C_e. The rate transport of the drug to the opening, R', is given by Eq. (6) and the rate of transport away from the opening, R, is given by Eq. (7).

$$R' = \frac{DAL}{\pi}(C_s - C_b) = 2D\Theta L (C_s - C_b) \quad \text{... Eq. (6)}$$

$$R = \frac{DaL}{h}(C_b - C_e) \quad \text{... Eq. (7)}$$

Considering that sink conditions prevail, i.e., $C_e = 0$ and setting Eq. (7) equal to Eq. (8) it can be shown that the rate of drug release at the steady state is described by Eq. (9)

$$R = \frac{2DaL\Theta C_s}{a + 2\Theta h} = \frac{DLC_s}{\frac{h}{a} + \frac{1}{2\Theta}} \quad \text{... Eq. (8)}$$

where D is the diffusion coefficient. It is clear from Eq. (8) that the release rate of the drug will be constant in a constant environment, i.e. when h is constant.

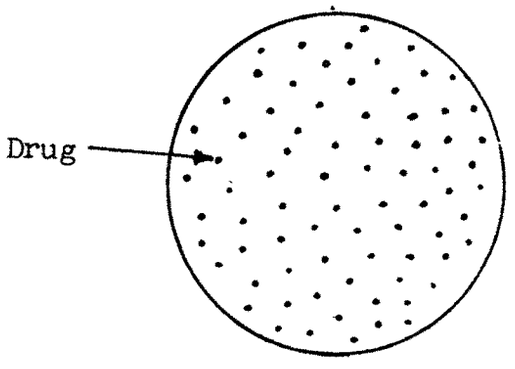
An analysis of theoretical behaviour of the above proposed zero-order drug delivery system was done by Lipper and Higuchi (49). Equations describing drug release with time are developed using physically realistic models. The theory agrees well with the experimental data and indicate that the drug release from the device is nearly, although not rigorously, zero order.

Mechanism of Dissolution Methods : Dissolution process can be considered similar to diffusion controlled process where the rate of diffusion from the solid surface to the bulk of the solution through an unstirred liquid film is the rate limiting step. In this case the dissolution process at the steady state would be described by Eq. (9).

$$\frac{dc}{dt} = K_D A (C_s - C) \qquad \ldots \text{ Eq. (9)}$$

where, $\frac{dc}{dt}$ is the dissolution rate, A is the surface area, C_s is the saturation solubility of the drug, C is the concentration of the drug in the bulk of the solution and K_D is the dissolution rate constant equal to D/Vl where D is the diffusion coefficient, l is the thickness of the unstirred liquid film and V is the volume of the dissolution medium. In such a system the availability is approximately proportional to the solubility of the drug in the dissolution media, C_s, provided constant area and diffusional pathlength

are maintained. After all the solid is gone the concentration difference driving the diffusion process decreases at the same rate as the drug is released. A common type of dissolution controlled dosage form is depicted in Scheme 6.



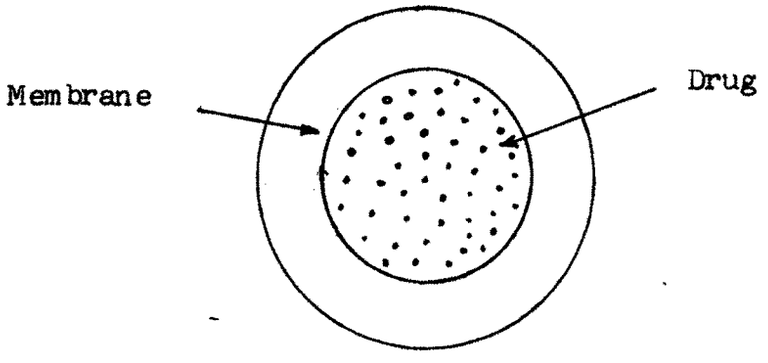
Scheme : 6. Dissolution control of drug release via drug impregnated ercsion.

In the situation shown in the scheme, it can be either drug impregnated sphere as might be obtained by microencapsulation or drug impregnated tablet which will be subjected to slow ercsion.

An alternative type of dissolution controlled dosage form is shown in Scheme 7.

In this case the drug is coated with a given thickness coating which is slowly dissolved in the contents of the GIT.

Complete erosion of the coat leads to an abrupt release of contained drug. If a dosage form consists of only three or



Scheme : 7. Dissolution control of drug release rate via thickness and dissolution rate of the membrane barrier coat.

four different thickness coats, one can expect pulsed dosing to occur, on the other hand, if a spectrum of different particle coats are employed in the dosage form, continuous release of the drug is expected. Hence controlled drug delivery systems designed based on the theory of dissolution fall in the category of (i) encapsulated and (ii) Matrix containing, systems.

Robinson (50) has presented a review on the different techniques and coating materials used and the different drugs which have been studied employing controlled drug delivery systems designed based on the principle of dissolution.

A.4 Methods Based on Ion Exchange

The method of ion exchange for controlled drug delivery system design relies only on the ionic environment of the resin containing drug for release characteristics and should therefore, be less susceptible to environmental conditions such as enzyme contact and pH at the site of administration. In practice, however, the release characteristics are governed by properties of the resin and the way in which the material is handled in the formulation. Since ion-exchange resins depend on ionic environment for their release of drug, this approach can be used to prepare liquid sustained release products, which indeed are available in the market.

Theory - Resins are water-insoluble agents containing salt forming groups in the repeating position on the resin chain. Either cationic or anionic groups can be used to produce the desired ion-exchange resin. The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin with the drug solution in a chromatography chamber or by keeping the resin in contact with the drug solution for extended period of time. The drug resin is then washed to remove contaminants and dried to form particles or beads.

Because the drug containing resin is insoluble and

extensively cross linked, it is difficult to picture a diffusion controlled exchange of drug with an ionic species in solution to provide drug to the absorption pool. Nevertheless, when a high concentration of appropriately charged ions is in contact with the ion-exchange group, the drug molecule is exchanged and diffused out of resin to bulk solution as shown below :

$$\text{Resin } \left[N(CH_3)\right]^+ X^- + Z^- \rightleftharpoons \text{Resin } \left[N(CH_3)\right]^+ Z^- + X^-$$

OR

$$\text{Resin } (SO_3^-)\ A^+ + B^+ \rightleftharpoons \text{Resin } (SO_3^-)\ B^+ + A^+$$

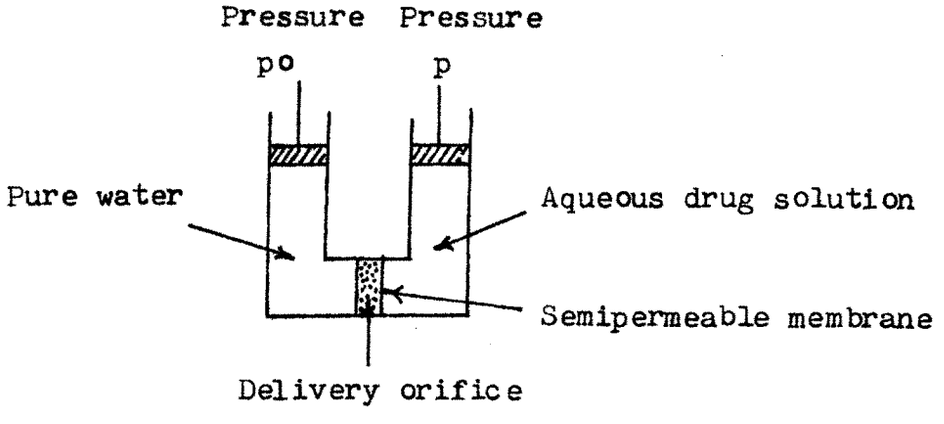
where X^- and A^+ are the drug molecules.
Eluting ions must diffuse into the resin matrix and establish equilibrium with ionic resin group, before the eluted ion can diffuse out. As with all the diffusion processes the area of diffusion and diffusional pathlength are important to the rate of diffusion. However, the presence of solvent in the matrix of the resin as well as the structural rigidity of the resin i.e. cross-linking, influences the rate of drug diffusion. For this reason the porosity of the resin and the size of the bead or particle must be controlled during the formulation process.

This approach to controlled drug delivery system

requires the presence of ions in solution and therefore, oral route is ideal route of administration of such systems in this context. However, the variability in diet, water intake, GIT content and composition make this constant ionic content unlikely. Nevertheless, oral products providing this principle do provide for prolonged release of drugs. Perhaps the rate-limiting step for drug release from these resins is diffusion of the drug out of the resin matrix. This would tend to minimize the variability of ionic content and its influence on drug release rate.

A.5 Methods Based on Osmotic Pressure

A recent publication by Theeuwes (51) reported on the application of osmotic pressure principles in the construction of a sustained release tablet. Scheme 8 represents the controlled drug delivery system designed, based on the



Scheme : 8. Osmotic pressure controlled drug delivery system.

principle of osmotic pump. Basically the system operates in the following manner : semipermeable membrane placed around a tablet, particle or drug solution allows 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.

Theory - The key to the system is the ability of the drug solution inside the tablet to attract water by osmosis through the semipermeable coating. The tablet imbibes fluid at a constant rate determined by the membrane permeability and by osmotic pressure of the core formulation. Since the drug solution is contained within a confined space, it will be pumped out of the tablet or particle through the orifice in the coat at a controlled rate equal to the volume uptake. This delivery rate is constant as long as excess solid is present inside the tablet and declines parabolically towards zero once the concentration falls below saturation. Thus controlling the rate of water inbibition controls the rate of drug delivery as explained by Eq. (10).

$$\frac{dV}{dt} = \frac{kA}{l} (\Delta\Pi - \Delta P) \qquad \ldots \text{ Eq. (10)}$$

Where $\frac{dV}{dt}$ is the flow rate of water into the capsule, k, A and l are membrane permeability, area and thickness respectively;

$\Delta\Pi$ is the osmotic pressure difference, and

ΔP is the hydrostatic pressure difference.

An important aspect to the success of this type of delivery system, apart from the polymeric coat and core formulation, is the size of the delivery orifice. Two conditions must be met in order for the system to be effective.

i) The orifice must be smaller than the theoretical maximum size to minimize the contribution to the delivery rate made by solute diffusion through the orifice.

ii) The orifice must be sufficiently large to minimize the hydrostatic pressure inside the system.

Too small an orifice will depress the delivery rate over and above the desired constant delivery. 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. (52) reported the use of automated laser drilling in making accurate and precise, exit pore for indomethacin in designing an elementary osmotic pump.

Use of laser in designing controlled drug delivery systems as a future possibility has been recently proposed (53). A brief account of laser and its application follows.

B. Lasers

B.1 History of Laser Development

The proposal that particles of light with energy of a particular frequency could stimulate atomic electrons to emit radiant energy as light of the same frequency was made by Albert Einstein in 1917. This phenomenon is the key to the operation of the laser. The name "laser", in fact, is an acronym for light amplification by stimulated emission of radiation.

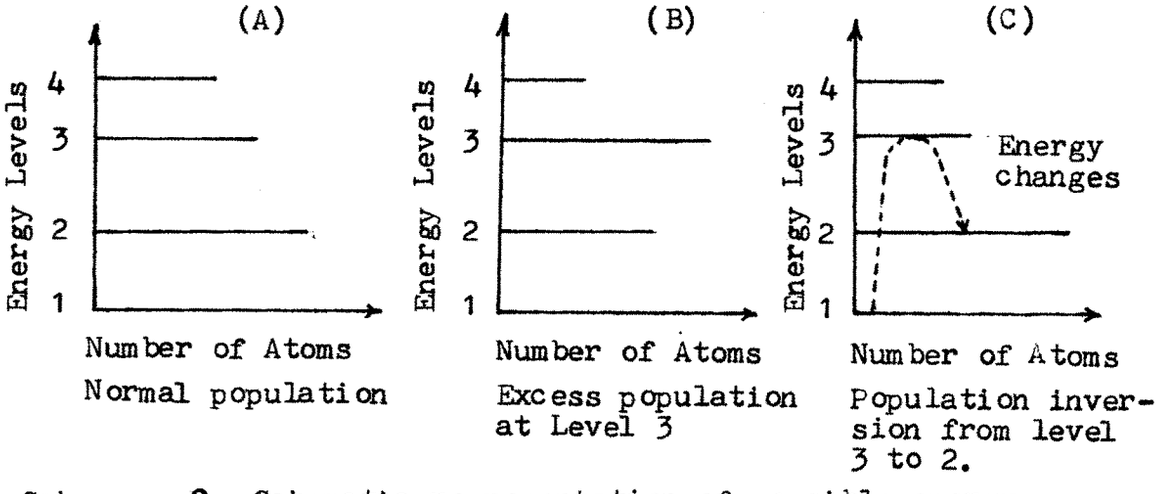
It was not until 1958 that C.H. Tawnes and A.L.Shawlow published a proposal that the principles employed in microwave amplification by stimulated emission of radiation to produce the maser could be extended to the amplification of light. A few years later T.H.Maiman had achieved the first operating laser. It consisted of a ruby rod, with mirror ends, that was surrounded by a helical flash lamp. Shortly after this Helium-Neon (He-Ne) gas laser was developed. Soon many more materials were found that could serve as active lasing media.

The credit for the development of the first Carbon dioxide (CO_2) gas laser goes to C.K.N.Patel, who worked at Bell Laboratories, U.S.A.. Three years later in 1966, the first industrial CO_2 gas laser was built by engineers at Coherent Radiation Laboratories, U.S.A..

B.2 The Lasing Process

The simplified description of the lasing process could be opposite of absorption. At heart the lasing phenomenon is the ability of photons to stimulate the emission of other photons, each having the same wavelength and direction of travel as the original.

According to quantum theory, atoms and molecules have discrete energy levels and can change from one level to another in discontinuous jumps. The energy change required for a jump is provided by the atom's absorption or emission of a burst of electromagnetic radiation. The radiation frequencies involved and the energy spacings between the levels are characteristic of an atom and thus differ from element to element.

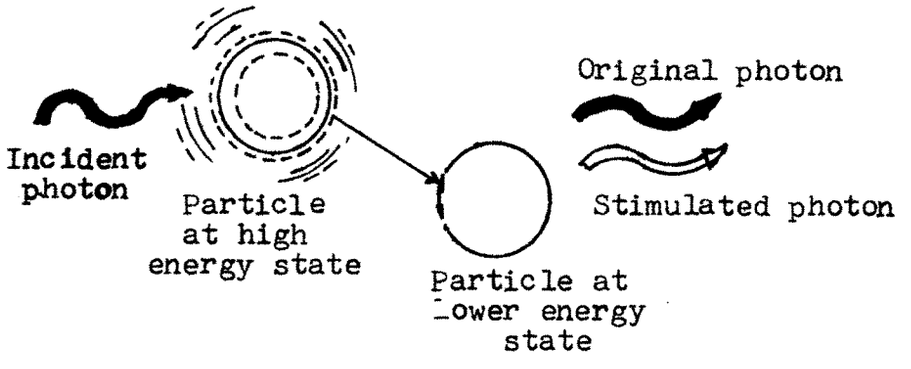


Scheme : 9. Schematic representation of possible energy states of an atom and population inversion principle.

Suppose the material is in a normal state of equilibrium under a given set of conditions as shown in Scheme 9(A). If the light falls on the material in such a state, some electrons are raised to a higher energy level and some electrons change to a lower level, but the net result is an increase in overall energy state of the atoms, because there is a net absorption of light by the material. If the material radiates energy, there is a net decrease in number of electrons at high level as compared to those at lower levels.

If it is desired to amplify light, a material with population distribution as indicated in Scheme 9(A) must be affected to increase the number of electrons at higher energy levels as shown in Scheme 9(B), with excess population at level 3. This is done by radiating energy of proper frequency into the material and it is known as population inversion because the normal state is inverted and produces more atoms with level 3 energy than with level 2 energy. Now the material is primed and is ready to emit light, when it is properly triggered by radiation of appropriate frequency. When so triggered the level 3 energy changes to level 2 energy as shown in Scheme 9(C), resulting in emission of light. In a laser cavity such emitted photons are trapped between highly polished and parallel mirrors, forcing them

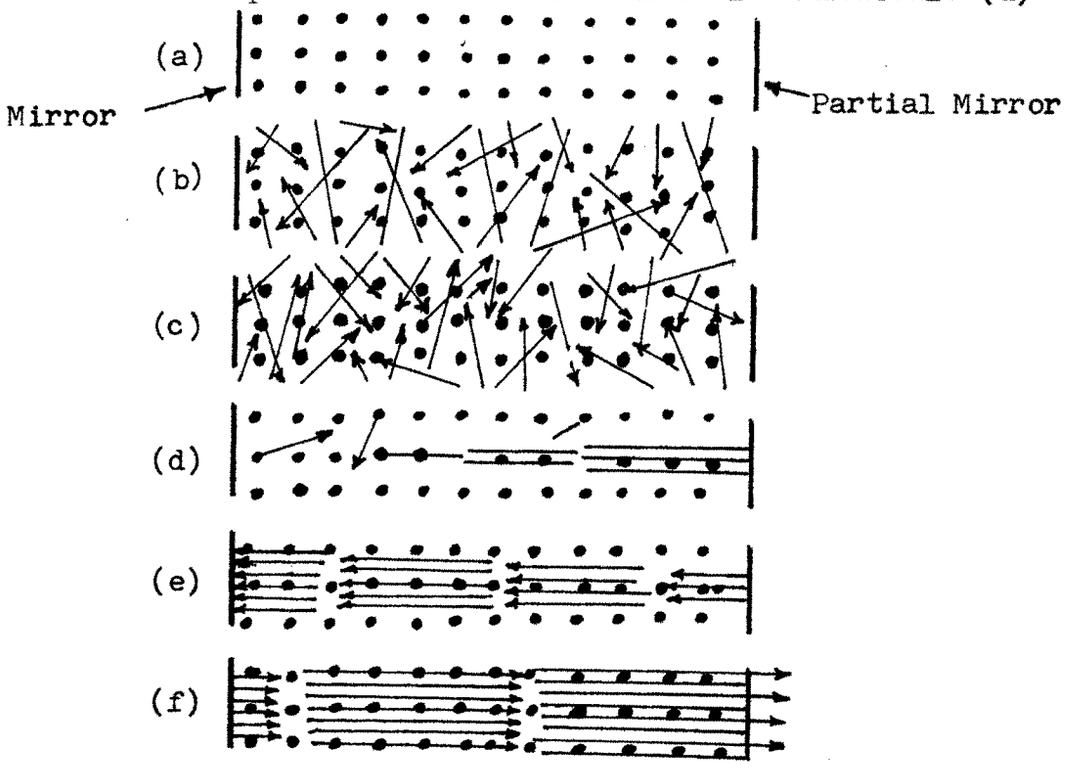
to bounce back and forth in the cavity. Whenever a photon collides with another excited particle of the same wavelength the second particle will also be stimulated to emit a photon that is identical in wavelength, phase and spatial coherence to the first (Scheme 10). Both photons are now capable of stimulating the emission of more photons like themselves and these two become a part of the growing wave between the mirrors.



Scheme : 10. Schematic representation of stimulated emission.

The phenomenon of growing wave of the photons between the mirror could be explained by the consideration of the following lasing sequence as shown in Scheme 11 (a-e). In (a), the molecules of the lasing medium are in the ground state. When excitation voltage is applied to the medium, many molecules are excited to a higher energy state and photons are emitted spontaneously (b, c).

If an emitted photon collides with an excited molecule (d)



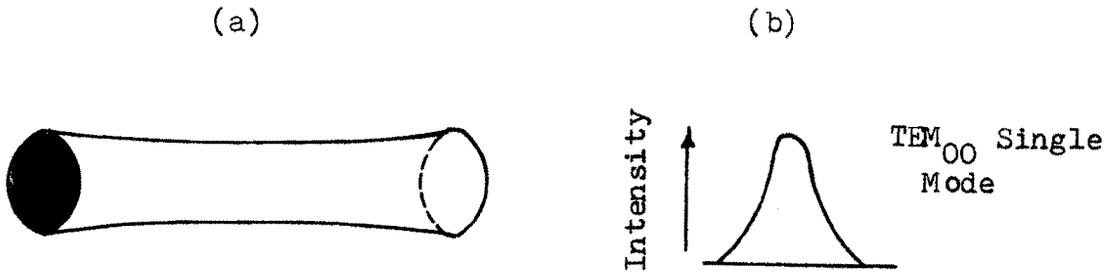
Scheme : 11. Events in a laser resonator, growing wave of photons.

stimulated emission occurs as explained earlier. Stimulated emission now proceeds as each of the photons is now capable of causing the production of more photons. Photon motion can be in any direction, but those which happen to travel parallel to the tube axis will strike an end mirror and be reflected back along the same axis. It is these photons which build up the coherent, single frequency light wave in the tube as they bounce back and forth between the mirrors, stimulating the emission of more and more identical

photons in a chain reaction. Some of these photons (f) pass through the partially transmissive mirror contributing to the laser output, while the others continue to oscillate in the resonator generating more photons. This phenomenon will continue as long as a population inversion is maintained among the molecules of the lasing medium. If the laser is in the pulsed mode the output emission is in short bursts, but if it is in continuous wave (CW) mode, the light is continuous.

Transverse Beam Modes - The photons oscillating from one end of the resonator to the other constitute electromagnetic energy which forms an intense electromagnetic field. The shape of this field is critically dependent not only on photon wavelength but also on mirror allignment, curvature and spacing, and bore diameter of the laser tube.

This field can assume many different cross-sectional shapes, termed transverse electromagnetic (TEM) modes, but only certain modes or mixtures of them, are useful for processing of materials. The different types of TEM modes include : TEM_{00}, TEM_{01}, TEM_{11}, etc. of which TEM_{00} mode (Gausian mode) shown in Scheme 2(a) is ideal for cutting, drilling and welding operations because it produces beam that can be focused to a minimun spot size for every high



Scheme : 12. TEM_{00} (Gausian) electromagnetic mode and distribution of power across the beam.

power density. The TEM_{00} mode has most of the energy distributed at the center as shown in Scheme 12(b) and hence is more efficient tool for cutting and drilling than does the more fragmented power distribution in the case of other TEM modes.

B.3 Properties of Laser

The output from a lasing process i.e. the laser beam have the following characteristic features.

i) Monochromatic - It occupies very narrow band on the spectrum.

ii) Coherent - The radiant energy is disciplined with the photons emitted uniformly with respect to time and space.

iii) Very low divergence - The laser beam is perfectly collimated with a typical axial divergence of only

1 to 2 milliradians. A laser with this low divergence can have an intensity (also called power density) of several hundred watts per square centimeter. The beam can be focussed by a lens to a small spot, the size of which is theoretically limited only by beam divergence and diameter, light wavelength and laser focal length.

iv) Brightness

v) Polarization.

It is these unique properties of the laser which make it the tool of choice for accurate and precise drilling operations and other relevant specific applications.

B.4 Fundamental Requirements for Lasing

All the lasers include three fundamental elements.

(i) a lasing medium - one which provides atoms, ions or molecules that support light amplification.

(ii) an energy source - to excite the medium.

(iii) an optical resonator - to provide feedback of the amplified light.

All the materials cannot qualify as lasing media since a successful lasing medium must be excitable enough to achieve a condition of population inversion i.e. more photons must be generated by the medium than are being absorbed. A number of materials including solids, liquids and gases will support light amplification in this manner. Depending on the type of the lasing medium used, lasers can be classified into different types.

B.5 Types of Lasers and their Applications

Table 1 gives a summarized account of the laser application, types of lasers used and the relevant laser properties which aid a particular application (denoted by the symbol '✓').

B.6 CO_2 Gas Laser

Since CO_2 gas laser was used in this study, a more detailed discussion on CO_2 gas laser is given below.

The basic elements of a CO_2 gas laser as shown in Scheme 13 consists of a mixture of carbon dioxide, nitrogen and helium gases filled in a discharge tube forming the lasing medium, high voltage electrical discharge as an energy source to excite the medium and two mirrors, one

Table I.1 : Different Types of Lasers and Their Applications.

Type of Laser used*	Property of laser which aids the relevant application						Applications
	Mono-chroma-ticity	Low Diver-gence	Single or low order mode	Coherent Nature	High Power	Efficiency	
He - Ne	✓		✓	✓			Precision measurement of length
He - Ne	✓	✓					Surveying
Nd-YAG; Ga As		✓			✓		Range Finding
He - Ne	✓						Velocity Measurement
Ruby, Nd:YAG,CO_2	✓	✓			✓	✓	Drilling
CO_2	✓	✓			✓	✓	Cutting
CO_2, Ruby, Nd:YAG	✓	✓			✓	✓	Welding
Ruby, Argon ion	✓	✓	✓	✓			Ophthalmology
Ruby;Nd:YAG,He-Ne	✓			✓			Holography
He - Ne, GaAs	✓	✓					Communication
CO_2	✓	✓	✓	✓			Surgery
Ruby			✓	✓		✓	Surface Sterilization

* Basically two types (1) Gas laser (2) Solid State

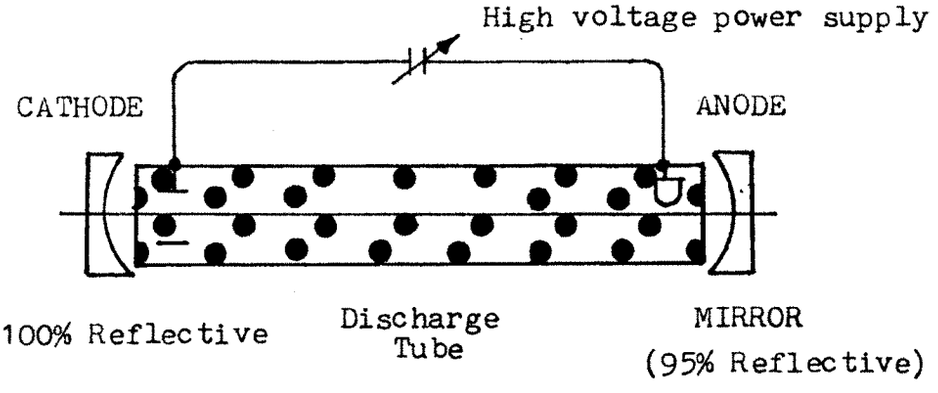
(1) <u>Gas Lasers</u>

Argon
Carbon dioxide (CO_2)
Helium-Neon (He-Ne^2)

(2) <u>Solid State</u>

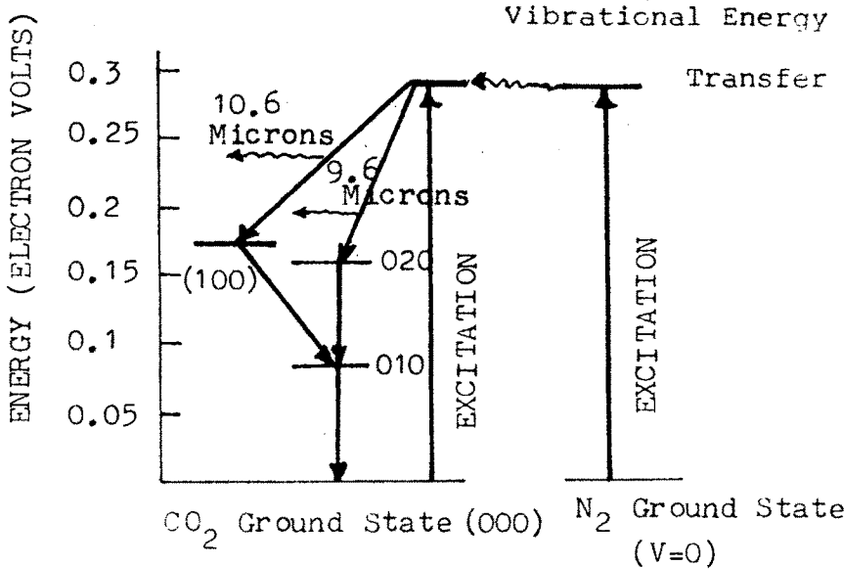
Synthetic Ruby
Gallium-Arsenide (Ga:As
Neodymium:Yitrium,Aluminium, Garnet (Nd-YAG)

100% reflective and the other 95% reflective arranged opposite to each other forming the optical resonator to provide feed back of the amplified light.



Scheme : 13. Basic CO_2 laser configuration.

There are several electron energy states above the ground state which CO_2 molecule can temporarily occupy (Scheme 14).



Scheme : 14. Energy Levels of CO_2 System.

The excitation begins at the right with nitrogen (N_2) molecule and is transferred to the CO_2 molecule at the top left when a CO_2 molecule decays from highest energy state marked by 001, to an intermediate level, marked by 100 or 020, the energy released during the transition has a wavelength of either 10.6 or 9.6 microns, depending on the size of the jump. The 001 to 100 jump being shorter, produces longer wavelength, It is also the more efficient transition for CO_2 molecules; for this reason the CO_2 beam is utilized at, and characterized by, its 10.6 μm wavelength.

When CO_2 molecules are excited by a high-voltage electrical discharge in a pure environment, each level receives a share of the molecule, but the lower energy level aims the most, preventing the formation of a population inversion.

To make population inversion possible, the CO_2 medium must be modified in some way. This is done by mixing N_2 gas molecule with carbon dioxide. Helium (He) is also included in the mixture to increase the thermal conductivity of the lasing medium. As shown in the scheme 14, one of the high energy states of N_2 molecules is very close on the spectrum to the 001 level of CO_2 molecule. As a result, some N_2 molecules are able to supplement the 001-level CO_2 population through resonance transfer of energy. Since no

coincidence energy levels occur between the two gases at lower energy states, the high 001 population is increased over lower levels, achieving the necessary population inversion.

C. Research Envisaged

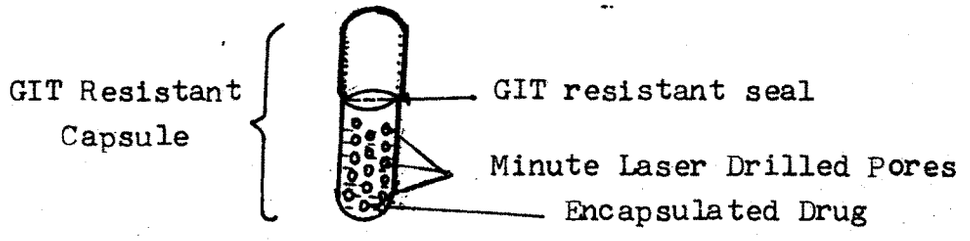
The literature survey reveals that the potential use of laser in the field of communication, industry, medicine etc. has been well established by now, however, its use in pharmacy has not been explored to any significant extent. The attempts to use laser in pharmacy, till recently have been restricted to limited fields like aerosol valve drilling (54) and surface sterilization (55), with the exception of a recent report by Theeuwes et al. (52) of using automated laser drilling in making exit pore for indomethacin, in designing rather sophisticated controlled drug delivery system, based on the principle of an elementary osmotic pump.

In view of the present trend and the need of a developing country like India, to better utilize the already known drugs, an attempt has been made in this study to employ indigenously available laser technology and naterials in designing a new controlled release drug delivery system based on the combined

principle of dissolution and diffusion, without involving much of sophistication.

C.1 Hypothesized Design of the System

The hypothesized system as shown in the scheme below consists of a GIT resistant hard gelatin capsule, with minute laser drilled pores made on the wall of the capsule,



Scheme : 15.

Schematic representation of the hypothesized new controlled drug delivery system.

encapsulating the drug and sealed with a suitable GIT resistant material. Unlike a conventional capsule, this system when administered orally will not disintegrate under GIT conditions, but will release the drug slowly through minute laser drilled pores made on the wall of the capsule. The release rate of the drug may be controlled by varying the number and diameter of the drilled pores and hence

varying the total surface area available for the release of the drug.

C.2 Proposed Mechanism

The system is expected to work on the combined principle of dissolution and diffusion, with different mechanism predominating at different steps after oral administration of the system, almost similar to one which works on the principle of encapsulated diffusion contrcl where the drug is enclosed in a porous film (41-46).

Step 1 (Dissolution) - When the system is orally administered the fluid in the GIT penetrates into the capsule through the minute laser drilled pores. The capsule imbibes the fluid at a constant rate determined by porcsity i.e. number and diameter of laser drilled pores and may be by the capillary action of the powder content encapsulated. The fluid that has made an entry into the capsule would dissolve the drug resulting in the formation of a saturated solution of the drug inside the capsule, creating a concentration gradient for the subsequent diffusion process. One of the important factors governing this step would be the solubility of the encapsulated drug in the GIT fluid that has made an entry into the capsule.

Step 2 (Diffusion) - Since the drug solution inside this capsule is confined to a small space with a positive

concentration gradient prevailing, the drug will slowly diffuse out of the capsule at a rate equal to the volume of the liquid entering the capsule which once again is a function of total surface area available for the transport i.e. the diameter and number of drilled pores. During the process of diffusion some of the laser drilled pores may be allowing the entry of the GIT fluid while others might act as exit pores for the solution of the drug. At equilibrium the volume of the liquid entering the capsule may be equal to the volume being released out and the system may be expected to release the drug following zero-order kinetics.

An important aspect to the success of this system, considering the proposed mechanism would be the size and number, the accuracy and precision of the laser drilled pores.

The unique property of CO_2 gas lasers like monochromatic and coherent nature of the beam, possibility of focussing the beam to a small spot using an appropriate lens, accurate and precise control over the drilled minute pores and large scale commercial production possibilities, apart from the local availability of the facility; has made it the tool of choice for the present study.

C.3 Objectives of the Present Study

Thus the objectives of the present study were to :

(i) design a new controlled drug delivery system employing laser and standardize the system with respect to preparation of GIT resistant capsule and laser drilling technique using an appropriate model drug;

(ii) use this new drug delivery system in designing slow release capsule;

(iii) use the suitably modified form of the new drug delivery system in designing sustained release capsule; and

(iv) work out the commercial and economic feasibility report on use of laser in designing a new controlled release drug delivery system as envisaged herein, in a pharmaceutical industry.

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