CHAPTER I

INTRODUCTION

Increasing competition among pharmaceutical industries and pressure from persons of the health professions and government officials to demonstrate clinical effectiveness of their drug delivery systems has undoubtedly increased interest in the whole area of drug dosage forms (1-6). Thus although new drugs and their derivatives still receive priority from most of the pharmaceutical manufacturers, there is an increasing interest in the development of new drug delivery systems (7-10) such as prolonged action dosage forms (11-14), and improvement of old ones. Another reason that has provoked interest in prolonged action dosage forms, has been the rapid growth of polymer technology and its application (15-18).

I. CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Controlled action drug dosage forms have been available for years. Speedy antacids and quick analgesics are proprietary drugs whose controlled action, in these cases, fast acting, have long been extolled in intensive advertising campaigns. The twelve hour antihistaminic tablet and the eight hour aspirin tablet have been developed (19-21) as proprietary drugs where extended or sustained release of the active ingredients simplifies the drug regimen.

The development pharmacist of today has numerous techniques for preparing therapeutic formulation with regulated release or activation of the desired ingredients. These techniques vary from chemical modification of the drug, for example, making it more or less soluble in gastric juices, to the inclusion of a myriad of additives or excipients, thereby influencing construction of the final drug form. The types and construction of many of the prolonged action oral drug delivery systems are discussed in several reviews (22-25). Generally, the types of construction fall into the following broad categories : encapsulated beads or pellets, matrix tablets, modified enteric coated dosage forms, ion exchange resin complexes, and slightly soluble salts or complexes. Examples of prolonged action systems for other routes of drug entry include transdermal drug delivery system (26,27). Occusert (28,29), uterine therapeutic system (30), and parenteral controlled drug delivery systems such as oily solutions and suspensions, emulsions, aqueous suspensions, use of polymers to complex (or absorb) drug molecules in solution and/or to increase the viscosity of the medium, emulsions and implants (22-25). Newer controlled release drug delivery systems are osmotic delivery systems (31-33), liposomes for controlled drug delivery systems (34,35), transdermal systems (36), magnetic modulation systems (37), etc..

The need for a controlled release preparation often arises as a result of drug properties such as a short biological half life, local irritation, or extensive metabolism, or perhaps through the nature of the disease state for patient compliance reasons (38-42). In considering a drug for this mode of drug delivery, certain criteria have to be examined and evaluated. These are the physico-chemical, pharmacokinetic, and biological characteristics of the drug. With each drug property there is a range of values that lends itself to the design of sustained release products, and outside this range the design becomes more difficult, or, in the extreme, prohibitive. Extremes of aqueous solubility, oil/water partition coefficient, erratic absorption characteristics, multi-compartment distribution and binding, extensive metabolism/degradation of the drug during its transit from the point of drug delivery to the target area, and narrow therapeutic index are some of the limiting factors in formulating an effective sustained release product (43-45). Theoretically, each of these limitations can be overcome and successful controlled drug delivery can be accomplished by using physical, chemical, and biomedical engineering approaches, alone or in combination.

Spansule sustained release dosage form was introduced as early as in 1950s. Since then, there have been numerous

studies on the release of active drugs from this type of preparation (46-49) and also on the clinical effectiveness of these products in general (50-52). Examples of coated beads or granules include antihistaminics (51), belladonna alkaloids (50), phenothiazines (53), antihypertensives (52), cardiac muscle dialators (54), anorexigenic agents (55), steroidal anti-inflammatories (56), and nonsteroidal anti-inflammatories such as aspirin (20).

There are several ways to prepare drug coated beads or granules. A common procedure is to coat nonpareil seeds with the drug and follow this with either a slowly dissolving wax or polymer coat of varying thickness. Such coating can also be applied through microencapsulation wherein the drug solution or crystal is encapsulated with a coating substance. There are available a variety of slowly dissolving coatings such as those based on various combinations of carbohydrate sugars, cellulose, polyethylene-glycols, polymeric materials and waxes (57).

An alternate approach is to compress the drug with a slowly dissolving carrier into a tablet form. The rate of drug availability from such tablet dosage form may be controlled by the rate of penetration by the dissolution fluid. To this end, the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability

of the tablet and particle surface can play important roles in the drug release rate profile. The porosity of the tablet i.e. surface area available, can be altered in a compressed tablet by varying compression force, adhesion between adjacent particles and size and shape of the particles. In addition, hydrophobic fillers can be added to decrease the effective porosity because fewer pores will be penetrated by eluting fluid. Various examples of matrix tablets have been cited in the literature (58-60).

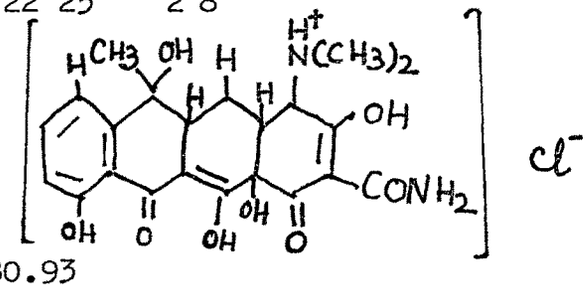
A. TETRACYCLINE HYDROCHLORIDE

History :

The development of tetracycline antibiotic was the result of a systematic screening of soil specimens collected from many parts of the world for antibiotic-producing micro-organisms. The first of the compounds, chlortetracycline, was introduced in 1948. Two years later oxytetracycline became available. Elucidation of the chemical structure of these agents furnished the basis for the production of a third member of this group, tetracycline in 1952 (61).

Molecular formula : $C_{22}H_{25}Cl\,N_2O_8$

Molecular structure



Molecular weight : 480.93

Physical Properties :

Tetracycline hydrochloride is a crystalline, faint yellow, odourless, slightly bitter compound. It is freely soluble in water, moderately soluble in methanol, ethanol and insoluble in ether and hydrocarbon solvents. The aqueous solution becomes turbid because of hydrolysis. The potency is affected in solution of pH below 2, and is destroyed rapidly by alkali hydroxide solutions (62).

Mechanism of Action :

Recent investigations into mode of action of tetracyclines (63,64) lend support to previous observations (65,66) that they inhibit the protein synthesis of sensitive bacteria. This inhibition is reported to interfere with variety of biochemical systems : cell wall synthesis (67), biosynthesis of bacterial respiratory systems (68), and similar systems (69). The details of the extensive studies in this field have been reviewed by Weisblum and Davies (70).

Antimicrobial Spectrum :

The tetracyclines possess wide range of antimicrobial activity against gram positive and gram negative bacteria. They are also effective against some microorganisms innately insensitive to many chemotherapeutic agents, such as Rickettsiae, Mycoplasma, Chlamydia and Amoeba. They are not

active against any of the true viruses, yeasts, or fungi (71,72).

Absorption, Distribution and Excretion :

The tetracyclines are incompletely and variably absorbed from the stomach and upper part of the intestinal tract and greater in fasting state. Absorption of these agents is impaired to variable degree by milk and milk products, and particularly by the concomitant administration of aluminium hydroxide, sodium bicarbonate, calcium and magnesium salts, and iron preparations (73). The mechanisms responsible for the decreased absorption appear to be chelation and an increase in the gastric pH (74).

After a single oral dose peak plasma concentrations are attained in 2 to 4 hours. Tetracycline has plasma half life of 8-10 hours and it is frequently administered two to four times daily. The administration of 250 mg of tetracycline hydrochloride every six hours produces peak plasma concentration of approximately 3 µg/ml (75, 76).

The volume of distribution of the tetracyclines is relatively larger than that of the body water, indicating sequestration in some tissues. Tetracycline is bound to plasma proteins upto 65%, however, the values reported in literature are variable (77).

Most tetracyclines are excreted primarily by kidneys and can be recovered unchanged from the urine. Variable amounts are eliminated in the faeces. All tetracyclines are concentrated in the liver and excreted in the bile, with considerable reabsorptive cycling from the gastro-intestinal tract. Because of enterohepatic circulation, tetracyclines may be detected in the blood for several days after treatment is discontinued (77).

Untoward Effects :

Various skin reactions, including morbilliform rashes, urticaria, fixed drug eruptions, and generalised exfoliative dermatitis, may follow the use of any of the tetracyclines. Among the more severe allergic responses are angioedema and anaphylaxis; anaphylactoid reactions can occur even after the oral use of these agents. Other effects that may have their origin in hypersensitivity are burning of eyes, cheilosis, brown or black coating of the tongue, atrophic or hypertrophic glossitis, pruritus ani or vulvae, and vaginitis; these effects often persist for weeks or months after cessation of tetracycline therapy. Fever of varying degree and eosinophilia occur when these agents are administered.

All tetracyclines have relatively low toxicity at usual dosage levels. Gastrointestinal disturbances

(anorexia, heartburn, nausea, vomiting, flatulence and most often diarrhoea) occur in about 10% of patients receiving 2g or more of tetracycline or the equivalent daily. This increases somewhat on prolonged administration. Other undesirable reactions of the various tetracyclines include dryness of mouth, hoarseness, stomatitis including vesiculopapilar oral lesions, glossitis including black hairy tongue, pharyngitis, dyspepsia, enterocolitis, proctitis, and inflammatory lesions caused by candidal overgrowth of the vulvovaginal and perianal regions. Most of these reactions result from suppression of normal enteric flora with overgrowth of other organisms. Tetracycline hydrochloride is thought to have an antianabolic effect, which may produce negative nitrogen balance and increase blood urea levels. However, this is of no clinical importance when usual doses are given to patients with normal renal function.

The tetracyclines may cause liver damage that is sometimes associated with pancreatitis, particularly when large doses (2g or more daily) are administered intravenously. Tetracyclines should also be avoided during pregnancy because they are attributed to embryonic and growing osscous tissue where they form a calcium orthophosphate complex. Colouration of teeth has also been reported on prolonged use. The tetracyclines can cause a rare condition known as pseudotum

orcerebri. Vertigo may also be observed after use of tetracyclines. Tetracyclines delay blood coagulation and may potentiate the effect of coumarin type anticoagulants. Blood dyscariasis, including neutropenia and hemolytic anemia, have occurred rarely following administration of the tetracyclines (72).

Therapeutic uses :

The tetracyclines have been used extensively both for the treatment of infectious diseases and as an additive to animal feeds to facilitate growth.

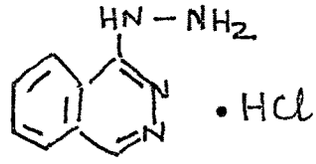
Tetracyclines are used in Rickettsial infections, nonspecific urethritis, chlamydia (Lymphogranuloma venereum, Psittacosis, inclusion conjunctivitis, Trachoma), Mycoplasma pneumonia, Bacillary infections (like Brucellosis, Tularemia, Cholera and others), coccal infections, venereal infections, urinary tract infections, amebiasis, chronic obstructive pulmonary disease, intestinal disease, acne etc. (71,72).

B. HYDRALAZINE HYDROCHLORIDE

History :

The effectiveness of hydralazine and similar hydrazino compounds for the treatment of hypertension was first reported by Gross et al. (78) in 1950. Methods of synthesis were published by Druey and Ringier (79) in 1951.

Molecular formula : $C_8H_9Cl\,N_4$



Molecular structure

Molecular weight : 196.68

Physical Properties :

Chojnacki et al. (80) investigated the crystal properties of hydralazine hydrochloride. Recrystallised from water, the crystals were found to be yellow, monoclinic, with unit cell a = 9.408, b = 14.529, c.= 6.643°A, β = 103.59° , Z = 4. It is freely soluble in water, soluble in methanol and ethanol and poorly soluble in 2-propanol, chloroform, ethyl ether (anhydrous), ethyl acetate and acetonitrile. The melting point of hydralazine hydrochloride is near 273°C (81,82).

Mechanism of Action :

Early studies on hydralazine attributed its antihypertensive effect successively to specific renal vasodilation and to an action on the CNS. However, present evidence indicates that the major action of hydralazine is direct relaxation of vascular smooth muscle. The effect on arterioles is greater than on veins. In man intraarterial

is more effective than intravenous administration in raising skin temperature and blood flow to the extremities. Intravenous injection causes a greater vasodilation in limbs to which vasomotor control has been chronically impaired by sympathectomy or by spinal cord section than in normally innervated limbs. Patients with chronic spinal cord transections as high as T_1 to T_5 and normal blood pressures respond to small doses of hydralazine with a drop in diastolic pressure comparable to that induced in normal subjects (83).

Cardiac stimulation by hydralazine probably involves a reflux response to the fall in blood pressure; but it is somewhat more marked than would be expected on this basis alone and is not well correlated with changes in blood pressure. Tachycardia can be induced by very small doses injected into the cerebral ventricles (84), and hydralazine tachycardia can be prevented by ganglionic or β-adrenergic blocking agents.

Recently Worcel et al. (85) have reported pre and post synaptic effects of hydralazine on arterial smooth muscle, and their role in the hypotensive action of drug.

Pharmacological Properties :

All major effects of hydralazine are on the cardio-vascular system. In both, laboratory animals and man,

adequate doses decrease arterial blood pressure, diastolic often more than systolic, and peripheral vascular resistance. The drug decreases heart rate, stroke, volume, and cardiac output. The preferential dialation of arterioles, as compared to veins, minimizes postural hypotension and promotes the increase in cardiac input. The effect of hydralazine develops gradually over 15 to 20 minutes even after intravenous administration. Splanchnic, coronory, cerebral, and renal blood flows increase unless the fall in blood pressure is very marked. Glomerular filtration, renal tubular function, and urine volume are not consistantly affected. However, hydralazine can cause retension of sodium and water and decreased urine volume. Hydralazine usually increases renin activity in plasma presumably as a result of increased secretion of renin by the renal juxtaglomerular cells in response to reflex sympathetic discharge. Vascular resistance in the cutaneous and muscle beds may decrease, but this is usually in parallel with the fall in blood pressure and blood flow does not increase (86,87).

Absorption, Metabolism and Excretion :

Because of extensive first pass metabolism in the liver, the bioavailability of hydralazine is relatively less after oral administration. Results of studies measuring the urinary excretion of radioactivity after the oral

administration of ^{14}C - hydralazine (88-90) indicate that 52 to 90% of the dose is ultimately found in the urine. Studies using non-selective assay technique indicate that peak 'apparent' hydralazine concentrations usually occur within 1 hour of administration of commercially available tablets (91-94). Even more rapid absorption occurs when the drug is administered as an aqueous solution with the peak 'apparent' hydralazine concentration appearing as early as 15 minutes after dosing (93,95). It can be metabolised by multiple pathways, but acetylation seems to be major route(91). The acetylation phenotype of a patient appears to be an important determinant of the bioavailability of the drug. Rapid acetylators have lower bioavailability (about 30%) than do slow acetylators about (50%) after oral administration of hydralazine. The simultaneous ingestion of food and hydralazine can increase the bioavailability of the drug (96).

Animal studies (97-100) indicate that hydralazine derived ^{14}C is found in high concentrations in the kidney, liver, blood, lung, adrenals, and arteries.

Hydralazine is extensively metabolised and only small amounts (1 to 15%) are found in urine even when non-selective assay procedures were used (89,90,93,101,102-104). The elimination half life of hydralazine in plasma ranges from 2 to 8 hours (averaging 3 hours) and other pharmacokinetic

parameters have been reported by various workers (89,90,93,96,105).

Untoward Effects :

The incidence of untoward effects of hydralazine therapy is high headache, palpitation, anorexia, nausea, dizziness, and sweating are common. Nasal congestion, flushing, lacrimation, conjunctivitis, paraesthesias, oedema, tremors, and muscle cramps occur less frequently. Drug fever, urticaria, skin rash, polyneuritis, gastro-intestinal hemorrhage, anemia, and pancytopenia are rare, but require termination of hydralazine therapy. A drug induced lupus like syndrome occurs in 10 to 20% of patients who receive prolonged therapy with hydralazine at doses exceeding 400 mg daily. This syndrome can also occur at doses of 200 mg per day or less.

Therapeutic Uses :

The oral form of hydralazine is rated as effective for treatment of essential hypertension, probably effective for treatment of hypertension associated with acute glomerulo-nepheritis, and possibly effective for treatment of hyper-tension associated with pre-eclampsia in order to prevent acute convulsant toxemia. The parenteral form is effective for treatment of some severe forms of hypertension where

the drug cannot be given orally, probably effective in treatment of pre-eclampsia and acute glomerulonepheritis.

Recently, hydralazine has been found to be effective in reducing afterload in the treatment of congestive heart failure (106,107), severe aortic insufficiency (108), and after valve replacement (109) or other cardiac surgery (110).

The use of hydralazine has now been optimized by concurrent administration of an inhibitor of the β-adrenergic nervous system; thereby both tachycardia and increased secretion of renin are prevented. When used concurrently with a thiazide and a β-adrenergic blocking drug, hydralazine is effective in small doses for long periods and it does not often cause the symptoms that previously limited its use (87).

II. RESEARCH ENVISAGED :

Tetracycline hydrochloride and hydralazine hydrochloride have been selected for the present study. Incomplete absorption (111), peaks and troughs in its blood levels due to high and frequent dosing (112), incidence of side effects due to high dosing (113) and prolonged therapy necessitate formulating controlled release drug delivery systems of tetracycline hydrochloride. Although a few sustained release products of the drug have

appeared in market (Sustamycin capsules - MCP Pharmaceuticals, U.K., Tetrabid Organon - Organon, U.K.), these being proprietary products, the information on the formulation aspects is negligible. Tetrabid, a prolonged action tetracycline hydrochloride (0.25 g) preparation, was reported to be equally effective when compared to the standard tablet in the treatment of acne vulgaris. This prolonged action formulation could be administered at one half the daily dose compared to the conventional tablet, hence reducing the possible incidence of undesirable side effects (114). Another study reported efficacy of sustained release tetracycline in the treatment of gonorrhoea (115). The slow release dosage forms of hydralazine hydrochloride will permit large hydralazine dose to be administered less frequently and reduce the fluctuations in blood levels and the incidence of side effects (116).

Thus tetracycline hydrochloride and hydralazine hydrochloride emerge out as potential candidates for the design of controlled release dosage form. In the present study it was thought worthwhile to attempt formulation of beads of these drugs which could be suitably coated with release controlling material(s) and subsequently, after encapsulation, could be used as a dosage form. Beads of uniform spherical shape are assumed to be better for uniform and reproducible coating, so as to control the drug

release. Such beads of drugs will be prepared by using a pelletar and marumerizer. The second approach in the present study was to formulate controlled release matrix tablets, basically because this lends to feasibility of accommodating large dose of the drug in a single unit. This is of particular relevance to drugs having relatively larger dose.

The plan of work for present investigation was therefore proposed to proceed on the following lines :

1) Development or modification of analytical methods for estimation of the drug wherever necessary to meet the requirements of present investigation.

2) Development of procedure to prepare beads of the selected drugs.

3) Coating of the beads by spray technique and air suspension coating device.

4) Study the factors affecting release of drug from beads such as excipients, coating materials etc..

5) Development of controlled release matrix tablets of selected drugs.

6) Study the factors affecting release of drug from tablets such as matrix material, excipient etc..

7) Evaluation of the prepared samples for the *in vitro* release pattern of drug.

8) *In vivo* evaluation of promising products in dogs/ human subjects.

9) Stability studies of satisfactory products of selected drugs.

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