Chapter 2

LITERATURE REVIEW

2.1 INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed for sustained release systems, the oral route has received the most attention. The types of controlled release systems employed for oral administration include almost every currently known theoretical mechanisms for such applications. This is due to the fact that there is more flexibility in dosage design and constraints, such as sterility and potential damage at the site of administration, are minimized. Controlled release drug delivery means not only prolonged duration of drug delivery, but also implies predictability and reproducibility of drug release kinetics(1). The goal in designing controlled delivery systems is to reduce the frequency of dosing and/or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Several reports have been presented on the use of hydrophilic polymers, especially, cellulose ethers, in the formulation of controlled/sustained release dosage forms(2) . Efforts have been made to explore newer polymeric materials for their potential as matrix formers in controlled release systems, which include the naturally occurring polysaccharide gums. Guar gum, a naturally occurring macromolecular galactomannan polysaccharide, has very high intrinsic viscosity, easy availability at low cost and non-ionic characteristics. These factors favour its potential for use as a matrix former.

2.2 GUAR GUM (GG)

Guar flour; Decorpa; Jaguar; Gum cyamopsis; Burtonite V-7-E.

GG has been in commercial production since 1953. GG was originally developed as a replacement for locust bean gum. However, it soon became obvious that although both gums are galactomannans, there are significant differences in their chemical composition and behaviour. Locust bean gum

requires cooking at elevated temperatures to achieve maximum viscosity, while GG will hydrate in cold water. There has been rapid growth in its consumption since its commercial introduction in 1953, due to the fact that guaran functions not only as traditional viscosity builder for water systems, but also as hydrogen-bonding, reagent-type chemical for such industries as mining and paper making. The gum, a non-ionic neutral polysaccharide, is a galactomannan.

Source :

Guar, drought resistant legume of genus cyamopsis (*Cyamopsis tetragonolobus*) is native of India, where it is used for food and feed (3). GG is obtained from the endosperm of guar seeds(4).

Physical Properties :

GG is a pale yellowish-white colored powder with characteristic odor and gummy taste. It forms viscous, colloidal dispersions (solutions) when hydrated in cold water; viscosities can be measured with a rotational shear type viscometer such as Brookefield synchrolectric viscometer. Viscosity is dependent on time, temperature, concentration, pH, ionic strength and type of agitation(5). The optimum rate of hydration is between pH 7.5 and 9.0. The viscosity of 1% w/v aqueous solutions ranges from 2000 to 22,500 cps: the sol is thixotropic. Finely milled powders are difficult to disperse. It requires 2 - 4 hours in water at room temperature to develop maximum viscosity.

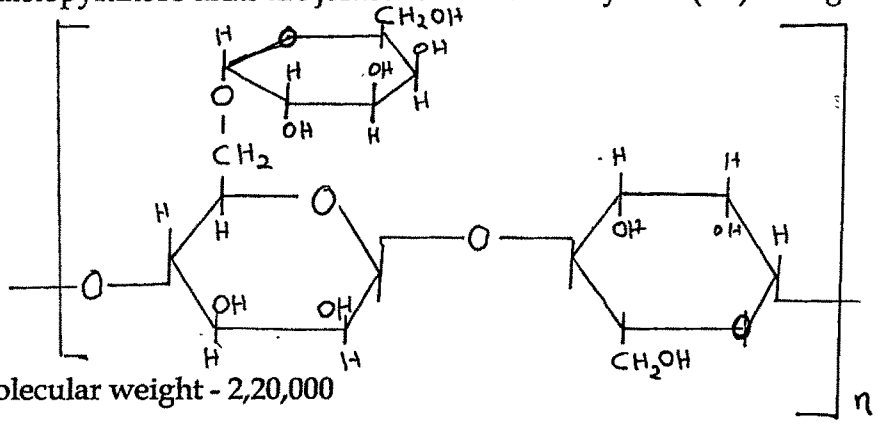
Chemical Properties :

Purified commercial guar gum was reported to contain ash 0.1%; η_{rel} 6.14 for 0.202% and 602 for 0.745% dispersion, $[\alpha]$ + 52.3°, reducing value 15.2 mg Cu/g (6). Fractional analysis of guar represented a galactomannan

polysaccharide containing 34.5% d-galactose anhydride and 63.4% d-mannose anhydride(7).

Structure :

GG, a d-mannoglycan (1:2) is a straight chain mannan with a single-membered galactose branches on almost every alternate mannose unit. The d-mannopyranose units are joined by β ⟶ (1:4) linkages and single d-galactopyranose units are joined to this chain by α → (1:6) linkages as shown -



Molecular weight - 2,20,000

Presence of α-d-glycosidic linkages was indicated by its rapid acid hydrolysis with accompanying decrease in specific rotation and by hydrolysis under the action of diastase(8).

Stability :

GG is stable in solution over a pH range of 1 - 10.5. Prolonged heating results in degradation of viscosity. Bacteriological stability can be improved by the addition of mixture of 0.15% methyl and 0.02% propyl paraben or by 0.1% benzoic acid or sodium pentachlorophenate.

Incompatibilities have been observed with acetone, alcohol, tannins, strong acids and alkalis. Borate ions present in dispersing water prevent hydration of guar. The addition of borate ions in hydrated solution

produces cohesive gel, which prevents further hydration. The gel can be liquefied by reducing pH below 7.0(9).

Applications :

GG was originally developed as replacement for locust bean gum. However, it soon became obvious that although both gums are galactomannans, there are significant differences in their chemical composition and behaviour. Applications have been reported to indicate both the conventional uses of the hydrophilic colloid as viscosity builder and water binder and also its specialised uses which depend on chemical composition and molecular configuration. Some of them include its use as depressant and auxiliary reagent to increase the recovery of purified ore in mining industry, as a flocculant or settling agent to concentrate ores and tailings in mining industry, as filter aid, industrial water treatment, as a thickener and binder of free water in foods, in cosmetics and pharmaceuticals(10,11). The paper industry has become one of the largest users of galactomannans where it is used as wet end additive for filter retention and in size press or calender operations. The use of GG in explosives has also been reported(12).

Studies on modifications of GG :

GG has been modified chemically and physically by many researchers to get products of desired properties for different applications which can be listed as under-

Hydrolysis:

- Hydrolysis of a complex polysaccharide is successfully done by stepwise degradation with acids of increasing strengths. Acidic, enzymatic and alkaline hydrolysis of GG have been reported (13,14,15,16). Guaran, the water-soluble component of guar flour, which contains 34.5% d-galactose anhydride and 63.4% d-mannose anhydride, undergoes rapid

acid hydrolysis indicating presence of α-d-glycosidic linkages. Enzyme α-d-galactosidase produces specific hydrolysis of GG producing intermediate amount of galactose. Enzymatically modified gums are able to form gels due to smooth unsubstituted mannan regions in the modified galactomannan.

- Characterisation of hydrolysed gum and the hydrolysis products have been done using suitable analytical techniques and various mono, di- and oligo- saccharides have been isolated. The hydrolysed gum has been characterised by determination of liberated sugars which can act as a measure of degree of hydrolysis. There are several methods for estimation of reducing sugars(17). Of the many colorimetric methods proposed , the Somogyi (in both titrimetric and colorimetric modifications), the phenol-sulphuric acid method and the anthrone colorimetric method are widely used. Viscosities of the gum solutions can also act as an indicator to the degree of hydrolysis, which reduces with increased hydrolysis.

Oxidation:

- Periodic acid and its salts (generally sodium and less often potassium) are mainly used in the carbohydrate chemistry for the oxidation of α-glycol groups. Small amounts of periodate preferentially oxidize the galactose group leaving the mannose chain intact(18,19,20). The oxidised products after treatment with bisulphite were successfully used as wet end paper additives.

Methylation:

- Methylation has been used as a technique in oligosaccharide and polysaccharide structure analysis, as well as a method of assignment of ring size. The procedures for methyl ether formation involve the use of methylating agents like dimethylsulphate in conjunction with strong alkali, which serves a catalytic role as well. More drastic techniques have been employed such as the use of sodium and liquid

ammonia to form alkali metal salts followed by treatment of the intermediate methyl iodide. The use of highly polar solvents like dimethylsulphoxide which do not solvate hydroxyl groups permit reaction to proceed with favourable kinetic rates under relatively mild conditions. The problems involved in methylation of natural products include the liability of the compounds to the methylating conditions, solubility of higher molecular weight compounds and relatively low efficiency of the heterogeneous methylating reactions. Some chain cleavage in case of several oligosaccharides may take place. The methylation of given compound will involve both steric and kinetic factors. In such case, methods for methylation are usually employed on empirical basis. Several reports on methylation of GG are available (21 - 25).

Other modifications:

- Various other modifications of GG include the synthesis of carboxyalkyl ethers, aminoethyl ethers and esters(26, 27, 28). The dialdehyde gum has been used as wet end and dry strength additives (29). Co-precipitation with gelatin from hydroalcohol gave slowly hydratable gum(30). Guar galactomannan was modified by treatment with an α-d-galactosidase prepared from lucerne seeds. On incubation for 2 hours this enzyme removed >75% of galactose from guar galactomannan with no concurrent decrease in viscosity. It was observed that guar galactomannan with reduced galactose-mannose ratio (<20:80) has better interaction properties (31).
- Guar galactomannan polysaccharide has been successfully grafted with polyacrylamide side chains by solution polymerisation technique using redox initiator. By grafting a flexible but easily degradable polyacrylamide polymer on rigid and shear stable but with poor drag reducing polysaccharide, it was possible to develop highly drag reducing, effective shear and biodegradation resistant drag reducing agents. The

structural changes taking place in the macromolecule due to grafting were confirmed by comparing the rheological behaviour of grafted GG solutions with that of commercial and purified GG solutions (32).

2.3 CONTROLLED DRUG DELIVERY SYSTEMS

Over the past 35 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focussed on the development of sustained/controlled release drug delivery systems. Administration of drugs in conventional dosage forms (except via intravenous infusion at constant rate) often results in see-saw fluctuations of drug concentrations in systemic circulation and tissue compartments. Drug concentrations can be maintained within a narrow therapeutic range by the use of controlled-release drug delivery systems which will also minimize the incidence and severity of adverse side effects. The controlled release systems for oral use include those designed simply to delay the release of drug (for example an enteric coated system), as well as more complicated systems in the form of matrix tablets, coated pellets, osmotic pumps, etc., designed to release the drug over an extended period of time, either in a continuous manner (sustained release) or as a series of pulses (timed release). A sustained release product may be considered one in which the drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug(33). To maintain a given level of activity the net effect of product construction and physiological factors is such that drug becomes available for absorption

at constant rate which is equal to the disappearance rate in the body after absorption.

In order to develop sustained or controlled release oral delivery systems the formulation scientists face the difficulties of restraining and localising the system at the targeted areas of the GIT. Controlled/sustained release preparations using alternative routes have been formulated but oral route still remains the most desirable.

Matrix Formers :

Hydrophilic polymer matrices, widely used today in the formulation of sustained release dosage forms, were first used in 1962(34). The method described involved mixing a drug with a non-digestible hydrophilic gum such as hydroxypropylmethyl cellulose(HPMC) followed by compressing the mixtures into tablets. When such a tablet was exposed to water or digestive fluids initial drug release occurred, followed by the hydration and gelation of gum at the tablet liquid interface, resulting in viscous gel barrier layer which retarded further drug release. Thereafter, several reports have been presented on the use of hydrophilic polymers, especially, cellulose ethers, as delaying matrices. Huber *et al* (35) investigated the use of sodiumcarboxymethylcellulose and HPMC as delaying agents. The successful use of HPMC in the production of prolonged release tablets is well documented(36).

Efforts were made to explore newer matrices other than cellulose derivatives. Baveja *et al* (37) have examined some natural gums and mucilages as sustaining materials for tablet dosage forms. Vinny Dhopeshwar *et al* (38) evaluated xanthan gum as matrix former for the preparation of sustained release tablets. Talukdar *et al* (39) studied the influence of direct and wet granulation, gum concentration, addition of binder, pH, ionic strength,

rotation speed, and surfactant on the drug release from xanthan gum matrix tablets.

Chitosan-reinforced alginate beads were prepared and the release patterns of coloring matter held within them were investigated by Murata *et al* (40). Drug release kinetics from carbomer matrices were studied by Durrani *et al* (41). A study and design of sustained release tablets containing oxazepam was reported by Ferreira *et al* (42). Rick *et al* (43,44) explored the possible application of scleroglucan hydrophilic matrix and the factors influencing drug release from this natural polymer hydrophilic matrix. A swelling measurement device was designed by Panomsuk *et al* (45) to observe the axial swelling direction of a matrix containing various types of hydrophilic cellulose derivatives. The release kinetics of caffeine and potassium chloride representing poorly soluble and water soluble drugs from PVP matrices were studied using different mathematical models by Arini *et al* (46). Ethyl cellulose matrix controlled release tablets of a soluble drug were prepared and studied by Katikaneni *et al* (47).

In Vitro and _In Vivo_ Evaluation of Controlled Drug Delivery Systems :

In vitro evaluation:

A review of current literature reveals that a formidable task facing a researcher in his/her successful development of a viable controlled release drug delivery device and experimental assessments of the controlled-release rate profile of drugs from the device is the proper design of an *in vitro* drug elution system that permits accurate evaluation and mechanistic analysis of the controlled release profiles. Variables, such as analytical sensitivity for drug assay, long-term maintenance of sink condition, hydrodynamic characteristics of solution diffusion, reproducibility of sampling and the volume and temperature of the system, have to be carefully evaluated during the

initial stage of design and precisely controlled during the operation. Many designs of *in vitro* drug elution systems have been devised and used (48).

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the *in vitro* test system. Apparatus 1 (basket) or Apparatus 2 (paddle) may be more useful at higher rotation frequencies (e.g. Paddle at 100 rpm). Apparatus 3 (reciprocating cylinder) has been found to be essentially useful for bead type of modified-release dosage forms. Apparatus 4 (Flow cell) may offer advantages for modified release dosage forms that contain active ingredient having very limited solubility. Apparatus 5 (paddle over disk) and Apparatus 6 (cylinder) have been shown to be useful for evaluating and testing transdermal dosage forms (49).

At least three test times are chosen to characterize the *in vitro* drug release profiles. An early time point, 1 to 2 h, is chosen to show that potential dose dumping is not probable. An intermediate time point is chosen to define the *in vitro* release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug(49).

In vivo evaluation:

In the development of a controlled release drug delivery system for long-term controlled administration of a therapeutic agent, it becomes necessary once a satisfactory *in vitro* drug-release profile has been achieved, to conduct the *in vivo* evaluations of the mechanisms, and rate profiles of drug release at the target site(s) of treatment or

administration in appropriate animal models to establish *in vitro-in vivo* correlation.

The *in vivo* evaluations of controlled release drug delivery systems vary from one type of drug delivery systems to another; depending on the biomedical applications projected, proper animal models and site(s) of administration have to be selected. It may be possible to use plasma drug concentration data alone as a basis for the approval of a modified-release preparation, in cases where there is a well-defined relationship between the plasma concentrations of the drug or active metabolites and the clinical response (therapeutic and adverse). The types of pharmacokinetic studies that should be conducted are a function of how much is known about the active drug entity, its clinical pharmacokinetic and biopharmaceutic properties and whether pharmacokinetic studies are intended to be the sole basis for product approval. As a minimum (1) a single dose crossover study for each strength of a modified - release dosage form and (2) a multiple dose, steady state, study using the highest strength of modified release dosage form, are required to characterize the product.(49).

In vitro-in vivo correlation:

The term *in vitro-in vivo* correlation first appeared in pharmaceutical literature as a result of the awareness of the concepts of bioavailability and of *in vitro* dissolution rate determinations. The term *in vitro-in vivo* correlation refers to the establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form. The relationship between the two properties, biological and physicochemical, is then expressed quantitatively.

Numerous attempts have been made to correlate one or more pharmacokinetic parameters determined from *in vivo* studies of products with the amount released in a given time in an *in vitro* dissolution test. Three correlation levels have been defined and categorized in United States Pharmacopoeia. The concept of correlation level is based upon the ability of the correlation to reflect the entire plasma drug concentration-time curve that will result from administration of a given dosage form. It is the relationship of the entire *in vitro* dissolution curve to the entire plasma level curve that defines the correlation. (49)

Drug Release Characteristics and Modeling :

A fair amount of attention has been given in the literature to gain a mechanistic understanding of drug release from sustained release preparations and the factors affecting it. Many mathematical models have been used to describe the release of drugs from the matrices. Higuchi(50) obtained a mathematical relationship for cases where the drug particles are dispersed in a homogeneous uniform matrix which acts as the diffusional medium and where the drug particles are incorporated in an essentially granulated matrix and released by the leaching action of the penetrating solvent.

Dissolution rate may be defined as the amount of active ingredient in a solid dosage form dissolved in unit volume under standardized conditions of liquid/solid interface temperature and media composition (51). The traditional mathematical expression for this definition is the Noyes-Whitney equation -

$$dw/dt = K \cdot S \ (C_{sat} - C_{sol})$$

dw/dt = dissolution rate; K = dissolution constant; S = surface area of solid; C_{sat} = concentration of saturated solution; C_{sol} = concentration at any given time.

By keeping the volume of solvent large with respect to saturation point (at least five to ten times as large) sink conditions are approximated.

The bioavailability of drug does not necessarily have any close relationship with the dissolution characteristics. A rapidly dissolving drug, for example, may not exhibit bioavailability correlation with dissolution test data, unless the formulation of the drug or manufacturing procedure have been designed specifically to impede dissolution. The use of dissolution characteristics to predict bioavailability of a solid dosage form is therefore, not universal, nevertheless dissolution characteristics vary with factors of formulation and manufacturing processes.

Ritger and Peppas (52) presented an empirical equation which can be used to analyse data of Fickian and non-Fickian diffusional release from non-swellable polymeric delivery systems -

$$M_t/M_\alpha = K\, t^n$$

where M_t/M_∞ is fractional solute released into the penetrating solvent (dissolution medium); K is a constant which incorporates the properties of the macromolecular polymeric system and the drug; and n is the diffusional exponent, which characterizes the drug transport mechanism. When the exponent n = 0.5, the drug diffuses through and is released from the polymer with a quasi Fickian diffusion mechanism, even though there is swelling of the polymer and dynamic macromolecular relaxations. For n > 0.5, an anomalous non-Fickian solute diffusion is observed. The special case of n = 1 has gained importance due to its potential application in the development of swelling-controlled drug delivery system with zero order kinetics. This

mechanism of solute transport is known as pseudo-case II solute transport (41).

Ford *et al* (53) considered the relationships as predicted by the above equation for the release of promethazine hydrochloride for HPMC matrices as inappropriate. The introduction of lag period was essential to describe accurately the quantity of drug released. The equation -

$$M_t/M_\infty = K(t - l)^n + K'(t - l)^{2n}$$

incorporates a lag period (l), kinetic constants (K and K') for diffusion and erosion controlled release and a diffusional exponent (n). It produced best fit of the data as evaluated by information criteria and unweighted sum of squares.

Percolation theory, based on the formation of clusters and on the existence of site or bond percolation phenomena, is a new mathematical tool that allows for explanation of the release process. The probability at which a cluster just percolates a system is termed percolation threshold(54). The concept of percolation theory and percolation thresholds have been applied to study the release behaviour from inert matrix systems (55,56).

Factors Affecting Drug Release Characteristics :

Many variables are involved in determining the relationship between the amount of drug administered and that ultimately available at the target sites of action. Reports of mechanistic analysis of controlled release of drugs revealed that partition coefficient (K); diffusivities (D_s, D_p); solubilities (C_s, C_p); diffusional path thickness (δ_p, δ_d) and other system parameters play various rate-determining roles in the controlled release of drugs from the delivery systems (57). The effects of various rate-controlling system parameters have been studied by many researchers. Lapidus and Lordi (58,59) investigated the influence of temperature, diluents and polymer type

on release patterns and applicability of Higuchi equations with respect to the drug availability from hydratable factors on the kinetics of drug release from matrix tablets. They showed that the rate constants may be described in terms of physicochemical properties of the tablet constituents and the degree of compression. Bamba *et al* (60) studied the release mechanisms in gel forming sustained release preparations. The release rate of drug from such preparations could be limited by one of the following factors - (a) the permeation of water, (b) gelation rate, (c) the dissolution rate of drug in the penetrating water, (d) the diffusion rate of drug in the gel and (e) the Higuchi porous penetration. They concluded the release mechanism as being limited by the rate of water penetration and back diffusion of the dissolved substance, whereas gelation rates and actual dissolution rate of drug are not rate determining. They noted the insensitivity of the matrix system to nature of the excipients and pH of the dissolution liquid.

Salomon and co-authors (61,62) investigated both the influence of excipient viscosity, drug-gum ratio, compression force, particle size, electrolyte concentrations and tablet thickness on the release of a highly soluble salt from HPMC matrix. Ford *et al* (63) examined the release of promethazine hydrochloride, propranolol hydrochloride and aminophylline from HPMC matrices. The effects of several factors related to formulation, fabrication and physicochemical characteristics of some bronchodilators from compressed hydrophilic polymeric matrices and their correlation with molecular geometry were studied by Baveja *et al* (64). The effect of HPMC on water penetration into a matrix system was studied by Wan *et al* (65). Mitchell *et al* (66) studied the influence of substitution type on the performance of methyl cellulose and HPMC gels and matrices. Mandal(67) investigated the influence of binding solvents on drug release from HPMC tablets.

Drug containing matrices are a simple and economic method to achieve sustained release of drugs, particularly for oral applications. Often, these matrices, whether formed by traditional methods such as drug compression with inert excipients or made using polymers by more exotic processing, are viewed as simple structures which act as simple diffusional barriers. It is obvious that dissolution processes are also important in these systems. The goal has been to specifically achieve constant release rate. It is immediately apparent that constant rate of release cannot be easily achieved since the diffusion path length changes rapidly, the geometry may not be favourable and the balance between diffusion and dissolution may not yield the proper control. As a result, investigators have considered methods to modify matrices for achieving constant-rate release from heterogeneously loaded (that is, a solid, pure drug phase exists) matrices. Lee(68) has considered using initial position dependent concentration profiles while Harland *et al* (69) have considered the effect of dissolution vs diffusion control to achieve constant rate delivery. In addition, an effect not commonly noted is that the transport characteristics can change appreciably in matrices due to alteration of the porosity of these matrices as depletion of the drug occurs. Chang *et al* (70) suggested that a constant flux and hence a constant drug release rate, can be maintained if the increase in the diffusivity of the drug is fast enough to offset the decrease in the concentration of dissolved drug near the surface as the drug is depleted. The possible use of modified starches in the formulation of sustained release preparations have been reported (71).

A novel class of phase-erosion controlled release devices based on semicrystalline polymers was developed. For preparation of these systems, a drug was dissolved in a dilute polymer solution, the system was cast or molded and exposed to an annealing procedure leading to significant crystallization of the polymer carrier. Drug release from such systems is

controlled by the rate of the crystal dissolution in water or biological fluids. The degree of crystallinity of the polymer carrier can be varied by heat treatment and is the controlling factor of the drug release rate from such systems. A molecular interpretation of the overall release process has been presented by Mallapragada *et al* (72).

The ultimate goal of controlled release formulations is to optimise the drug delivery. Optimisation of drug delivery aims at supplying drug in a predictable and reproducible manner at required site, at the required rate, for required time, with minimum inconvenience to the patient.

2.4 PROFILE OF DRUGS

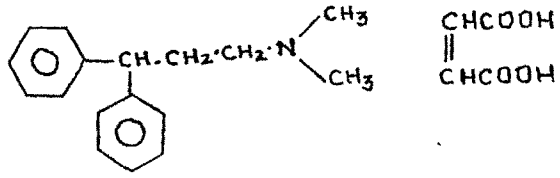
The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targetted areas of gastrointestinal tract(GIT). Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to dose dumping phenomenon. Drugs like chlorpheniramine maleate, diltiazem hydrochloride and phenylpropanolamine hydrochloride which are freely/highly water soluble play leading roles in their respective field of therapy. For better patient compliance and minimisation of side-effects, attempts have been made to design long acting devices in the form of sustained or controlled release preparations to deliver these drugs.

2.4.1 CHLORPHENIRAMINE MALEATE (CPM) (73)

CPM is a histaminic H_1-receptor antagonist which is given by mouth for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders. It is a common ingredient of cough and cold preparations.

Molecular Formula : $C_{16}H_{19}ClN_2.C_4H_4O_2$

Molecular structure :



Molecular Weight : 390.87

Physical properties :

CPM is white odourless crystalline powder, soluble as 1 in 4 of water, 1 in 10 of alcohol and of chloroform; slightly soluble in ether. Incompatibility has been reported with calcium chloride, kanamycin, noradrenaline acid tartarate, pentobarbitone sodium and iodipamide meglumine.

Pharmacokinetics :(74)

CPM is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentration occurring about 2.5 to 6 hours after administration by mouth. CPM appears to undergo considerable first pass metabolism. About 70% of chlorpheniramine in the circulation is bound to plasma proteins. There is wide interindividual variation in the pharmacokinetics of chlorpheniramine, values ranging from 2 to 43 hours have been reported for the half life.

CPM is extensively metabolised. Metabolites include desmethyl- and didesmethyl chlorpheniramine. Unchanged drug and metabolites are excreted primarily in the urine, excretion is dependent on urinary pH and flow-rate. Only trace amounts have been found in the faeces. A duration of action of 4 to 6 hours has been reported, this is shorter than may be predicted from pharmacokinetic parameters.

Therapeutic uses :

CPM is an alkylamine derivative with the actions and uses of the histamine H_1-receptor antagonists. It is a potent antihistamine and causes a moderate degree of sedation: it also has antimuscarinic activity. CPM is used for the symptomatic relief of hypersensitivity reaction including urticaria and angioedema, rhinitis and conjunctivitis and in pruritic disorders. It is a common ingredient of compound preparations for symptomatic treatment of coughs and common cold.

Adverse reactions :

A significant proportion of patients do experience sedation; side effects involving CNS stimulation are more common. There have been isolated reports of blood dyscrasias after administration of CPM; these include agranulocytosis, thrombocytopenia, pancytopenia and aplastic anaemia. Haemolytic anaemia has occurred after administration of dexchlorpheniramine maleate.

Methods for estimation of CPM : (75)

Various methods are available for the determination of CPM, which may be listed as under-

Acid base titration:

- Acid base titrations were performed potentiometrically using nonaqueous solvents with 0.1N $HClO_4$ as the titrant. Titration as an assay method is cited in USP where CPM is titrated with perchloric acid in acid media. An aqueous titration assay has also been proposed that involves the basic titration of excess hydrochloric acid that was not taken by the free base.

Colorimetric methods:

- Among the earliest was the formation of Reinecke salt which was dissolved in acetone and the absorbance was read. Several variations of

the Jones and Brady reaction have been studied. The general reaction involves formation of an adduct through attack on the pyridine ring by cyanogen bromide but further complexation with aniline is possible with many n-(2-pyridyl)antihistamines. The reaction is an adaptation of Koenig reaction.

Polarography:

- CPM exhibits a 2-electron reversible reduction that requires two protons to be consumed. The procedure recommends that the assay be run in 0.2M sulphuric acid(pH - 0.7) and a sample concentration from 10^{-5} - 10^{-3}.

Spectrometric and fluorometric methods:

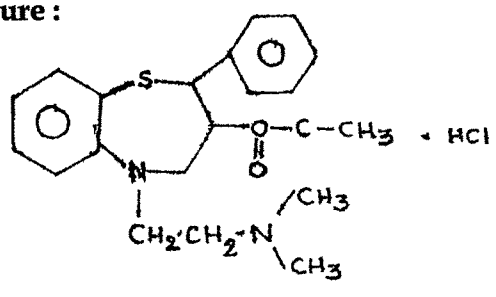
- Analytical fluorescence techniques have been used for analysis of CPM. UV spectroscopy has been used for the estimation of CPM in injectables and in syrups.

2.4.2 DILTIAZEM HYDROCHLORIDE (DIL) (76)

Diltiazem is a calcium-channel blocker with peripheral and coronary vasodilator properties. It lowers blood pressure and has some effect on cardiac conduction. It is given by mouth in the treatment of angina pectoris and the management of hypertension and has been tried in patients with myocardial infarction with equivocal results. It is generally well-tolerated although headache, oedema, gastro-intestinal disturbances and rashes may occur.

Molecular formula : $C_{22}H_{26}N_2O_2S.HCl$

Molecular Structure :



Molecular Weight : 450.98

Physical properties :

A white odourless crystalline powder or small crystals, freely soluble in water, chloroform, formic acid and in methyl alcohol; sparingly soluble in dehydrated alcohol; insoluble in ether. The degradation of diltiazem *in vitro* was enhanced in acid pH and at elevated temperature: about 25% of sample was lost after 24 hours at 37°, whereas there was no appreciable loss at 25°.

Pharmacokinetics :

Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first pass hepatic metabolism. After oral administration of a solution of diltiazem peak plasma levels are reached in 38 minutes after dosing, t-max is approximately 3 hours. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolised in the liver; one of the metabolites, desacetyldiltiazem has been reported to have 25-50% of the activity of the parent compound. The half-life is reported to be about 3 to 5 hours. Approximately 2 to 4 % of a dose is excreted in urine as unchanged diltiazem with the remainder being excreted as metabolites in bile and urine.

Therapeutic uses :

DIL is a calcium channel blocking agent. It is a peripheral and coronary vasodilator with very limited negative ionotropic activity but its vasodilator properties are less marked than those of nifedipine. Unlike nifedipine, diltiazem inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes. Diltiazem is used in the management of chronic stable (classical) and vasospastic (e.g. Prinzmetals') angina pectoris and has

also been used, alone or in combination, in the management of hypertension.

Adverse Effects :

Treatment with diltiazem is generally well tolerated. Headache, oedema, hypotension, dizziness, flushing, nausea and gastro-intestinal disturbances (including anorexia, vomiting, constipation or diarrhea, taste disturbances and weight gain) may occur. Rashes, possibly due to hypersensitivity, are normally mild and transient, but in few cases erythema, multiforme or exfoliative dermatitis has developed. Diltiazem may depress cardiac conduction and has occasionally led to atrioventricular block, bradycardia and rarely asystole or sinus arrest.

Estimation of DIL :(77)

Identification testing of DIL drug substance and product can be accomplished by uv absorbance analysis, infrared spectroscopy and by elemental weight determination of carbon, hydrogen, nitrogen, chlorine and sulphur.

Electrochemical analysis:

Ion-selective Electrodes: The use of ion-selective electrodes as a rapid, inexpensive method for the determination of diltiazem has been explored. Detection limits of 10^{-5} or lower are attainable.

Adsorptive stripping voltammetry and Flow amperometry: Voltammetric procedures can be used for trace measurements of diltiazem. Diltiazem exhibits both reductive and oxidative voltammetric responses. The adsorptive stripping is accomplished with a static mercury drop in conjunction with a stripping analyzer.

Chromatographic Analysis:

High-performance Liquid Chromatography: A stability-indicating HPLC procedure may be used for the identity testing of DIL. The retention

time(RT) of the major peak in the sample chromatogram should correspond to that of the DIL reference standard(RS).

Capillary zone electrophoresis: A micellar electrokinetic chromatographic method allows the separation of optically isomeric DIL using bile salts as chiral surfactants. Separation is achieved using a fused-silica capillary tube and a voltage upto +25KV. Detection is achieved on a column using UV absorption at 210 nm.

Spectrophotometric analysis:

Colorimetry: A colorimetric method, involving the reaction of diltiazem with cobalt thiocyanate in acidic media, is available which allows the estimation of diltiazem alone and in solid dosage forms.

Specific Rotation: The specific rotation $[\alpha]^{25}_{D}$, is determined with freshly prepared 1% solutions of DIL in water. The specific rotation for DIL bulk drug ranges between +112.0 and +114.0.

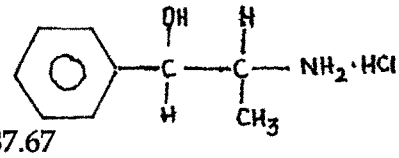
Direct Ultraviolet Spectrophotometry: DIL is characterised by an absorption maximum at approximately 235 nm. This absorption can be used as the basis for the quantitative determination. The assay is performed by comparing the absorbance of the sample dissolved in 0.1N HCl to a standard of a known concentration in 0.1N HCl. The absorbance for the drug product is calculated by subtracting the absorbance of the excipients similarly prepared in 0.1N HCl from the absorbance recorded for the drug product.

2.4.3 PHENYLPROPANOLAMINE HYDROCHLORIDE (PPA) (78)

PPA is an indirectly acting sympathomimetic agent. Its main clinical use is as a nasal decongestant, where it may be used alone or in combination with other agents usually orally, for the symptomatic relief of cold. Adverse effects of PPA are essentially those of adrenergic stimulation; additionally hypersensitive reactions and stimulation of CNS have occurred.

Molecular Formula : $C_9H_{13}NO$

Molecular structure :



Molecular weight : 187.67

Physical properties :

PPA is a white or almost white crystalline powder with a slight aromatic odour. B.P. solubilities are 1 in 2.5 of water, 1 in 9 of alcohol, practically insoluble in dichloromethane.

Pharmacokinetics :

PPA is readily and completely absorbed from GIT, peak plasma concentration being achieved about an hour or two after oral administration. In urinary excretion studies, with human subjects, it was found that approximately 90% of the drug was excreted predominantly unchanged in 24 hours. The mean elimination half life of PPA in man has been reported as 3.9 hours and the elimination rate constant as 0.18 $hour^{-1}$.

Therapeutic uses :

PPA is largely an indirect-acting sympathomimetic agent with an action similar to that of ephedrine but is less active as a CNS stimulant. It is given orally for the symptomatic relief of nasal congestion.

Adverse effects :

Sympathomimetics produce a wide range of adverse effects, most of which mimic the results of excessive stimulation of the sympathetic nervous system. These include central effects of sympathomimetic agents like fear, anxiety, restlessness, tremor, insomnia, confusion, irritability and psychotic

states. Appetite may be reduced and vomiting may occur . Other effects that may occur with sympathomimetic agents include difficulty in micturition and urinary retention, dyspnoea, weakness, altered metabolism including disturbances of glucose metabolism, sweating and hypertension. Headache is also common.

Methods of Analysis:(79)

UV Spectrophotometric Analysis:

Periodate oxidation of PPA has been used. The sample to be determined is placed in a separatory funnel, sodium bicarbonate and sodium metaperiodate are added and the solution is allowed to stand for about 15 min. 0.1M hydrochloric acid is added and then the solution is extracted with hexane. The extract is filtered and the absorbance determined at 242 nm in 1 cm cuvette using hexane as reference. The amount of oxidation product of PPA is determined by comparison of the sample absorbance of PPA RS treated in the same manner. Ether and chloroform have also been used for the extraction of the derivative.

Colorimetric Analysis:

PPA can be reacted with ninhydrin in a citrate buffer at an elevated temperature and determined colorimetrically at 570 nm. An ion pair extraction technique using an acidic dye, bromothymol blue, has been utilized and the resulting chloroform extract determined at 420 nm.

Spectrofluorimetric Analysis:

PPA has been determined by measuring its fluorescamine derivative, 4-phenyl-spiro[furan-2(3H),1'-phthalan]-3,3'-dione, at 480 nm with the excitation wavelength being at 398 nm. The reaction favours a pH of 9 for optimal reactivity.

Titrimetric Analysis:

After extraction of PPA from alkaline aqueous solution with chloroform, shaking with saturated sodium chloride solution and back extracting with an excess of sulphuric acid, the excess acid is titrated with a standard sodium hydroxide solution using methyl red as indicator.

Chromatographic Analysis:

- *Column Chromatography*: A weakly basic anion exchange resin, Amberlite R-45, was found to be suitable for the separation of PPA from various dosage forms and yielded 99.6% recovery of the drug which was then determined titrimetrically.
- *Paper Chromatography*: A descending paper chromatography using Whatman No. 1 paper has been reported. The solvent system consisted of 1:1 mixture of butanol (saturated with 1M hydrochloric acid) and methanol. After spraying with Dragendorff's reagent, the resulting orange-red spots were quantitatively determined by densitometry.

Various other chromatographic methods of analysis have been reported including Gas chromatography, HPLC and TLC.

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