
CHAPTER - ONE

I N T R O D U C T I O N

CHAPTER - 1

INTRODUCTION

Research in Drug Industry - An International Scenario :

It is a basic characteristic of the Pharmaceutical Industry's world wide that it is the most Research & Development intensive industry. The present status of the international pharmaceutical industry and the advances in therapy available today are primarily due to the very high innovational inputs deployed by the leading multi-national pharmaceutical companies.

In 1982, there were 20 companies in the world, whose turnover exceeded a Billion US \$, and these companies each spend significantly over \$ 100 million per year on R & D, most of it on basic research for the discovery and development of new drugs. Such expenditure constitutes 10 percent of the annual sales turnover of these companies. It has been the experience of these companies that for investments of this order of magnitude, industrial units need a sustained and guaranteed profitability from their existing business, since drug research is inherently risky, complex and time consuming. In 1980, it was estimated that on an average the direct cost of development of a single new drug was \$ 15 to \$ 20 million, if one adds to this the indirect costs of failures, the total economic cost would come

to around \$ 60 million and an elapsed time of 10 to 12 years for the discovery and marketing of a successful new drug. Escalating costs, increased regulatory controls, higher standards for new drugs, the rapid obsolescence of new products and extended elapsed times from laboratory to final approval have further led many companies in recent years to devote their attention to fewer therapeutic areas(1).

If the present trend continue, real expenditure by industry on R & D will have to treble by 1990 and completion of a single new pharmaceutical research project could take 15 to 20 years and the development cost of a single new drug entity could conceivably escalate to Rs.70 crores. It is clear that only the largest multinational companies can engage themselves in basic research for the development of new drugs and that too only for a selected and small number of therapeutic indications.

The developing countries will continue to depend on the developed countries for the know-how for manufacturing basic drugs. The research in these countries will confine to developing formulations suitable to the local environments and modification of existing formulation.

Indian Drug Industry

Today the Indian Drug Industry accounts for less than 2% of the world production of pharmaceuticals although we have 15% of the world's

population. Against the global production of US \$ 96,800 million drugs during the year 1986, India produced drugs valued at US \$ 1,700. Even today only a fraction of the population receive benefits of the modern medicines which are primarily in the urban areas. The Government is making efforts to extend this facilities to the rural areas through health care programme.

A country like India has certain specific problems which are primarily due to over low economic standard, insufficient sanitation, scarcity of drinking water, malnutrition etc. The majority of the people suffer primarily from the following diseases :-

- i) Tuberculosis
- ii) Leprosy
- iii) Malaria
- iv) Gastro enterities
- v) Blindness
- vi) Filariasis
- vii) Worm infestation

In addition, because of high birth rate, arrangements are to be made for immunisation of children of various ages. Because of constant efforts made by the Government both infant mortality rate and death rate have been brought down. As a signatory to the Alma-Ata delegation of WHO in 1978, India has adopted 'Health for All' as the goal for

the nation. The pharmaceutical industry has a vital role to play in the 'Health for All' programme by providing good quality medicines to all those who need them at prices that are reasonable. The NCAER* has estimated, on the basis of certain assumptions, that Rs.16,000 crores worth of medicines (at 1979-80 prices) would be needed by the end of the century. This is almost eight times the current production. Hence the pharmaceutical industry in India is poised for higher growth in the coming years (2).

Sulpha Drugs :

In India, Sulpha drugs are most commonly used in various formulations. Among the eleven bulk drugs of Sulpha group, Sulphamethoxazole has the highest growth rate of 15% per annum. While the demand for other bulk drugs of Sulpha group expected to grow at the rate of 5%(3).

The demand for Sulphamethoxazole is estimated to grow from the level of 270 MTs per annum during 1982-83 to 720 MTs per annum during 1989-90.

In view of the high growth rate of consumption and wide usage, the research study has been based on Sulphamethoxazole.

A study was made of the effects of various binders and binder concentration on the physical properties of the fluidized bed

granulation. Binders investigated gelatin U.S.P., Acacia, providone & hydroxy-propyl-cellulose. Binder formula weight had the following effects :

- a) Increase average granule size
- b) Decrease granule friability
- c) Increased interparticulate porosity
- d) Decreased granule flowability(4).

Uniform tablets were made by using a 10% w/w paste of the various starches as a binding agent. Disintegration times and the dissolution rates were determined. The general plain starches were found to be better than their combinations as far as in Vitro dissolution rate is concerned. Barley was found to be the best starch binder with lowest disintegration time (27 sec) and highest release (53.0%)(5).

The influence of various drug excipient [Sulfadiazine (I) and lactose] ratios on the vitro release of the drug was studied. Greater release was obtained for I from the tablet form than the pure drug powder(6).

Comparative bio-availability study of trimethoprim and Sulphamethoxazole in co-trimoxazole preparation - Dissolution studies by different methods. The dissolution of cotrimoxazole (400 mg of Sulphamethoxazole & 80 mg trimethoprim) was studied and the results obtained with the U.S.P. paddle and basket method were compared.

Few differences were observed between the two methods(7).

The activity of hydroxy propyl cellulose (II) as a binder in tablet formulations was investigated. A crystalline active principle (Sulfathiazole), with weak solubility in both water and alcohol was chosen in order to avoid any binding activity from the drug itself. The influence of the method of preparation, binder concentration, molecular weight of (II) nature of the solvent and viscosity of the granulating dispersion on granulation and tablet characteristics were studied(8).

The binding properties, during granulation of a wide range of excipients with aspirin (III) was studied. During direct compression all the binders tested assured homogenous distribution of (III) and a good cohesion and good disintegration of the resulting tablets. When wet granulation was used Avicel pH 10.2 (cellulose micro crystalline) carboxy methyl cellulose, ethyl cellulose and carboxy methyl starch gave the best results(9).

Carboxy Methyl Cellulose :

Effect of degree of polymerization and substitution of tablet disintegration and dissolution of Sulphamethoxazole tablets were studied with highly polymerized grades of carboxy methyl cellulose and found effective with the compound having a high degree of polymerization

and a small number of carboxy methyl groups(10).

A facorially designed experiment was carried out to study the influence of diluents like lactose, carboxy methyl starch, sodium lauriyl sulphate (IV) and magnesium stearate (V) on the in vitro dissolution rates of nitrofurantoin, oxcytetracycline and tetracycline hydrochloride hard gelatin capsules. Analysis of variance confirmed that although the main factors of diluent type, diluent concentration and the absence and presence of both (V) and (IV) were highly significant, the existance of interactions between the factors prevented exact quanttitative prediction of the influence of each factor. There appears however, to be a strong indication that the invitro drug release of capsule formulations can be related to the solubility of the drug(11).

The influence of the concentration of lactose magnesium stearate and sodium lauryl sulphate on the invitro dissolution and the drug content of hard gelatin capsules, filled under conditions which result in a maximum tapped bulk density was evaluated by factorially designed experiment. The study show an important influence of lactose concentrations on drug release and capsule filling, and the large changes in response which can occur by the addition of a wetting agent(12).

The dissolution profiles of prednisone, digoxin and griseofulvin in simulated GI fluids were determined after solvent deposition or ball

milling with 3 commercially available grades of amorphous silicon dioxide. The study revealed evidence of drug entrapment, larger average pore diameters, produced trituration with slowest dissolution rates(13).

The release of paracetamol and chloramphenical, suspended in liquid paraffin to an underlying aqueous layer was investigated as a function of particle size, concentration, and the presence of additives in the liquid paraffin. The study revealed - release to be independent of particle size, concentration and degree of coverage of the interface by particles. Addition of water to the suspensions increased the degree of agglomeration and reduced the degree of interfacial coverage but did not change the release rate. Dioctyl-Sodium-Sulfosuccinate 0.2% also had no effect on release rate, but in combination with water an increase in rate was observed(14).

The influence of salts on the flocculation state of suspension of benzocaine and butamben stabilized by several poly oxyethylene nonyl phenols as characterised by apparent viscosity, refiltration rate and sedimentation was studied. The effectiveness of the salts in promoting flocculation was in the order Sodium Sulphate > Magnesium Sulfate > Sodium Chloride > Calcium Chloride which, follows the lyotropic series indicating that the action of the salts involved dehydration of the lyophilic chains of the surfactants(15). The wetting of Salicylic acid and paracetamol powders by aqueous solutions of polysorbate

80 (Tween 80) and Sodium lauryl sulphate were determined by measuring the contact angles. Low concentrations of surfactants caused an improvement in the wetting was seen. Absorption of the surfactant at the solid/liquid interface may account for this(16).

Some factors influencing the invitro release of phenytoin from formulations - Ingeneral the release pattern from capsule was more complex than that from tablets. Formulation variables which affected release were particle size, packing of the capsule and the nature of the diluent. The formation of insoluble drug salts from adjuvants used in preparing drug delivery system appeared to be a possible factor in the biopharmaceutical variability of the drug(17).

Dissolution rate of Sulfamethoxazole utilizing sugar glass disperisions. Results showed a marked increase in the dissolution rate of sulphamethoxazole in the solid dispersions as compared with that of drug alone. During the fusion process, an interaction took place between the drug and the sugar forming a complex. In vitro bacteriological activity of the dispersion was not changed by the interaction with sugars(18).

Effects of addition of Magnesium stearate in Rifampicin Capsules. Magnesium stearate decreased the dissolution rate of Rifampicin sieved through 42-80 mesh screen, but accelerated the dissolution rate when passed through 200 mesh screen(19).

Comparison of the physical properties of some Sulfacetamide eye ointments commercially available in the U.K. - The rheology, particle size distribution and drug release, measured by dissolution and agar diffusion technique of five eye ointments containing sulphacetamide sodium were studied. Although particle size distributions of the two official ointments were similar, their consistency and drug release patterns were different. All ointments exhibited shear break down during continuous shear rheology. A linear relationship was found between the quality of drug release by agar diffusion technique, and the amount dissolved after 60 minutes. The official ointments released more slowly and in most case to a lesser extent than the other three formulations(20).

The absorption of drug substances is a most important factor in the selection of the appropriate route of administration in the design of the most efficacious dosage forms and therefore in drug therapy. Drugs are most frequently taken by oral administration. The majority are taken for the systemic drug effects that result after absorption from the various surfaces along the gastro intestinal tract. The oral route is considered the most natural uncomplicated convenient and safe means of administering drugs. Drugs are administered by the oral route in a variety of pharmaceutical forms, each with inherent therapeutic advantages that result in their selective use by physicians. The most popular forms are tablets, capsules suspensions and various pharmaceutical solutions. Briefly tablets are solid dosage forms

prepared by compression or moulding and contain medicinal substances with or without suitable diluents, binders, disintegrants, coatings colorants and other pharmaceutical adjuncts(21). Capsules are solid dosage forms in which the drug substance and such appropriate pharmaceutical adjuncts as fillers are enclosed in either a hard or a soft shell which is generally composed of a form of gelatin(22). Generally drug materials are released from capsules faster than from tablets. Suspensions are preparations of finely divided drugs held in suspension through out a suitable vehicle. Suspensions have the advantage over solid dosage forms in that they are presented to the body in fine particle size, ready for the dissolution process immediately upon administration(23).

Dosage form considerations in gastro intestinal absorption, the dosage form in which the drug is administered, the influence of additives on its physico chemical properties often have a profound influence on the rate of absorption and availability of the drug. The effect of the dosage form on absorption rate and physiological availability depends on the rate at which it releases the drug content, there in, into biological fluids.

Tablets :

Tablets in general should have a certain degree of tensile strength, provide uniform dose of medicaments, posses disintegration and

dissolution characteristics(24). Of the additives added none is more critical than the binder used to form the granulation, for it is largely the binder which is fundamental to the granulation, particle size uniformity, adequate hardness, ease of compression and general quality of the tablet.

A granule is an aggregation of component particles that is held together by the presence of finite strength(25). The strength of the wet granule is due mainly to the surface tension of liquid and capillary forces. These forces are responsible for initial agglomeration of the wet powder. Upon drying the dried granule will have strong bonds resulting from fusion and curing of the adhesive or binder. Under these conditions vanderwaals forces are of sufficient strength to produce a strong dry granule. Measurement of granule strength are aimed at estimating the relative magnitude of attractive forces, seeking to hold the granule together. The resultant strength of the granule is of course dependent on the base material, the kind and amount of granulating agent used. Granule strength and friability are important as these effect changes in particle size, distribution of granulation and consequently compressibility into cohesive tablets. Granule friability can also affect unit dose precision in some tablet systems. When such systems undergo friability breakdown, the drug may preferentially separate from the granules and as particle size separation occurs the tablets containing higher level of fines also contain a higher concentration of the drug.

In tablets particularly it is significant that the rate of dissolution has been shown to correlate closely with the bio-availability of the drug. Unfortunately a single granulation property can influence many different tablet properties while degrading others. In addition, adding to the complexity of property relationships is the fact that many different granulation properties, alone and as interactions effects often influence a single tablet property(26-30).

Binders or adhesives are added to tablet formulations to add cohesiveness to powders, there by providing the necessary bonding to form granules, which under compaction form a cohesive mass or compact referred to as a tablet(31-35). The formation of granules aids in the conversion of powders of widely varying particle sizes of granules which may more uniformly flow from the hopper to the feed system, and uniformly fill the die, cavity. The primary criterion when choosing a binder is its compatability with the other tablet components. Secondly it must impart sufficient cohesion to the powders to allow for normal processing-sizing, lubrications compression and packaging, yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredient for absorption. Final tablet characteristic such as dissolution, rate, disintegration time, porosity, friability, capping tendency and hardness are of fundamental physico-chemical properties of interest to the development pharmacist(36,37). Therefore granulation characteristics are of interest

and the most universally measured are those bulk density, some assessment of flow, degree of compaction in tablets and porosity(38).

Capsules :

Rate of absorption of certain drugs from hard gelatin capsules may be highly dependent on formulations(39,40). Assuming basic principles the availability of a drug for gastro intestinal absorption from a well formulated capsule will be better than or equal to the availability from a tablet dosage form, provided the fine particles placed in a capsule are not subjected to compression and possible fusion which would reduce the specific surface area-provided the particles in a capsule are intimately wet by the biological fluids, a large effective surface area will be available for dissolution(41).

It is important to have a suitable diluent in a capsule dosage form of a poorly soluble drug. An inert hydrophillic diluent serves to disperse the hydrophobic drug particles, increase the permeation rate of aqueous fluid to the content of the gelatin capsule, minimize clumping of the drug particles in contact with the biological fluids and optimize effective surface area, presence of a wetting agent in addition to a hydrophillic diluent is often advantageous, provided the drug is stable in stomach. Diluent must have no tendency to absorb or interact with the drug.

Factors that may influence absorption from capsule dosage forms include particle size, selection of diluents and fillers, absorption or other interactions of drug and filler and crystal form. Magnesium stearate is a commonly used lubricant in capsule and tablet making, to facilitate the flow of the drug fill into tableting or encapsulating machinery. Although small amounts of Magnesium stearate are generally used (frequently less than 1%) the water proofing characteristics of this insoluble material can pose a problem to the penetration of solid dosage form by the gastro-intestinal fluids intended to dissolve it. This obstacle to water and fluids penetration can delay the dissolution of the drug and its absorption. The practice of adding a surfactant in capsule and tablet formulations to facilitate the wetting of drug substance by the bathing gastro intestinal fluids is a widely followed procedure in industry. The advantage of adding a wetting agent to capsule formulation of Lithium Carbonate to enhance dissolution has been demonstrated. Even in instances in which Magnesium stearate or some other water insoluble lubricant is not used in capsule formulation, when the gelatin shell of capsule dissolves, liquid must displace the air that surrounds the dry powder within the capsule and penetrate the drug before the capsule fill can be dispersed and dissolved.

Powders of poorly soluble drugs have a tendency to float on the surface of the fluid and agglomerate to further minimize air-liquid contact and if wetting does not occur readily, dissolution is delayed.

Whether it be the presence of a lubricant, surfactant or some other pharmaceutical expient, formulation can influence the bio-availability of a drug substance and can account for difference in drug effects which may be encountered between two capsule products of same medicinal substance.

Suspensions :

The effects of several variable - nature of the vehicle, electrolyte type and concentration of surfactant upon the physical properties of sulphagaunidine suspensions have been investigated. It was shown that the concept of controlled flocculation may be usefully applied to the formulation of pharmaceutically acceptable suspension of the drug(42,43). The general physico-chemical principle applicable to caking and flocculation in pharmaceutical systems are reviewed and are related to practical formulation problems. The increasing use of suspensions as a form of pharmaceutical preparation has emphasized the need for further evaluation of the factors controlling the physical stability and bio-availability of these systems. The investigation of their physical and chemical properties stands as a challenge to the Industrial pharmacist and research worker because many problems arise in the design and manufacture of pharmaceutical suspension (44,45).

There are many considerations in the development and preparation

of a pharmaceutically elegant suspension. In addition to therapeutic efficacy, chemical stability of the components of the formulation, permanency of the preparation and esthetic appeal of the preparation - desirable qualities in all pharmaceutical preparations - a few other features apply more specifically to the pharmaceutical suspensions(46).

- a) A properly prepared pharmaceutical suspension should settle slowly and should be readily redispersed upon the gentle shaking of the container.
- b) The characteristics of the suspension should be such that the particle size of the suspension remains fairly constant throughout long periods of undisturbed standing.
- c) The suspension should pour readily and evenly from its container(47).

These main features of a suspension, depend upon the nature of the dispensed phase, the dispersion medium and pharmaceutical adjuncts(48,49).

Sulphamethoxazole oral suspension U.S.P. are marketed under the name Gantanol suspension (Roche) 500 mg/5 ml. They come under the class of Anti bacterials (Non-antibiotic Anti-infectives). These Sulfa-drug suspensions are bacteriostatic agents particularly useful in the

treatment of urinary tract infections. Sulfonamides competitively inhibit bacterial synthesis of folic acid and para-aminobenzoic acid.

Ointments :

The vehicle or bases provide convenient means of maintaining the drug at or close to the topical absorption site. It is doubtful if vehicles used for dermatological preparation can promote the absorption of drugs that are not themselves absorbable, but the composition of the vehicle can markedly affect the release and absorption of absorbable drugs(50,51).

The vehicle controls the drug activity, the rate of diffusion in the vehicle, and the partition coefficient between the vehicle and skin(52). A high affinity of the bases for the drug is not desirable. Drugs that complex or bind to components of the vehicle are released into the skin very slowly. Release of the drug is favoured by using a vehicle that is a poor solvent for the drug. A high stratum Corneum - Vehicle partition coefficient, encourages the process of transfer of drug into the epidermis. The partition coefficient may be altered by including various solvent (such as alcohol and propylene glycol) in the vehicle. Hydro carbon ointment vehicles have an occlusive action on the skin, but emulsion bases are less occlusive. Insoluble powders such as Zinc oxide reduce the occlusive properties by their uptake of water and by providing a large surface area for evaporation.

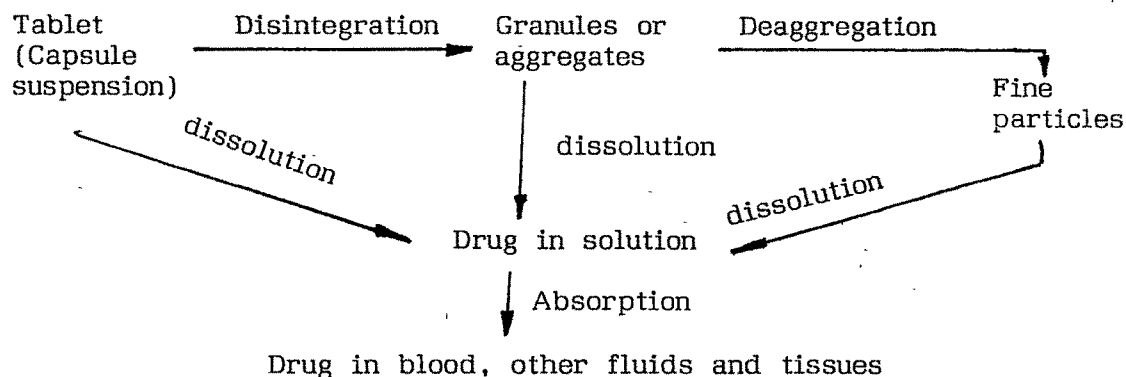
Although the various factors that influence percutaneous absorption of drugs are becoming better understood, it is not yet possible to select the best vehicle for a drug solely from a knowledge of their respective physico-chemical properties. The vehicle is chosen on the basis of practical experience with selected formulations using a quantitative or semi quantitative measurement of drug penetration.

Bioavailability :

Bioavailability of a drug depends on various factors, such as the dissolution behaviour, the time of stay in the absorption section of G.I.T., the absorption rate constant, and special physiological factors. The therapeutic performance of a drug is often determined by the dynamics of its release from a dosage form. The processes involved when a oral dosage form is administered is shown in Scheme "A" (53,54).

SCHEME "A"

Oral Dosage forms.



Since a drug has to be dissolved before it is available for absorption in the gastro-intestinal tract, in-vitro dissolution tests have been developed to assess the dissolution behaviour of the drug under conditions that simulate the in-vitro environment.

The dependence of the rate of absorption on the dissolution characteristics of a solid drug in the gastro intestinal tract is an important bio-pharmaceutical problem(55). The sartorius solubility simulator was developed for the invitro investigation of this.

Comparative experiments have shown that with the help of solubility simulator the rate of dissolution of drugs in the human gastro-intestinal tract, the resulting absorption characteristics can be reproduced. The solubility simulator is used in the development of pharmaceuticals containing drugs in solid form (viz. tablets, granulations, powder, suspensions etc.). Whose effectiveness is known to depend upon physical factors such as type of auxilliary substance, the surface of drug particles. Tests on such preparations provide information as to whether the rate of absorption is substantially reduced by the dissolution process.

Factors which are of special importance for the dissolution and absorption of a drug in the various section of G.I.T. - pH value, liquid volume, time of stay, mixing. On the other hand, surface tension, viscosity and the enzymes of the gastric and intestinal juices

are of little importance.

Drugs administered orally in a solid dosage form must first go into solution in the gastro intestinal tract since only dissolved drugs can pass through the gastro intestinal wall and enter the body. The concentration of the dissolved drug in the G.I.T. is however constantly being reduced as dissolved drug passes into the body. This results in a greater or lesser increase in the rate of dissolution. This mutual interaction of absorption and dissolution is an important biopharmaceutical aspect.

In contrast to the dissolution of drugs, which seldom obeys simple laws (such as the Noyes whitney rate equation, the Hixon - Cromwell cube root law) due to the complex influencing factors and properties of formulations, the rate of absorption from a specific section of the G.I.T. can be described by a simple equation deduced from Ficks law of diffusion ignoring any back transport.

The Sartorius solubility simulator in which solid dosage forms go into solution under conditions which closely simulate those in which absorption effect is also taken into consideration. The solubility characteristic curve supplies information about the effect of the physico chemical properties of a drug or its pharmaceutical formulation on its dissolution behaviour and also on any differences between different formulations.

The absorption characteristic curve on the other hand describes whether and to what extent the uptake of a drug into the body has been influenced by the dissolution behaviour in the G.I.T. or by the pharmaceutical formulation(58).

The dissolution profile of a disintegrating oral dosage form is typically a sigmoid curve. The corresponding rate of dissolution is initially zero, then increases until it reaches a maximum and decreases back to zero. During the period that the dissolution rate is increasing, surface area is generated by disintegration. After the peak, the disintegration process approaches the final stage and dissolution is the rate determinant for the decrease of surface area. If disintegration of the tablet is rapid as compared to the dissolution process, then the portion of the curve having positive curvature may become quite abbreviated. If the dissolution profile of the tablet is obtained by intermittent sampling, this portion is often unobserved and is reported as a lag period.

Equations have been used to fit dissolution curves and provide parameters which facilitate the storage of data and the comparison between various formulations. Generally speaking such equation are obtained either empirically or semi empirically and no theoretical basis is available.

Aims and Significance :

The sulpha drugs are most commonly used in various formulations. Among the eleven bulk drugs of sulpha group, sulphamethoxazole has the highest growth rate of 15% per annum, while the demand for other bulk drugs of sulpha group is expected to grow at the rate of 5%. The demand for sulphamethoxazole is estimated to grow from the level of 270 mts per annum during 1982-83 to 720 mts. per annum during 1989-90. In view of high growth rate in consumption and wide usage, the research study has been based on sulphamethoxazole and sulphacetamide.

Dosage form considerations in gastro intestinal absorption, the dosage form in which the drug is administered, and its properties, the role played by additives in the formulation often have a profound influence on the rate of dissolution, absorption and availability of the drug.

In the present times sulphamethoxazole serves as an antibacterial and is available in the form of tablets, capsules, suspension in combination with trimethoprim in the ratio 5:1. It is marketed under various brand names with varying combination of additives. Not much of thought is being given to what extent the additives of the formulation play a significant role on its physico chemical properties which in turn often have a profound influence on the stability, rate

of absorption and availability of the drug.

A thorough investigation of literature on the "Effect of additives" on different drug dosage forms led to the following conclusion, that although work has been done on the effect of additives on dosage form design, not much work has been done with sulphamethoxazole and sulphacetamide in particular. Therefore there is a need for a complete data regarding bioavailability of sulphamethoxazole from different oral dosage forms such as tablets, capsules and suspensions. In order to study the release rate of a sulpha drug from a ointment dosage form sulphacetamide could be the drug of choice.

Present Investigation :

The present thesis involves five chapters.

CHAPTER I INTRODUCTION

CHAPTER II EFFECT OF BINDERS ON SULPHAMETHOXAZOLE TABLETS

Five batches of sulphamethoxazole tablets were prepared using different binders viz. starch, acacia, ethyl cellulose, sodium carboxy methylcellulose and providone (polyvinyl pyrrolidone P.V.P.) with water in 3% (dry basis) concentration. Comparative data

show that granules prepared with PVP have the best flow properties, minimum angle of repose, percentage fines and compressibility. While granule of sodium carboxy methyl cellulose could not be compressed into well defined tablets. Tablets containing starch as a binder posses all quality feature. Tablets from acacia however gives a poor dissolution profile. Ethyl cellulose have less effective granule formation leading to poor quality of tablets. Rank correlation with respect to solubility and absorption characteristics according to granulating agent in the formulation are as starch > ehylcellulose > P.V.P. > acacia.

CHAPTER III EFFECT OF ADDITIVES ON SULPHAMETHOXAZOLE CAPSULES

Formulations of Sulphamethoxazole Capsules are prepared and their physico chemical properties have been determined. Formulation of Sulphamethoxazole in combination with Corn starch and silicon dioxide have highest solubility and dissolution characteristics. However, formulation with silicon dioxide and dicalcium phosphate results a poor dissolution profile. Sulphamethoxazole capsules without additives showed higher weight variation and erroneous bioavailability

pattern. Formulations incorporating silicon dioxide as lubricant has a good flow property. Minimum weight variation was observed with dicalcium phosphate, magnesium stearate and aerosol O.T. A good dissolution and absorption characteristic is observed in formulation with dicalcium phosphate and magnesium stearate in the presence of sodium lauryl sulphate. Rank correlation with respect to bioavailability studies are as Batch V > Batch VIII > Batch I > Batch III.

CHAPTER IV EFFECT OF ADDITIVES ON SULPHAMETHOXAZOLE SUSPENSIONS

Suspensions of Sulphamethoxazole are prepared with the various combinations of additives viz. vehicles, suspending agents, wetting agents, electrolytes and preservatives. Sedimentation studies indicated that formulation IV have a marked increase in the sedimentation volume, clear supernatant fluid with very good redispersability. It has a comparatively high viscosity at negligible shear, however have a poor dissolution profile. Suspension III show low sedimentation volume, severe caking and poor redispersability. Suspension showed Newtonian behaviour when subjected to shearing rate. Dissolution profile

indicated slow release rate over a period of 30 min. Suspension II showed great degree of particle particle interaction, resulting in the formation of aggregates thereby leading to quick settling and increased sedimentation rate. Suspension I, II, showed 100% release of the drug within 15 min. Rank correlation in selection of a best combination of Sulphamethoxazole suspension is Suspension I > Suspension IV > Suspension II > Suspension III.

CHAPTER V EFFECT OF ADDITIVES ON SULPHACETAMIDE OINTMENTS

Five different formulations of sulphacetamide sodium ointment was prepared using different ointment bases. Formulation II, showed certain degree of stiffness when applied on to the skin. The other formulations namely Formulation I, III, IV and V, showed good spreadability characteristics. There was no visible signs of irritancy from any of the formulations. Rank correlation with respect to release rate studies are Formulation V > Formulation II > Formulation IV > Formulation I > Formulation III. For details see Table II.