"DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLET OF TIANEPTINE SODIUM"

Dissertation Submitted to

THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY

Chennai-600032

In Partial fulfillment for the award of the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled "**DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLET OF TIANEPTINE SODIUM**" submitted by student bearing **Reg.No-261510260**to The Tamilnadu Dr. M. G. R. Medical University, Chennai, for the partial fulfillment of the degree of MASTER OF PHARMACY was evaluated by us during the examination held on……

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CERTIFICATE

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DECLARATION

The work presented in this dissertation entitled, "**DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLET OF TIANEPTINE SODIUM**" was carried out by me, under the direct supervision **of Dr.V.KAMALAKKANNAN, M.Pharm.,Ph.D** Associate. Professor, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

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ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru J.K.K. Nattaraja Chettiar, providing us the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson Smt. N. Sendamaraai, B.Com., Managing Director Mr. S. Omm Sharravana, B.Com., LLB., J.K.K. Nattraja Educational Institutions, Komarapalayam for their blessings, encouragement and support at all times.

It is most pleasant duty to thank our beloved Principal Dr. R.SAMBATHKUMAR, M.Pharm., Ph.D., J.K.K.Nattraja College of Pharmacy, Komarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

I express my whole hearted thanks to my guide Dr.V.KAMALAKKANNAN M.Pharm.,Ph.D Associate.Professor , Department of Pharmaceutics, for suggesting solution to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

My sincere thanks to Dr. R. Shanmuga Sundaram, M.Pharm., Ph.D., Vice Principal and Professor and Head of the Department, Department of Pharmacology, Dr. Kalaiarasi., M.Pharm.,Ph.D Asst.Professor, Department of Pharmacology, for their valuable suggestions during my project work.

It is my privilege to express deepest sense of gratitude toward Dr.M. Senthilraja, M.Pharm., Ph.D., Professor and Head, Department of Pharmacognosy and Mrs. P. MeenaPrabha, M.Pharm.,Asst.Professor, Department of Pharmacognosy for their valuable suggestions during my project work.

My sincere thanks to Dr. M. Vijayabaskaran, M.Pharm., Ph.D., Assistant Professor

and head Department of Pharmaceutical chemistryMrs. S. Gomathi, M.Pharm., Lecturer, Department of Pharmaceutical chemistry and for their valuable suggestions and inspiration.

My sincere thanks to Dr.N. Venkateswaramurthy, M.Pharm.,Ph.D Professor and Head, Department of Pharmacy Practice. Mrs. K. Krishna Veni, M.Pharm.,Asst.Professor, Department of Pharmacy Practice, for their help during my project.

My sincere thanks to Dr.V.Sekar, M.Pharm., Ph.D., Professor and Head of The Department of analysis, , and Dr.I.Caroline nimila,M.Pharm.,Ph.D., Assistant Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to Dr. S. Bhama, M.Pharm.,Ph.D Associate Professor, Mr. R. Kanagasabai, B. Pharm. M.Tech., Assistant Professor, Mr. K. Jaganathan, M.Pharm., Asst.Professor, Department of Pharmaceutics, Mr. C. Kannan M.Pharm., Asst.Professor, Department of Pharmaceutics for their valuable help during my project.

I greatly acknowledge the help rendered by Mrs. K. Rani, Office Superintendent, Mrs. V. Gandhimathi, M.A., M.L.I.S., Librarian, and Mrs. S. Jayakala, B.A., B.L.I.S., Asst. Librarian for their co-operation.

My special thanks to all the Technical and Non Technical Staff Members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

Mrs. G.ROHINI

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LIST OF ABBRIVATIONS

API	-	Active pharmaceutical ingredient
° C	-	Degree centigrade
Conc	-	Concentration
CDER	-	Center for Drug Evaluation and Research
cm	-	Centimeter
DT	-	Disintegration time
DC	-	Drug content
FDTs	-	Fast dissolving tablets
FT-IR	-	Fourier Transform Infrared
g	-	Gram
GIT	-	Gastrointestinal tract
hr	-	Hour
IR	-	Infra Red
IgE	-	Immuno globulin E
IP	-	Indian Pharmacopoeia
IODs	-	Intraoral drugs
Kg	-	kilo gram
KBr	-	Potassium bromide
m. p.	-	Melting Point
MDTs	-	Mouth dissolving tablets
min	-	Minutes
mg	-	milli gram

ml	-	milli liter
mm	-	milli meter
MCC	-	Microcrystalline cellulose
NDDS	-	novel drug delivery systems
nm	-	nano meter
ODTs	-	Orodispersible tablets
PEG	-	Poly ethylene glycol
pH	-	Hydrogen ion concentration
QD	-	Quick dissolve
QoL	-	Quality of life
rpm	-	Revolution per minute
sec.	-	Second

CONTENTS

1. INTRODUCTION

1.1. ORAL SOLID DOSAGE FORMS – A CONVENIENT DRUG DELIVERY SYSTEM

The conventional oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drugs candidates and formulation. The popularity of oral route is attributed to patient acceptance, ease of administration,[1-2] accurate dosing, cost effective manufacturing methods, and generally improve shelf life of the product. In fact the development of a pharmaceutical product for oral drug delivery, irrespective of its physical form (solid, semisolid, or liquid dosage form) involves varying contents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal physiology[1]

Oral solid dosage forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled release and sustained release drug delivery system have been developed. Although these new systems are in fast progression, for many drugs and therapeutic indications, conventional oral solid immediate release drug delivery systems provided satisfactory clinical performance with an appropriate balance of efficacy and safety.

The major drawbacks in developing a controlled release and sustained release drug delivery systems are outlined as given below:

1.1.1.Drawbacks in Controlled Release and Sustained Release Drug Delivery System.

Decreased systemic availability[3] when compared with immediate release conventional dosage forms due to incomplete release, increased first pass metabolism, increased instability, and insufficient residence time for complete release, site-specific absorption, and pH-dependantsolubility. Poor*in-vitro in-vivo* correlation.Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by patient and thus, increased risk of toxicity.

Difficulty in retrieval of drug is in case of toxicity, poisoning and hypersensitivity reactions. Reduced potential for dosage adjustment of drugs normally administered in varying strengths. Higher cost of formulation.

1.2.ORAL SOLID DOSAGE FORMSAS GENERIC PRODUCT DEVELOPMENT

Oral solid dosage forms such as tablets or capsules can be developed into an immediate release or modified release generic product. A generic drug product, is also referred as a multisource Pharmaceutical product, is essentially identical to the brand name drug product in terms of active ingredient, strength, dosage form, route of administration, quality, safety, efficacy, performance characteristics, and therapeutic identification[5]

The development of a single dosage oral tablet requires six key decisions and they are listed below

- Reference listed drug (RLD or innovator drug)
- Active material
- Non-active ingredients
- Container- closure system

- Comparative dissolution procedure
- Bioequivalence to the RLD

1.3. IMMEDIATE RELEASE ORAL SOLID DOSAGE FORMS

Immediate release solid oral dosage forms are formulations of tablets, capsules that are designed to disintegrate and release the drug in absence of any controlling features such as coatings or other formulation techniques[6]

1.3.1. Tablets

Compressed tablets are defined as solid-unit dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

Reasons for preferring tablets as dosage forms are

- Accurate dosage
- Good physical and chemical stability.
- Cost effective
- Elegant appearance and patient compliance.

1.3.1.1. Advantages of tablets

- They provide an accurately measured dose and low content variability of the unit dose.
- They are of low manufacturing cost.
- They are easy to package and ship.
- They are simple to identify.
- Manufacturing processes and techniques provide tablets certain special release products such as enteric and delayed release products[7]

1.3.1.2. Disadvantages

- Some drugs may cause local irritation effect harmful to gastrointestinal mucosa.
- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression.

1.3.2. Excipientsused in Formulation of Tablets

The excipients used in formulation of tablets are

1.3.2.1. Diluents

They are bulking agents added to the active ingredient in sufficient quantity to make a reasonably sized tablet. Examples: Lactose, Sucrose, Dextrose, Mannitol, Sorbitol, Starch, Microcrystalline Cellulose, Calcium phosphate (dibasic and tribasic)

1.3.2.2. Binders

Binders or Adhesives are the substances that promote cohesiveness. It is utilized for converting powder into granules through a process known as Granulation. Examples: Gelatin, Glucose, Methylcellulose, Water, Acacia, Polyvinyl pyrrolidone, Sorbitol.

1.3.2.3. Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture and is added in the dry state prior to compression. The most commonly used glidants are colloidal silicon dioxide (Cabosil®, Cabot®) and syloid. They are used in

concentration less than 1%. Talc is also used and may serve the dual purpose of lubricant/glidant.

1.3.2.4. Lubricants

Lubricants are the substance which prevent adhesion of the tablet material to the surface of the dies and punches, reduce inter particle friction, facilitate an easy ejection of tablets from the die cavity and improves rate of flow of granules. Commonly used lubricants are Talc, Magnesiumstearate, Calcium stearate, Stearic acid, Hydrogenated vegetable oil and PEG. The quantity of lubricant significantly varies from 0.1 to 5%.

1.3.2.5. Disintegrants

Disintegrants are the substances added to a tablet to facilitate its break up or disintegration after administration. Examples: Starch1500(5to15%w/w), AvicelpH101,102 (Microcrystalline cellulose (5 to15 %w/w), Sodium starch glycolate, Polyvinyl pyrrolidone (PVP) and cross linked Polyvinyl pyrrolidone, Sodium Carboxy methyl cellulose, Croscarmellose sodium, Low substituted hydroxyl cellulose.

1.4. TABLET EVALUATION TESTS

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interactions between tablet components may alter the physical tablet properties, and greatly affect the bioavailability of the tablet system[8]

There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size,

shape, thickness, weight, hardness, disintegration and dissolution characters. The diameters and shape depends on the die and punches selected for the compression of tablets.

1.4.1. General Appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance, control of lot to lot uniformity and general tablet to tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablets size, shape, color, presence or absence of odor, taste, surface textures, physical flaws and consistency.

1.4.1.1. Shape and size

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process. At a constant compressive load, tablet thickness varies with changes in die fill, particle size distribution and packing of powder mix being compressed and with tablet weight, while with a constant die fill,thickness varies with variation in compressive load. The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within a ± 5% variation of a standard value. The physical dimensions of the tablet along with the density of the material in the tablet formulation and there proportions, determine the weight of the tablet. The size and shape of the tablet can also influence the choice of tablet machine to use, the best particle size for

granulation, production lot size that can be made, the best type of tableting processing that can be used, packaging operations and the cost of production.

The USP has provided limits for the average weight of uncoated compressed tablets.

Table1 :Weight variation requirements as per USP

Average weight	% difference
130 mg or less	10
More than 130 mg through 324mg	7.5
More than 324mg	5

1.4.1.2 Organoleptic properties

Color is a vital means of identification for many pharmaceutical tablets and is also usually important for consumer acceptance. The color of the product must be uniform within a single tablet, from tablet to tablet and from lot to lot. Non uniformity of coloring not only esthetic appeal but could be associated by the consumer with non uniformity of content and general poor product quality. Reflectance spectrophotometry, tristimulus colorimetric measurements and micro reflectance photometer have been used to measure color uniformity and gloss on tablet surface.

Odor may also be important for consumer acceptance of tablets and can provide an indication of the quality of tablets as the presence of an odor in a batch of tablets could indicate a stability problem, such as the characteristic odor of acetic acid in degrading aspirin tablets.Taste is also important for consumer acceptance of certain

tablets(chewable tablets)and many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product

1.4.2. Content Uniformity

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and un coated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50 mg or smaller sizes. Tablet monographs with a content uniformity requirement do not have weight variation requirements. For content uniformity test, representative samples of 30 tablets are selected and 10 are assayed individually. At least 9 must assay within ± 15% of the declared potency and non may exceed ±25 %

1.4.3. Mechanical Strength of Tablets

The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information is useful in the selection of excipients. An excessively strong bond may prevent disintegration and subsequent dissolution of a drug. Weak bonding characteristics may limit the selection and/or proportion of excipients, such as lubricants, that would be added to the formulation. The mechanical properties of pharmaceutical tablets are quantifiable by the friability, hardness or crushing strength, crushing strength friability values, tensile strength and brittle fracture index[9]

1.4.4 Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4 min of this treatment or 100 revolutions the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is the measure of tablet friability. The value is expressed as percentage. A maximum weight loss of not more than 1 % of the weight of the tablets being used during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have fewer tendencies to cap where as thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress.

1.4.5. Hardness or Crushing Strength

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet

production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packing and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg. Tablet hardness has been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

1.4.6. Tensile Strength

A non-compendial method of measuring the mechanical strength of tablets that is now widely used id the tensile strength. This is the force required to break a tablet in a diametral compression test. The radial tensile strength, T, of thetablets can be calculated from the equation

$$T=2F/pdH$$

Where F is the load needed to break the tablet, and d and H are the diameter and thickness respectively. Several precautions must be taken when using the equation. Various factors e.g. test conditions, deformation properties of the material, adhesion conditions between compact and its support and tablet shape may influence the measurements of the tensile strength.

1.4.7. Disintegration

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms. The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and the bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37^0c, preferably in a 1L beaker. For compressed uncoated tablets, the testing fluid is usually is water at 37 ^{0} c but some monographs direct that simulated gastric fluid be used. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets. For most uncoated tablets, the BP requires that the tablets disintegrate in 15 min(although it varies for some uncoated tablets) while for coated tablets, up to 2 h may be required. The individual drug monographs specify the time disintegration must occur to meet the Pharmacopoeial standards.

1.4.8. Dissolution

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms and is now

developing into a tool for predicting bio availability, and in some cases, replacing clinical studies to determine bio equivalence. Dissolution behavior of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between *in vitro* dissolution rate of many drugs and their bio availability has been demonstrated and is generally referred to as *in vitro-in vivo* correlation, IVIVC.

For many drugs, particularly those that are poorly soluble in the gastric fluid, the rate limiting step in the absorption process is the dissolution rate and a dissolution rate determination can therefore be a useful guide to comparative bio availability. Since drug absorption and physiological availability depend on the availability of the drug substance in a dissolved state, suitable dissolution characteristics are important property for a satisfactory tablet. The dissolution test measures the amount of time required for certain percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It describes a step towards physiological availability of the drug substance, but it is not designed to measure the safety or efficacy of the tablet being tested. It provides *invitro* control procedure to eliminate variation among production batches. The dissolution medium must be aqueous and the pH of the medium should be controlled and should simulate *invivo* conditions. The dissolution medium should be 0.1 M HCL and pH 6.8 buffer to simulate the bio logical extremes. The possible role of bile salts in absorption of highly in soluble drugs suggests the inclusion of physiological concentrations of sodium taurocholate in the mildly acid or alkaline media. Studies have shown that low agitation must be used (i.e. in the order of 50 rpm)and that the tablet must not be subjected to abrasion in keeping with the mild agitation in the gastrointestinal tract.

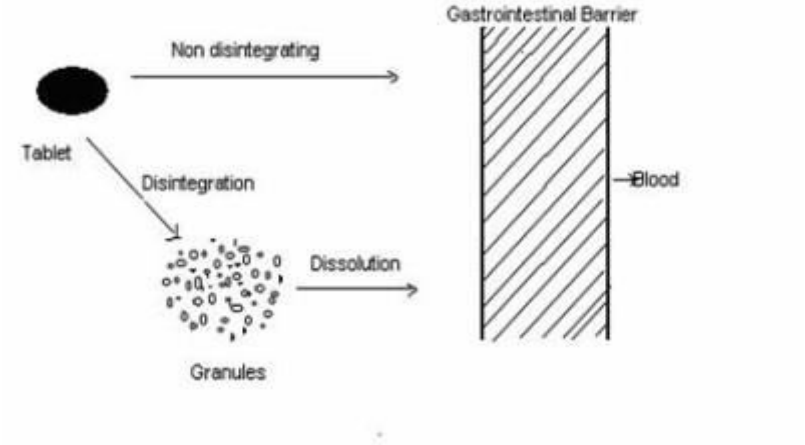


Fig. 1:Schematic diagram of the dissolution process

Dissolution kinetics is important in determining the bio availability of a drug. Levy and some other workers reported that the dissolution rate controls the rate of buildup of certain drugs in the blood stream. It was thus recognized that *in-vitro* dissolution kinetics provides useful information on the availability of drugs and their subsequent therapeutic effects in *vivo*. This lead to the inclusion of dissolution tests in the United States NF XIII (1970) and USP XVIII (1970)monographs for one capsule and 12 tablet preparations.

1.4.8.1. Discriminative pH method for dissolution of tablets.

Immediate release dosage forms are designed to allow drugs to dissolve freely in the GI contents, with no intention of prolonging the dissolution or absorption of drugs upon administration. IR products could be rapidly dissolving or slowly dissolving depending on the intrinsic dissolution rate of the drug substances. For a rapidly dissolving product, more than 85 % of API is expected to dissolve within 30 min in ≤ 900 ml of aqueous medium.

According to FDA draft guidance document, entitled "Waiver of *In-Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutical Classification System" for waivers of an *in-vivo* relative bioavailability study, dissolution should be greater than 85 % in 30 min in the three recommended dissolution media (acidic media, such as 0.1 N HCL or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer and a pH 6.8 buffer or Simulated Intestine Fluid USP without enzymes). For waivers of *in-vivo* bio equivalent, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products.

2. LITERATURE REVIEW

2.1PAST WORK ON TIANEPTINE SODIUM

Fuad Lechin *et al*., 2009, investigated the effects of tianeptine, a drug which enhances 5-HT uptake during the oral glucose tolerance test. They found that the drug triggered significant and sustained insulin rises which were opposite to the plasma glucose decreases. The fact that significant nor adrenaline/adrenaline (NA/Ad) plasma ratio paralleled insulin rises throughout the test is consistent with the excitatory role played by the peripheral neural sympathetic activity[11]

Sevgi Tatar and Zeynep, 2008, developed a method which involves formation of colored chloroform extractable ion-pair complexes of tianeptine with bromophenol blue (BPB), bromocresol green (BCG), bromothymol blue (BTB) and methyl orange (MO) in acidic medium. Beer's law is obeyed in the concentration ranges 3.0—12.0, 4.0—16.0, 4.0—14.0 and2.0—10.0mgml_1 with BPB, BCG, BTB and MO, respectively. The detection limit of tianeptine was found to be1.8mgml_1 for BPB, 2.0 for BCG, 2.0mgml_1 for BTB and 1.0mgml_1 for MO[12]

Dresse *et al*., 1988, studied influence of a test meal on the absorption and disposition of tianeptine (Stablon), a new antidepressant, was investigated in 12 healthy subjects in a two-way, randomized, open cross-over study. Single 12.5-mg oral doses of tianeptine were administered following a night of fasting or immediately after a standardized breakfast. When subjects received tianeptine under fasting conditions the lag time before absorption onset, and the time of the maximum plasma concentration were 0.55 +/- 0.26 hours and 1.29 +/- 0.29 hours, respectively. The maximum plasma concentration was 322 +/- 44 ng/mL, and the total area under the curve 994 +/- 248 ng/hr/mL[13]

Loo et al., 1990, demonstrated its ant depressive clinical efficacy in several double-blind versus reference drug trials. A multicentre open trial, including depressed

patients enabled us to evaluate the safety of tianeptine and to control the maintenance of the therapeutic efficacy in the course of its long-term prescription[14]

Dalery *et al*., 2001, compared the efficacy and acceptability of tianeptine vs placebo in the long-term treatment of unipolar major recurrent depression, 268 hospitalized and ambulatory patients meeting DSM III-R criteria for major depression with a 21-item Hamilton depression rating scale (HDRS) score ≥ 17 and at least one episode in the previous 5 years received tianeptine in a 6-week multicenter open study.[15]

Wagstaff and Ormrod DSpencer , 2001, studied Tianeptine as an antidepressant agent with a novel neurochemical profile. It increases serotonin (5-hydroxytryptamine, 5-HT) uptake in the brain (in contrast with most antidepressant agents) and reduces stress-induced atrophy of neuronal dendrites. Like the selective serotonin reuptake inhibitors (SSRIs) and in contrast with most tricyclic antidepressant agents, tianeptine does not appear to be associated with adverse cognitive, psychomotor, sleep, cardiovascular or bodyweight effects and has a low propensity for abuse[16]

Doaa Ahmed El-Setouhy *et al*., 2008, formulated orodispersible film(s) of the antidepressant drug tianeptine sodium to enhance the convenience and compliance by the elderly and pediatric patients. The novel film former, lycoat NG73 (granular hydroxypropyl starch), along with different film-forming agents (hydroxypropyl methyl cellulose, hydroxyethyl cellulose, and polyvinyl alcohol), in addition to three film modifiers, namely, maltodextrin, polyvinyl pyrrolidone K90 and lycoat RS780 (pregelatinized hydroxypropyl starch) were evaluated. Eight formulae were prepared by the solvent-casting method, and were evaluated for their *in vitro* dissolution characteristics, *in vitro* disintegration time, and their physico-mechanical properties[17]

Michaela Bulaceanu *et al*., 1988, examined photo chemically induced fluorescence (PIF) properties of tianeptine and some of its metabolites were investigated in acidic (pH 2.3) water–alcohol mixtures at room temperature. Two PIF methods were developed, including bulk solution and flow injection analysis (FIA). Linear calibration plots were established over a concentration range of more than one order of magnitude. Limits of detection ranged from 15 ng ml^{-1} for FIA-PIF to 25 ng ml^{-1} in bulk solution. The RSDs were between 3 and 5%. The PIF methods were applied to

the determination of tianeptine in a pharmaceutical preparation with recoveries varying from 96 to 106% in bulk solutions and from 98 to 106% for FIA-PIF[18]

Niederhofer *et al*., 2003, observed twelve male children (7.3 ± 3.3 years) with autistic disorder, diagnosed by ICD-10 criteria, completed a placebo-controlled, double-blind crossover trial of tianeptine, which lasted for 12 weeks. Subjects were included in the study if their eye contact and expressive language was inadequate for their developmental level. Subjects had not tolerated or responded to other psychopharmacological treatments (neuroleptics, methylphenidate, clonidine or desipramine).Tianeptine were modestly effective in the short-term treatment of irritability in some children with autistic disorder[19]

Salvadori *et al*., 1990, studied the disposition of the antidepressant tianeptine and its MC_5 metabolite (pentanoic acid analogue of tianeptine) was studied following a single 12.5 mg oral dose of tianeptine sodium salt in 20 patients with chronic renal failure. In 12 patients (group I) having a creatinine clearance of less than 19 $mlmin^{-1}$ the pharmacokinetics parameters for tianeptine and MC_5 metabolite were determined and compared with those obtained in a matched control group (group II). The other 8 patients (group III) were functionally anephric and were studied during 1 dialysis to assess the haemodialysis clearances of tianeptine and MC_5 metabolite. The comparison between groups I and II showed that renal failure did not appear to affect the disposition of parent tianeptine[20]

Tatar Ulu and Sevgi, 2007, used sensitive and selective high-performance liquid chromatographic method has been developed for the determination of tianeptine (Tia) in tablets. The method is based on derivatization of Tia with 4-chloro-7-nitrobenzofurazan (NBD-CI). A mobile phase consisting of acetonitrile-10 mM orthophosphoric acid (pH 2.5, 77 + 23) was used at a flow rate of 1 mL/min on a C1a column. The Tia-NBD derivative was monitored using a fluorescence detector, with emission set at 520 nm and excitation at 458 nm. Gabapentin was selected as an internal standard. Linear calibration graphs were obtained in the concentration range of 45-300 ng/mL The lower limit of detection (LOD) was 10 ng/mL at a signal-to-noise ratio of 4. The lower limit of quantitation (LOO) was 45 ng/mL[21]

Vadachkoria *et al*., 2009, surveyed a total of 24 patients (male volunteers), consumers of opiates in the past and suffering from Tianeptine abuse, were under clinical observation. The age range of patients was from 21 to 33 years. Tianeptine consumption history was 5 months duration on the average. The daily dose of preparation was 40 tablets (500 mg intravenous injections on the average). Patients used Tianeptine in combination with antihistamines (Promethazine, Suprastin). Research was carried out with the use of clinical, psychological and laboratory methods[22]

Grasela and Fiedler, 2002, predicted the ability of population pharmacokinetic parameters of tianeptine, obtained from a mixed effect analysis of pre-marketing pharmacokinetic studies, was evaluated using tianeptine plasma concentrations obtained during a large multi-center post-marketing surveillance study[23]

Daniel Ginestet, 1997, studied the efficacy of tianeptine in the treatment of major depressive episodes was assessed in three double-blind placebo-controlled studies. In a first double-blind study comparing tianeptine (37.5 mg/day) with placebo, 126 patients with Major Depression or a Depressed Bipolar Disorder were treated for 42 days, 60% of these patients fulfilled DSM-III-R criteria for melancholia[24]

Salvadori *et al*., 1990, applied a balanced 3 way cross-over study involving 12 young healthy volunteers (6 men and 6 women) was used to determine the pharmacokinetic parameters of the antidepressant tianeptine following a single dose administered by oral and intravenous route. The influence of alcohol on the pharmacokinetics of tianeptine when given *per os* was also investigated. Kinetic parameters of metabolite MC_5, the C_5 side chain beta–oxidation product of tianeptine, were simultaneously determined[25]

Royer *et al.*, 1988, conducted a study by following oral administration in the fasting healthy subject, the mean maximum concentration of tianeptine is 334 +/-79 ng/ml. Absorption of tianeptine from the tablet form is rapid and complete. Maximum plasma concentration is obtained by the first hour following administration (0.94 +/- 0.47 h). Absolute bioavailability is 99 +/- 29%. Tianeptine is thus rapidly and completely absorbed in the tablet form and is not subject to first-pass effect.

Distribution of tianeptine in the body is characterized by the following: its rapidity, the mean distribution half-life being about 0.7 h, its limited extent, the apparent volume of distribution being about 0.8 L/kg (0.77 +/- 0.31 L/kg), and protein binding, which averages 93.8 +/- 2.4%. Elimination of tianeptine is characterized by a short mean half-life of 2 h 30 min (2.5 +/- 1.1 h) and by renal excretion of 0.4 ml/min (0.4 +/- 0.4 ml/min). Tianeptine is extensively metabolized[26]

Guillem and Lepine, 2003, reported on a tianeptine dependence lasting for eighteen months in a 42 year old patient. The patient had a previous history of addiction to opiates, amineptine, cocaine and alcohol. He also had a family history of addiction to alcohol and opiates. Tianeptine was prescribed for a major depressive disorder. The patient alleged a "flash sensation" like with heroin since the very first doses with a physical and psychological well-being sensation, better psychomotor performances and transient mood elation. His addiction to tianeptine was immediate and heavy[27]

Koen Schruers and Eric Griez, 2004, suggested that increased 5-HT availability is important for the anti-panic effect of serotonergic drugs and in maintaining the response to selective serotonin reuptake inhibitors (SSRIs). Tianeptine is an antidepressant with 5-HT reuptake enhancing properties (i.e. the opposite pharmacological profile to that of SSRIs). Therefore, no effect would be expected in panic disorder. The aim of the present study was to compare the effect of tianeptine with that of paroxetine, a selective 5-HT reuptake inhibitor with demonstrated efficacy in panic disorder, on the vulnerability to a laboratory panic challenge in panic disorder patients[28]

Guelfi, *et al*., 1989, conducted a study on 265 adult outpatients with dysthymic disorder (DSM-III) associated with clinically manifest anxiety (according to FDA criteria) were included in a multicenter, randomized double-blind study. The trial consisted of three phases: placebo pretreatment phase and inclusion in the trial, treatment phase, placebo post treatment phase. Patients were treated in mono therapy for 42 days with a mean dosage of 3 tablets per day corresponding to 37.5 mg/day of tianeptine or 75 mg/day of amitriptyline respectively[29]

Mathieu Boiret *et al.,* 2011, developed a near infrared (NIR) method for determination of tablet potency of active pharmaceutical ingredient (API) in a complex coated tablet matrix. The calibration set contained samples from laboratory and production scale batches. The reference values were obtained by high performance liquid chromatography (HPLC) and partial least squares (PLS) regression was used to establish a model. The model was challenged by calculating tablet potency of two external test sets. Root mean square errors of prediction were respectively equal to 2.0% and 2.7%[30]

Hantzberg *et al.,* 1987, concerned the use of a new antidepressant, tianeptine, as a treatment of depressive and/or amotival syndrome, in 30 drug addicts, detoxified from opiates. From a thymoanaleptic point of view, 85% of the patients exhibit a positive result after 28 days of treatment with 37.5 mg/day. These good results are confirmed by the evolution of the Hamilton Depression Rating Scale global score, which significantly decreases from D0 to D14 and from D14 to D28. The acceptability of the antidepressant is good. Anticholinergic side-effects are very uncommon. Tianeptine appears devoid of any obvious psycho stimulant or sedative effect[31]

2.4. PAST WORK ON IMMEDIATE RELEASE TABLETS

Abhay Gupta *et al*., 2009, investigated correlation between disintegration and dissolution for immediate release tablets containing a high solubility drug and to identify formulations where disintegration test, instead of the dissolution test, may be used as the acceptance criteria based on International Conference on Harmonization Q6A guidelines. A statistical design of experiments was used to study the effect of filler, binder, disintegrating agent, and tablet hardness on the disintegration and dissolution of verapamil hydrochloride tablets[32]

Biljana Govedarica *et al*., 2011, demonstrated the best tablet properties with coated paracetamol (mass of tablets, diameter, height and mechanical strength, friability RSD<2%).Furthermore, coated paracetamol in combination with both investigated superdisintegrants such as Vivasol® and Polyplasdone® XL-10 shows faster disintegration time and dissolution rate in comparison to paracetamol for direct

compression. Eventually, the major advantages of the formulation with coated paracetamol for industrial production are decrease of friability and superiority in terms of flowability, compressibility, quick disintegration and dissolution. Regarding the results, coating of PAR particles is beneficial for the manufacturing of tablets with immediate release[33]

Kyriacos Soula and Dimassi Hani, 2009, studied the critical formulation/process factors were the type and concentration of microcrystalline cellulose, the ratio of lactose to microcrystalline cellulose, the concentration of croscarmellose, and the compression force. A two-step approach was implemented. First an optimization study was performed to determine the type of microcrystalline cellulose and its ratio to lactose. Subsequently, a final optimization formulation study was performed based on the results obtained in the preliminary study. Data were analyzed using the SPSS 15 (Statistical Software for Social Sciences). The differences in means between the formulation and the targeted product[34]

Parikh, 2010, attempted to develop solid oral formulations of Telmisartan which can be prepared using less complicated and expensive processes and fulfill all prerequisites for pharmaceutical use, i.e. long-lasting stability of the formulation under different climatic conditions and sufficient solubility of the active substance for sufficient gastrointestinal absorption in the slightly acidic and neutral pH region. Preferably, the formulations should have immediate release characteristics and a dissolution showing no essential pH dependency within the physiological relevant pH interval of the gastrointestinal tract[35]

Hu*et al*., 2006, optimized the formulation of immediate release tablet. The immediate release tablet was prepared by using dry granules. The preparation was optimized by using orthogonal design which took the flow property of granules, the hardness, the disintegrating time and the dissolution rate of the tablet as indices. The optimized formulation contained 40% microcrystalline cellulose, 10% sodium carboxymethyl starch and 15% dextrin. The hardness disintegrating time and T50 of the tablet were 4.5 kg, 3 min, 5 min respectively[36]

2.5. PAST WORK DONE ON EXCIPIENTS

Gohel *et al*., 2007, used superdisintegrants are sodium starch glycolate, crospovidone, and croscarmellose sodium. Like diluents, each superdisintegrant has strengths and weaknesses. In the present investigation, the preparation and evaluation of co processed disintegrant containing crospovidone and sodium starch glycolate was explored. The reasons for the selection of crospovidone are as follows: better compressibility compared with other superdisintegrants, high capillary activity, pronounced hydration capacity, and little tendency to form gels. Moreover, the rate and extent of liquid uptake and swelling of crospovidone (Polyplasdone XL 10) are not reduced in 0.1 N hydrochloric acid when compared with aqueous medium. The aqueous medium (water) represents disintegration medium and 0.1 N HCl represents gastric environment. Sodium starch glycolate was chosen because of its high swelling capacity. Moreover, the disintegrant efficiency of sodium starch glycolate is unimpaired by the presence of hydrophobic excipients such as lubricants[37]

Ganesh Chaulang *et al*., 2008, investigated enhancement of the dissolution profile of furosemide using solid dispersion (SD) with crospovidone (CPV) by using kneading technique. 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio[38]

Phake and Anderson, 1990, studied the effect of crospovidone on the characteristics of wet granulated acetaminophen was investigated. Power blends of acetaminophen and crospovidone were wet granulated using hydroxypropyl methylcellulose as the binder and water as the granulating liquid. The sieve analysis data showed that as the level of crospovidone in the powder blend increased, there was an increase in the amount of fines in the particle distribution of the dried granulations. The bulk densities of formulae containing a higher level of crospovidone were generally lower although no clear trend was seen for the tap density values.. The results of this study indicate that an interaction of both mechanisms may be responsible for the effect of crospovidone on the characteristics of wet granulated acetaminophen[39]

Sangmesh Torne *et al*., 2010, studied fast disintegrating tablets of taste masked ondansetron hydrochloride were prepared by direct compression method with a view

to enhance patient compliance. Taste masking was done by complexing ondansetron hydrochloride with eudragit EPO in ratio 8:2. Two superdisintegrant i.e. crospovidone and croscarmellose sodium were used in different combination ratio[40].

Suhas *et al*., 2010, developed mouth dissolving tablets of losartan potassium were design with a view to enhance the patient compliance and provide a quick onset of action. Losartan potassium is an angiotensin receptor antagonist, used in the management of hypertension. It has low bioavailability due to its first pass metabolism. Hence the main objective of the study was to formulate mouth dissolving tablets of losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug. Mouth dissolving tablets prepared by direct compression and using super disintegrants like Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration.[41]

Ferrero *et al*., 1997, studied the efficiency of croscarmellose sodium (Ac-Di-Sol®) in a direct compression formulation containing a poorly water soluble drug at high dosage was investigated. An experimental design with two variables, applied pressure and concentration of Ac-Di-Sol®, allowed the evaluation of micro structural, mechanical and disintegration properties of the tablets. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure[42]

Piyush Patel*et al*., 2009, determined if a solid dispersion of furosemide in sodium starch glycolate (SSG) would enhance the dissolution properties of the drug. Solid dispersion of furosemide in SSG was prepared in ratios of 1:1 and 1 (furosemide):2 (SSG) by kneading method Tablets containing the solid dispersion were formulated and their dissolution characteristics compared with commercial furosemide tablets[43]

Vineet Bhardwaj*et al*., 2010, aimed to prepare fast disintegrating tablets of Amlodipine Besylate by using different disintegrants and to evaluate the effect of increasing Amlodipine Besylate load on the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment of angina and hypertension. The superdisintegrant used in this study were Kollidon CL, Ac-Di-Sol and Sodium Starch Glycolate in varying concentrations (2%, 4%, 6%) [44]

3. AIM & OBJECTIVE

The main aim of the current study was to formulate Tianeptine sodium tablets and to evaluate.

Immediate release tablets are most widely used dosage forms. These products are designed to disintegrate in the stomach followed by their dissolution in the fluids of the gastro intestinal tract.

Tianeptine is a selective serotonin reuptake enhancer (SSRE) drug used for treating major depressive episodes (mild, moderate, or severe). It is having a half-life of 2.5 h and used at a dose of 12.5 mg.

Currently, Tianeptine is approved in France and manufactured and marketed by Laboratoires Servier SA, it is also marketed in a number of other European countries under the trade name "Coaxil" as well as in Asia and Latin America as "Stablon" and "Tatinol" but it is not available in the UK.

The objective of the study was,

- To develop tianeptine sodium immediate release tablets to achieve faster dissolution to match the innovator product Stablon 12.5 mg.
- Another objective of the study is to evaluate dissolution profiles of these tablets in discriminating dissolution mediums to ensure its bioequivalence.

4. PLAN OF WORK

- Literature survey
- Selection of materials and methodology
- Compatibility study of drug with various excipients using DSC.
- Preparation of Tianeptine sodium immediate release tablets
- Evaluation of tablet granules and tablets prepared for the following:

Precompression parameters:

- Angle of repose
- Bulk density
- Tapped density
- Hausner's ratio
- Carr's compressibility index

Post compression parameters:

- Hardness
- Disintegration time
- Content uniformity
- Friability
- Weight variation
- *In vitro* dissolution studies
- Drug content estimation by HPLC
- Accelerated stability studies

5. DRUG PROFILE& EXCIPIENTS PROFILE

5.1 DRUG PROFILE

Chemical name: [3-chloro-6-methyl-5, 5-dioxo-6, 11-dihydro-(c, f)-dibenzo-(thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt.

Structure:

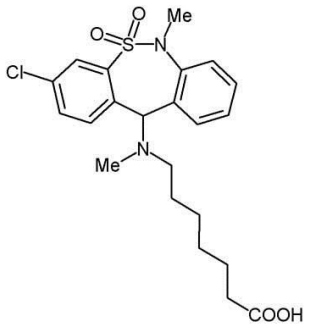


Fig 2: Structureof Tianeptine

Molecular formula: $C_{21}H_{24}ClN_2NaO_4S$

Molecular weight: 458.9 g/mol

Strength: 12.5 mg

Description: white coated tablet.

Pharmaceutical Classification: Antidepressant

Bioavailability: 70-99%

Metabolism: Hepatic

Half life: 2.5 h

Excretion: renal

Mechanism of action: Initial studies found that upon acute and sustained administration, tianeptine decreased the extracellular levels of serotonin. However tianeptine has low affinity for serotonin transporters, so this effect appears to be indirect However, co administration of tianeptine and fluoxetine inhibited tianeptine's effect on long-term potentiation in

hippocampal CA1 area. In contrast to SSRIs and tricyclic antidepressants, tianeptine modestly enhances the mesolimbic release of dopamine, but it is also unclear how this occurs because tianeptine itself has no effect on dopamine transporters, nor does it affect D1, D2, D3, D4 and D5 receptors

Dosage and administration: 1 tablet 3 times a day before the main meals of the day.

Adverse Effects:Gastralgia, abdominal pain, dryness of the mouth, anorexia, nausea, vomiting, flatulence Insomnia, drowsiness, nightmares, asthenia Tachycardia, extra systole, precordialgia Dizziness, headaches, faintness, trembling, upsets Respiratory discomfort, tightness of the throat Myalgia, lumbago

Pharmacokinetics: Gastro intestinal absorption is rapid and complete. Distribution is rapid and is associated with a high level of protein binding (approx. 94%). Molecule is extensively metabolized in the liver by the processes of beta-oxidation and N- demethylation. Elimination is characterized by a short terminal half life of 2.5 hr, only a very slight excretion of parent compound (8%) via the kidneys and an essentially renal route of excretion for the metabolites.

In elderly subjects: Pharmacokinetic studies performed in chronically treated elderly patients (age over 70 yrs) demonstrated an increase of 1 hr in the elimination half life.

In subjects with hepatic insufficiency: Studies have shown that the effects of chronic alcoholism on the pharmacokinetic parameters are negligible, even when alcoholism is associated with cirrhosis of the liver.

In subjects with renal insufficiency: Studies have shown an increase of 1 hr in the elimination half life.

5.2. EXCIPIENTS PROFILE

5.2.1. Talc

Nonproprietary names

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

Synonyms

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Imperial, Luzenac Pharma, magnesium hydrogen metasilicate, MagsilOsmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore, talcum.

Chemical Name

Talc

Empirical formula

$Mg_6 (Si_2O_5)_4(OH)_4$

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional category

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant

Table 2: Uses of talc

Use	**Concentration (%)**
Dusting powder	90.0-99.0
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

Applications in pharmaceutical formulation or technology

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations. In a novel powder coating for extended-release pellets,and as an adsorbant.

- Talc is used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Stability and storage conditions

Talc is a stable material and may be sterilized by heating at 160˚C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds[10]

5.2.2. Magnesium stearate

Nonproprietary names

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

Synonyms

Dibasic magnesium stearate, magnesium distearate, magnesiistearas, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt, Synpro 90

Chemical name

Octadecanoic acid magnesium salt

Empirical formula

$C_{36}H_{70}MgO_4$

Molecular weight

591.24 g/mol

Structural formula

$[CH_3 (CH_2)_{16}COO]_2Mg$

Functional category

Tablet and capsule lubricant

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Applications in pharmaceutical formulation or technology

- It is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25%- 5.0% w/w.
- It is also used in barrier creams.

Stability and storage conditions

Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

5.2.3. Mannitol

Nonproprietary names

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP: Mannitol

Synonyms

Cordycepic acid, C*PharmMannidex, E421, Emprove, manna sugar, D mannite, mannite, mannitolum, Mannogem, Pearlitol

Chemical name

D-Mannitol

Empirical formula

$C_6H_{14}O_6$

Molecular weight

182.17 g/mol

Structural formula

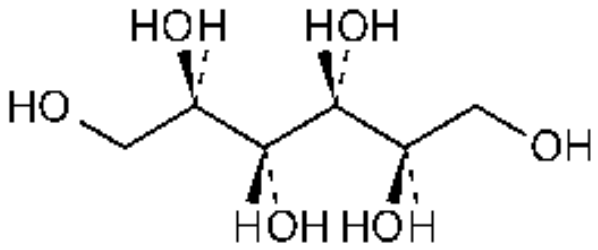


Fig 3: Structure of Manitol

Functional category

Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Applications in pharmaceutical formulation or technology

- In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.
- Mannitol may be used in direct-compression tablet applications for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily.
- Specific tablet applications include antacid preparations, glyceryltrinitrate tablets, and vitamin preparations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and mouth feel.

- In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.
- Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v).
- It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,[11] and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.
- Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure.

Stability and storage conditions

Mannitol is stable in the dry state and in aqueous solutions.The bulk material should be stored in a well-closed container in acool, dry place.

Incompatibilities

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.
- Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution.
- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.

5.2.4. PVP K_{30}

Nonproprietary names

BP: Povidone

JP: Povidone

PhEur: Povidone

USP: Povidone

Synonyms

E1201, Kollidon, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone, polyvinylpyrrolidone, povidonum, Povipharm, PVP, 1- vinyl-2-pyrrolidinone polymer.

Chemical name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical formula

(C6H9NO)n

Molecular weight

2500–3000000 g/mol

Structural formula

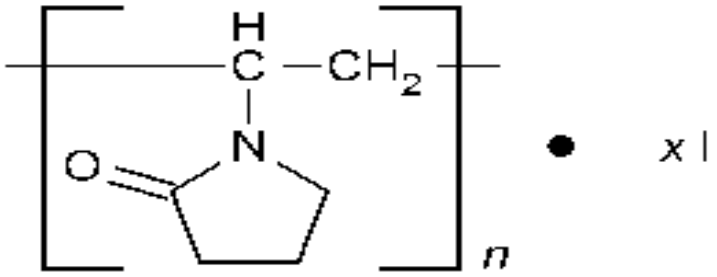


Fig 4: Structure of PVP K_{30}

Table 3: uses of Povidone

USE	**CONCENTRATION (%)**
Carrier for drugs	10-25
Dispersing agent	Upto 5
Eye drops	2-10
Suspending agent	Upto 5
Tablet binder, tablet diluent, or coating material	0.5-5

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are

manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Applications in pharmaceutical formulation or technology

- In tableting, povidone solutions are used as binders in wet-granulation processes.
- Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro alcoholic solutions.
- Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.
- Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.
- Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.
- The solubility of a number of poorlysoluble active drugs may be increased by mixing with povidone.
- Special grades of pyrogen-free povidone are available and have been used in parenteral formulations.

Stability and storage conditions

Povidone darkens to some extent on heating at 150˚C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130˚C, steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

5.2.5. HPMC K_4M

Nonproprietary names

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

Synonyms

Benecel MHPC, E464, hydroxypropyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, MHPC, Pharmacoat, Tylopur, Tylose MO.

Chemical name

Cellulose hydroxypropyl methyl ether

Molecular weight

10000–1500000 g/mol

Structural Formula

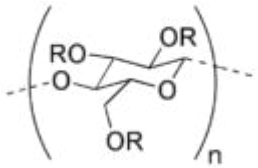


Fig 5: Structure of HPMC R = H or CH_3 or $CH_2CH(OH)CH_3$ **K_4M**

Functional category

Bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended-release agent, film-forming agent, foaming agent, granulation aid, modified-release agent, mucoadhesive, release-modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained-release agent, tablet binder, thickening agent, viscosity-increasing agent.

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder

Applications in pharmaceutical formulation or technology

- Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.
- In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.
- Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.
- Hypromellose is also used as a suspending and thickening agent in topical formulations

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–90˚C, depending upon the grade and concentration of material. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

5.2.6. Crospovidone

Nonproprietary Names

BP: Crospovidone

PhEur: Crospovidone

USP-NF: Crospovidone

Synonyms

Crospovidonum, Crospopharm, crosslinkedpovidone, E1202, Kollidon CL, Kollidon CL-M, Polyplasdone XL, PolyplasdoneXL-10, polyvinylpolypyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula

(C6H9NO)n

Molecular Weight

>1 000000 g/mol

Structural Formula

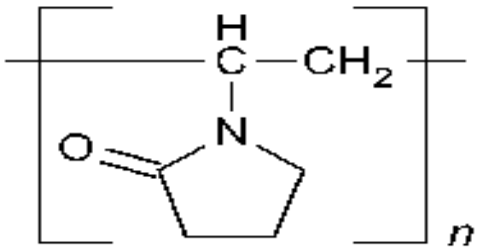


Fig 6: Structure of Crospovidone

Functional Category

Tablet disintegrant

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Applications in Pharmaceutical Formulation or Technology

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods.
- Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer.

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

5.2.7. Croscarmellose Sodium

Nonproprietary Names

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

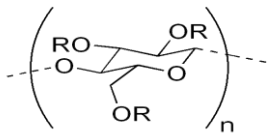
Synonyms

Ac-Di-Sol, carmellosumnatricumconexum, crosslinkedcarboxymethylcellulose sodium, Explocel, modified cellulose gum, NymcelZSX, Pharmacel XL, Primellose, SolutabandVivasol.

Chemical Name

Cellulose, carboxymethyl ether, sodium salt, crosslinked

Structural Formula



R = H or CH_2CO_2H

Fig 7: Structure of Croscarmellose Sodium

Functional Category

Tablet and capsule disintegrant

Description

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Applications in Pharmaceutical Formulation or Technology

- Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.
- When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized.
- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table 4: Uses of croscarmellose sodium.

Use	**Concentration (%)**
Disintegration in capsules	10-25
Disintegration in tablets	0.5-5.0

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30˚C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not

compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

5.2.8. Sodium Starch Glycolate

Nonproprietary Names

BP: Sodium Starch Glycolate

PhEur: Sodium Starch Glycolate

USP-NF: Sodium Starch Glycolate

Synonyms

Carboxymethyl starch, sodium salt, carboxymethylamylumnatricum, Explosol, Explotab, Glycolys, Primojel, starch carboxymethyl ether, sodium salt, Tablo, Vivastar P

Chemical Name

Sodium carboxymethyl starch

Structure

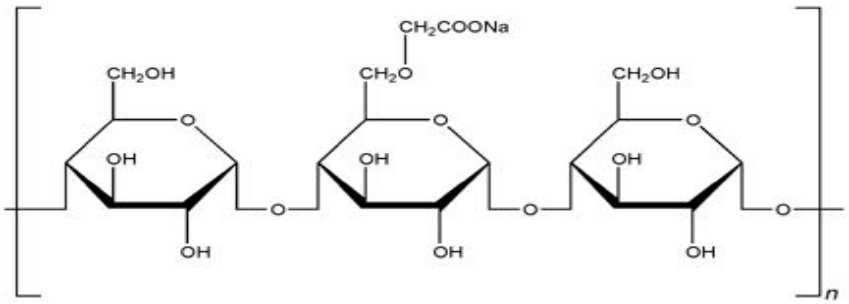


Fig 8: Structure of Sodium Starch Glycolate

Functional Category

Tablet and capsule disintegrant

Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The granules show considerable swelling in contact with water.

Applications in Pharmaceutical Formulation or Technology

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.

- The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient.
- Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.
- Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired.
- Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

6. MATERIALS

6.1.1. List of equipment used

Table 5: List of equipment and manufacturers

INSTUMENT	**SUPPLIER**
Weighing balance	Sartorius
Electronic balance	Essae DS-852
Mechanical stirrer	Vision labs
Tray dryer	Millennium equipment Pvt. Ltd(METD-6G)
Tapped density apparatus	Electro lab (ETD-1020)
Compression machine	Rimekkarnavathi
Hardness testing apparatus	Pharmag tester
Friability test apparatus	Electro lab friabilator
Disintegration tester(USP)	Electro lab(ED-2AL)
Dissolution test system	Electro lab
Rapid mixer granulator	Saral engineering(RMG5-15)
HPLC	RS spectra

6.1.2. List of materials used

Table6: List of materials and their suppliers

CHEMICAL	**SUPPLIER**
Tianeptine sodium	RA chemPharma Ltd, Hyd, India
Mannitol	Roquette, Pune, India
Croscarmellose sodium	FMC biopolymer, Mumbai, India
PVP K-30	Anshul agencies, Mumbai, India
HPMC K4M	Colorcon, Pune, India
Sodium starch glycolate(glycol YS)	Signet chemicals, Hyd, India
Magnesium stearate	Ferro chemicals, Mumbai, India
Talc	Signet chemicals, Hyd, India
Crospovidone(Polyplasdone XL-10)	Signet chemicals, Hyd, India

6.2. METHODOLOGY

6.2.1. Preformulation Studies

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system[45]

6.2.1.1. Angle of repose

The angle of repose of API powder was determined by funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in a way that, it measures 2.5 cm from the surface level. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.[46]

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Table 7: Flow Properties and Corresponding Angle of Repose

Flow property	**Angle of repose**
Excellent	25-30
Good	31-35
Fair aid not needed	36-40
Passable- may hang up	41-45
Poor must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

6.2.1.2. Bulk density

The powder sample was screened through sieve No.18 and the sample equivalent to 25 gm was weighed and filled in a 100 mL graduated cylinder and the powder was leveled and the unsettled volume, V_0 was noted. The bulk density is calculated in g/cm3 by the formula.

Bulk density = M/V_0

Where, M = Powder mass

V_0 = apparent unstirred volume

6.2.1.3. Tapped density

The powder sample under test was screened through sieve No.18 and the weight of the sample equivalent to 25 gm was filled in a 100 mL graduated cylinder. The mechanical tapping of cylinder was carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 was noted. The difference between two tapping volume was less than 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm3 by the formula.

$$\text{Tapped density} = M/V_f$$

Where, M =weight of sample power taken

V_f = tapped volume

6.2.1.4. Compressibility index

The Compressibility Index of the powder blend was determined by Carr's compressibility index to know the flow character of the powder. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TD-BD)/TD] \times 100$$

6.2.1.5. Hausner's ratio

The ratio of tapped density to bulk density of the powder is called the Hausner's ratio. It is calculated by the following equation.

$$H = \rho T / \rho B$$

Where, ρT = tapped density, ρB = bulk density

Table 8: Scale of Flowability

Compressibility index (%)	Flow character	Hausner's ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

6.2.2. Assay of Tianeptine Sodium by HPLC

6.2.2.1. Preparation of mobile phase

52 volumes of acetonitrile and 48 volumes of a 2 g/l solution of sodium lauryl sulphate were mixed and pH was adjusted to 2.5 using phosphoric acid.

6.2.2.2. Preparation of diluent

Degassed mixture of water and methanol were prepared in the ratio of 50:50 and filtered

6.2.2.3. Preparation of standard solution

50 mg of Tianeptine sodium working standard was weighed and transferred into a 100 mL volumetric flask, to that 70 mL of diluents were added and sonicated to dissolve the content. Volume was made up to the mark with the diluent. 5 mL of

above solution was transferred into a 50 mL volumetric flask and vol made up to the mark with diluent. The prepared solution was filtered through 0.45 µ nylon membrane filter paper.

6.2.2.4. Preparation of sample solution

50 mg of Tianeptine sodium fine tablet powder was taken into a 100 mL volumetric flask and 70 mL of diluents were added, sonicated for 20 min with intermittent shaking and vol was made up to the mark with diluents. The prepared solution was passed through 0.45µ nylon filter paper. 5 mL of above solution was transferred into a 50 mL volumetric flask and made up to the mark with diluents. The solution was filtered through 0.45µ nylon filter paper.

6.2.2.5. Chromatographic conditions

Column: inertsil ODS-2,150 mm x 4.6 mm x 5 µm or its equivalent

Flow rate: 1.0 mL/min

Wave length: 220 nm

Column temperature: 30˚C

Injection volume: 10 µl

Run time: 15 min

6.2.2.6. Procedure

10µl of diluents, six replicate injections of standard solution and two injections of sample solution were separately injected into the chromatograph, chromatograms were recorded and the peak responses were measured.

Content was calculated using the formula

A_T Std. wt 5 100 50 P

…… X …… X ….. X …… X ……. X …… X AW = mg/tab

A_S	100	50	Sample wt	5	100

A_T = peak area of Tianeptine sodium in sample solution

A_S = average peak area of Tianeptine sodium in standard solution.

Stdwt = weight of Tianeptine sodium standard

Sample wt. = weight of the sample.

P = potency

AW = average weight of the tablets

6.2.3. Compatibility studies

Compatibility studies were conducted to investigate and predict physico chemical interaction between drug substance and excipients and therefore to select suitability of chemically compatible excipients. Preformulation studies are carried out with the objective of ascertaining the incompatibility of the excipients used in the existing formulation and to avoid any excipient, which is incompatible with the drug in the final formulation.

Table9: Composition of blends for compatibility study

Batch no.	**Composition**
TIB001	Tianeptine sodium+ Mannitol+ HPMC+ Povidone+ CCS+ Talc+ Mg stearate
TIB002	Tianeptine sodium+ Mannitol+ HPMC+ Povidone+ CP+ Talc+ Mg stearate
TIB003	Tianeptine sodium+ Mannitol+ HPMC+ Povidone+ SSG+ Talc+ Mg stearate

3.2.4. Manufacturing procedure

All the ingredients were weighed as per the manufacturing formula, sifted through #50 and collected separately.

6.2.4.1. Dry mixing

Intragranular materials were mixed for 3 minutes in a polybag.

6.2.4.2. Granulation

To this blend binder solution was added slowly within 3 minutes.

6.2.4.3. Drying and sizing

After complete addition of binder solution, mixing was continued for another two minutes to break the lumps. This wet mass was transferred into tray drier and dried at 45˚C. After semi drying this material was passed through mesh no #12 and drying was continued upto 2 hours. The granules were passed through mesh no #18.

6.2.4.4. Prelubrication

Super disintegrants were passed through mesh no # 40 and added to the above granules in a sandwich manner and blended for 3 min using polybag.

6.2.4.5. Lubrication

To this blend magnesium stearate and talc (passed through mesh no #60) were added and blended for 2 minutes.

6.2.4.6. Tablet compression

Tablets were compressed using compression machine with lubricated blend, employing appropriate punch toolings.

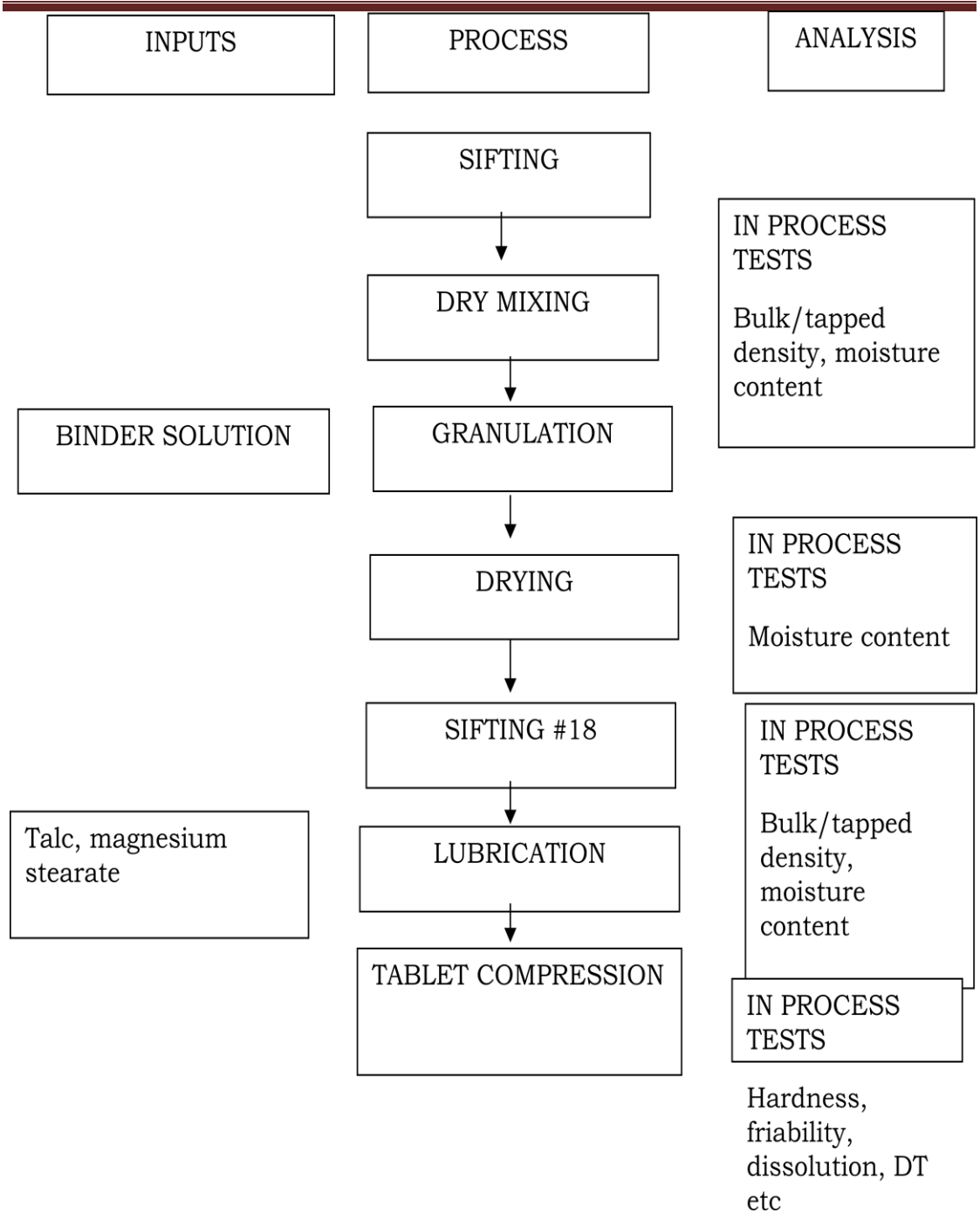


Fig. 9: Flow chart for the manufacturing process

Table10: Formulae of Tianeptine sodium IR tablets prepared

Ingredients (mg)	**Formulations**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Tianeptine sodium	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mannitol	133.7	130.3	128.6	133.7	130.3	128.6	133.7	130.3	128.6
Polyplasdone XL	2.55	4.25	8.5	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	2.55	4.25	8.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	2.55	4.25	8.5
Povidone	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
Purified water	QS	QS	QS	QS	QS	QS	QS	QS	QS
Hypromellose	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Polyplasdone XL	2.55	4.25	1.7	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	2.55	4.25	1.7	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	2.55	4.25	1.7
Magnesium stearate	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
talc	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4

6.2.5. Evaluation Parameters

6.2.5.1. Thickness

The thickness of the tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

6.2.5.2. Weight variation

Twenty tablets were randomly selected from each batch and individually weighed .The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

6.2.5.3. Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\% = \frac{\text{Initial wt} - \text{final wt}}{\text{Initial wt}} \times 100$$

6.2.5.4. Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºc and observed over the time described in the individual monograph. To fully satisfy the test the tablets disintegrate completely into a soft mass having no palpably firm core.

6.2.5.5. Dissolution

The dissolution studies of the prepared tablets were carried using Electro lab apparatus II. Dissolution was performed in 900 mL of water, 6.8 pH buffer, pH 4.5 acetate buffer and in CDER recommended media i.e. 0.1 N Hcl at 37 ±0.5˚C at 100 rpm. An auto sampler, coupled to the dissolution apparatus was programmed to withdraw and replace 10 mL of the dissolution media at 15, 30, 45, 60 and 90 min.

Preparation of standard solution

35 mg of tianeptine sodium working standard was weighed and transferred to 100 mL volumetric flask. 50 mL of methanol was added and sonicated to dissolve the content.1 mL of the above solution was taken and 50 mL of media was added. The above solution was filtered through 0.45 µ nylon membrane filter paper.

Procedure

10 µl of diluents, five replicate injections of standard solution and two injections of sample solution were injected into the chromatograph and the peak areas were measured from the chromatograms.

Chromatographic conditions

Column: inertsil ODS-2,150 mm x 4.6 mm x 5 µm or its equivalent

Flow rate: 1.0 mL/min

Wave length: 220 nm

Column temperature: 30˚C

Injection volume: 50 µl

% labeled amount of tianeptine sodium dissolved

A_T WS 5 900 P 100

= …… X …… X ….. X ……. X ……. X ……

A_S	100	100	100	label claim in mg

A_T = peak area of Tianeptine sodium in sample solution

A_S = average peak area of Tianeptine sodium in standard solution.

Ws = Weight of tianeptine sodium working standard taken in mg.

P = potency.

3.2.5.6. Stability Studies

The selected batch was kept at 40°C with 75% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

7.RESULTS AND DISCUSSION

7.1. PREFORMULATION STUDIES

7.1.1. Drug-Excipient compatibility study

Table11: Results on drug – excipient compatibilities studies – TIB001

SN	Test conditions	Day 0	Day 15			Day 30		
			25°C/60 %RH	30°C/75 %RH	40°C/75 %RH	25°C/60 %RH	30°C/75 %RH	40°C/75 %RH
1	PA	WCC	WCC	WCC	WCC	WCC	WCC	WCC
2	Assay (%)	100	103.7	102.2	104.4	102.8	103.5	104.3

WCC= White colored crystalline powder; PA= Physical appearance

Table 12: Results on drug – excipient compatibilities studies – TIB002

SN	Test conditions	Day 0	Day 15			Day 30		
			25°C/60 %RH	30°C/75 %RH	40°C/75 %RH	25°C/60 %RH	30°C/75 %RH	40°C/75 %RH
1	PH	WCC	WCC	WCC	WCC	WCC	WCC	WCC
2	Assay (%)	102	103.0	104.8	104.8.0	103.0	104.9	105.7

WCC= White colored crystalline powder; PA= Physical appearance

Table 13: Results on drug – excipient compatibilities studies – TIB003

S N	Test conditions	Day 0	Day 15			Day 30		
			25°C/60 %RH	30°C/75 %RH	40°C/75 %RH	25°C/60 %RH	30°C/75 %RH	40°C/75 %RH
1	PA	WCC	WCC	WCC	WCC	WCC	WCC	WCC
2	Assay (%)	105.3	103.8	100.6	103.6	105.1	105.5	106.1

WCC= White colored crystalline powder; PA= Physical appearance

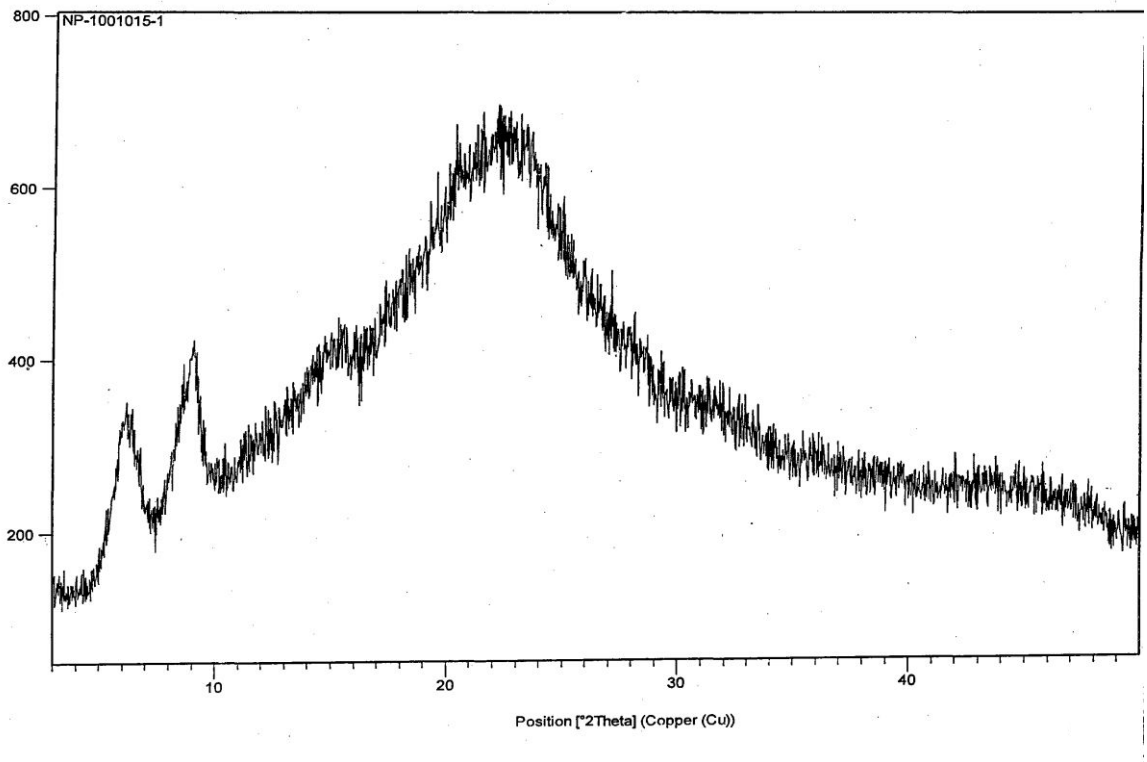


Fig. 10: XRD of Tianeptine sodium (API)

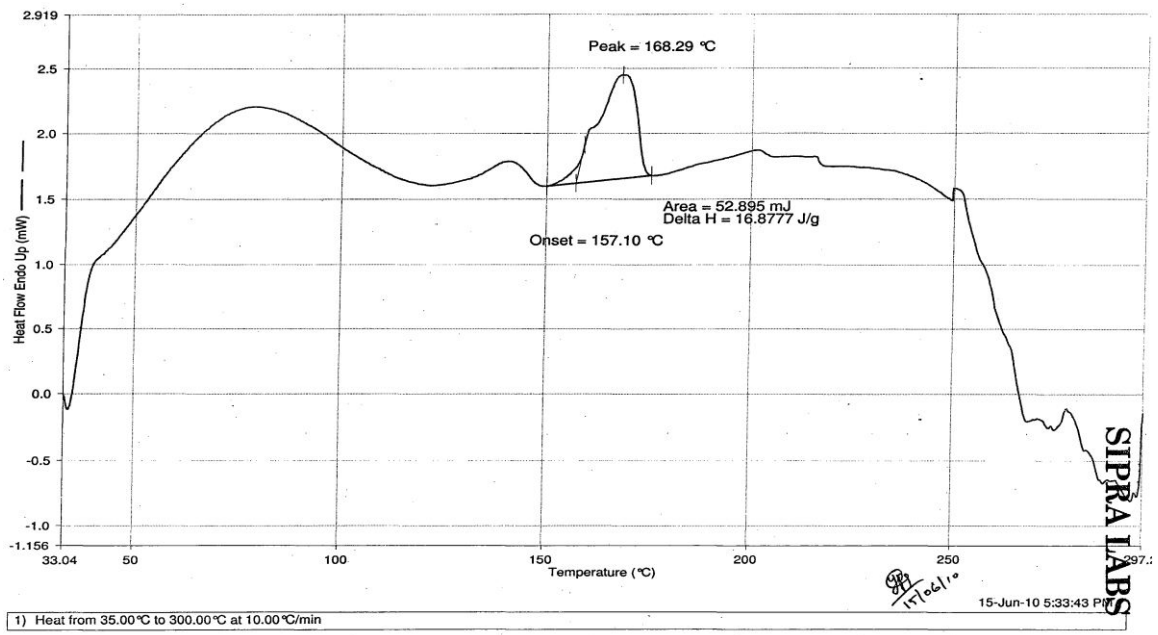


Fig. 11: DSC of Tianeptine (API)

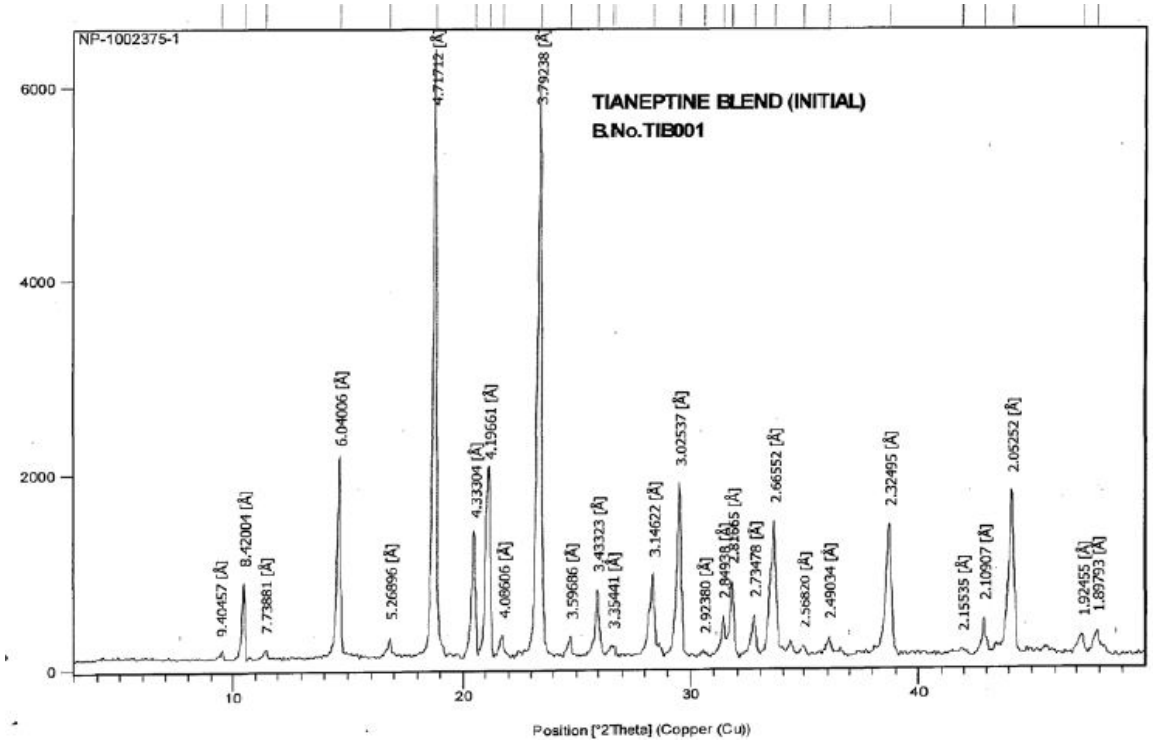


Fig. 12: XRD of TIB001 (day 0)

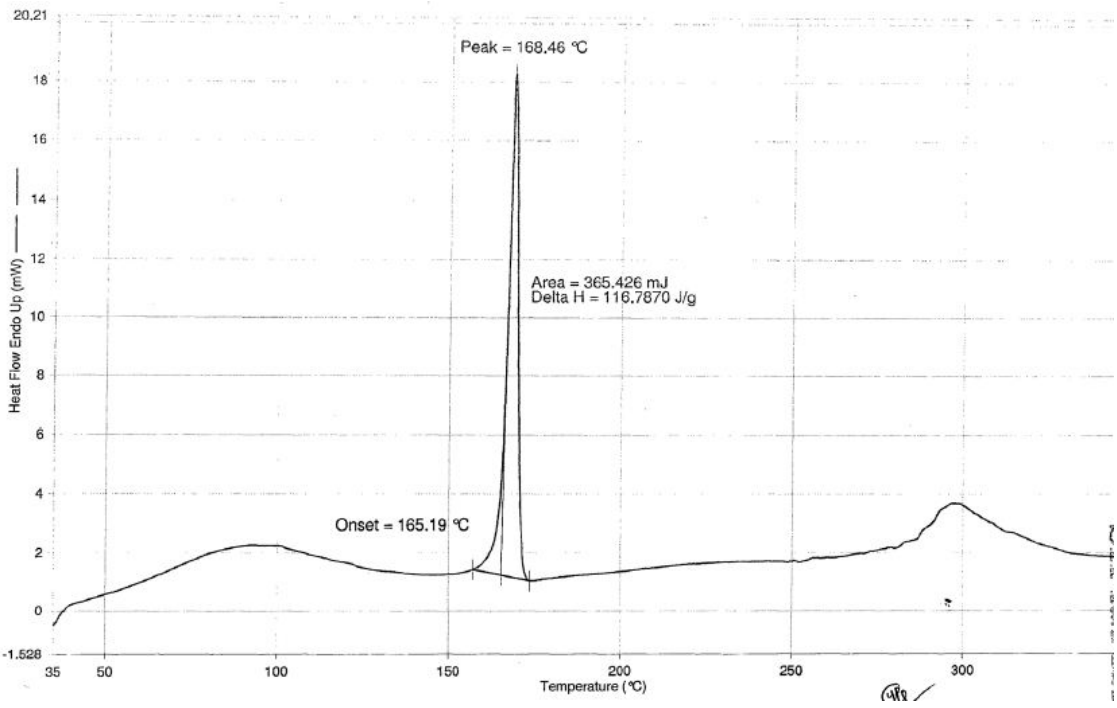


Fig.13: DSC of TIB001

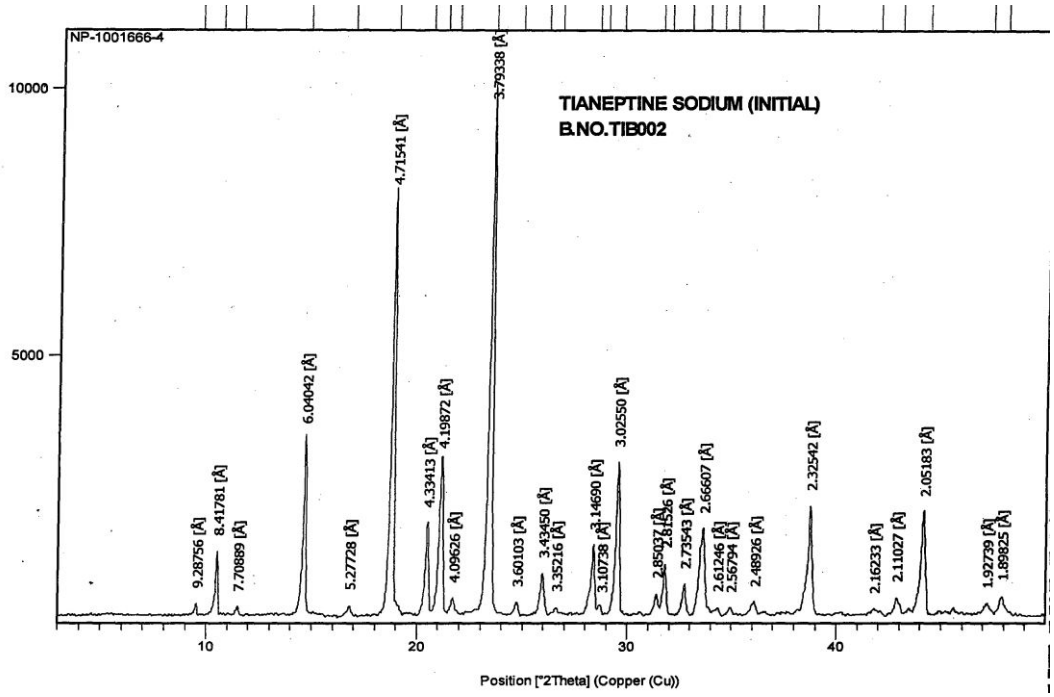


Fig.14: XRD of TIB002

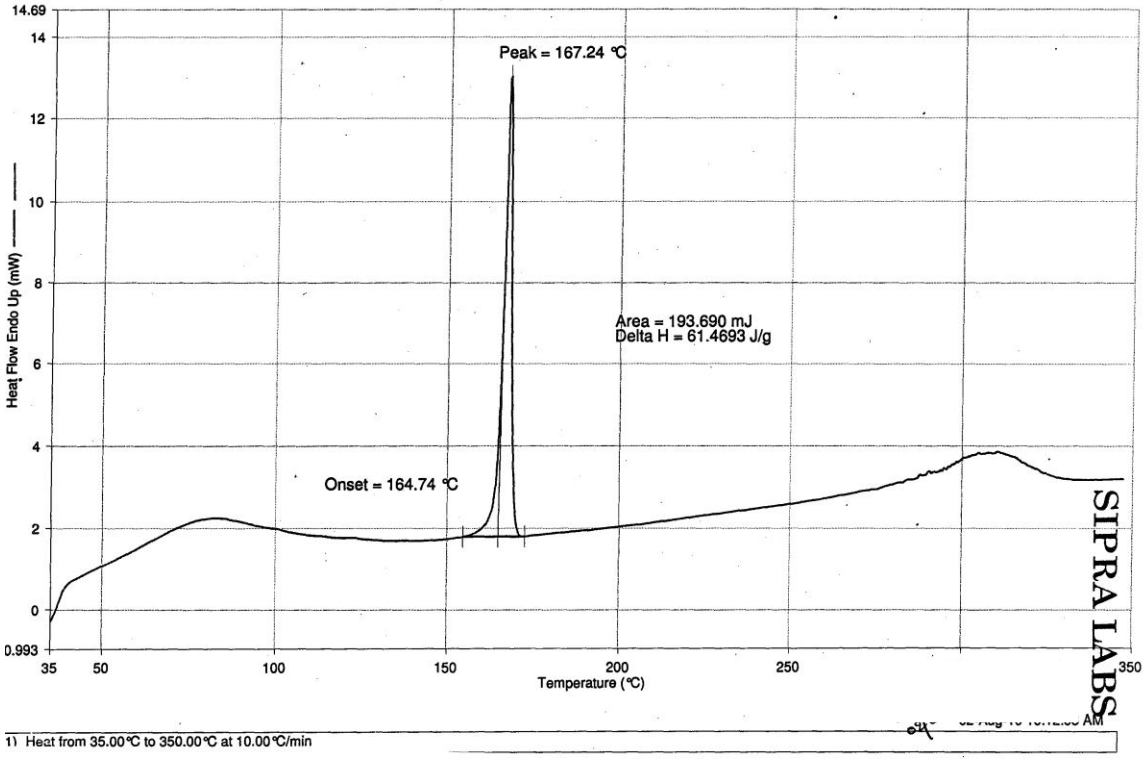


Fig.15: DSC of TIB002

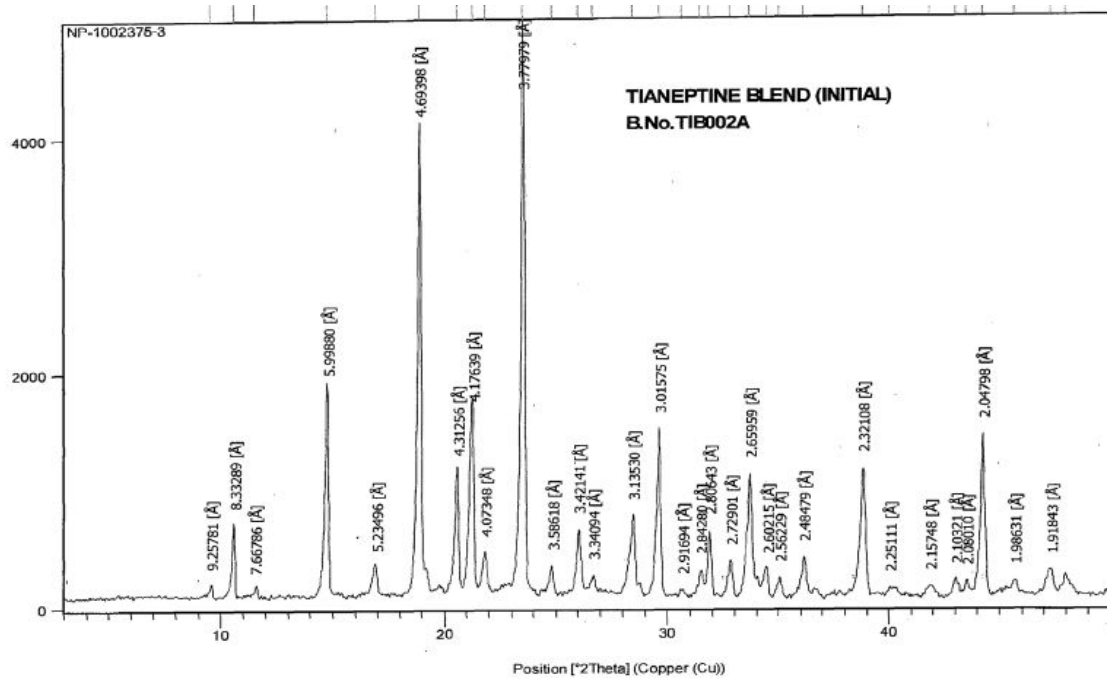


Fig.16: XRD of TIB003

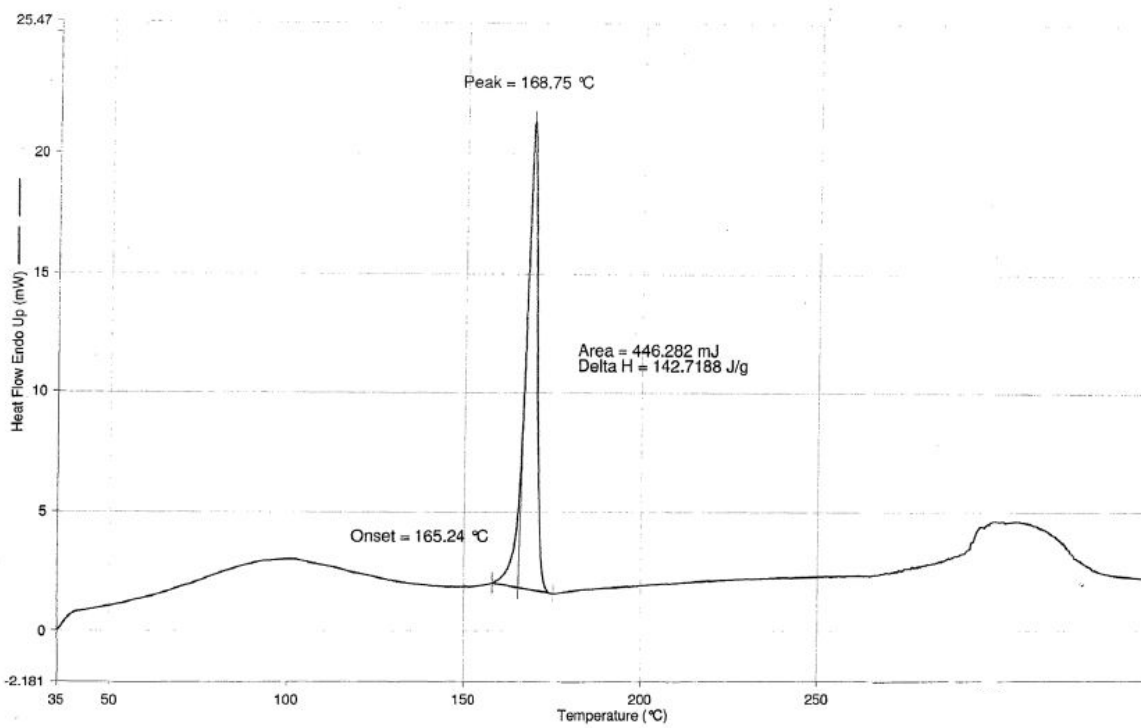


Fig.17: DSC of TIB003

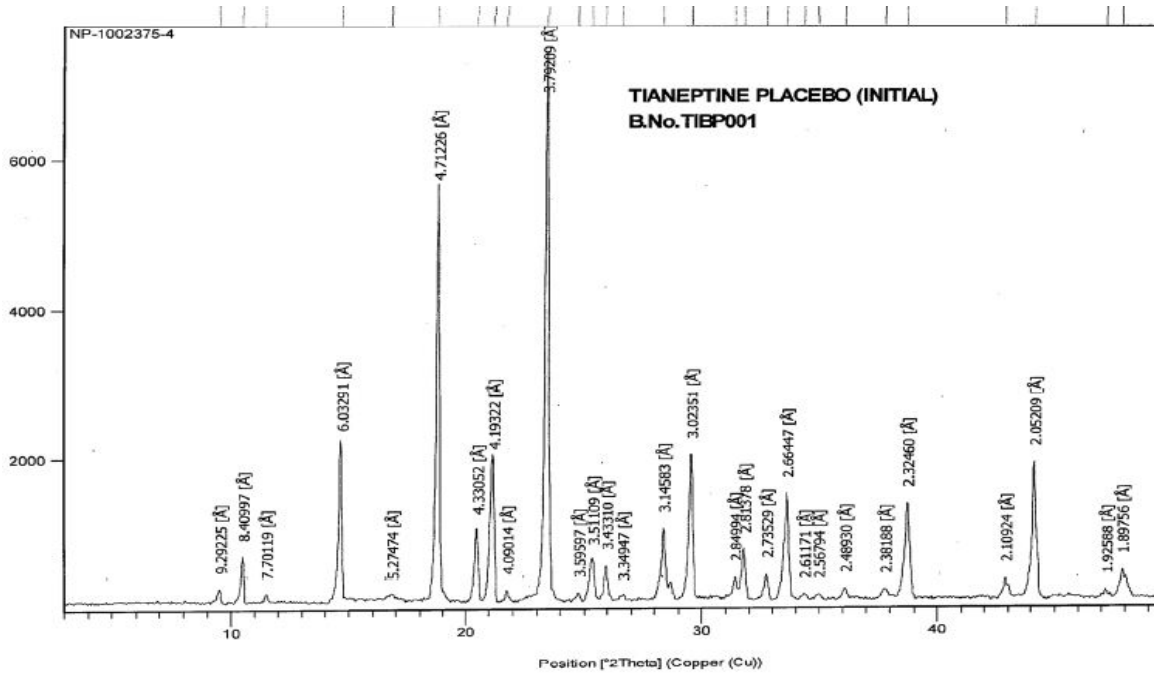


Fig.18: XRD of Placebo

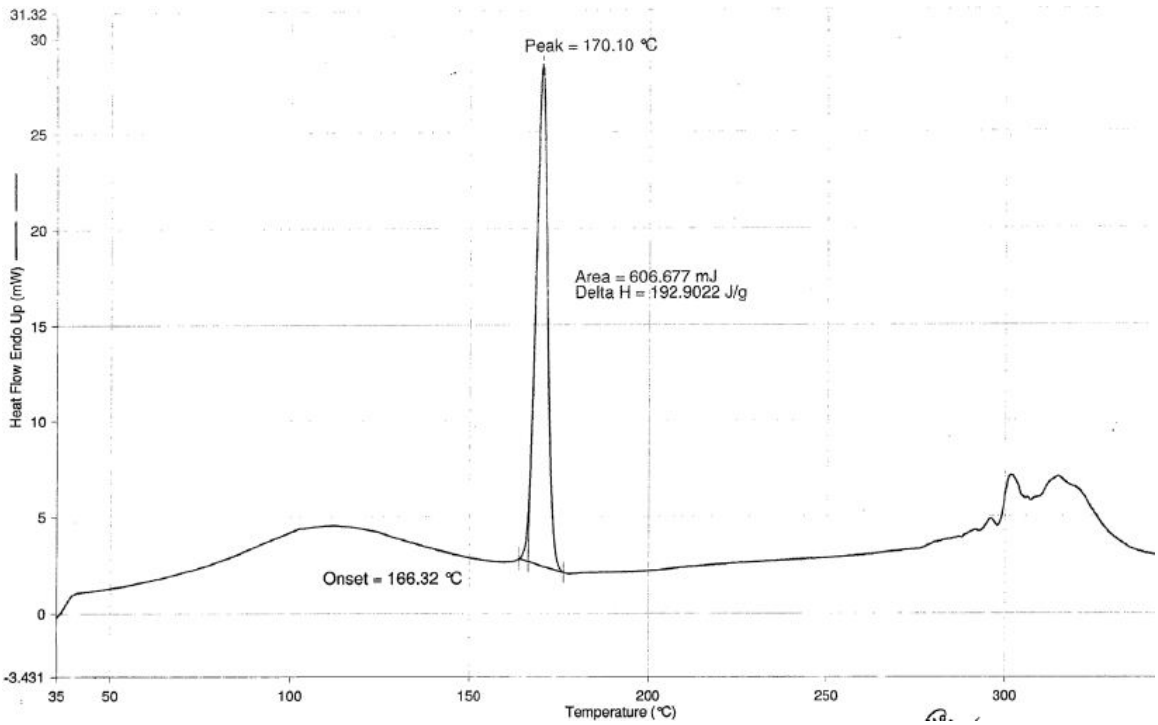


Fig. 19: DSC of placebo

The preformulation studies indicated that the assay of the blends were consistent, at all conditions, indicating that the drug was stable in the blend for the duration of the study.

Further the XRD of API showed that the API is predominantly crystalline, and the corresponding DSC showed endothermic transition around 170˚C. However, the delta H values were around 12 to 16. The low J/g value is indicative of the fact that the drug is predominantly crystalline.

The DSC of the blend and that of Stablon showed a sharp endothermic transition around 169˚C, which could be attributed to mannitol, as the melting point of mannitol is between 165 to 170 ˚C.

The DSC and XRD studies were also suggestive of lack of any interaction (solid state) of drug with the selected excipients.

Table14: Preparation of standard graph of tianeptine sodium

LEVEL (%)	CONCENTRATION	PEAK AREA
20	0.0028	395032
50	0.007	987580
80	0.0112	1580129
100	0.014	1875161
120	0.0168	2370193

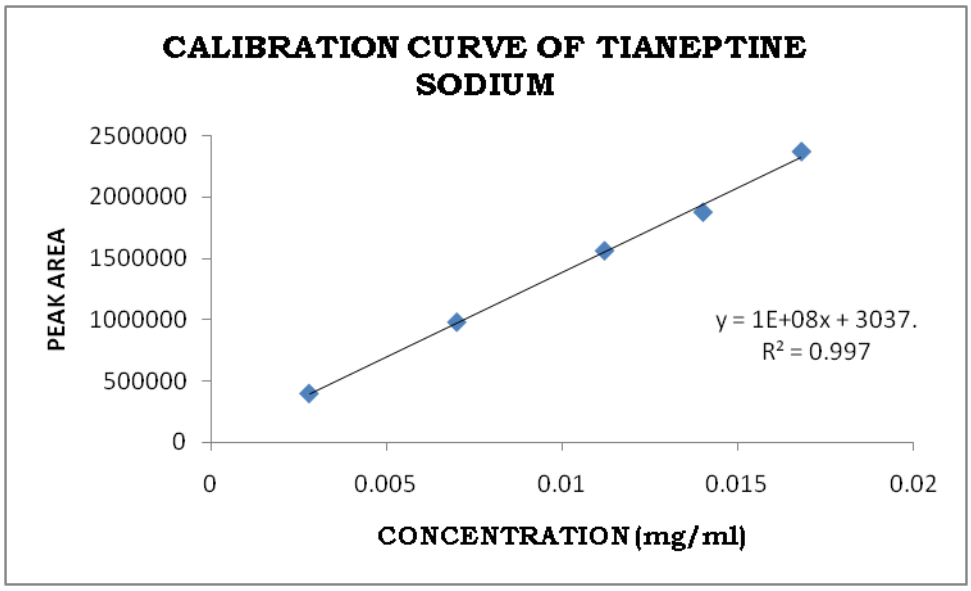


Fig.20: Calibration curve of Tianeptine sodium

Table15: Powder characteristics of the formulations F1-F5

Evaluation parameters	F1	F2	F3	F4	F5
Bulk density (g/cc)	0.445±0.01	0.460±0.02	0.466±0.02	0.488±0.05	0.503±0.09
Tapped density (g/cc)	0.521±0.05	0.523±0.03	0.532±0.04	0.568±0.04	0.586±0.11
Hausner's ratio	1.07±0.11	1.13±0.09	1.15±0.09	1.16±0.08	1.16±0.08
Angle of repose	34.9±2.30	34.54±2.07	33.39±3.20	34.05±3.25	33.17±2.60
Carr's index (%)	18.0±4.90	17.2±3.00	17.4±4.00	17.2±3.80	15.1±5.80
All the values are expressed as mean ± S.D; No. of trails (n)=6					

Table16: Powder characteristics of the formulations F6-F9

Evaluation parameters	F6	F7	F8	F9
Bulk density (g/cc)	0.512±0.11	0.462±0.07	0.508±0.10	0.486±0.10
Tapped density (g/cc)	0.574±0.12	0.545±0.08	0.584±0.13	0.563±0.10
Hausner's ratio	1.12±0.08	1.18±0.10	1.14±0.07	1.16±0.09
Angle of repose	34.74±3.30	33.78±2.50	36.18±2.20	35.14±3.00
Carr's index (%)	16.7±4.30	19.4±3.00	14.6±4.50	17.2±4.10

All the values are expressed as mean ± S.D; No. of trails (n)=6

Table17: Evaluation of post compression parameters of F1-F5

Test	Stablon	F1	F2	F3	F4	F5
Weight variation (mg)	169	169.2±2.30	169.9±2.50	170.2±1.70	169.9±2.10	170.5±1.90
Thickness (mm)	3.5	3.63±0.09	3.89±0.07	3.68±0.15	3.87±0.05	3.89±0.02
Hardness (kg/cm^2)	7.2	7.1±0.76	6.2±0.20	7.1±0.80	6.7±0.80	7.1±0.80
Friability (%)	0.12	0.12±0.90	0.12±0.67	0.15±0.84	0.14±0.79	0.12±0.52
Disintegration time(min)	3.30	3.15 ±3.80	3.10±4.10	3.00±2.30	3.60 ±3.60	2.55±2.10
Content uniformity (%)	101.0	100.5	100.1	100.0	99.3	99.8

All the values are expressed as mean ± S.D; No. of trails (n) =6

Table18: Evaluation of post compression parameters of F6-F9

Test	Stablon	F6	F7	F8	F9
Weight variation (mg)	169	169.9±2.2	170.3±2.1	170.2±2.0	169.7±1.8
Thickness(mm)	3.5	3.78±0.01	3.79±0.03	3.67±0.03	3.76±0.03
Hardness(kg/cm^2)	7.2	7.2±0.8	7.5±0.3	6.9±0.3	6.5±0.2
Friability (%)	0.12	0.14	0.15	0.14	0.12
Disintegration time(min)	3.30	2.10±2.4	3.30±3.4	3.17±2.5	3.10±3.0
Content uniformity (%)	101.0	101.0	99.5	100.5	100.0

All the values are expressed as mean ± S.D; No. of trails (n)=6

Table19: Dissolution profiles of tianeptine IR tablets in 0.1 N Hcl

Time (min)	Percentage of tianeptine dissolved									
	Stablon	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0	0
5	62.1	53.0±0.9	67.8±0.87	57.1±1.3	59.0±1.4	65.5±1.5	77.0±1.3	50.0±0.9	51.3±2.0	53.2±1.6
10	84.3	66.7±1.4	79.4±1.5	85.9±1.1	68.0±0.6	72.7±0.5	87.7±1.5	87.6±1.2	87.9±1.7	89.1±0.7
15	88.1	75.6±1.3	88.5±1.8	88.9±1.5	77.4±0.9	84.0±0.7	91.0±1.1	98.8±0.98	97.9±0.83	99.0±1.32
30	95.9	89.6±1.43	94.4±1.4	94.6±0.87	84.5±1.43	90.1±1.53	95.4±0.68	99.4±0.71	98.0±1.43	99.3±0.91
45	99.0	95.5±1.43	94.9±1.75	97.1±2.0	90.4±0.93	92.5±0.75	97.8±1.34	102.1±1.37	100.9±0.67	102.7±0.85
60	100.4	98.5±1.32	98.9±1.76	96.8±0.87	97.4±0.99	98.1±1.41	98.8±1.8	105.8±1.21	102±0.86	97.8±1.11
f1	-	9.6	3.4	2.6	10.0	6.3	4.6	7.1	5.6	6.4
f2	-	49.82	71	76.5	49.87	59.5	59.4	56.5	59.8	59.1

All the values are expressed as mean ± S.D; No. of trails (n)=6

Table20: Dissolution profiles of tianeptine IR tablets in pH 4.5 acetate buffer

Time (min)	Percentage of tianeptine dissolved									
	Stablon	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0	0
5	93	70.6±1.21	90.8±1.54	83.2±1.87	75.6±0.98	81.1±0.65	87.4±1.54	58.4±1.74	64.7±1.47	71.4±0.68
10	92.2	85.4±0.98	100±1.35	94.4±1.74	82.1±1.95	84.2±1.78	89.8±0.93	81.1±1.57	85.4±1.34	87.6±0.65
15	92.4	91.5±1.43	102.2±1.68	98.3±1.48	84.5±0.69	86.5±1.57	91.4±1.54	91.1±0.96	92.4±0.67	91.9±1.56
30	92.5	97.5±1.22	103.9±1.76	99.1±1.97	92.9±0.85	94.7±1.43	95.1±1.59	94.1±0.69	95.6±0.43	97.8±1.75
45	93.9	98±1.54	105±1.83	99.0±0.97	97.6±0.69	95.4±0.58	96.0±1.82	100.1±1.48	102.1±2.0	104.5±1.798
60	94	99.0±1.4	105±1.53	100.8±0.83	98.0±0.71	97.1±0.63	96.1±1.76	101.5±1.48	99.8±1.68	104.1±0.91
f1	-	8.3	9.7	6.5	8.2	6.19	3	11.7	11.7	9.9
f2	-	49.8	51.4	59.8	51.9	58.9	75.4	40.7	45.1	48.0

All the values are expressed as mean ± S.D; No. of trails (n)=6

Table21: Dissolution profiles of tianeptine IR tablets in pH 6.8 phosphate buffer

Time (min)	Percentage of tianeptine dissolved									
	Stablon	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0	0
5	75.4	75.2±1.98	86.2±1.53	75.2±1.78	76.7±0.86	82.1±0.59	86.7±0.18	69.1±1.59	71.1±1.63	75.4±1.53
10	87	85±0.63	101.5±1.54	93.3±1.83	86.1±0.99	88.4±0.32	90.3±1.43	81.1±1.67	81.5±1.37	87.1±1.87
15	91.6	89.8±0.92	103.2±0.72	97.1±0.69	88.4±1.76	91.8±0.92	93.8±0.72	86.7±1.84	89.1±1.31	88.4±1.66
30	98.3	94.9±1.31	102.7±0.72	98.7±1.41	92.0±0.86	96±0.65	98±0.72	92.9±1.49	95.1±1.52	94.8±0.92
45	99	96.3±1.46	103.2±1.75	98.7±0.93	97.1±0.74	98.9±0.49	98.8±1.64	100.9±1.65	102.7±0.87	103.1±0.69
60	99	95.7±1.43	103.2±0.48	97.3±0.38	97.0±1.75	99.0±0.73	98.4±1.87	100.1±1.71	103.4±0.39	102.7±0.63
f1	-	2.5	9.3	2.7	2.9	2.0	3.3	4.8	3.7	2.75
f2	-	78.6	51.5	72	74	75.3	65	65.9	71.1	75.2

All the values are expressed as mean ± S.D; No. of trails (n)=6

Table22: Dissolution profiles of tianeptine IR tablets in water

Time(min)	Percentage of tianeptine dissolved									
	Stablon	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0	0
5	72	56.7±1.63	81.3±1.54	80.8±1.32	68.2±1.43	74.4±1.76	76.8±0.74	54.1±0.74	69.1±0.81	72.5±1.15
10	88.6	80.8±1.31	93±1.56	95.5±1.48	79.4±0.46	81.4±1.67	82.8±0.28	67.1±0.71	77.9±1.43	
15	93	87.1±0.43	95.9±0.63	97.7±1.74	80.8±1.65	82.9±1.49	84.1±1.46	79.1±1.82	85.6±1.54	81.1±1.36
30	94	93.6±0.97	92.8±1.76	98.5±1.67	81.1±1.45	84.1±1.41	87.4±1.81	89.1±2.0	91.5±0.72	89.5±0.54
45	95	96.4±1.13	100.3±1.42	99±1.43	80±0.43	82.5±0.47	86.4±1.98	94.5±1.32	94.5±1.56	94.8±1.75
60	95.6	98.4±1.65	99.8±1.69	100.1±1.12	81.4±1.82	81.2±1.03	87.7±0.34	99.1±0.72	99.8±1.19	100.8±1.06
f1	-	6.3	5.1	6.3	12.7	10	8	11.7	5.3	6.2
f2	-	55.9	63.8	61.4	46.2	49.5	56.7	88.5	61.5	56.9

All the values are expressed as mean ± S.D; No. of trails (n)=6

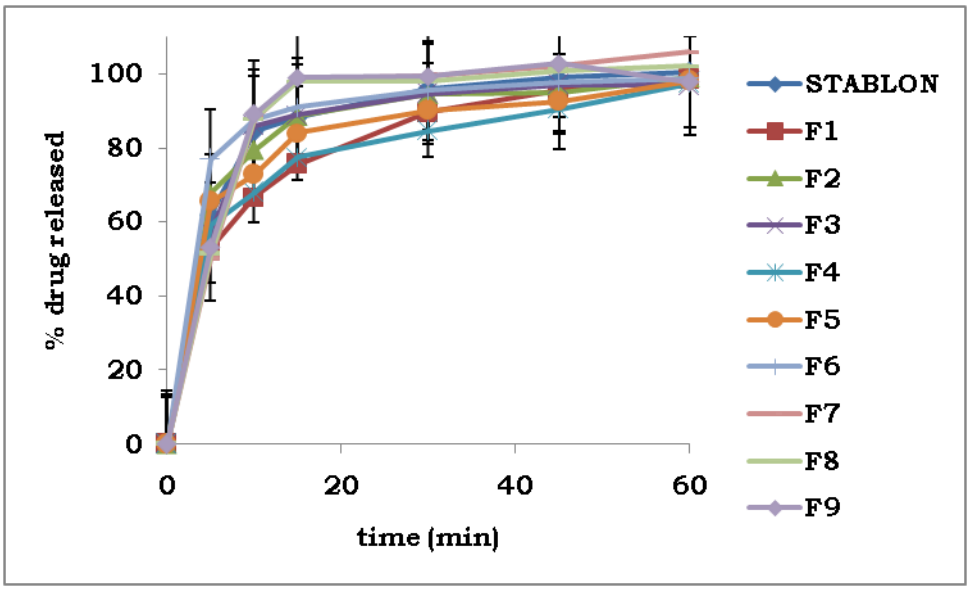


Fig.21: Dissolution profiles of Stablon and tianeptine IR tablets in 0.1 N Hcl

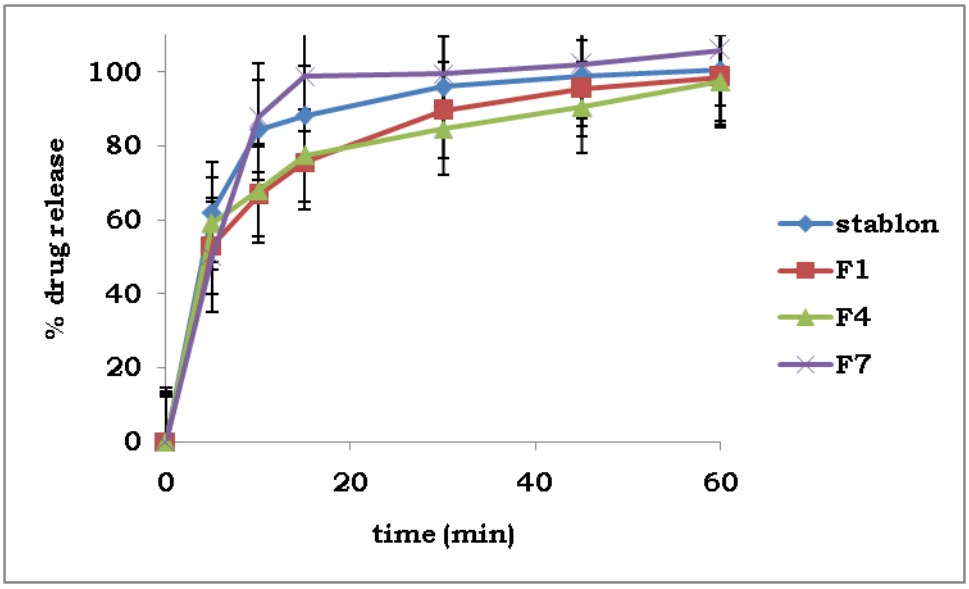


Fig.22: Dissolution profiles of tianeptine IR tablets at 3% concentration of different super disintegrants

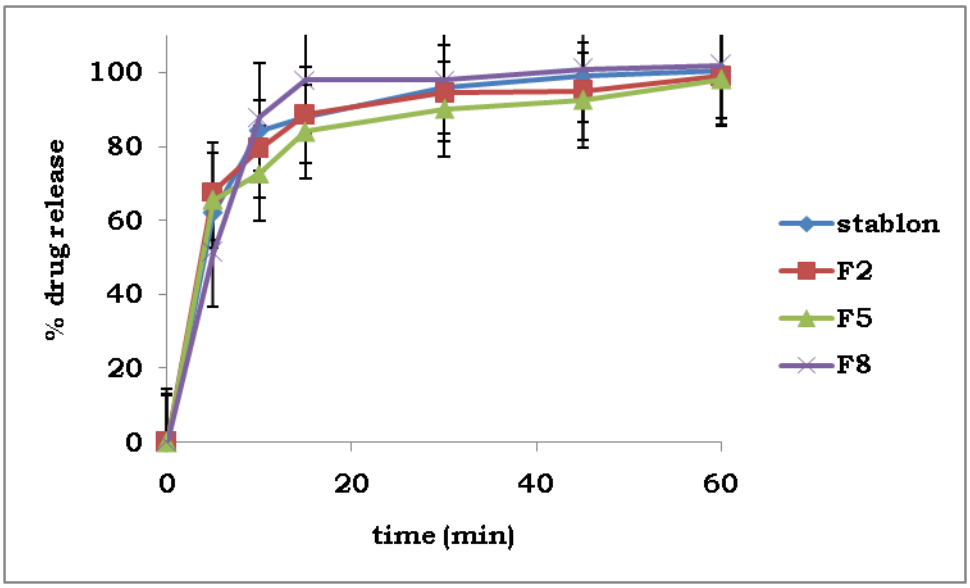


Fig.23: Dissolution profiles of tianeptine IR tablets at 5% concentration of different super disintegrants

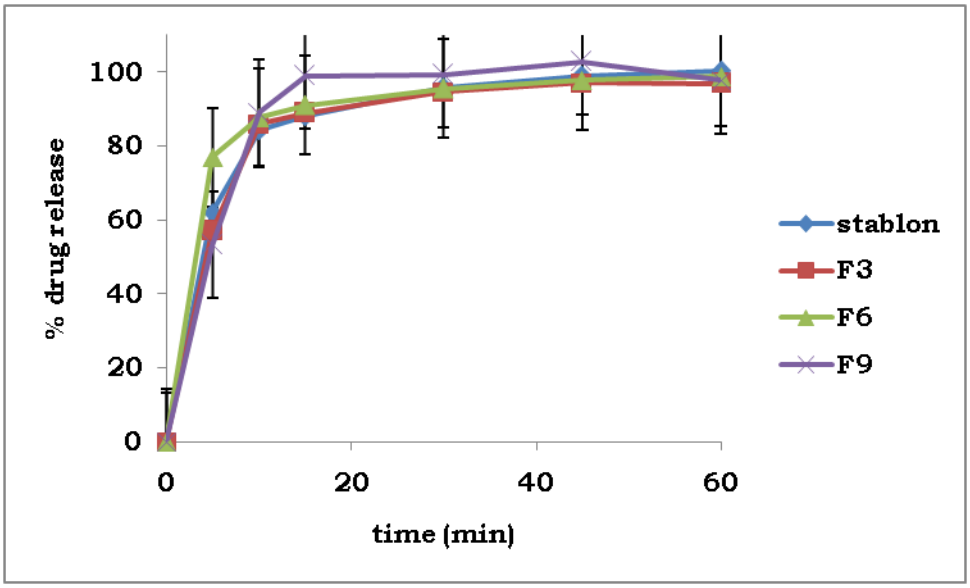


Fig.24: Dissolution profiles of tianeptine IR tablets at 6% concentration of different super disintegrants

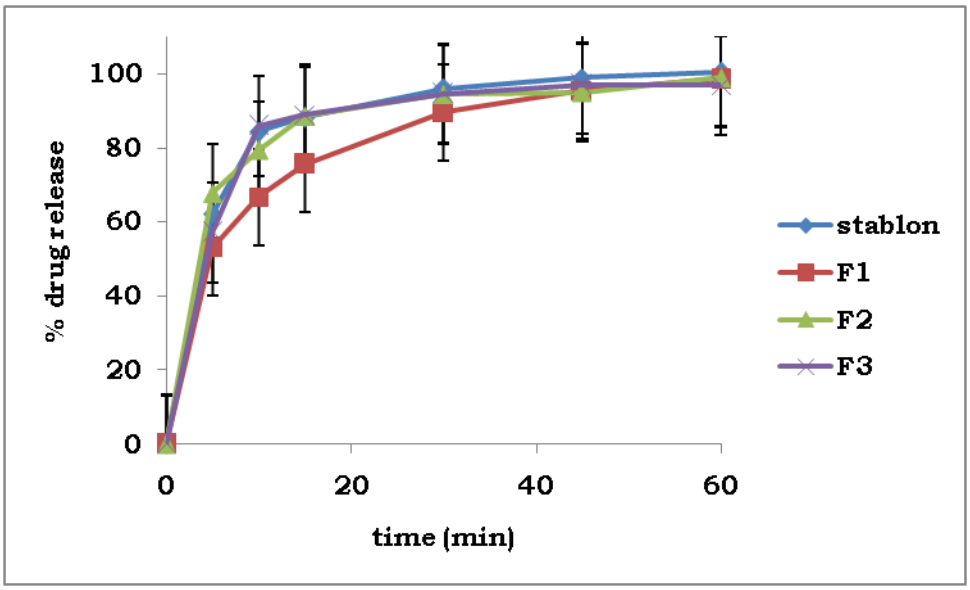


Fig.25: Dissolution profiles of tianeptine IR tablets at different concentrations of crospovidone

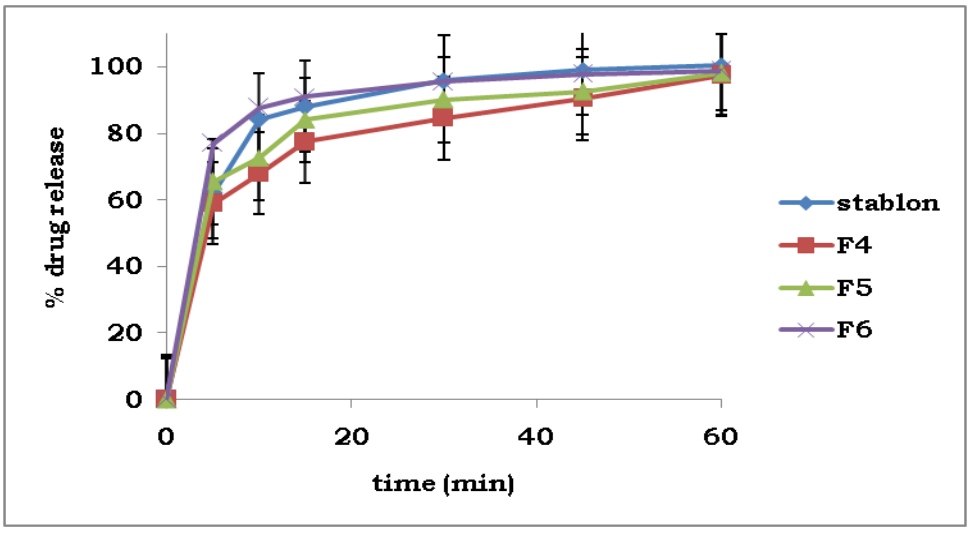


Fig.26: Dissolution profiles of tianeptine IR tablets at different concentrations of croscarmellose sodium

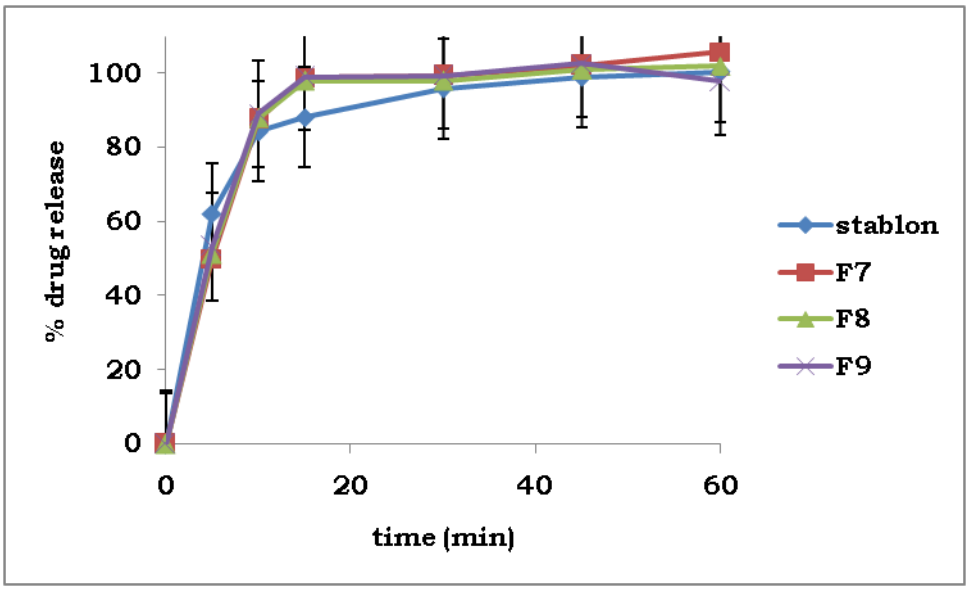


Fig.27: Dissolution profiles of tianeptine IR tablets at different concentrations of sodium starch glycolate

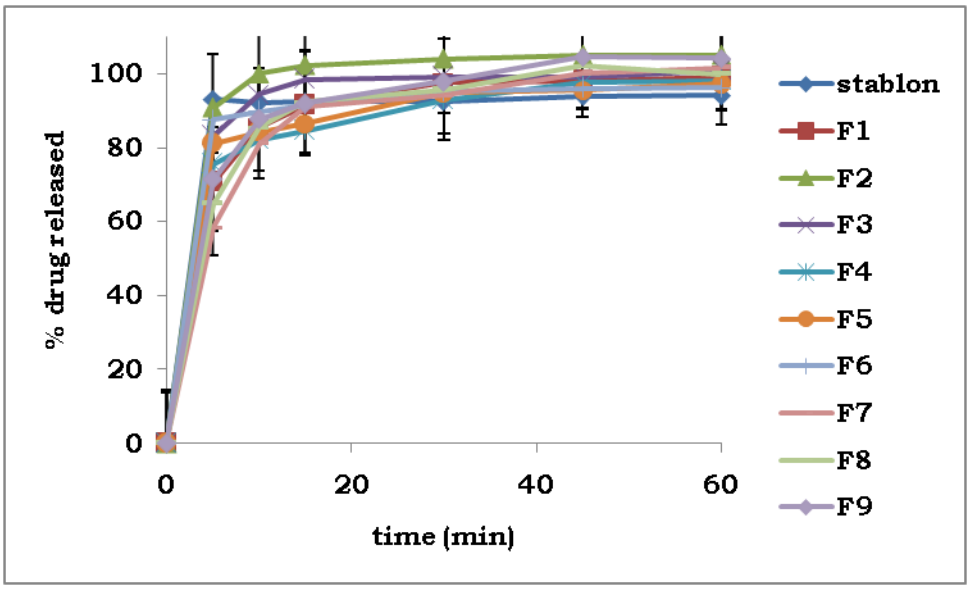


Fig.28: Dissolution profiles of Stablon and tianeptine IR tablets in acetate buffer pH 4.5

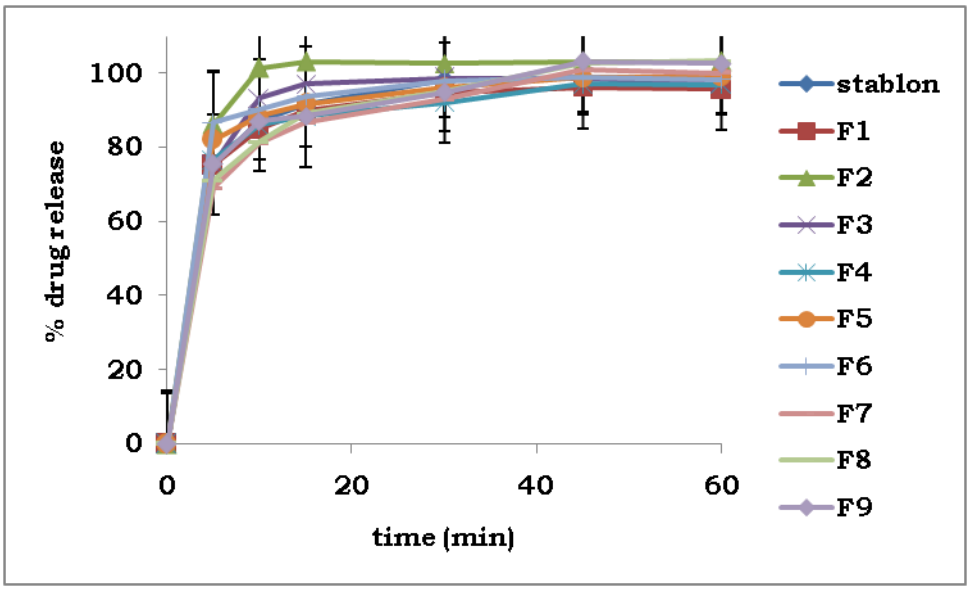


Fig.29: Dissolution profiles of Stablon and tianeptine IR tablets in phosphate buffer pH 6.8

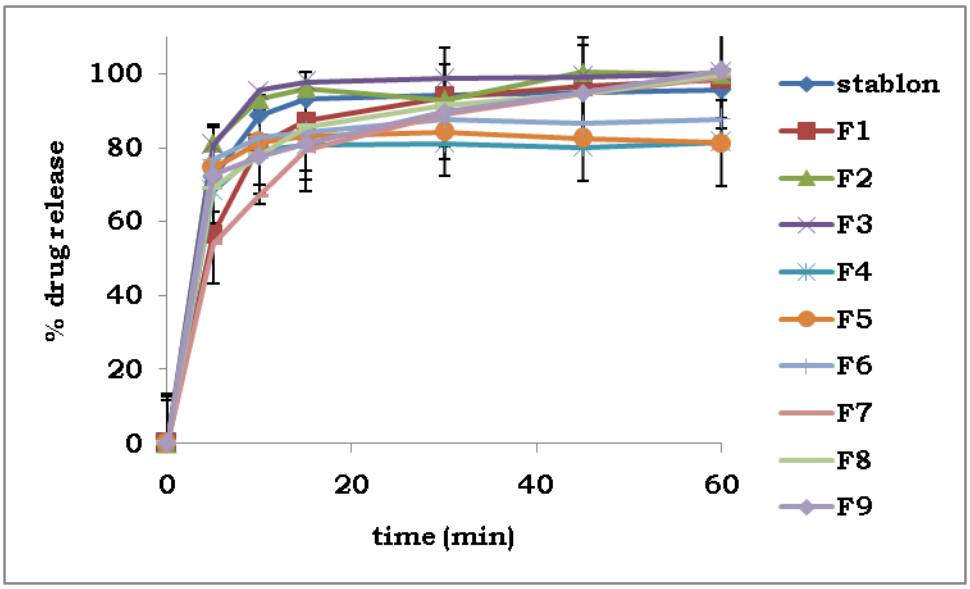


Fig.30: Dissolution profiles of Stablon and tianeptine IR tablets in water

Table23: Dissolution parameters of Tianeptine sodium IR tablets prepared (F1-F4)

Parameters		Formulations				
		Stab	**F1**	**F2**	**F3**	**F4**
T_{50}% (min)	**M1**	4.00	5.00	2.75	4.25	3.75
	M2	2.00	3.50	1.75	3.00	3.50
	M3	3.50	3.25	3.00	3.00	3.00
	M4	3.00	4.50	2.00	2.75	4.00
T_{80}(min)	**M1**	9.00	19.50	10.50	9.00	20.00
	M2	4.00	13.25	4.00	4.50	8.25
	M3	7.00	7.75	4.75	6.50	6.75
	M4	6.75	9.75	4.75	4.75	14.00
DE_{30} (%)	**M1**	77.74	67.55	77.75	77.1	68.09
	M2	84.82	80.87	91.84	87.14	77.67
	M3	82.17	80.35	91.35	85.12	79.60
	M4	81.26	75.35	86.69	86.57	71.80
PD_{10}	**M1**	84.30	66.70	79.40	85.90	68.00
	M2	93.00	85.40	100.0	94.40	82.10
	M3	87.00	85.00	101.50	93.30	86.10
	M4	88.60	80.80	93.00	95.50	79.40

Table24: Dissolution parameters of Tianeptine sodium IR tablets prepared (F5-F9)

Parameters		Formulation					
		Stab	**F5**	**F6**	**F7**	**F8**	**F9**
T_{50}% (min)	**M1**	4.00	3.00	3.00	5.00	4.00	5.00
	M2	2.00	3.25	3.00	4.50	3.50	3.50
	M3	3.50	3.25	3.00	3.75	3.75	3.50
	M4	3.00	1.75	2.00	4.50	3.50	3.00
T_{80}(min)	**M1**	9.00	13.50	6.50	8.50	8.75	8.50
	M2	4.00	4.75	4.50	9.75	8.50	7.25
	M3	7.00	5.00	4.50	9.50	9.25	7.00
	M4	6.75	9.25	7.75	11.25	11.5	12.5
DE_{30} (%)	**M1**	77.74	73.55	81.63	80.71	80.33	81.54
	M2	84.82	80.05	83.77	77.14	79.71	81.58
	M3	82.17	83.01	85.26	77.15	78.9	80.25
	M4	81.26	74.62	76.48	68.84	75.9	74.42
PD_{10}	**M1**	84.30	72.70	87.70	87.60	87.90	89.10
	M2	93.00	84.20	89.80	81.10	85.40	87.60
	M3	87.00	88.40	90.30	81.10	81.50	87.10
	M4	88.60	81.40	82.80	67.10	77.90	77.60

Note:

M1-0.1 N Hcl

M2-Acetate buffer pH 4.5

M3-Phosphate buffer pH 6.8

M4-Purified water

Table 25: Dissolution of optimized formulation maintained for stability with 0.1 N Hcl

Time (min)	% Drug release in at 40°C/75 RH			
	Initial	**1st month**	**2nd month**	**3rd month**
0	0	0	0	0
5	77.0	77.4	77.2	77.1
10	87.7	87.6	87.4	87.3
15	91.0	89.9	89.7	89.6
30	95.4	95.2	95.1	94.9
45	97.8	97.6	97.5	97.3
60	98.8	98.7	98.6	98.4

Table 26: Dissolution of optimized formulation maintained for stability with pH 4.5 Acetate buffer

Time(min)	% Drug release in at 40°C/75 RH			
	Initial	**1st month**	**2nd month**	**3rd month**
0	0	0	0	0
5	87.4	87.3	87.2	87.1
10	89.8	89.6	89.4	89.3
15	91.4	91.3	91.2	91.1
30	95.1	95.0	94.8	94.7
45	96.0	95.9	95.8	95.6
60	96.1	96.0	95.9	95.8

Table 27: Dissolution of optimized formulation maintained for stability with pH 6.8 Phosphate buffer

Time(min)	% Drug release in at 40°C/75 RH			
	Initial	1st month	2nd month	3rd month
0	0	0	0	0
5	86.7	86.5	86.4	86.3
10	90.3	90.2	90.1	89.9
15	93.8	93.7	93.6	93.5
30	98.8	98.7	98.6	98.5
45	98.0	97.9	97.8	97.7
60	98.4	98.4	98.3	98.2

Table 28: Dissolution of optimized formulation maintained for stability with water

Time(min)	% Drug release in at 40°C/75 RH			
	Initial	1st month	2nd month	3rd month
0	0	0	0	0
5	76.8	76.6	76.5	76.4
10	82.8	82.6	82.4	82.3
15	84.1	83.9	83.7	83.6
30	87.4	87.3	87.2	87.1
45	86.4	86.3	86.2	86.1
60	87.7	87.5	87.4	87.3

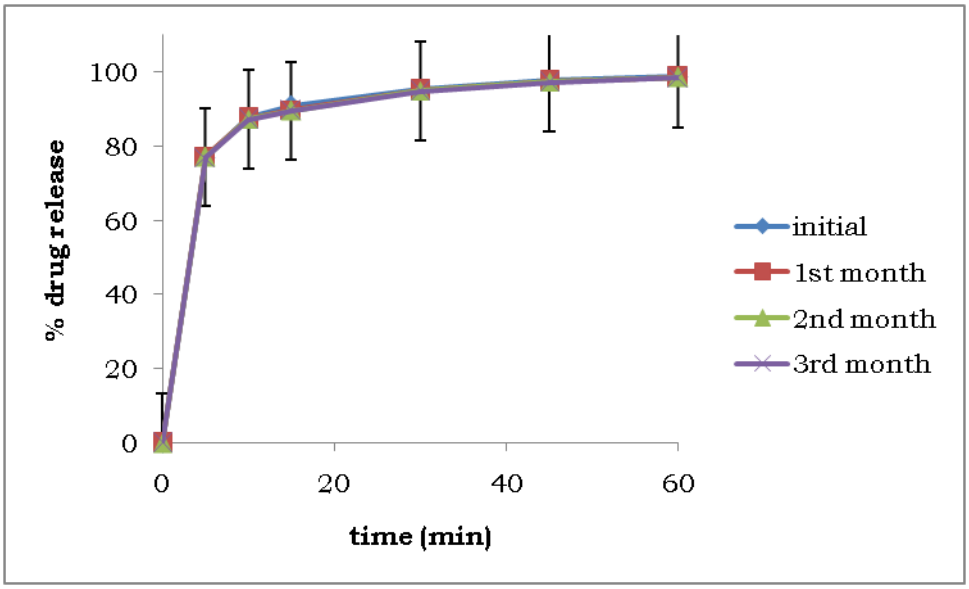


Fig.31:Comparative dissolution data of stability samples in 0.1 N Hcl

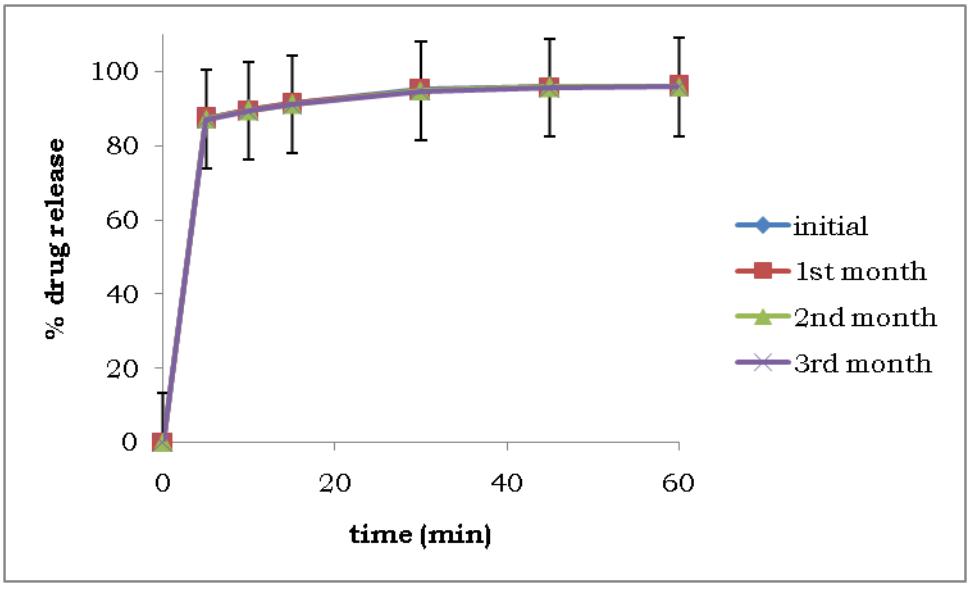


Fig.32:Comparative dissolution data of stability samples in Acetate buffer pH 4.5

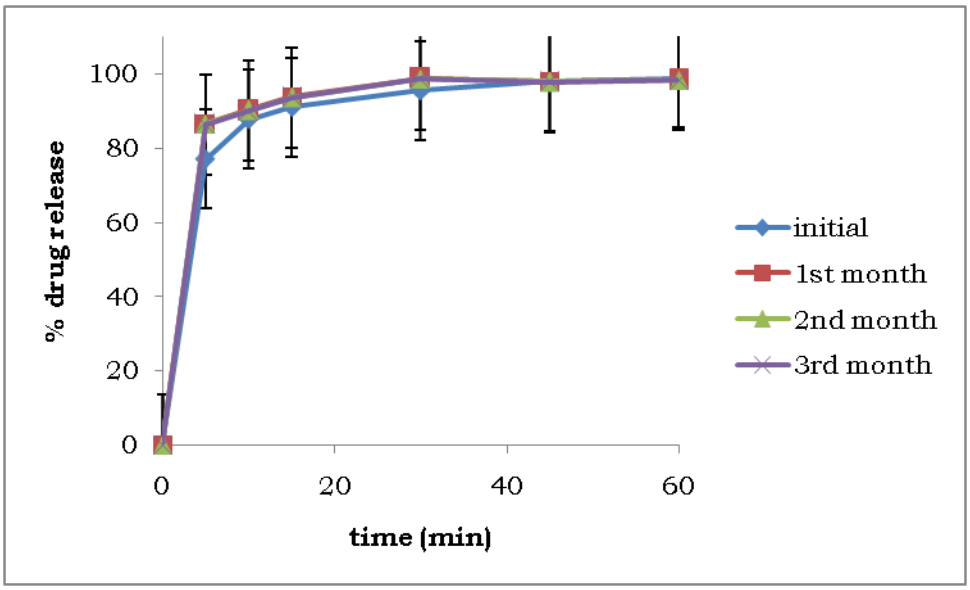


Fig.33: Comparative dissolution data of stability samples in Phosphate buffer pH 6.8

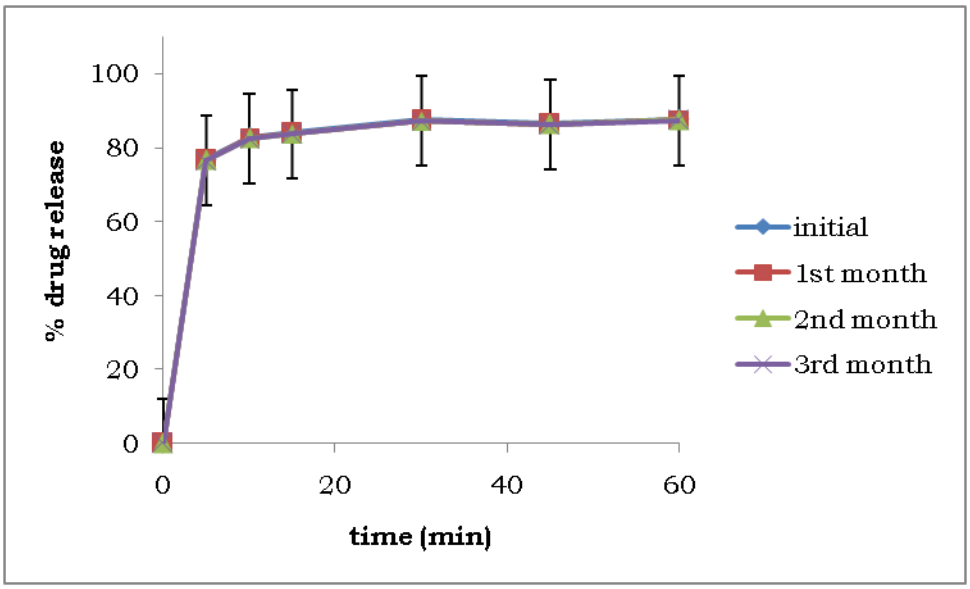


Fig.34:Comparative dissolution data of stability samples in water

No incompatibilities between tianeptine sodium, mannitol, povidone, hypromellose, super disintegrants (CP, SSG, and CCS), magnesium stearate and talc had been observed. Immediate release tablets containing 170 mg of tianeptine were prepared by using different proportions (3%, 5%, 6%) of croscarmellose sodium, crospovidone, sodium starch glycolate by wet granulation method. Hardness of the tablets was in the range of 6.0-7.5. Weight loss in the friability test was less than 0.2% in all the cases. All the IR tablets prepared contained tianeptine within 100±2.5% of the labeled claim. All the tablets disintegrated rapidly in the USP disintegration test.

The disintegration time was dependent on the type of disintegrant used and as the disintegration is rapid they are considered suitable for immediate release. Polyplasdones are densely cross-linked homopolymers of *N*-vinyl 2-pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration. Visually, tablets formulated with Polyplasdones could be seen to rapidly disintegrate into more or less uniform fine particles, while tablets formulated with croscarmellose sodium and sodium starch glycolate appear to disintegrate much more slowly into more or less uniform coarse particles.

Tablets containing croscarmellose sodium and sodium starch glycolate seemed to swell immediately. This was in accordance with earlier findings where tablets prepared with croscarmellose sodium and sodium starch glycolate showed tremendous swelling before disintegration (Gorman *et al*.1982, Wan & Prasad 1989, Yen *et al*. 1997). Further the rapid swelling of these tablets upon wetting may partly be attributed to the recovery of deformation. As per the results it is evident that tablets containing CP as disintegrant at a concentration of 6% disintegrated more rapidly followed by tablets containing CCS and SSG.

***In vitro* dissolution studies**

Generally, the recommended dissolution media for *in vitro* dissolution testing can be used to guide formulation development and it is typically non discriminatory between formulation ingredients. Usually, drug release from immediate release tablets as used in the study, is driven more by the medium than the formulation ingredients. Discriminatory dissolution profiles are highly desirable for distinguishing between products having differences in pharmaceutical attributes (formulation or manufacturing process differences) as in the case in the present study, where in the difference in the formulation was with respect to disintegrant used and their concentrations.

Tianeptine dissolution profiles of the IR tablets in the recommended medium and discriminating mediums are given in table 5.9, 5.10, 5.11, 5.12 and shown in figs 5.12-5.21. Dissolution parameters of the tablets are summarized in table 5.13, 5.14. Results have show that the tablets prepared with CP showed faster dissolution than the corresponding tablets prepared with CCS or SSG, in both the four media as also was evidenced by the $t_{50\%}$ and $t_{80\%}$ values. It is evident from the results that as the concentration of super disintegrant increased, dissolution rate was also increased. All the tablets except F2 and F4 exhibited not less than 85% dissolution in 0.1 n Hcl indicating that bioavailability of these tablets is not limited by dissolution.

Tablets prepared by 6% CCS exhibited lesser $t_{50\%}$ and $t_{80\%}$ values in all the media indicating that F6 is superior to remaining formulations. F6 exhibited highest DE30 and PD10 values in 0.1 N Hcl, where as in other media's F2 exhibited higher values indicating that CP at 5% concentration is also effective for preparation of Tianeptine IR tablets. At all the concentrations CCS achieved faster dissolution compared to other super disintegrants at the same concentration and CP exhibited overlapping results with CCS and innovator Stablon.

CP exhibited faster dissolution at 5% concentration, CCS at 6% concentration and SSG exhibited similar dissolution rates at all concentrations. The results clearly demonstrate the superiority of CCS to enhance the release of the drug even in the

discriminatory medium, and shows that the choice of the super disintegrant and its concentration has a significant impact on drug dissolution. A similar trend was observed for the tablets and the difference was not very apparent between the tablets containing CCS and CP as disintegrants. All the formulations except the F4 exhibited greater than 85% dissolution at 30 min in all the media indicating that they can be considered as waivers of in vivo relative bioavailability study and from f1, f2 values it is obvious that formulation F1-F6 exhibited similar dissolution profiles with that of innovator under the dissolution test conditions defined for rapidly dissolving products, they can be considered as waivers of in vivo bio equivalence according to FDA draft guidance.

8. SUMMARY

The main objective of the study is to develop tianeptine IR tablets using various super disintegrants in different concentrations to achieve faster dissolution to match the innovator product Stablon-170 mg. Tablets were prepared by incorporating the super disintegrants at 3, 5, 6 % w/w. Tablet blends were prepared and micromeritic studies were carried out for those blends. Pure and formulated products of tianeptine were evaluated by HPLC at a wave length of 220 nm using inertsil ODS column. From the results obtained by HPLC, the calibration curve was constructed having regression value of 0.997. Assay values of the formulations were observed in the range of 99.3 to 101%. Compatibility studies were performed and it was observed that all the super disintegrants used were compatible with the drug. Dissolution studies were performed and it was found that formulation F6 have shown best results and comparable with the innovator (Stablon).

CONCLUSION

From the above experimental results it can be concluded that:

Immediate release tablets of tianeptine sodium can be prepared by using CCS, CP and SSG at different concentrations.

Immediate release tablets showed release depending on the concentration of the super disintegrant and also on the type of mechanism of disintegration of the super disintegrants CCS, SSG and CP.

Tablet dimensions, weight and breaking force have no significant difference between tablets with different disintegrants.

The DSC, XRD spectra's revealed that, there was no interaction between the drug and the disintegrants. From the study it is evident that a promising immediate release tablet formulation can be developed. Further in vivo investigation is required to establish efficacy of this formulations.

The study indicated that the dissolution rate increased with an increase in the super disintegrant concentration and significant results were observed with CCS even in discriminating media's and apparent difference in dissolution rate was not observed between tablets formulated with CP and SSG.

The study also indicated that all the formulations except F4 are bio waivers for in vivo relative bio availability study and formulations F1-F6 can be considered as waivers of in vivo bio equivalence study according to FDA guidelines.

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CERTIFICATE

DECLARATION

ACKNOWLEDGEMENT

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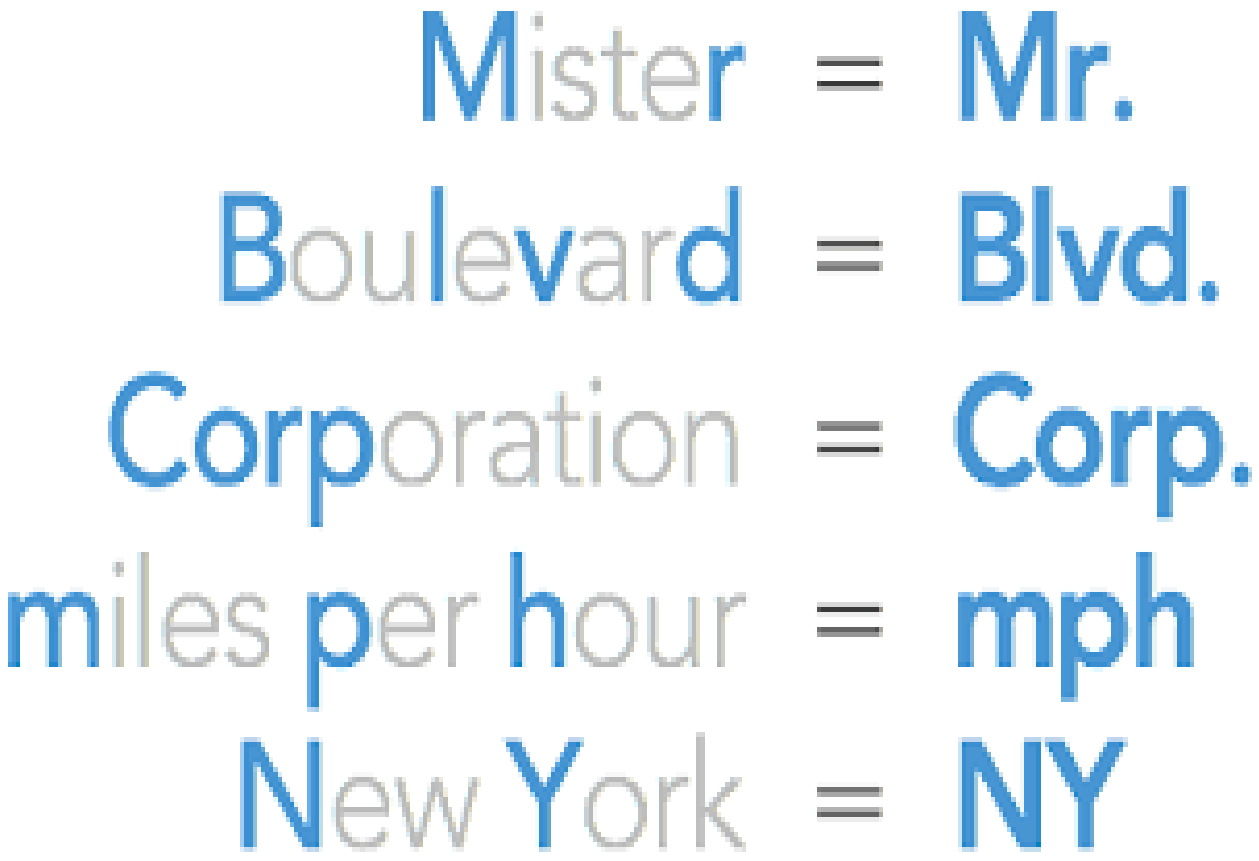

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