FORMULATION AND EVALUATION OF GALANTAMINE HYDROBROMIDE EXTENDED RELEASE CAPSULES

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register Number: 26111002

UNDER THE GUIDANCE OF

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All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF GALANTAMINE HYDROBROMIDE EXTENDED RELEASE CAPSULES-24mg"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of pharmacy in Pharmaceutics** is a bonafide research work done by **Register Number: 26111002** under my Guidance in the Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2012-2013.

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DECLARATION

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CONTENTS

ABBREVATIONS

API	Active pharmaceutical Ingredient
BCS	Biological Classification System
CI	Compressibility Index
DDS	Drug Delivery System
EC	Ethyl cellulose
ER	Extended Release
FBC	Fluid Bed Coater
FTIR	Fourier transformer infrared spectroscopy
GI	Gastro Intestinal Tract
HBR	Hydro bromide
HDPE	High Density Poly Ethylene
HPLC	High performance liquid chromatography
HPMC	Hydroxy propyl methyl cellulose
HR	Hausner Ratio
ICH	International Conference for Harmonisation
IP	Indian Pharmacopoeia
IPA	Iso Propyl Alcohol
IR	Immediate Release
MRI	Magnetic Resonance Imaging
PEG	Poly ethylene glycol
PET	Positron Emission Tomography
RH	Relative Humidity
RPM	Rotation Per Minute
SPECT	Single Photon Emission Computed Tomography
SR	Sustained Release
USP	United States Pharmacopoeia
WHO	World Health Organisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Sec	Seconds

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I. INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery[1]. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

1.1. Oral drug delivery: [2, 3, 4, 5]

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

For the past decades, there has been enhanced demand for patient complaint dosage forms. As a result the demand for the technologies has been increased 3 fold annually. Since the development cost of new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms are difficulty to swallow.

1.2. Modified Drug Delivery Systems [8]

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release occurs only after some time of the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment or to increase patient compliance and convenience of administration.

1.3. Classification[7]:

Modified Release dosage form may be classified as

- **Extended Release**
- **Sustained Release**
- **Controlled Release**
- **Delayed Release**
- **Site Specific Targeting**
- **Receptor targeting.**

1.3.1. Extended Release (ER):

This type of oral Drug delivery system allows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

1.3.2. Sustained Release (SR):

This term Extended or Sustained is constantly used to describe a pharmaceutical dosage form formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is Sustain in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained. In orally administered dosage forms, this duration is in hours and critically depends on the residence time of the dosage form in GI tract, where as in the case of injectables this period may vary from days to months.

1.3.2a. Advantages of ER/SR Dosage Forms [11]:

- Improved patient compliance due to reduced frequency of drug administration.
- The blood level oscillations characteristic of conventional dosage forms is reduced.
- A less obvious advantage that the total amount of drug administered can be reduced, thus maximizing availability with minimum dose.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form.
- The safety margin of high potency drugs can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Reliable therapy.

1.3.2b. Disadvantages: [11]

- Administration of Extended Release(ER) medication does not permit the prompt termination of therapy.
- Less flexibility in adjusting dosage regimen.
- Sustained release forms are designed for normal population, i.e., on the basis of biological half-lives. Consequently, disease states that alter drug disposition, significant patient variation, and so forth are not accommodated.
- Economic factors.

1.3.2c. Drug candidates that is suitable for ER/SR Dosage Forms:

- Should be effectively absorbed in small intestine.
- Biological half life should lie within 1-12hours.
- Dosage that is not titrated according to individual.
- Small doses(<1g)

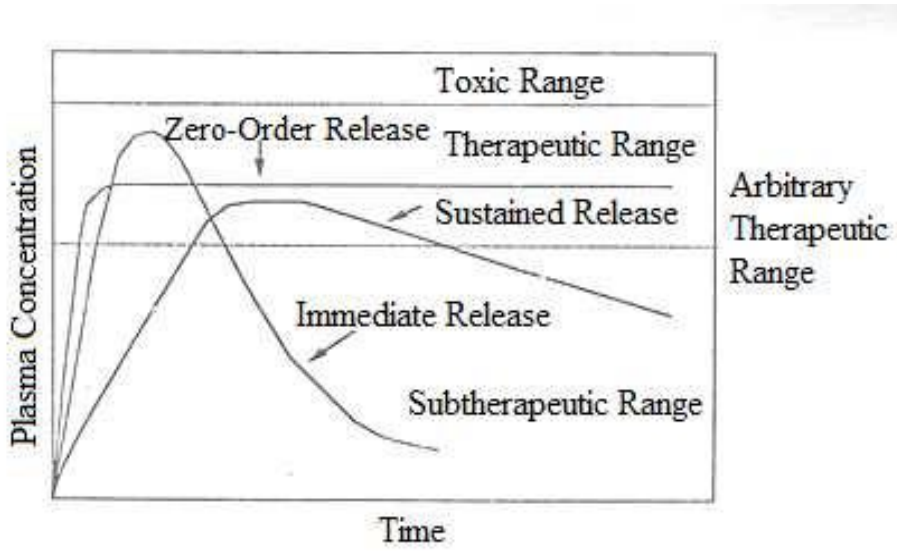

Fig:1.1 Plasma Dug Concentration Profiles for Conventional Tablet Formulation.

a. Extended/Sustained Release Formulation and a Zero Order Controlled Release Formulation.

ER/SR system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before its release, Eg: Enteric coated tablet or capsules.

The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body organ over an extended time in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process urinary excretion, enterohepatic recycling, sweat, fecal and so on. Since, for most of the drugs these elimination processes are first order, it can be said that a certain blood level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period. This is represented mathematically as following,

$$\text{Rate in} = \text{Rate out} = k_{\text{elim}} \times C_d \times V_d$$

Where C_d is the desired drug level,

V_d is the volume of distribution and

k_{elim} is the rate constant of drug elimination from the body.

1.3.3. PHYSICOCHEMICAL FACTORS INFLUENCING ORAL EXTENDED-RELEASE DOSAGE FORM DESIGN [13, 14]

a. Dose size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5- 1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

b. Ionization, *pka* and aqueous solubility:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined.

Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the Gastro Intestinal tract will be limited by dissolution of the drug. So it is obvious that the

solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

c. Partition Coefficient:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

d. Stability:

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and, hence, is subject to degradation.

1.3.4. BIOLOGICAL FACTORS INFLUENCING ORAL EXTENDED-RELEASE DOSAGE FORM DESIGN [13, 14]

- Biological half life.
- Absorption.
- Metabolism.

a. Biological half life:

The usual goal of an oral Extended Release product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 10 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

b. Absorption:

Since the purpose of forming a SR/ER product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption

should be approximately 3-4 hours otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period.

Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, ER preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds is to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bioadhesive materials.

c. Metabolism:

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Extended-Release dosage form is,

- Drug should have low half-life(<5 hrs)
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR/ER dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented.

1.3.5. Controlled Release Dosage:

Controlled Release dosage form is generally accomplished by attempting to obtain "zero- order" release from the dosage form which is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained Release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent).

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

a. Continuous release systems [13]

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various systems under this category are as follows:

1. Dissolution controlled release systems

2. Diffusion controlled release systems

3. Dissolution and diffusion controlled release systems

4. Ion exchange resin- drug complexes

5. pH dependent formulation

6. Osmotic pressure controlled systems

b. Delayed transit and continuous release systems[13]

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to retain in the stomach and hence the drug present therein should be stable in gastric pH. Systems included in this category are mucoadhesive systems and size based systems.

1.3.6. Delayed Release [15, 16]

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Delayed Release oral dosage forms can control where the drug is to be released, e.g. when the dosage form reaches the small intestine (Enteric-coated dosage forms) or the colon (colon-specific dosage forms).

Delayed Release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example Enteric-coated tablets and pulsatile-release capsules.

Delayed Release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of time.

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical sustained release solid oral dosage forms today include Tablets, Capsules, Granules and Pellets.

Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.4. ALZHEIMER'S DISEASE [23, 24, 25]

Alzheimer's disease also known in medical literature as Alzheimer disease, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss. As the sufferer declines

they often withdraw from family and society. Gradually, body functions are lost, ultimately leading to death.

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain. Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease.

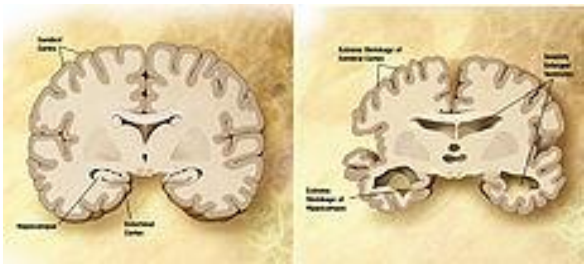

Fig:1.2 Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right). Differential characteristics are pointed out.

Characteristics:

The disease course is divided into four stages, with progressive patterns of cognitive and functional impairments

Pre-dementia:

The first symptoms are often mistakenly attributed to ageing or stress. Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfils the clinical criteria for diagnosis of Alzheimers disease.

Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory(Memory of meanings and Concept relationships)

can also be symptomatic of the early stages of Alzheimers disease. Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease.

Early stage:

In people with Alzheimers disease the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small portion of them, difficulties with language, executive functions, perception (Agnosia), or execution of movements (Apraxia) are more prominent than memory problems. Alzheimers disease does not affect all memory capacities equally. Older memories of the person's life (Episodic memory), facts learned (Semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat) are affected to a lesser degree than new facts or memories.

Moderate stage:

Progressive deterioration eventually hinders independence; with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (Paraphasias). Reading and writing skills are also progressively lost. Complex motor sequences become less coordinated as time passes and Alzheimers disease progresses, so the risk of falling increases During this phase, memory problems worsen, and the person may fail to recognise close relatives

Advanced stage:

During this last stage of Alzheimers disease, the person is completely dependent upon caregivers. Language is reduced to simple phrases or even single

words, eventually leading to complete loss of speech. Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common results. People with Alzheimers disease will ultimately not be able to perform even the simplest tasks without assistance. Muscle mass and mobility deteriorate to the point where they are bedridden, and they lose the ability to feed themselves.

a. CAUSES OF THE DISEASE:

The cause for most Alzheimer's cases is still essentially unknown (except for 1% to 5% of cases where genetic differences have been identified). Several competing hypotheses exist trying to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, which proposes that Alzheimers disease is caused by reduced synthesis of the neurotransmitter acetylcholine.

b. PATHOPHYSIOLOGY

Neuropathology:

Alzheimer's disease is characterized by loss of neurons and synapses in the cerebral cortex and certain sub cortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Studies using MRI and PET have documented reductions in the size of specific brain regions

in people with Alzheimers disease as they progressed from mild cognitive impairment to Alzheimer's disease

Disease mechanism:

The amyloid hypothesis traditionally points to the accumulation of beta amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ionhomeostasis, induces programmed cell death (Apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.

Genetics of the disease:

The vast majority of cases of Alzheimer's disease are sporadic, meaning that they are not genetically inherited although some genes may act as risk factors. On the other hand around 0.1% of the cases are familial forms of autosomal dominant (not sex-linked) inheritance, which usually have an onset before age 65. This form of the disease is known as Early onset familial Alzheimer's disease

c. DIAGNOSIS

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions. Advanced medical imaging with Computed Tomography (CT) or Magnetic Resonance Imaging(MRI), and with Single Photon

Emission Computed Tomography (SPECT) or Positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. Moreover, it may predict conversion from prodromal stages (Mild cognitive impairment) to Alzheimer's disease

d. PREVENTION

At present, there is no definitive evidence to support that any particular measure is effective in preventing Alzheimers disease. Global studies of measures to prevent or delay the onset of Alzheimers disease have often produced inconsistent results. Although cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of Alzheimers disease, The components of a Mediterranean diet, which include fruit and vegetables, bread, wheat and other cereals, olive oil, fish, and red wine, may all individually or together reduce the risk and course of Alzheimer's disease.

Pharmaceutical Management:

Five medications are currently approved by regulatory agencies such, as U.S.Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the cognitive manifestations of Alzheimers disease.

Acetylcholinesterase[6] inhibitors (Tacrine, Rivastigmine, Galantamine and Donepezil) and the other (Memantine) is an NMDA receptor antagonist. No drug has an indication for delaying or halting the progression of the disease**.** The

most common side effects are nausea and vomiting both of which are linked to cholinergic excess.

1.5. PELLETS[17]

Pellets are defined as defined as multiple unit dosage forms which are small (0.5 mm to 1.5 mm), free flowing, spherical particulates formed by agglomeration of powders or granules of drug substances and excipients using appropriate processing equipment. Pellets are also used to describe small rods with aspect ratio of close to unity.

1.5.1. Advantages:

- Pellets are more advantageous in developing controlled release dosage forms other than single-unit dosage forms.
- High flexibility in designing oral dosage forms
- They can be divided into different strengths without formulation or process changes
- They can be blended to deliver incompatible bioactive agents simultaneously and provide different release profiles at the same or different sites in the GI tract.
- Pellets taken orally can disperse freely in the GI tract, maximize drug absorption, minimize local irritation of mucosa by certain irritant drugs
- Reduced inter and intra-patient variability.

1.5.2. Pelletization Techniques[18,19]:

The most commonly used and intensively investigated pelletization processes are powder layering, solution/suspension layering, and extrusion-spheronization.

a. Powder Layering:

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the binding liquid and dry powder, it generally requires specialized equipment. The primary equipment-related requirement in a powder-layering process is that the product container should have solid walls with no perforations to avoid powder loss beneath the product chamber before the powder is picked up by the wet mass of pellets that is being layered on.

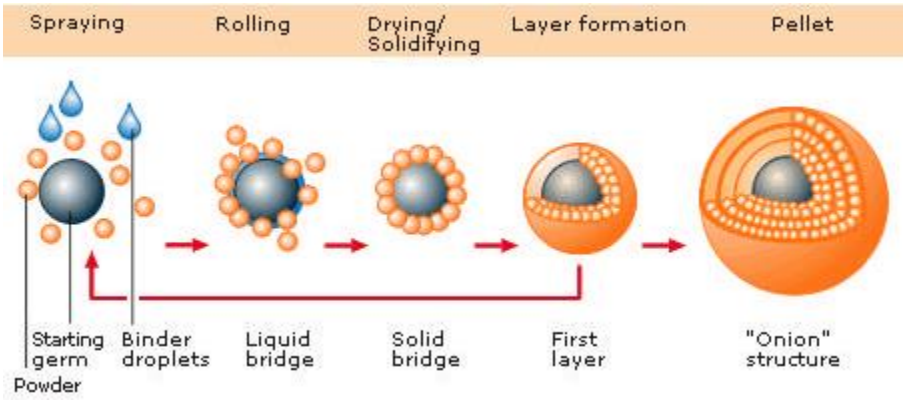

Fig:1.3. Scheme of steps involved in pelletization by Layering.

b. Solution Layering:

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which

may be inert materials or crystals/granules of the same drug. In principle, the factors that control coating processes apply to solution or suspension layering and, as a result, require basically the same processing equipment. Consequently, conventional coating pans, fluid-bed centrifugal granulators, and Wurster coaters have been used successfully to manufacture pellets. The efficiency of the process and the quality of pellets produced are in part related to the type of equipment used.

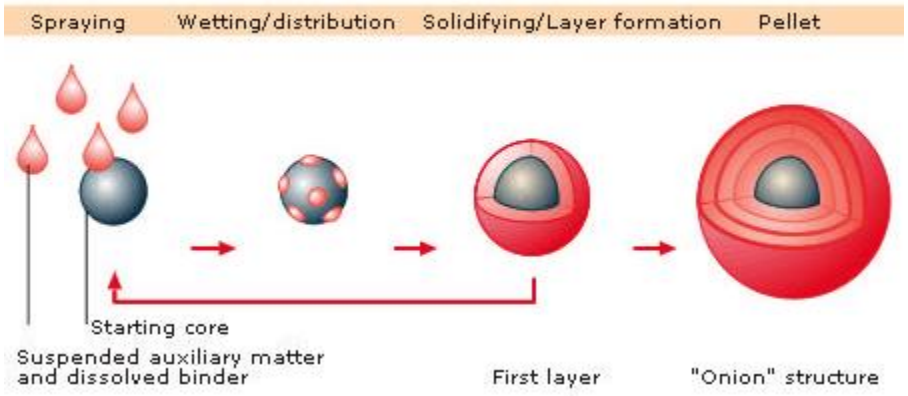

Fig:1.4 Scheme of stages involved in pelletization by suspension or solution Layering

i. Conventional Coating Pan:

In this technique the granules are placed in the coating pan and the coating solution is sprayed on the granules by atomizer with pressure.

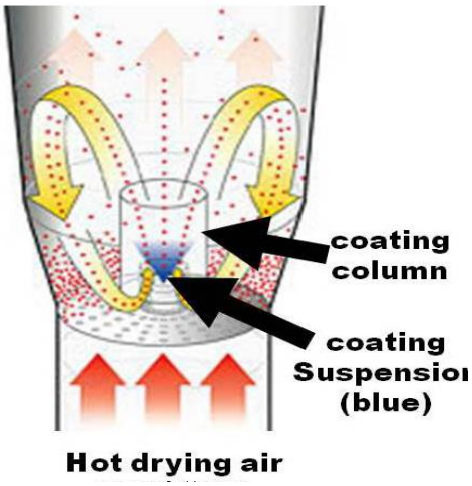

Fig:1.5 Fluidized Bed processing.

ii. Fluidized Bed Processing:

1. Beads are pushed through the coating column by hot air.
2. While moving through the coating column, beads are sprayed with coating suspension.
3. As beads circulate through the bed, the coating suspension dries and leaves a layer of solids on the bead.

c. Extrusion-Spheronization:

It is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening. The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that, can be easily extruded. The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and are pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally,

owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved**.**

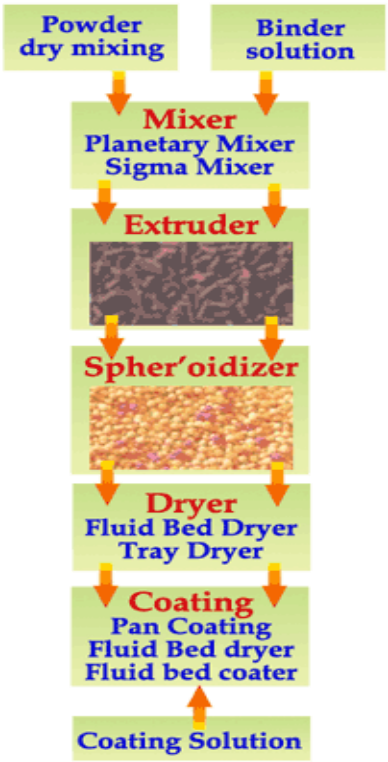

Fig:1.6 Scheme of pelletization stages in Extrusion and Spheronization.

d. Other Pelletization methods

Other pelletization methods such as globulation, agitation and compaction (compression) are also used, although in a limited scale, in the preparation of pharmaceutical pellets.

Globulation, or droplet formation, consists of two related processes, spray drying and spray congealing.

Spray drying is the process in which drugs in the suspension or solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs.

Spray congealing is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate- and controlled-release pellets can be prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables.

Compression is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing.

Balling is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid.

Capsules[12]

Capsules are solid dosage forms in which the drug or a mixture of drugs is enclosed in hard or soft gelatin capsules. These shells made up of gelatin and this can be intended for oral administration. These are available in various sizes, shapes and capacity.

Types of capsules

1. Hard gelatin capsules
2. Soft gelatin capsules

1. Hard gelatin capsules

These sizes are designed by in numbers.

Table:1.1 Capsule sizes and their fill weights

S.No	Size of capsules	Volume in ml	Fill weight in mg
1	000	1.37	615-1370
2	00	0.95	430-950
3	0	0.68	305-680
4	1	0.50	225-500
5	2	0.37	165-370
6	3	0.30	135-300
7	4	0.21	95-210
8	5	0.13	60-130

2. Soft gelatin capsules:

These are classified depending upon the sizes and capacities.

The number represents capacities in minims

1) Round-1,2,3,4,,5,6,7,8,9,28,40,40T,80T and 90T.

2) Oval-1,2,3,4,,5,6, 7..5,10,12,16,20,40,60,80,85 and 110.

3) Oblong-3,4,5,6,8,9.5,11,14,16,20,90 and 360.

4) Tube-5,6,8,17.5,30A,30B,35,45,55,65,90,160,250,320 and 480.

5) Misc-6, 17, 30, 35, 60 and 80.

Capsules Standards and limits:

Description:

It should comply with specifications of product.

Content of active ingredients:

Limit: 90 to110% of label claim or as per in house limit.

Uniformity of weight[4]

Table:1.2. Content uniformity limits(USP)

Average weight of capsules content	**Percentage deviations allowed**
less than 130mg	10%
130 to 320mg	7.5%
320mg or more	5.0%

Disintegration test:

a. Hard gelatin capsules:

Disintegration time shall not be more than 30 min.

b. Soft gelatin capsules:

Disintegration time shall not be more than 60 min.

c. Enteric capsule:

Acidic media –shall not disintegrate in 2hrs and in alkaline medium capsules shall disintegrate within 30 min.

Standard length for hard gelatin capsules in mm

Table:1.3. Capsules lock length in mm.

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Size	Cap	Body
0	10.68-11.68	18.22-19.22
1	9.51-10.51	16.22-17.22
2	8.67-9.67	14.84-15.84
3	7.73-8.73	12.98-13.98
4	6.97-7.97	11.84-12.84

Microbial limits:

Total microbial count, not more than 1000grams of the capsules shell. Atleast One gram of capsules shell be free from E.coli and Salmonella.

Loss on drying:

Between 12.5% and 16% detrained on 0.3 gram of shell by drying in oven at 105^0C for 4 hrs or to constant weight.

Reason for selecting capsules:

The Galantamine in tablet form of three times dose per a day the prior art may cause problems in patients with swallowing difficulty for adults and childrens.

This drawback is avoided with the use of multiparticulate formulations, since they may be dispersed in liquids at the movement of the administration.

It should be kept in mind that pharmaceutical compositions formulated in tablets are subject to variations in their physicochemical properties such as hardness, disintegration time, and dissolution time and also on dissolution rate due to the compression process involved in their production. Such variations are of course undesirable in extended release Galantamine capsules, since the prediction of the dissolution rate is an extremely important factor for the efficiency of the formulation.

Finally Extended release multiparticulate formulations of Galantamine of the invention advantageously provide a better drug release at the gastrointestinal tract compared with single tablets formulations and the dosing frequency will be reduced. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency.

II.LITERATURE REVIEW

- **Timo Erkinjuntti, et al [28](2002)** Proved robust evidence for the effectiveness of cholinergic treatments such as galantamine (Reminyl IR) in AD suggests its potential use in the treatment of dementias related to preclinical evidence supports this rationale. Galantamine, which has a unique dual cholinergic mode of action, may be of particular benefit in Vascular Dementia and AD with Cognitive Vascular Dementia.

- **Patrick Vigneault, Sarah Bourgault, et al [29](2012)** Galantamine is a reversible inhibitor of acetylcholinesterase and an allosteric-potentiating ligand of the nicotinic acetylcholine receptors. It is used for treating mild-to-moderate Alzheimer's disease. Interestingly, QT interval prolongation on the electrocardiogram (ECG), malignant ventricular arrhythmias and syncope have been reported with Galantamine.

- **Alexis Kays Leonard, et al [30](2005)** studied and developed an intranasal (IN) formulation of the acetyl cholinesterase inhibitor galantamine, Various approaches were examined to this end, including adding co-solvents, cyclodextrins, and counterion exchange. Of these, replacement of bromide ion with lactate or gluconate, resulted in a dramatic drug solubility increase, more than 12-fold. NMR confirmed the molecular structure of new drug salt forms. The *in vivo* studies confirmed that IN galantamine achieves systemic blood levels comparable to those of conventional oral administration.

- **Khatavkar UN, et al [31](2011)** Developed and evaluated in vivo of novel monolithic matrix mini tablets approach to control the release of Galantamine Hydrobromide (GAH) in comparison with desired release profile to the Innovator formulation Razadyne(®) ER capsules. The direct compression method was employed for preparation of matrix mini tablets as against reservoir multiparticulate pellets of innovator formulation. It was found that increase in the concentration of high viscosity hydroxypropylcellulose (HPC) results reduction in release rate. In vivo prediction was done by Wagner-Nelson method. Prediction errors were estimated for C(max) and area under curve (AUC) and found to be not exceeding 15%. These results suggest that novel monolithic matrix approach could be suitable technique to formulate controlled release GAH.

- **Patent number-7955622 [32]:** Controlled Release galantamine formulations, including controlled release particles, pellets, granules, and spheres are prepared by using sugar pellets as core, HPMC as Binder cum retardant and Ethyl Cellulose as Sustain Polymer.

- **Ben Seltzer, et al [33](2010)** An extended release form of the cholinesterase inhibitor (ChEI) drug galantamine (galantamine-ER) was developed, chiefly to increase adherence to medication regimes in patients with mild-to-moderate Alzheimer's disease (AD). Except for predicted differences in ($_{Cmax}$) and $_{tmax}$, comparable doses of once daily galantamine-ER and regular, immediate release galantamine, (galantamine-IR), are pharmacologically equivalent. A 24-week randomized, double-blind, placebo-and active-

controlled, multicenter phase III trial, which compared galantamine-IR, galantamine-ER and placebo in subjects with mild to moderate score range, Since its release onto the market galantamine-ER has enjoyed wide popularity and a recent surveillance study suggests that it has the highest 1-year persistence rate of all the ChEIs.

- **Olin J, Schneider L, et al** [34]**(2001)** was isolated from several plants, including daffodil bulbs, but is now synthesized. Galantamine is a specific, competitive, and reversible acetylcholinesterase inhibitor., which were similar to those seen in earlier antidementia AD trials, and consisted primarily of mildly to moderately impaired outpatients. In this magnitude for the cognitive effect is similar to other cholinesterase inhibitors including donepezil, rivastigmine, and tacrine.
- **Guk-Hee Suh, et al** [35]**(2004)** Studied in the Korean population rapidly aging and the nurnber of Koreans with Alzheimer's disease (AD) steadily growing, treatment of AD is becoming an increasing concern. Galantamine hydrobromide, a dual acetylcholinesterase inhibitor and allosteric modulator of nicotinic receptors, is being studied in the treatment of the disease.
- **Hugo Geerts, et al** [36]**(2005)** suggest a role for cholinergic stimulation, especially the 7-nicotinic acetylcholine receptors (nAChR), amyloid mediated neurotoxicity. There is substantial evidence that these effects occur by upregulation of the protective protein bcl-2 and are mediated via 7-nicotinic acetylcholine receptors. suggesting a neuroprotective effect for galantamine mediated by 7-nicotinic receptors are worthy.

- **Patent No-0142193** [37]: substantially claims that galantamine formulations include Microcrystalline cellulose, lactose, starch colloidal silicon dioxide, crospovidone, Hydroxy propyl methyl cellulose, propylene glycol, talc and titanium dioxide.

III. AIM AND OBJECTIVE

The aim and objective of the present study was to develop extended release Galantamine capsules and these were compared with the Innovator product (Razadyne).

The purpose of the present work was aimed at the following objectives.

- The dosing frequency is also reduced by formulate into capsules.
- Even though in market Galantamine tablets and gels is available we can formulate pellets because of pellets are having good flow properties in intestine and less cost of production for formulation.
- The main aim of the present study was to extended release Galantamine capsules of 16 hours release for to reduce the dosing frequency when compared with the Immediate Release tablet for treating Alzheimer.
- To achieve this goal we have to formulate and evaluate the capsules. The formula will be finalized by comparing the in-vitro dissolution profile with that of the marketed product.

IV. PLAN OF WORK

- **Step: 1 Preformulation Study**
  - API Characterization
    - Physical Appearance
    - Solubility studies
    - Sieve Analysis
  - Drug-Excipient Compatibilty Studies
    - Physical Compatibility
    - FT-IR Spectrophotometry
  - Analytical Method Development
- **Step: 2 Selection Of Coating Technology**
- **Step: 3 Formulation Development**
- **Step: 4 Evaluation of Pellets**
  - Physical Description
  - Sieve Analysis
  - Bulk Density and Tap Density
  - Percentage Moisture Content

- **Step: 5 Evaluation of Capsules**
  - Weight Variation
  - Content Uniformity
  - Lock Length
  - Assay by HPLC
  - Dissolution by HPLC
- **Step: 6 Comparison of Dissolution profile of trial formulations with Innovator.**
- **Step: 7 To perform Stability Studies of Selected Formulation.**

V. DRUG PROFILE

Galantamine[25]:

Galantamine is a cholinesterase inhibitor that has been used to reverse the muscular effects of gallamine triethiodide and tubocurarine, and has been studied as a treatment for Alzheimer's disease and other central nervous system disorders.

Chemical IUPAC Name:

(4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydro bromide.

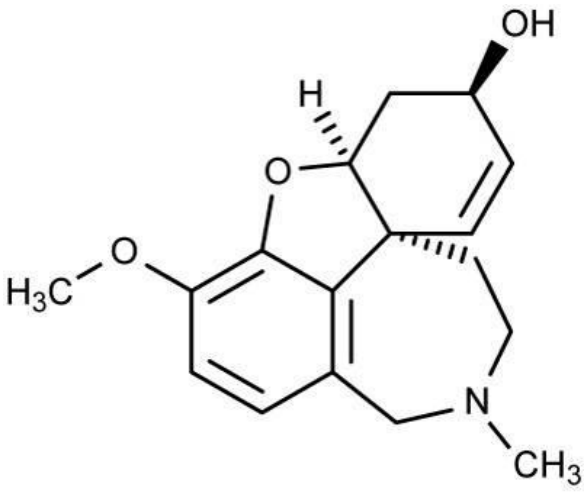


Fig: 5.1 Molecular Structure

Chemical Formula: $C_{17}H_{21}NO_3$

Molecular Weight: 287.15

State: White Crystalline Solid

Melting Point: 269-270^{0}C

Partition Coefficient: Log P =1.39

Dissociation Constant: Pka= 8.2

Purity: ≥98%.

BCS Class: II

Solubility:

Sparingly soluble in aqueous buffers and water, soluble in Sodium hydroxide

Chemical Class: Benzofurans derivative.

Therapeutic Class: Cholinesterase Inhibitor.

Storage:

Store the drug in a closed container at room temperature, away from heat, moisture, and direct light.

Stability: ≥2years at 25^{0}C

Indication:

For the treatment of mild to moderate dementia of the Alzheimer's type and also been investigated in patients with mild cognitive impairment, who did not meet the diagnostic criteria for Alzheimer's disease.

Pharmacology:

Galantamine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. An early pathophysiological feature of Alzheimer's disease that is associated with memory loss and cognitive deficits is a deficiency of acetylcholine as a result of selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus. Galantamine is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetyl cholinesterase.

Mechanism of action:

Galantamine's proposed mechanism of action involves the reversible inhibition of acetylcholinesterase, which prevents the hydrolysis of acetycholine, leading to an increased concentration of acetylcholine at cholinergic synapses. Galantamine also binds allosterically with nicotinic acetylcholine receptors and may possibly potentiate the action of agonists (such as acetylcholine) at these receptors.

Dosage:

Dosing differs accordingly with the dosage form, and also indication.

5.1. PHARMACOKINETICS:

5.1.1.Absorption:

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the capsule was the same as the bioavailability of an oral solution. Food did not affect the AUC of Galantamine but Cmax decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution of Galantamine is 175 L.

5.1.2. Distribution:

The plasma protein binding of Galantamine is 18% at therapeutically relevant concentrations. In whole blood, Galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of Galantamine is 1: 2.

5.1.3. Metabolism:

Galantamine is metabolized by hepatic Cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of Galantamine, and inhibitors of both pathways

increase oral bioavailability of Galantamine modestly O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged Galantamine and its glucuronide accounted for most of the sample radioactivity.

5.1.4. Excretion:

Galantamine Hydro bromide Extended Release capsules on oral administration, about 20% of the dose was excreted as unchanged Galantamine in the urine in 24 hours, representing a renal clearance of about 65 mL/min, about 20–25% of the total plasma clearance of about 300 ml/min.

Elimination half-life: 7 hours, allowing once daily administration in a clinical setting.

Special Populations:

Elderly

Data from clinical trials in patients with Alzheimer's disease indicate that Galantamine concentrations are 30–40% higher than in healthy young subjects.

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg

Galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUC increase of unchanged Galantamine compared to extensive metabolizers.

Hepatic Impairment:

Following a single 4 mg dose of Galantamine tablets, the pharmacokinetics of Galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5–6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7–9), Galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment.

Gender and Race:

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Galantamine Hydrobromide, but a population pharmacokinetic analysis indicates (n= 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n= 1029 White, 24 Black, 13 Asian and 23 others) did not affect the clearance of Galantamine Hydrobromide.

Renal Insufficiency:

Following a single 8 mg dose of Galantamine tablets, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers.

5.2. DRUG-DRUG INTERACTIONS

Use with Anticholinergics:

Galantamine Hydrobromide has the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors:

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine

Cimetidine and Ranitidine

Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either Cimetidine (800 mg daily) or Ranitidine (300 mg daily). Cimetidine increased the bioavailability of Galantamine by approximately 16%. Ranitidine had no effect on the PK of Galantamine.

5.3. INNOVATOR CHARACTERIZATION

Brand Name : Razadyne ER Capsules

Batch No OJG001

Mfg by: Ortho-Mcneil Neurologics, Belgium, Olen

Physical Characteristics

Capsule Size : 1

Capsule Colour : Caramel Colour Cap and body

Pellets Shape : Spherical

Pellets Colour : Shining White

Average Fill Weight : 294.37mg

% Moisture Content : 0.8

Assay : 101.7%

VI. MATERIALS AND METHODS

Table:6.1 Materials List

Ingredients	Manufacturer	Category
Galantamine	Aurobindo Pharma, Hyderabad	API
HPMC E5	Colourcon, Goa.	Retardant
PEG 6000	Clarient, Mumbai.	Solubilizer
Ethyl Cellulose	Shandong, China.	Extended Release Coating
Sugar Spheres	Prime Health Care Ltd, Chennai.	Core pellets
Isopropyl Alcohol	Rankem, Faridabad.	Solvent
Water	Rachem, Hyderabad.	Solvent

6.1.1. EXCIPIENT PROFILE [20]

Table:6.2 HYPROMELLOSE

Synonyms	Benecel, HPMC, Methocel, Hydroxy propyl methyl cellulose
Description	White or creamy white fibrous or granular, odourless, tasteless powder
Functional Categories	Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent viscosity builder
Solubility	Soluble in cold water, forming a viscous colloidal solution, practically insoluble in mixtures of ethanol and dichloromethane, mixtures of alcohol and water
pH	5.5-8.0 for a 1%w/w aqueous solution
Bulk Density	0.341 g/cm^3
Tapped Density	0.557 g/cm^3
Melting Point	Browns at 190-200^oC Chars at 225-230^oC
Moisture Content	Absorbs moisture from the atmosphere
Stability and Storage Conditions	Stable between pH 3-11, should be stored in a well-closed container in a cool and dry place
Incompatibility	Incompatible with some oxidizing agents
Applications	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

Table:6.3 SUGAR SPHERES

Synonyms	Non-pareil; Non-pareil seeds; NPTAB; Nu-Core; Nu-Pareil PG; sugar seeds; Suglets
Description	Approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch
Functional Categories	Tablet and capsule diluent.
Solubility	solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.
Density	1.57–1.59 g/cm3 for Suglets less than 500 μm in size; 1.55–1.58 g/cm3 for Suglets more than 500 μm in size.
Storage	Sugar spheres are stable when stored in a well-closed container in a cool, dry place.
Applications	Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations

Table:6.4 POLY ETHYLENE GLYCOL-6000

Synonyms	Polyethylene glycol, Macrogol.
Chemical Name	***ά-*** Hydro-ω-Hydroxypoly-(oxy-1,2-ethanediyl)
Description	Their odor is faint and sweet. Grades of 6000 and above are available as fee-flowing milled powders
Functional Categories	USP-Suppository base, Solvent, tablet and/or capsule lubricant, ointment base and pharmaceutical aid.
Solubility	All grades are soluble in water and miscible in all proportions with other PEGs (after melting if necessary), aqueous solutions of higher molecular weight grades may form gels.
Melting point	PEG -6000: 55-63^{0}C PEG -1000: 37-40^{0}C PEG -1500:44-48^{0}C
Storage	Oxidation may occur if PEGs are exposed for long periods to temperatures exceeding 50^{0}C. Storage under nitrogen will reduce the possibility of oxidation.
Incompatibilities	With solid grades of, Phenobarbital forms water in soluble complex (by hydrogen bonding)
Applications	Gelling agent, Solubilizer, Tabelt binder and Tablet film coating.

Table:6.5 ETHYL CELLULOSE

Synonyms	Ethyl cellulose, Ethocel
Description	A tasteless free flowing white to light powder.
Functional Categories	Tablet binder, coating agent
Solubility	Insoluble in water, glycerin and propylene glycol but insoluble in varying degrees in certain organic solvents, depending upon the ethoxyl content.
Stability and storage condition	It is resistant to alkalis both dilute and concentrated and to salt solutions. It is more sensitive to acidic materials than are cellulose esters Ethylcellulose should be stored between 70C and 320C in a dry area away from all sources of heat. Store in a well closed container
Incompatibilities	Incompatable with paraffin wax and microcrystalline wax
Applications	Tablet binder, Tablet coating material, Thickening agent in creams and lotions or gel.

Table:6.6 ISO PROPYL ALCOHOL

Synonyms	Isopropanol, Alcohol Isopropylieum , petrohol, dimethylcarbinol, 2-propan-2-ol, Sec-propyl alcohol.
Description	Transparent, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone and a slightly bitter taste.
Functional Categories	Local disinfectant.
Melting point	$88.5^{0}C$
Stability and storage condition	Store in a tight container remote from heat and protected from light.
Incompatibilities	Oxidizing agents like hydrogen peroxide and nitric acid decompose isopropyl alcohlol. It may be slated out form aqueous mixtures by the addition of sodium salts etc.
Applications	Disinfectant Degreasing in Lotions Solvent for Film Coating Cosmetics Tablet Granulation

6.2. EQUIPMENTS USED

Table No:6.7 Equipments List

NAME	**MANUFACTURER**
Electronic Weighing Balance	Essae DS-852, Bangalore.
Fluidised Bed Processor	Pharmatech UFBM-3, Vasai.
Mechanical Stirrer	REMI Electrotechnik RQ1291D, Thane.
Capsule Filling Machine	Pam Pharmaceutical MFD112, Mumbai.
KF Titrator	Metrohm, 787 KF Titrino, India.
Tray Drier	Millenium Equipment METD-64, Hyderabad.
UV Apparatus(Double Beam)	Shimadzu UV2450, USA.
Dissolution Apparatus	Electrolab ED2AL, Mumbai.
HPLC Apparatus	Shimadzu LC-2010C, USA.
Electronic Sieve shaker	SWECO, Mumbai.
Automatic capsule filling machine	Rimek formulations, Mumbai.

6.3 EXPERIMENTAL WORK

6.3.1. PREFORMULATION STUDIES[10]:

a. API Characterization:

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, melting point, particle size and compatibility.

Physical Appearance:

The appearance of the API is done by visual observation

Solubility Studies:

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently the therapeutic efficacy of the pharmaceutical product. The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved.

Sieve Analysis:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve are stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom).

Procedure:

A series of sieves are arranged in the order of their decreasing pore diameter (increasing sieve number) such as sieve number 20, 30, 40, 60, 100 and 200. 100 grams of drug is weighed accurately and transferred to sieve number 20 which were kept on top. The sieves are shaken for about 5-10 minutes. Then the drug retained on each sieves is taken, weighed separately and amount retained is expressed in terms of percentage.

b. Drug - Excipient Compatibility Studies:

Compatability studies are carried out to study the possible interactions between Galantamine and other active ingredients

Procedure:

The compatibility studies are carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of mixture can be exposed to different storage conditions like $40^{o}C \pm 2^{o}C$ /75% RH ±5% and control samples were to be kept at $2\text{-}8^{o}C$. They are tested with respect to their physical and chemical aspects. These samples are collected at regular intervals and subjected to FT-IR.

Table:6.8 Conditions for compatibility studies[24]

S.No.	Storage Condition	Samples packed in	Sampling Periods in weeks
1	Accelerated 40 ^{o}C±2 ^{o}C /75% RH ±5%	3 Double polythene bags	1W,2W,3W,4W
2	Refrigeration 2-8^{o}C	1 Double polythene bag + 1 glass vessel	1W,2W,3W,4W,

FT-IR Spectrophotometric Method:

It is performed by Potassium bromide pellet method. Potassium bromide is dried in oven at 45°C before analysis. The pure drug is triturated with Potassium bromide and pellet is prepared by setting the pressure to 100 kg/cm^2 for 2 minutes. The obtained pellet is analyzed in Burker FTIR Tensor Model, Germany. Potassium bromide background was obtained initially before analysis of test samples. The same procedure is repeated for analysis of drug and Hydroxy Propyl Methyl Cellulose E5, Ethyl Cellulose$_{N45}$, also drug and excipient mixture free from moisture content are used for analysis.

6.3.2. Analytical Method Development:

a. Determination of absorption maxima (λ_{max}) for Galantamine

Standard stock solution containing 100 µg/ml of Galantamine Hydrobromide was prepared in Distilled water. From the stock, different aliquots were taken and diluted to 10 ml mark with same solvent to obtain series of concentrations. The solutions were scanned on Spectrophotometer in the UV range 200-400 nm. Galantamine Hydrobromide showed absorbance maxima at 289 nm.

b. Preparation of standard curve for Galantamine Hydrobromide .

100 mg of Galantamine Hydrobromide was dissolved in 100 ml calibrated volumetric flask and completing to volume with P^H 6.5 phosphate Buffer. From this 10ml pipette out in 100 ml calibrated volumetric flask and dilution was made with P^H 6.5phosphate Buffer. From this solution 2 ml, 4ml, 6ml, 8ml…up to 10ml was pipette out in different 10 ml volumetric flask and this was finally diluted with P^H 6.5phosphate Buffer to 10ml. The absorbance was noted λ_{max} of 289nm.

6.3.3. METHOD OF MANUFACTURING

a. Fluidised Bed Processing:

Raw Material Dispensing:

Accurately weighed quantities of raw materials, measured quantities of solvents are dispensed.

Coating Solution Preparation:

HPMC E5 is dissolved in specific quantity of Water Add all other ingredients along with drug are added to it, which are stirred under mechanical stirrer at 1600-1900RPM.The above two solutions are mixed by stirring.

Filtration:

The solution is filterd through #150 mesh, to remove any lumps or visible particles.

Drug Loading:

Accurately weighed sugar spheres (cores) are transferred into Fluid Bed Processor (FBP). These cores are coated with drug solution uniformly.

Sieving:

Finally these dried pellets are sieve to obtain pellets of uniformity with required size.

Barrier Coating:

HPMC E5 is dissolved in specific quantity of Water. PEG-6000 are added to it, which are stirred under mechanical stirrer at 1600-1900RPM.Transfer the Drug loaded pellets to FBP for Barrier coating.

Extended Release Coating:

Ethyl Cellulose N_{45} is dissolved in specific quantity of Iso Propyl Alcohol, PEG-6000 are added to Water, which are stirred under mechanical stirrer at 1600-

1900RPM. The above two solutions are mixed by stirring. Transfer the barrier Coated pellets to FBP for ER coating.

Sieving and Drying:

Finally these dried pellets are sieved to obtain pellets of uniformity with required size and dried.

Capsule Filling:

The weight of pellets equivalent to 24mg Galantamine are filled into hard gelatin capsules of size.1 by capsule filling machine.

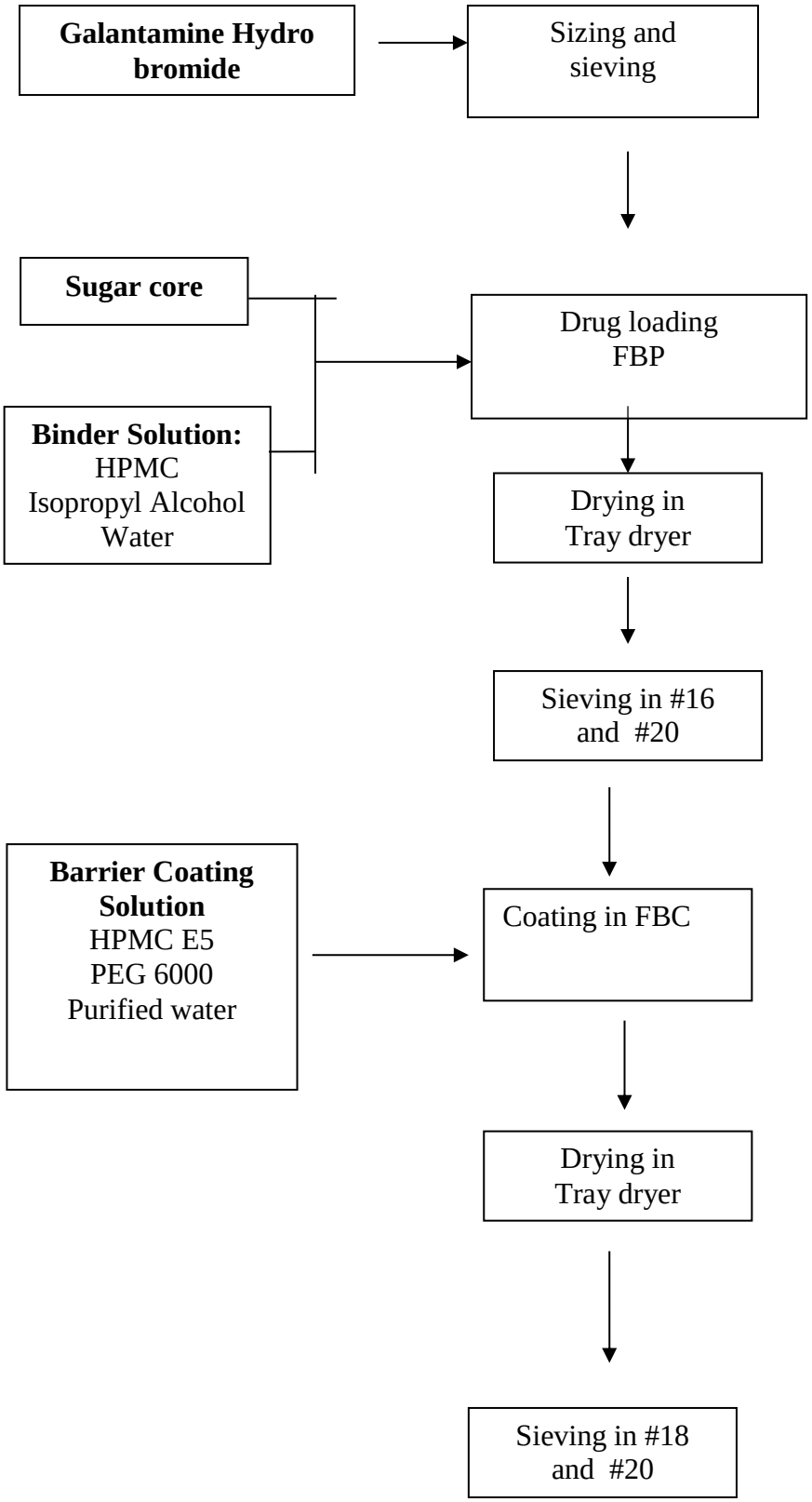
Process Control Parameters:

Spray Gun	**:**	Needle
Spray Type	**:**	Bottom spray
Spray Rate	**:**	5ml/min
Spray Pump RPM	**:**	2-6 rpm
Inlet Temperture	**:**	39 °C
Bed Temperature	**:**	37 °C
Outlet Temperture	**:**	31-33 °C
Air Presssure	**:**	1Kg/cm^2

6.3.4. Formulation Development

Galantamine Hydrobromide extended release capsules were prepared. The process was displayed in the following flow chart.

MANUFACTURING PROCESS FLOW CHART



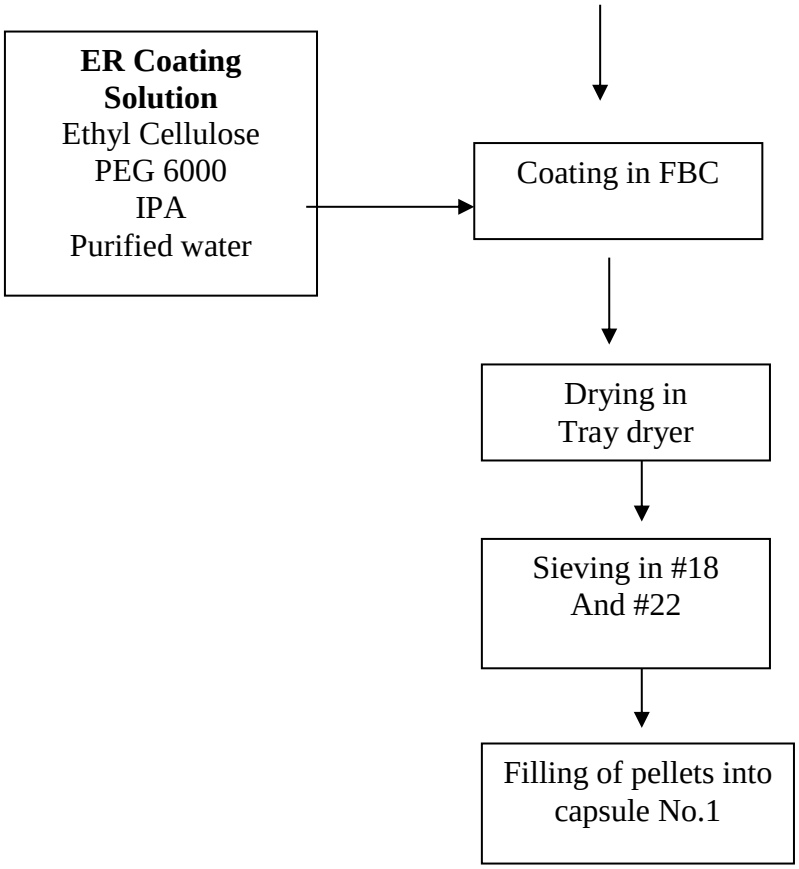


Fig:6.1. Manufacturing flow chart for extended release capsules

FORMULATION TRAILS

Formulation studies Galantamine Hydrobromide extended release capsules are based on pre formulation data of various excipients were selected and their compilation was shown in the following Table.6.9.

Table No. 6.9 Formulae and their quantities as per w/w: 350grams Batch

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Galantamine Hydrobromide	35.87	35.87	35.87	35.87	35.87	35.87	35.87	35.87	**35.87**
2	Sugar Pellets(18≠22)	273.2	273.2	273.2	273.2	273.2	273.2	273.2	273.2	**273.2**
3	HPMC E_5	8	9	10	11	12	16	15	14.5	**14**
4	I.P.A	239	239	239	239	239	239	239	239	**239**
4	Water	239	239	239	239	239	239	239	239	**239**
Barrier Coating										
5	HPMC E_5	15	12	14	10	14	14	14	14	**14**
6	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
7	Purified Water	260	260	260	260	260	260	260	260	**260**
ER coating										
10	Ethyl cellulose	17.5	16.5	15.5	8	8	12	9.5	10	**10.5**
11	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
12	I.P.A	197.4	197.4	197.4	197.4	197.4	197.4	197.4	197.4	**197.4**
13	Purified Water	296	296	296	296	296	296	296	296	**296**

Pellets were evaluated by physical and chemical parameters. Characteristics like Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose, sieve analysis and assay carried out for core pellets, coated pellets. The results were presented in the form of Table.7.16 in results.

Loading of Galantamine Hydrobromide Pellets in Capsules

To prepare Galantamine capsules 24mg by taking Galantamine Hydrobromide pellets 24 mg from the formulation F9 is taken and filled.

Procedure

1. Before filling pellets into capsules the parameters like Bulk density, Tappered density, Angle of repose, are evaluated.

2. Size'1' capsules were selected for capsule formulation which has Purple color capsule shell.

3. The pellets were loaded in hard gelatin capsules No.1 with Automatic capsule filling machine.

4. Coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 24 mg Galantamine Hydrobromide.

Stability Study[24]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

Storage conditions[24]

Stability samples are stored at

Accelerated : 40±2°C/75±5% RH

Intermediate: 30±2°C/65±5% RH

Long term : 25±2°C/60±5% RH

Testing Intervals for

Accelerated: Initial, 1, 2, 3 and 6 months

Long term: Initial, 3, 6, 9, 12, 18, 24 and 36 months.

Intermediate: Initial, 3, 6, 9 and 12 months**.**

The formula of F9 was optimized and selected for evaluation studies. Further stability study was done for F9.

In general significant change for a drug product is defined as

- A 5% change in assay from its initial value or failure to meet the acceptance criteria for when using biological or immunological procedures.
- Any degradation products exceeding its acceptance criterion.
- Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. e.g. size, shape and dose delivery per activation however some changes in physical attributes may be accepted under accelerated condition and as appropriate for the dosage form.
- Failure to meet the acceptance criterion for pH.
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.

Studies like moisture content, assay, dissolution studies were carried out for a period of 2 months. Initial stage, at the end of first month and second month, the above said parameters were carried out at 25^{O}C/60%RH, 30^{O}C/65% RH and 40^{O}C/75%RH.

6.3.5. EVALUATION OF CAPSULES

Weight variation test[26]

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 5 %.

Lock Length[26]

It was tested by using Vernier calipers.

Disintegration

The compendial disintegration test for hard and soft capsules follows the same procedure and uses the same apparatus. The capsules are placed in the basket rack assembly, 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 capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

Dissolution[26]

Procedure

For capsules place 500ml of dissolution medium in each vessel and allow the medium to equilibrate to a temperature of 37 ± 0.5 ºC. Place one capsule in each of the Paddle and operate the apparatus at 50 rpm for specific time. With draw 10ml of the solution from each vessel and replace with equal volume of fresh dissolution

medium at specific time intervals. Filter the solution through 0.45microns membrane filter and discard first few ml of the filtrate. Dissolution study was carried out in pH 6.5 buffer for 0^{st}, 2^{th}, 6^{th}, 12^{th} and 16^{th} hours and assay was done by HPLC method.

Table: 6.10. **Dissolution Parameters**

Apparatus	USP Type-II (Paddle)
Volume	500 ml
RPM	50
Medium	pH 6.5 phosphate Buffer at 37ºC
Drug release time	0^{th} Hour
	2^{th} Hour
	6^{th} Hour
	12^{th} Hour
	16^{th} Hour

Assay by HPLC [27]

Mobile Phase Reagents:

Solution A: Methanol and buffer Solution (1:19) AR Grade

Solution B: Acetonitrile and methanol(19:1) HPLC grade

Preparation of P^H 6.8 Phosphate buffer:

5.34g/L of dibasic sodium phosphate dehydrate in water. Adjust with phosphoric acid to a pH of 6.5

Preparation of Mobile Phase:

Filtered and degassed mixture of buffer and acetonitrile in the ratio of 30:70 v/v is prepared.

Preparation of Blank Solution:

Accurately weighed quantity of about 33mg of placebo powder is transferred into 100ml volumetric flask, 60ml diluents is added, sonicated for 15minutes and made upto the mark with diluent. 5.0ml of the resulting solution is transferred into a 50ml volumetric flask and made up to the mark with diluent. The solution is filterd through 0.45µm Nylon filter.

Preparation of Standard Solution:

Accurately weighed quantity of about 24mg of Galantamine Hydrobromide working standard is transferred into 100ml volumetric flask, 60ml diluents is added, sonicated for 15minutes and made up to the mark with diluent. 5.0ml of the resulting solution is transferred into a 50ml volumetric flask and made up to the mark with diluents. The solution is filtered through 0.45µm Nylon filter.

Preparation of Sample Solution:

Accurately weighed quantity of powdered pellets equivalent to 24mg of Galantamine Hydrobromide is transferred into 100ml volumetric flask, 60ml diluents is added, sonicated for 15minutes and made upto the mark with diluent. 5.0ml of the resulting solution is transferred into a 50ml volumetric flask and made upto the mark with diluent. The solution is filterd through 0.45µm nylon filter.

Chromatographic Conditions:

Column **:** Hypersil BDS C18, 4.6mm×10cm; 3-µm L1 packing

Flow Rate **:** 1.5 ml/min

Wave Length **:** 230 nm

Column Temperature **:** 35°C

Injection Volume **:** 20µl

Run Time **:** 6minutes.

System Suitability:

The peak responses are recorded for standard solution. The relative standard deviation for five replicate standard solution injections should not be more than 2%. The tailing factor for Galantamine Hydrobromide peak should not be more than 2.0. Theoretical plates for Galantamine Hydrobromide peak should not be less than 2000.

Procedure:

20µl, five replicate injections of standard solution and two injections of sample solution are injected. The chromatograms are recorded and the peak response is measured. The assay is calculated by using following formula.

$$\%\text{Drug Content} = \frac{Ru}{Rs} \times \frac{W_S}{100} \times \frac{5}{50} \times \frac{100}{W_T} \times \frac{P}{5} \times \frac{100}{100} \times \text{Label claim}$$

Where,

Ru = Peak area of Galantamine Hydrobromide in sample solution

Rs = Average peak area of Galantamine Hydrobromide in standard solution

W_S = Amount of Galantamine Hydrobromide taken in working standard (mg)

W_T = Amount of sample (mg)

P = Potency of Galantamine Hydrobromide working standard used.

Moisture permeation test

The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules.

The degree and rate of moisture penetration is determined by packing the dosage unit together with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating desiccating absorption of moisture) and comparing the pre and post weight of the packaged unit and also by the Karl Fisher Titration Equipme

VII. RESULTS AND DISCUSSIONS

In the present study Nine formulations with variable coating polymers are used and the capsules are prepared and evaluated for physico-chemical, invitro dissolution studies. The formulated batches trails were shown in Table 6.9.

7.1. Preformulation Studies

Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The Bulk density and Tapped density was found to be 0.248 g/ml and 0.328 g/ml respectively.

A simple indication of ease with which a material can be induced to flow is given by application of a compressibility index. The value for Compressibility index of Galantamine Hydrobromide was found to be 24.39% that reflect the poor flow property of Galantamine Hydrobromide , which was supported by the Hausner ratio of 1.322.

The physical characterization of the Polymer was done by evaluating them for the physical characteristics such as Bulk density, Tapped density, Compressibility index, and Hausner's ratio and Angle of repose.

a) Melting Point Determination:

Melting point of Galantamine Hydrobromide was found to be in the range 269-270^{o}c, which complied with Pharma Euro standards, indicating purity of the drug sample.

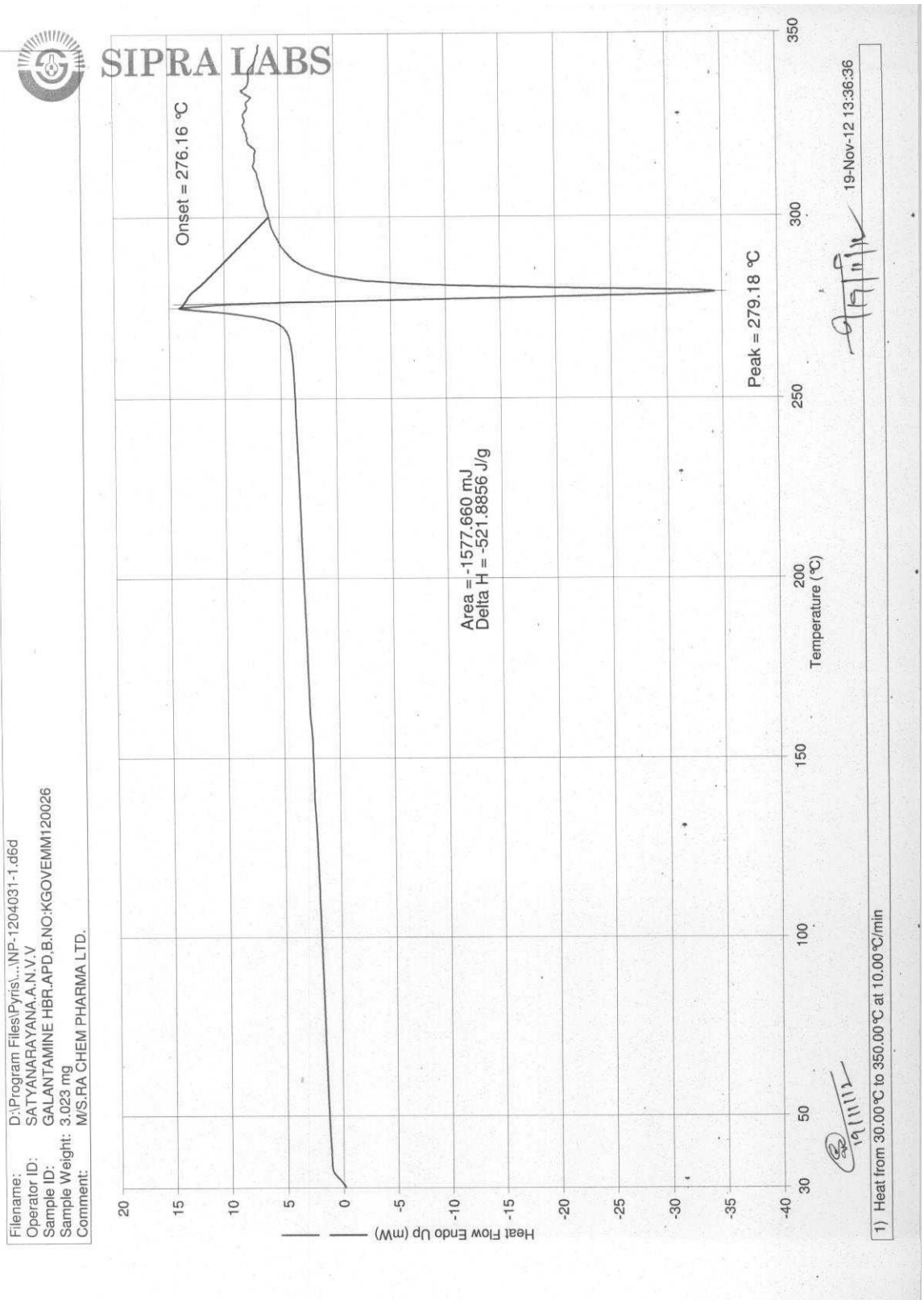


Fig:7.1. DSC Of Galantamine Hydrobromide

b) Solubility:

Galantamine Hydrobromide was found to be slightly soluble in water, freely soluble in Sodium hydroxide Solution, Insoluble in Ether, Alcohol and Methylene chloride.

c) Compatibility Study:

Compatibility studies were performed using FT-IR spectrophotometer. The FT-IR spectrum of pure drug and physical mixture of drug and polymer were studied.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. The Spectra for formulation is shown in below.

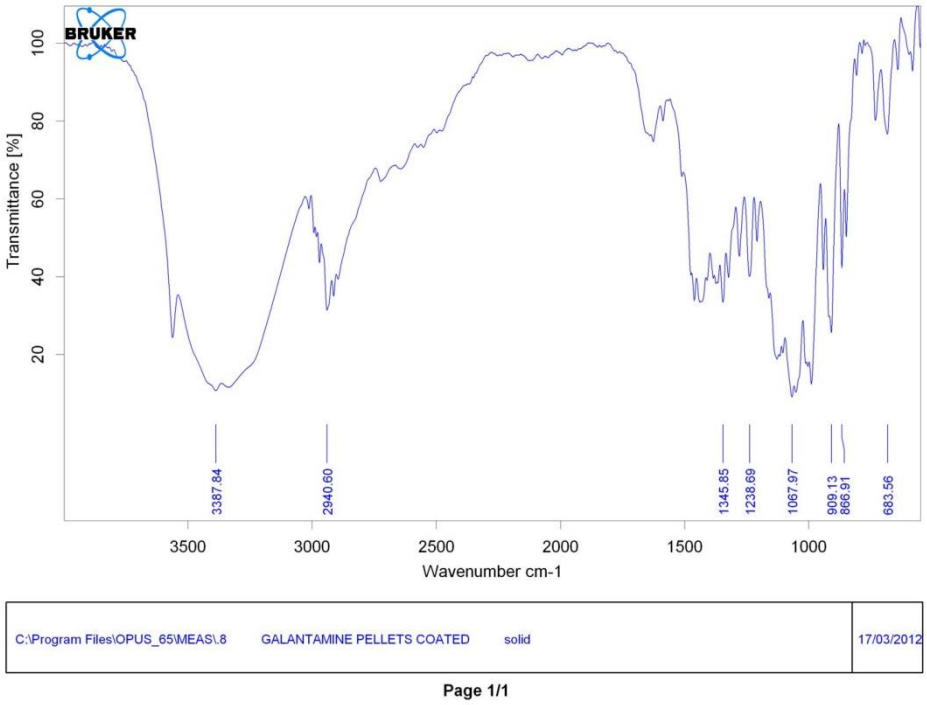


Fig:7.2. FT-IR Spectrum of Optimized Product(F9).

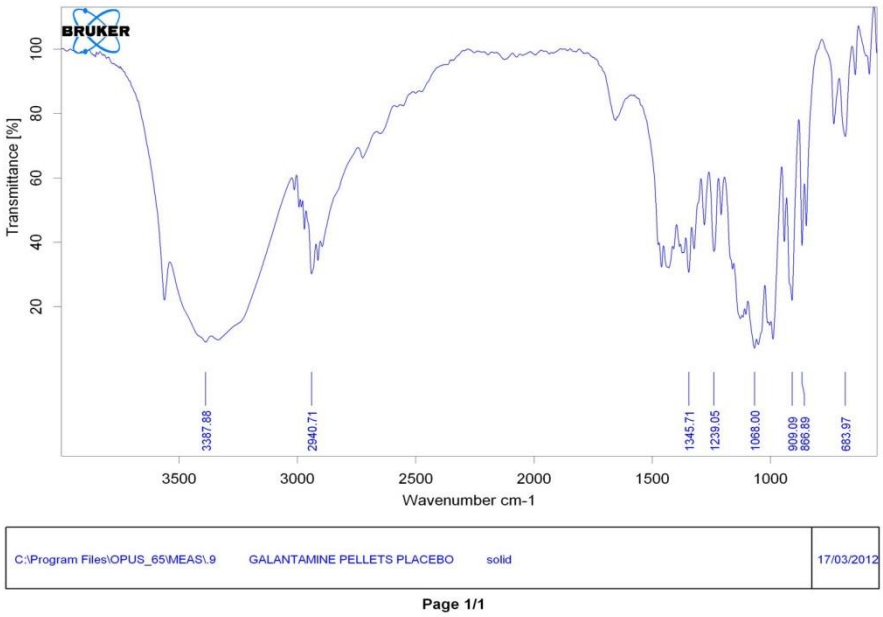


Fig:7.3. FT-IR Spectrum of Placebo Pellets

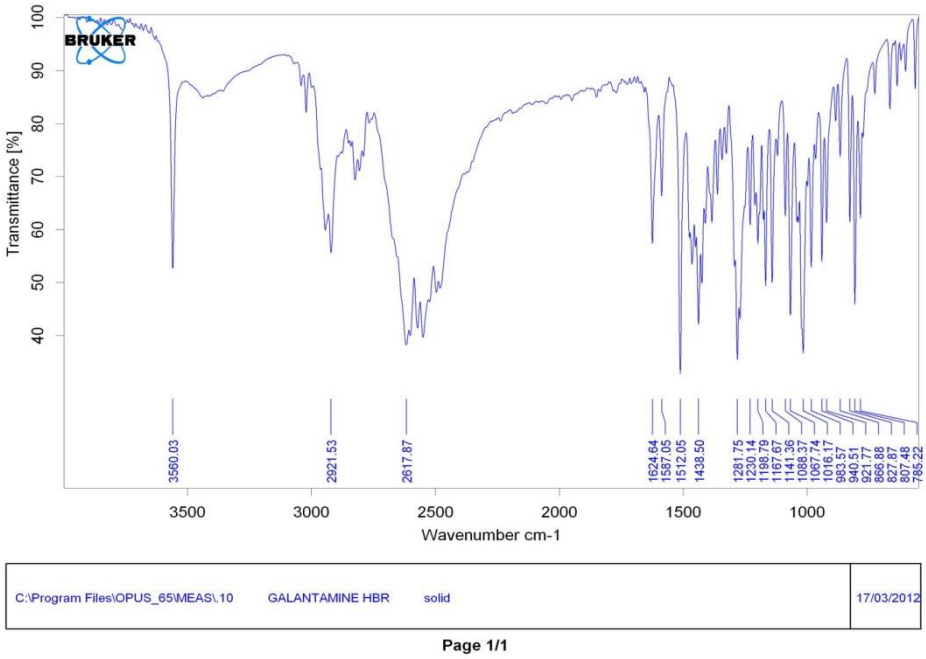


Fig:7.4. FT-R Spectrum of Pure Drug

d) Physical properties:

Physical properties of Galantamine Hydrobromide and polymers like Bulk density, Tapped density, Compressibility index and Hausner's ratio and Angle of repose result is shown below table.

Table:7.1. Physical properties of Galantamine hydrobromide

Bulk density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index	Hausner's Ratio	Angle of repose
0.248	0.328	24.39 %	1.322	26.04^0

e) Sieve analysis:

Table:7.2. Sieve analysis values of Galantamine Hydrobromide drug

Sieve No	Empty sieve(gm)	Sample sieve(gm)	Difference (gm)	%Retained	%Cumulative Retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2

#60	287.2	297.4	10.2	10.2	11.4
#80	245.0	268.2	23.2	23.2	34.6
#100	274.0	299.0	25.0	25.0	59.6
#200	270.0	310.0	40.0	40.0	99.6
Receiver	348.8	349.0	0.2	0.2	99.8

Weight of sample=100gm

Through this sieve analysis we came to know that as large quantity of powder was retained on sieve No. 200, which indicates poor flow of the drug. Flow property and particle size are inversely proportional to each other as Galantamine Hydrobromide has fine grade of particles, it has poor flow. Hence the Galantamine Hydrobromide has poor flow property.

7.2. Preparation of standard curve of Galantamine Hydrobromide

Preparation of P^H 6.5 phosphate Buffer

5.34g/l of Dibasic Sodium Phosphate Dihydrate in water. Adjust with phosphoric acid to 6.5P^H

Standard Curve of Galantamine Hydrobromide in P^H 6.5 phosphate Buffer

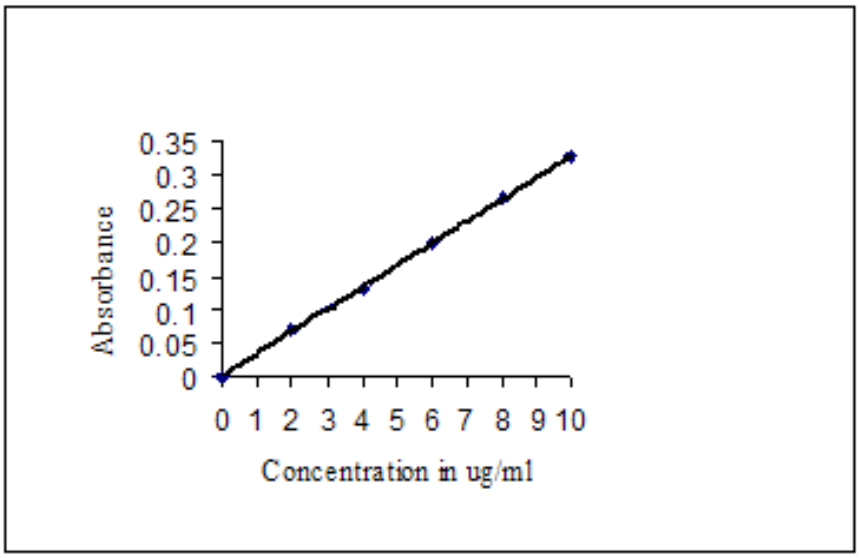
100 mg of Galantamine Hydrobromide was dissolved in 100 ml calibrated volumetric flask and completing to volume with P^H 6.5 phosphate Buffer. From this 10ml pipette out in 100 ml calibrated volumetric flask and dilution was

made with P^H 6.5phosphate Buffer. From this solution 2 ml, 4ml, 6ml, 8ml…up to 10ml was pipette out in different 10 ml volumetric flask and this was finally diluted with P^H 6.5phosphate Buffer to 10ml. The absorbance was noted λ_{max} of 289nm. The absorbance values are shown in Table 7.3.

Standard curve of Galantamine Hydrobromide was determined by plotting absorbance V/s concentration at 289 nm. and it follows the Beer's law. The results were show in table no. and the R^2 value is 0.9994 and slope is 0.0267.

Table:7.3. Standard curve values of Galantamine Hydrobromide

S.No	Concentration µg/ml	Absorbance at 289nm
0	0	0.00
1	2	0.06
2	4	0.132
3	6	0.212
4	8	0.268
5	10	0.327



Y=0.02673x+0.0007. $R^2 = 0.9994$

Fig:7.5. Standard Curve of Galantamine Hydrobromide

7.3. Determination of $\lambda_{max\ of}$ Galantamine Hydrobromide by UV spectrum

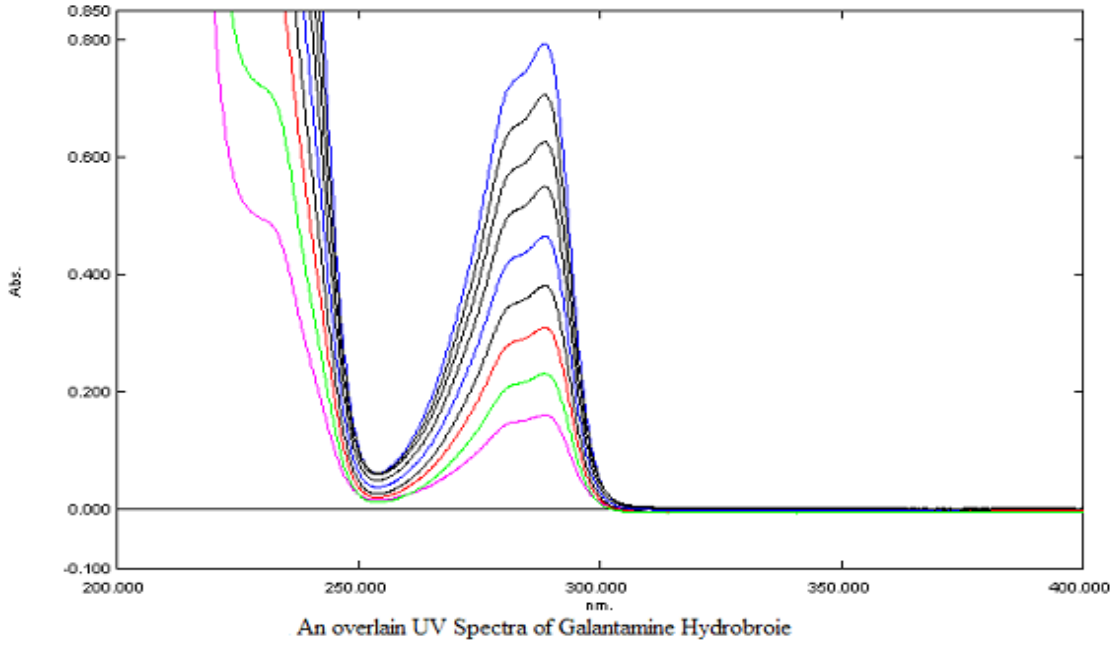


Fig:7.6. UV Spectrum of Galantamine Hydrobromide

The λ_{max} of Galantamine Hydrobromide is determined by UV spectrum the graph indicates that the maximum absorbance is observed at 289nm and it is the λ_{max} of Galantamine Hydrobromide.

Compatibility studies:

The compatibility studies were carried out at 25^0C/60% RH and 40^0C/75% RH for 0, 2 and 4 weeks. With respect to physical and chemical aspects, they were tested and there is no drug-excipients interactions are observed.

Table:7.4. Compatibility study of Drug and Excipients

S. No.	Drug and Excipients	Initial Physical Description	25°C / 60% RH and 40°C / 75% RH (Closed)		
			1st Week	2nd Week	4th Week
1	Galantamine HBr	White crystalline powder	*	*	*
2	Galantamine HBr + Sugar spheres	Off-white powder contain spherical pellets	*	*	*
3	Galantamine HBr + Ethyl cellulose N-45	Off-white powder	*	*	*
4	Galantamine HBr +	white powder contain	*	*	*

	Poly ethylene glycol 6000	crystalline material			
5	Galantamine HBr + HPMC E_5	Off-white powder	*	*	*
6	Galantamine HBr + Isopropyl alcohol	Off-white thick mass	*	*	*
7	Galantamine HBr + Purified Water	Off-white thick mass.	*	*	*
8	Galantamine HBr + Sugar spheres + Ethyl cellulose N-45 + HPMC + Polyethyleneglycol-6000+ Isopropylalcohol + Purified Water.	Off-white powder containing lumps	*	*	*

Note: Star mark (*) indicates that there is no interaction between drug and excipients at 25° C/60% RH, 40°C/75% RH.

Trial batches formulae and their quantities as per W/W:350grams Batch

Note: Drug is taken as overage to compensate the drug loss during drug layering process.

7.4. DISSOLUTION STUDIES

F-1 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.5. In-vitro dissolution profile of formulation F1

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	F1
0	0	0.00
2	38.35	60.49
6	67.72	87.88
12	81.35	93.24
16	90.09	98.65

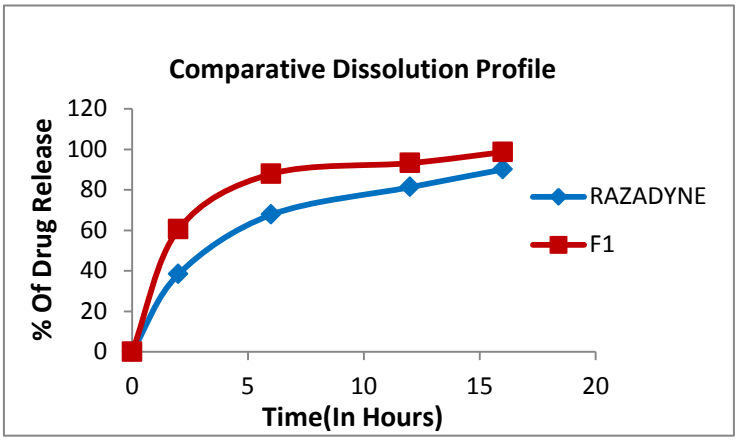


Fig:7.7. Comparative dissolution profile of formulation F1

Observation:

Based on the above results, the shape of the pellets is not uniform. During drug loading temperature was maintained below 22ºC. The pellets size and strength is good and release was more relatively.

Conclusion

The size and strength of the pellets are good and coating margin is around 17% is there for further development and to increase the HPMC ratio drug loading.

F-2 Dissolution Profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.6. Invitro dissolution profile of formulation F2

Time (Hrs)	**Percentage of Drug release**	
	Razadyne ER	**F2**
0	0	0.00
2	38.35	48.17
6	67.72	82.12
12	81.35	88.33
16	90.09	89.04

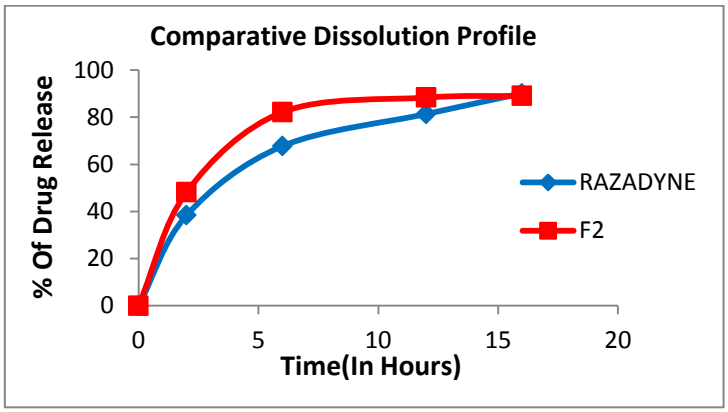


Fig:7.8. Comparative dissolution profile of formulation F2

Observation and Conclusion

Based on the above results, Concentration of the Ethyl cellulose N45 and HPMC to be increased to attain the desired drug release.

F-3 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.7. Invitro dissolution profile of formulation F3

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	F3
0	0	0
2	38.35	42.17
6	67.72	72.12
12	81.35	78.33
16	90.09	89.04

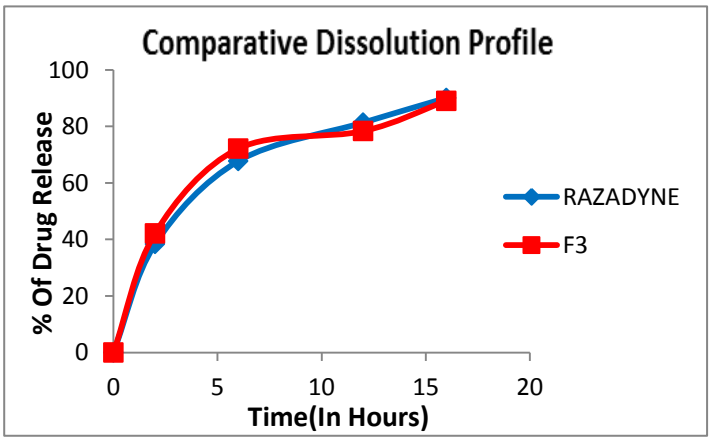


Fig:7.9. Comparative dissolution profile of formulation F3

Observation and Conclusion

Based on the above results, Concentration of the Ethyl cellulose N45 and HPMC to be reduced to attain desired drug release.

F-4 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.8. Invitro dissolution profile of formulation F4

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	F4
0	0	0
2	38.35	52.04
6	67.72	68.12
12	81.35	74.60
16	90.09	80.62

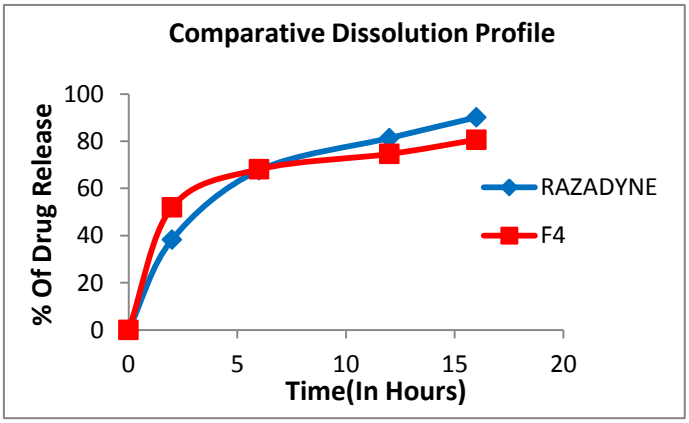


Fig:7.10. Comparative dissolution profile of formulation F4

Observation

Based on the above results, the When we decreased the concentration of ethyl cellulose N45 and reducing the concentration of HPMC the changes in release in final and first hour. (Razadyne ER).

Conclusion

To overcome this problem we have planned to coat only with Ethyl cellulose N45 with decreasing HPMC level to get the more release in the final hour.

F-5 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.9. Invitro dissolution profile of formulation F5

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	F4
0	0	0
2	38.35	61.01
6	67.72	101.01
12	81.35	100.68
16	90.09	100.10

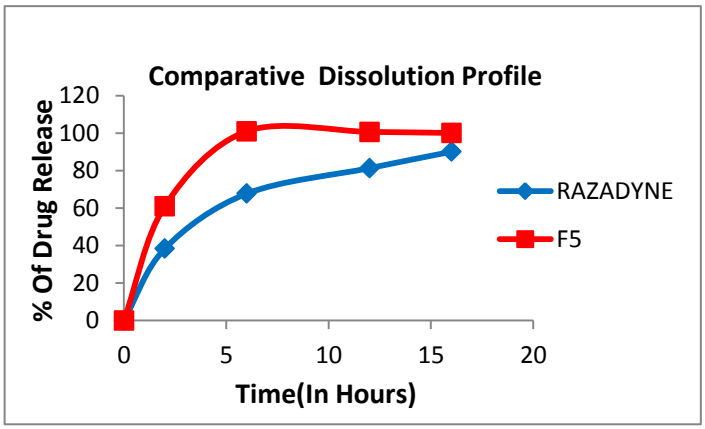


Fig :7.11. Comparative dissolution profile of formulation F5

Observation

Based on the above results, the concentration of Ethyl cellulose N45 to be increased to get the desired release.

Conclusion

To get the desired release we have to increase Ethyl cellulose N45 and the HPMC to be reduced to check the release changes in the starting point.

F-6 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.10. Invitro dissolution profile of formulation F6

Time (Hrs)	**Percentage of Drug release**	
	Razadyne ER	**F6**
0	0	0
2	38.35	28.61
6	67.72	57.86
12	81.35	74.58
16	90.09	81.77

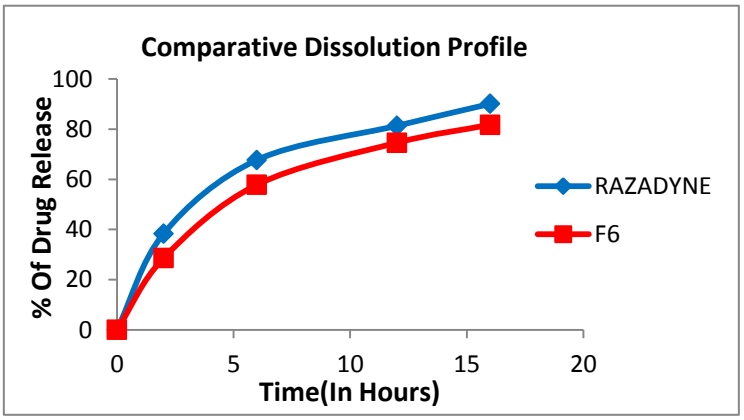


Fig:7.12. Comparative dissolution profile of formulation F6

Observation

Based on the above results, the starting release in lower limit so the concentration of the HPMC is high so that has to reduce which retarteds release.

Conclusion

Because the sustained release polymer what we are coating as a second layer will give some of the effect on the 6.5 pH Acid media, by using the HPMC polymers as a Inner layer we can overcome.

F-7 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.11. Invitro dissolution profile of formulation F7

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	**F7**
0	0	0
2	38.35	52.39
6	67.72	76.82
12	81.35	82.06
16	90.09	89.62

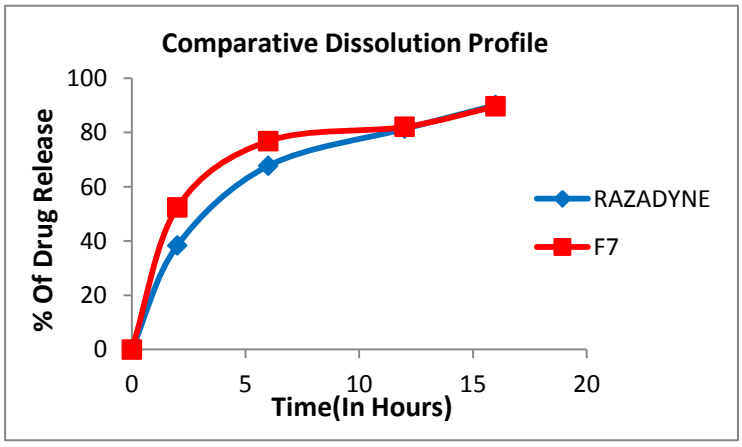


Fig:7.13. Comparative dissolution profile of formulation F7

Observation

Based on the above results, the ethyl cellulose N45 concentration to be increased.

Conclusion

To get the desired release we can increase the concentration of ethyl cellulose concentration.

F-8 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.12. Invitro dissolution profile of formulation F8

Time (Hrs)	**Percentage of Drug release**	
	Razadyne ER	**F8**
0	0	0
2	38.35	42.28
6	67.72	62.85
12	81.35	79.34
16	90.09	87.23

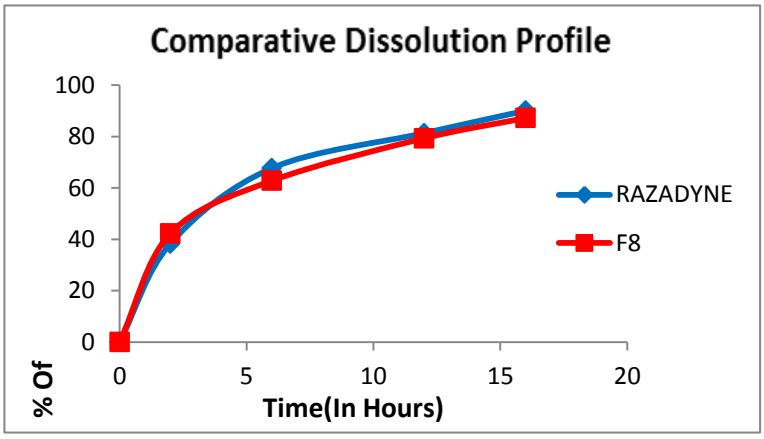


Fig:7.14. Comparative dissolution profile of formulation F8

Observation

Based on the above results, we have to increase ethyl cellulose concentration but the shape, size and strength of the pellets is good.

Conclusion

This formula is repeated from the core to confirm the formula.

F-9 Dissolution profile

(Conditions: pH 6.5 phosphates buffer, 500 ml, 50 rpm and Apparatus II)

Table:7.13. Invitro dissolution profile of formulation F9

Time (Hrs)	Percentage of Drug release	
	Razadyne ER	F9
0	0	0
2	38.35	38.25
6	67.72	66.94
12	81.35	80.97
16	90.09	89.68

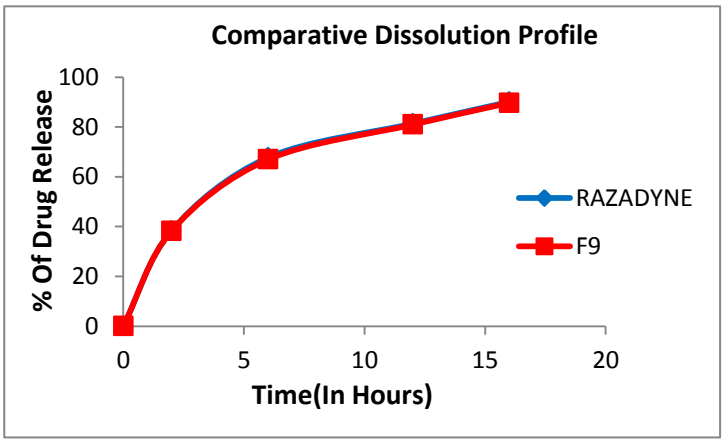


Fig No.7.15. Comparative dissolution profile of formulation F9

Observation

Based on the above results, the release, shape, size and strength of the pellets is good and we got reproducible results.

Conclusion

This formula is finalized for further optimization batch.

Table:7.14 Invitro dissolution profile of formulations F1-F9

S.No	Time in hrs	Percentage drug release								
		Razadyne ER	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0	0
2	2	38.35	60.49	48.17	42.17	52.04	61.01	28.61	52.39	42.28	38.25
3	6	67.72	87.88	82.12	72.12	68.12	101.01	57.86	76.82	62.85	66.94
4	12	81.35	93.24	88.33	78.33	74.60	100.68	74.58	82.06	79.34	80.97
5	16	90.09	98.65	89.04	89.04	80.62	100.10	81.77	89.62	87.23	89.68

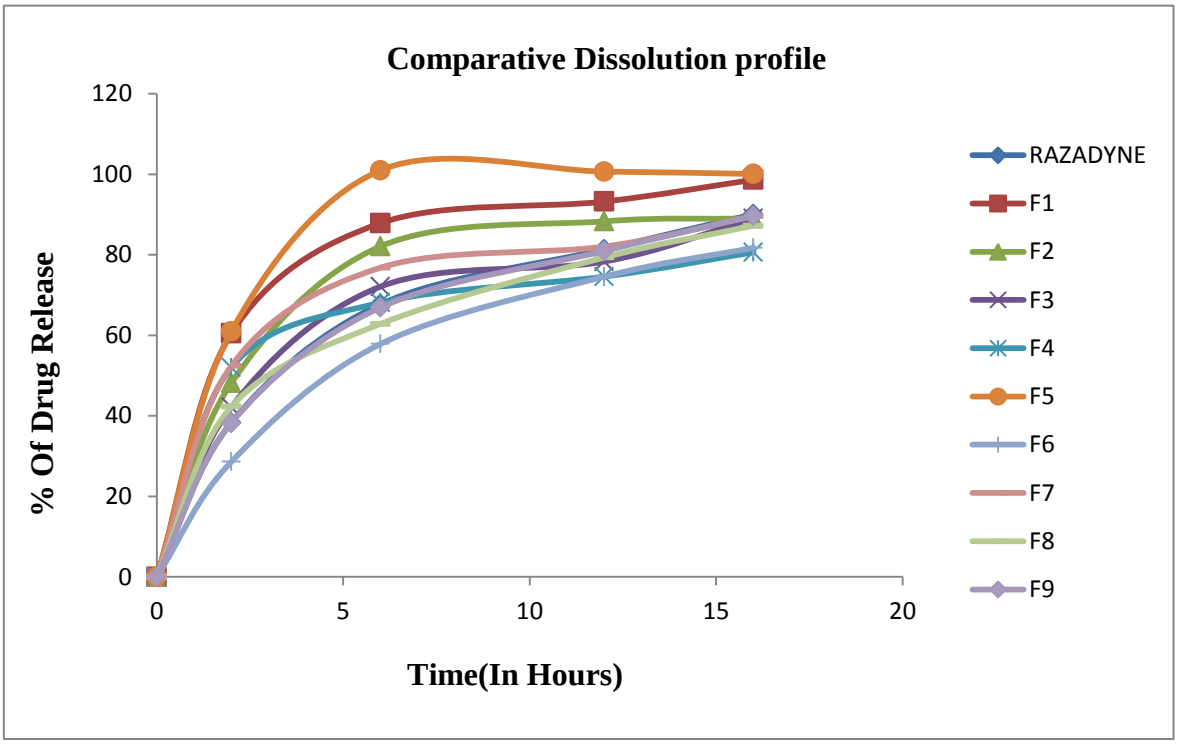


Fig:7.16. Comparative dissolution profile of formulations F1-F9

CHARACTERISTICS OF PELLETS FOR TRIAL F9

Table:7.15. Charecterstics of pellets formulation F9

Core pellets	Results
Yield (Limit-NLT 97%)	99.6%
Bulk density	0.648 g/ml
Tapped density	0.658 g/ml
Compressibility index	1.519
Angle of repose	26.04^0
Hausner's ratio	1.015

Sieve analysis for 100 gm for uncoated	
# 16 passed	99 g
# 20 retained	99 g
#16 passed and 20 retained	99 g
coated pellets	
Yield (Limit-NLT 96%)	99%
Sieve analysis for 100 gm	
#16 passed	98 g
#20 retained	98 g
# 16 passed and 20 retained	98 g
Bulk density	0.673 g/ml
Tapped density	0.684 g/ml
Compressibility index	1.70
Angle of repose	27.46^0
Hausner's ratio	1.01

Loading of coated pellets into capsules

The pellets after checking physical parameters this can be filled into capsules No.1 by using automatic capsule filling machine and the weight of capsule can be checked in filling of pellets into capsules.

The percentage weight variation of capsules is given as 5% to the total fill weight of capsule No.1 with sugar dummy pellets of same (#18-22 #) size.

7.5. EVALUATION OF CAPSULES

Weight variation

The uniformity of dosage units may be demonstrated by determining weight variation or content uniformity. The weight variation method is as follows.

Hard gelatin capsules

Table:7.16. Weight variation of all formulations of F1-F9

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Weight variation	275.7	288.4	324.2	252.4	261.2	292.4	299.6	298.4	300.6

Standard Deviation: 21.98932

7.5.1 Content Uniformity:

Assay by HPLC [29]

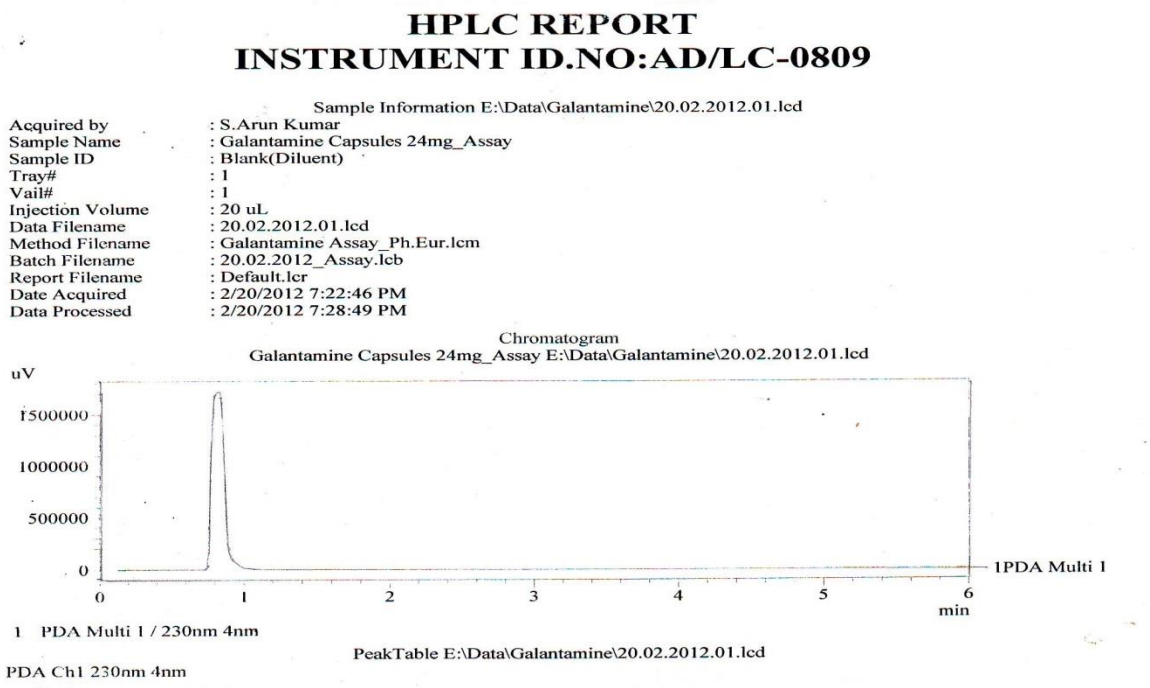


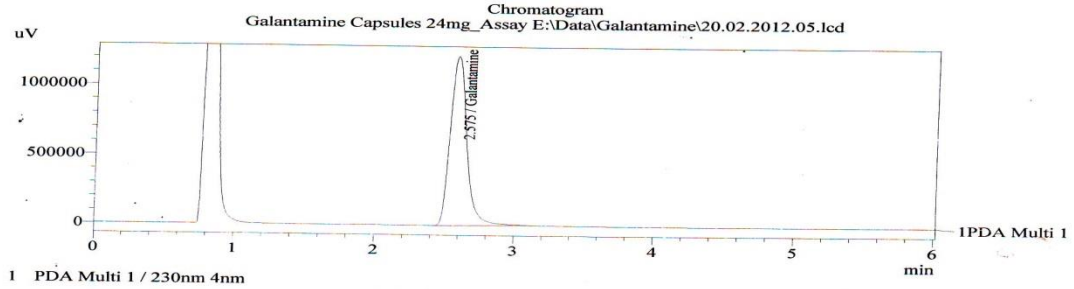
Fig:7.17 HPLC Chromatogram of Blank

RA CHEM PHARMA LTD
HPLC REPORT
INSTRUMENT ID.NO:AD/LC-0809

Sample Information E:\Data\Galantamine\20.02.2012.05.lcd

Acquired by	: S.Arun Kumar
Sample Name	: Galantamine Capsules 24mg_Assay
Sample ID	: GACXE/N/11/006 Assay spl_1
Tray#	: 1
Vail#	: 3
Injection Volume	: 20 uL
Data Filename	: 20.02.2012.05.lcd
Method Filename	: Galantamine Assay_Ph.Eur.lcm
Batch Filename	: 20.02.2012_Assay.lcb
Report Filename	: Default.lcr
Date Acquired	: 2/20/2012 7:49:00 PM
Data Processed	: 2/20/2012 9:11:14 PM

Chromatogram
Galantamine Capsules 24mg_Assay E:\Data\Galantamine\20.02.2012.05.lcd



1 PDA Multi 1 / 230nm 4nm

PeakTable E:\Data\Galantamine\20.02.2012.05.lcd

PDA Ch1 230nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1	Galantamine	2.57	10168076	100.00
Total			10168076	100.00

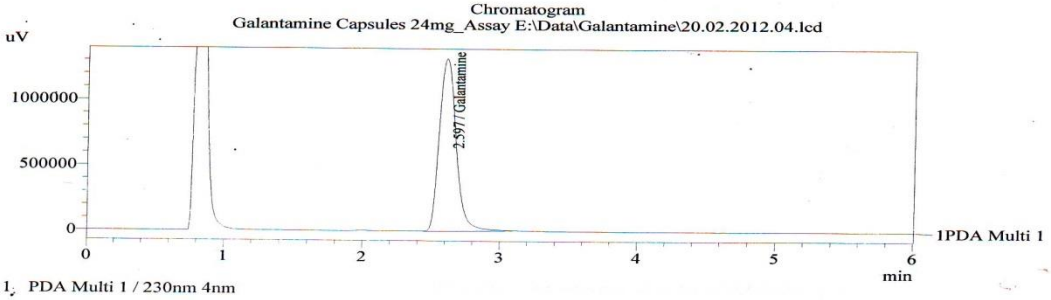
Fig:7.18 HPLC Chromatogram of Sample

RA CHEM PHARMA LTD
HPLC REPORT
INSTRUMENT ID.NO:AD/LC-0809

Sample Information E:\Data\Galantamine\20.02.2012.04.lcd

Acquired by	: S.Arun Kumar
Sample Name	: Galantamine Capsules 24mg_Assay
Sample ID	: Assay Standard Inj`3
Tray#	: 1
Vail#	: 2
Injection Volume	: 20 uL
Data Filename	: 20.02.2012.04.lcd
Method Filename	: Galantamine Assay_Ph.Eur.lcm
Batch Filename	: 20.02.2012_Assay.lcb
Report Filename	: Default.lcr
Date Acquired	: 2/20/2012 7:42:27 PM
Data Processed	: 2/20/2012 9:11:09 PM

Chromatogram
Galantamine Capsules 24mg_Assay E:\Data\Galantamine\20.02.2012.04.lcd



1 PDA Multi 1 / 230nm 4nm

PeakTable E:\Data\Galantamine\20.02.2012.04.lcd

PDA Ch1 230nm 4nm

Peak#	Name	Ret. Time	Area	Theoretical Plate#	Tailing Factor
1	Galantamine	2.6	11246913	2050	1.4
Total			11246913		

Fig:7.19 HPLC Chromatogram of Standard

The amount of active ingredient determined by assay is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed with no unit outside the range of 70% to 125% of label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes and all the capsules are within the range of USP.

Table:7.17. Content uniformity percentage of formulations F1-F9

S.No	F1	F2	F3	F4	F5	F6	F7	F8	F9
Strength 200mg	109.9%	108.7%	105.0%	102.5%	104.2%	95.7%	100.6%	98.9%	99.0%

Standard Deviation of Content Uniformity: 4.8075

Disintegration test

Table:7.18. Disintegration values of all formulations F1-F9

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Disintegration time in min.	4.30	4.50	4.40	5.10	4.50	4.50	4.55	5.05	4.25

Standard Deviation Disintegration: 0.30219

Moisture permeation test

The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules

Table:7.19. Moisture content values of all formulations F1-F9

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Moisture content	3.2%	2.9%	3.2%	3.6%	3.3%	2.9%	2.3%	1.8%	1.75%

Standard Deviation Moisture content: 0.6685

7.6. STABILITY STUDIES

Stability studies are to be carried out as per ICH guidelines for F9 batch of this product at long term, Intermediate and Accelerated storage conditions.

Table:7.20. Evaluation parameter values at different temperature conditions

S.No	Parameter	Stability conditions at		
		25°C	30°C	40°C
1	Assay	100.13%	100.05%	100.10%
2	Moisture content	1.72 %	1.75%	1.85 %
3	Disintegration time in minutes	4.30	4.25	4.20

Capsules Specification Parameters

After filling of pellets into capsule, the parameters of capsules are observed.

Table:7.21.Capsules specification parameters

Parameters	**Results**
Strength	**24mg**
Description	Size '1' hard gelatin capsules, with white transparent body and Bluecap containing white to off white spherical pellets of 18-20# size.
Capsule size	1
Weight of 10 filled capsules (gm)	3.007 gm
Weight of individual capsules (mg)	299.6, 298.4, 302.4, 299.6, 304.0, 298.6 299.6, 304.2, 302.0, 299.4
Locked length (mm)	17.4, 17.6, 18.2, 17.8, 18.2, 17.5, 17.6, 17.4, 17.9, 18.1

Standard deviation of Galantamine Extended Release Capsules: 2.267

IIX SUMMARY AND CONCLUSION

- The active pharmaceutical ingredient Galantamine Hydrobromide was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study" , and the results obtained with selected excipients showed good compatibility with Galantamine Hydrobromide drug.

- Galantamine Hydrobromide coated pellets were formulated by using commercially available sugar pellets and Galantamine Hydrobromide coated capsules were filled by Automatic capsule filling machine with various excipients. The optimization procedures aided in the stabilization of the formula and in the formulation of the Galantamine Hydrobromide Extended release capsules.

- The Stability of the capsules and pellets were determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH and 25ºC ± 2 ºC/ 60% ± 5% RH, and 30ºC±2ºC/65±5% RH conditions for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for content uniformity, assay, disintegration and dissolution studies. By the stability studies, the formulated Galantamine Hydrobromide extended release capsules and pellets proved to be stable throughout the period of the storage.

- The Galantamine Hydrobromide extended release pellets were loaded in size 1 hard gelatin capsules. It showed good results in formulation of stable

dosage. The dissolution profile of the prepared Galantamine Hydrobromide extended release capsules were compared with that Reminyl extended release capsules (Razadyne ER) of the product.

- The release was found nearer in the case of pellets loaded in capsules. And dissolution profile of Galantamine Hydrobromide extended release capsules were compared with that of innovator (Razadyne ER). The release was found similar to that of innovator. So the prepared product was said to be equivalent with innovator.

- When coated pellets in capsule come to discussion of dosage form extended release showed better drug release.

- Extended release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. Because of Small size pellets enter into the systemic circulation in very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more when compared with the innovator (Razadyne ER) sample.

- The release in the starting hours is controlled by increasing the concentration of Ethyl cellulose N-45 in the formulations in F9 formula and the HPMC is also increased.

- Even though Galantamine Hydrobromide tablets and capsules, gels available in market the formulation of F9 was shows better results with innovator

product and the formulation process will be easy, safe and effective.

- Finally I conclude that extended release pellets in capsule of formulation F9 has relevant drug release rate rather than innovator and it has better stability, Bioavailability than the innovator.

FUTURE SCOPE

- In vivo evaluation of present study.
- Development of extended release dosage form of Galantamine Hydrobromide by using Novel polymers.
- Development of new method in the formulation process focusing on Alzheimer's disease for effective Treatment.

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