"FORMULATION DEVELOPMENT OF EXTENDED RELEASE TABLET OF AN ANTI-MUSCARINIC AGENT"

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IN

PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

BY

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UNDER THE GUIDANCE OF

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May 2014

CERTIFICATE

*This is to certify that the dissertation work entitled "**FORMULATION DEVELOPMENT OF EXTENDED RELEASE TABLET OF AN ANTI-MUSCARINIC AGENT**" submitted by Ms. Darshi Shah with Regn. No. (12MPH103) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Intas Pharmaceuticals Ltd, Ahmedabad under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.*

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DECLARATION

I hereby declare that the dissertation entitled **"Formulation Development Of Extended Release Tablet Of An Anti-Muscarinic Agent"**, is based on the original work carried out by me under the guidance of Mr. Amit Aggarwal, Head, Process Development Lab, Intas Pharmaceuticals Ltd and Dr. Dhaivat Parikh, Assistant Professor, Department of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Date: 15th MAY **DARSHI SHAH**

Place: Institute of Pharmacy,
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LIST OF ABBREVIATIONS

ABBREVIATIONS	FULL NAME
OAB	Over Active Bladder
QbD	Quality by Design
QTPP	Quality Target Product Profile
ER	Extended Release
CQA	Critical Quality Attributes
CMA	Critical Material Attributes
UI	Urinary Incontinence
Mg	Milligram
Mg	Microgram
Tab	Tablet
HDPE	High Density Polyethylene
RLD	Reference Listed Drug
NMT	Not More Than
NLT	Not Less Than
FDA	Food and Drug Administration
RSD	Relative Standard Deviation
LOD	Loss on Drying
ml	Milliliter
µl	Microliter

FORMULATION DEVELOPMENT OF EXTENDED RELEASE TABLET OF AN ANTI-MUSCARINIC AGENT

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ABSTRACT

Nowadays the oral route represents the predominant and most preferable route for drug delivery. Over-active bladder (OAB) is associated with a strong desire to urinate and correlates with an over-active detrusor muscle. ASTONT2013 is widely used as an anti muscarinic agent. Conventional dosage form of ASTONT2013 exhibits side effects like dry mouth (most common), constipation, urinary retention, etc. Hence, to overcome side effects, once a day formulation was developed to maintain drug therapeutic level and for better patient compliance. The aim of the present investigation was to systematically formulate and optimize tablet which follows zero order kinetics using quality by design (QbD) approach. Initially tablets were formulated after identifying critical quality attributes. Tablets were formulated by direct compression method by using different grades of HPMC. However, release profile did not comparable with the innovator. Hence, release of drug was delayed by applying coat of pH dependent polymer. Results revealed that optimized batch was found within the acceptable range. The second approach was explored to develop delayed release using hydrophobic agent. However, using alone hydrophobic agent, drug release could not be delayed. Hence, incorporation of hydrophobic agent (Gelucire 43/01) with hydrophilic matrix (HPMC) was investigated. These both factors were scientifically studied using Design of Experiment (DoE). 3^2 factorial design was employed to optimize the ratio of Gelucire 43/01 and HPMC K 100 M. The optimize batch was developed by validated model from the desired response region. Hence, the aim of present study was to formulate once a day dosage form of ASTONT2013 by employing two different approaches. From the above result it can be concluded that, by employing pH dependent coat over matrix tablet gave better delayed release profile than by incorporating hydrophobic agent with matrix tablet.

AIM OF INVESTIGATION

- The oral route represents the predominant and most preferable route for drug delivery. Unlike parenteral dosage forms, it allows ease of administration, therefore, better patient compliance.
- The oral dosage form must be designed in such a way that there is minimal effect of extreme pH ranges, the presence or absence of food, degradative enzymes and motility of the gastrointestinal tract.
- Extended release drug delivery system releases drug in a slow manner over an extended period of time and maintains therapeutic levels for longer time.
- Urinary incontinence (UI) is defined as the involuntary loss of urine. Overactive bladder (OAB)/ urge incontinence is a type of UI, which is associated with a strong desire to urinate and correlates with an overactive detrusor muscle. People with overactive bladder experience inappropriate contractions of the bladder during the storage phase of the micturition cycle. These contractions increases rate of micturition frequency, a strong desire to urgency, and urine loss.
- Hence, extended release formulation for the treatment of OAB is required for better patient compliance and overcome dose related side effects.
- An anti-cholinergic agent used for treatment of OAB includes tolterodine tartrate, ASTONT2013, trospium, solifenacin, dorifenacin and fesoterodine. Among all these durgs, reports suggest that the tolterodine and ASTONT2013 is the best in terms of controlling adverse effect and low cost of the treatment as most drugs lack functional selectivity for the bladder and use may be limited because of their adverse effects.
- Additionally, ASTONT2013 is indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with neurological conditions (i.e., spina bifida). These agents have also been used to treat voiding disorders in patients with spinal trauma or other neurological diseases.
- The innovator product for treatment of OAB makes use of osmotic controlled release oral drug delivery system (OROS) technology.
    - **But OROS technology has the following limitations:**

- ➔ Requirement of a special equipment for drilling an orifice in the dosage form and for that reason it is costly;
- ➔ Variation in the residence time of the system in the body due to gastric motility and food intake;
- ➔ Dose dumping in case of inefficient coating process.

- Thus, there arises a need for developing a formulation which provides a similar drug release profile and overcomes the limitations of OROS technology.
- Hence, two approaches were investigated to achieve drug release similar to innovator:
  1. Formulation of Matrix tablets applying enteric coat using pH-dependent polymer. By applying enteric coat there will be negligible drug release during initial hours similar as innovator drug release profile and controlled release in basic medium up to 24 hours. And it will also minimize the first pass metabolism of drug.

  2. Formulation of matrix tablets using hydrophilic polymer with incorporation of hydrophobic agent (Gelucire 43-01). Addition of hydrophobic agent can retard drug release in initial hours and hydrophilic polymer will act as a rate controlling polymer.
- Thus, the main objective of the study was to formulate and develop a robust controlled release formulation of ASTONT2013 by using two approaches and comparing them with innovator.

2.1 ORAL DRUG DELIVERY SYSTEM

- **Modified release oral drug delivery system**

- Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. Disadvantage of immediate release DDS is fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects.

Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. [1,2,3,4]

Oral modified release delivery systems are most commonly used for,

1) Delayed release (e.g., by using an enteric coating);
2) Extended release (e.g. zero-order, first-order, etc.);
3) Programmed release (e.g., pulsatile, triggered, etc.) and
4) Site specific or timed release (e.g., for colonic delivery or gastric retention).

Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics. [1, 5]

Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. [1, 6]

- **Extended release oral drug delivery system**

- Extended release formulations make the drug available over extended time period after oral administration.
- The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly, formulation helps to avoid the side effects associated with high concentrations.
- The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.[7, 8, 9]

Advantages: [8, 9]

Extended release products have the following advantages:

a) They maintain therapeutic concentrations over prolonged periods.

b) They avoids the high blood concentration.

c) They have the potential to improve the patient compliance.

d) They reduce the toxicity by slowing drug absorption.

e) They increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.

f) They minimize the local and systemic side effects.

g) They improve the treatment efficacy.

h) They minimize drug accumulation with chronic dosing.

i) They provide less use of total drug.

j) They improve the bioavailability of few drugs.

- **Drug properties, which are suitable for, extended release formulation.[8, 9]**

a) Physiochemical properties of the drug: The following physico-chemical properties are desired for a drug candidate to be suitable for extended release formulation,

1. Aqueous solubility: >0.1mg/ml
2. Drug stability in vivo: High enough, such that the drug remains stable during its release from the system.
3. Protein binding: Drug with high protein binding does not require release modification
4. Drug pKa& ionization at physiological pH: pKa for acidic API= 3.0 - 7.5,pKa for Basic API = 7.0 - 11.0
5. Mechanisms and sites of absorption: Mechanism of absorption should not be active type and absorption window should not be narrow
6. Molecular size and diffusivity: Molecule size should be small (100-400 D) so it can be easily diffused through polymer matrix
7. Dose size: <300mg

b) Biological properties of drug: The following biological properties are desired for a drug candidate to be suitable for extended release formulation,

1. Distribution: Active Pharmaceutical Ingredient (API) with small volume of distribution is suitable.
2. Metabolism: API should be metabolized with intermediate speed.
3. Half-life of drug: 2 - 8 hrs.
4. Margin of safety: High enough so dose dumping does not cause any serious side effect.
5. Plasma concentration response relationship: API having linear relationship.

2.2URINARY INCONTINENCE[10, 11]

- Urinary incontinence (UI) is defined as the involuntary loss of urine. UI occurs when the pressure within the bladder increases that within the urethra during the filling phase. Overactive bladder (OAB)/ urge incontinence is a type of UI, which is associated with a strong desire to urinate and correlates with an overactive detrusor muscle.
- People with overactive bladder experience inappropriate contractions of the bladder during the storage phase of the micturition cycle. These contractions increase rate of micturition frequency, a strong desire to urgency, and urine loss.
- An extrapolation of the figures provided by Decision Resources, results that around 24 million people affected by overactive bladder/ urge incontinence in 2001 in 5 European countries i.e. UK, France, Germany, Italy, and Spain and 17 million in United States, making it more prevalent than asthma (15 million), osteoporosis (10 million), diabetes mellitus (7 million) or Alzheimer disease (4 million). [12, 13]

- **Pathology of urinary incontinence**

- Normal micturition (urination) depends on several factors working synchronously. Many pathological processes and age-related changes can result in UI.
- Control of urination primarily depends on the detrusor and sphincter muscles plus associated structures.

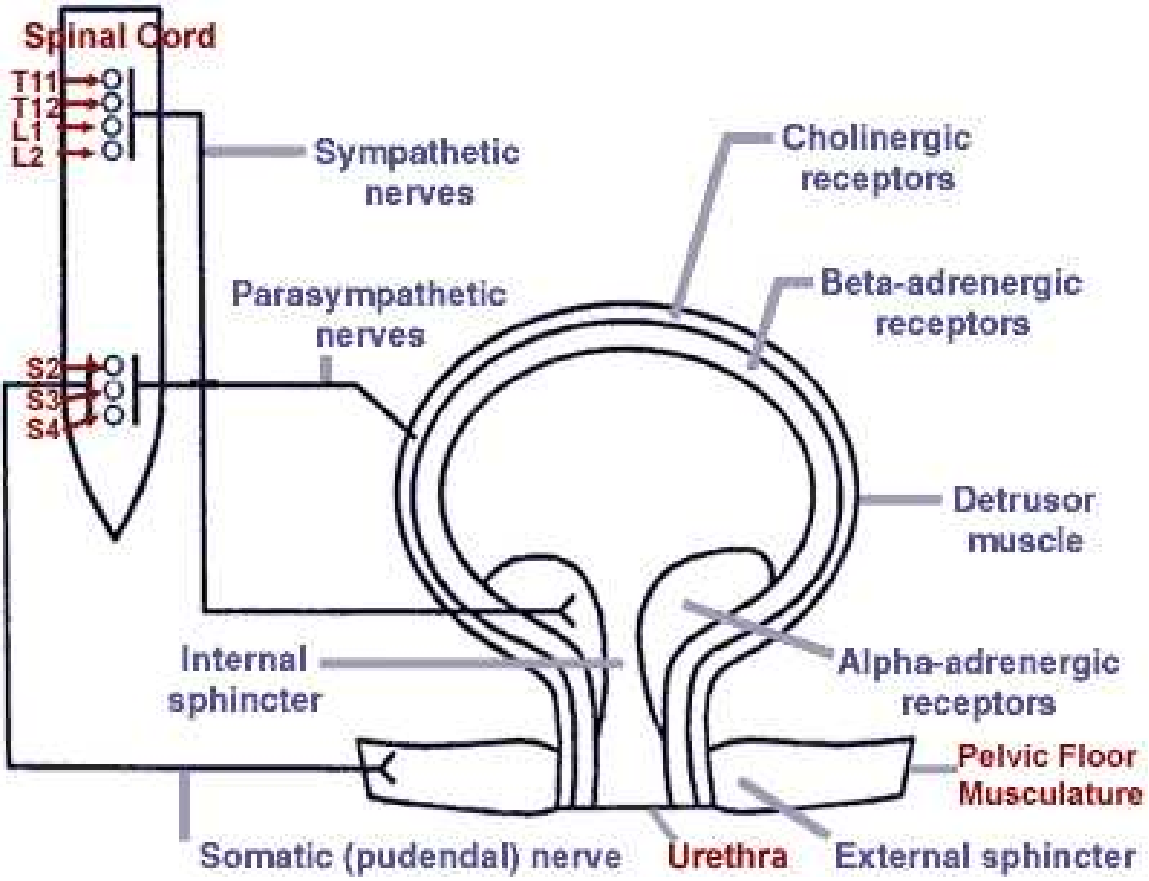


Fig 2.1. Pathology of urinary incontinence

- Detrusor muscle: Multilayered contractile bladder muscle can allow filling until distension triggers voiding urge. Cortical activity as well as spinal and pelvic (cholinergic) nerves control voiding. When the bladder has filled with 200-400mL of urine, urge to void is perceived. During micturition (voiding), it is the parasympathetic nervous system which causes a release of acetylcholine, which in turn, results in detrusor contractions. Detrusor contraction may be inhibited by damage or interference with this system directly or by medications blocking cholinergic, prostaglandin or calcium channel activity.

- Sphincter muscles: Internal and external sphincter functions depend on integrity of muscle, innervations, and anatomic relationship (angle of the bladder to the urethra). Appropriate angulations and integrity of structures prevent urine loss when intra-abdominal pressure increases. Regarding innervations: alpha-adrenergic activity causes sphincter contraction (retention of urine) whereas beta-adrenergic activity causes sphincter relaxation (leakage) of urine (and obviously blocking agents cause the reverse!)

Contributions of aging to UI: urinary incontinence is one of the geriatric syndromes and is not inevitable or accepted as a normal age-related change. However, several changes that accompany aging do contribute to a predisposition toward the development of UI.

2.3 INTRODUCTION TO TECHNIQUE[14, 15]

- A polymer coating is often applied to enhance the tablet's appearance or to make the tablet smoother and easier to swallow and to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life).

- Coating may be applied to multiple range of oral solid dosage form, including tablets, capsules, multiparticulates and drug crystals.

- When coating composition is applied to a batch of tablets in a coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied.

The coating process is usually a batch operating task consisting of the following phases:

- Identification of batch and Recipe selection (film or sugar coating)
- Loading/Dispensing (accurate dosing of all required raw materials)
- Warming
- Spraying (Both application and rolling are carried out simultaneously)
- Drying
- Cooling
- Unloading

➢ **Enteric coating**

- An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine.
- Coating changes from a sticky liquid to tacky semisolid and eventually to non-sticky dry surface pans.
- The enteric coated polymers remain unionise at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibres.

- There are four reasons for putting such a coating on a tablet[16]

Protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics).

To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate).

For the delivery of drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.

To provide a delayed-release component for repeat action.

Required for minimizing first pass metabolism of drugs.

- Ideal properties of enteric coating material :

- Resistance to gastric fluids
- Susceptible/permeable to intestinal fluid
- Compatibility with most coating solution components and the drug substrate
- Formation of continuous film
- Nontoxic, cheap and ease of application

2.4 QUALITY BY DESIGN (QBD)[17,18,19]

- QBD is mandatory from 2013 by USFDA, before that formulation were developed by trial and error methods by varying one factor at a time. This is time consuming process and difficult to optimize all parameters.
- Recently USFDA introduced use of quality by design approaches for systemic development of formulation. The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.
- Quality by design comprised of tools which include Design of Experiments (DOE), Risk Assessments and Process Analytical Technology (PAT). According to quality by design, one need to identify the most important parameter elaborately termed as Critical Quality Attributes (CQA).
- By focussing on those critical quality attributes one can change the quality, safety and efficacy of the product.

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality.

❖ For applying QBD approach following direction of plan is needed:

- Quality Target product profile (QTPP)
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements.

What is QTTP? [20]

- The QTPP is a patient and labelling centred concept, it can be thought of as the "user interface" of the drug product. Thus a generic version and its reference product would be expected to have the same QTPP. A generic product may use a different formulation or design to implement the TPP. The characteristics and performance tests of a drug product would depended on the particular implementation and may differ between a generic and reference product.
- These can include the route of administration, dosage form and size, maximum and minimum doses, pharmaceutical elegance (appearance), and target patient population (paediatric formulations may require chewable tablets or a suspension). Common aspects of drug product quality are implicitly in the QTPP.

What is CQA?

- Critical quality attributes (CQAs) as physical, chemical, biological or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.

What is a Process Parameter? [21]

- There is confusion about what is a process parameter. Previously, some have defined a critical process parameter (CPP) as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

What Is a Control Strategy?

- A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented to ANDA to commercial production.

What Is Design Space?

- In the presence of interacting critical process parameters a design space is one approach to ensure product quality although it is not a check-box requirement. The current definition of design space is "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."

What is PAT?

- Application of PAT may be part of a control strategy. ICH Q8(R) identifies one use of PAT as ensuring that the process remains within an established design space. In a more robust process, PAT can enable active control of CPP, and if there is variation in the environment or input materials the operating parameters can be adjusted to keep the CMA under control to ensure quality.

2.5 PROFILE OF DRUG[22]

- **Profile of Drug ASTONT2013**

- Molecular weight: 393.95 g/mol

- Pharmacopeial stats: Official in United States Pharmacopeia 36 National Formulary 31

- BCS class: Class 1

- Category:
  Muscarinic antagonists
  Antispasmodics
  Anticholinergic agents
  Parasympatholytics
  Genitourinary smooth muscle relaxants

- Description: White, crystalline, odourless powder

- Melting Point:125°C (124°– 129°C)

- Storage: Preserve in well-closed containers

- Solubility: Freely soluble in water and in alcohol, very soluble in methanol and in chloroform, soluble in acetone, slightly soluble in ether, very slightly soluble in hexane.

- Pharmacology: **Drug ASTONT2013** exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).By inhibiting particularly the M1 andM2 receptors of the bladder, detrusor activity is markedly decreased.

- Pharmacodynamics: Antispasmodic, anticholinergic agent indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Drug X relaxes bladder smooth muscle. Drug X exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. Anti-muscarinic activity resides predominantly in the R-isomer.

- Pharmacokinetics:
  - Absorption: Rapidly absorbed from gastrointestinal tract
  - Distribution: Volume of distribution is 193L.
    Protein Binding is 91% to 93%
  - Metabolism: Hepatic Metabolism, primarily by CYP3A4
  - Elimination: Less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the N-desethyl metabolite form.

2.6 EXCIPIENTS DESCRIPTION

❖ **Lactose monohydrate:**[23]

- Non-proprietary Names

  BP: Lactose monohydrate

  PhEur: Lactosum monohydricum

  JP: Lactose

  USPNF: Lactose monohydrate

- Chemical Names and CAS Registry Number

  O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate[64044-51-5]

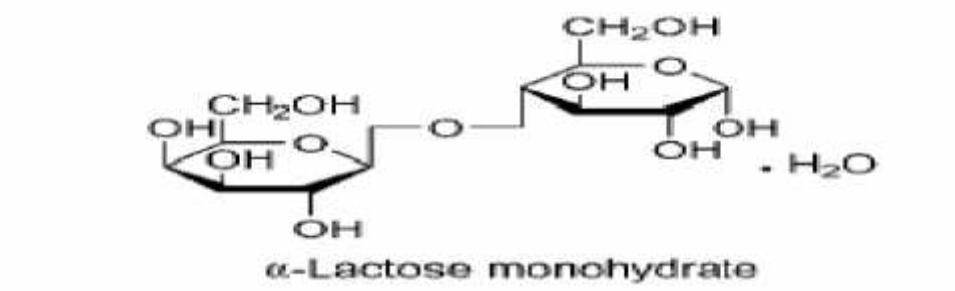
- Empirical Formula

  $C_{12}H_{22}O_{11}$-H_2O

- Molecular Weight

  360.31 g/mol

- Structural Formula



α-Lactose monohydrate

- Functional Category

  Binding agent; diluents for dry-powder inhalers; tablet binder; tablet and capsule diluents.

- Applications in Pharmaceutical Formulation or Technology

  - Lactose is widely used as a filler or diluent in tablets and capsules.

  -Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a Lactose monohydrate, containing small amounts of anhydrous lactose.

  - Direct-compression grades are often used to carry lower quantities of drug and these permits tablets to be made without granulation.

  - Other directly compressible lactose are spray-dried lactose and anhydrous lactose

- Description

  Lactose occurs as white to off-white crystalline particles or powder.

  Lactose is odourless and slightly sweet-tasting.

- Stability and Storage Conditions

  Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions.

- Typical Properties

Angle of repose	33^0 for Pharmatose DCL 15; 32^0 for Tablettose 70 and Tablettose 80.
Melting point:	201–202^0 C
Moisture content:	4.5–5.5% w/w water content
Solubility	Water 1 in 5.24, Practically insoluble in ether, chloroform and ethanol
Density (true)	1.545 g/cm3

- Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown colored products.

❖ **Microcrystalline cellulose[24]**

- Nonproprietary Names

  BP: Microcrystalline cellulose

  JP: Microcrystalline cellulose

  PhEur: Cellulosum microcristallinum

  USPNF: Microcrystalline cellulose

- Synonyms

  Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; F ibrocel; Pharmacel;Tabulose.

- Chemical Name and CAS Registry Number

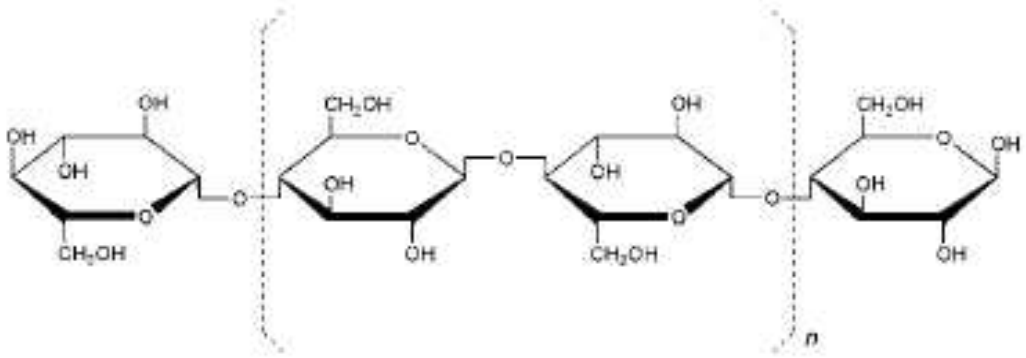
  Cellulose [9004-34-6]

- Empirical Formula and Molecular Weight

  $(C6H10O5)_{n\ \_36\ 000}$

  where n =220.

- Structural Formula



- Functional Category

  Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Uses of Microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsulebinder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluents	20–90

- Applications in Pharmaceutical Formulation or Technology

  -Microcrystalline cellulose is widely used as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes

  -Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

- Description

  -Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

  -It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Angle of repose	$49^0$for Ceolus KG; 34.4^0 for Emcocel 90M
Melting point:	260–270^0 C
Moisture content:	less than 5% w/w.
Solubility	slightly soluble in 5% w/v sodium hydroxide solution;, Practically insoluble in water , most organic solvents.
Density (true)	1.512–1.668 g/cm3

- Stability and Storage Conditions

  The bulk material should be stored in a well-closed container in a cool, dry place.
- Incompatibilities

  Microcrystalline cellulose is incompatible with strong oxidizing agents.

❖ **Hypromellose[25]**

- Nonproprietary Names

  BP: Hypromellose

  JP: Hydroxypropylmethylcellulose

  PhEur: Hypromellosum

  USP: Hypromellose
- Synonyms

  Hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methylhydroxypropylcellulose; Metolose.
- Chemical Name and CAS Registry Number

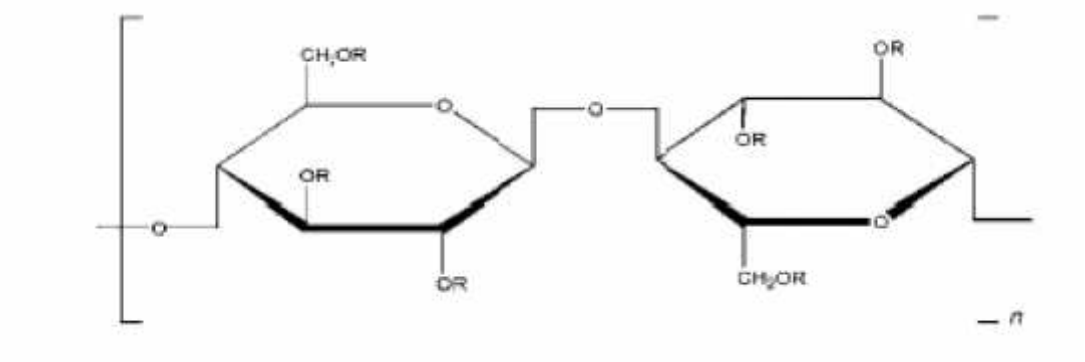
  Cellulose hydroxypropyl methyl ether [9004-65-3]
- Empirical Formulas and Molecular weight

  -Hypromellose as a partly O methylated and O-(2-hydroxypropylated) cellulose.

  -It contains methoxy and hydroxypropoxy groups.

  Molecular weight - 10 000–1 500 000 g/mol.

- Structural Formula



where R is H, CH3, or CH3CH(OH)CH2

- Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Use	Concentration (%)
Tablet binder	2-5% w/w
High-viscosity grades may be used to retard the release of drugs from a matrix	10–80% w/w
Film-forming solutions to film-coat tablets.	2–20% w/w
Thickening agent	0.45–1.0% w/w

- Applications in Pharmaceutical Formulation or Technology

In oral products, hypromellose is primarily used as a tablet binder, in film coating and as a matrix for use in extended-release tablet formulations.

- Description

Hypromellose is an odourless and tasteless, white or creamy white fibrous or granular powder.

Melting point	170–180^{0}C
Moisture content	Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
Solubility	Soluble in soluble in cold water, insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol
Density (true)	1.326 g/cm^3

- Stability and Storage Conditions

  -Hypromellose powder is a stable material, although it is hygroscopic after drying.

  -Aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative

- Incompatibilities

  Hypromellose is incompatible with some oxidizing agents.

❖ **Opadry OY-29020 clear[26]**

- Opadry OY-29020 coatings are fully formulated, one-step, PVA (polyvinyl alcohol)-based aqueous film coatings that offer a high level of moisture protection and improved final product color stability combined with fast coating process times.

- OpadryOY-29020 clear is a ready mixture which comprises of fine homogenous mixture of seal coating components.
- The ingredients of Opadry Clear are as follows:

Opadry OY-29020 clear quantitative composition

Opadry	OY-29020 clear
Ingredients	% w/w
Hypromellose6 cps	90.910
Macrogol 400	9.090

❖ **AcrylEZE 93 O 575001 Grey**[27]

- Acryl-EZE® is a fully formulated, dry enteric acrylic coating system dispersible in water, for the application of an enteric film coating to multi-particulate solid dosage forms.
- Combining the benefits of a fully formulated coating system with a globally accepted enteric polymer (EUDRAGIT L100-55*), Acryl-EZE is readily dispersible in water for easy application.
- The enteric coating provides consistent, reproducible delayed release profiles. Acryl-EZE is a fully formulated, dry acrylic-enteric coating system, dispersible in water, for the application of a delayed release film coating to solid dosage forms such as tablets, granules and beads.
  - Key Characteristics

- Acrylic polymer for proven enteric performance.
- Ready formulated powder.
- Easy to dispense and disperse- only 20 minutes preparation time.

- ACRYL-EZE is a ready mixture which comprises fine homogenous mixture of enteric coating components.
- The ingredients of ACRYL-EZE are as follows:

Acryl-EZE 93O575001 Grey quantitative composition

Acryl-EZE	93O575001 Grey
Ingredients	% w/w
Methacrylic acid copolymer type-C	40
Talc	37.25
Titanium dioxide	14.69
Tri ethyl citrate	4.8
Colloidal anhydrous silica	1.25
Sodium bicarbonate	1.2
Ingredients	% w/w
Iron oxide yellow	0.02
Sodium lauryl sulfate	0.5
Iron oxide black	0.29

- Recommended Storage Condition

  Store product below 30ºC and less than 75% relative humidity (RH).

❖ Gelucire 43/01[28]

- Gelucire are polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol (PEG).
- Each component presents different affinity for water and act as surfactant and co surfactant. Di- and triglycerides are lipophilic in nature
- Depending on the chemical composition of gelucire they are used for different purposes.
  - **Low HLB gelucire can be used to reduce the dissolution rate of drugs**
  - High HLB gelucire can be used for faster release of drugs

- In the designation of gelucire names, for example, Gelucire 43/01, 43 indicates melting point and 01 indicates its HLB value.

TYPE	CHEMICALNAME	USE
43/01	Glycerol esters of saturated C12-C18 fatty acids	Excipient, vehicle, consistency building and fatting agent

➢ Advantages of Gelucire[29]

The lipidic materials like Gelucire are considered as an alternative to the polymers used in the sustained release formulation because of some advantages like;

- The have low melt viscosity
- Absence of toxic impurities such as residual monomer catalysts and initiators
- Potential biocompatibility
- Biodegradability and prevention of gastric irritation by forming a coat around the gastric irritant.

2.7 PRESENT STATUS [30]

- Over active bladder (OAB) is associated with a strong desire to urinate and correlates with an over active detrusor muscle.
- Anti-cholinergic agents are used for treatment of OAB which acts by competitively antagonizing the M-2 (muscarinic receptor) present in various smooth muscles.
- Medicines used to treat OAB are tolterodine tartrate, trospium, solifenacin, dorifenacin and fesoterodine. Among all these medicines, reports suggested that tolterodine was found to be the best in terms of cost of treatment and with least adverse effect.
- As most drugs lack functional selectivity for the bladder and produce adverse effects like dryness of mouth, dryness of eye and constipation, their usefulness might be limited.
- **Treatment of OAB using immediate release formulation of drug X lead to severe adverse effects like dryness of mouth, dryness of eye and constipation, due to frequent dosing. This problem could be overcome by adapting once-a-day modified release formulation (i.e. extended release system).**

3.1 Literature survey on Controlled Release Formulation

Liu Q et al in their research, " Zero-order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro-retentive system" have designed a composite gastro-retentive matrix for zero-order delivery of highly soluble drug alfuzosin hydrochloride (10mg), that has potential to enhance bioavailability and site-specific delivery to the proximal small intestine. A composite gastro-retentive matrix for zero-order delivery of highly soluble drug alfuzosin hydrochloride (10 mg) has been designed and characterized. Two systems containing polyethylene oxide (PEO), hydroxypropylmethylcellulose (HPMC), sodium bicarbonate, citric acid and polyvinyl pyrrolidone were dry blended and compressed into triple layer and bi-layer composite matrices. Dissolution studies using the USP 27 paddle method at 100 and 50 rpm in pH 2.0 and 6.8 were performed using UV spectroscopy at 244 nm, with automatic sampling over a 24 h period using a marketed product as a reference to calculate the "f_2" factor. Textural characteristics of each layer, the composite matrix as a whole, and floatation potential were determined under conditions similar to dissolution. Percent matrix swelling and erosion along with digital images were also obtained. Both systems proved to be effective in providing prolonged floatation, zero-order release, and complete disentanglement and erosion based on the analysis of data with "f_2" of 68 and 71 for PEO and HPMC based systems, respectively. The kinetics of drug release, swelling and erosion, and dynamics of textural changes during dissolution for the designed composite systems offer a novel approach for developing gastro-retentive drug delivery system that has potential to enhance bioavailability and site-specific delivery to the proximal small intestine.[31]

Carelli V. et al have performed extensive research in evaluating silicone based matrix containing a cross linked polyethylene glycol as a controlled drug delivery system for potential oral application. They have shown that a silicone based matrix containing dispersed medicated granules of crosslinked polyethyleneglycol with high swelling capacity has the potential to release in-vitro, substantial fractions of drugs of different solubilities within 6 hours at controlled rates. Papaverine-HCl, clonidine-HCl and salicylamide are the model drugs used.[32]

Sakr F.et al developed a "Programmable drug delivery system for oral administration". The device was in the form of a non-digestible oral capsule (containing drug in a slowly eroding matrix for controlled release) and was designed to utilize an automatically operated geometric obstruction that kept the device floating in the stomach and prevented it from passing through the remainder of the GIT. In-vitro long-term drug delivery from a prototype model was studied using levon or gestril as a model drug. Zero-order release could be maintained for periods ranging between 5 and 20 days before the geometric obstruction was triggered off.[33]

Krogel I. et al, developed a multi functional matrix drug delivery system surrounded by an impermeable cylinder. In the study, drug release increased with a reduced HPMC viscosity grade, higher aqueous drug solubility, decreased HPMC content and increased surface area of the matrix.[34]

KrishnaiahY et al have designed oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets. The present study is carried out to design oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets. Trimetazidine dihydrochloride was chosen as a model drug because of its high water solubility. Matrix tablet granules containing 30% (M1), 40% (M2) or 50% (M3) of guar gum were prepared by the wet granulation technique using starch paste as a binder. Three-layer matrix tablets of trimetazidine dihydrochloride were prepared by compressing on either side of guar gum matrix tablet granules of trimetazidine dihydrochloride.[35]

3.2 Literature survey on Quality by Design

Robert W. Bondi Jr. et al described the modern philosophy for pharmaceutical drug product development and manufacturing beginning with the identification of core regulatory documents that define cGMPs for the twenty-first century, process analytical technology (PAT) and quality by design (QbD). The critical role of PAT in a successful QbD environment was documented, providing an overview of important multivariate mathematical techniques and modern analytical technologies for process monitoring that facilitate process understanding and ultimately process control. The concept of design space was considered, describing the relationship between critical process parameters (CPPs) and critical quality attributes (CQAs). A discussion of control models provided a perspective on how such models function to ensure that CPPs and other process variables were maintained in a state of control within the working range that corresponds to the desired set of CQAs. Finally, the chapter provided considerations regarding how the pharmaceutical industry may achieve return-on-investment (ROI) while achieving advanced process control and real-time release (RTR) by capitalizing on manufacturing efficiencies.[36]

Siegfried Adam et al combined Quality by Design (QbD) and Discrete Element Model (DEM) simulation-approach is to characterize a blending unit operation by evaluating the impact of formulation parameters and process variables on the blending quality and blending end point. Understanding the variability of both the API and the excipients, as well as their impact on the blending process are critical elements for blending QbD. In a first step, the QbD-methodology was systematically used to (1) establish the critical quality attribute content uniformity and to link this CQA to its surrogate blend homogeneity, (2) identify potentially critical input factors that may affect blending operation quality and (3) risk-rank these factors to define activities for process characterization. Subsequently, a DEM-simulation-based characterization of the blending process was performed. A statistical evaluation is finally presented, relating blend homogeneity of systems with low particle number to the regulatory requirements. Data were then used to map out a three-dimensional knowledge space, providing parameters to define a design space and set up an appropriate control strategy.[37]

Naseem A. Charoo applied quality by design (QbD) approach to the development of dispersible tablets. Critical material and process parameters were linked to the critical quality attributes of the product. Variability was reduced by product and process understanding which translates into quality improvement, risk reduction and productivity enhancement. The risk management approach further lead to better understanding of the risks, ways to mitigate them and control strategy was proposed commensurate with the level of the risk. Design space in combination with pharmaceutical quality management system provided for flexible regulatory approaches with opportunity for continuous improvement that benefits patient and manufacturer alike. The development of dispersible tablet was proposed in the current study through a QbD paradigm for a better patient compliance and product quality. The quality target product profile of a model biopharmaceutical class II drug was identified. Initial risk analysis led to the identification of the critical quality attributes. Physicochemical characterization and compatibility studies of the drug with commonly used excipients were performed. Experiments were designed with focus on critical material and process attributes. Design space was identified and risk factors for all the possible failure modes were below critical levels after the implementation of control strategy. Compliance to the design space provided an opportunity to release batches in a real time. In conclusion, QbD tools together with risk and quality management tools provided an effective and efficient paradigm to build the quality into dispersible tablet.[38]

Sumit Kumar et al explored Quality by Design (QbD) principles to understand spray drying process for the conversion of liquid nanosuspensions into solid nano-crystalline dry powders using indomethacin as a model drug. The effects of critical process variables: inlet temperature, flow and aspiration rates on critical quality attributes (CQAs): particle size, moisture content, percent yield and crystallinity were investigated employing a full factorial design. A central cubic design was employed to generate the response surface for particle size and percent yield. Multiple linear regression analysis and ANOVA were employed to identify and estimate the effect of critical parameters, establish their relationship with CQAs, create design space and model the spray drying process. Inlet temperature was identified as the only significant factor (p value <0.05) to affect dry powder particle size. Higher inlet temperatures caused drug surface melting and

hence aggregation of the dried nano-crystalline powders. Aspiration and flow rates were identified as significant factors affecting yield (p value <0.05). Higher yields were obtained at higher aspiration and lower flow rates. All formulations had less than 3% (w/w) moisture content. Formulations dried at higher inlet temperatures had lower moisture compared to those dried at lower inlet temperatures.[39]

3.3 Literature survey on Over Active Bladder

Naoki Yoshimura and et al explored that in addition to current drug therapies, we also present preventive rather than reactive therapy. We promote the idea of afferent blockade, a revised treatment approach targeting afferent nerves that control the bladder. It would be more desirable to prevent the micturition reflex that initiates overactive bladder. A number of afferent blockade drugs now in development can prevent the bladder from contracting involuntarily. Treating the patient with overactive bladder via this approach would allow the possibility of lower drug doses with fewer side effects as well as greater efficacy. Anticholinergic agents that suppress muscarinic receptors in bladder smooth muscles are by far the most useful pharmacological agents for managing overactive bladder and urge incontinence. Although an abundance of drugs is available for overactive bladder, for many drugs estimated efficacy is based on preliminary open studies rather than on controlled clinical trials. However, the drug effect in an individual may be empirically important. In developing countries most bladder relaxant drugs discussed are not available, mainly due to economical reasons, which make pharmacological treatment of overactive bladder difficult in these countries.[40]

Eric S. Rovner et al suggested that overactive bladder (OAB) is a chronic condition that often requires long-term treatment to maintain control of symptoms. A range of therapeutic options are available; however, antimuscarinic agents form the mainstay of treatment. It is well documented that the immediate-release (IR) formulations of these agents have equivalent efficacy in relieving OAB symptoms. However, tolterodine demonstrates a more favourable tolerability profile, particularly in terms of the frequency and severity of dry mouth. Due to the development of novel drug delivery systems, extended-release (ER) formulations of both oxybutynin and tolterodine are now available, permitting once-daily dosing. The convenience of once-daily dosing of antimuscarinic agents would be expected to improve patient compliance and further relieve the symptoms of OAB. Clinical studies with the ER formulations of these agents demonstrate potential clinical advantages over their respective IR forms in terms of either efficacy or tolerability or both.[41]

Richard Scheife et al suggested that anticholinergic drugs are available for the treatment of OAB, including tolterodine, trospium chloride, and propiverine (not available in the United States). The total anticholinergic drug burden may also be important in determining the potential for CNS adverse effects. The spectrum of anticholinergic CNS adverse effects ranges from drowsiness to hallucinations, severe cognitive impairment, and even coma. The immediate-release (IR) and extended-release (ER) formulations of anticholinergic agent have been associated with cognitive impairment. In the only published clinical trial that was identified, no significant differences in CNS adverse effects were observed between the IR and ER formulations of tolterodine. There were few clinical data on the use of propiverine in patients with OAB. Trospium chloride has shown favourable CNS tolerability in post marketing surveillance studies.When considering treatment choices for patients with OAB, particularly the elderly, the potential CNS adverse effects of each anticholinergic agent must be weighed against the severity of OAB symptoms.[42]

3.4 Literature survey for Enteric Coating

Elnazeer I. et al explored that the aim of this study was to develop a delayed-release matrix pellet containing atenolol as active pharmaceutical ingredient. The matrix additionally contained trisodium phosphate dodecahydrate as alkalizing pore-former agent to enhance the dissolution of the atenolol at pH 6.8. The delayed release was ensured by coating with a gastro-resistant polymer. For this purpose, an acryl EZE MP aqueous dispersion was used, which is suggested in the literature for pellet coating. Before this functional film coating, a protective polymer layer was developed, to prevent direct contact between the alkalizing layer and the acryl EZE. The results of in vitro dissolution tests demonstrated that the double-coated pellet preparation is a delayed-release solid dosage form. Enteric-coated pellets as dosage forms are especially suited for the administration of drugs which are not stable in the gastric fluids or which can cause irritation of the gastric mucosa and which are absorbed in the duodenum or upper intestine Several commercially available polymers are suitable for the coating of pharmaceutical dosage forms, and some can be used to control the drug release kinetics. However, it is often difficult to adjust a particular release profile to the pharmacokinetic characteristics of the drug. Different formulation and processing parameters can be varied in order to optimize the drug release patterns, e.g. coating level, type polymers, etc., but these variations are often restricted because reasonable film properties must be provided and production on a large scale must be feasible. To overcome these restrictions, polymer blends can be used as coating materials controlling drug release.[43]

Kathrin Nollenberger et al Poly(meth)acrylate coatings for pharmaceutical applications were introduced in 1955 with the launch of EUDRAGIT® L and EUDRAGIT® S, two types of anionic polymers. Since then, by introducing various monomers into their polymer chains and thus altering their properties, diverse forms with specific characteristics have become available. Today, poly(meth)acrylates function in different parts of the gastrointestinal tract and/or release the drug in a time-controlled manner. This article reviews the properties of various poly(meth)acrylates and discusses formulation issues as well as application possibilities. Over the years, numerous oral dosage forms using poly(meth)acrylate coatings have been introduced, employing not only simple

coatings but also combining poly(meth)acrylates to achieve specific release profiles. Advances have included innovative formulations as well as new technologies in product development. One example is ready-to-use polymer mixtures combined with color matching possibilities, which are quicker to prepare and allow customization. These types of polymer systems contain all the necessary excipients in a powder mixture that only needs to be stirred into a solution prior to coating.[44]

G Crotts suggested that the purpose of this study was to define coating conditions for the enteric coating of a highly water soluble, acidic tablet core. Acidic tablet cores containing a marker drug were separated into three groups and seal coated to coverage gains. By employing a 'color coding' scheme, the different seal coated tablets could be coated simultaneously to reduce the number of experiments and eliminate potential differences that may exist during separate coating processes. In addition, an allotment of each coded tablet type was sequentially numbered with a marker pen, weighed, and recorded in order to identify the precise level of enteric coating as well as to monitor the variability of a given coating operation. The tablets were coated with five Eudragit® L30D-based enteric formulations containing different amounts of plasticizer (10–20 parts) and talc (10–50 parts). During each enteric coating process, a predetermined amount of labeled tablets were removed after attaining 6, 8, and 10% weight gains. The labeled tablets were re-weighed, sorted, and then tested using USP disintegration and dissolution methods. Weight gain measurements of individual tablets indicated low coating variability (6.2% RSD) during the enteric coating processes. Dissolution results revealed that all enteric coat formulations inhibited drug release for 2 h in 0.1 N HCl. In contrast, it was found that tablets without a seal coat failed the USP disintegration test. In addition, seal coated tablets exhibited ca. 1.5–5 fold greater drug release at most intermediate sampling time points in phosphate buffer, pH 6.8, than tablets without a seal coat, suggesting that the dissolution of the latter was delayed by the generation of an acidic microenvironment at the interface of the enteric coat/acidic tablet core. Prior to enteric coating an acidic, highly water soluble substrate, a seal coat barrier should be applied to prevent retardation in drug release. A simple strategy utilizing color coding and tablet marking can be employed to test the effect of a seal coat, evaluate enteric coating formulations and process with minimal experimentation and analyses.[45]

3.5 Literature survey on Hydrophobic Agent

Prashant Upadhyay et al studies on biological macromolecules lipid-Gelucire based sustained release gastroretentive multiparticulates of metformin hydrochloride (MH) were developed by dispersing MH in melted Gelucire 39/01and 43/01 using the melt granulation technique while fast release solid dispersions gastroretentive multiparticulates of glibenclamide (GLB), poorly soluble drug were developed using Gelucire 50/13 and PEG200, 400, 4000, 6000 as carrier at different ratios. Percent drug entrapment of MH was 99.6 ± 0.35% and in vitro floating ability was 11.3 ± 0.47 h. Model dependent analysis shows that zero order kinetics was followed while drug release mechanism was anomalous diffusion controlled. Combination of ethylcellulose, methylcellulose and microcrystalline cellulose with Gelucire were explored for release of drug The low bioavailability (50–60%) and short plasma half-life (1.7–4.5 h) of MH make the development of sustained-release gastroretentive dosage forms desirable using Gelucire 39/01 and 43/01.[46]

Melike Uner et al explored that solid lipid ketoprofen micropellets (SLKM) at different drug/beeswax ratios [(1:1) and (1:2)] were prepared by emulsion congealing technique and then compressed into tablets. Ketoprofen in solid state was incorporated into the melted beeswax at 90 °C and the mixture was emulsified in the hot aqueous. Tween® 80 solution by stirring at a constant rate. The SLKM were obtained by cooling the coarse emulsion down to room temperature and filtering. Drug entrapment efficiency and particle size analysis by laser diffractometry (LD) were determined, and existence of a drug–lipid interaction was investigated by differential scanning calorimetry (DSC) on the SLKM, before being compressed into the tablets by direct compression method. Finally, in vitro release studies were performed and the release kinetics of the waxy tablets were calculated.[47]

Dasharath M. Patel et al suggested that the purpose of this research was to develop and optimize a controlled-release multiunit floating system of a highly water soluble drug, ranitidine HCl, using Compritol, Gelucire 50/13, and Gelucire 43/01 as lipid carriers. Ranitidine HCl– lipid granules were prepared by the melt granulation technique and

evaluated for in vitro floating and drug release. Ethyl cellulose, methylcellulose, and hydroxypropyl methylcellulose were evaluated as release rate modifiers. A 3^2 full factorial design was used for optimization by taking the amounts of Gelucire 43/01 (X1) and ethyl cellulose (X2) as independent variables, and the percentage drug released in 1(Q1), 5(Q5), and 10 (Q10) hours as dependent variables. The results revealed that the moderate amount of Gelucire 43/01 and ethyl cellulose provides desired release of ranitidine hydrochloride from a floating system. Thus, the major objective of the present study was to design floating sustained-release granules with a low drug:lipid ratio. To achieve a lower drug:excipient ratio and good floating ability, the hydrophobic grade of the lipid excipient Gelucire(Gelucire 43/01) was selected.[48]

4.1 MATERIALS AND METHODS

- Various materials and equipments were used to carry out the experimental work. The list of materials and equipments used are given in the table 4.1 and 4.2 respectively.

Table: 4.1 List of materials

Name of Material	Manufacturer/ Supplier
Lactose monohydrate(DCL-11)	DMV Fonterra, Goch, Germany
Microcrystalline cellulose (Avicel 102)	FMC Biopolymer Philadelphia,USA
Iron oxide black	RohaDyechem, Mumbai, India.
Ferric oxide yellow	Rockwood Italia, Los Angeles, USA
Ferric oxide red	Rockwood Italia, Los Angeles, USA
Hydroxypropylmethyl cellulose	Dow Chemicals, Mumbai, India
Purified talc	Luzenac Val Chesone, Porte, Italy.
Colloidal anhydrous silica	Evonik, Mumbai, Italy.
Magnesium stearate	Merck Limited, Mumbai, India.
Opadry OY-29020 clear	Colorcon, Goa, India
Acryl 93O575001 grey	Colorcon, Goa, India
Opacode black S-1-17823	Colorcon, Goa, India

Table: 4.2 List of equipments

Name of equipment	Make and model
Octagonal Blender	Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India.
Electronic weighing balance (PG 403-S)	Mettler Toledo, Denver Instrument, India.
Double rotary tablet compression machine (CMB4-35 station)	Cadmach Machinery Co Ltd., Ahmedabad.
Coating machine	Solace Coater, Vadodara, India
Dissolution Test Apparatus (TDT-06T)	Electrolab, Mumbai, India.
HPLC	Shimadzu Corporation, Kyoto, Japan
Stability chamber	Newtronics, Mumbai, India.
UV spectrophotometer (1800)	Shimadzu Corporation, Kyoto, Japan.

4.2 PREFORMULATION STUDIES

4.2.1 CHARACTERIZATION OF ASTONT2013

- ASTONT2013 is official in US Pharmacopeia, and was analyzed as per the specifications given in the Pharmacopeia.The drug substance was procured from Harman Finochem Limited., Aurangabad.
- The tests for ASTONT2013 were conducted as mentioned in the Pharmacopeia and are shown in Table 4.3.

Table: 4.3 Tests and specification of ASTONT2013

Sr. No.	Tests	Limits	Observations
1	Description	White, crystalline & odorless powder.	White, crystalline & odorless powder.
2	Solubility	Freely soluble in water and in alcohol, very soluble in methanol and in chloroform, soluble in acetone, slightly soluble in ether, very slightly soluble in hexane	Freely soluble in water and in alcohol, very soluble in methanol and in chloroform, soluble in acetone, slightly soluble in ether, very slightly soluble in hexane
3	Identification (A) By infrared absorption (B) By HPLC	The infrared absorption spectrum of the substance being examined should be concordant with the Infrared absorption spectrum of ASTONT2013 working standard The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in chromatogram of standard preparation, as obtained in assay.	FTIR graph is presented in Fig. 4.1. The retention time of peak in the chromatogram of sample preparation is matching with the peak of chromatogram of standard.

Sr. No.	Tests	Limits	Observations
4	Melting range	Between 124°C and 129°C	125° C
5	Loss on drying	Not more than 3.0% w/w	1.10%
9	Related compounds (By HPLC)	A) ASTONT2013 related compound A : Not more than 0.15% w/w B) Any other single impurity : Not more than 0.10% w/w C) Total impurities : Not more than 1.0% w/w	Related compounds were found to be within the specified limits.
10	Assay (By HPLC)	Not less than 97.0% w/w and not more than 102.0%	99.8%
12	Particle size (by Malvern master sizer)	A) d(0.1) : Not more than20µ B) d(0.5) : Between 40µ to 80µ C) d(0.9) : Between 160µ to 210µ	A) d(0.1): 7.91 µ B) d(0.5): 43.74µ C) d(0.9): 192.31µ

FTIR spectroscopy: The FTIR spectra of ASTONT2013 is shown in fig.4.1

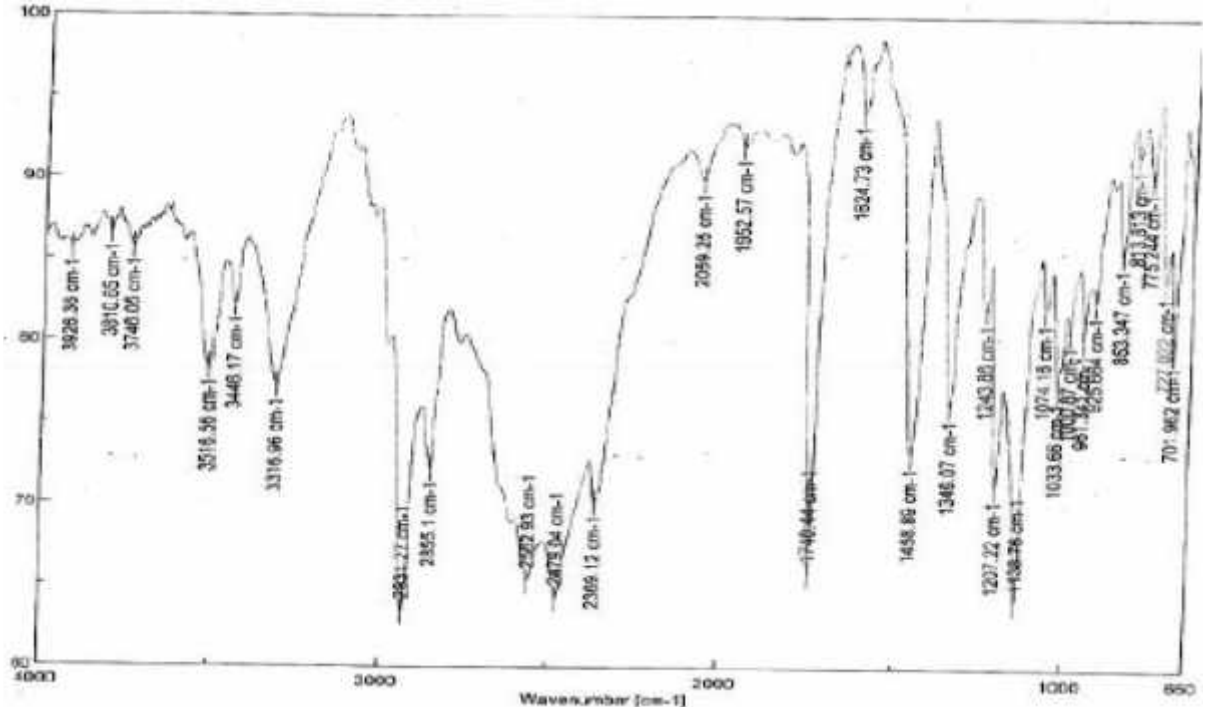


Fig. 4.1: FTIR spectra of ASTONT2013

Interpretation of the peaks is given in table no. 4.4

Table: 4.4 Interpretation of FTIR studies

Wave Number (cm^{-1})	Assignment of functional group	Intensity of peak
3316.96	OH (free hydroxyl)	M
2931.27	C-H(Aromatic)	M
2855.1	C-H(Aliphatic)	W
2369.12	C≡H (Alkynes)	M
1740.44	>C=O(Ester carboxyl)	S
1458.89	C=C (Aromatic ring stretch)	M
1243.86	Tertiary aliphatic amines	W
1207.22	Tertiary aliphatic amines	W
1138.76	Conjugated Ester	S
1033.66	Aromatic in-plane bend	W

Where W- Weak peak, M- Medium peak, S- Strong peak

- **Conclusion:**

  From the interpretation of FTIR studies, it confirms that the test sample is ASTONT2013.

4.2.2 PHYSICO-CHEMICAL ANALYSIS OF ASTONT2013

The ASTONT2013 was analyzed for its physico-chemical characteristics as per USP and the results are depicted in table 4.5.

Table: 4.5 Results: Physico-chemical analysis of ASTONT2013

Sr. No.	Tests	ASTONT2013	Limits
1	Description	White, crystalline, odorless powder	White, crystalline, odorless powder
2	Loss on drying	1.10 %	Not more than 3.0% w/w
3	Assay	99.8 %	Not less than 97.0% w/w and not more than 102.0%
4	Related compounds		
	ASTONT2013 related compound A	0.040%	Not more than 0.15%
	Any other single impurity	0.077%	Not more than 0.10%
	Total impurities	0.328%	Not more than 1.0%

4.2.3 PARTICLE SIZE DETERMINATION AND FREQUENCY DISTRIBUTION OF ASTONT2013

- Particle size determination of the ASTONT2013 was carried out using Malvern particle sizer. Malvern works on the principle of laser diffraction which gives accurate results for particle size determination.
- Particle size was determined by placing 1 g of ASTONT2013 in the duct of Malvern particle size analyzer.
- As per the patent of innovator product, the particle size of ASTONT2013 in the formulation should be greater than 150 µm.
- The results of particle size and frequency distribution are provided in table no.4.6

Table: 4.6 Particle size specification of ASTONT2013

Method	Specifications
Particle size (By Malvern master sizer)	d(0.1) : Not more than 20µ d(0.5) : Between 40 and 80µ d(0.9) : Between 160 and 210µ

The particle size of ASTONT2013 was determined as per the procedure mentioned above, and the results are shown in table 4.7 and figure 4.2

Table: 4.7 Results: Particle size distribution

Method	Specifications	RN0344
Particle size (By Malvern master sizer)	d(0.1) d(0.5) d(0.9)	7.91 µm 43.74 µm 192.31 µm

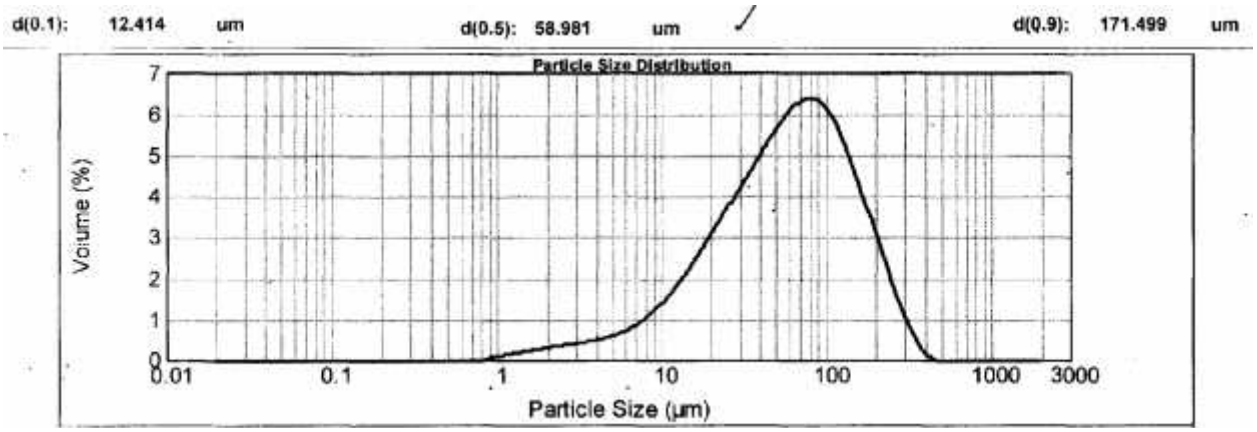


Fig. 4.2: Frequency distribution of particle size of ASTONT2013

- **Conclusion:**

  The results shows that the particle size of ASTONT2013 determined were within the in-house specifications. Hence, ASTONT2013 could be selected for formulation trials.

4.2.4 Flow properties

- Flow property of the ASTONT2013 was determined by calculating parameters such as bulk density, tapped density, compressibility index and Hausner's ratio.

➢ Bulk density and tapped density

- 10 g powder was placed in 100 ml measuring cylinder. Volume occupied by the powder was noted down as V_0, without disturbing the cylinder. Then cylinder was fitted in instrument and 10 taps were performed. After 10 taps, volume was noted down as V_a. Again after 500 taps volume was noted down as V_b. Finally after 1250 taps volume was noted as V_c. The difference between V_b and $V_c$is less than or equal to 2 mL, V_c is tapped volume. Bulk density and tapped density were calculated using following formulas:

  Bulk density (g/mL) = weight of sample in grams / V_0

  Tapped density (g/mL) = weight of sample in grams / Vc

- Compressibility index
  - Tapped and apparent bulk density measurements were used to estimate the compressibility of the material.

Compressibility index = 100*(Tapped density-Bulk density)/Tapped density

- Hausner's ratio
  - It is the ratio of bulk volume to tapped volume or tapped density to bulk density.

Hausner's Ratio = Tapped Density / Bulk Density

The results of flow properties of ASTONT2013 are provided in table no 4.8.

Table: 4.8:Results:Micromeritics of ASTONT2013

Sr. No.	Tests	Results
1.	Bulk density	0.43 g/mL
2.	Tapped density	0.67 g/mL
3.	Carr's index	35.82%
4.	Hausner's ratio	1.56

- **Conclusion:**

  The flow property of ASTONT2013 is very poor as indicated by Hausner's ratio and Compressibility index.

4.2.5 pH DEPENDENT SOLUBILITY STUDIES

- pH dependent solubility study of ASTONT2013 from both the batches were carried out in water, 0.1N hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The results are provided in table no 4.9.

Preparation of buffer solutions:

1. 0.1N hydrochloric acid- 8.5 mL of conc. HCl was mixed with 700 ml of distilled water. Volume was made upto 1000 mL with distilled water.
2. pH 4.5 acetate buffer- 2.99 g of sodium acetate was weighed in 1000 ml volumetric flask. 14 mL of acetic acid solution, was added and the volume was made up with distilled water.
3. pH 6.0 phosphate buffer- 50 mL of the monobasic potassium phosphate solution was prepared in a 200 ml volumetric flask. 22.4 mL of 0.2M NaOH, was added and the volume was made up with distilled water.

Table: 4.9 Results: Solubility of ASTONT2013 in different medium

Sr. No.	Medium	Saturation solubility (mg/mL)	Remarks*
		ASTONT2013	
1	Distilled water	271.577	Sink Condition
2	0.1N HCl	248.600	Sink Condition
3	Acetate buffer 4.5 pH	263.345	Sink Condition
4	Phosphate buffer 6.0 pH	263.318	Sink Condition

*Sink condition achieved if solubility is > 0.05 mg/mL

- **Conclusion:**

  ASTONT2013 shows pH independent solubility. This indicates that the sink condition can be maintained throughout the gastrointestinal tract.

4.2.6 HYGROSCOPIC STUDIES

- To check the hygroscopicity, the ASTONT2013 was directly exposed in an open petri dish placed in a desiccators containing saturated solution of ammonium sulphate and having humidity levels 80-90% RH and maintained at 25°C. The mass gain due to moisture absorption was monitored at 24 h.
- Percentage increase in mass was calculated using the following expression:

$$(m_3-m_2)/(m_2-m_1)*100$$

Where,

m_1 – weigh of petridish; m_2 – weight of petridish containing substance being studied

m_3 – weight of petridish containing substance being studied after 24 hr.

Results:

ASTONT2013

m1 : 42.808 gm

m2 : 43.818 gm

m3 : 43.829 gm

- So, as per the equation, percentage increase of moisture content was found to be 1.09%.
- Conclusion:
  According to result obtained, it can be concluded that ASTONT2013 is slightly hygroscopic in nature.

4.3 INNOVATOR CHARACTERIZATION

- Details of the innovator product and its physical characteristics are mentioned in table 4.10 respectively

Table: 4.10 Product details of innovator product

Generic name	ASTONT2013extended release tablets 15 mg
Dosage form	Extended release tablet
Label claim	Each tablet contains 15 mg ASTONT2013 in a controlled-release formulation.
Mfg. by	Alza Corporation, Vacaville, CA
Marketed in	USA
Exp. date	02/2014
Indications covered in leaflet	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Treatment of pediatric patients aged 6 years and older with symptoms of detrusor over activity associated with a neurological condition (e.g., spina bifida).
Inactive Ingredients	Cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxyl toluene
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture and humidity.
Packaging	100 CC, HDPE square bottle with child resistant cap and ORICAP desiccant
Pack style	Pack of 100 tablets.

Table: 4.11 Physical characterization of innovator product

Tablet description	Grey coloured, round, biconvex, coated tablets imprinted with "15XL" on one side and plain on other side mark with laser drill on any side.
Tablet shape	Round shaped
Tablet dimensions (mm)	7.45
Embossing details	Imprinted with "15XL" on one side and plain on other side mark with laser drill on any side.
Avg. weight (mg)	187.62
Thickness (mm)	4.5

4.3.1 CHARACTERIZATION OF INNOVATOR PRODUCT

- The physicochemical characteristics of innovator product were evaluated and the results are table 4.12

Table: 4.12 Characterization of innovator product

Sr. No.	Strength	15 mg
	Batch No.	1CG604
	Exp. Date	May 2014
	Analysis Date	14/06/2013
1.	Average weight (mg)	187.4
2.	Assay (%)	100.0
3.	Related substances	
	Related Compound A	0.022%
	Single max unknown	0.048%
	Total impurities	0.085%
4.	Loss on drying (%)	1.46

4.3.2 IN-VITRO DRUG RELEASE OF INNOVATOR PRODUCT

Table: 4.13 Results: *in-vitro* drug release in

0.1N HCl followed by pH 6.0 phosphate buffer + 0.2% SLS

Time (Hrs)	Cumulative percent release
0.1 N HCl	
1	1
2	3
pH 6.0 phosphate buffer + 0.2% SLS	
2	12
4	24
6	38
8	52
10	64
12	75
14	82
16	87
20	87

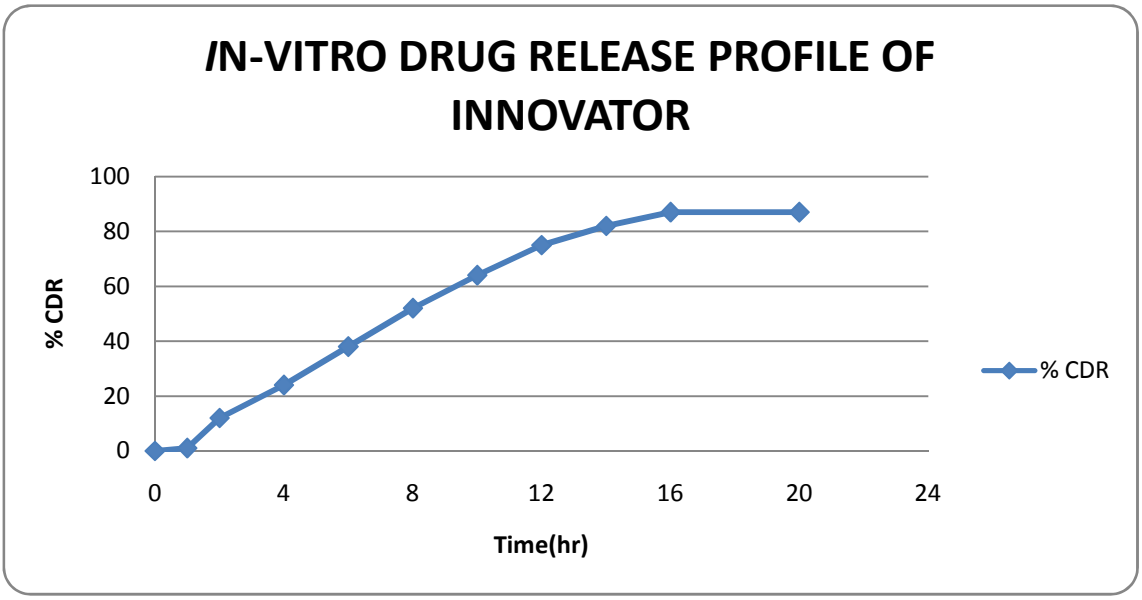


Fig:4.3 *in-vitro* drug release in

0.1N HCl followed by pH 6.0 phosphate buffer + 0.2% SLS

4.4 FORMULATION OF EXTENDED RELEASE TABLETS

Extended release tablets can be formulated using various technologies. Widely used commercially viable technologies are monolithic matrix system and coating controlled extended release system. The choice of the technology depends upon the target *in-vitro* profile which in turn depends upon desired *in-vivo* performance. The major factors that affect the performance *in-vitro* and *in-vivo* of an extended-release tablet are type of system and nature along with concentrations of polymers used to develop an extended release tablet. There are various manufacturing techniques like direct compression, dry granulation and wet granulation used for fabrication of extended release tablets.

Direct compression approach is the simplest and involves least process variables that may impact the quality of the product. Moreover, whenever gelling polymers are used in formulation, it is best to use direct compression as manufacturing technique since it has minimal impact on the properties of naive polymer. Therefore it was decided to initiate product development using direct compression approach.

Formulation was designed considering the following factors:

1) *Dissolution release rate*: The choice of technology, polymer and manufacturing process was selected considering the fact that, reference product utilizes osmosis as dissolution mechanism leading to almost perfect zero-order release pattern.
2) *Trade dress selection*: In order to match the trade-dress, formulation was pseudo-dose proportional and employed look-a-like strategy.
3) *Functional coat*: Preliminary evaluation of reference product dissolution suggested that it required to have partial enteric coating on tablets in order to control release in 0.1 N HCl.
4) *Requirement of seal coat*: A barrier coat was required in between core and enteric coat so that enteric coat did not perturb the core matrix formulation characteristics and lead to irreproducible release pattern.
5) *Product identification*: The limitation for debossing on tablets imposed by large amount of coating onto the core tablets lead to the selection of imprinting as a tool

for differentiation between strengths. Accordingly appropriate tooling was selected for compression. Moreover the strengths were differentiated at each stage that might lead to use of colorants.

4.4.1 FORMULATION DESIGN

Considering the limitation imposed by patents and technology used by reference product formulation design involved:

1. *A hydrophilic matrix tablet*: Choice of hydrophilic polymer to formulate a matrix tablet was guided by some of the patents of ALZA corp., (US 6,262,115, and 6,117,453) along with the Mylan's available formulation of 5 mg and 10 mg strength.
2. *A barrier coat*: ASTONT2013 exhibited good aqueous solubility and core contained hydrophilic polymers. An aqueous enteric coating over such a core lead to erratic dissolution profiles, therefore a seal coat was applied in between core and enteric coat.
3. *Enteric coat*: The release rate of innovator product in acidic pH was minimal for first two hours and pharmacokinetic profile of innovator, it was decided to apply enteric coat. Moreover it was practically impossible to obtain near zero release for first two hrs with a hydrophilic matrix formulation.

4.5 DRUG-EXCIPIENTS COMPATIBILITY STUDY

Compatibility studies of ASTONT2013 with different excipients were carried out by accelerated thermal stress study.

The vials were incubated at 40°C/75% RH for 1 month, 60°C, 30°C/65% RH and 25°C/60% RH for 1 month. Samples were observed at the end of 1 month and physical description was recorded.

Table:4.14 Compatibility studies of ASTONT2013 and excipients in accelerated condition

Sr. No.	Samples	Ratio
1.	ASTONT2013	1
2.	ASTONT2013 + Microcrystalline cellulose	1:10
3.	ASTONT2013 + HPMC	1:5
4.	ASTONT2013 + Magnesium stearate	1:0.5
5.	ASTONT2013 + Talc	1:1
6.	ASTONT2013 + Lactose	1:10
7.	ASTONT2013 + Sodium chloride	1:5
8.	ASTONT2013 + Polyethylene glycol	1:0.5
9.	ASTONT2013 + Colloidal anhydrous silica	1:0.5
10.	ASTONT2013 + Mannitol	1:10
11.	ASTONT2013 + Methacrylic acid copoylmer	1:1
12.	ASTONT2013 + Cellulose acetate	1:2
13.	ASTONT2013 + Polyethylene oxide	1:10

Drug excipient compatibility studies were performed as per the procedure mentioned above and the results are shown in table 4.15 .

Table: 4.15 Results:Drug excipients compatibility studies

Condition	ASTONT 2013 : Excipient (Ratio)	Description	Related substances (%)			% Assay
			Related Comp A	Single unk. Imp.	Total imp	
ASTONT2013						
Initial	1:0	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.000	0.000	0.000	100.0
ASTONT2013 + Microcrystalline Cellulose						
Initial	1:10	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.033	0.000	0.033	100.0
40°C, 75% RH, Open, 1M		White powder	0.053	0.000	0.053	99.9

ASTONT2013 + HPMC						
Initial	1:5	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.042	0.000	0.042	100.0
ASTONT2013 + Magnesium stearate						
Initial	1:0.5	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.064	0.000	0.064	99.9
ASTONT2013 + Talc						
Initial	1:1	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.031	0.000	0.031	100.0
ASTONT2013 + Lactose						
Initial	1:10	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0

ASTONT2013 + Sodium chloride						
Initial	1:5	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.000	0.000	0.000	100.0
ASTONT2013 + Polyethylene glycol						
Initial	1:0.5	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		Lump formation	0.000	0.401	0.401	99.6
40°C, 75% RH, Open, 1M		Lump formation	0.032	0.000	0.032	100.0
ASTONT2013 + Colloidal anhydrous silica						
Initial	1:0.5	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.000	0.000	0.000	100.0

ASTONT2013 + Mannitol						
Initial	1:10	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		Lump formation	0.036	0.000	0.036	100.0

ASTONT2013 + Methacrylic acid copoylmer						
Initial	1:1	White powder	0.000	0.000	0.000	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.000	0.000	0.000	100.0
ASTONT2013 + Cellulose acetate						
Initial	1:2	White powder	0.033	0.000	0.033	100.0
50°C, Closed, 1M		White powder	0.000	0.000	0.000	100.0
40°C, 75% RH, Open, 1M		White powder	0.033	0.000	0.033	100.0

ASTONT2013 + Polyethylene oxide						
Initial	1: 10	White powder	0.000	0.071	0.071	99.9
50°C, Closed, 1M		Lump formation	0.106	0.191	0.297	99.7
40°C, 75% RH, Open, 1M		Lump formation	0.086	0.000	0.086	99.9

Conclusion:

- No significant increase in the impurity levels was observed with studied excipients except with polyethylene glycol and polyethylene oxide. Based on the results, it is concluded that the attempt is made to avoid the use of polyethylene glycol and polyethylene oxide in formulation and if at all needed the ratio of these excipients shall be selected in such a way that they will have minimal impact on generation of impurity. Moreover direct interaction of such excipients with ASTONT2013 shall be avoided.

4.6 MANUFACTURING PROCESS:

- The manufacturing process employed in preparation of extended release tablets of ASTONT2013 is mentioned below:

  - Step 1: Dry Mix:

ASTONT2013 and excipients used to formulate hydrophilic matrix system (such as lactose monohydrate, microcrystalline cellulose, hydroxypropylmethyl cellulose, colloidal anhydrous silica and/or purified talc) were co-sifted through 40# sieve.

Iron oxide black was sifted through 100# sieve and mixed with the above sifted dry mix for 20 min. in a blender.

  - Step 2: Blending:

Colloidal anhydrous silica and purified talc were co-sifted through 40# sieve and mixed with dry mix prepared in step-1 for 10 min. in a blender.

  - Step 3: Lubrication:

Magnesium stearate was sifted through 60# sieve and mixed with blend prepared in step-2 for 5 min in a blender.

  - Step 4: Compression:

The lubricated blend was compressed in compression machine with D tooling.
Upper punch: 7.10 mm, round shaped, standard concave, plain
Lower punch: 7.10 mm, round shaped, standard concave, plain
Die: 7.10 mm

  - Step 5: Seal coating:

Preparation of seal coating solution: Opadry OY-29020 Clear was dispersed in isopropyl alcohol followed by addition of dichloromethane and stirred for 45 minutes. The dispersion was passed through # 100 sieve.
Procedure for seal coating: The core tablets were loaded in a coating pan and preheated for 5 minutes at intermittent rotation. The process parameters set for seal coating are mentioned in table 4.16. The tablets were further coated with the above coating dispersion to achieve a weight gain of 6.0% w/w of core tablet.

Table: 4.16 Seal coating process parameters

Sr. No.	Parameters	Required parameters	Initial set parameters
1	Inlet temperature (°C)	51 to 57	52
2	Exhaust temperature (°C)	39 to 41	38
3	Product bed temperature (°C)	39 ± 41	40
4	Pan speed (rpm)	3-7	4
5	Atomization air pressure (Mpa)	2	2
6	Gun to bed distance (in.)	8-15	10
7	Spray rate (g/mL)	1.5-2.5	2
8	Cubic feet per meter (CFM)	20-26	24

- After completion of seal coating, the tablets were post dried at intermittent rotation for 30 minutes.

o Step 6: Enteric coating

Preparation of enteric coating solution: Acryl – EZE 93O575001 Grey was dispersed in purified water and stirred for 45 minutes.

Procedure for enteric coating: The core tablets were loaded in a coating pan and preheated for 5 minutes at intermittent rotation. The process parameters set for enteric coating are mentioned in table 4.17 .The tablets were further coated with the above coating dispersion to achieve a weight gain of 12.0% w/w of seal coated tablet.

Table: 4.17 Enteric Coating process parameters

Sr. No.	Parameters	Required parameters	Initial set parameters
1	Inlet temperature (°C)	48 to 54	52
2	Exhaust temperature (°C)	38 to 42	40
3	Product bed temperature (°C)	39 to 43	41
4	Pan speed (rpm)	2-3	2
5	Atomization air pressure (Mpa)	2	2
6	Gun to bed distance (in.)	8-15	10
7	Spray rate (g/mL)	1.5-2.5	2
8	CFM	20-26	24

After completion of enteric coating, the tablets were dried at intermittent rotation for 60 minutes.

4.7 QUALITY TARGET PRODUCT PROFILE (QTPP) & CRITICAL QUALITY ATTRIBUTES (CQA)

- Based upon the above clinical and pharmacokinetic characteristics of innovator tablets as per the product label, and characterization of innovator product tablets in-vitro drug release and physicochemical characteristics, a QTPP was defined to guide the development of a generic extended release tablet that is therapeutically equivalent to the RLD (Reference Listed Drug).

The QTPP for the ASTONT2013 extended release tablet USP 15 mg extended release tablets is defined in Table 4.18.

Table: 4.18 Quality Target Product Profile (QTPP) for the ASTONT2013 extended release tablet USP 15 mg

QTPP Element	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: Same dosage form
Dosage design	Extended-Release tablet	Extended-Release design needed to meet label claims.
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	15 mg	Pharmaceutical equivalence requirement: Same strength
Stability	24-month shelf-life at room temperature.	Needed for commercialization
Drug product	Physical Attributes	Pharmaceutical equivalence

quality attributes	Average Net content	requirement: Meeting the same or compendial or other applicable (quality) standards (i.e., identity, dissolution ,assay, purity, and quality)
	Identification	
	Assay	
	Uniformity of Dosage Units	
	Dissolution	
	Degradation product	
	Loss on Drying	
	Microbial Limits	
	Related solvents	
Container closure system	Suitable container closure system to achieve the target shelf-life and to ensure tablet integrity during shipping	HDPE bottle pack selected based on similarity to the RLD packaging. Child resistant cap is needed.
Administration	The recommended starting dose is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.	As per the information provided in RLD labeling

- From the QTPP, we identified Critical Quality Attributes (CQAs) of the drug product which are summarized as shown in Table.4.19

Table: 4.19 Critical and non-critical quality attributes of ASTONT2013the extended release tablet

Drug Product Quality Attributes	Target	Is this critical?	Justification of Criticality
Appearance	Color and shape acceptable to the patient and similar to RLD. No visual defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to develop product with color, shape, and appearance similar to RLD and ensure patient acceptability.
Odor	No unpleasant odor	No	Odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
Size	Size acceptable to the patient and similar to RLD	No	Tablet size is set similar to RLD. It is standard size with ease of swallowing as well as patient acceptance and compliance with treatment regimens. Therefore, it is not critical.
Score/Imprint Configuration	Imprinting on tablet	No	Unique identification
Average Net Content	Target weight ± 3%	No	Formulation and process variables are unlikely to impact this CQA.

Identification	Positive for ASTONT2013	No	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity.
Assay	97.0% to 102.0% of label claim	Yes	Variability in assay will affect safety and efficacy.
Uniformity of Dosage Units	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy.
Degradation Products/ Related Compounds	Any other impurity: NMT 0.10% Total impurities: NMT 1.0%	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH requirements till shelf-life. Limit of known impurity & any other impurity can be kept higher then ICH limits to meet the limit of drug substance as per USP monograph.

Drug release	Similar drug release profile as RLD using USP recommended dissolution method	Yes	Both formulation and process affect drug release. Failure to meet the dissolution specification can impact bioavailability. So, it is critical to meet this specification and match drug release profile to RLD.
Loss on drying	Not more than 3.0% w/w	No	Limited amounts of water in oral solid dosage forms will not impact patient safety or efficacy.
Microbial Limits	Meet relevant pharmacopoeia Criteria	No	Non-compliance with microbial limits will impact patient safety. In this case, the risk of microbial growth is low because dry granulation process used during manufacturing process. Therefore, formulation and process variables are unlikely to impact this CQA.

NMT: Not more than

- During pharmaceutical development all attributes in the QTPP are monitored. The following drug product CQAs were identified for explicit tracking in risk assessment: Assay, Impurities, CU, Dissolution. The criteria for inclusion in this list of CQAs were that these attributes had the greatest potential to be altered by process parameters or formulation variables.

4.7.1 RISK ASSESSMENT OF POTENTIAL IMPACT OF API ATTRIBUTES ON DRUG PRODUCT CQAS

- A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The same relative risk ranking system was used throughout pharmaceutical development. For each risk assessment performed, the rationale for the risk assessment tool selection and the details of the risk identification, analysis and evaluation are available to the FDA Reviewer upon request.

- To identify variables for further a risk assessment study was conducted. The risk assessment included prior knowledge and experience with related formulations and information about ASTONT2013 from literatures. Because the final manufacturing process was not established at the time of this risk assessment, changes that could be mitigated by adjustments to the manufacturing process were related as lower risk. These factors would be recognized during process development if required. In the risk assessment process, quantitative risk priority numbers were mapped onto three categories. (High, Medium and Low)

Table 4.20 Risk assessment of Potential Impact of excipients on drug Product CQA's

Drug product CQAs	Formulation variables →			
	Diluent level	HPMC Level	Colloidal Anhydrous Silica Level	Magnesium Stearate Level
Assay	Low	Low	Low	Low
Uniformity of Dosage Units	Low	Low	Low	Low
Degradation Products	Low	Low	Low	Low
Dissolution	Low	High	Low	Low

Low Risk : No further Investigation is needed;

Medium Risk : Further investigation may be needed in order to reduce the risk;

High Risk : Further investigation is needed.

Table 4.21: Risk assessment justification

Excipients Attributes	Drug Product CQAs	Justification
Diluent	Assay	Since the level of Diluents directly compressible grade used is low and its impact on flow is minimal, it is unlikely to impact assay and uniformity of dosage units. The risk is low.
	Uniformity of Dosage Units	
	Degradation Products	Diluent is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Dissolution	Since the level of Diluent is low it is unlikely to impact dissolution. The risk is low.
Hydroxy propyl methyl cellulose (Polymer)	Assay	Since the dry granulation process is followed with using high viscosity and low viscosity grade controlled release polymer HPMC. Impact on flow is minimal; it is unlikely to impact assay & uniformity of dosage units. The risk is low.
	Uniformity of Dosage Units	
	Degradation Products	HPMC is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Dissolution	Concentration of HPMC level can impact dissolution via release of drug from matrix formation. So HPMC level will affect the dissolution profile. The risk is high.
Colloidal anhydrous silica (Glidant)	Assay	Generally, colloidal anhydrous silica enhances blend flowability. A low level of colloidal anhydrous silica is not likely to impact assay and uniformity of dosage units. The risk is low.
	Uniformity of Dosage Units	
	Degradation Products	Colloidal Anhydrous Silica is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Dissolution	Colloidal anhydrous silica has less impact on dissolution. Since the level of Colloidal anhydrous silica used is low hence it is unlikely to impact dissolution as ASTONT2013 is BCS class I. The risk is low.

Magnesium Stearate (Lubricant)	Assay	Since the level of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and uniformity of dosage units. The risk is low.
	Uniformity of Dosage Units	
	Degradation Products	Magnesium stearate is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Dissolution	Magnesium Stearate level is low and may not impact dissolution as ASTONT2013 BCS class I. The risk is low.

- Trial with varying quantities of the tabulated excipients was evaluated in optimization part.

4.7.2 PROCESS RISK ASSESSMENT

- A good formulation also must be easy to manufacture and must produce good products consistently. After the formulation is optimized, more studies must be conducted to optimize the manufacturing process. A typical manufacturing process for a tablet product includes blending, milling, lubrication and compression, coating. Each processing step involves several process parameters. For a given formulation, critical processing steps must be thoroughly evaluated so that a robust manufacturing process can be defined. This process usually starts after the formulation is selected. This entire process is usually called manufacturing process development and optimization.

Table 4.22: Tablet manufacturing process flow variables

Process	Variables	Responses
Lubrication	Mixing time	Blend Uniformity
Tabletting	Low, optimum & high Hardness of tablets	Physical parameters , content uniformity and Dissolution
Coating	Different percentage of coating	Weight gain, Physical parameters and dissolution

Table 4.23: Risk assessment of Potential Impact of Process on drug Product CQA's

Drug product CQA	Process Attribute		
	Lubrication	Compression	Coating
Assay	Low	Medium	Low
Uniformity of Dosage Units	High	High	Low
Dissolution	Low	High	High

Low Risk : No further Investigation is needed;

Medium Risk : Further investigation may be needed in order to reduce the risk;

High Risk : Further investigation is needed.

- Trial with varying quantities of the tabulated excipients was evaluated in optimization part.

Table 4.24: Risk assessment justification

Process	Drug Product CQAs	Justification
Lubrication	Assay	Lubrication time can directly impact assay and blend uniformity which can finally impact content uniformity of tablets and it also has impact on dissolution so risk is high and the dose is very low. So impact of lubrication time on Blend uniformity and dissolution needs to be studied. However it has no impact on Assay & degradation products so risk is low.
	Uniformity of Dosage Units	
	Dissolution	
Compression	Assay	Tablet press speed and feeder speed may impact the flow of the blend into the die cavity. Although good flowability was achieved during optimization of the prototype formulation, the risk of compression process variables to impact tablet assay is medium.
	Uniformity of Dosage Units	Segregation may occur during compression due to vibration as well as poor flow from the hopper to feeder frame and, ultimately, into the die cavity. The risk of compression process variables to impact tablet CU is high. Hence further studies to be conducted.
	Dissolution	Excessive compression force may impact the drug release profile as the formulation is extended release dosage forms. The risk of compression process variables to impact drug release is high. Hence further studies needs to be conducted.
Coating	Assay	Percentage coating can directly impact on dissolution so risk is high. However it has no impact on Assay & Uniformity of Dosage Units so risk is low
	Uniformity of Dosage Units	
	Dissolution	

4.8 EVALUATIONOF TABLETS

- The formulated tablets of ASTONT2013 were subjected to the following evaluation parameters.

4.8.1Weight variation: Twenty tablets were weighed individually and the average weight was determined. The percent deviation was calculated and checked for weight variation. The Pharmacopeial standards for weight variation of a tablet is shown in table no 4.25.

Table: 4.25 Standards for weight variation test

Average weight of tablet	% deviation
130 mg or less	10
More than 130 mg but less than 324 mg	7.5
324 mg or more	5

4.8.2Thickness measurement: The thickness of prepared tablets was measured using a vernier caliper. Five tablets from each batch were used for this test. The mean and standard deviation of each batch was calculated.

4.8.3Hardness test: Tablet hardness (tablet crushing strength) is defined as the force required for breaking a tablet in a diametric compression test. Tablets required a certain amount of hardness or strength to withstand mechanical shocks of manufacturing, packaging, and shipping. Hardness of 5 tablets from each batch was measured using Monsanto hardness tester.

4.8.4Friability test: Friability test was performed to assess the effect of friction and shock, which may often cause tablet to chip, cap or break. Friability of the tablets was determined using Roche friabilator (Erection and Instrumentation Engineers). This device subjected the tablets to combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropped the tablets at a height of 6 inches in each revolution. Tablets were weighed and placed in the friabilator and were subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed.

The friability (f) was calculated using following formula:

$$\text{Friability (\%)} = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} * 100$$

4.8.5 Uniformity of content: A tablet was placed in 250 ml volumetric flask. To it5 ml of water was added and kept aside for 5 min. 100ml of diluent was added and sonicated for 15 min. Solution was diluted to 250ml with diluents. Solution was centrifuged at 3000 rpm. Quantitatively a volume of clear supernatant was diluted to obtain a solution having concentration of 0.2 µg ASTONT2013 per ml.

4.8.6*In-vitro*dissolution studies: The tablets were evaluated for *in-vitro* drug release in USP dissolution apparatus. The conditions used for dissolution study are provided in table no. 4.26.

Table: 4.26: Dissolution conditions

USP dissolution apparatus	Type-II (Paddle type)
Media	0.1 N HCl for 2 Hrs, pH 6.0 + 0.2 % SLS 900ml for 2,4,14,20 Hrs.
Volume of dissolution medium	900 ml
Speed of paddle rotation	50 rpm
Sampling point (h)	2,4,6,8,10,12,14,16,20
Temperature	37 ± 0.5ºC

4.8.7*In-vitro* alcohol dose dumping: For alcohol dose dumping study (1) 900 ml of 0.1 N HCl and (2) 900 ml 40% v/v ethanol in 0.1 N HCl were selected to mimic the effect of alcohol on drug release. Dissolution test parameters were set as follows,

- Temperature : 37.0 ± 0.5ºC
- Rotational speed : 100 rpm
- Apparatus type :Paddle

The dissolution system was combined with an automatic sampling and analyzing. Samples of 10 ml were withdrawn at every 15 min for 2 hrs. ASTONT2013 was measured by reverse phase HPLC.

Qualification criteria for alcohol dose dumping study were

1) Drug release in alcoholic medium should be similar with drug release in non-alcoholic medium, if a first criterion is not met then

2) Drug release in alcoholic medium should be less than or comparable to that of the reference product (As per USFDA guidelines on alcohol dose dumping study).

4.8.8Assay: Ten tablets were taken and as per USP procedure final concentration is prepared equivalent to 0.1mg/mL of ASTONT2013, evaluated using HPLC.

Procedure:

- Buffer: A solution containing 6.67 g/L of monobasic potassium phosphate and 8.55 g/L of dibasic potassium phosphate
- Mobile phase: Acetonitrile and *Buffer* (49:51)
- Standard solution: 0.1 mg/mL of USP ASTONT2013 in *Mobile phase*
- Sample solution: 0.1 mg/mL of ASTONT2013 in *Mobile phase*
- Chromatographic system:
  - Mode: Liquid Chromatography
  - Detector: UV at wavelength 210 nm
  - Column: 4.6-mm × 7.5-cm; 3-µm or 3.5-µm packing L7
  - Column temperature: 45°C
  - Flow rate: 1 mL/min
  - Injection volume: 10 µL

4.8.9Stability studies: The accelerated stability study for tablets were performed by placing the tablets in HDPE bottles(with 1 g silica gel canister (desiccant) with child resistant cap) from optimized and stability batch at40ºC temperature and 75% RH and at 25ºC temperature and 60% RH for three months. At the end of each month, tablets were evaluated for drug release profile (dissolution test) and drug content (assay).

4.9FORMULATION TRIALS

Table: 4.27: Trials of batches F1 to F5

Trials	F1	F2	F3	F4	F5
Batch size	1100				
Part I- Dry mix					
Drug X	15				
HPMC K 15 M	40	20	-	-	-
HPMC K 4 M	-	-	40	20	-
HPMC 100 LV CR	50	50	50	50	90
HPMC K 100 M	-	-	-	-	10
Lactose monohydrate	24	34	24	34	20
MCC 101	30	40	30	40	25
Iron oxide black	0.072				
Part II- Blending					
Talc	1.5				
Aerosil	1.5				
Part III- Lubrication					
Magnesium stearate	2				
Target wt. per tablet (mg)	165				

Table: 4.28: Evaluation Parameters of batches F1 to F5

Trial	F1	F2	F3	F4	F5
Physical parameters					
Average Weight (mg)	165	166	165	166	165
Thickness (mm)	3.98-4.10	4.01-4.23	4.00-4.19	3.98-4.07	4.01-4.20
Hardness (N)	85-118	93-108	90-106	95-109	100-113
Friability (%)	Nil	Nil	Nil	Nil	Nil
Dissolution Results					
Time Points	Reference Product % drug release	0.1N HCl followed by pH 6.0 Phosphate buffer with 0.2%SLS			
0.1N HCl media					
1	1	0	0	0	0	0
2	3	5	6	9	5	1
pH 6.0 phosphate buffer with 0.2 % SLS					
2	12	8	9	11	10	8
4	24	10	12	14	13	9
14	75	31	39	42	45	68
20	87	42	51	61	67	81

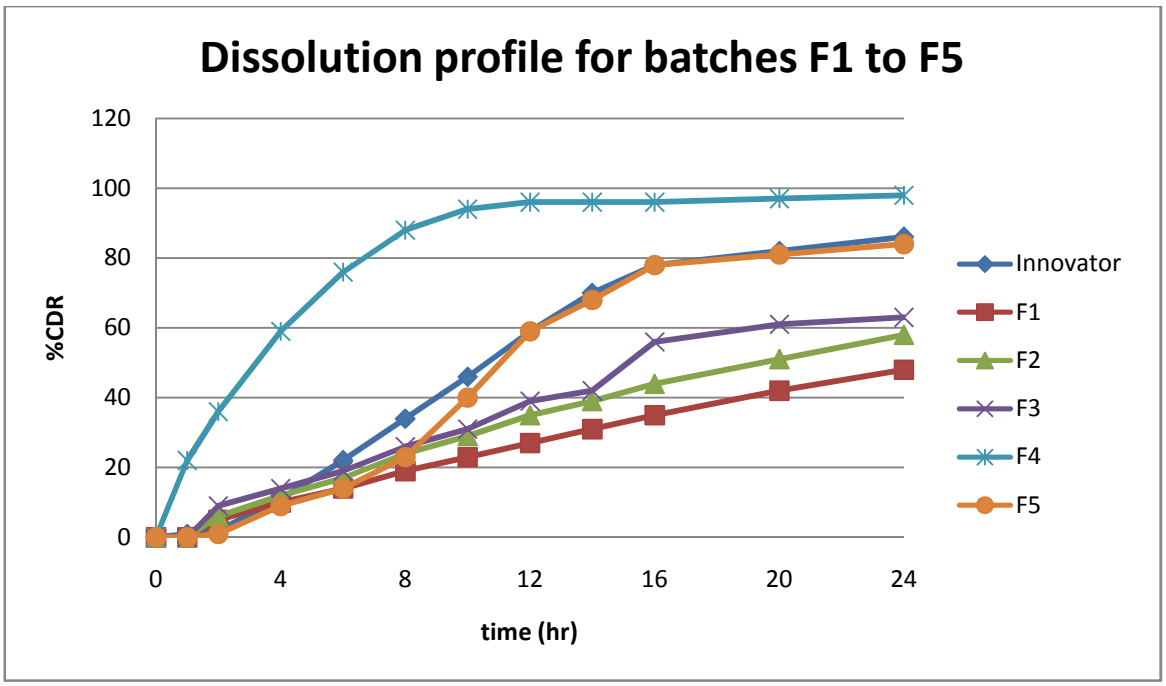


Fig 4.4: Dissolution Profile of batches F1 to F5

- **Discussion**

  From the above results, it was concluded that all F1 to F5 batches shows slower dissolution profile than the innovator. In batches F1 to F4 HPMC K 4 M and HPMC K 15 M could not controlled the release as an innovator. As they would hydrate faster so drug would release slowly from the matrix. Hence, slow hydrating polymer was incorporated in F5 trial. In F5 trial HPMC 100 LV CR quantity was very high, which retard the release of drug in initial hours. As it was fast hydrating polymer, drug would not be able to release in initial hours.

  Hence, further trials were executed by taking different ratio of fast hydrating and slow hydrating polymer.

Table: 4.29: Trials of batches F6 to F10

Trials	F6	F7	F8	F9	F10
Batch size	1100				
Part I- Dry mix					
Drug X	15				
HPMC K 15 M	-	-	-	-	-
HPMC K 4 M	-	-	-	-	-
HPMC 100 LV CR	80	50.0	40	-	40
HPMC K 100 M	20	40.0	30	50	40
Lactose monohydrate	20	25	32	42	25
MCC 101	25	30	43	53	40
Iron oxide black	0.072				
Part II- Blending					
Talc	1.5				
Aerosil	1.5				
Part III- Lubrication					
Magnesium stearate	2				
Target wt. per tablet (mg)	165				

Table: 4.30: Evaluation Parameters of batches F6 to F10

Trial		F6	F7	F8	F9	F10
Physical parameters						
Average Weight (mg)		165.820	165.000	165.000	165.823	165.654
Thickness (mm)		3.97-4.14	4.00-4.15	3.90-4.05	4.24-4.32	3.82-3.89
Hardness (N)		98-110	100-115	90-105	90-110	90-100
Friability (%)		Nil	Nil	Nil	Nil	Nil
Dissolution Results						
Time Points	% Drug Release	0.1N HCl followed by pH 6.0 Phosphate buffer with 0.2%SLS				
	Reference Product					
0.1N HCl media						
1	1	0	2	3	2	0
2	3	2	6	6	5	1
pH 6.0 phosphate buffer with 0.2 % SLS						
2	12	5	8	10	6	11
4	24	8	12	13	10	13
14	75	54	44	44	32	43
20	87	77	61	58	43	56

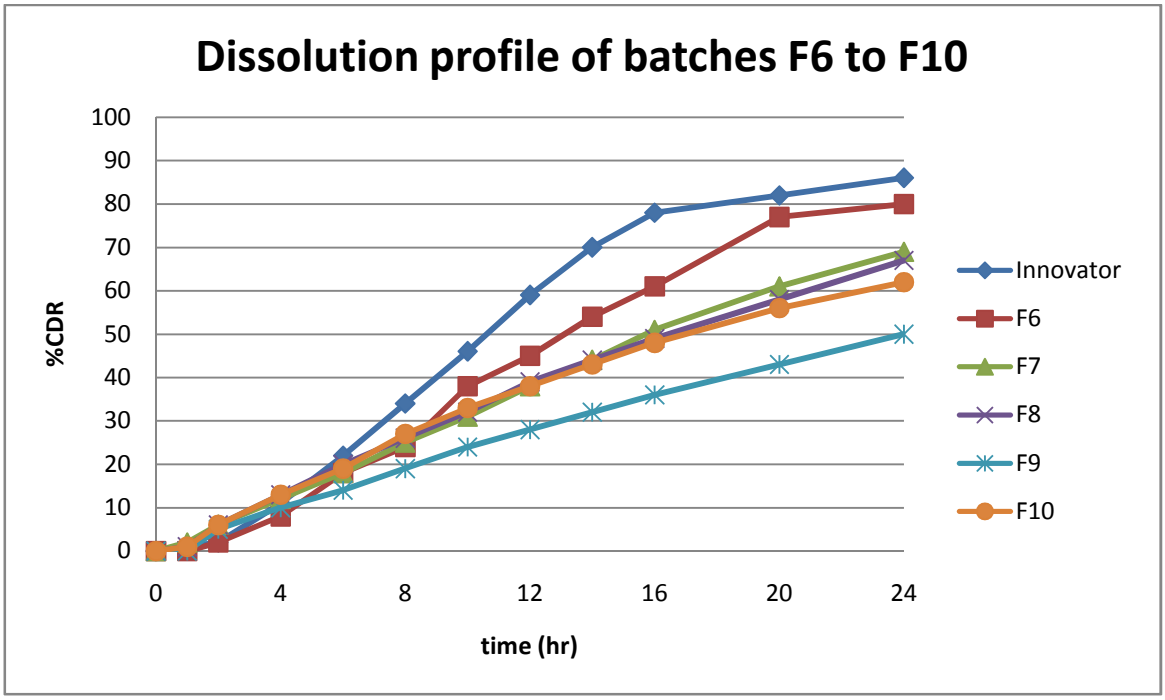


Fig 4.5: Dissolution Profile of batches F6 to F10

- **Discussion**

  From the above results it was observed that F6 to F10 batches were showed slow release profile than the innovator.F6 to F8 batches gave faster release respectively in initial hours, as HPMC 100 LV CR quantities would decrease respectively. Though it would retard the release in latter hours as HPMC K 100 M quantities would increase respectively in F6 to F8 batches. Hence, F10 batch gave slow release of drug in initial 2 hours and also controlled the release till 20 hours. However, it would not match with an innovator. Hence, further trials incorporating HPMC 100 LV CR and HPMC K 100 M was executed.

Table: 4.31: Trials of batches F11 to F14

Trials	F11	F12	F13	F14
Batch size	1100			
Part I- Dry mix				
Drug X	15			
Lactose monohydrate	20	26	28	30
MCC 101	45	32	34	36
HPMC 100 LV CR	45	55	45	45
HPMC K 100 M	35	35	40	37
Iron oxide black	0.072			
Part II- Blending				
Talc	1.5			
Aerosil	1.5			
Part III- Lubrication				
Magnesium stearate	2			
Target wt. per tablet (mg)	165			

Table: 4.32: Evaluation Parameters of batches F11 to F14

Trial		F11	F12	F13	F14
Target wt. per tablet (mg)		196.072	196.072	207.265	207.265
Physical parameters					
Average Weight (mg)		196	198.6	201	200
Thickness (mm)		4.05-4.12	4.15-4.22	4.22-4.28	4.20-4.30
Hardness (N)		95-110	95-110	100-110	100-110
Friability (%)		Nil	Nil	Nil	Nil
Dissolution Results					
Time Points	% Drug Release	0.1N HCl followed by pH 6.0 Phosphate buffer with 0.2%SLS			
	Reference Product				
0.1N HCl media					
1	1	0	0	0	0
2	3	0	0	0	0
pH 6.0 phosphate buffer with 0.2 % SLS					
2	12	20	15	22	18
4	24	37	28	38	34
14	75	74	65	84	75
20	87	92	84	99	92

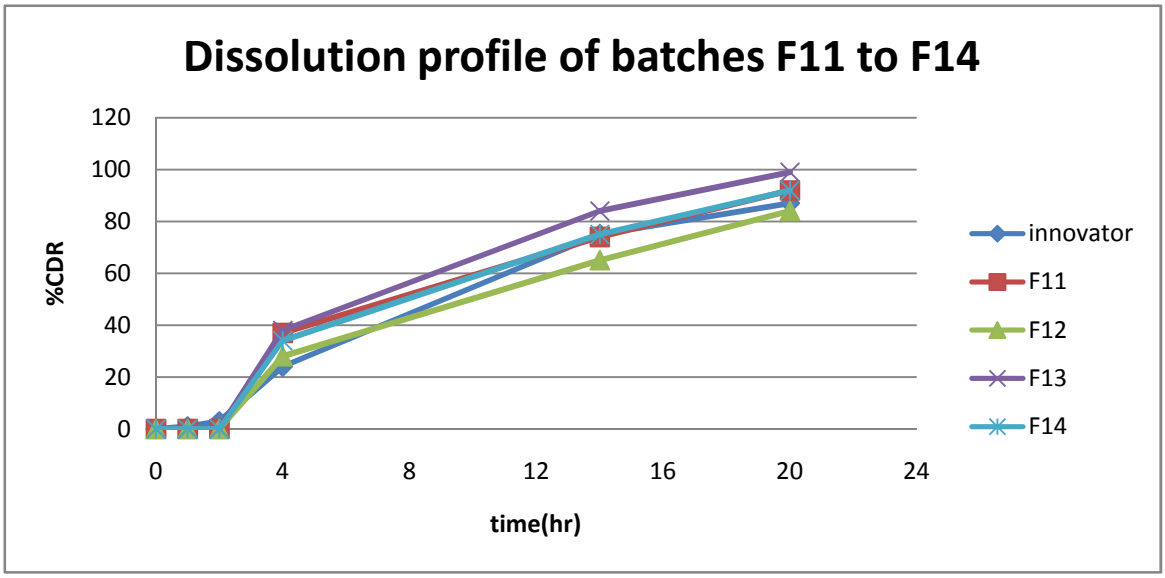


Fig 4.6: Dissolution Profile of batches F11 to F14

- **Discussion**

  From the above results it can be concluded that by varying quantities of HPMC K 100 M and HPMC 100 LV CR F14 batch gave similar dissolution profile as an innovator. As it would retard release in first two hours and also delayed the drug release till twenty hours. Hence, F14 batch was optimized batch from above trials.

4.9.1 OPTIMIZATION OF HARDNESS LEVEL ON DRUG DISSOLUTION OF OPTIMIZED BATCH F14:

The tablets were formulated following the procedure mentioned above But the compression of tablet in step-4, was carried out at 3 different hardness levels i.e. low, optimum and high.

Table No. 4.33: Hardness challenge

Batch No.	**14A**	**14B**	**14C**
Parameters	Minimum	Optimum	Maximum
Average weight (mg)	163-166	162-166	163-167
Hardness (N)	40-50	90-100	120-130
Thickness (mm)	4.00-4.10	3.87-3.92	3.79-3.85
Friability (% w/w)	0.21	Nil	Nil
Dissolution: pH 6.0 Phosphate Buffer with 0.2% SLS, Paddle, 50 rpm, 900 ml			
Time points (hrs)	Cumulative % drug dissolved		
2	28	20	25
4	48	35	38
6	66	50	52
8	76	58	64
10	82	61	72
12	90	72	79
14	95	80	85
16	98	81	92
20	100	98	95

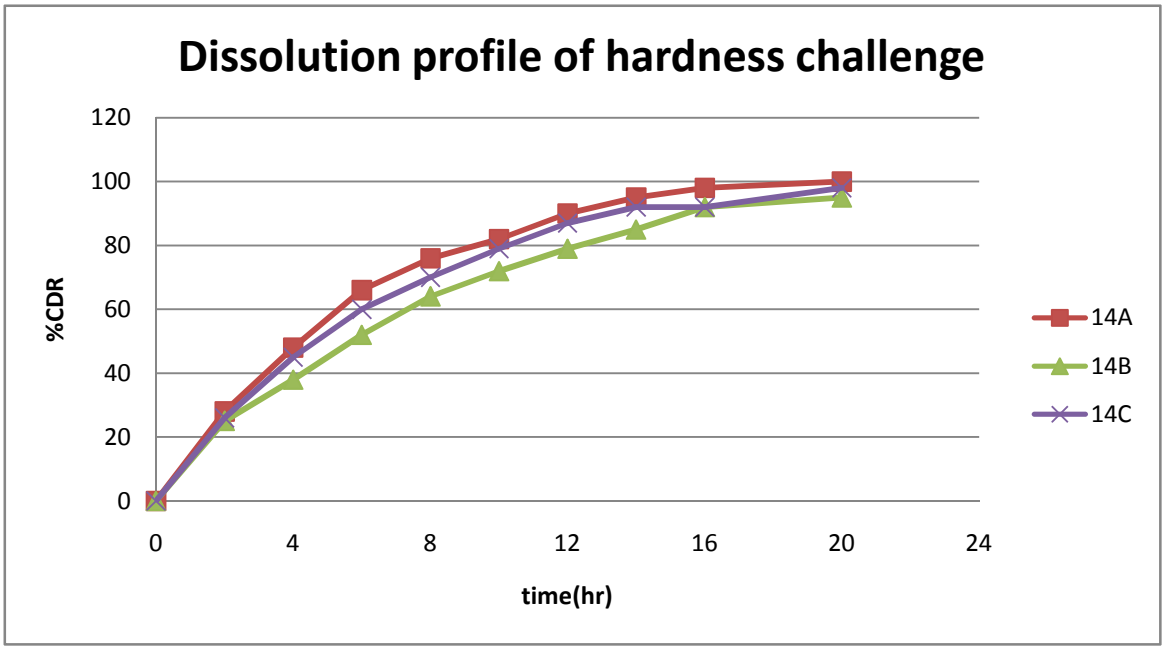


Fig 4.7: Dissolution profile of hardness challenge

- **Discussions :**

  Hardness challenge was executed to evaluate relation between hardness and dissolution. Based on above results of dissolution and physical parameters, it can be concluded that obtained hardness for given strength shows no significant effect on dissolution, indicating hardness range should be finalized on the range of minimum to maximum hardness.

4.9.2OPTIMIZATION OF BLENDING TIME ON BLEND UNIFORMITY ON OPTIMIZED BATCH F14

The tablets were formulated following the procedure mentioned above. But the dry mix prepared in step-1 was blended in a blender for different time intervals i.e. 10, 20 and 30 min.

Table No. 4.34: Optimization of Blending time

Batch no	**14D**	**14E**	**14F**
Blending time	10 min	20 min	30 min
Parameters			
Average weight (mg)	167-169	166-169	167-170
Thickness (mm)	3.68-3.78	3.86-3.91	3.70-3.80
Hardness (N)	100-110	90-105	100-110
Friability (% w/w)	Nil	Nil	Nil
Blend assay (%)	96.0	100.8	96.9
Tablet assay (%)	94.0	98.0	95.1
Content uniformity			
Minimum %	76.0	98.0	92.0
Maximum %	97.0	103.0	97.0
Mean %	89.0	100.0	94.0
% RSD	29.7	4.1	8.5

- **Discussion:**

  Blend uniformity at lubrication different stage that total mixing time between **10 minutes to 30 minutes** gives good blend uniformity without affecting dissolution of tablets. However, based on tablet assay, blend assay and RSD data lubrication time of 20 minutes was finalized.

4.9.3OPTIMIZATION OF SEAL COATING ON DRUG DISSOLUTION OF OPTIMIZED BATCH F14

The tablets were formulated following the procedure mentioned above. But in step-5, the tablets were further coated with the seal coating dispersion to achieve different weight gain of 4%, 5% and 6% w/w of core tablet.

Table No. 4.35: Optimization of Seal Coating

Batch no.	**14G**	**14H**	**14I**
% Seal coating (weight gain)	4%	5%	6%
Test parameters			
Average weight (mg) – Core tablets	168.2	165.7	167.9
Average weight (mg) – Seal coated tablets	174.9	173.9	179.9
% weight gain	4%	5%	6%
Dissolution: pH 6.0 phosphate buffer with 0.2% SLS, Paddle, 50 rpm, 900 ml			
Time points (hrs)	Cumulative % drug dissolved		
2	39	28	26
4	57	47	45
6	71	61	60
8	81	72	70
10	88	80	79
12	93	85	84
14	97	90	88
16	99	92	91
20	102	95	93
22	102	96	93

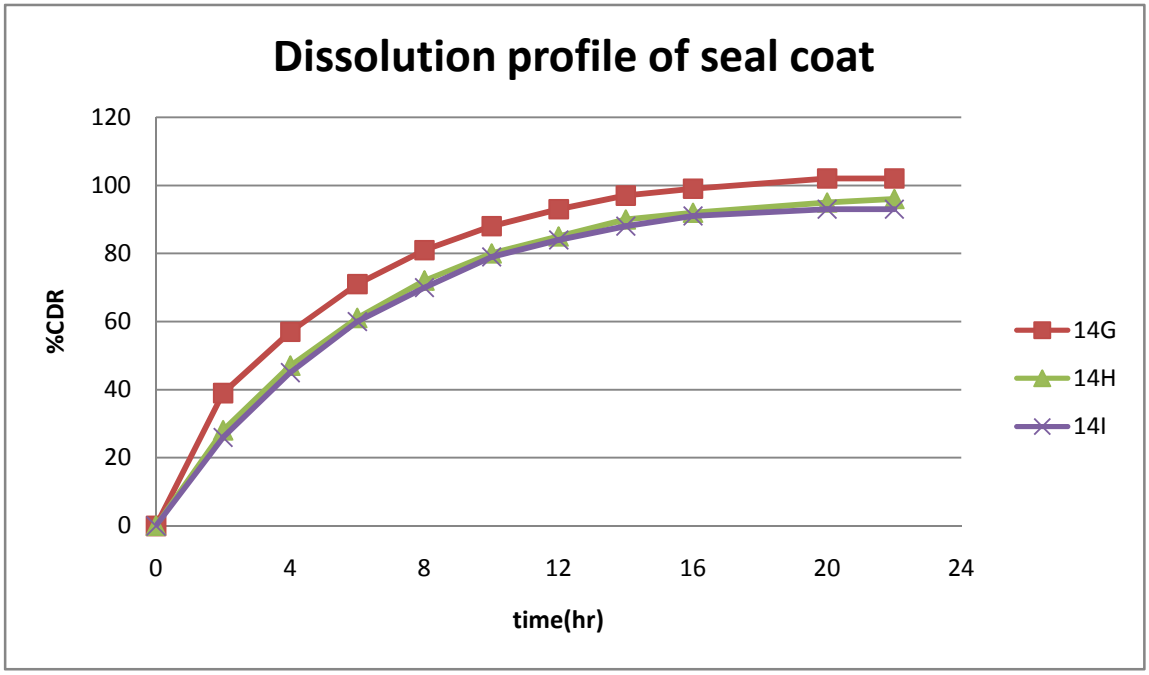


Fig.4.8: Dissolution profile of seal coat

- **Discussion:**

Based on above results of dissolution and physical parameters, it can be concluded that applied seal coat for given concentration shows significant effect on dissolution, indicating concentration range of seal coat below 6% showed faster drug release. Hence, 6% seal coat level would finalized.

4.9.4OPTIMIZATION OF ENTERIC COATING ON DRUG DISSOLUTION OF OPTIMIZED BATCH F14:

The tablets were formulated following the procedure mentioned above. But in step-6, the tablets were further coated with the enteric coating dispersion to achieve different weight gain and slow drug release at initial 2 hours of 10%, 11% and 12% w/w of seal coated.

Table No. 4.36: Optimization of Enteric Coating

Batch No.	**14J**	**14K**	**14L**
% Enteric coating (weight gain)	10.0%	11.0%	12.0%
Test parameters			
Average weight (mg) – Seal coated tablets	175.8	173.0	179.2
Average weight (mg) – Enteric coated tablets	195.1	192.9	200.7
% weight gain	11.0%	11.5%	12.0%
Dissolution: 0.1 N HCl, Paddle, 50 rpm, 900 ml followed by			
Time Points (hrs)	Cumulative % drug dissolved		
1	0	0	0
2	0	0	0
Dissolution: pH 6.0 phosphate buffer with 0.2% SLS, Paddle, 50 rpm, 900 ml			
2	26	20	18
4	45	37	34
6	60	51	48
8	70	63	59
10	79	72	68
12	87	80	75
14	92	87	81
16	92	91	86
20	98	97	92

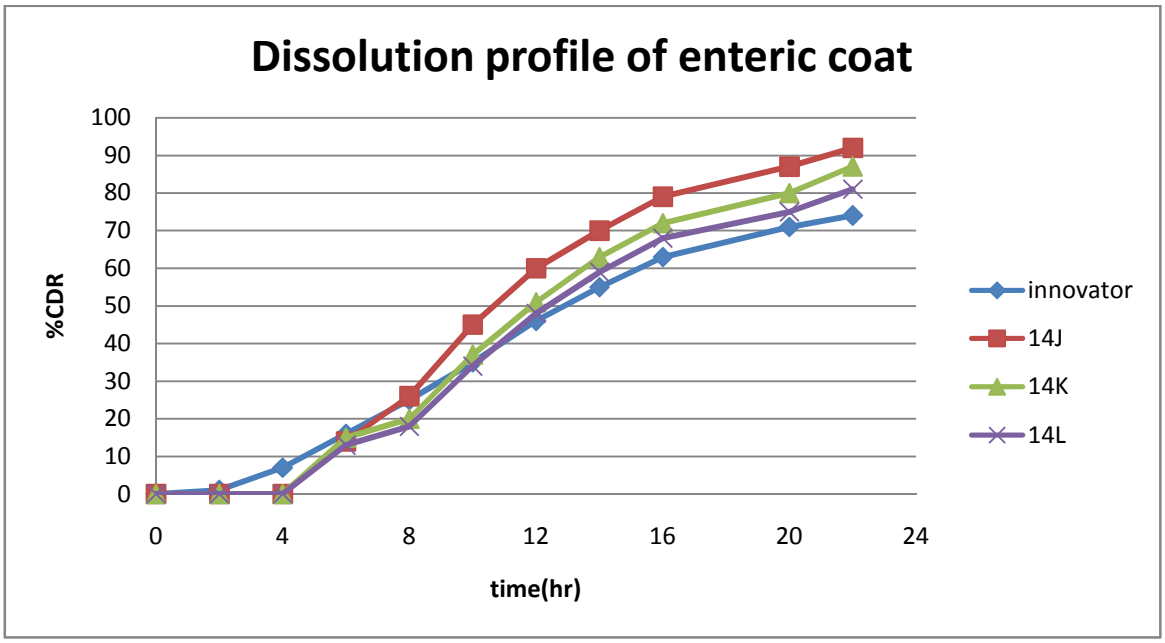


Fig.4.9: Dissolution profile of Optimization of enteric coat

- **Discussion:**

Based on above results of dissolution and physical parameters, it can be concluded that applied enteric coat for given concentration shows no significant effect on dissolution. However, in 10% and 11% enteric coat, weight gain of tablet would not be gained similar as an innovator. Moreover, the release rate of batch 14L (12%) showed similar dissolution profile to the innovator and gained optimized weight gain. Thus, an enteric coating of around 12% weight gain will be considered as optimized.

4.9.5 REPRODUCIBLE BATCH OF OPTIMIZED BATCH F14

Reproducibility of optimized batch was done and evaluated.

Table No. 4.37: Reproducible batch

Trial		**F14R**
Target wt. per tablet (mg)		207.265
Physical parameters		
Average Weight (mg)		202
Thickness (mm)		4.20-4.30
Hardness (N)		100-110
Friability (% w/w)		Nil
Dissolution Results		
Time Points	% Drug Release	0.1N HCl followed by pH 6.0 Phosphate buffer with 0.2%SLS
	Reference Product	
0.1N HCl media		
1	1	0
2	3	0
pH 6.0 Phosphate buffer with 0.2 % SLS		
2	12	18
4	24	34
14	75	75
20	87	92

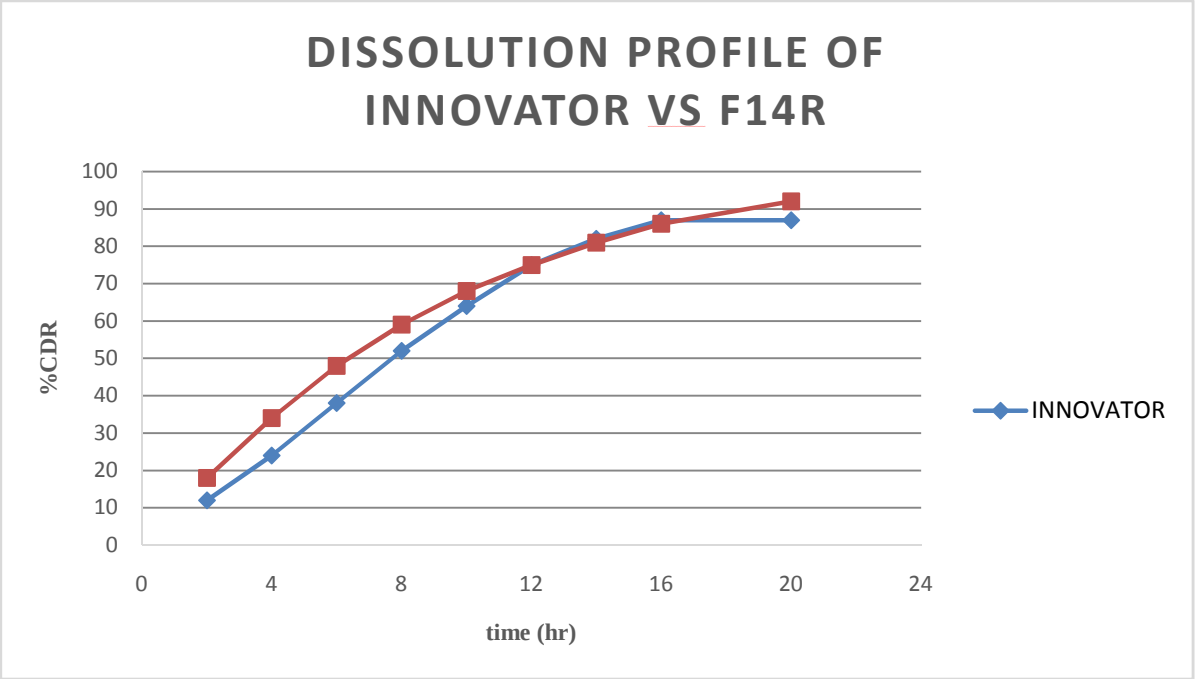


Fig 4.10 Reprodicible Batch F14R

- **Discussion:**

  On the basis of dissolution results, F14R batch showed similar results as the innovator release profile. Thus, reproducibility was validated.

4.9.6 ALCOHOL DOSE DUMPING STUDY FOR OPTIMIZED BATCH F14 WITH COMPARISON TO INNOVATOR PRODUCT

- Medium: 0.1 N HCl + alcohol USP 40%

  Speed:50 rpm

Table No. 4.38 :Alcohol Dose Dumping Study

Time (min)	% cumulative Drug Release	
	Innovator Product	F14AD
15	0	0
30	0	0
45	0	0
60	0	2
75	2	3
90	5	6
105	8	7
120	12	9

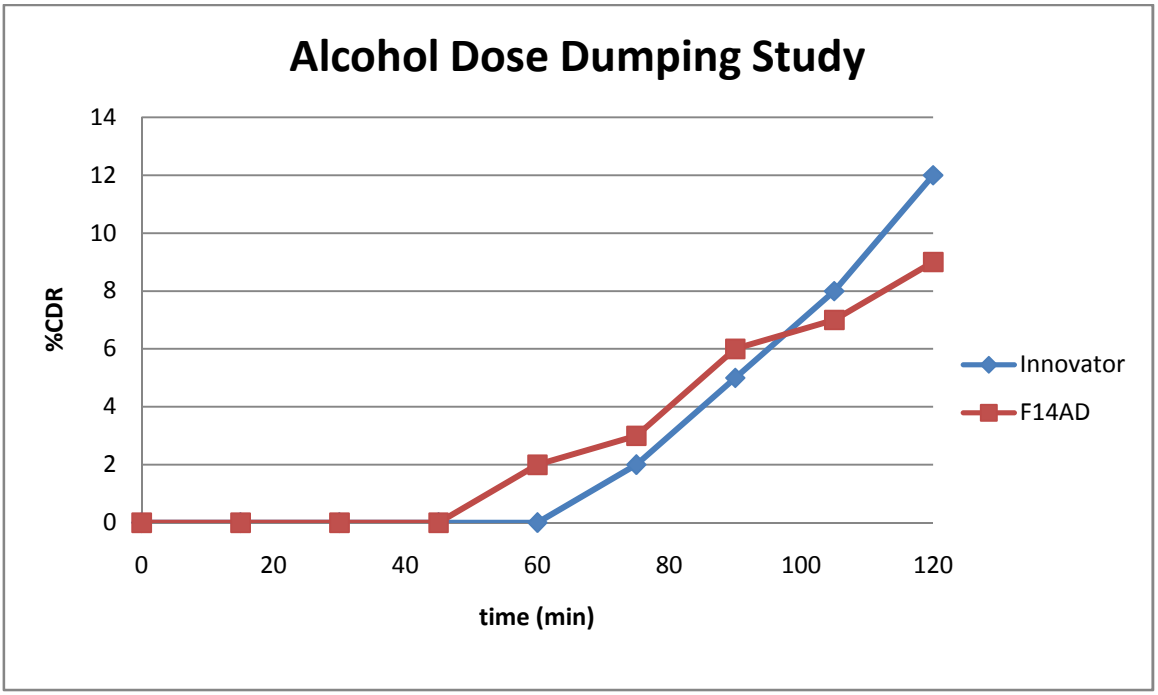


Fig 4.11: Alcohol Dose Dumping Study

- **Discussion:**

  In alcohol media drug release of optimized batch is less than the innovator drug release profile.

4.9.7STABILITY STUDIES OF F14

Table No.4.39 Stability Studies Of F14

Sr. No.	Tests	Initial	40°C / 75 % RH	
			1M	3M
1	Description	Grey colored round biconvex coated tablets plain on both sides.	Grey colored round biconvex coated tablets plain on both sides.	Grey colored round biconvex coated tablets plain on both sides.
2	Assay	98.9	98.8	98.1
3	Dissolution (0.1N HCl followed by pH 6.0 phosphate buffer + 0.2% SLS)			
	2 hrs (acid)	0	0	0
	2 hrs (Buffer)	18	17	18
	6 hrs (Buffer)	48	45	46
	14 hrs (Buffer)	82	78	80
4	Related Substances			
	Related Compound A	0.053	0.059	0.059
	Unknown Impurity	0.028	0.034	0.027
	Total impurities	0.081	0.093	0.097
5	Loss on drying (%)	4.69	3.52	3.02

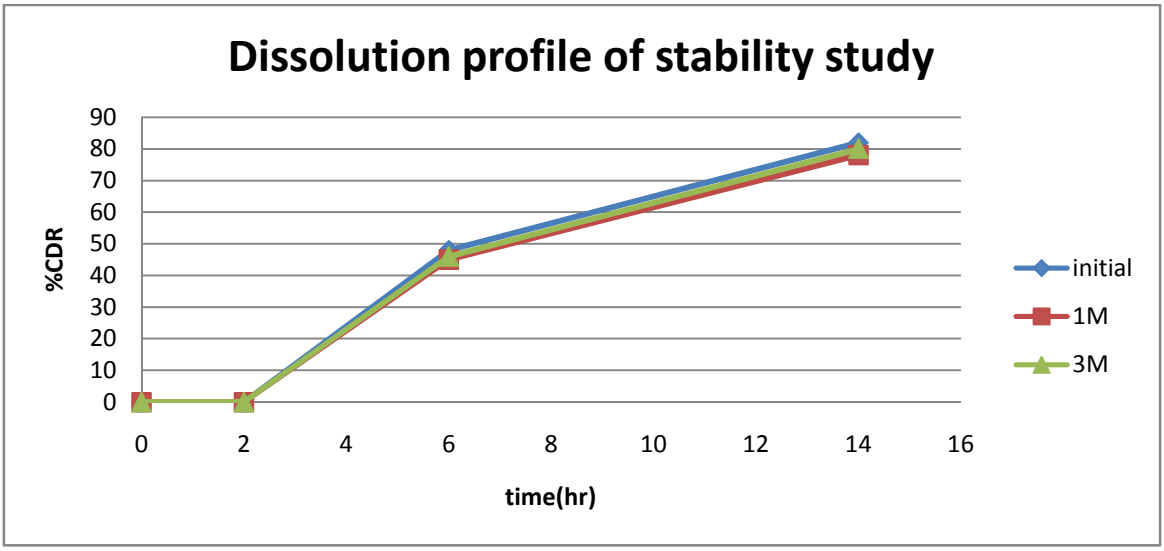


Fig 4.12 Stability Studies Of F14

- Discussion:

  Drug AST0NT2013 ER tablets USP 15 mg were found stable in HDPE bottle during 3 months stability at 40°C/75% RH and 25°C/60% RH.

4.9.8STATISTICAL ANALYSIS OF THE OPTIMIZED FORMULATION

Release profiles of Drug ASTONT2013 and Innovator were compared by calculating statistically derived mathematical parameter, "similarity factor" (f_2), using predicted in vitro release profile as the reference (section 3).

The equation of similarity factor is :

$$f_2 = 50 * \log \{ [1 + \frac{1}{n} \times \sum_{t=1}^{n} R_t - T_t ^2]^{-0.5} \times 100 \}$$

Where,

R_t and T_t = percent Drug AST04 dissolved at each time point for the reference and test product,

n = number of dissolution sample times,

t = time sample index.

If the two profiles are identical, f_2 is 100. Values of $f_2 \geq 50$ indicate similarity of two dissolution profiles.

- **Conclusion**

Similarity factor (f_2) values for Drug AST0NT2013 and Innovator when compared with predicted release profile are **60.2**. Ideally the f_2 values must fall in the range of 50-100. Thus, the release profile of the developed formulation was similar to the Innovator release profile. Dissimilarity factor (f_1) values for Drug AST0NT2013 and Innovator when compared with predicted release profile are **7.68**.

4.9.10 Drug Release Kinetic Model:

Table No.4.40: Drug Release Kinetic Model

Batches	Zero order	First order	Higuchi	Korsmeyer-peppas	Hixon-crowell
Innovator	0.9975	0.9358	0.7944	0.9988	0.9704
F14	0.9733	0.9269	0.9225	0.9946	0.9687

- **Discussion:**

  From the above results it was concluded that product batch F14 was follow Korsmeyer-peppas reaction, that is diffusion from matrix. From that n was calculated and its value is 1.023, which indicated drug ASTONT2013 follows zero order kinetics.

4.10 UPDATED RISK ASSESSMENT OF THE FORMULATION VARIABLES:

Acceptable ranges for the high risk formulation variables have been established. Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated.

Table 4.41: Updated risk assessment of the formulation variables

Drug product CQAs	HPMC K100M Level	Colloidal Anhydrous Silica Level	Magnesium Stearate Level
Assay	Low	Low	Low
Uniformity of Dosage Units	Low	Low	Low
Degradation Products	Low	Low	Low
Dissolution	Low*	Low	Low

* Updated from initial

Low Risk : No further Investigation is needed;

Medium Risk : Further investigation may be needed in order to reduce the risk;

High Risk : Further investigation is needed.

Table 4.42: Updated risk assessment of the process variables

Parameters	Range studied	Target Selected	Purpose of control
Lubrication time	10 to 30 minutes	20 minutes	To achieve uniformity of blend.
Hardness	50– 120N	100 – 110 N (Target 100 N)*	To achieve satisfactory physical attributes and dissolution.

4.11 MATERIALS AND METHODS

- Various materials and equipments were used to carry out the experimental work. The list of materials and equipments used are given in the table 5.1 and 5.2 respectively.

Table: 4.11 List of materials

Name of Material	Manufacturer/ Supplier
Hydroxypropylmethyl cellulose (K100 M)	Central Drug house Pvt. Ltd, India
Gelucire 43/01	Gattefosse, Mumbai, India.
Microcrystalline cellulose (Avicel 101)	Central Drug house Pvt. Ltd, India
Purified talc	Central Drug house Pvt. Ltd, India
Colloidal anhydrous silica	Central Drug house Pvt. Ltd, India
Magnesium stearate	Central Drug house Pvt. Ltd, India
Sodium hydroxide	Central Drug house Pvt. Ltd, India
Potassium dihydrogen phosphate	Central Drug house Pvt. Ltd, India

Table: 4.12 List of equipments

Equipment/ Machine	Supplier/Manufacturer
UV/VIS Double beam Spectrophotometer	Shimadzu UV-1800, Japan
pH meter	Analab scientific instruments, India
Tablet Dissolution tester USP	Electrolab TDT-08L, India
Rotary tablet machine	Rimek, Karnavati Engineering Pvt. Ltd, India
Electronic weighing balance	Citiweigh- Tejas exports, India
Hardness tester	Thermonik, Campbell electronics DHT-250, India
Fribility tester	Roche Friability tester, Switzerland
Magnetic stirrer	Remi Equipment Pvt. Ltd, India
Hot air oven	EIE InstrumentsPvt. Ltd, India
FTIR	Jasco FTIR 6100 Type A, Japan

4.12 DETERMINATION OF STANDARD CURVE OF ASTONT2013

- Determination of UV absorption maxima(λ_{max}) of ASTONT2013

  The absorption maxima of ASTONT2013 are reported as 258 nm, in the literature. The absorption maxima of the drug were validated by scanning the known concentrations between 400 nm to 200 nm.

- Calibration curve plotting for ASTONT2013

A. Calibration curve plotting of ASTONT2013 in pH 1.2 (0.1 N HCl containing 2% SLS):

Stock solution of 100 µg/ml was prepared in 0.1 N HCl (containing 2% SLS) by dissolving 20 mg drug in 100 ml 0.1 N HCl. Suitable aliquots were taken from it and diluted with 0.1 N HCl to get final concentration of 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 µg/ml.

B. Calibration curve plotting of ASTONT2013 in pH 6.0 phosphate buffer:

Stock solution of 100 µg/ml was prepared methanol by dissolving 20 mg drug in 100 ml of methanol. Suitable aliquots were taken from it and diluted with buffer to get final concentration of 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 µg/ml.

❖ **Spectrophotometric estimation of** ASTONT2013

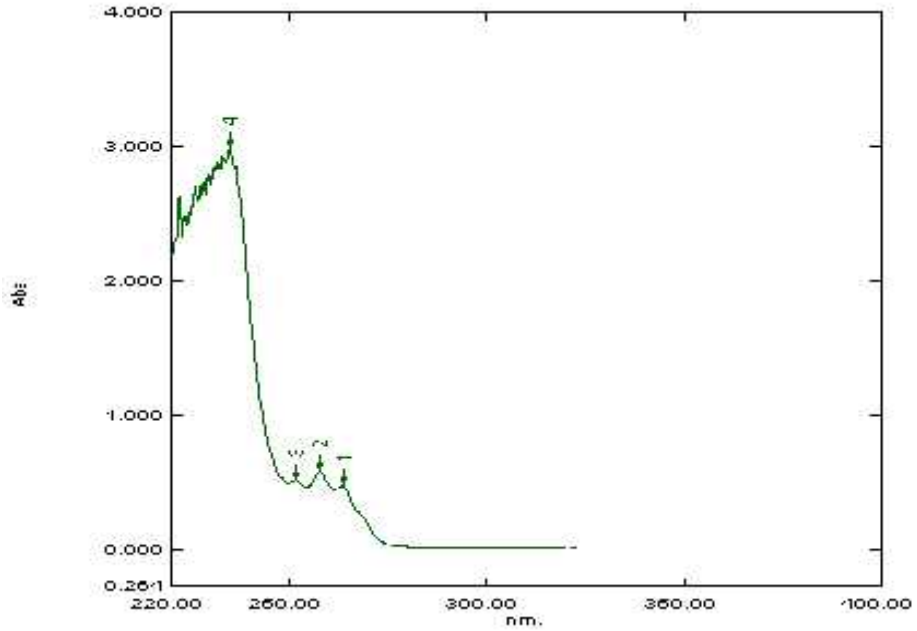


Fig 4.11 Estimation of ASTONT2013 in 0.1 N HCl

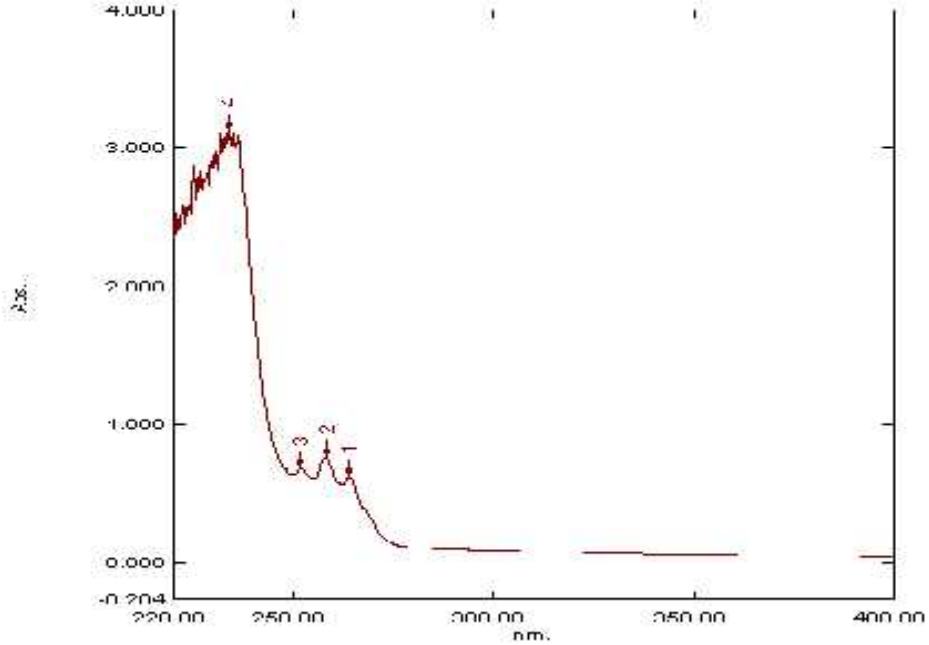


Fig 4.12 Estimation of ASTONT2013 in pH 6.0 phosphate buffer

- STANDARD CURVE OF ASTONT2013 IN 0.1 N HCl (λmax-258 nm)

Table: 4.13 Standard Curve Of ASTONT2013 in 0.1 N HCl

Concentration µg/ml	Absorbance 1	Absorbance 2	Absorbance 3	Average
400	0.264	0.266	0.264	0.264
500	0.316	0.318	0.318	0.318
600	0.378	0.379	0.38	0.379
700	0.441	0.443	0.445	0.444
800	0.496	0.496	0.495	0.496
900	0.568	0.568	0.569	0.569
1000	0.614	0.613	0.613	0.614
1100	0.698	0.698	0.699	0.698
1200	0.751	0.752	0.752	0.752
1300	0.804	0.804	0.804	0.804

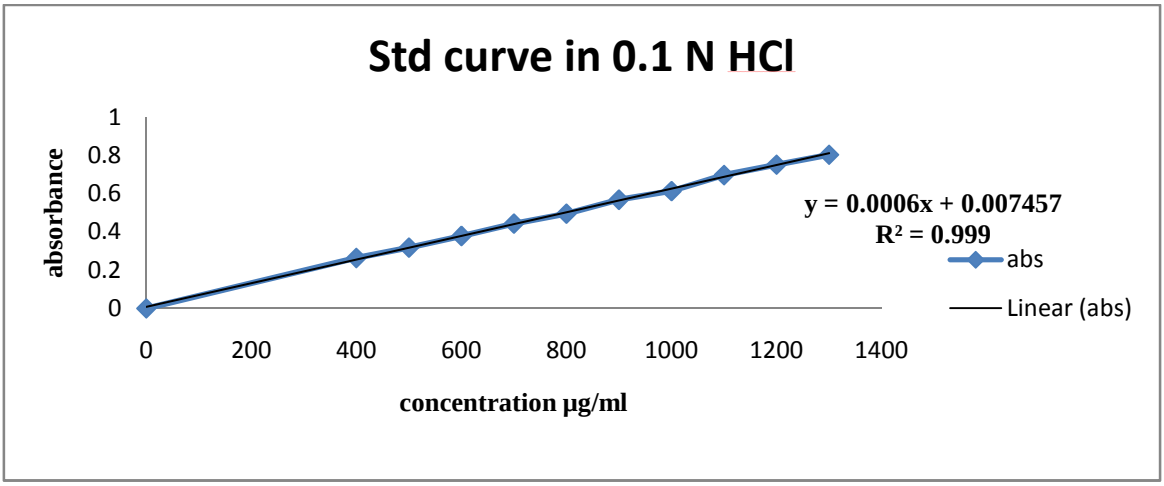


Fig.4.13 Standard Curve of ASTONT2013 in 0.1 N HCl

Regression parameter	**Value**
Correlation coefficient	0.999
Slope	0.0006
Intercept	0.007457

- STANDARD CURVE OF ASTONT2013 IN pH 6.0 PHOSPHATE BUFFER (λmax-258 nm)

Table no.:4.14 standard curve of ASTONT2013 in Ph 6.0 phosphate buffer

Concentration µg/ml	Absorbance 1	Absorbance 2	Absorbance 3	Average
100	0.116	0.117	0.117	0.117
200	0.215	0.215	0.214	0.215
300	0.324	0.325	0.324	0.324
400	0.402	0.403	0.403	0.403
500	0.488	0.488	0.487	0.488
600	0.549	0.55	0.549	0.549
700	0.65	0.651	0.651	0.651
800	0.704	0.703	0.703	0.703
900	0.761	0.76	0.761	0.761
1000	0.836	0.837	0.837	0.837

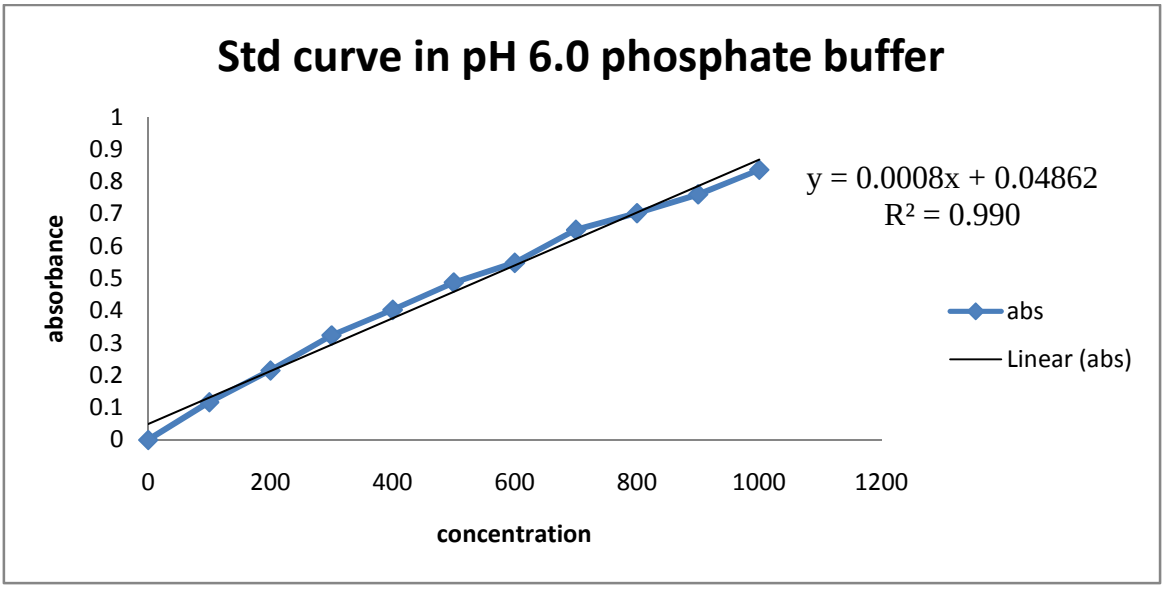


Fig.4.13 Standard Curve of ASTONT2013 in pH 6.0 phosphate buffer

Regression parameter	**Value**
Correlation coefficient	0.990
Slope	0.0008
Intercept	0.04862

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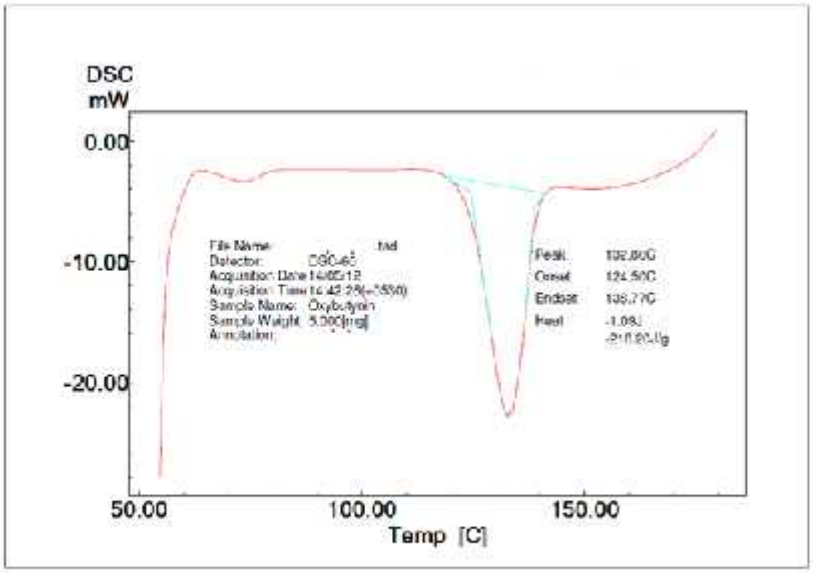
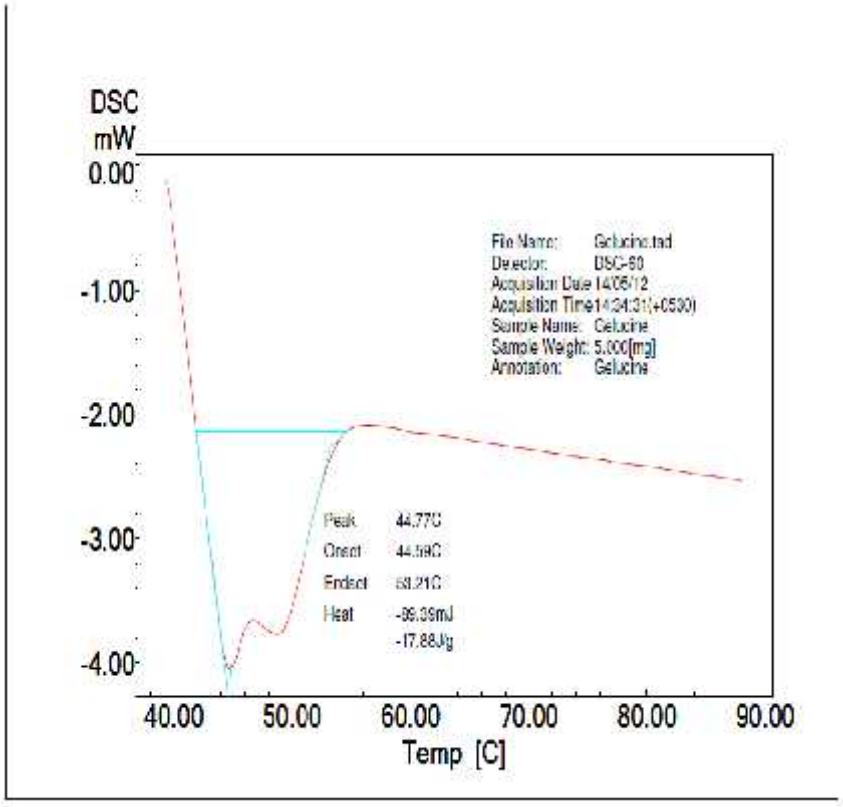
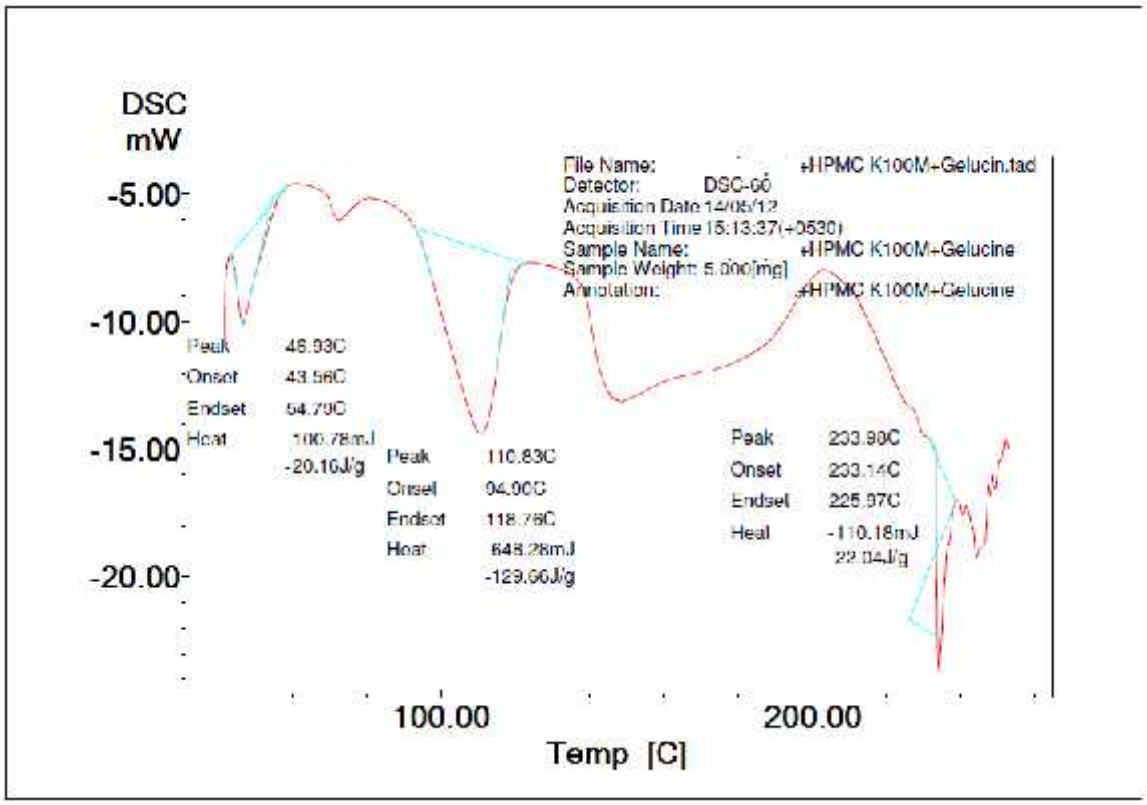
❖ **DRUG EXCIPIENT COMPATIBILITY:**



(A) DSC graph of drug ASTONT2013



(B) DSC graph of Gelucire 43/01



(C)DSC graph of mixture

- **CONCLUSION:**

  From the above graphs of DSC, it was concluded that excipients did not change the drug peak after thermally induced decomposition. No transition was observed after melting under the hot stage microscope.

4.13 MANUFACTURING PROCESS

The manufacturing process employed in preparation of extended release tablets of ASTONT2013 is mentioned below:

- Step 1: Dry Mix:

ASTONT2013 and excipients used to formulate hydrophilic matrix system, microcrystalline cellulose, hydroxyl propyl methyl cellulose (K100 M), colloidal anhydrous silica, purified talc, magnesium stearate were co-sifted through 40# sieve.
Dry mix for 10 min in poly bag.

- Step 2: Melt granulation:

Melt lipid at 40^0C. Add step 1 powder to melted lipid and stir it vigorously. Cool down it to room temperature. And mix for 10 min.

- Step 3: Compression:

The lubricated blend was compressed in compression machine with D tooling.

4.14 EVALUATIONOF TABLETS

- The formulated tablets of ASTONT2013 were subjected to the following evaluation parameters.
- Hardness, thickness Friability were measured as mentioned in section 4.7
- *In-vitro* dissolution studies: The tablets were evaluated for *in-vitro* drug release in USP dissolution apparatus. The conditions used for dissolution study are provided in table no.

Table: 4.15: Dissolution conditions

USP dissolution apparatus	Type-II (Paddle type)
Media	0.1 N HCl for 2 hrs,pH 6.0 + 0.2 % SLS.
Volume of dissolution medium	250 ml
Speed of paddle rotation	50 rpm
Sampling point (h)	2,4,6,8,10,12,14,16,20
Temperature	37 ± 0.5ºC

4.15 PRELIMINARY TRIALS

Table No.4.16: Trials of Batches D1 to D4

Trials	D1	D2	D3	D4
Weight	mg/tab			
Batch size	20 tab			
Drug	15	15	15	15
Gelucire 43/01	-	-	15	30
Bees wax	15	30	-	-
HPMC K 100 M	-	-	-	-
Avicel 101	115	100	115	115
Mg stearate	2			
Col silica	1.5			
Talc	1.5			
Total weight	165			

Table No.4.17: Evaluation Parameters of Batches D1 to D4

Trials	D1	D2	D3	D4
Average weight (mg)	167-169	166-169	167-170	165-170
Thickness (mm)	3.68-3.78	3.86-3.91	3.70-3.80	3.71-3.84
Hardness (N)	70-82	69-78	65-76	58-62
Friability (% w/w)	Nil	Nil	Nil	Nil

- **Discussion:**

  -The main aim of study was to develop a tablet formulation which releases drug in controlled manner. It has been reported that hydrophobic agent can controlled the release of drug. Hence different hydrophobic agents (LIPIDS) were screened to control release of ASTONT2013 from the tablets.

  -The in vitro drug release study of batches D1 to D4 containing bees wax and Gelucire 43/01 was not able to control the release of drug. Batch D1 to D4 containing Bees wax and Gelucire in different amounts gave 100% drug release at the end of 2 hours. Thus lower concentrations of lipids were incorporated with hydrophilic polymer in further batches to decrease the drug release.

Table No.4.18: Trials of Batches D5 to D8

Trials	D5	D6	D7	D8
Weight	mg/tab			
Batch size	20 tab			
Drug	15			
Gelucire 43/01	30	45	-	15
HPMC K 100 M	45	30	75	60
Avicel 101	115	100	70	100
Mg stearate	2			
Col silica	1.5			
Talc	1.5			
Total weight	165			

Table No.4.19: Evaluation Parameters of Batches D1 to D4

Trials	D7	D8
Average weight (mg)	167-169	166-169
Thickness (mm)	3.68-3.78	3.86-3.91
Hardness (N)	84-93	80-85
Friability (% w/w)	Nil	Nil

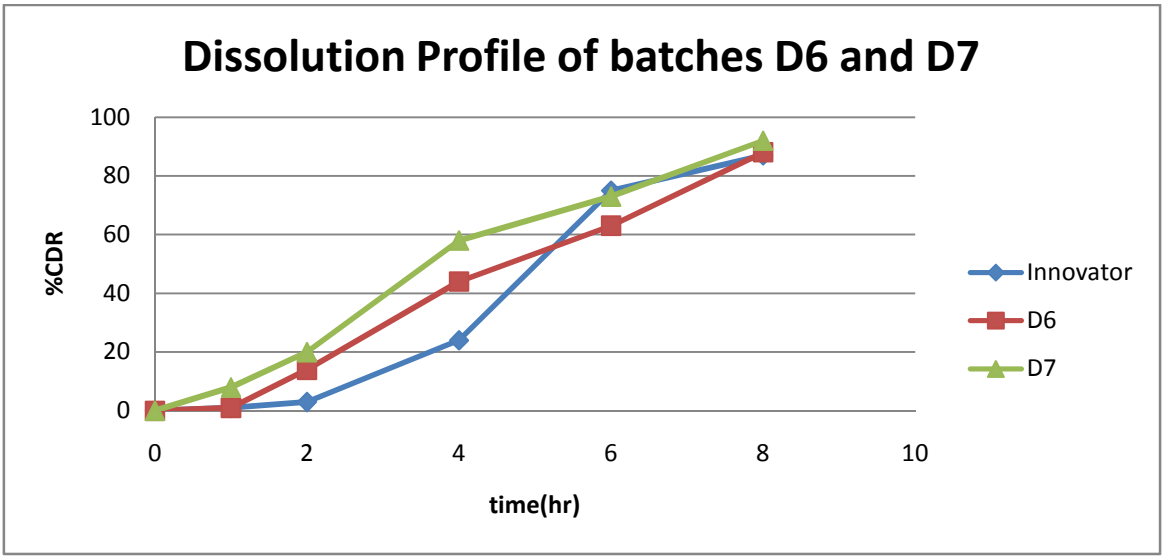


Fig.4.15 Dissolution Profile of batches D6 and D7

- **Discussion:**

  In batch D5 and D6 concentration of Gelucire 43/01 was high. Due to high amount of Gelucire tablet could not be compress. Thus, hydrophilic polymer HPMC K 100 M was incorporated to delay the drug release. Batch D8 showed better result than D7. In batch D8 incorporation of Gelucire 43/01 with HPMC K 100 M exhibit delayed release as compare to D7, in which alone hydrophilic matrix was incorporated.

4.16 OPTIMIZATION OF FORMULATION OF ASOTNT2013 BY 3^2 FACTORIAL DESIGN

- The optimization techniques, on the basis of a few experiments and statistical analysis of the results of trial batches can provide an efficient and economical method for the prediction of the optimal concentration.
- From the trial batches, two independent variables were found to affect drug release significantly. Hence by applying 3^2 full factorial design, influence of two independent variables:

X1: amount (mg) of Gelucire 43/01 and

X2 : amount (mg) of HPMC K 100 M were studied over five dependent variables like percentage cumulative drug release at 2 hrs **(Y_1)** , 4 hrs **(Y_2)**, 6 hrs **(Y_3), 14 hrs (Y4) and Hardness**. Layout and composition of 3^2 full factorial design are shownin table5.10 and 5.11

Table No.4.10 Uncoded Value

Sr. No	X1	X2
1	-1	-1
2	0	-1
3	+1	-1
4	-1	0
5	0	0
6	+1	0
7	-1	+1
8	0	+1
9	+1	+1
10	0	0

Table 4.11Translation of Coded Levels In Actual Units

Independent variables		Real value (%)		
		Low (-1)	**Medium (0)**	**High (1)**
X1	amount (mg) of Gelucire 43/01	10	15	20
X2	amount (mg) of HPMC K 100 M	50	60	70

Sr. No.	**X1**	X2	**%CDR 2 hrs**	**%CDR 4 hrs**	**%CDR 6 hrs**	**%CDR 14 hrs**	**HARDNESS**
1	10	50	35.1	42.78	62.22	96.29	83
2	15	50	32.82	40.21	60.72	91.9	77
3	20	50	29.38	35.43	57.87	84.12	60
4	10	60	29.1	37.64	52.04	85.96	81
5	15	60	20.82	30.01	41.36	81.33	81
6	20	60	19.07	25.21	38.59	62.27	61
7	10	70	17.66	21.11	42.41	78.23	88
8	15	70	15.13	20.26	41.59	68.71	79
9	20	70	12.32	18.29	25.49	49.49	56
10	15	60	19.42	31.23	40.30	82.14	81

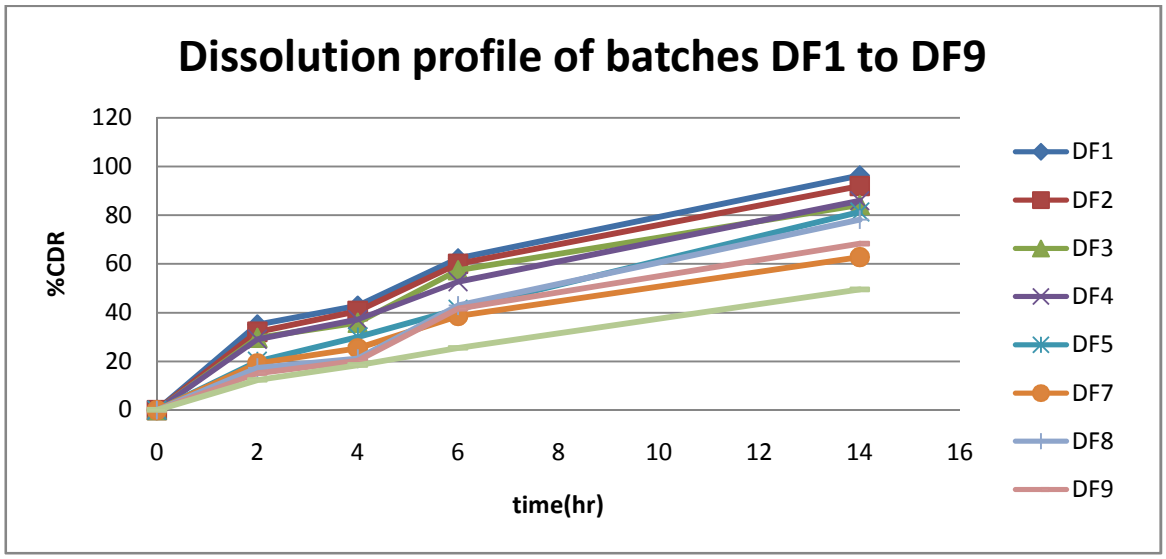


Fig4.16 Dissolution Profile of Batches DF1 To DF9

After measuring the dependent variables either simple linear, interactive, polynomial or quadratic models was evolved by carrying out multiple regression analysis of the data and F statistics to identify statistically significant terms.

Linear equation: $\mathbf{R = b_0 + b_1X_1 + b_2X_2}$

Interactive equation: $\mathbf{R = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2}$

Polynomial equation: $\mathbf{R = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2}$

Quadratic equation: $\mathbf{R = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$

Where, R is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity.

4.16.1 EVALUATION OF FACTORIAL DESIGN BY CHECK POINT BATCH:

- The application of the desirability function combines all the responses in one measurement and gives the possibility of predicting optimum levels for the independent variables. The desirability function was used for optimization of the formulation. During optimization of formulations, the responses have to be combined in order to produce a product of desired characteristics. The method was adopted to calculate the desirability of individual dependent variable and overall desirability by taking geometric mean. The batch having highest overall desirability (near to 1) value should be considered as an optimum batch. For this, range of all the dependent variables were selected which would satisfy the criteria of the formulation. Combinations of all the possible different levels of both independent variables which satisfied the above criteria and having the desirability near to 1 was selected as check point batch. The check point batch was evaluated for the three responses.

4.16.2 Effect of independent variables on dependent variables

Table 4.12 Summary of each factor effect and its p-values for response Y1, Y2 and Y3.

Factor	Y_1		Y_2		Y_3		Y_4		Y_5	
	Factor Effect	P value	Factor Effect	P value	Factor Effect	P value	Factor Effect	P value	Factor Effect	P value
X_0	17.93	0.0001	20.72	0.0050	43.18	0.0060	83.77	0.0031	79.93	0.0025
X_1	-9.18	*<0.0001*	-9.77	*0.0008*	-12.62	*0.0009*	-12.77	*0.0009*	-12.50	*0.0003*
X_2	-1.87	*0.0083*	-3.46	*0.0310*	-5.89	*0.0142*	-10.65	*0.0019*	0.50	*0.6649*
X_1X_2	0.35	*0.5037*	1.88	*0.2206*	-2.39	*0.2399*	-4.14	*0.0810*	-2.25	*0.1615*
X_1^2	6.55	*0.0004*	6.49	*0.0188*	4.32	*0.1300*	-1.10	*0.6609*	-7.86	*0.0102*
X_2^2	-1.06	*0.1603*	-1.70	*0.3733*	-0.34	*0.8880*	-6.91	*0.0416*	-0.86	*0.6440*

* Indicate the value is insignificant at p> 0.05 and does not affect the responses.

Variables which had p value less than 0.05, significantly affect the responses.

Here, p- values of A & B were less than 0.05 for all the responses and hence both factors significantly affected all the responses either positively or negatively based on their factor effect value.

Table No.4.13: Summary of calculated ANOVA parameters

Parameter	SS	Df	MS	F value	p - value	Remarks
Y_1	627.29	5	125.46	141.97	0.0001	Significant
Y_2	757.47	5	151.49	22.47	0.0050	Significant
Y_3	1230.28	5	246.06	20.44	0.0060	Significant
Y_4	1850.48	5	370.10	29.06	0.0031	Significant
Y_5	1114.56	5	222.91	32.38	0.0025	Significant

Table No.4.14 Results of statistical parameters of responses

Parameter	Y_1	Y_2	Y_3	Y_4	Y_5
SD	0.94	2.60	3.47	3.57	2.62
Mean	21.22	23.60	45.56	78.96	74.70
R^2	0.9944	0.9656	0.9623	0.9732	0.9759
Adjusted R^2	0.9874	0.9227	0.9153	0.9397	0.9458

4.16.2 EFFECT OF INDEPENDENT VARIABLES ON % CDR AT 2 HRS (Y1):

Figure (A)& (B) show the contour plot & 3D surface plot for Y_1, Y_2, Y_3, Y_4, Y_5, suggesting the effect of variables as described above.

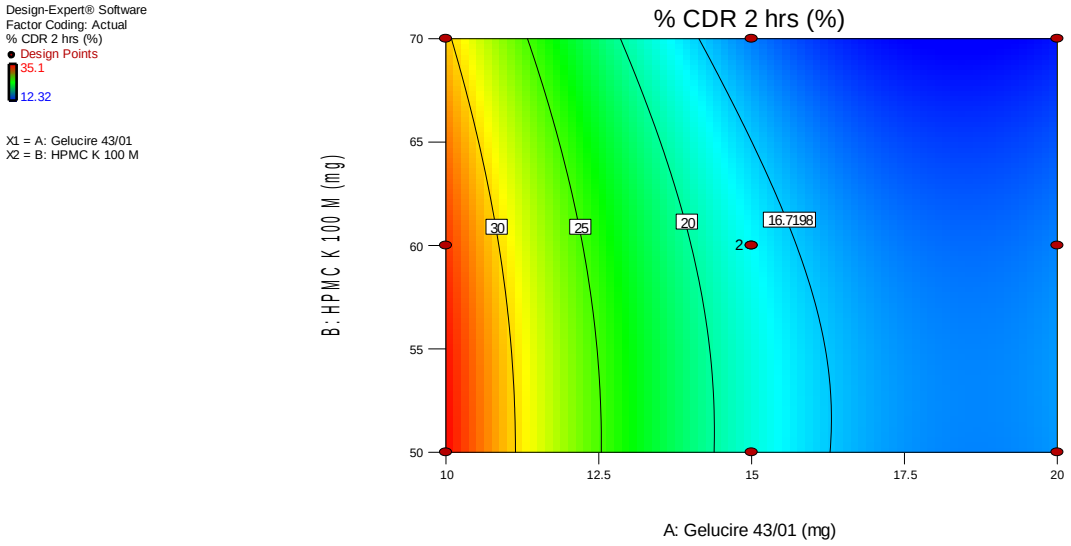


Figure 4.7 (A) Contour plot for response Y_1

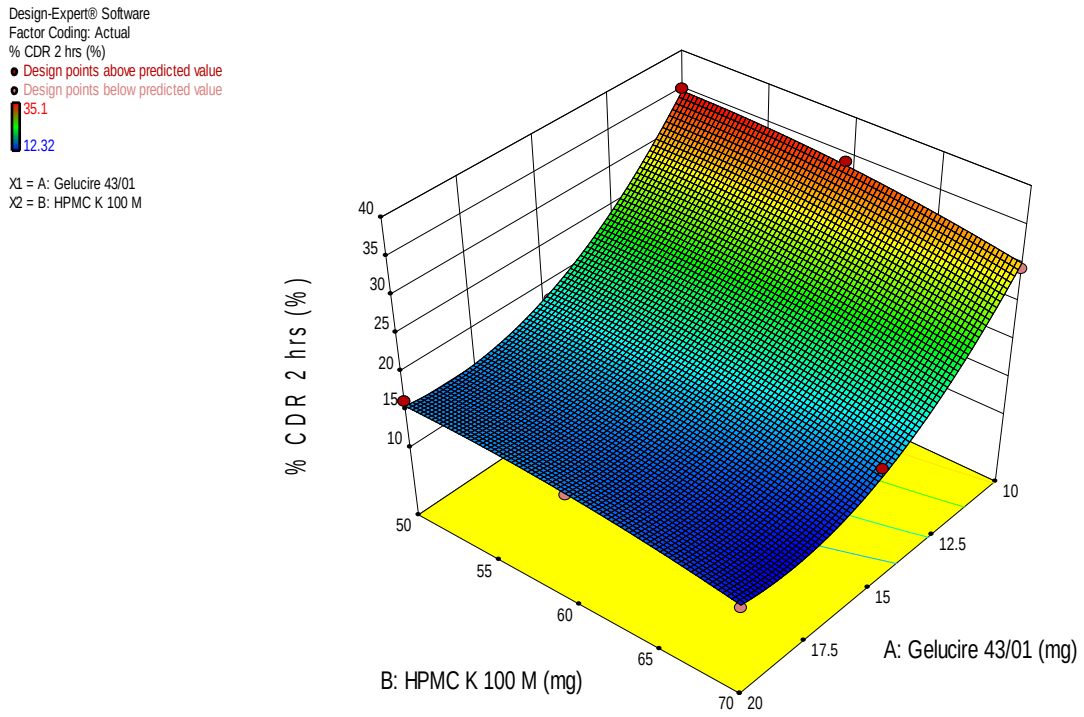


Figure 4.7 (B) 3D surface plot of response Y_1

- **Discussions:**

  Reduced ANOVA equation for %CDR 2 hrs

  % CDR 2 hrs=+17.93+(-9.18)* X_1 +(-1.86)* X_2+6.55* X_1^2

- The significance levels of the coefficients of X_1X_2, X_2^2 were found greater p value. Therefore they were omitted from the full model to generate a reduced model. The coefficients of X_1, X_2, X_1^2 were found to be significant at $p<0.05$; hence, they were retained in the reduced model.
- From equation, factor value of X_1 was -9.18 and X_2 was -1.87 which indicates X_1 Had more effect on % CDR at 2 hours than X_2
- Negative sign of both factors indicates that if amount of both factors increased, % CDR at 2 hours was decreased.

4.16.3 EFFECT OF INDEPENDENT VARIABLES ON % CDR AT 4 HRS (Y_2):

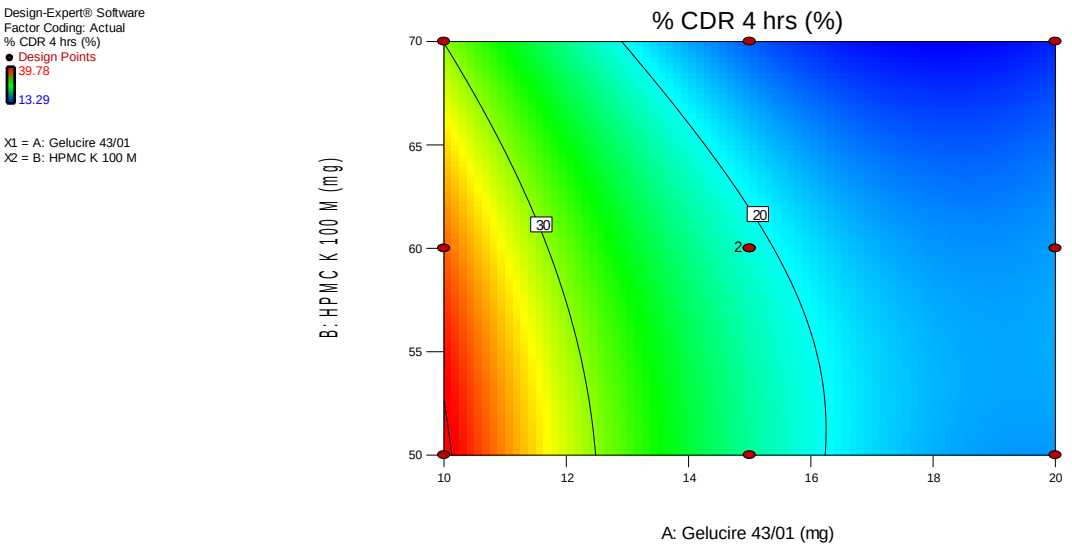


Figure 4.8 (A) Contour plot for response Y_2

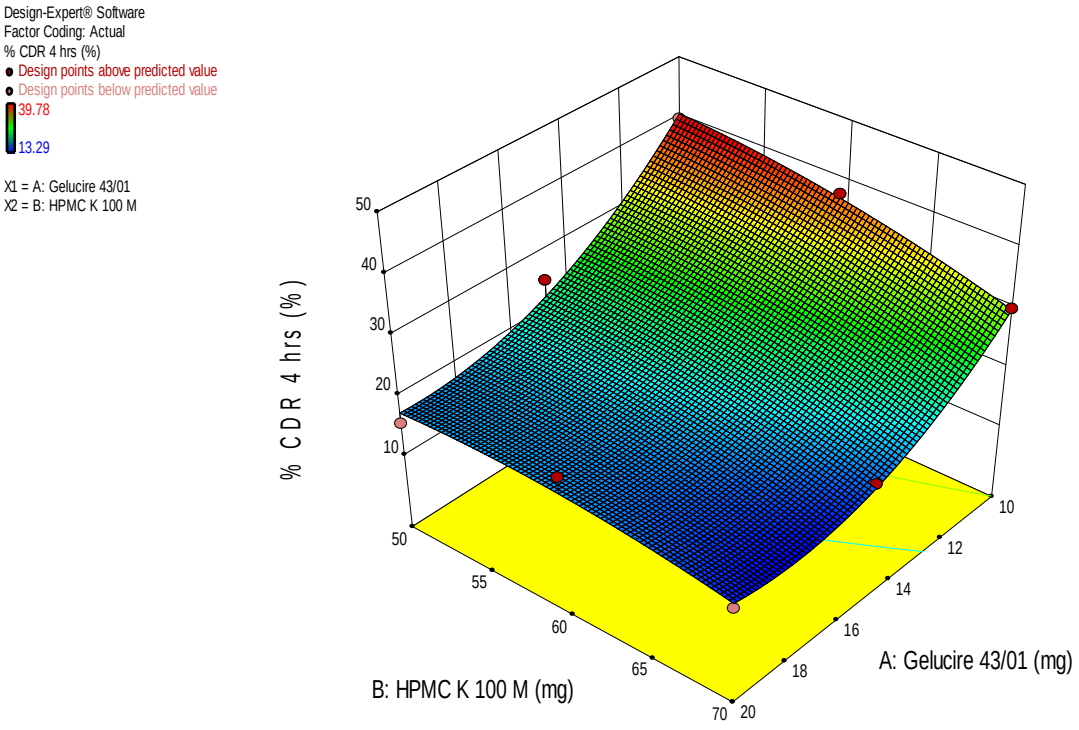


Figure 4.8(B) 3D surface plot of response Y_2

- **Discussions:**

  Reduced ANOVA equation for %CDR 4 hrs

  %CDR 4 hrs=+20.72+(-9.77)* X_1 +(-3.46)* X_2+6.49* X_1^2

- The significance levels of the coefficients of X_1X_2, X_2^2 were found greater p value. Therefore they were omitted from the full model to generate a reduced model. The coefficients of X_1, X_2, X_1^2 were found to be significant at $p<0.05$; hence, they were retained in the reduced model.
- From equation, factor value of X_1 was -9.77 and X_2 was -3.46 which indicates X_1 Had more effect on % CDR at 4 hours than X_2
- Negative sign of both factors indicates that if amount of both factors increased, % CDR at 4 hours was decreased.

4.16.4 EFFECT OF INDEPENDENT VARIABLES ON % CDR AT 6 HRS (Y_3):

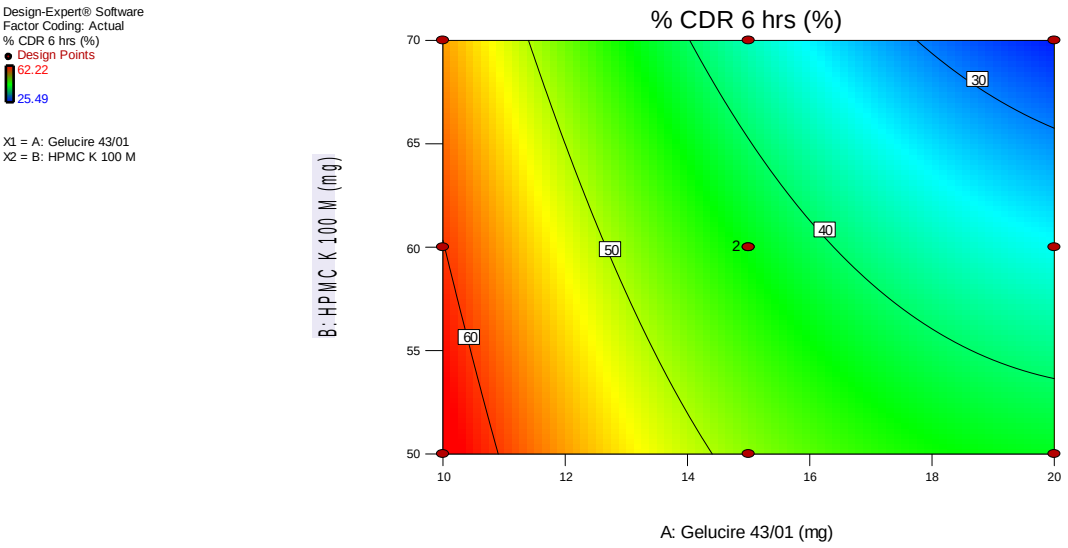


Figure 4.19(A) Contour plot for response Y_3

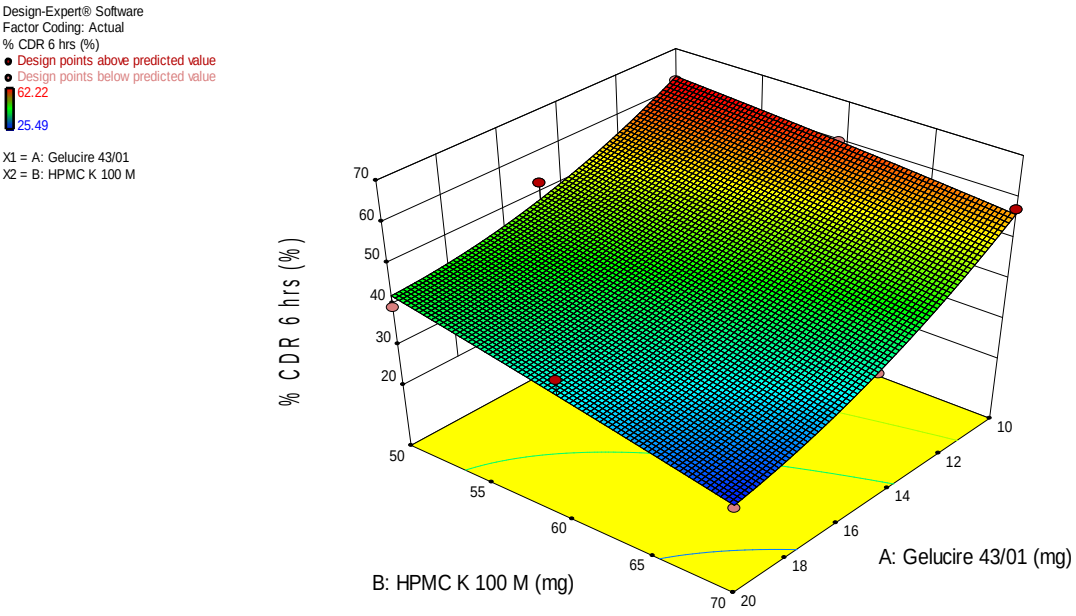


Figure 4.19(B) 3D surface plot of response Y_3

- **Discussions:**

  Reduced ANOVA equation for %CDR 6 hrs

  % CDR 6 hrs=+43.18+ (-12.62)* X_1 + (-5.89)* X_2

- The significance levels of the coefficients of X_1X_2, X_2^2, X_1^2 were found greater p value. Therefore they were omitted from the full model to generate a reduced model. The coefficients of X_1 and X_2, were found to be significant at $p<0.05$; hence, they were retained in the reduced model.
- From equation, factor value of X_1 was -12.62 and X_2 was -5.89 which indicates X_1 Had more effect on % CDR at 6 hours than X_2
- Negative sign of both factors indicates that if amount of both factors increased, % CDR at 6 hours was decreased.

4.16.5 EFFECT OF INDEPENDENT VARIABLES ON % CDR AT 14 HRS (Y_4):

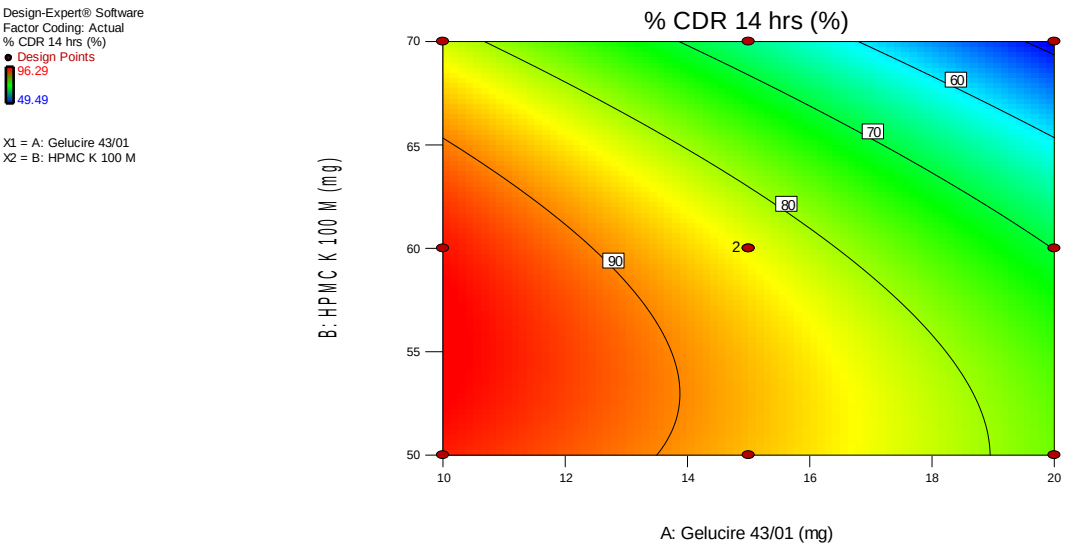


Figure 4.10(A) Contour plot for response Y_4

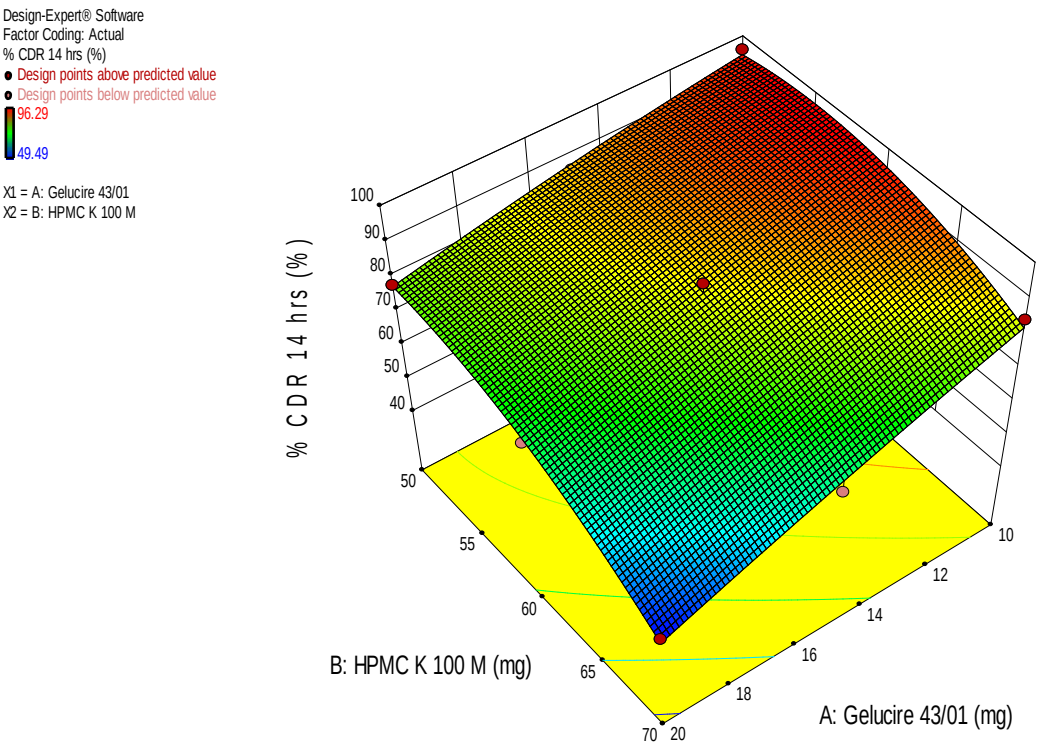


Figure 4.10(B) 3D surface plot of response Y_4

- **Discussions:**

  Reduced ANOVA equation for %CDR 14 hrs

  % CDR 14 hrs= +83.77+ (-12.77)* X_1 +(-10.65)* X_2+(-4.14)* X_1 X_2+(-6.91)* X_2^2

- The significance levels of the coefficients of X_1X_2, X_2^2, X_1^2 were found greater p value. Therefore they were omitted from the full model to generate a reduced model. The coefficients of X_1 and X_2, were found to be significant at $p<0.05$; hence, they were retained in the reduced model.
- From equation, factor value of X_1 was -12.77 and X_2 was -10.65 which indicates X_1 had more effect on % CDR at 14 hours than X_2. However, X_2 also had significant effect on drug release at 14 hours. Thus, now HPMC K 100 M was enough hydrated to give delayed release in later hours.
- Negative sign of both factors indicates that if amount of both factors increased, % CDR at 14 hours was decreased.

4.16.6EFFECT OF INDEPENDENT VARIABLES ON HARDNESS (Y_5):

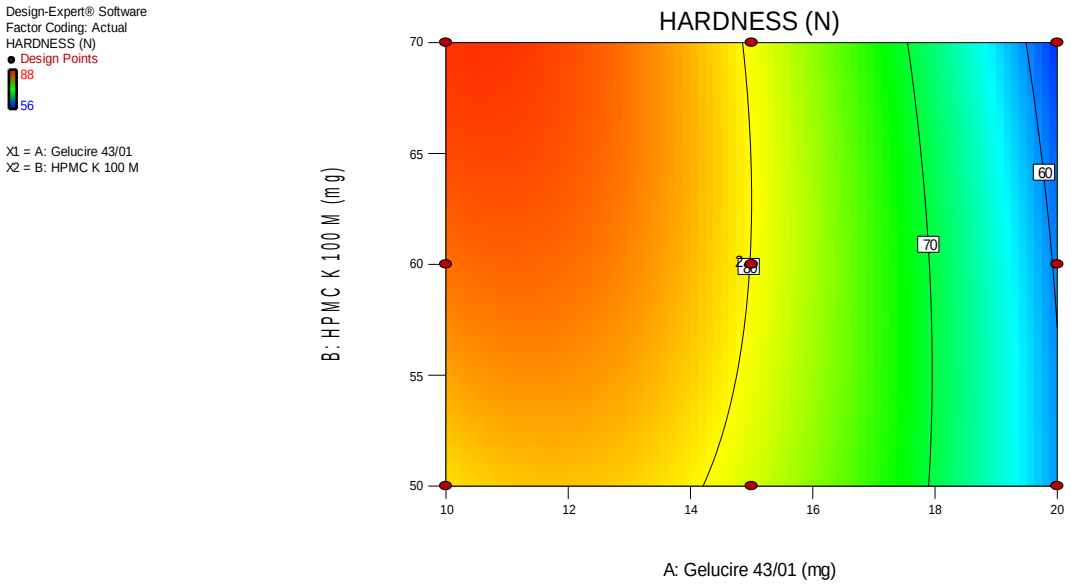


Figure 4.11(A) Contour plot for response Y_5

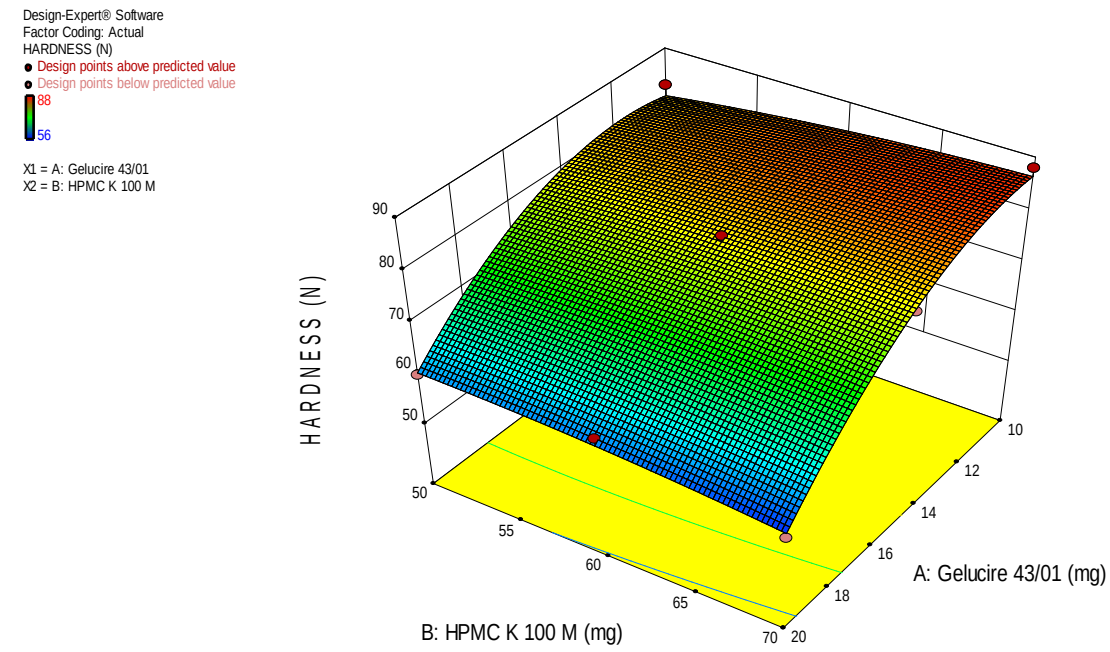


Figure 4.11 (B) 3D surface plot of response Y_5

- **Discussion:**
- Reduced ANOVA equation for hardness **HARDNESS=+79.93+ (-12.50)*** X_1**+ (-7.86)* X^2**

- The significance levels of the coefficients of X_1X_2, X_2^2, X_2 were found greater p value. Therefore they were omitted from the full model to generate a reduced model. The coefficients of X_1 and X_1^2 were found to be significant at $p<0.05$; hence, they were retained in the reduced model.
- From equation, factor value of X_1 was -12.50 and X_1^2 was -7.86 which indicates X_1 had significant effect on hardness. However, X_2 had not any effect on hardness. Thus, it was concluded that Gelucire 43/01 had critical role in formulation as per hardness concern.
- Negative sign of X_1 factors indicates that if amount of X_1 factors increased, hardness was decreased.

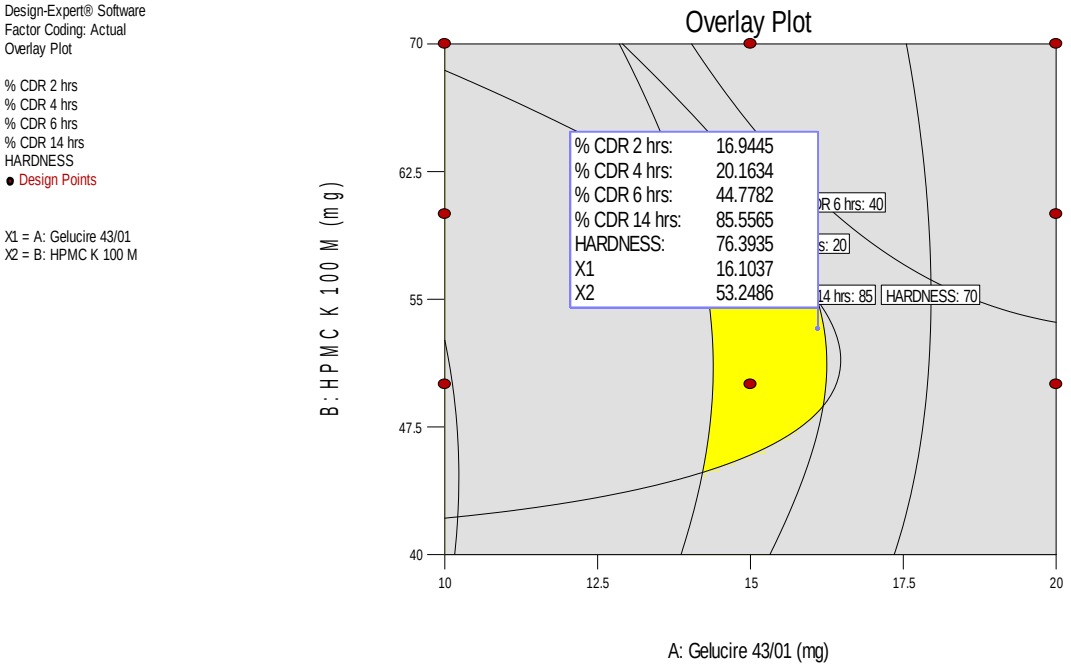


Fig No.4.12 Overlay Plot of Design

- After incorporating the criteria, an overlay plot would give design space region from which optimized batch was selected and performed.

Table No 4.15 Optimized Batch From Overlay Plot

Factor	Name	Level	Low Level	High Level
A	Gelucire 43/01	16.10	10.00	20.00
B	HPMC K 100 M	53.42	50.00	70.00

Table No 4.16 Results of Optimized Batch from Overlay Plot

ANOVA equation	Predicted	Obtained
% CDR 2 hrs=+17.93+(-9.18)* A+(-1.86)* B+0.35* AB+6.55* A^2+(-1.06) *B^2	16.94306	15.13
% CDR 4 hrs=+20.72+(-9.77)* A+(-3.46)* B+1.88* AB+6.49* A^2+(-1.70)* B^2	22.18451	22.36033
% CDR 6 hrs=+43.18+(-12.62)*A+(-5.89)*B+ (2.39)* AB+4.32* A^2+(-0.34)* B^2	44.1763	44.84048
% CDR 14 hrs=+83.77+(-12.77)* A+(-10.65)* B+(-4.14)* AB+(-1.10)* A^2+(-6.91)* B^2	85.5933	84.01868
HARDNESS=+79.93+(-12.50)* A+0.50* B+(-2.25)* AB+(-7.86)* A^2+(-0.86)* B^2	76.3459	74

- Conclusion
- From the overlay plot, optimized batch was formulated and evaluated.

  And the results were found to be matched with the predicted values.

  Thus, the mathematical model which was incorporated, was validated.

4.17 STATISTICAL ANALYSIS OF THE OPTIMIZED FORMULATION

Release profiles of Drug ASTONT2013 and Innovator were compared by calculating statistically derived mathematical parameter, "similarity factor" (f_2), using predicted in vitro release profile as the reference (section 3).

The equation of similarity factor is :

$$f_2 = 50 * \log \{ [1 + \frac{1}{n} \times \sum_{t=1}^{n} R_t - T_t ^2]^{-0.5} \times 100 \}$$

Where,

R_t and T_t = percent Drug AST04 dissolved at each time point for the reference and test product,

n = number of dissolution sample times,

t = time sample index.

If the two profiles are identical, f_2 is 100. Values of $f_2 \geq 50$ indicate similarity of two dissolution profiles.

- **Conclusion**

Similarity factor (f_2) values for Drug AST0NT2013 and Innovator when compared with predicted release profile are **68.92**. Ideally the f_2 values must fall in the range of 50-100. Thus, the release profile of the developed formulation was similar to the Innovator release profile.

PART-1 COATED MATRIX EXTENDED RELEASE TABLET

- The aim of the project was to formulate and evaluate an extended release dosage form of Drug ASTONT2013 for the treatment of overactive bladder by applying quality by design approach.The objective of the study was to develop once-a-day extended-release tablet compared to commercially available thrice-a-day immediate release formulation for better patient compliance. This would also reduce dose-dependent adverse effects due to less variation in the plasma concentration compared to immediate release. The intention of the current project was also to match the drug release profile of the formulated extended release matrix tablet with that of the innovator product having OROS technology. Hence, provides a cost-effective therapy for treatment of urinary incontinence.

- Preformulation studies of ASTONT2013 were performed, the results revealed that the ASTONT2013 is having poor flow and slightly hygroscopic in nature. Various excipients such as lactose monohydrate, microcrystalline cellulose, purified talc, colloidal anhydrous silica, methacrylic acid copolymer, cellulose acetate and magnesium stearate and controlled release matrix polymers such as hypromellose K100 M and hypromellose K 100 LV CR were found to be compatible with ASTONT2013.

- Formulation was performed by applying enteric coat over matrix tablet to get similar dissolution profile. Seal coat was applied so that enteric coat would not perturb the core. Critical quality attributes were decided, to execute quality in final product from initial stage.

- Formulation trials included screening of high viscosity hypromellose and low viscosity hypromellose. From which HPMC 100 LV CR (45 mg) and HPMC K 100 M (37 mg) were selected to give controlled drug release. 6% Seal coat was optimized as below 6% faster drug release would be there. Enteric coat of 12% would optimize as, at that concentration initial hours drug release was near to zero. Moreover, 12 % of an enteric coat gave target weight gain. Hardness challenge was executed to

evaluate relation between hardness and dissolution. Based on tablet assay, blend assay and RSD data lubrication time of 20 minutes was finalized. The optimized batch was selected on the basis of similar dissolution profile to innovator and similarity factor F2 which is 60.2.

- Tablets from batch F14 and innovator product were subjected to stability studies as per ICH guidelines. Results revealed that Drug AST0NT2013 ER tablets USP 15 mg were found stable in HDPE bottle during 3 months stability at 40°C/75% RH and 25°C/60% RH.

- From the study it was concluded that F14 (stabilized formulation) achieved all quality targets described in quality target profile and the said formulations were close to innovator product in terms of drug content, drug release profile and stability. Hence, robust product was developed.

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PART-2 WAX MATRIX EXTENDED RELEASE TABLET

- The objective was to develop a once-a-day extended-release tablet of a ASTONT2013 for the treatment of overactive bladder. The aim of the project was to control the release of ASTONT2013 by use of hydrophobic agent. As in innovator drug release profile there was no drug release in initial hours. It was suggested that to employ hydrophobic agent.

- Hydrophobic agent would incorporate a drug so that it would release slowly. Hydrophobic agents such as bees wax, carnuba wax, Ggelucire were screened in formulation trials. However, in initial trials alone use of hydrophobic agent could not controlled the drug release. Hence, further trials were performed by employing polymer matrix with hydrophobic agent.

- Form the different hydrophobic agents which were screened Gelucire 43/01 was optimized. Gelucire 43/01 was incorporated with high viscosity polymer that was HPMC K 100 M. However, initially concentration of gelucire 43/01 was higher. Thus, tablets could not be compress. By decreasing concentration of gelucire 43/01 and increasing concentration of HPMC K 100 M gave controlled release of ASTONT2013.

- Gelucire 43/01 and HPMC K 100 M, these both factors were scientifically studied using Design of Experiment (DoE). 3^2 factorial design was employed to optimize the ratio of Gelucire 43/01 and HPMC K 100 M. Results of design revealed that Geluicre 43/01 could controlled the release of drug in initial hours. After that when HPMC K 100 M hydrated, it would controlled the release of drug. However, alone Gelucire 43/01 could impact the hardness. The optimize batch was developed by validated model from the desired response region. The optimized batch was selected on the

basis of similar dissolution profile to innovator and similarity factor F2 which is 68.92.

- Optimized batch developed from design gave similar results to predicted results. Hence, product developed from employing hydrophobic and hydrophilic agents could control the release of drug ASTONT2013.

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