FORMULATION DEVELOPMENT AND EVALUATION OF MYCOPHENOLATE SODIUM 360mg DELAYED-RELEASE TABLETS

Dissertation submitted to

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MASTER OF PHARMACY

IN

PHARMACEUTICS

By

REG. NO: 26113901

Under The Guidance of

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APRIL-2013

CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF MYCOPHENOLATE SODIUM 360mg DELAYED-RELEASE TABLETS "** was carried out by **Reg. No: 26113901** in the Department of Pharmaceutics, **Arulmigu Kalasalingam College of Pharmacy**, Krishnankovil, affiliated to the Tamilnadu Dr M.G.R Medical University, Chennai. This work was guided and supervised by **Mr.V.SIVAKUMAR, M.Pharm, (PhD)** Assistant Professor, Department of Pharmaceutics.

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EVALUATION CERTIFICATE

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CONTENTS

INTRODUCTION

The past two decades witnessed enormous research and development in the field of medicine and pharmacy. Research, development and sales of drug delivery systems are increasing at rapid pace throughout the world. This worldwide trend will intensify in this decade as cuts in public health expenses demand lower costs and higher efficiency. To meet this demand, many efficient drugs currently in use have to be reformulated within the delivery system that can be value-added for optimal molecular activity.

Now a significant awareness in the scenario has been observed that instead of searching for new drugs using random hit or miss approach, the development of superior drug delivery system which enhance the therapeutic efficacy of conventional drugs by controlling the release rate or by targeting to the tissue site may be an effective approach to improve the efficacy of the chemotherapeutic agent.

With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal[1].

There are two ways to accomplish this goal,

1. Development of new, better and safer drugs with long half-lives and large therapeutic indices
2. Effective and safer use of existing drugs through concepts and techniques of controlled and targeted delivery systems[2]

PRINCIPLES OF DOSAGE FORM DESIGN

Drugs are rarely administered solely as pure chemical substances, but are almost given as formulated preparations. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation[3].

Before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These factors can be broadly grouped in to 3 categories,

1. Biopharmaceutical considerations (Factors affecting absorption of drugs)
2. Drug related factors (Physical and Chemical properties of the drug)
3. Therapeutic considerations (Disease to be treated and Patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc…), the tablet dosage form is the most widely used. Compressed tablets are defined as solid unit dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

Advantages of Tablets:

The primary potential advantages of tablets[4] are

- ✓ They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- ✓ The cost is lowest of all oral dosage forms.
- ✓ They are the lightest and most compact of all.

- ✓ They are in general the easiest and cheapest to packaging and shipment.
- ✓ Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- ✓ They may provide the greatest ease of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- ✓ They lend themselves to certain special release profile products, such as enteric or delayed release products.
- ✓ They are better suited to large scale production than with other unit oral dosage forms.
- ✓ They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

Disadvantages:

Inspite of all these advantages, tablets also possess some disadvantages[4]. The disadvantages of tablets include the following

- ✓ Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- ✓ Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

- ✓ Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating.

CLASSIFICATION OF TABLETS

Tablets are classified in different ways[5]. They are

a) **Classification based on mode of administration**

1) Tablets to be swallowed
2) Chewable tablets
3) Tablets used in oral cavity
   a. Buccal tablets
   b. Sublingual tablets
   b. Troches and lozenges
   c. Dental cones
4) Tablets administered other than oral route
   a. Implants
   b. Vaginal tablets / suppositories

b) **Classification based on drug manufacturing process**

1) Standard compressed tablets
2) Multiple compressed tablets
   a. Compression – coated tablets
   b. Layered tablets
3) Coated tablets
4) Molded tablets (Tablet triturates)

c) **Classification based on drug release profile**

1) Fast Dissolving tablets

2) Immediate Release tablets

3) Controlled Release tablets (Sustained Release tablets)

4) Delayed Release tablets (Enteric coated tablets)

d) **Tablets used to prepare solutions**

1) Effervescent tablets

2) Dispersible tablets

TABLET EXCIPIENTS:

The excipients are classified according to the function, they perform in the tablet[4]. They include the following.

a) Fillers / Diluents

b) Binders

c) Disintegrants

d) Lubricants

e) Glidant

f) Anti-adherents / anti-adhesives

S.No	CATEGORY	DEFINITION	EXAMPLES
1	Fillers / Diluents	They are the bulking agents which are inert substances added to active ingredient in sufficient quantity to make a reasonably sized tablet.	Lactose, Sucrose, Dextrose, Mannitol, Sorbitol, Starch, Micro crystalline Cellulose, Calcium carbonate, Calcium phosphate (dibasic and tribasic).
2	Lubricants	These agents are required to prevent adherence of the granules to the punch or dies.	Metal stearates (0.5 to 2% of Ca, Mg, Zn), Stearic acid fine powder (1 to 3%), Talc and Starch 1500 (5 to 10%), PEG 4000 and 6000 (2 to 5%)
S.No	**CATEGORY**	**DEFINITION**	**EXAMPLES**
3	Binders	These are glue that holds the powder together to form granules. They are adhesives added to tablet formulation to provide cohesiveness required for bonding together granules, under compaction to form tablets.	Gelatin, Glucose, Methylcellulose, Water, Acacia, Starch paste, Alcohol, Polyvinylpyrrolidone, Sorbitol.
4	Disintegrants	These agents are added to tablet formulation / granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in aqueous environment.	Starch USP (5 to 20%w/w), Starch 1500(5 to15%w/w), Avicel pH 101,102 (Microcrystalline cellulose 5 to 15%w/w), Sodium starch glycollate (Explotab 2 to 8% w/w), PVP and cross linked PVP (0.5 to 10%w/w), Sodium Carboxyl Methyl cellulose.
5	Glidants	These are materials that improve the flow characteristics of granulations by reducing inter particulate	Aerosil (Colloidal Silicon dioxide) (0.1 to0.5%w/w), Talc (1 to 5%w/w) and Syloid.

		friction.	

TABLET MANUFACTURING PROCESS:

An outline of the various steps involved in the manufacturing of tablets[6] by different methods is mentioned below,

Wet Granulation	Dry Granulation	Direct Compression
Milling of drugs and excipients	Milling of drugs and excipients	Milling of drugs and excipients
Mixing of milled products	Mixing of milled products	Mixing of milled products
Preparation of the binder solution	Compression in to large hard tablets called slugs	Tablet compression
Mixing binder solution with powder mixture to form wet mass	Screening of slugs	
Coarse screening of wet mass	Mixing with lubricant and disintegrating agent	
Drying moist granules	Tablet compression	
Screening dry granules with lubricant and disintegrant		
Mixing Screened granules with lubricant and disintegrant		
Tablet compression		

The various process involved in the manufacturing of tablet are,

- ✓ Mixing

- ✓ Granulation
- ✓ Drying
- ✓ Milling / Sizing
- ✓ Compression
- ✓ Coating
- ✓ Packing

Mixing:

Mixing is defined as to put together (substances / things / one substance / thing with another) in one mass assemblage with more or less through diffusion of the constituent elements among one another. The three main mechanisms involved in mixing are diffusion, convection and shear.

Types of mixers:

a) Batch type:

Double cone blender, V- Shaped, Barrel, Planetary, Ribbon, and Fluid bed Granulator, Fluidized bed dryer.

b) Continuous:

Zig zag mixer.

Granulation:

Granulation is any process of size enlargement whereby small particles are gathered together into large permanent aggregates to render them in to free flowing state.

Reasons for granulation:

- ✓ Render the material free flowing
- ✓ Densify material
- ✓ Prepare uniform mixtures that do not separate
- ✓ Improve compression characteristics of drug
- ✓ Control the rate of drug release
- ✓ Removes dust
- ✓ Improve appearance of the tablet

Types of granulation:

- ✓ Wet Granulation.
- ✓ Dry Granulation.
- ✓ Direct Compression.

Wet Granulation – Schematic Representation:

Drug → Grind → Adjuvant → Blend → Binder Addition → Agglomerate → Pellets

Tablet¯ Compress ¬ Lubricate ¬ Blend ¬ Screen ¬ Dry

The equipment widely used for wet granulation process is "RAPID MIXER GRANULATOR".

Dry Granulation – Schematic Representation:

Drug → Grind → Adjuvant → Blend → Pellet [Compaction] → Crush → Screen

¬

Tablet ¯ Compress ¬ Lubricate ¬ Blend

Direct Compression Schematic Representation:

Drug → Grind → Adjuvants → Blend → Compress → Tablet

Drying:

Drying is defined as removal of water / other liquid from a solid / semisolid mass by evaporative process.

The various equipments used for drying are

- ✓ Tray Dryer
- ✓ Turbo tray dryer
- ✓ Fluidized Bed Dryer
- ✓ Spray Dryer

Compression:

Compression is defined as a process of applying pressure to a material. In Pharmaceutical tabletting an appropriate volume of granules in to die cavity is compressed between upper punch and lower punch to consolidate the material into a single solid matrix, which is subsequently ejected from the die cavity as "INTACT TABLET"

The equipments used for compression are

- Single Punch Tablet Compression Machine
- Rotary Tablet Compression Machine.

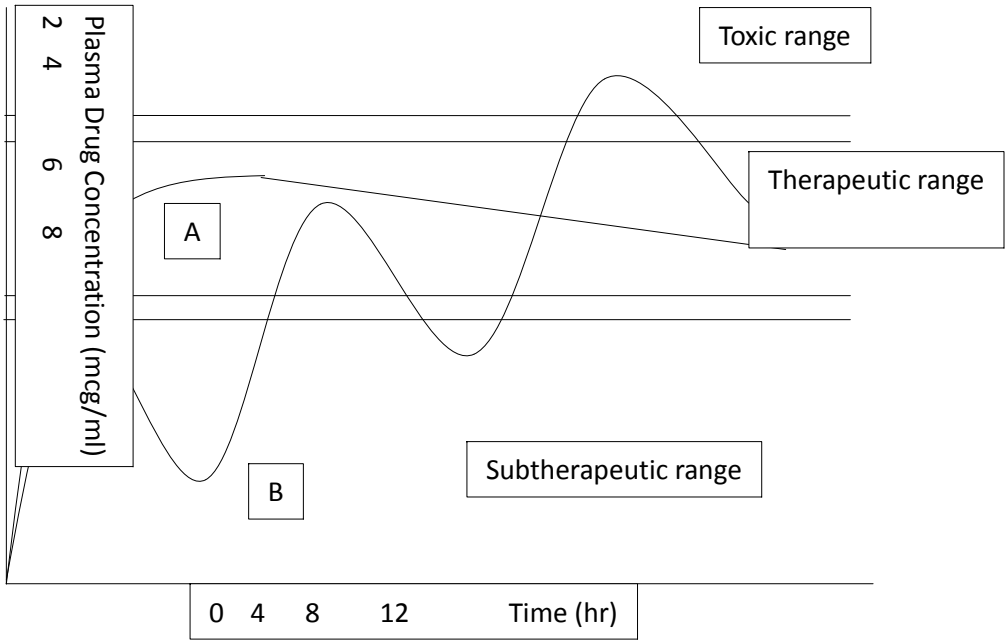
THE SUSTAINED RELEASE CONCEPT

Sustained release, sustained action, prolonged action, controlled release, extended action are the terms used to identify drug delivery systems that are designed to achieve a prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The extended, slow release of controlled release drug products produces a relatively flat, sustained plasma drug concentration that avoids toxicity (from high drug concentrations) or lack of efficacy (from low drug concentrations)[7].

The desirable therapeutic advantages of a sustained release form are,

1. Frequency of drug administration is reduced and thus patient compliance can be improved.
2. The blood level oscillation characteristics of multiple dosing of conventional dosage forms is reduced.
3. Total amount of drug administered can be reduced, thus maximizing availability within minimum dose.
4. Safety margin of high potency drugs can be increased, and the incidence of both local and systemic adverse effects can be reduced.
5. Overall, administration of sustained release forms enables increased reliability of therapy[1b].

There are various approaches in delivering a therapeutic substance to the target site in a sustained release fashion. Microspheres, which are matrix systems containing drug throughout (either in solution or microcrystalline form) the structure are potential candidates for oral sustained release [8].



Typical plasma drug concentration versus time profiles for an ideal sustained release microencapsulated product (A) and conventional dosage form (B) repeatedly given orally[9].

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pellets for prolonged release of a drug and was presumably the forerunner to the development of the coated particle approach [10].

With many drugs, the basic goal of therapy is to achieve a steady state blood on tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of the therapeutic effect in the face of uncertain fluctuations in the In-vivo environment in which drug release takes place [11].

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release are terms to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over and extended period of time after administration of a single dose.

Oral injection has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release of systems the oral route of administration has received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route[12].

MODIFIED RELEASE SYSTEMS

To overcome the potential problems associated with conventional drug therapy modified release systems were developed and may be divided into four categories [13].

1. Sustained release

a. Controlled release

b. Prolonged release

2. Site specific release
3. Receptor
4. Delayed release

Sustained release system

Sustained release are that which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.

Controlled release system

An ideal controlled drug delivery system is that which delivers the drug at predetermined rate, locally or systemically for the predetermined period of time. Thus maintaining constant drug level in blood or target tissue.

Site specific and receptor release system

Site specific and receptor release and targeted release system refers to targeting of the drug directly to a certain biological location.

Prolonged release system

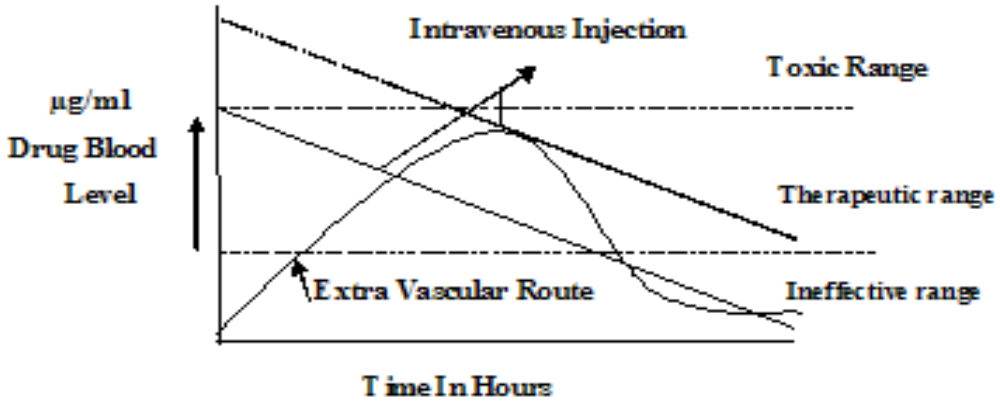
Prolonged release system, prolongs the duration of action without maintaining a constant drug blood level.

Conventional dosage forms are associated with many side effects such as the initial dose may not be adequate enough to reach the therapeutic range to elicit pharmacological response. Besides this the repeated drug administration at the equal intervals may result in severe side effects. These problems of conventional dosage forms are overcome by controlled drug delivery systems since sustained release dosage forms usually consists of two parts an immediately available dose to establish the blood level quickly and a sustaining part that contains several times the therapeutic dose for protracted drug levels

In conventional drug therapy it can be seen from the figure that the administration of drug by either intravenous injection or an extravascular route e.g. orally, intramuscularly or rectally does not maintain drug blood level within the therapeutic range for an extended period of time. The short action is due to the inability of conventional dosage forms to control temporal delivery [13].

FIGURE – 1

Drug Blood Level Vs Time Profile for Intravenous injections (eg. Dextrose and Sodium Chloride Injections) and extra vascular route of administration (Acetaminophen tablet given orally)



Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery or drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its case of administration as well as the traditional belief that by oral administration the drug it as well absorbed as the foodstuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form (solid, semisolid, or liquid dosage form), involves varying extents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal (GI) physiology [14].

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the counter markets are mostly the immediate-release type, which are designed for immediate release of drug for rapid absorption. Because of their clinical advantages over immediate-release pharmaceutical products containing the same drugs, sustained-release pharmaceutical products, such as those formulated on the basis of spansule coating technology, have over their introduction into the marketplace. Recently, a new generation of pharmaceutical products, called controlled-release drug delivery systems, such as those developed form the osmotic pressure-activated drug delivery system, have recently received regulatory approval for marketing and their pharmaceutical superiority and clinical benefits over the sustained-release and immediate-release pharmaceutical products have been increasingly recognized.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration. Irrespective of the mode of delivery immediate, sustained or controlled release and the design of dosage forms (either solid dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology. Therefore, a fundamental understanding of various disciplines including GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systematic approach to the successful development of an oral pharmaceutical dosage form (or drug delivery system). The more sophisticated a delivery system the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any, case the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects: (i) physicochemical, pharmacokinetic and pharmacodynamics characteristics of the drug, ii. the anatomic and physiologic

characteristics of the gastrointestinal tract and iii. physicomechanical characteristics and the drug delivery mode of the dosage form to be designed.

Although it is often impractical to alter the physicochemical, pharmacokinetic and or pharmacodynamics characteristics of a drug to be delivered by a chemical approach, such as the synthesis of an analog or medically undesirable to modify the anatomic and physiologic characteristics of the gastrointestinal tract, the design of a controlled-release oral dosage form by optimization of dosage form characteristics with GI anatomy and physiology taken into consideration could provide some opportunity to rationalize the systemic delivery of drugs and maximize their therapeutic benefits.

The term “Controlled-release oral dosage form: is not new to most people working in various fields of pharmaceutical research and development. In fact, approximately 30 years ago, the U.S. Food and Drug Administration (FDA) published regulatory requirements for controlled-release products. Unfortunately there has been a proliferation of controlled-release dosage forms on the marketplace that may have little rationale and provide no advantages over the same drugs in conventional dosage forms. Over the last decades there has also been an increase in the use of controlled-release labeling claim.

Potential Advantages of Sustained Drug Therapy

Sustained drug therapy is used for the following purposes [11]

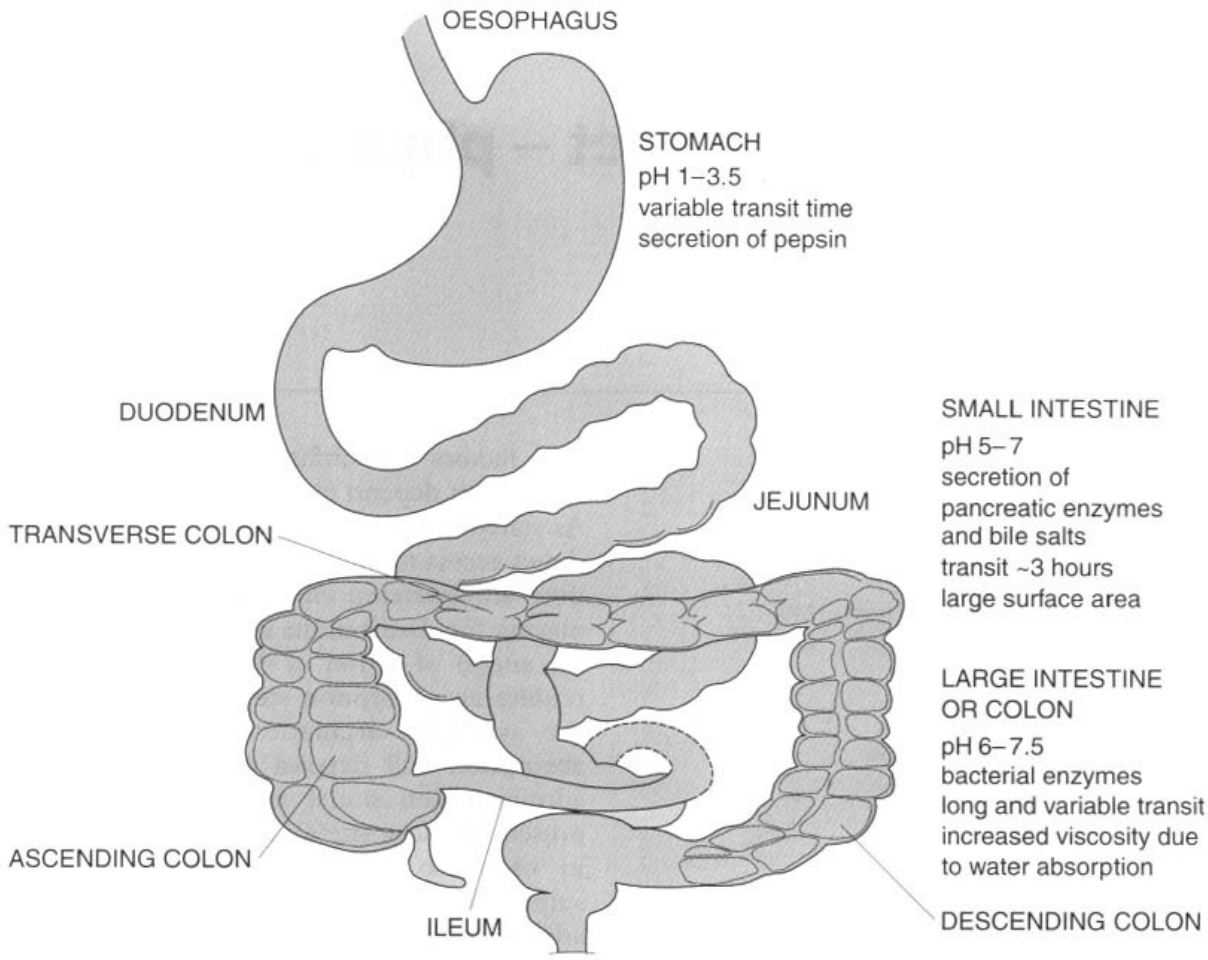
1. Patient compliance due to reduction in frequency of dosing
2. Employ minimum drug
    a. Minimize or eliminates local and systemic side effects.
    b. Obtain less potentiating or reduction in drug activity with chronic use.
    c. Minimize drug accumulation with chronic dosing.
3. Improve efficacy in treatment
    a. Cure or control condition more promptly
    b. Improve control of condition.

DELAYED RELEASE SYSTEM[17]

Delayed release systems are those that used repetitive intermittent dosing of the drug from one or more immediate release units incorporated into single dosage form.

Definition:

Delayed-Release tablets that are intended to resist the gastric fluid and to release their active substance in the in the intestinal fluid. Usually they are prepared from granules or particles already covered with a gastro-resistant coating or in certain cases by covering tablets with a gastro-resistant Enteric coated tablets.



For tablets covered with a gastro-resistant coating carry out the test for disintegration with the following modifications. Use 0.1M Hydrochloric Acid as a liquid. Operate the apparatus for 2 hours, without the discs and examine the state of the tablets. The time of resistance to the acid medium varies according to the formulation of the tablets to be examined. An authorized deviation is not less than 2 hours. No tablet shows signs of either disintegration or cracks that would allow to escape of the contents. Replace the acid by phosphate buffer solution P^H 6.8 and add a disc to each tube. Operate the apparatus for 60 minutes and examine the state of the tablets. If the tablets comply because of adherence to the discs, repeat the test a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

ENTERIC COATING TECHNIQUE:

This technique is used to protect the tablet core from disintegration in the acid environment of the stomach for one or more of the following reasons:

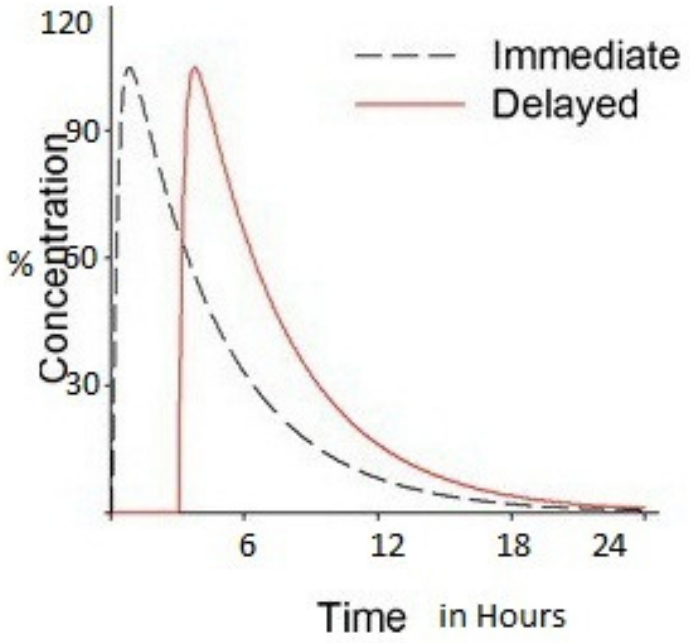
- ✓ Prevention of acid attack on active constituents unstable at low pH;
- ✓ To protect the stomach from the irritant effect of certain drugs;
- ✓ To facilitate absorption of a drug that is preferentially absorbed distal to the stomach.

The following polymers are among those commonly used for the purposes of enteric coating:

- ✓ Cellulose acetate phthalate
- ✓ Polyvinyl acetate phthalate
- ✓ Suitable acrylic derivatives.

Because they possess free carboxylic acid groups on the polymer backbone, they exhibit a differential p^H solubility profile. They are almost insoluble in aqueous media at low p^H, but as the p^H rises they experience a sharp, well denned increase in solubility at a specific pH, e.g. p^H 5.2 for cellulose acetate phthalate.

COMPARISON CHART FOR DELAYED-RELEASE WITH IMMIDIATE RELEASE DOSAGE FORM



REVIEW OF LITERATURE

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- **Staatz, Christine E, Tett, Susan E**[19] This review aims to provide an extensive overview of the literature on the clinical pharmacokinetics of mycophenolate in solid organ transplantation and a briefer summary of current pharmacodynamic information. Strategies are suggested for further optimisation of mycophenolate therapy and areas where additional research is warranted are highlighted. Mycophenolate has gained widespread acceptance as the antimetabolite immunosuppressant of choice in organ transplant regimens. Mycophenolic acid (MPA) is the active drug moiety.
- **L Chan, S Mulgaonkar, R Walker**[20] Patient-Reported Gastrointestinal symptom burden and health-related quality of Life following Conversion from Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium.

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to improve mycophenolic acid -related upper gastrointestinal adverse events by delaying the release of mycophenolic acid until reaching the small intestine.

- **K Budde, P Glander, BK Kramer, W Fischer**[22] Conversion From Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium in Maintenance Renal Transplant Recipients Receiving Tacrolimus. Clinical, Pharmacokinetic and Pharmacodynamic activity.

- **G Crotts, A Sheth, J Twist, I Ghebre-Sellassie**[23] Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acidic tablet core should be applied to prevent retardation in drug release.

- **Ciancio G, Sageshima J, Burke GW, Rosen A, Miller J**[24] A Randomized Trial Comparing Tacrolimus/ Mycophenolate Mofetil (CellCept) Versus Tacrolimus/Enteric-Coated Mycophenolate Sodium (Myfortic) In First Renal Transplants Induced With Both Daclizumab And Thymoglobulin. With Steroid Avoidance.

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- **W.Arns**[26] Noninfectious Gastrointestinal Complications of Mycophenolic Acid Therapy. Mycophenolic acid , a reversible inhibitor of inosine 5″-monophosphate dehydrogenase (IMPDH), selectively inhibits T- and B-cell proliferation. Mycophenolic acid exposure correlates inversely with the risk of acute rejection. Mycophenolate mofetil is an immediate-release formulation of Mycophenolic Acid that is absorbed in the stomach and small intestine.

- **Theodore W. Perry, Uwe Christians, James F. Trotter, Jamie Bendrick-Peart**[27] Mycophenolate mofetil is one of the major immunosuppressive agents used in liver transplantation recipients. In an attempt to mitigate one of the most common side effects of Mycophenolate mofetil (gastrointestinal symptoms), enteric-coated mycophenolate sodium was developed. In this study, we report the pharmacokinetic profile of enteric-coated mycophenolate sodium in stable liver transplantation recipients administered a single 720 mg dose.

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- **Massari P, Duro-Garcia V, Girón F, Hernández E, Juárez F, Castro C, Toledo M**[30] Safety assessment of the conversion from mycophenolate mofetil to mycophenolate sodium in stable renal transplant recipients. Full dose tolerability with enteric coated mycophenolate sodium.

- **Dumortier J, Gagnieu M-C, Salandre J, Guillem P, Adham M, Boillet O**[31] Conversion from Mycopenolate mofetil to enteric-coated Mycopenolate sodium in liver transplant patients presenting gastrointestinal disorders.

- **Bjarnason I.**[32] Enteric coating of mycophenolate sodium: a rational approach to limit topical gastrointestinal lesions and extend the therapeutic index of mycophenolate.

- **Fanak et al., (2012)**[33] reported that physical and chemical stability of Mycophenolate Mofetil (MMF) suspension prepared at the hospital. Suspension formulations were prepared from both tablets and capsules forms of MMF. Thereafter the stability parameters such as pH, microbial control, thermal and physical stability and particle sizes were evaluated. The amount of MMF, in the suspension was measured at various time points by HPLC. According to the obtained results in this study, capsule-based suspension was stable for as long as 14 days at 5°C.

- **Kathleen et al., (2012)**[34] reported that race and drug formulation influence on Mycophenolic acid pharmacokinetics in stable renal transplant recipients. The Journal

of Clinical Pharmacology. Mycophenolic acid clearance and dose-normalized area under the concentration-time curve 0-12 (AUC) were determined. Mixed model statistics evaluated the main effects of race, drug formulation, and interaction of race and drug formulation (R × D) with albumin, cyclosporine trough, renal function, and diabetes and enterhepatic recirculation. The findings concluded that race influences MPA exposure between MMF and EC-MPS and may warrant therapeutic monitoring during formulation conversion.

- **Hari and Karen et al., (2012)** [35] reported that current state of renal transplant immunosuppression: Present and future. World Journal of Transplant 2012; 2(4): 51-68. Regimens designed to limit or eliminate calcineurin inhibitors and/or corticosteroid use are actively being pursued. An ideal immunosuppressive regimen limits toxicity and prolongs the functional life of the graft. This article contains a critical analysis of clinical data on currently available immunosuppressive strategies and an overview of therapeutic moieties in development.

- **Zeher, et al., (2011)**[36] reported that efficacy and safety of enteric-coated Mycophenolate sodium in combination with two glucocorticoid regimens for the

treatment of active lupus nephritis. This exploratory study suggests that EC-MPS may facilitate glucocorticoid reduction without loss of efficacy in patients with active lupus nephritis, but results require confirmation in a controlled, longer-term study versus the current standard of care.

- **Esquivel et al., (2010)** [37] reported that comparison of dissolution properties of 2 enteric-coated formulations containing Mycophenolate sodium: Myfortic vs Femulan. For both formulations, mycophenolate sodium content was within the 90% to 110% range of the label claimed dose, and no impurities were present as determined at high-performance liquid chromatography. Mycophenolate sodium release was assayed by applying the US Pharmacopeia apparatus 2 dissolution test at 2 different pH values (1.2 and 6.8) to mimic conditions in the stomach and the small intestine, respectively. At pH 1.2, mycophenolate sodium release was less than 2%, with respect to the label claimed dose, for both formulations. At pH 6.8, mean (range) mycophenolate sodium release with Myfortic was 104.9% (104.0%–105.6%), and with femulan was 62.3% (51.3%–67.7%); the difference between formulations achieved statistical significance

- **Sarah et al., (2010)** [38] reported that therapeutic drug monitoring of mycophenolate mofetil and enteric-coated mycophenolate sodium in patients with systemic lupus erythematosus. MPA AUC between 0 and 12 h ($AUC_{0–12h}$), C_{max}, T_{max}, and 12-h trough concentrations (C_{12h}) were determined. Means of dose-normalized MMF– or EC-MPS–MPA C_{max} were 64.6 ± 25 and 61.4 ± 27.1 h mg/l, respectively. MPA T_{max} for EC-MPS was longer and more variable than for MMF. MMF-MPA $AUC_{0–12h}$ and C_{12h} were correlated ($r = 0.78$, $p = 0.0001$), but EC-MPS–MPA C_{max} and single concentrations were weakly correlated. A limited-sampling strategy (LSS) combining C_{max} and C_{12h} gave satisfactory predictive performance to estimate MPA $AUC_{0–12h}$ after EC-MPS administration.

- **Dario et al., (2007)** [39] reported that Pharmacokinetics of Mycophenolate sodium and comparison with the Mofetil formulation in stable kidney transplant recipients. Patients who were taking the enteric-coated formulation had mycophenolic acid time of occurrence for maximum drug concentration that ranged from 0 to 480 min and higher dosage-adjusted mycophenolic acid trough levels compared with patients who were given mycophenolate mofetil. Conversion from the enteric-coated formulation of mycophenolate sodium to mycophenolate mofetil resulted in an improvement of the mycophenolic acid kinetics profiles.

- **Budde et al., (2004)** [40] reported that enteric-coated Mycophenolate sodium: safe conversion from mycophenolate mofetil in maintenance renal transplant recipients.

Enteric-coated mycophenolate sodium (EC-MPS) is an advanced formulation delivering mycophenolic acid (MPA), developed with the objective of improving MPA-related upper GI adverse events. A pivotal, 12-month, phase III, randomized, multicenter, double-blind, double-dummy, parallel group study investigated whether stable renal transplant patients can be converted from MMF to EC-MPS therapy without compromising tolerability or efficacy.

- **Maurizio et al., (2004)** [41] reported that enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. An enteric-coated formulation of mycophenolate sodium (EC-MPS; myfortic) has been developed with the aim of improving the upper GI tolerability of mycophenolic acid. Within 12 months, 15.0% of EC-MPS patients and 19.5% of MMF patients required dose changes for GI adverse events (p=ns). Enteric-coated-MPS 720 mg b.i.d. is therapeutically equivalent to MMF 1000 mg b.i.d. with a comparable safety profile.

- **Monica et al., (2004)** [42] reported that Mycophenolate sodium versus Mycophenolate mofetil: A review of their comparative features. From the findings, this study

concludes that considering the limited number of studies comparing these two agents, it is difficult to establish significant concluding remarks of the advantages of using ECMS over MMF. What is obvious, however, is that ECMS does represent an alternative to the significant number of patients suffering from the common gastrointestinal intolerance reported with MMF. Whether ECMS's consistent capacity to achieve the target AUC (0-24) of >30 μg/ml is of clinical relevance needs further investigation.

- **Nashan et al., (2004)** [43] reported that conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant patients: Preliminary results from the myfortic prospective multicenter study. Enteric-coated mycophenolate sodium (EC-MPS) is a new formulation delivering mycophenolic acid developed with the aim of improving upper GI tolerability. A large prospective, open-label, multicenter program (myPROMS: myfortic PROspective Multicenter Study) is underway to determine the efficacy and safety of EC-MPS, in combination with cyclosporine microemulsion in a large population of de novo and maintenance renal transplant recipients. The preliminary data summarized here are from two subprotocols, which investigated the benefits of converting maintenance renal transplant patients receiving MMF to EC-MPS. The 3-month interim analyses suggest

that the conversion from MMF to EC-MPS is well tolerated in maintenance renal transplant recipients.

- **Budde et al., (2003)** [44] reported that enteric-coated Mycophenolate sodium can be safely administered in maintenance renal transplants patients from the results of a 1 – year study. American Journal of Transplantation 2003; 4: 237-243. The study concluded that renal maintenance patients can be converted from MMF to EC-MPS without compromising the safety and efficacy profile associated with MMF.

- **William et al., (2003)** [45] reported that immunosuppression with Mycophenolic Acid: One size does not fit all. An enteric-coated formulation of mycophenolate sodium (Myfortic) is in the final stages of drug development. Presumably the enteric coating avoids upper GI tract toxicity and delivers the drug more distally, where it may be absorbed better. Randomized blinded trials are in progress, but thus far there is no evidence that this formulation has a better efficacy or side effect profile than MMF.

- **Schuurman et al., (2002)** [46] reported that Mycophenolate sodium: tolerability and efficacy in transplantation in the rat. Mycophenolate sodium (MPS) is in clinical development as an enteric-coated formulation to alleviate this gastrointestinal adverse effect. Accompanying this development, MPS and MMF were evaluated in a tolerability study in rats and in efficacy studies in rat allo- and xenotransplantation

models. The minimal effective dose to prevent rejection of a kidney or heart allograft or a hamster heart xenograft is a daily dose of 10-20 mg/kg MPS, at which dose the first adverse side effects can be observed: the compound at 40 mg/kg is not tolerated. This window is even narrower for MMF than for MPS, and in most models, a minimal effective MMF dose could not be established. The window between optimal immunosuppression and adverse side effects is larger when the compounds are given in combination with cyclosporine A: in all models investigated combinations were established yielding long-term survival without histologic signs of rejection and without signs of side effects. Thus, the combination of an IMPDH inhibitor (MPS, MMF) and a calcineurin inhibitor (cyclosporine A) enables fine-tuning in achieving optimal immunosuppression avoiding drug side effects.

AIM

The aim of formulation development was to formulate Mycophenolate sodium Tablets 360mg (Enteric coated), which are robust, stable and bio-equivalent to the Generic product of **Myfortic 360mg** Tablets marketed by **Novartis pharma stein AG** which is used as Reference Listed Product for comparison & Developmental studies. Product development was carried out on Mycophenolate sodium Tablets 360mg. All the critical process parameters identified at development stage were confirmed and proved that the process is capable of producing a drug product of the required quality with the proposed process & product parameters.

OBJECTIVE

The objective of the present study is to:

- To develop a formulation of Delayed-Release tablets of Mycophenolic acid of strength 360mg which shall be bioequivalent to Reference product.
- To develop a best processing method using different grades of excipients.
- To develop a seal coating and enteric coating formula by various weight buildup.
- To develop and evaluate the in-vitro dissolution release of the prepared tablets and to compare with the Reference product.
- Data characterization and compilation of the final formulated product.

PLAN OF WORK

- Literature survey
- Reference product evaluation
- Pre-formulation Studies
- Drug-Excipients Compatibility Studies – For selection of compatible excipients.
- Formulation development for core tablet.
- Formulation development for seal coating.
- Formulation development for enteric coating.
- Formulation development for dissolution comparable with Innovator product.
- Stability studies of finalized product

Physical and chemical evaluation of test product

- Weight variation
- Thickness
- Hardness
- Friability
- Disintegration
- Dissolution
- Related Substances

DRUG PROFILE

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Each Enteric coated Tablet contains:

Mycophenolic acid …… 360mg.

FORMULATION STUDIES

Mycophenolate sodium Tablet is indicated as an immunosuppressant drug used to prevent rejection in organ transplantation. It was initially marketed as the prodrug mycophenolate mofetil (MMF) to improve oral bioavailability. More recently, the salt mycophenolate sodium has also been introduced.

MANUFACTURER FOR ACTIVE SUBSTANCE

The active substance has been procured from Biocon Ltd. India/Concord Ltd India.

COMPONENTS OF DRUG PRODUCTS:

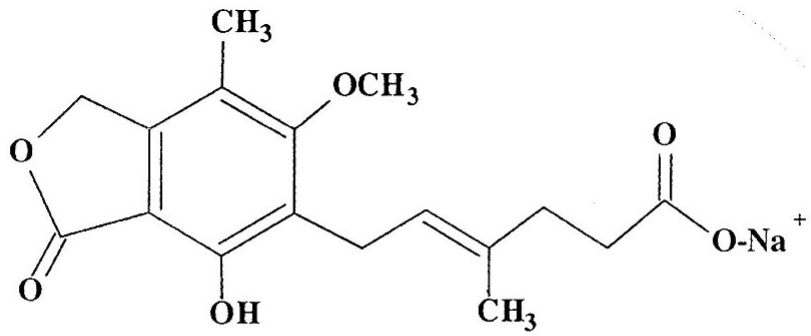
Physico-Chemical characterization of Mycophenolate sodium:

Mycophenolate sodium is an off white crystalline hygroscopic powder. It is slightly soluble in methanol and very slightly soluble in water.

Molecular Formula: $C_{17}H_{20}O_6$

Molecular weight : 320.34 $g \cdot mol^{-1}$

Chemical Structure:



Sodium mycophenolate, (Sodium 1,3- dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate), $C_{17}H_{19}O_6Na$

PHARMACOLOGY[15]

Mycophenolate sodium (MPS) is an enteric coated, delayed release monosodium salt of Mycophenolate Acid (MPA). The active ingredient, MPA, was first discovered in 1896 as a

fermentation product of several Penicillium species. While it was initially studied as an antibiotic, it was in the early 1970's that MPA was demonstrated to suppress antibody responses and prolong skin-graft survival in mice. Inhibitors of inosine monophosphate dehydrogenase (IMPDH) are effective immunosuppressants and MPA is a potent, selective, uncompetitive and reversible inhibitor.

In vitro studies have demonstrated that only free MPA is available to inhibit IMPDH after NADH (nicotinamide adenine dinucleotide) is released but before XMP which is the committed step in *de novo* guanosine nucleotide synthesis. The structure of IMPDH also indicates that MPA inhibits the enzyme by simultaneously mimicking the nicotinamide portion of the NAD cofactor and a catalytic water molecule. Clinical studies have shown MPA to be 4.8 times more active against type-II IMPDH than type-I, thereby increasing its selectivity toward activated lymphocytes. Enteric-coated MPS was developed for the potential to reduce MPA-associated side effects such as nausea, vomiting, dyspepsia, abdominal pain and discomfort based on the hypothesis of sharing a similar mechanism of GI toxicity with that of non-steroidal anti-inflammatory agents (NSAIDs). Preliminary studies showed that MPA is a potent uncoupler of mitochondrial oxidative phosphorylation similar to NSAIDs.

PHARMACOKINETICS[15]

ABSORPTION

In vitro studies demonstrated that the enteric-coated mycophenolic acid tablet does not release mycophenolic acid under acidic conditions (p^H less than 5) as in the stomach but is highly soluble in neutral p^H conditions as in the intestine. Following mycophenolic acid oral administration without food in several pharmacokinetic studies

conducted in renal transplant patients, consistent with its enteric-coated formulation, the median delay (t_{lag}) in the rise of mycophenolic acid concentration ranged between 0.25 and 1.25 hours and the median time to maximum concentration (T_{MAX}) of mycophenolic acid ranged between 1.5 and 2.75 hours. In comparison, following the administration of mycophenolate mofetil, the median T_{MAX} ranged between 0.5 and 1 hour. In stable renal transplant patients on modified cyclosporine-based immunosuppression, GI absorption, and absolute bioavailability of mycophenolic acid following the administration of mycophenolic acid delayed-release tablet was 93% and 72%, respectively. Mycophenolic acid pharmacokinetics is dose proportional over the dose range of 360mg to 2,160mg. In the early post transplant period, mean mycophenolic acid AUC and C_{MAX} were approximately one-half of those measured 6 months post transplant. The trials in other solid organ transplant types; heart and liver, have demonstrated equivalent pharmacokinetic parameters relative to MMF. There is significant intra and inter-patient variability in pharmacokinetic parameters which is dependent on organ type, concurrent immunosuppressive therapy and weeks post-transplant.

DISTRIBUTION

The mean (± SD) volume of distribution at steady state and elimination phase for MPA is 54 (± 25) L and 112 (± 48) L, respectively. MPA is highly protein bound to albumin, >98%. The protein binding of mycophenolic acid glucuronide (MPAG) is 82%. The free MPA concentration may increase under conditions of decreased protein binding (uremia, hepatic failure, and hypoalbuminemia).

METABOLISM

MPA is metabolized principally by glucuronyl transferase to glucuronidated metabolites. The phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG), is the predominant metabolite of MPA and does not manifest pharmacological activity. The acyl glucuronide is a minor metabolite and has comparable pharmacological activity to MPA. In

stable renal transplant patients on cyclosporine, USP (MODIFIED) based immunosuppression, approximately 28% of the oral Myfortic dose was converted to MPAG by presystemic metabolism. The AUC ratio of MPA:MPAG:acyl glucuronide is approximately 1:24:0.28 at steady state. The mean clearance of MPA was 140 (± 30) mL/min.

ELIMINATION[23]

The majority of MPA dose administered is eliminated in the urine primarily as MPAG (>60%) and approximately 3% as unchanged MPA following MPS administration to stable renal transplant patients. The elimination half-life of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.

EFFECTS OF FOOD[24]

The effect of a high fat meal compared to the fasting state has been assessed. There was no effect on MPA AUC, along with a 33% decrease in C_{MAX} and a significant delay in T_{MAX}.[26]

DRUG INTERACTION

The following drug interaction studies have been conducted with Mycophenolate sodium 360mg enteric coated tablets.

- ✓ ***Gastroprotective agents:*** Antacids with magnesium and aluminum hydroxides
- ✓ ***Proton Pump inhibitors:***
- ✓ ***Cholestyramine and Drugs that Bind Bile Acids:***
- ✓ ***Oral Contraceptives:*** levonorgesterol
- ✓ ***Live Vaccines:*** Influenza vaccination

ADVERSE REACTION

The principal adverse reactions associated with the administration of Mycophenolate sodium include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

THERAPEUTIC DRUG MONITORING[23]

Therapeutic drug monitoring in the context of MMF and MPS has been defined as a diagnostic method that assigns drug concentration values, based on studies relating patient outcome measurements to drug concentrations, to predict efficacy (usually a lowered rate of graft rejection) or toxicity (short-term or long-term) in individual patients.[27] Renal function and drug related side effects has been found for the 12hours dose interval MPA AUC_{0-12} and the pre-dose trough MPA concentration. Maximum plasma concentration (Cmax) (>30mg/L) and AUC values (>microgram*h/ml) for MPA are associated with a lower risk of renal allograft rejection; while levels of therapeutic exposure >60-70 microgram*h/ml are associated with a significant proportion of patients withdrawing from treatment due to adverse events, mainly GI intolerability.

DOSAGE AND ADMINISTRATION

MPS is available in 180mg and 360mg enteric coated tablets.12 Because of this coating the tablets should not be crushed. The pharmacokinetic behavior of MPA and MPAG previously described in this document require that both MPS and MMF be administered twice daily. The dosage of MPS tablets was designed such that a 720mg dose of MPS would provide the nearest molar equivalent of MPA provided by 1000mg of MMF. The MMF daily dose of 1000mg BID is accepted based on the results of pivotal trials that have shown this to be the accepted dose for prophylaxis in renal transplantation.7 Daily doses of MPS 720mg and MMF 1000mg are utilized for liver transplant recipients while higher doses of MPS 2160mg and MMF 3000mg are used for heart transplant recipients.

EXCIPIENT PROFILE

Excipients are selected based on the excipients of Reference Product. Apart from the Reference product excipients other excipients are selected based on the proposed composition & possible use of them.

LACTOSE MONOHYDRATE

Nonproprietary Names

- BP: Lactose monohydrate
- PhEur: monohydricum Lactosum
- JP: Lactose
- USPNF: Lactose monohydrate

Chemical Name

O-β-d-Galactopyranosyl-(1→4)-α-d-glucopyranose monohydrate

Empirical Formula

$C_{12}H_{22}O_{11}·H_2O$

Functional Category

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

Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluents in tablets.

Description

Lactose is white to off-white crystalline particles or powder, odorless and slightly sweet-tasting. In the solid state, lactose appears as various isomeric forms, the stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous and stable α-lactose anhydrous.

Stability and Storage Conditions

Mold growth and brown coloration may occur under humid conditions. Lactose should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Lactose is also incompatible with amino acids, aminophylline, amphetamines and lisinopril.

Safety

Adverse reactions to lactose are largely lead to cramps, diarrhea, distension, and flatulence

POVIDONE

Nonproprietary Names

- BP: Povidone
- JP: Povidone
- PhEur: Povidonum
- USP: Povidone

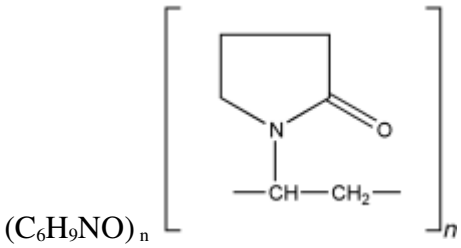
Synonyms

poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula



Functional Category

Disintegrant, dissolution aid, suspending agent and tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, Povidone is used as binders in wet-granulation processes and as coating agents.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder and freely soluble in acids, chloroform, methanol, and water practically insoluble in ether, hydrocarbons and mineral oil.

Stability and Storage Conditions

The powder is hygroscopic; it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

Safety

Povidone may be regarded as nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.

CROSPOVIDONE

Nonproprietary Names

- BP: Crospovidone
- PhEur: Crospovidone
- USP-NF: Crospovidone

Synonyms

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Functional Category

Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation method Crospovidone can also be used as a solubility enhancer dissolution rate.

Description

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

Stability and Storage Condition

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

Incompatibilities

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

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

MAIZE STARCH

Nonproprietary Names

- BP: Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch
- JP: Corn Starch, Potato Starch, Rice Starch, Wheat Starch
- PhEur: Maize Starch, Pea Starch, Potato Starch, Rice Starch, Wheat Starch
- USP-NF: Corn Starch, Potato Starch, Tapioca Starch, Wheat Starch

Synonyms

Amido; amidon; amilo; amylum; C*PharmGel; Eurylon; fecule; Hylon; maydis amylum; Melojel; Meritena; oryzae amylum; Pearl; Perfectamyl; pisi amylum; Pure-Dent; Purity 21; Purity 826; solani amylum; tritici amylum; Uni-Pure.

Chemical Name

Starch

Empirical Formula

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

Applications in Pharmaceutical Formulation or Technology

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

Description

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Stability and Storage Conditions

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under normal storage conditions. Starch solutions or pastes are physically unstable and are readily metabolized by microorganisms; they should therefore be freshly prepared when used for wet granulation. Starch should be stored in an airtight container in a cool, dry place.

Incompatibilities

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

Safety

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic and non irritant material.

PREGELATINIZED STARCH

Nonproprietary Names

- BP: Pregelatinised Starch
- PhEur: Starch, Pregelatinised
- USP-NF: Pregelatinized Starch

Synonyms

Amylum pregelificatum; compressible starch; C*PharmGel; Instastarch; Lycatab C; Lycatab PGS; Merigel; National 78-1551; Pharma-Gel; Prejel; Sepistab ST200; Spress B820; Starch 1500 G; Tablitz; Unipure LD; Unipure WG220.

Chemical Name

Pregelatinized starch

Empirical Formula

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation or Technology

Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and Disintegrant.

Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

COLLOIDAL ANHYDROUS SILICA

Nonproprietary Names

- BP: Colloidal Anhydrous Silica
- JP: Light Anhydrous Silicic Acid
- PhEur: Silica, Colloidal Anhydrous
- USP-NF: Colloidal Silicon Dioxide

Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

Chemical Name

Silica

Empirical Name

CiO_2

Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant, thermal stabilizer; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.

Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Stability and Storage Conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a p^H 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a p^H greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a p^H greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.

Incompatibilities

Incompatible with diethylstilbestrol preparations.

Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

MAGNESIUM STEARATE

Nonproprietary Names

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt

Empirical Formula

$C_{36}H_{70}MgO_4$

Functional Category

Tablet lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used as a lubricant.

Description

It is a very fine, light white, precipitated powder of low bulk density, having a faint odor of stearic acid with a characteristic taste and greasy to the touch and readily adheres to the skin. Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene.

Stability and Storage Conditions

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

Incompatibilities

Incompatible with strong acids, alkalis, iron salts and strong oxidizing materials.

Safety

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

CROSCARMELLOSE SODIUM

Nonproprietary Names

- BP: Croscarmellose Sodium
- JP: Croscarmellose Sodium
- PhEur: Croscarmellose Sodium
- USP-NF: Croscarmellose Sodium

Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name

Cellulose, carboxymethyl ether, sodium salt, crosslinked

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.

Description

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

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

HYPROMELLOSE

Nonproprietary Names

- BP: Hypromellose
- JP: Hypromellose
- PhEur: Hypromellose
- USP: Hypromellose

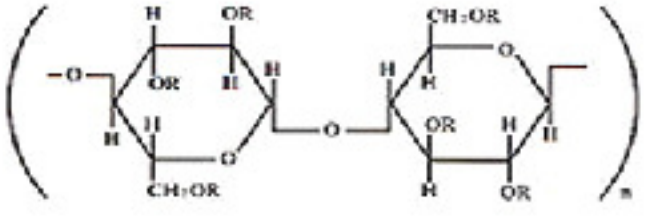
Synonyms

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

Chemical Name

Cellulose hydroxypropyl methyl ether

Empirical Formula



Partly O-methylated and O-(2-hydroxypropylated) cellulose.

Functional Category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent;

suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

Description

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

Stability and Storage Conditions

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

Incompatibilities

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

Safety

Hypromellose is widely used as an excipient in oral, opthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

EUDRAGIT® L 30 D-55

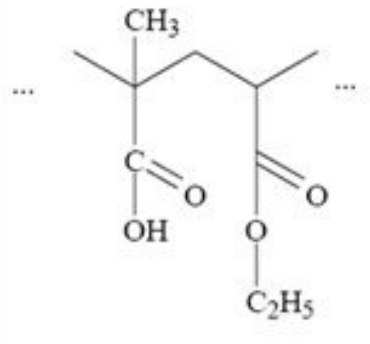
Nonproprietary Names

- Ph. Eur.: Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30%
- USP/NF: Methacrylic Acid Copolymer Dispersion - NF
- JPE: Methacrylic Acid Copolymer LD

Chemical name:

Poly(methacrylic acid-co-ethyl acrylate) 1:1

Empirical Formula



Acrylates Copolymer

Functional catagory

EUDRAGIT® L 30 D-55 is the aqueous dispersion 30% of anionic polymers with methacrylic acid as a functional group.

Applications in Pharmaceutical Formulation or Technology

- ✓ Effective and stable enteric coatings with a fast dissolution in the upper Bowel
- ✓ Granulation of drug substances in powder form for controlled release
- ✓ Site specific drug delivery in intestine by combination with EUDRAGIT® S grades
- ✓ Variable release profiles

Description

It is a milky-white liquid of low viscosity with a faint characteristic odour.

POLYETHYLENE GLYCOL

Synonyms

Breox PEG; Carbowax; Hodag PEG; Lutro E; PEG; polyoxyethylene glycol.

Chemical name

¬ -Hydro-α-hydroxy-poly(oxy-1,2-ethane-1-yl)

Empirical formula

$HOCH_2(CH_2OCH_2)_mCH_2OH$

Where m represents the average number of oxyethylene groups

Molecular weight

380 - 420

Functional category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in pharmaceutical formulation or technology

- Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations.

- Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases.

- Mixtures of polyethylene glycols can be used as suppository bases. Disadvantages of using polyethylene glycols are : they are chemically more reactive than fats.

- Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other

suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

- Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

- When used for thermoplastic granulations, a mixture of the powdered constituents with 10-15 % w/w PEG 6000 is heated to 70-75ºC. the mass becomes paste-like and forms granules if stirred while cooling.

- In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film forming polymers.

- Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets.

Description

The USPNF XVII describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids whilst grades 1000 and above are solids at ambient temperatures.

Moisture content

Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g PEG 4000 and above, are non hygroscopic.

Refractive index

n_D^{25} = 1.459 for PEG 200

n_D^{25} = 1.463 for PEG 300

n_D^{25} = 1.465 for PEG 400

n_D^{25} = 1.467 for PEG 600

Solubility

- All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary).

- Aqueous solutions of higher molecular weight grades may form gels; Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin and glycols.

- Solid polyethylene glycols are soluble in acetone, soluble in aliphatic hydrocarbons and there, but insoluble in fats, fixed oils and mineral oil.

MATERIAL AND METHODS

MATERIALS USED*:*

List of materials used for formulation of Mycophenolate sodium 360mg Delayed – Release Tablets

S.NO	INGREDIENTS	FUNCTION	SUPPLIER
1.	Mycophenolate sodium BP	Active ingredients	Biocon Ltd.
2.	Lactose monohydrate BP	Diluent	Signet
3.	Crospovidone (XL 10) BP	Disintegrant	FMC Bio Polymer
4.	Povidone K 30 BP	Binder	BASF
5.	Pregelatinised starch BP	Diluent / Disintegrant	RanQ Remidies
6.	Maize Starch BP	Diluent / Disintegrant	Maize Products
7.	Croscarmellose sodium BP	Disintegrant	FMC Bio Polymer
8.	Colloidal anhydrous silica BP	Glidant	Signet
9.	Magnesium stearate BP	Tablet Lubricant	Nitika
10.	Hypromellose (HPMC)	Film forming agent	Colorcon
11.	Polyethylene Glycol	Plastisizer.	Vasudha
12.	Isopropyl alcohol BP	Non aqueous solvent	Magnus Pharmaceutical
13.	Dichloromethane BP	Non aqueous solvent	
14.	Eudragit L30 D – 55 MS	Enteric Film forming agent	Evonik Products
15.	Purified Talc BP	Smoothening agent.	Signet
16.	Titanium dioxide BP	Opacifier	Kronos
17.	Ferric oxide yellow USP	Colorant	Kronos
18.	Ferric oxide red USP	Colorant	Kronos
19.	Sodium hydroxide BP	Alkaniser	RanQ Remidies
20.	Purified water	Aqueous solvent	In House

EQUIPMENTS USED:

List equipments used for formulation of mycophenolate sodium 360mg Delayed – Release tablets.

S.NO	EQUIPMENTS	MANUFACTURER
1.	Electronic Weighing Scale - 220 g	Shimadzu, Japan
2.	Electronic Weighing Scale –5kg & 30kg	Essae
3.	Disintegration tester	Electrolab
4.	Tapped volumeter	Erweka, Germany
5.	Electromagnetic Sieve shaker	Electrolab
6.	IR-Moisture Analyzer	Essae Taroka
7.	Bin Blender 30/10/5/2 Liters	Sams Techno Mech
8.	Rapid Mixer Granulator	Sams Techno Mech
9.	Fluid Bed Drier	Pam Glatt
10.	Multimill	Sams Techno Mech
11.	Vibro sifter (30' , 750 mm)	Sams Techno Mech
12.	Hardeness Tester	Erweka, Germany
13.	Friabilator	Electrolab
14.	Digital Vernier Caliber	Mitutoyo
15.	Mechanical Stirrer	Remi, Mumbai
16.	P^H Meter	Eutech
17.	De- Humidifier	Novita
18.	Compression Machine -10 station	Pacific Tools
19.	Coating machine – Conventional	Sams Techno Mech
20.	HPLC	Shimadzu Model No.SPD-10A
21.	UV visible spectrophotometer	Shimadzu, Japan
22.	Stability chamber- 40°C/75%RH	Thermolab, Maharashtra
23.	Stability chamber- 50°C/90%RH	Thermolab, Maharashtra

PREFORMULATION STUDY

Preformulation testing is the first step in the development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical

properties of a drug substance alone and when combined with excipients. The overall objective of Preformulation studies is to generate information useful to the formulator in developing a stable dosage forms.

API Characterization

Pre-formulation may be described as a phase of the research and development process, where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Pre-formulation studies were performed on the drug which includes solubility, Bulk density, Tapped density, Compatibility.

Physical Appearance

The API was observed for its color and physical state

Solubility

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a liquid solvent to form a homogeneous solution of the solute of the solute in the solvent. The solubility of a substance fundamentally depends on the used solvent as well as on temperature and pressure. The specified quantity of sample (1gm) was added into different quantity of solvent (methanol, alchol, chloroform, water, acetone, ethyl acetate) in room temperature.

Loss of drying:

Loss on drying was done using IR Moisture analyzer to check the moisture content in the test sample. The sample of about 1-2gm taken for analysis.

Bulk Density

The density of a powder is determined using volume meter. A known weight of sample is placed into a measuring cylinder and measured untapped Volume and its weight.

Pour (or Bulk) density=mass/untapped Volume.

Tapped density

Known weight of sample is placed into a measuring cylinder and 'tapped' (mechanically raised and lowered a set distance) until a consistent volume is reached which corresponds to the maximum packing density of the material.

Tapped density= mass/tapped volume

Hausner ratio and Carr's index

- ✓ The Hausner ratio and Carr's index are both measures of the flow properties of powders.
- ✓ A Hausner ratio of <1.25 indicates a powder that is free flowing

Whereas >1.25 indicates poor flow ability.

- ✓ The smaller the Carr's index the better the flow properties.
- ✓ 5-15 indicates excellent 12-16 good, 18-21 fair and >23 poor flow.

DRUG EXCIPIENTS COMPATIBILITY STUDIES

Drug–Excipient Compatibility Study

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added. The commonly used excipients are blended with the API in the varying ratios and subjected to accelerated condition (3 months in 40°C / 75 % RH), and at stress condition (1 month in 50°C / 90 % RH), the sample are monitored for any change in physical state, colour, odor, loss on drying and related substances. Any excipients contributing to such a change shall not be used in the formulation.

Selection of Excipients

The excipients are selected based on the excipients of reference product, apart from the reference product excipients other excipients are selected based on the proposed composition & possible use of them.

Sample preparation

Binary mixtures of the drug and excipients are prepared by placing the accurately weighed amounts of the drug and excipients in polybag and mixed till homogenous mixture is achieved. Then, these mixtures are filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals. These samples are charged at 50°C/90% RH and 40°C/75% RH conditions.

Storage conditions

Table No: Stability conditions and parameters for Drug–Excipients Compatibility Study

S.No	PARAMETERS	CONDITIONS				
		Initial	40°C/75% RH			50°C/90%RH
			1month	2month	3month	1month
1.	Physical appearance	✓	✓	✓	✓	✓
2.	Related Substances	✓	✓	✓	✓	✓
3.	Assay	✓	✓	✓	✓	✓

Sample analysis

All vials are inspected for the appearance, color and odour. The samples removed from 40°C/75% RH and 50°C/90% RH are analyzed as per the parameters mentioned in the above table.

FORMULATION DEVOLPMENT FOR CORE TABLET TRIALS

S.NO	NAME OF INGREDIENT	QTY/TABLET (mg)			
		F1	F2	F3	F4
Dry mix					
1.	Mycophenolate sodium BP*	384.70	384.70	384.70	384.70
2.	Lactose monohydrate BP**	134.80	130.65	120.60	122.20
3.	Croscarmellose Sodium BP	16.35	16.35	20.40	-----
4.	Crospovidone (XL10) BP	-----	-----	-----	16.80
Binder					
5.	Povidone K 30 BP	4.80	6.50	6.50	6.50
6.	Isopropyl alcohol BP	140.00	140.00	140.00	140.00
Lubrication					
7.	Maize starch BP	12.00	12.00	18.00	-----
8.	Pregelatinised starch BP	-----	-----	-----	20.00
9.	Colloidal anhydrous silica BP	3.15	4.20	4.20	4.20
10.	Magnesium stearate BP	4.20	5.60	5.60	5.60
Total Core Tablet weight		**560.00**			

*Actual quantity of Mycophenolate sodium BP to be dispensed in based on actual %purity.
** Quantity of excipients should adjust to the target filled weight.

FORMULATION DEVOLPMENT FOR SEAL COATING TRIALS

S.NO	NAME OF INGREDIENT	QTY/TABLET (mg)			
		S 1 **2.5%**	**S 2** **2.86%**	**S 3** **3.04%**	**S 4** **3.21%**
1	Hypromellose BP(5cps)	11.38	13.00	13.81	14.62
2	Polyethylene glycol BP	2.62	3.00	3.19	3.38
3	Isopropyl alcohol BP	140.00	160.00	170.00	180.00
4	Dichloromethane BP	140.00	160.00	170.00	180.00
Seal coating weight gain		**14.00**	**16.00**	**17.00**	**18.00**
Total seal coated tablet weight		**574.00**	**576.00**	**577.00**	**578.00**

FORMULATION DEVOLPMENT FOR ENTERIC COATING TRIALS

S.NO	NAME OF INGREDIENT	QTY/TABLET (Mg/tab)				
		E 1 8.68 %	E 2 9.55 %	E 3 10.42 %	E 4 11.28%	E 5 12.15 %
1.	Eudragit L30 D – 55 MS (100mg eq to 30mg solid)	116.62	128.38	140.00	151.62	163.38
2.	Polyethylene glycol BP	4.00	4.40	4.80	5.20	5.60
3.	Purified Talc BP	7.50	8.25	9.00	9.75	10.50
4.	Titanium dioxide BP	2.50	2.75	3.00	3.25	3.50
5.	Ferric oxide yellow USP	0.50	0.55	0.60	0.65	0.70
6.	Ferric oxide red USP	0.12	0.13	0.15	0.16	0.18
7.	Sodium hydroxide BP	0.38	0.41	0.45	0.49	0.52
8.	Water for NAOH BP (10 % w/w)	3.75	4.13	4.50	4.90	5.20
9.	Purified water BP for Color suspension	71.22	78.40	85.50	92.60	99.77
Enteric coating weight gain		**50.00**	**55.00**	**60.00**	**65.00**	**70.00**
Total coated tablet weight		**626.00**	**631.00**	**636.00**	**641.00**	**646.00**

FORMULATION DEVELOPMENT FOR COMPARABLE DISSOLUTION PROFILE TRIALS (CDP)

S.NO	NAME OF INGREDIENT	QTY/TABLET (mg)			
		D1	D2	D3	D4
Core Tablet Formula					
Dry mix					
1.	Mycophenolate sodium BP*	384.70	384.70	384.70	384.70
2.	Lactose monohydrate BP**	120.58	118.95	118.30	117.50
3.	Crospovidone (XL10) BP	16.80	16.80	16.80	16.80
Binder					
4.	Povidone K 30 BP	8.12	9.75	10.40	11.20
5.	Isopropyl alcohol BP	140.00	140.00	140.00	140.00
Lubrication					
6.	Pregelatinised starch BP	20.00	20.00	20.00	20.00
7.	Colloidal anhydrous silica BP	4.20	4.20	4.20	4.20
8.	Magnesium stearate BP	5.60	5.60	5.60	5.60
Total Core Tablet weight		**560.00**			
Seal Coating Formula					
9.	Hypromellose BP(5cps)	13.00	13.00	13.00	13.00
10.	Polyethylene glycol BP	3.00	3.00	3.00	3.00
11.	Isopropyl alcohol BP	160.00	160.00	160.00	160.00

12.	Dichloromethane BP	160.00	160.00	160.00	160.00
Seal coating weight gain		**16.00**			
Total seal coated Tablet weight		**576.00**			

*Actual quantity of Mycophenolate sodium BP to be dispensed in based on actual %purity.

** Quantity of excipients should adjust to the target filled weight.

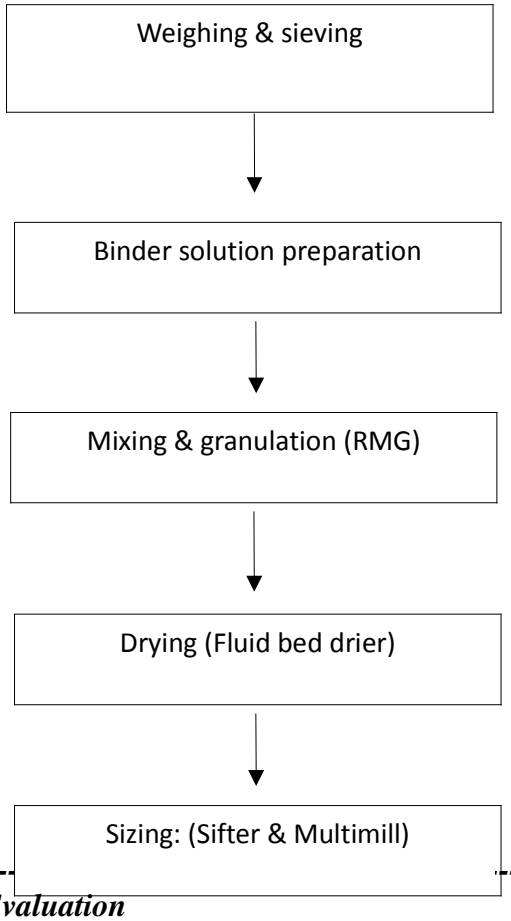
S.NO	NAME OF INGREDIENT	QTY/TABLET (mg)			
		D1	D2	D3	D4
Enteric Coating Formula					
1.	Eudragit L30 D – 55 MS (100mg eq to 30mg solid)	140.00	140.00	140.00	140.00
2.	Polyethylene glycol BP	4.80	4.80	4.80	4.80
3.	Purified Talc BP	9.00	9.00	9.00	9.00
4.	Titanium dioxide BP	3.00	3.00	3.00	3.00
5.	Ferric oxide yellow USP	0.60	0.60	0.60	0.60
6.	Ferric oxide red USP	0.15	0.15	0.15	0.15
7.	Sodium hydroxide BP	0.45	0.45	0.45	0.45
8.	Water for NAOH BP (10 % w/w)	4.50	4.50	4.50	4.50
9.	Purified water BP for Color	85.50	85.50	85.50	85.50

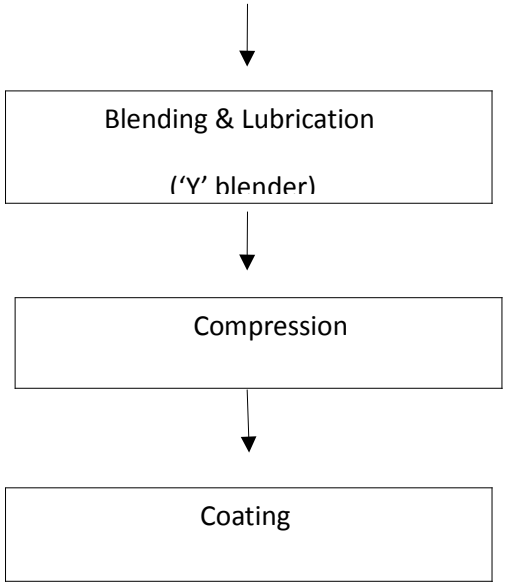
	suspension				
Enteric coating weight gain		**60.00**			
Total Enteric Coated Tablet weight		**636.00**			

INFORMATION ON DEVELOPMENT STUDIES:

Manufacturing procedure for Mycophenolate sodium tablets was optimized at various steps of formulation development. Studies were conducted using the most commonly used conventional wet granulation process. Results of wet granulation trials were encouraging. In-process parameters of compression, seal coating and enteric coating were satisfactory.

PROCESS FLOW DIAGRAM OF WET GRANULATION





MANUFACTURING PROCESS

1. POTENCY CALCULATION

*****Amount of the Mycophenolate sodium BP based on the 100% potency on anhydrous basis. Quantity of Mycophenolate sodium BP shall be calculated by using the formula given below.

$$\text{Quantity Mycophenolate sodium MS} = \frac{\text{Label claim (in mg)} \times 100 \times 100}{\text{Assay} \times (100 - \text{LOD})}$$

**Actual Quantity of Lactose monohydrate BP shall be calculated by using the formula given below.

Standard Quantity of (Mycophenolate sodium MS + Lactose monohydrate BP) - Actual Quantity of Mycophenolate sodium MS

Mycophenolate sodium 384.7mg = Mycophenolic acid 360mg

2. GENERAL INSTRUCTION

- ✓ Carry out all manufacturing activities at NMT 25°C & NMT 60% RH.
- ✓ Use talc free gloves and nose masks while all manufacturing activities.

3. DISPENSING

Carry out the dispensing of API and excipients of the batch in Dispensing Booth.

Packed in virgin polythene bag separately for each material.

4. DRY MIX SIFTING

i. Use Stainless Steel (S.S.) sieve of #30
ii. Collect sifted items in In-Process Containers (IPCs) lined with virgin polythene bag separately for each material.
iii. Check the cleanliness and the integrity of the sieves before and after use.
iv. Use talc free gloves and nose masks while sieving the materials.

Mycophenolate sodium BP

Sift using 30 # S.S. Sieve and collect in the S.S. bin.

Lactose monohydrate BP

Sift using 30 # S.S. Sieve and collect in the S.S. bin.

Maize starch BP

Sift using 30 # S.S. Sieve and collect in the S.S. bin.

Crospovidone (XL 10) BP

Sift using 30 # S.S. Sieve and collect in the S.S. bin.

4. DRY MIXING

Load the above sifted material in to Bin Blender and mix for 15 min at 25 RPM speed.

5. BINDER

Dispense and take Isopropyl alcohol BP. Dissolve Povidone BP (K 30) under mechanical stirring for 30 minutes.

6. WET GRANULATION

- ✓ Add 70 % of binder to dry mix present in RMG under slow speed for 2 minutes. Rake the mass in RMG, if necessary.
- ✓ Add remaining quantity of binder, continue mixing for 4 - 5 minutes with impeller at SLOW speed and chopper (if required) until desired wet mass obtained.
- ✓ If required add additional quantity of Isopropyl alcohol BP and mix for two more minutes.

7. DRYING OF GRANULES

Discharge the wet mass from RMG into Fluid Bed Drier Bowl by opening the discharge port and operating the impeller and chopper at SLOW speed. Operate the FBD as described in the Standard operating procedure.

CYCLE I: Distribute the material uniformly in the FBD bowl using S.S. paddle. Start the FBD and air-dry the wet mass without application of heat (steam valve to be kept closed) for 15 minutes.

CYCLE II: Rake the wet mass and continue drying the wet granules in FBD at an inlet temperature of 40 - 60°C (set at 55°C) for 30 minutes. Record the LOD result.

LOD Limit: Between 1.0 – 2.5 % W/W (target 1.5 % w/w)

LOD parameter :(105ºC)

If the LOD value obtained is within the specified range, take samples for LOSS ON DRYING (LOD) and test LOD at 105˚ C by IR moisture balance. Record the LOD result.

8. DRY SIFTING

Sift the dried granules through 20 # SS sieve using vibratory sifter. Collect the retention in a poly bag.

9. DRY MILLING

Pass the retention granules through multimill fitted with 1.5 mm screen Knives forward at slow speed. Collect the milled granules in the IPC bin and transfer to vibratory sifter. Repeat the dry shifting and do this process until the end of retention. Record the milling time and weighing detail of bin.

10. PRE LUBRICATION

i. Use Stainless Steel (S.S.) sieves of #30and #40
ii. Collect sifted items in In-Process Containers (IPCs) lined with virgin polythene bag separately for each material.
iii. Check the cleanliness and the integrity of the sieves before and after use.
iv. Use talc free gloves and nose masks while sieving the materials.
v. Transfer sifted Croscarmellose Sodium BP and Colloidal silicondioxide BP into the blender containing dried and milled granules.

Croscarmellose Sodium BP

Sift using 40 # S.S. Sieve and collect in the S.S. bin.

Colloidal silicondioxide BP

Sift using 30# S.S. Sieve and collect in the S.S. bin.

11. PRE LUBRICATION BLENDING

Load the above sifted material in to Bin Blender and mix for 15 min at slow speed.

12. LUBRICATION

i. Use Stainless Steel (S.S.) sieve of #60
ii. Collect sifted items in In-Process Containers (IPCs) lined with virgin polythene bag separately for each material.
iii. Check the cleanliness and the integrity of the sieves before and after use.
iv. Use talc free gloves and nose masks while sieving the materials.
v. Transfer sifted Magnesium Stearate BP into the Pre lubricated blend.

Magnesium stearate BP

Sift using 60 # S.S. Sieve and collect in the S.S. bin.

13. LUBRICATION BLENDING

Load the above sifted material in to Bin Blender and Blend for 3 min at slow speed.

Record the % yield of lubricated granules.

14. COMPRESSION (PUNCH&DIES):

i. Set the tablet compression machine by using respective punches and dies.
ii. Set the Compression machine for the following parameters
iii. Results for each parameter as per the Acceptance criteria shall be recorded for each batch at different hopper levels.
iv. Carry out all compression activities at NMT 25°C & NMT 60% RH.

15. PUNCH&DIES DETAILS

Upper Punch: 11.50 mm circular shape, concave plain on surface.

Lower Punch: 11.50 mm circular shape, concave plain on surface.

Dies : 11.50 mm.

In process Physical parameters Specifications (core):

Parameters	Specification
Appearance	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.
Target weight	560.0 mg
Average weight	560.0 mg ± 2.0 %
Uniformity of weight	Average weight ± 4.0%
Diameter	11.5 ± 0.2mm
Thickness	5.70 ± 0.2mm
Hardness	40 to 100 N
Disintegration Time	NMT 15 minutes
Friability	NMT 1% w/w

14. SEAL COATING SOLUTION PREPARATION

a) 10% overage is taken for compensating loss on coating.
b) Disperse Hypromellose BP (15 cps) in Isopropyl alcohol BP and stir for 15 minutes.
c) Dissolve Polyethylene glycol BP in Methylene dichloride BP.
d) Transfer the above two solution into the same beaker and stir for 15 minutes.
e) Prepared seal coating solution was filter with nylon cloth.
f) Store the filtered seal coating solution into well closed air tight container.

15. SEAL COATING OPERATION

i. Load uncoated tablets into coating pan and warm the bed temperature between 35-50°C.
ii. Load the coating suspension in coating suspension storage tank and start stirrer.
iii. Check the uniformity of mass of 20 coated tablets
iv. Operate the coating pan as described by the below Standard Operating Procedure

S.NO.	SEAL COATING PARAMETERS	LIMITS
1.	Pan speed	3 to 6 RPM
2.	Inlet air temperature	40 to 50°C

3.	Exhaust air temperature	35 to 50 ° C
4.	Automizing air pressure	2.0 to 4.0 kg/cm^2
5.	Spray gun nozzle diameter	1.5 mm
6.	Distance between spray gun & surface of the tablet bed	16 -20 inches

In process Physical parameters Specifications (Seal coating):

Parameters	Specification
Description of tablets	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.
Target weight	576.0 mg
Average weight	576.0 mg ± 2.0 %
Uniformity of weight.	Average weight ± 4.0%
Diameter	11.6 ± 0.2 mm
Thickness	5.8 ± 0.2mm
Disintegration Time	NMT 15 minutes

16. ENTERIC COATING SOLUTION PREPARATION

i. 10% overage is taken for compensating loss on coating.
ii. Disperse Eudragit L30 D – 55 IH in purified water BP.
iii. Dissolve sodium hydroxide BP in purified water. Slowly add this solution into above dispersed solution. After reaching 5.2 P^H sodium hydroxide solution should not be added.
iv. Add Talc BP, Titanium dioxide BP, Ferric oxide yellow USP, Ferric oxide red USP and Polyethylene glycol BP in purified water under colloidal mill. After 20 minutes transfer into above solution and stir for 10 minutes.
v. Prepared enteric coating solution was filter with nylon cloth.
vi. Store the filtered enteric coating solution into well closed air tight container.

17. ENTERIC COATING OPERATION

i. Load seal coated tablets into coating pan and warm the bed temperature between 35-50°C.

ii. Load the coating suspension in coating suspension storage tank and start stirrer.
iii. Check the uniformity of mass of 20 coated tablets.
iv. Operate the coating pan as described by the below Standard Operating Procedure.

S.NO.	ENTERIC COATING PARAMETERS	LIMITS
1.	Pan speed	3 to 6 RPM
2.	Inlet air temperature	40 to 50°C
3.	Exhaust air temperature	35 to 50 ° C
4.	Automizing air pressure	2.0 to 4.0 kg/cm^2
5.	Spray gun nozzle diameter	1.5 mm
6.	Distance between spray gun & surface of the tablet bed	16 -20 inches

In process Physical parameters Specifications (Enteric coating):

Parameters	Specification
Description of tablets	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
Target weight	636.00 mg
Average weight	636.00 mg ± 2.0 %
Uniformity of weight.	Average weight ± 4%
Diameter	11.8 ± 0.2mm
Thickness	6.0 ± 0.2mm
Disintegration Time	a) 0.1 M Hydrochloric acid - No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer - Disintegration NMT 45 minutes.

18. CONTAINER CLOSURE SYSTEM

The Tablets are packed in Alu-Alu blisters and PVDC blisters. These package materials are commonly used for oral solid forms and no special interaction studies were performed. The packaging materials are obtained from reliable, qualified suppliers. Results of stability studies confirm suitability of chosen primary packaging materials.

19. ALU/ALU BLISTER PACKING:

I. Set the sealing temperature of Alu-Alu Blister packing machine at 180 to 190ºC
II. Run the machine and pack the tablets. Take samples and send for leak test. Sampling quantity: 5 Blister.

S.NO	PARAMETERS	OBSERVATION
1	Thickness (mm)	6.2 mm
2	Diameter (mm)	11.9 mm

20. LEAK TEST PROCEDURE:

- ✓ Place the blisters to be leak tested into Desiccators containing a blue dye solution.
- ✓ Close the lid.
- ✓ Test pressure will be -60 Kpa for 60 seconds
- ✓ Observation should be At 180 to 190ºC - Not a single strip fail.

21. **DISSOLUTION APPARATUS PARAMETERS**

i. Method : USP dissolution apparatus-ll (paddle) method
ii. Temperature : 37°C ± 0.5˚C
iii. Dissolution medium : p^H 6.8 Phosphate buffer
iv. Volume : 1000ml
v. RPM : 50

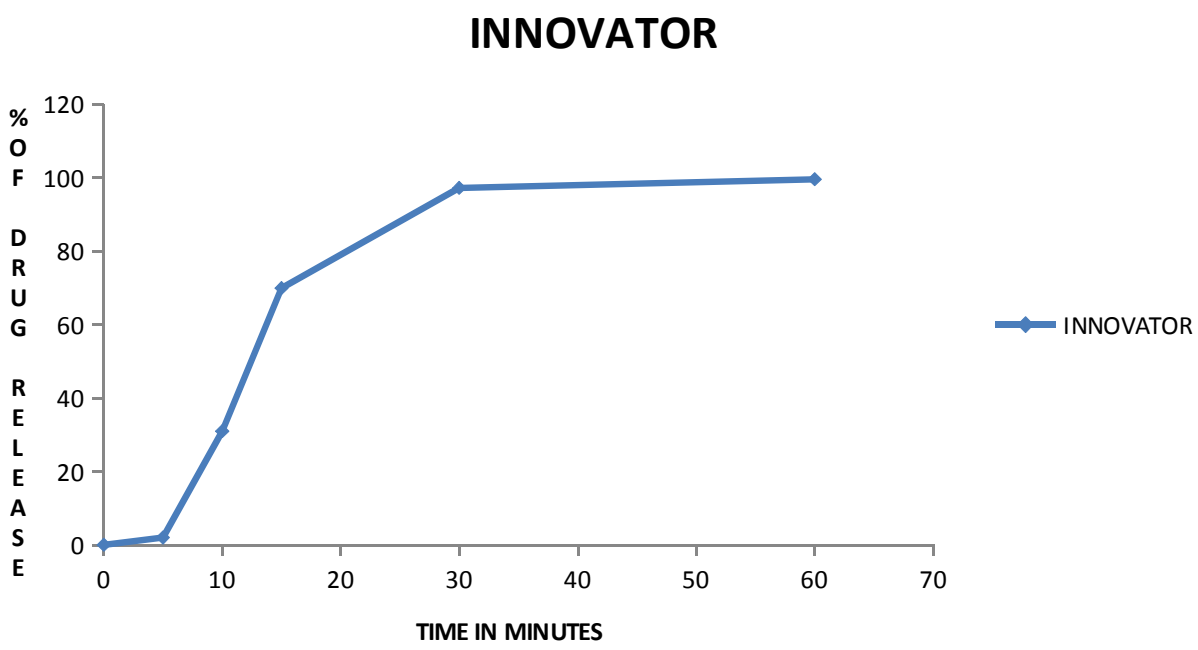
RESULT AND DISCUSSION

EVALUATION OF INNOVATOR PRODUCT

Product Name		**Myfortic®-360**		
Brand Name		**Novartis pharma stein AG**		
Lot No		**S0612**		
Exp. Date		**October 2014**		
Strength		360mg		
Description		Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.		
Storage Conditions		Store at a temperature below 30°C (86 F); Brief exposure to 40°C does not adversely affect the product. Protect from moisture.		
Physical Parameter				
Average weight of coated tablet(mg)		640.00	639.00	641.00
Core weight/Enteric weight (mg)		563/76	559/78	562/79
Thickness of coated tablet (mm)		6.05	5.99	6.12
Thickness of core tablet (mm)		5.68	5.66	5.71
Hardness (N)		56	63	71
Diameter mm		11.84	11.79	11.87
Disintegration Time	0.1 M Hydrochloric acid	No crack observed in 2 hours.		
	P^H 6.8 phosphate buffer	28 minutes 33 seconds to 34 minutes 56 seconds.		
Package Evaluation				
Pack Size		10 Tablets		
Packing Container		Alu-Alu blisters		
Printed Leaflet		Printed Leaflet attached on Carton Box		
Inactive Ingredients				
Lactose anhydrous, Maize starch, Povidone K 30, Croscarmellose Sodium, Colloidal silicon dioxide, Magnesium stearate, HPMC phthalate, Titanium dioxide, Ferric oxide red				

INNOVATOR DISSOLUTION PROFILE

S.NO	Time in Minutes	Innovator-Sample Myfortic® 360 Lot No:S0612
1.	0	0.00
2.	10	1.98
3.	20	30.94
4.	30	69.91
5.	45	97.23
6.	60	99.58



DRUG-EXCIPIENTS COMPATIBILITY STUDY

Sample & Ratio	Interval &Condition		Related substances					
			Imp A (%)	**Imp B (%)**	**Imp C (%)**	**Imp D (%)**	**Unknown Imp E (%)**	**Total Imp (%)**
Mycophenolate sodium 1:1	**INITIAL**		0.01	ND	ND	0.01	ND	**0.02**
	40°C/ 75%RH	**1M**	0.01	ND	ND	0.01	ND	**0.02**
		2M	0.01	ND	ND	0.01	ND	**0.02**
		3M	0.01	ND	0.01	0.01	ND	**0.03**
	1M 50°C/90%RH		0.01	ND	ND	0.01	ND	**0.02**
Mycophenolate Sodium+ Lactosemonohydrate 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/ 75%RH	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.01	0.01	0.01	0.01	ND	**0.04**
		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**
Mycophenolate Sodium + Crospovidone 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.0	0.0	0.0	0.01	ND	**0.04**

	75%RH		1	1	1			
		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**

Sample & Ratio	**Interval &Condition**		**Related substances**					
			Imp A (%)	**Imp B (%)**	**Imp C (%)**	**Imp D (%)**	**Unknown Imp E (%)**	**Total Imp (%)**
Mycophenolate Sodium + Povidone K30 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/ 75%RH	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.01	0.01	0.01	0.01	ND	**0.04**
		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**
Mycophenolate Sodium + PGS 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/ 75%RH	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.01	0.01	0.01	0.01	ND	**0.04**

		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**
Mycophenolate Sodium + Colloidal unhydrous silica 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/ 75%RH	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.01	0.01	0.01	0.01	ND	**0.04**
		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**

Sample & Ratio	**Interval &Condition**		**Related substances**					
			Imp A (%)	**Imp B (%)**	**Imp C (%)**	**Imp D (%)**	**Unknown Imp E (%)**	**Total Imp (%)**
Mycophenolate Sodium + Mg Stearate 1:1	**INITIAL**		0.01	0.01	0.01	0.01	ND	**0.04**
	40°C/ 75%RH	**1M**	0.01	0.01	0.01	0.01	ND	**0.04**
		2M	0.01	0.01	0.01	0.01	ND	**0.04**
		3M	0.01	0.01	0.01	0.01	0.01	**0.05**
	1M 50°C/90%RH		0.01	0.01	0.01	0.01	ND	**0.04**
Lactose mono	**INITIAL**		0.01	0.01	ND	ND	ND	**0.02**
	40	**1M**	0.01	0.01	ND	ND	ND	**0.02**

hydrate	**°C/ 75%RH**							
		2M	0.01	0.01	ND	ND	ND	**0.02**
		3M	0.01	0.02	ND	ND	ND	**0.03**
	1M 50°C/90%RH		0.01	0.01	ND	ND	ND	**0.02**
Crospovidone	**INITIAL**		0.01	ND	0.01	0.01	ND	**0.03**
	40°C/ 75%RH	**1M**	0.01	ND	0.01	0.01	ND	**0.03**
		2M	0.01	ND	0.01	0.01	ND	**0.03**
		3M	0.01	ND	0.01	0.02	ND	**0.04**
	1M 50°C/90%RH		0.01	ND	0.01	0.01	ND	**0.03**

Sample & Ratio	**Interval &Condition**		**Related substances**					
			Imp A (%)	**Imp B (%)**	**Imp C (%)**	**Imp D (%)**	**Unknown Imp E (%)**	**Total Imp (%)**
Povidone K30	**INITIAL**		0.01	0.01	ND	ND	ND	**0.02**
	40°C/ 75%RH	**1M**	0.01	0.01	ND	ND	ND	**0.02**
		2M	0.01	0.01	ND	ND	ND	**0.02**
		3M	0.01	0.02	ND	ND	ND	**0.03**
	1M 50°C/90%RH		0.01	0.01	ND	ND	ND	**0.02**
PGS	**INITIAL**		0.01	ND	0.01	0.01	ND	**0.03**

	40°C/ 75%RH	**1M**	0.01	ND	0.01	0.01	ND	**0.03**
		2M	0.01	ND	0.01	0.01	ND	**0.03**
		3M	0.01	ND	0.01	0.02	ND	**0.04**
	1M 50°C/90%RH		0.01	ND	0.01	0.01	ND	**0.03**
Colloidal unhydrous Silica	**INITIAL**		0.01	0.01	ND	ND	ND	**0.02**
	40°C/ 75%RH	**1M**	0.01	0.01	ND	ND	ND	**0.02**
		2M	0.01	0.01	ND	ND	ND	**0.02**
		3M	0.01	0.02	ND	ND	ND	**0.03**
	1M 50°C/90%RH		0.01	0.01	ND	ND	ND	**0.02**

Sample & Ratio	**Interval &Condition**		**Related substances**					
			Imp A (%)	**Imp B (%)**	**Imp C (%)**	**Imp D (%)**	**Unknown Imp E (%)**	**Total Imp (%)**
Magnesium Sterate	**INITIAL**		0.01	ND	0.01	0.01	ND	**0.03**
	40°C/ 75%RH	**1M**	0.01	ND	0.01	0.01	ND	**0.03**
		2M	0.01	ND	0.01	0.01	ND	**0.03**
		3M	0.01	ND	0.01	0.02	ND	**0.04**
	1M 50°C/90%RH		0.01	ND	0.01	0.01	ND	**0.03**
Mycophenolat	**INITIAL**		0.07	0.03	0.03	0.04	0.01	**0.18**

e Sodium+ All core formulation Excipents 1:1								
	40°C/ 75%RH	**1M**	0.07	0.03	0.03	0.04	0.01	**0.18**
		2M	0.07	0.03	0.03	0.04	0.01	**0.18**
		3M	0.07	0.03	0.03	0.04	0.02	**0.19**
	1M 50°C/90%RH		0.07	0.03	0.03	0.04	0.01	**0.18**
All core formulation Excipents 1:1	**INITIAL**		0.06	0.03	0.03	0.03	0.01	**0.16**
	40°C/ 75%RH	**1M**	0.06	0.03	0.03	0.03	0.01	**0.16**
		2M	0.06	0.03	0.03	0.03	0.01	**0.16**
		3M	0.06	0.03	0.03	0.04	0.01	**0.17**
	1M 50°C/90%RH		0.06	0.03	0.03	0.03	0.01	**0.16**
Mycophenolate sodium+All coating formulation Excipents (seal & enteric) 1:1	**INITIAL**		0.04	0.03	0.02	0.01	0.01	**0.11**
	40°C/ 75%RH	**1M**	0.04	0.03	0.02	0.01	0.01	**0.11**
		2M	0.04	0.03	0.02	0.01	0.01	**0.11**
		3M	0.04	0.03	0.02	0.01	0.02	**0.12**
	1M 50°C/90%RH		0.04	0.03	0.02	0.02	0.01	**0.12**

Standard Impurities and Limits

IMPURITIES	LIMITS
Impurity A	Not more than 0.15%
Impurity B	Not more than 0.15%

Impurity C	Not more than 0.15%
Impurity D	Not more than 0.15%
Impurity E	Not more than 0.10%
Total impurities	Not more than 0.5%

OBSERVATION AND CONCLUSION

All the excipients used in the Drug-Excipients compatibility study were found to be compatible and the Impurities were within the limits. Hence further formulation development studies are proceeded.

Characteristic of the formulation Trails F1, F2, F3 & F4

S.No	PARAMETERS	F1	F2	F3	F4
1.	Bulk density (g/ml)	0.47	0.46	0.47	0.48
2.	Tapped density (g/ml)	0.59	0.57	0.57	0.57
3.	Carr's index (%)	20.34	19.29	17.54	15.78
4.	Hausner's ratio	1.26	1.23	1.21	1.18
5.	Flow property	Poor	Fair	Fair	Good

PARTICLE SIZE DISTRIBUTION

S.NO	Sieve Analysis	Cumulative % of drug release			
		F1	F2	F3	F4
1.	# 40 mesh retention	30.00	28.00	27.00	27.00
2.	# 60 mesh retention	55.00	43.00	44.00	45.00
3.	# 80 mesh retention	68.00	56.00	58.00	58.00
4.	# 100 mesh retention	79.00	74.00	75.00	74.00
5.	# PAN	100.00	100.00	100.00	100.00

FORMULATION TRIAL -F1

OBSERVATION

The Carr's index and the Hausner's Ratio indicated that the blend has poor flow characters. To understand the powder behaviour the batch was taken further for compression.

It was observed that the blend had formed a cake in the feed frame and there were weight variations due to non uniformity of the powder flow.

CONCLUSION

It was planned to increase the binder concentration for better compressibility and increase the lubricant to improve flow property.

FORMULATION TRIAL -F2

Physical parameters observation for core tablet:

PARAMETERS	SPECIFICATION	OBSERVATION
Appearance	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.
Target weight	560.00 mg	560.00 mg
Average weight	560.00 mg ± 2.0 %	+1.32 % to -1.41%
Uniformity of weight	Average weight ± 4.0%	+3.21 % to -2.96%
Diameter	11.5 ± 0.2mm	11.51 to 11.52 mm
Thickness	5.70 ± 0.2mm	5.69 to 5.72 mm
Hardness	40 to 100 N	44.2 to 68.9 N
Disintegration Time	NMT 15 minutes	20 minutes 04 seconds
Friability	NMT 1% w/w	0.14%

OBSERVATION

The Carr's index and the Hausner's Ratio indicated that the blend has fair flow characters. To understand the powder behavior the batch was taken further for compression.

It was observed Disintegration time more than 20 minutes.

CONCLUSION

It was planned to increase the disintegrating agent concentration for improve disintegration.

FORMULATION TRIAL- F3

Physical parameters observation for core tablet:

PARAMETERS	SPECIFICATION	OBSERVATION
Appearance	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.
Target weight	560.0 mg	560.0 mg
Average weight	560.0 mg ± 2.0 %	+1.21 % to -1.82%
Uniformity of weight	Average weight ± 4.0%	+2.9 % to -3.15%
Diameter	11.5 ± 0.2mm	11.52 to 11.55 mm
Thickness	5.70 ± 0.2mm	5.68 to 5.73mm
Hardness	40 to 100 N	45.3 to 64.5 N
Disintegration Time	NMT 15 minutes	18 minutes 45 seconds
Friability	NMT 1% w/w	0.12%

OBSERVATION

The Carr's index and the Hausner's Ratio indicated that the blend has fair flow characters. To understand the powder behavior the batch was taken further for compression.

It was observed Disintegration time more than 18 minutes. Compare with previous trial same problem identified.

CONCLUSION

It was planned to replace following disintegrating agents Croscarmellose sodium instead of crospovidone and maize starch instead of pregelatinised starch.

FORMULATION TRIAL -F4

Physical parameters observation for core tablet:

PARAMETERS	SPECIFICATION	OBSERVATION
Appearance	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.	White to Off white color, circular shape, biconvex uncoated tablets plain on both side.
Target weight	560.0 mg	560.0 mg
Average weight	560.0 mg ± 2.0 %	+1.25 % to -1.95%
Uniformity of weight	Average weight ± 4.0%	+2.91 % to -3.15%
Diameter	11.5 ± 0.2mm	11.52 to 11.55 mm
Thickness	5.70 ± 0.2mm	5.68 to 5.76 mm
Hardness	40 to 100 N	46.2 to 64.5 N
Disintegration Time	NMT 15 minutes	6 minutes 20 seconds
Friability	NMT 1% w/w	0.18%

OBSERVATION

The Carr's index and the Hausner's Ratio indicated that the blend has good flow characters.

Physical parameters of core tablets passed in all specification limits.

CONCLUSION

Next trial planned to increase the batch size of **TRIAL-F4** formula and optimize the seal coating formula by various weight buildups.

FORMULATION TRIAL- S1

Physical parameters observation for seal coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.
2.	**Target weight**	574.00 mg	574.0 mg
3.	**Average weight**	574.00 mg ± 2.0 %	+1.45 % to -2.02%
4.	**Uniformity of weight.**	Average weight ± 4.0%	+3.11 % to -3.21%
5.	**Diameter**	11.55 ± 0.2 mm	11.48 to 11.58 mm
6.	**Thickness**	5.82 ± 0.2mm	5.81 to 5.84 mm
7.	**Disintegration Time**	NMT 15 minutes	6 minutes 30 seconds.

OBSERVATION

Physical parameters of seal coated tablets passed in all specification limits. But 2.5% weight buildup of seal coating formed an irregular thin layer in core tablet. It was not sufficient to protect the core tablet from moisture absorption during enteric coating process.

FORMULATION TRIAL -S2

Physical parameters observation for seal coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.
2.	**Target weight**	576.00 mg	576.0 mg
3.	**Average weight**	576.00 mg ± 2.0 %	+1.44 % to -1.98%
4.	**Uniformity of weight.**	Average weight ± 4.0%	+3.10 % to -3.24%
5.	**Diameter**	11.6 ± 0.2 mm	11.59 to 11.64 mm
6.	**Thickness**	5.8 ± 0.2mm	5.78 to 5.81 mm
7.	**Disintegration Time**	NMT 15 minutes	7 min 52 sec

OBSERVATION

Physical parameters of seal coated tablets passed in all specification limits. In this Seal coated tablets at the 2.86% weight buildup has laminated the core tablet properly.

FORMULATION TRIAL -S3

Physical parameters observation for seal coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.
2.	**Target weight**	577.00 mg	576.8 mg
3.	**Average weight**	577.00 mg ± 2.0 %	+1.44 % to -1.99%
4.	**Uniformity of weight.**	Average weight ± 4.0%	+3.12 % to -3.23%
5.	**Diameter**	11.6 2± 0.2 mm	11.6 to 11.66 mm
6.	**Thickness**	5.82 ± 0.2mm	5.78 to 5.86 mm
7.	**Disintegration Time**	NMT 15 minutes	15 min 52 sec

OBSERVATION

In this Seal coated tablets at the 3.04% weight buildup has laminated the core tablet properly. But disintegration time was more than 15 minutes.

FORMULATION TRIAL-S4

Physical parameters observation for seal coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.	White to off white color, circular shape, and biconvex seal coated tablets plain on both sides.
2.	**Target weight**	578.00 mg	578.2 mg
3.	**Average weight**	578.00 mg ± 2.0 %	+1.42 % to -1.62%
4.	**Uniformity of weight.**	Average weight ± 4.0%	+3.08 % to -3.18%
5.	**Diameter**	11.6 5± 0.2 mm	11.64 to 11.70 mm
6.	**Thickness**	5.83 ± 0.2mm	5.79 to 5.84 mm
7.	**Disintegration Time**	NMT 15 min	26 min 52 sec

OBSERVATION

In this Seal coated tablets at the 3.21% weight buildup has laminated the core tablet properly. But disintegration time was more than 26 minutes.

CONCLUSION

Seal coating of the **TRIAL-S2** sample tablets compiled with the all specification limits. Next trial planned to increase the batch size of **TRIAL-S2** and optimize the enteric coating formula by various weight buildups.

FORMULATION TRIAL-E1

Physical parameters observation for enteric coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
2.	**Target weight**	626.00 mg	626.00 mg
3.	**Average weight**	626.00 mg ± 2.0 %	+1.83 % to -1.91%
4.	**Uniformity of weight.**	Average weight ± 4%	+3.24 % to -3.08%
5.	**Diameter**	11.7 ± 0.2mm	11.69 to 11.74 mm
6.	**Thickness**	5.9 ± 0.2mm	5.86 to 6.02 mm
7.	**Disintegration Time**	a) 0.1M HCL – No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer- Disintegration NMT 45 minutes.	a) 0.1M HCL– crack observed in 56 minutes 30 seconds . b) Not performed.

Observation

8.68% weight buildup enteric coated tablets failed in Disintegration test at 0.1 M Hydrochloric acid – crack observed in 56 minutes and 30 seconds.

FORMULATION TRIAL-E2

Physical parameters observation for enteric coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
2.	**Target weight**	631.00 mg	631.00 mg
3.	**Average weight**	631.00 mg ± 2.0 %	+1.7 % to -1.98%
4.	**Uniformity of weight.**	Average weight ± 4%	+3.41 % to -3.52%
5.	**Diameter**	11.75 ± 0.2mm	11.71 to 11.82 mm
6.	**Thickness**	5.95 ± 0.2mm	5.94 to 6.08 mm
7.	**Disintegration Time**	a) 0.1M HCL– No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer - Disintegration NMT 45	a) 0.1M HCL – crack observed in 1 hour 35minutes 45 seconds. b) Not performed

		minutes.	

OBSERVATION

9.55% weight buildup enteric coated tablets failed in Disintegration test at 0.1 M Hydrochloric acid – crack observed in 1 hour 35 minutes 45 seconds.

FORMULATION TRIAL-E3

Physical parameters observation for enteric coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
2.	**Target weight**	636.00 mg	636.00 mg
3.	**Average weight**	636.00 mg ± 2.0 %	+1.81 % to -1.95%
4.	**Uniformity of weight.**	Average weight ± 4%	+3.31 % to -3.11%
5.	**Diameter**	11.8 ± 0.2mm	11.81 to 11.84 mm
6.	**Thickness**	6.0 ± 0.2mm	5.94 to 6.08 mm

7.	**Disintegration Time**	a) 0.1M HCL– No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer - Disintegration NMT 45 minutes.	a) 0.1M HCL– No crack observed in 2 hours. b) P^H6.8 phosphate buffer- 21 minutes 33 seconds to 24 minutes 56 seconds.

OBSERVATION

10.42% weight buildup enteric coated tablets compiled within the all specification limits.

FORMULATION TRIAL-E4

Physical parameters observation for enteric coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
2.	**Target weight**	641.00 mg	641.05 mg
3.	**Average weight**	641.00 mg ± 2.0 %	+1.78 % to -1.85%
4.	**Uniformity of weight.**	Average weight ± 4%	+3.23 % to -3.44%
5.	**Diameter**	11.85 ± 0.2mm	11.82 to 11.87 mm

6.	**Thickness**	6.05 ± 0.2mm	6.01 to 6.11 mm
7.	**Disintegration Time**	a) 0.1 M Hydrochloric acid – No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer - Disintegration NMT 45 minutes.	a) 0.1 M Hydrochloric acid – No crack observed in 2 hours. b) P^H 6.8 phosphate buffer - 53 minutes 30 seconds to 56 minutes 45 seconds.

OBSERVATION

11.28% weight buildup enteric coated tablets failed in disintegration test in P^H 6.8 phosphate buffer-observed more than 56 minutes 45 seconds.

FORMULATION TRIAL-E5

Physical parameters observation for enteric coated tablet:

S.NO	PARAMETERS	SPECIFICATION	OBSERVATION
1.	**Description of tablets**	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.	Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.
2.	**Target weight**	646.00 mg	646.00 mg
3.	**Average weight**	646.00 mg ± 2.0 %	+1.81 % to -1.95%
4.	**Uniformity of weight.**	Average weight ± 4%	+3.31 % to -3.11%
5.	**Diameter**	11.8 ± 0.2mm	11.81 to 11.84 mm
6.	**Thickness**	6.0 ± 0.2mm	5.94 to 6.08 mm

7.	**Disintegration Time**	a) 0.1 M Hydrochloric acid – No crack should be observed in 2 hours. b) P^H 6.8 phosphate buffer - Disintegration NMT 45 minutes.	a) 0.1 M Hydrochloric acid – No crack observed in 2 hours. b) P^H 6.8 phosphate buffer - 56 minutes 20 seconds to 1 hour 10 minutes 35 seconds.

OBSERVATION

12.15% weight buildup of enteric coated tablets failed in disintegration test in P^H 6.8 phosphate buffer-observed more than 1 hour 10 minutes 35 seconds.

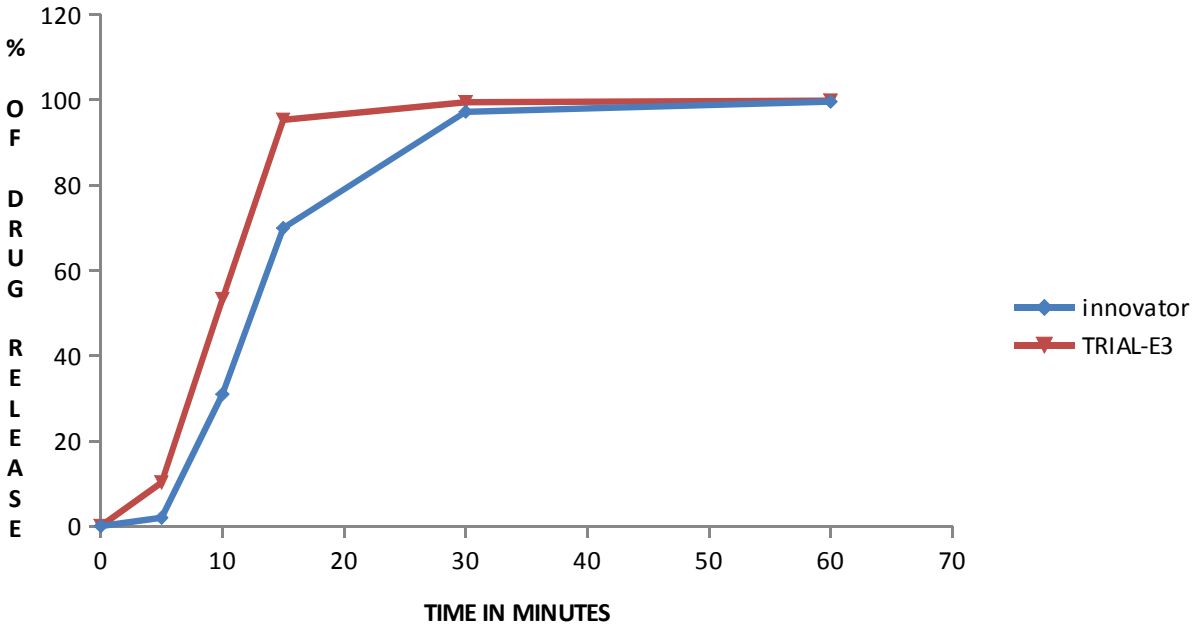
CONCLUTION

Enteric coating of the **TRIAL-E3** sample tablets compiled with the all specification limits. This trial sample tablets compare with innovator sample Dissolution profile (CDP).

DISSOLUTION PROFILE IN P^H 6.8 PHOSPHATE BUFFER

INNOVATOR $_{VS}$ TRIAL-E3

Time	**Innovator- Myfortic 360**	**TRIAL-E3**
0	0.00	0.00
10	1.98	10.20
20	30.94	53.27
30	69.91	95.33
45	97.23	99.47
60	99.58	99.83
Dissimilarity factor & Similarity factor		
F1	**Limit (0 to 15)**	**18.20**
F2	**Limit (50 to 100)**	**31.53**



CONCLUSION

Dissolution rate of **TRIAL-E3** was found to be more when compared with the Innovator product. Initial dissolution rate of the test product was found to be much faster than that of the innovator product. It was planned to increase the binder in various ratios was taken in **TRIAL-E3** formula to reduce dissolution rate to match with Innovator product dissolution profile.

PHYSICAL PARAMETERS FOR COMPARABLE DISSOLUTION PROFILE TRIALS (CDP)

PARAMETERS	OBSERVATION			
	D1	D2	D3	D4
Core Tablet				
Average weight	+1.19 % to -1.74%	+1.23 % to -1.89%	+1.21 % to -1.53%	+1.25 % to -1.95%

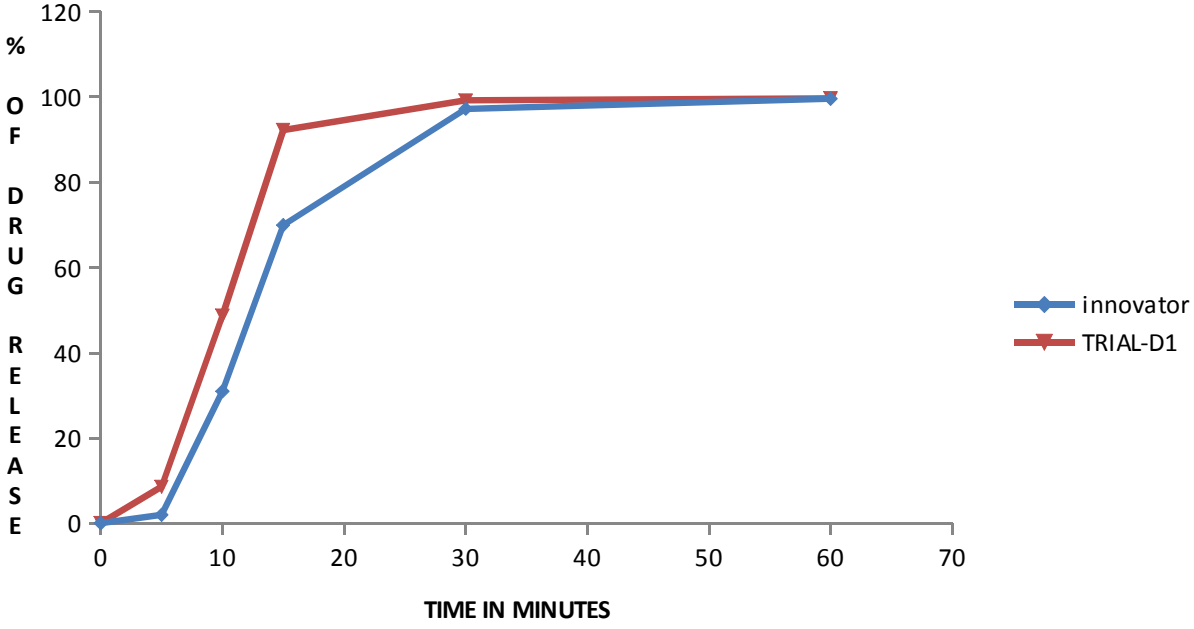
Uniformity of weight		+2.60 % to -3.11%	+2.75 % to -3.43%	+2.31 % to -3.03%	+2.91 % to -3.15%
Diameter		11.51 to 11.55 mm	11.51 to 11.53 mm	11.51 to 11.54 mm	11.52 to 11.55 mm
Thickness		5.68 to 5.76 mm	5.68 to 5.76 mm	5.69 to 5.72 mm	5.68 to 5.76 mm
Hardness		49..5 to 66.3 N	43.2 to 68.4 N	48.2 to 65.2 N	54.2 to 69.9 N
Disintegration Time		6 minutes 50 sec	7 min 30 second	08 min 55 sec	10 min 04 second
Friability		0.23%	0.18%	0.16%	0.12%
Seal coated Tablet					
Average weight		+1.37 % to -1.86%	+1.45 % to -1.86%	+1.51 % to -1.68%	+1.44 % to -1.98%
Uniformity of weight		+3.12 % to -3.14%	+3.26 % to -3.21%	+3.23 % to -3.14%	+3.10 % to -3.24%
Diameter		11.59 to 11.62 mm	11.59 to 11.61 mm	11.58 to 11.63 mm	11.59 to 11.64 mm
Thickness		5.75 to 5.81 mm	5.78 to 5.82 mm	5.79 to 5.80 mm	5.78 to 5.81 mm
Disintegration Time		8 min 30 sec	9 min 40 sec	10 min 55 sec	11 min 52 second
Enteric coated Tablet					
Average weight		+1.66 % to -1.85%	+1.68 % to -1.57%	+1.73 % to -1.86%	+1.81 % to -1.95%
Uniformity of weight		+3.27 % to -3.32%	+3.36 % to -3.43%	+3.29 % to -3.21%	+3.31 % to -3.11%
Diameter		11.79 to 11.85 mm	11.77 to 11.83 mm	11.78 to 11.81 mm	11.79 to 11.84 mm
Thickness		5.94 to 6.05 mm	5.96 to 6.04 mm	5.98 to 6.03 mm	5.94 to 6.08 mm
Disintegration Time	**0.1M HCL**	Passed	Passed	Passed	Passed
	P^H 6.8 PHO_4 Buffer	26 min 20 sec	28 min 40 sec	31 min 15 sec	34 min 54 second

DISSOLUTION PROFILE IN P^H 6.8 PHOSPHATE BUFFER

INNOVATOR $_{VS}$ TRIAL-D1

Time	Innovator- Myfortic 360	TRIAL-D1
0	0.00	0.00
10	1.98	8.56
20	30.94	48.67

30	69.91	92.21
45	97.23	99.17
60	99.58	99.65
Dissimilarity factor & Similarity factor		
F1	**Limit (0 to 15)**	**16.21**
F2	**Limit (50 to 100)**	**36.20**

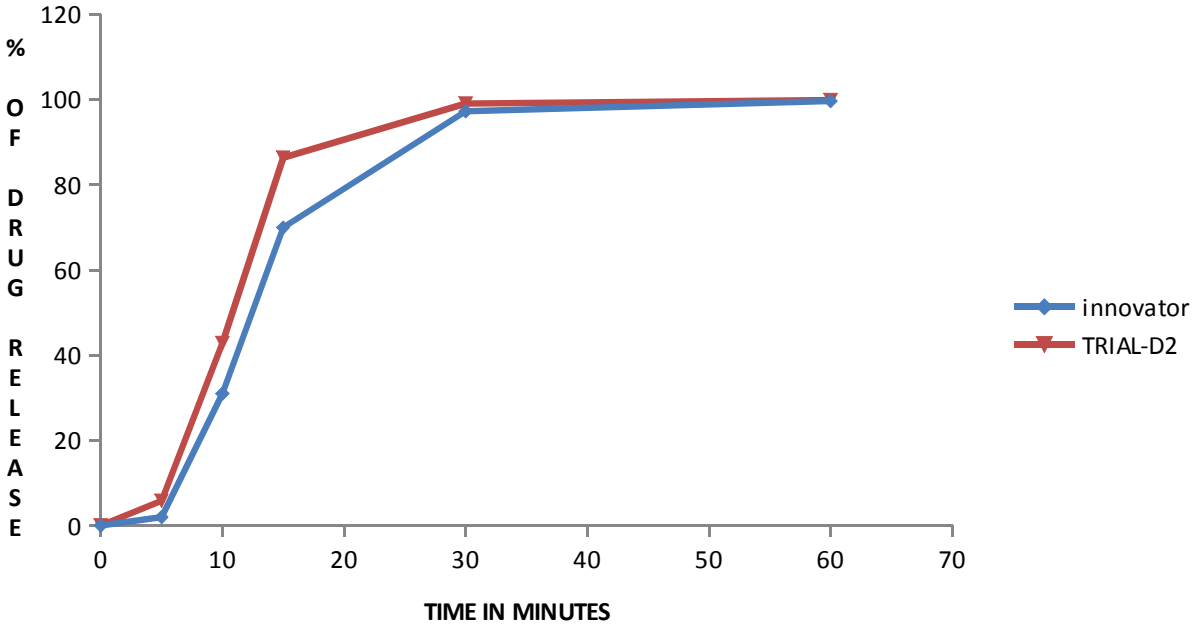


DISSOLUTION PROFILE IN P^H 6.8 PHOSPHATE BUFFER

INNOVATOR VS TRIAL-D2

Time	Innovator- Myfortic 360	TRIAL-D2

0	0.00	0.00
10	1.98	5.83
20	30.94	42.82
30	69.91	86.33
45	97.23	99.02
60	99.58	99.81
Dissimilarity factor & Similarity factor		
F1	**Limit (0 to 15)**	**15.81**
F2	**Limit (50 to 100)**	**43.60**

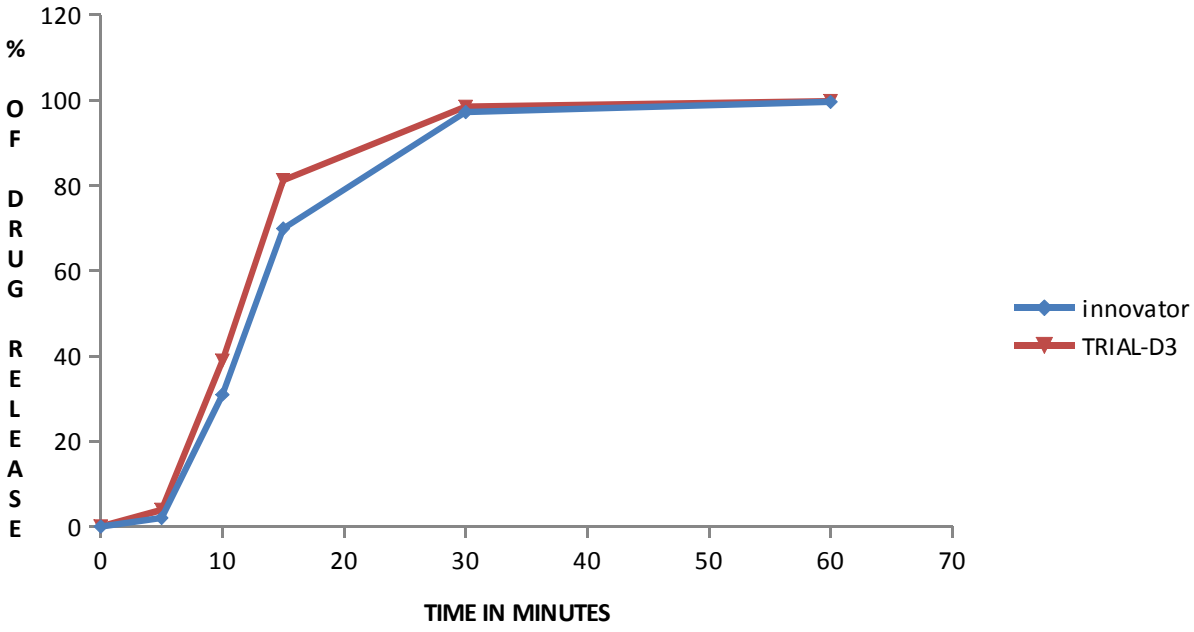


DISSOLUTION PROFILE IN P^H 6.8 PHOSPHATE BUFFER

INNOVATOR $_{VS}$ TRIAL-D3

Time	Innovator- Myfortic 360	TRIAL-D3
0	0.00	0.00

10	1.98	3.91
20	30.94	38.87
30	69.91	81.21
45	97.23	98.46
60	99.58	99.78
Dissimilarity factor & Similarity factor		
F1	**Limit (0 to 15)**	**9.59**
F2	**Limit (50 to 100)**	**46.50**

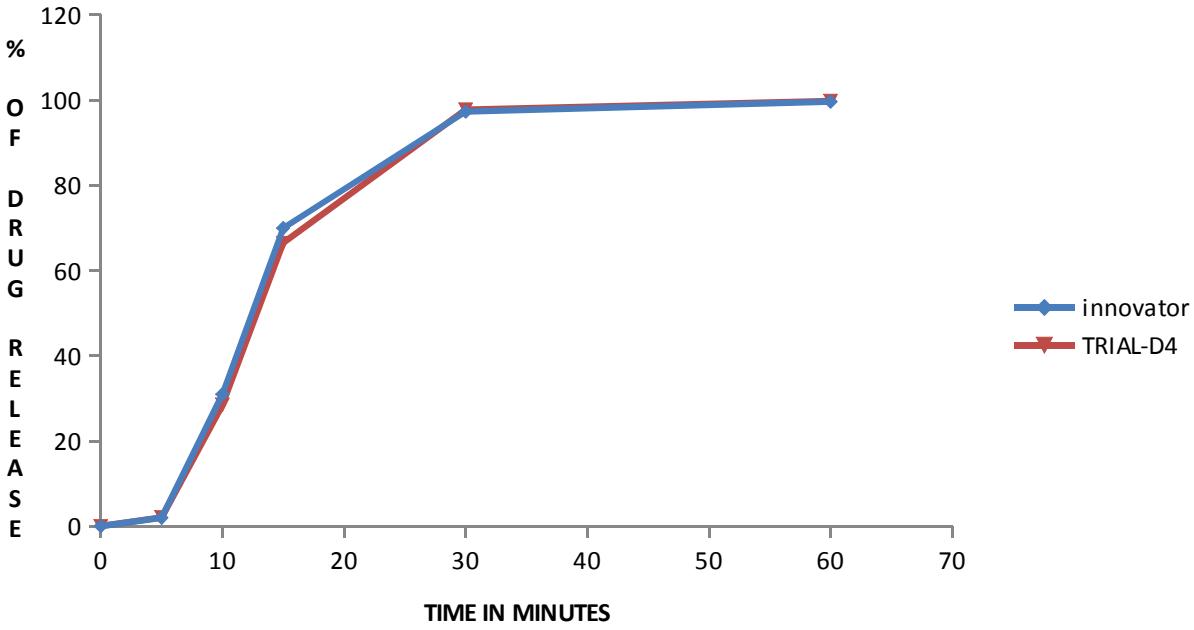


DISSOLUTION PROFILE IN P^H 6.8 PHOSPHATE BUFFER

INNOVATOR $_{VS}$ TRIAL-D4

Time	Innovator- Myfortic 360	TRIAL-D4

0	0.00	0.00
10	1.98	2.03
20	30.94	28.45
30	69.91	66.42
45	97.23	97.68
60	99.58	99.76
Dissimilarity factor & Similarity factor		
F1	**Limit (0 to 15)**	**7.16**
F2	**Limit (50 to 100)**	**62.92**



CONCLUSION

TRIAL-D4 drug release profile was found to be satisfactory and comparable with that of Innovator product. This is also confirmed by dissimilarity factor and similarity factor. Hence it was decided to pack the tablets in the proposed packaging method (Alu-Alu Blister). This packed sample tablets were loaded for stability assessment in 50°C/90%RH (stressed condition) for 1 month and at 40°C/75%RH (accelerated conditions) for 1 month.

STABILTY STUDIES

STABILTY STUDIES 50°C/90% & RH 40°C/75% RH					
TEST NAME		**LIMIT**	**INITIAL**	**1 MONTH**	
Description of tablets		Peach color, circular shape, and biconvex enteric coated tablets plain on both sides.		**50°C/ 90%RH**	**40°C/75%RH**
Avg. wt (mg)		636.00 mg ± 2.0 %	+1.66 % to -1.85%	+1.75 % to -1.87%	+1.68 % to -1.84%
Hardness (N)		40 to 100 N	66.4 to 78.5N	65.5 to 77.8N	67.2 to 79.9N
Thickness (mm)		6.0 ± 0.2mm	5.94 to 6.05 mm	5.95 to 6.04 mm	5.96 to 6.05mm
Disintegration time	**0.1M HCL**	No crack should be observed in 2 hours	Passed	Passed	Passed
	P^H6.8 PHO_4 Buffer	NMT 45 minutes.	34 min 54 sec	33 min 40 sec	34 min 25 sec
Dissolution Profile in P^H6.8 PHO_4 Buffer		**Time Interval**	**%Drug Release**		
		10	2.03	2.01	1.98
		20	28.45	29.55	30.21
		30	66.42	67.33	67.51
		45	97.68	97.52	97.56
		60	99.76	99.68	99.73
Assay		95 – 105 %	99.65	99.57	99.62
Known impurity		NMT 0.2%	0.16	0.11	0.17
Unknown Impurity		NMT 0.15%	0.02	0.01	0.02
Total Impurity		NMT 1.0 %	0.18	0.12	0.19

CONCLUSION

The 1 month stability data at stressed condition showed no characteristic changes when compared to the initial results which indicate the product is stable. The 1 month stability at accelerated condition was also found to be within the specified limits. The stability study loaded at stressed condition for 1 month reveals that the product is stable.

SUMMARY AND CONCLUSION

SUMMARY

Among the various routes of drug delivery system, Oral route is the oldest and most common route of drug administration. In oral administration, tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing and higher stability compared with oral liquids.

Mycophenolate sodium delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid. Mycophenolic acid is an immunosuppressive agent. Mycophenolic acid is an uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation to DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes.

The project work entitled "**Formulation Development and Evaluation of Mycophenolate Sodium 360mg Delayed-Release Tablets**" was carried out in the study. The study was mainly focused on the optimization of the formulation to meet the reference product characteristics, based on the excipients of reference product, the excipients were selected for Drug Excipient compatibility study trials. The binary mixtures were filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals and charged at 50°C/90% RH and 40°C/75% RH conditions. All the excipients used in the Drug-Excipients compatibility study were found to be compatible with API.

The development was initially started with various formulation trials by wet granulation method were formulated and evaluated to make a comparable product with the reference product.

In formulation **TRIAL-F3** formulated by hand granulation, was found that the disintegration time more than 18 minutes. Hence a next formulation **TRIAL-F4** was planned to replace following disintegrating agents Croscarmellose sodium instead of crospovidone and maize starch instead of pregelatinised starch.

TRIAL-F4 blend has good flow characters and physical parameters of core tablets passed in all specification limits. Next trial planned to increase the batch size of **TRIAL-F4** formula and optimize the seal coating formula by various weight buildups.

In seal coating optimization sample was collected from the coating pan in various weight buildups. **TRIAL-S2 (**2.86% weight buildup) sample tablets compiled with the all physical parameter of seal coating specification limits. Next trial planned to increase the batch size of **TRIAL-S2** and optimize the enteric coating formula by various weight buildups.

In enteric coating optimization sample was collected from the coating pan in various weight buildups. **TRIAL-E3 (**10.42% weight buildup) sample tablets compiled with the all physical parameter of enteric coating specification limits. This trial sample tablets compare with innovator sample Dissolution profile.

Dissolution rate of **TRIAL-E3** was found to be more when compared with the Innovator product. Initial dissolution rate of the test product was found to be much faster than that of the innovator product. It was planned to increase the binder in various ratios was taken in **TRIAL-E3** formula to reduce dissolution rate to match with Innovator product dissolution profile.

In **TRIAL-D4** drug release profile was found to be satisfactory and comparable with that of Innovator product. This is also confirmed by dissimilarity factor and similarity factor. Hence it was decided to pack the tablets in the proposed packaging method (Alu-Alu Blister).

TRIAL-D4 Alu-Alu blister packed sample tablets were loaded for stability assessment in 50°C/90%RH (stressed condition) for 1 month and at 40°C/75%RH (accelerated conditions) for 1 month.

The 1 month stability data at stressed condition showed no characteristic changes when compared to the initial results which indicate the product is stable. The 1 month stability at accelerated condition was also found to be within the specified limits. The stability study loaded at stressed condition for 1 month reveals that the product is stable.

CONCLUSION

TRIAL-D4 formulated tablets formula finalized, after passing of bio-equivalence and stability. The formulated tablets have to be studied for physico-chemical characteristics and stability for 6 months. Also the formulated tablets are to be submitted for bio-equivalence study with reference listed drug.

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ABBREVIATIONS

R&D	:	Research and Development
RLD	:	Reference Listed Drug
Ph.Eur.	:	European Pharmacopoeia
BP	:	British Pharmacopoeia
USP	:	United State Pharmacopoeia
COA	:	Certificate Of Analysis
DMF	:	Drug Master File
IPC	:	In-Process Containers
CDP	:	Comparative Dissolution Profile
MS	:	Manufacturer specification
MPA	:	Mycophenolic Acid
MPS	:	Mycophenolate sodium
MPAG	:	Mycophenolic Acid Glucuronide
HPLC	:	High Pressure Liquid Chromatography
LOD		Loss On Drying
FBD	:	Fluidized Bed Drier
API	:	Active Pharmaceutical Ingredient
NLT	:	Not Less Than
NMT	:	Not More Than
IMPDH	:	Inosine Monophosphate DeHydrogenase
RMG	:	Rapid Mixer Granulator
RM	:	Raw Material
BCS	:	Biopharmaceutical Classification System