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Development and Optimization of Oral Disintegrating Tablets of Esomeprazole Enteric Coated Pellets by QbD Approach

Shubhangee Tomar[1], Komal Patel[2]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutics, Gujarat Technological University, Ahmedabad, Gujarat, India
[2]Department of Pharmaceutical Analysis, Faculty of Quality Assurance, Gujarat Technological University, Ahmedabad, Gujarat, India

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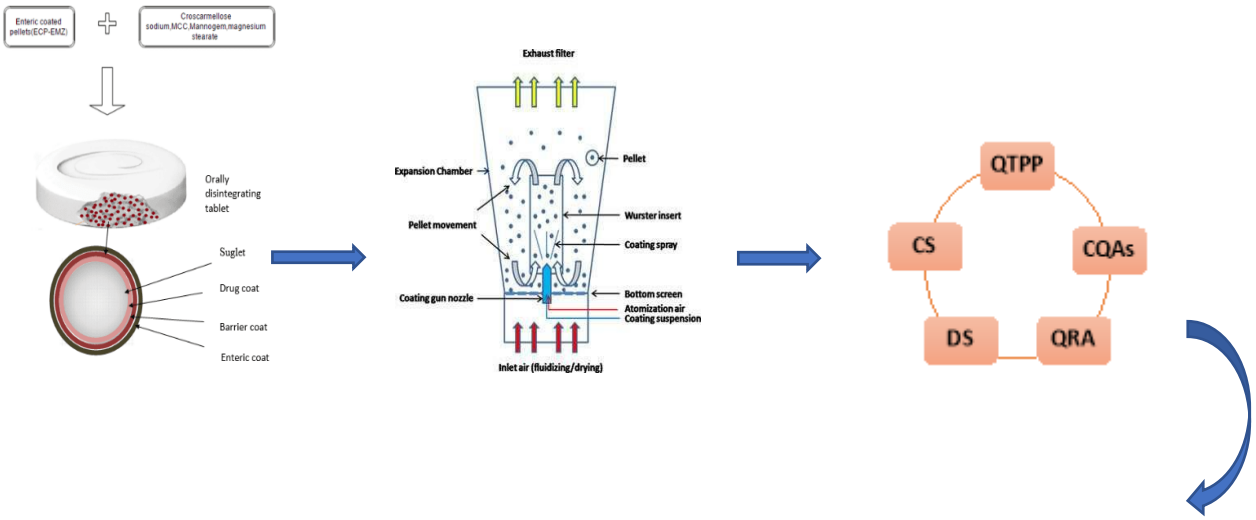
ABSTRACT

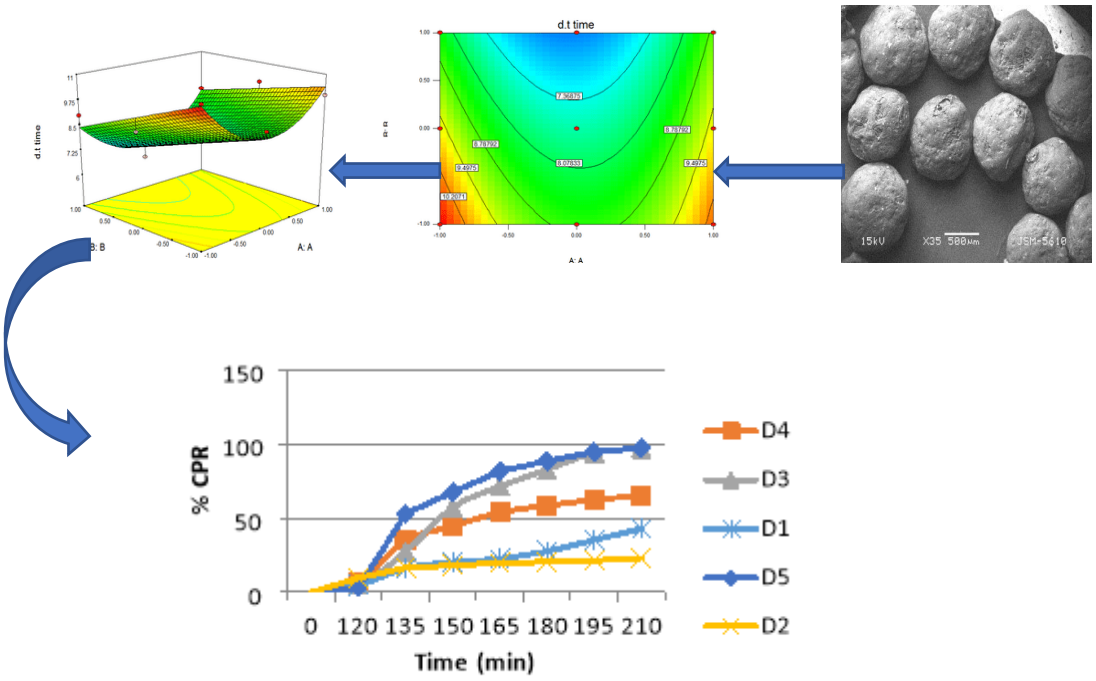
Background: The present study aims to Develop and optimize Oral disintegrating tablets (ODTs) containing enteric coated Esomeprazole Magnesium pellets. QbD Approach was applied to investigate Critical Quality Attributes and Critical Process Parameters that ensure Quality of the product. Formulation of enteric coated pellets was done by coating on non-peril seeds in Fluid Bed Coater. Coating was done in three consecutive layers. First layer contains drug Esomeprazole Magnesium and HPMC E5/Kollicoat IR as film forming polymer. Second coat was done to prevent interaction of drug to enteric coat; also, it acts like a base for enteric coat to be more appropriate. Third coat was done with enteric coating polymer Eudragit L30D55. Optimized pellets were characterized for their sphericity, flow properties, SEM analysis, cumulative percentage drug release, drug content, % yield and % drug load. ODTs were prepared by direct compression of pellets with superdisintegrant ODTs were optimized by applying Design of Experiment. Validation of optimized batch was done by check point method. Characterization of ODTs was done for their Hardness, Friability, Tablet size, thickness, content uniformity, cumulative percentage drug release, SEM analysis and intactness of the pellets.

Results and Conclusions: Optimized enteric coated pellets having Drug content 66.02 mg/0.5 gm pellets, 13.2 % drug load, 66.26 % yield, less than 5 % CPR up to 2 hours and almost 90 % CPR in the next 1 hour, were used for further preparation of ODTs. prepared ODTs had shown minimum Disintegration time, less than 10 % drug release up to 2 hrs and at least 85 % drug release in the next hour was achieved. In order to demonstrate clinical benefits the formulation can be manufactured at large scale to provide enough quantities for a clinical trial and to investigate the In Vivo performance.

KEY WORDS: Oral Disintegrating Tablets, Enteric coated pellets, Esomeprazole Magnesium, Quality by Design, Design of Experiments

Graphical Abstract:





Background

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Some novel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral administration. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts.

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute**.**

Mechanism of oral disintegrating tablets

ODTs are formulated in such a way that they disperse, dissolve, or disintegrate rapidly in oral cavity, allowing release of the medication from the dosage form without water. This is due to rapid water absorption into the core of the tablets, rapid disintegration of tablets and dissolving water soluble tablet components which leads to rapid dissolution of the tablets. Dissolved medication either swallowed or subjected to pregastric absorption which may lead to increasing the rate and extent of drug absorption and may decrease hepatic metabolism.

Technologies used for manufacturing of orally disintegrating tablets

Various processes can be employed to formulate ODTs including Conventional Technologies and Patented Technologies. Conventional Technologies include Freeze Drying or Lyophilization, Direct Compression, Molding Molded Tablets, Mass Extrusion, Melt Granulation, Phase Transition Process, Sublimation and Patented Technologies Include Zydis®, Orasolv, Durasolv, Wowtab, Cotton Candy Technology, Oraquick, Nanocrystal Technology, Shear Form Technology, Pharmaburst Technology, Frosta Technology.

Introduction To Enteric Coating

An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. Commonly-used enteric coatings may be made from: Methacrylic acid copolymers, Cellulose acetate (and its succinate and phthalate version), Polymethacrylic acid/acrylic acid copolymer, Hydroxypropyl methyl cellulose phthalate, Polyvinyl acetate phthalate, Hydroxyethyl ethyl cellulose phthalate, Cellulose acetate tetrahydrophtalate, Acrylic resin, Shellac.

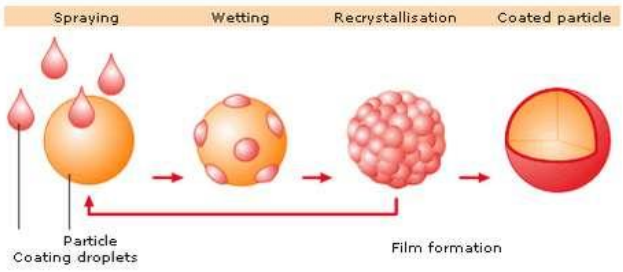
Introduction To Drug

Esomeprazole magnesium belongs to the family of proton pump inhibitors (PPIs) which inhibits gastric acid secretion. Esomeprazole, the stereospecific S-isomer of Omeprazole, is the first proton pump inhibitor (PPI) to be developed as a single isomer for use in the treatment of acid-related diseases. This optical isomer is subject to less first-pass

metabolism and lower plasma clearance than Omeprazole, thereby offering higher systemic bioavailability. Early studies have shown Esomeprazole achieves greater and more sustained acid control than Omeprazole, with a similar tolerability and safety profile. Furthermore, Esomeprazole shows a more rapid onset of acid-suppression effect than Omeprazole and less inter-individual variation in acid control. Additionally, a recent crossover study demonstrated that Esomeprazole at a standard dose of 40 mg once daily provides more effective control of gastric acid at steady state than standard doses of Pantoprazole, Lansoprazole and Rabeprazole in patients with symptomatic Gastroesophageal reflux disease (GERD). In addition, Esomeprazole treatment yields higher erosive Esophagitis healing rates and provides sustained resolution of heartburn in more patients than any other currently available.

Introduction To Fluid Bed Coater

Spray coating can be used for all fluid bed systems, be it in batch or continuous operation or if the film is applied from a sprayed solution, suspension or hot melt. For this processing option the parameters have to be chosen to avoid agglomeration, i.e. liquid bridges between the air suspended particles



QbD Approach

Quality by Design (QbD) is a modern, scientific approach that formalizes product design, automates manual testing, and streamlines troubleshooting. It uses a systematic approach to ensure quality by developing a thorough understanding of the compatibility of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insight upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified. QbD has four key components, Defining the Product Design Goal, Discovering the Process Design Space, Understanding the Control Space, Targeting the Operating Space

QbD Components

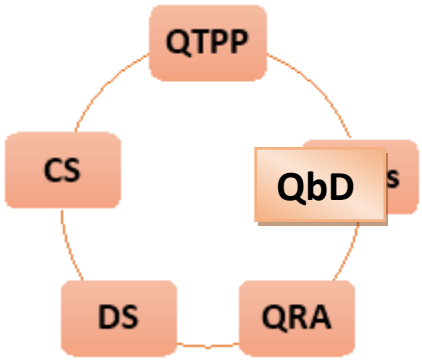


Figure 0.1: Components of QbD

- ✓ Quality target product profile (QTPP)
- ✓ List of critical quality attributes (CQAs)
- • List of critical material attributes of drug and excipients (CMAs)
- • List of critical process parameters (CPPs)
- ✓ Quality risk assessment (QRA)
- ✓ Design space (DS)

A control strategy (CS)that ensures the product reliability meets its predefined objectives.

QTPP
A prospective summary of the quality characteristics of a drug product that will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

Design Space

Design Space is the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

CQA FOR ENTERIC COATED PELLETS

- Cumulative drug release
- Drug content
- % yield

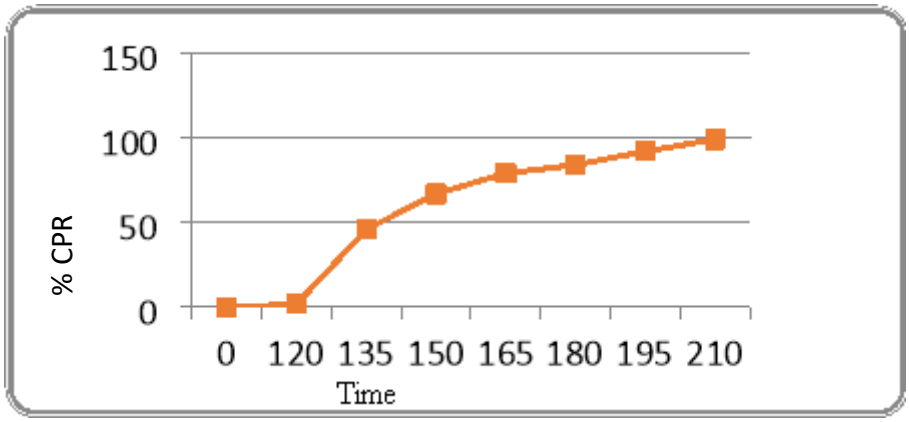


Figure 0.2: Target profile

Target profile

- ✓ No release up to 2 hrs in 1.2 pH
- ✓ Not less than 85 % release within 1 hr in 6.8 pH
- ✓ maximum drug load and maximum % yield

CRITICAL MATERIAL ATTRIBUTES. . . .

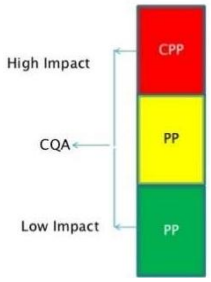
Critical quality attributes related to material

Raw material attributes: Hygroscopicity, Solubility of the drug

Intermediate: Flow property of pellets, Drug content

CRITICAL PROCESS PARAMETERS . . .

A process parameter is a Critical Process Parameter when it has high impact on a CQA. CCPs are responsible for ensuring the right CQA. CPPs are identified from a list of potential PPs using risk assessment and experimental work. For coating process critical process parameters are: Spray rate, Air flow, Input temperature, Humidity (blower speed) inside the chamber, Product temperature, Coating efficiency



CQA FOR ODTs: Disintegration time, Hardness, Intactness of pellets (by measuring drug release), Content uniformity(potential), Drug content

Target profile

- Disintegration time less than 1 min
- No change in release profile, that will be checked by similarity factor

CRITICAL MATERIAL ATTRIBUTES . . .

- Hydrophilicity of Superdisintegrant
- Water Insolubility of MCC

CRITICAL PROCESS PARAMETERS . . .

- Blending
- Compression force (potential)
- Speed of machine (potential)

Quality risk assessment

A risk assessment was performed to evaluate the impact that each attribute could have on the drug product CQAs. The relative risk that each attribute presents was ranked as high, medium and low. Quality risk assessment for pellets and tablets is shown in

Quality risk assessment for pellets

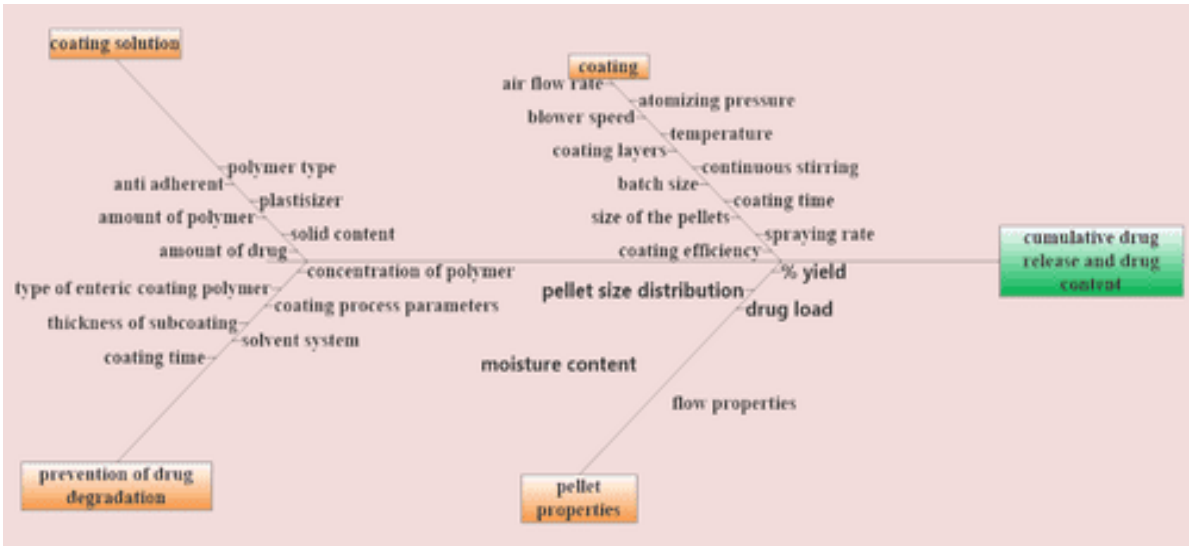


Figure 0.3: ISHIKAWA Diagram for enteric coated pellets

Quality risk assessment for ODT

Figure 0.4: ISHIKAWA Diagram for ODT

EXPERIMENTAL WORK

Materials Used: Esomeprazole Magnesium (Lupin Pharmaceutical Ltd), HPMC E5LV Premium (Chem Dyes Corporation), Kollicoat IR White II (BASF, The Chemical Company), Mannogem-EZ (SPI Pharma), Talc (Signet Chemical Corporation Pvt. Ltd), NP Suglets 600/710 (25/30 mesh) (The Dow Chemicals), Magnesium Stearate (Bombay Tablets, Gandhinagar), Eudragit L30-D55 (Evonic), Microcrystalline cellulose(Celphere CP 305) (Asahi Kasei)

Instruments and Equipments Used: Analytical Weighing balance (Sartorius CP 1245, Germany or RepTech® and Axis, India), Digital pH meter (Electro Quip (Labtronik), India), Magnetic stirrer(REM's magnetic stirrer), FTIR (FTIR-8400S, Shimadzu), UV spectrophotometer (UV-1800,scimadzu,Japan), Digital Micromter (Mututoyo), Fluid Bed Coater (Cronimach), Dissolution Apparatus (Electrolab Ltd., TDT 06-T, Mumbai, India), Disintegration Aapparatus (Electrolab ED-2 Bowl USP, Mumbai), Hardness Tester (Monsanto), Roche's Friabilator(Model EF2, Electrolab Ltd, Mumbai, India), Stability chamber TH (325S/G, Thermo lab equipment, Thane, India), Rotary Tablet Press Machine (Cadmach Machinery, Ahmedabad. India)

Analytical estimation of Esomeprazole Magnesium

Esomeprazole magnesium is official in Indian Pharmacopoeia 2014. It was analyzed by UV Spectrophotometer. pH 6.8 Phosphate Buffer was prepared by adding 50.0 ml of 0.2 M potassium dihydrogen phosphate, in a 200 ml volumetric flask, to it, 22.4 ml of 0.2 M sodium hydroxide was added and then volume was made up. For the Preparation of stock solution, 10 mg of Esomeprazole Magnesium was accurately weighed and dissolved in 100 ml of phosphate buffer pH 6.8 in a volumetric flask. The solution was filtered using Whatman's filter paper. This solution has 100 µg/ ml strength. Preparation of different concentrations of EMZ for calibration curvewas done by dilution method. From the prepared stock solution (100 µg /ml), 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 ml of solution was pipette out in 10 ml volumetric flask and diluted up to mark with phosphate buffer pH 6.8 to prepare a concentration range from 5 to 30 µg /ml. Absorbance of each solution was measured at 301 nm using UV-Visible Spectrophotometer

Determination of λmax

One of the dilutions (10 µg /ml) was selected and scanned in the wavelength range of 200- 400 nm to get the UV spectrum of the EMZ. From that scan, characteristic wavelength which shows maximum absorbance, λ_{max} was picked out. **Figure 0.5**

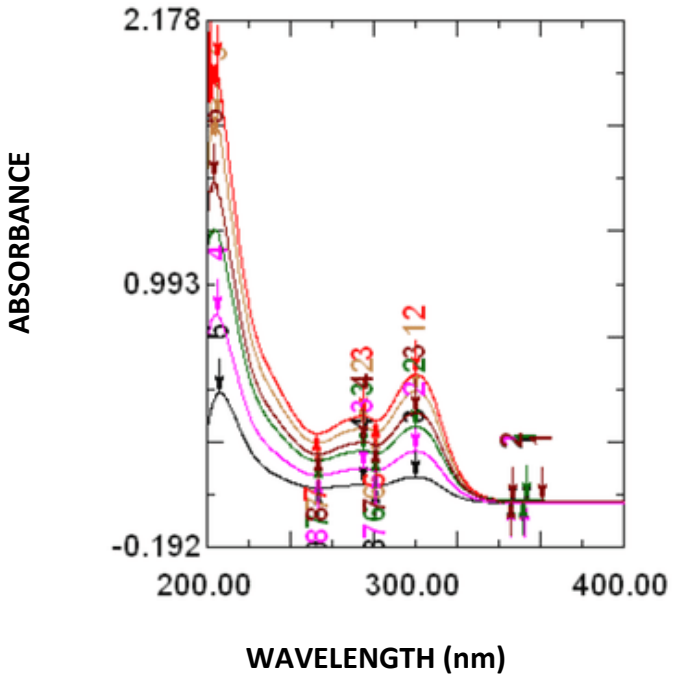


Figure 0.5: Scanning of spectra

PREFORMULATION STUDY

Organoleptic evaluations

For evaluation of organoleptic properties, color, odor and taste of drug were observed and recorded by using descriptive terminologies. According to organoleptic profiling of drug, observations were recorded as shown in Table 12.

Saturation solubility study

Solubility was determined by Shake Flask Method. The compound was added in surplus to a certain medium and shaken at a predetermined time, usually 24 h or longer. The saturation was confirmed by observation of the presence of

un-dissolved material. After filtration of the slurry, sample for analysis was taken; the amount of solute in the sample was determined by UV spectroscopy. Solubility was checked for distilled water, methanol and phosphate buffer pH 6.8.

Hygroscopicity

Accurately weighed amount of Esomeprazole magnesium was exposed to different humidity conditions of 60 % RH, 65 % RH, AND 75 % RH in different chambers. The amount of water absorbed was measured.

Micromeritical properties

Angle of repose and Compressibility Index were determined using bulk density and tapped density data

Drug Excipient compatibility study

FTIR study:

The FTIR of pure drug and physical mixture of it with other formulation ingredients in possible maximum concentration were measured using Fourier Transform Infrared Spectrophotometer (Model FTIR-8400S, Shimadzu, Japan). The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm-1.

DSC study:

Differential Scanning Calorimetry (DSC) is a thermoanalytical technique that is used to demonstrate the energy phenomena produced during heating or cooling of a substance (or a mixture of substances) and to determine the changes in enthalpy and specific heat and the temperatures at which these occur. Method: Samples were placed in pierced aluminum pans and hold for 1 min at 500°C and then heated gradually at 100C min-1 from 500°C to 2500°C. The onsets of melting points were calculated by the instrument.

FORMULATION AND DEVELOPMENT OF ODTS OF ESOMEPRAZOLE ENTERIC COATED PELLETS

FORMULATION AND DEVELOPMENT OF ENTERIC COATED PELLETS CONTAINING ESOMEPRAZOLE (ECP-EMZ)

- *PROCEDURE FOR PREPARATION OF ENTERIC COATED PELLETS CONTAINING DRUG*
- *Drug loading*

Specified quantity of suglets (non-pareil seeds) was weighed accurately. 400 ml of solvent (ethanol: water:: 9:1) was taken in a beaker and kept for continuous stirring under mechanical stirrer. Specified quantities of HPMC E5, talc, glycerin were added slowly to form uniform coating solution (**Error! Reference source not found.**). Now Esomeprazole was added and stirring was continued for 15 min. Suglets were charged in fluid bed coater chamber, and coated with the prepared coating solution containing Esomeprazole. Dried drug loaded pellets were collected and weighed to calculate coating efficiency. Process parameters were kept as shown in **Error! Reference source not found.**

- *Barrier coating*

200 ml of solvent (ethanol: water::9: 1) was taken in a beaker and kept for stirring under mechanical stirrer. Specified quantities of HPMC E5, talc and glycerin were added slowly to form uniform coating solution (**Error! Reference source not found.)**. Drug loaded pellets were coated with the above prepared coating solution (containing no drug) in the fluid bed coater (**Error! Reference source not found.**). Dried barrier coated pellets were collected and weighed to calculate coating efficiency.

- *Enteric coating*

100 ml purified water and 70 ml of Iso propyl alcohol were taken in a beaker and kept for stirring under mechanical stirrer. Specified quantity of enteric coating polymer i.e. Eudragit L30 D-55 (30 %) dispersion, talc and glycerin were added slowly to isopropyl alcohol-water mixture. stirring was continued for 30 minutes (till no solid residue remained) (**Error! Reference source not found.)**.now barrier coated pellets were coated with prepared enteric coating solution in fluid bed coater (**Error! Reference source not found.**). Dried enteric coated pellets (ECP-EMZ) were collected and weighed to calculate coating efficiency.

***Note**: coating solution must be kept on magnetic stirrer to give even composition of coat all the time while coating in the fluid bed coater.*

- *DEVELOPMENT OF FORMULATION ALONG WITH VARIATION IN OPERATING PROCESS PARAMETERS*

In order to prepare enteric coated pellets of desired criteria different types of coating solutions were prepared in which coating polymer itself, concentration of polymer, and ratio of polymer to drug was varied. Two types of polymer were screened, Hydroxy propyl methyl cellulose and Kollicoat IR, Operating process parameters were also varied

simultaneously parameters that were changed are: Atomization pressure of air flow, Blower speed or air flow, Input temperature, Output temperature, Flow of coating solution.

CHARACTERIZATION OF PELLETS

- Pellet size: Size of the pellets was measured using sieving method.
- Aspect ratio: Aspect ratio or Elongation measures sphericity of pellets. The maximum and minimum diameter of pellets was measured by digital micrometer. Aspect ratio was determined by following formula:

$$\text{Aspect ratio} = d_{max} / d_{min}$$

Where d_{max} & d_{min} are maximum & minimum diameters of pellets respectively.

- *Flow property: Flow property of enteric coated pellets was determined using Angle of repose and Compressibility index.*
- Drug Content: 0.5 gm of pellets was dissolved in 20 ml of Methanol. 1 ml of this solution was taken in a 10 ml volumetric flask and diluted up to the mark; again 1 ml of last dilution was taken and diluted up to mark. The absorbance of this solution was measured using UV Visible spectrophotometer.
- Drug load: It is the amount of drug coat to the total amount of pellets. It was calculated using formulae

$$\text{Drug load} = \frac{\text{amount of drug coated on pellet}}{\text{Amount of pellets}} * 100$$

- % yield: It shows how much drug have been coated to the pellets

$$\% \text{ Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} * 100$$

- Scanning electron microscopy

Morphology of pellets was determined using scanning electron microscopy. In this study sample was mounted on copper stubs and coated with a gold – platinum mixture in a sputter coater. Sample was then scanned using Cambridge stereo scan S90B Electron microscope, and micrograph was taken at a range of magnifications in order to determine morphology as well as to calculate pellet mean diameter and standard deviation around the mean.

- Drug release study: 0.5 gm of pellets were weighed and transferred to dissolution flask, containing 900 ml of 0.1N HCl (pH 1.2). The temperature was adjusted previously to 37ºC± 0.5ºC. Samples for first 2 hrs were collected and simultaneously replaced with medium. Now pellets are withdrawn from the flask and mereplaced the medium with phosphate buffer pH 6.8 and collect the samples for remaining 1.5 hrs and filter through 0.45µ membrane filter replace the sample quantity with the medium. The absorbance is measured at 271nm by using UV-spectrophotometer.

50.0 ml of the 0.2 M potassium chloride was added to 200-ml volumetric flask, 85 ml of 0.2 M hydrochloric acid was then added to it and then water was added to make up volume.

DEVELOPMENT AND CHARACTERIZATION OF ORAL DISINTEGRATING TABLETS OF ESOMEPRAZOLE PELLETS

- *PREPARATION OF ORALLY DISINTEGRATING TABLETS CONTAINING ECP-EMZ*

ODTs were prepared using direct compression method. Specified quantities of Enteric coated pellets, magnesium stearate, croscarmellose sodium, microcrystalline cellulose and mannogem-EZ (mannitol) were blended together in a plastic bag. After mixing, the resultant mixture was compressed using a rotary tableting machine.

METHOD OF PREPARATION

DIRECT COMPRESSION METHOD

Enteric coated pellets equivalent to 20 mg of drug was mixed with specified quantities of MCC, magnesium stearate, croscarmellose sodium and mannogem (mannitol) in a plastic bag, by simple tumbling, followed by compression of the blend was done.

Table 0.1 : Formulation for preparation of tablets

Ingredients	Category
Enteric coated pellets	Contains drug

Croscarmellose sodium	Superdisintegrant
MCC	Diluent
Magnesium stearate	Lubricant
Mannogem-EZ (mannitol)	Diluent/good mouth Feel

Table 0.2 : Different compositions of formulation

Ingredients	**I**	**II**	**III**
Enteric coated pellets(ECP-EMZ)	50	50	50
MCC	125	150	175
Croscarmellose sodium	10	15	20
Mannogem-EZ	q.s.	q.s.	q.s.
Magnesium stearate	7.5	7.5	7.5

All the ingredient quantities were taken in mg.

➢ *OPTIMIZATION OF ODTs*

DESIGN OF EXPERIMENT

➢ APPLICATION OF 3^2 FULL FACTORIAL DESIGN

In the present study a 3^2 full factorial design was used to optimize orally disintegrating tablet formulations. In contrast to traditional trial and error method that involves numbers of batches and hence requires much efforts and time, factorial design is an efficient method of developing a complex formulation with minimum number of batches in shortest period of time. It will also indicate the relative significance of selected variables and their interactions. In this design, two independent variables were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations.

➢ FACTOR AND LEVEL SELECTION

The objective of this study was to develop an optimized oral disintegrating tablet formulation with sufficient hardness which would disintegrate within 30 sec. To achieve this objective, the contribution of independent formulation variables was examined. Two independent variables, the concentration of Superdisintegrant croscarmellose sodium (X_1) and the concentration of MCC (X2) were set at three different levels. High and low levels of each factor were coded as 1 and -1, respectively and the medium level as zero. The levels of these formulation variables were chosen on the basis of literature review and the results were obtained from the preliminary studies conducted. In addition to factor and levels, dependent variables were also selected for the evaluation of the factorial design batches. The dependent variable measured was disintegration time (Y).

INDEPENDENT VARIABLES:

X_1: Concentration of superdisintegrant (CCS)

X_2: Concentration of MCC

DEPENDENT VARIABLES:

Y: Disintegration time

Table 0.3 : Actual values for 9 runs

Run	**X_1**	**X_2**
1	15	175

2	10	150
3	20	175
4	20	150
5	15	125
6	10	175
7	10	125
8	15	150
9	20	125

- Construction of contour and 3D surface plots

The quadratic model obtained from the regression analysis is allowed to build a 3- dimensional surface plot by Design Expert® software in which the dependent variable R was represented by a curvature as a function of Xi. The relationship between the individual response and independent variables can be directly visualized from the contour plots.

The application of the desirability function combines all the responses in one measurement and gives the possibility of predicting optimum levels for the independent variables. The desirability function was used for optimization of the formulation. During optimization of formulations, the responses have to be combined in order to produce a product of desired characteristics. The method was adopted to calculate the desirability of individual dependent variable and overall desirability by taking geometric mean. The batch having highest overall desirability (near to 1) value should be considered as an optimum batch. For this, range of all the dependent variables were selected which would satisfy the criteria of Oral disintegrating tablet formulation. In the case of ODTs, disintegration time less than 30 sec and hardness in the range of 3-4 kg/cm2 is acceptable. So, range of both the dependent variables should be selected such that it would satisfy these criteria's. Combinations of all the possible different levels of both independent variables which were satisfied the above criteria and having the desirability near to 1 was selected as check point batch

CHARACTERIZATION OF ODTS

- **MICROMERITICAL PROPERTIES:**
  The Micromeritical properties were measured as per section 5.4.4

- **CONTENT UNIFORMITY**
  The tablet (n=3) was placed in 100 ml of phosphate buffer (pH 6.8). After complete solubilisation, the solution was diluted appropriately, filtered and analyzed at 301 nm using UV-Visible Spectrophotometer (Shimadzu UV-1800). The average of three tablets was taken as the content of drug in one tablet. Esomeprazole tablets should contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Esomeprazole.

- **HARDNESS**
  The hardness of the tablets was determined using hardness tester (Monsanto).

- **FRIABILITY**
  Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche's Friabilator was used for this purpose. Weighed tablets were placed in the friabilator, which was then operated at 25 rpm for 4 min. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\% \text{ Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

- **THICKNESS**
  Thickness of the tablet was measured using digital micrometer

- **TABLET SIZE**
  Hardness of the tablet was measured using digital micrometer

- **IN VITRO DISINTEGRATION TEST**
  Disintegration time was determined using USP disintegration apparatus in simulated salivary fluid. The volume of medium was 900 ml and temperature was 37±0.5°C. Time in seconds was noted down for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured.

- **WETTING TIME**
  Five circular tissue papers of 10cm diameter were placed in a Petri dish with a 10cm diameter. Ten milliliters of water containing a water-soluble dye was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time .

- **INTACTNESS OF THE PELLETS WITHIN TABLET**
  Intactness of the pellets was checked by applying similarity factor (f_2) between the release profile of pellets before compression and tablet after compression . Release profiles were compared by calculating statistically derived mathematical parameter, "Similarity factor" (f_2).

Where R_t and T_t are percent drug dissolved at each time point for the pellets before compression and after compression into tablet, respectively, n is the no. of dissolution sample times and t is time sample index.

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

- SCANNING ELECTRON MICROSCOPY

As described previously

- **STABILITY STUDY OF OPTIMIZED BATCH**
  Stability studies were carried out for optimized batch to check any morphological or physicochemical changes. Sample was exposed to 75% RH and a temperature of 45-50ºC for 1 month in stability chambers. The tablets were evaluated for hardness, % friability, wetting time, in vitro disintegration time and drug content.

- COMPARISON WITH MARKETED PRODUCT
  The optimized tablet formulation was compared with marketed tablets in % drug release. Method used for comparison was same for the two sets of samples.

Description of the marketed product:

Esomeprazole Magnesium Tablet I.P. - Nexpro - 40

Each enteric coated tablet contains: Esomeprazole Mg Trihydrate equivalent to Esomeprazole 40 mg

Colors: red oxide of iron and TiO_2

Dose: as directed by physician

wallow whole tablet, do not crush or chew, Store at a temperature not exceeding 30ºC Protected from light and moisture, Keep out of reach of children, Mfg by: Torrent pharmaceuticals ltd, Mfg lic no.-M/563/2010

RESULTS & DISCUSSIONS

1.Preformulation study

0.1 Preformulation results

S.N.	Parameter	Experimental result
1.	Color	White to almost white crystalline powder
	Odor	Characteristic
2.	Taste	Bitter
3.	Angle of repose	27.47º
4.	Compressibility index	14.89
5.	Saturation solubility study Water Methanol Phosphate buffer	 Slightly soluble Soluble Freely soluble
6.	Hygroscopicity	Slightly hygroscopic

From the above results it could be seen that Esomeprazole magnesium had Angle of repose 27.47º and Hausner's ratio 1.175, which indicated that Esomeprazole magnesium was found to be good in flow. Hence for the development of the dosage form of the drug, there was no need to improve flow property of the drug. Solubility results showed good solubility in methanol, slightly soluble in water and soluble in phosphate buffer pH 6.8.

Drug - Excipient compatibility study

Drug - Excipient compatibility studies include experiments under conditions typical for the handling, formulation, storage and administration of a drug candidate as well as stability in presence of other excipients. The findings of these study revealed that drug is compatible with proposed excipients at different conditions. It was expected that the drug does not degrade when exposed to GI tract.

FTIR

FTIR spectrum of Esomeprazole magnesium is characterized by the absorption band of Sulphonyl group, Methylene C-H band, Secondary amine C-N stretch, Alkyne C-H band, Aromatic C-H out of plane band, and Methoxy group **(Table 0.2)**. The presence of characteristic peaks of drug in the FTIR spectra of physical mixture (Drug: polymer) indicates the absence of chemical interaction between the drug and the polymers employed in the study. FTIR study confirms no interaction between drug and excipient.

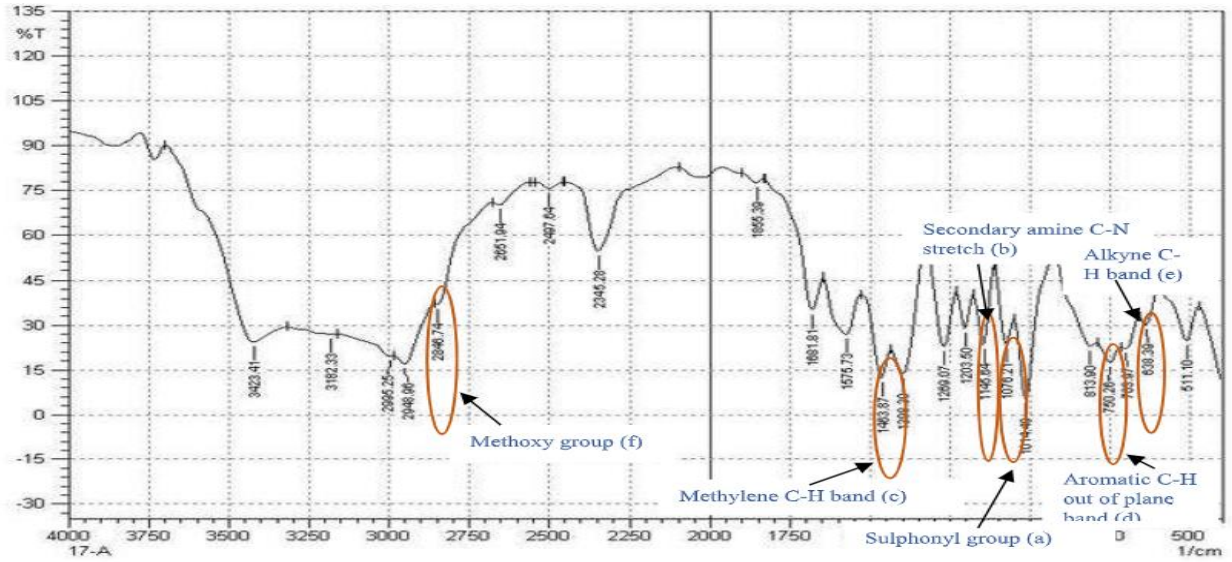


Figure 0.1: FTIR Spectra of Drug Esomeprazole Magnesium [A]

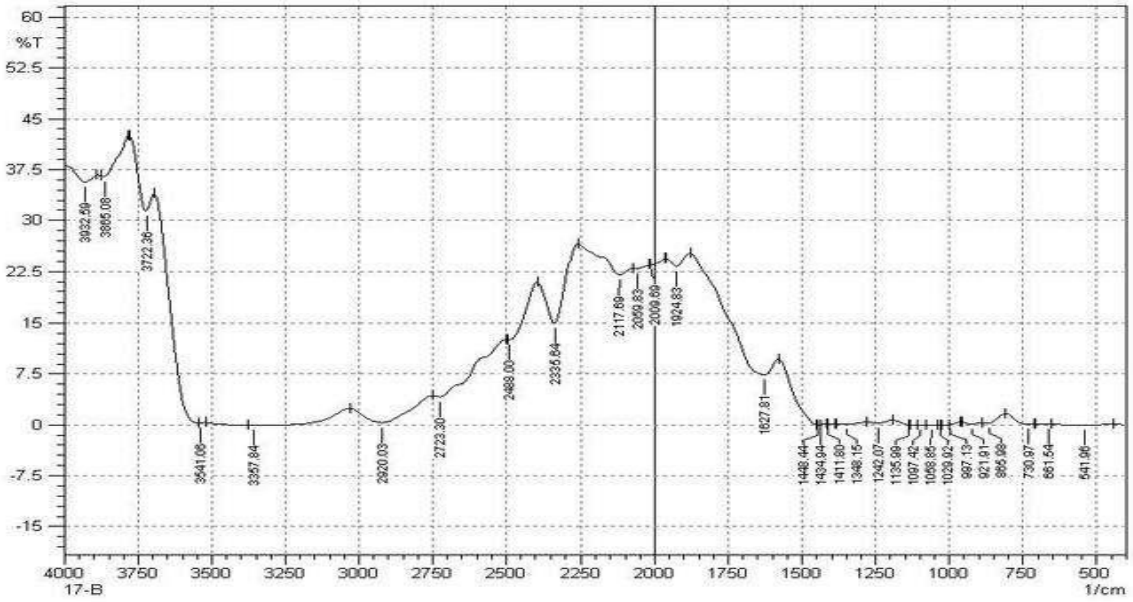


Figure 0.2 FTIR Spectra of Drug + Suglet [B]

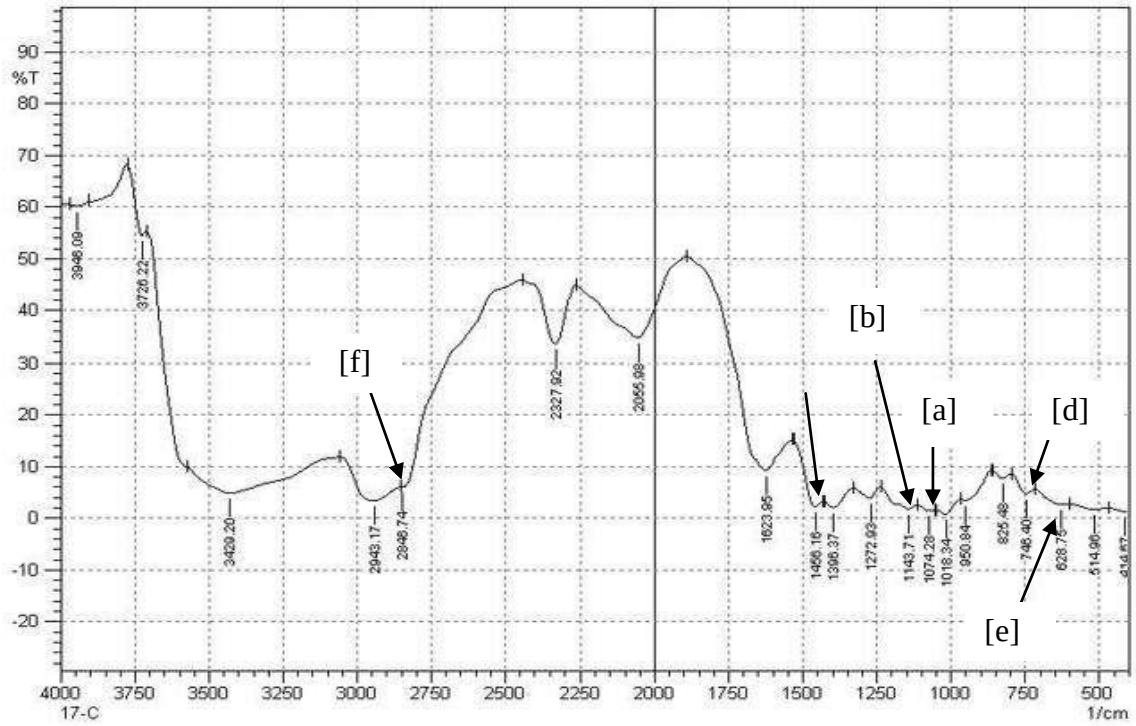


Figure 0.3: FTIR Spectra of Drug + HPMC [C]

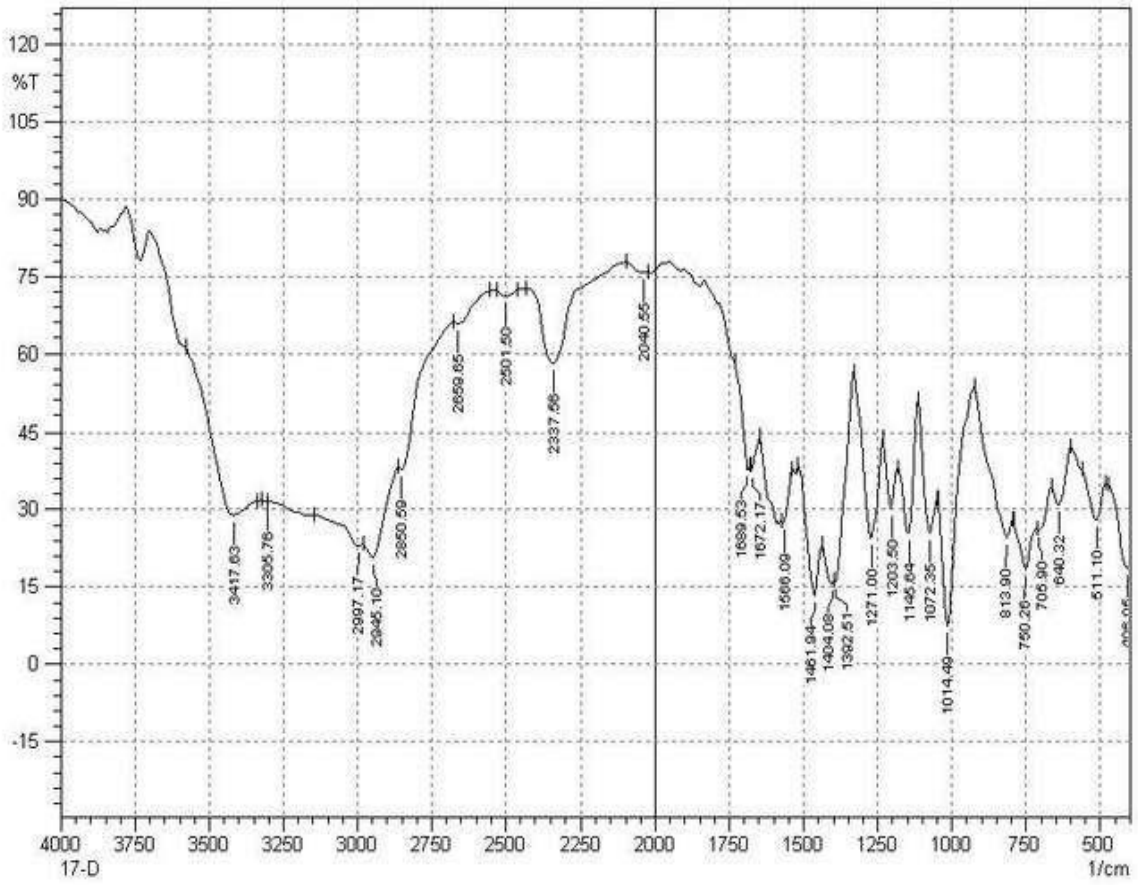


Figure 0.4: FTIR Spectra of Drug + Kollicoat [D]

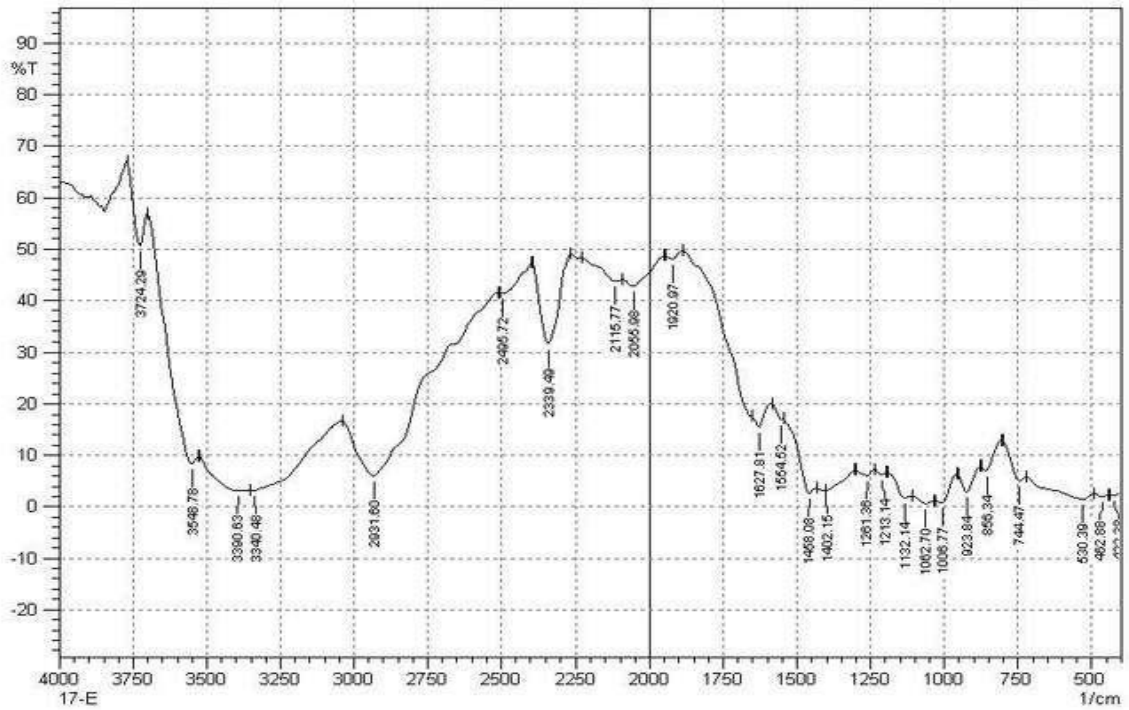


Figure 0.5: FTIR Spectra of Drug + Suglet + HPMC [E]

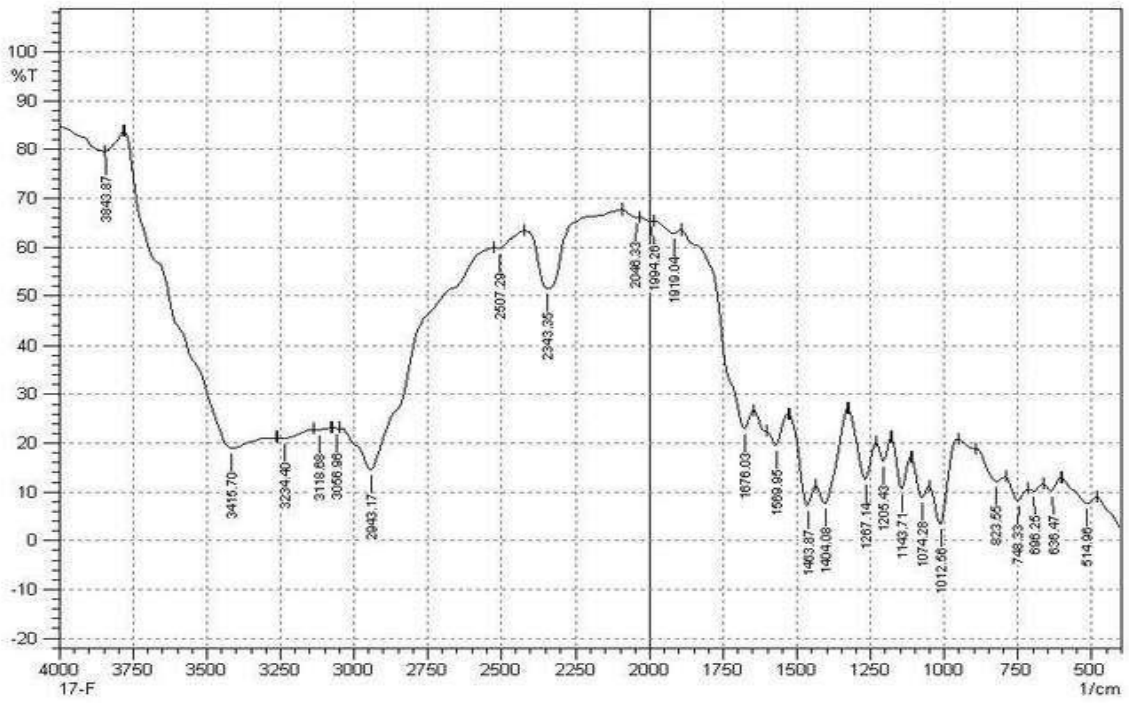


Figure 0.6: FTIR spectra of Drug + Suglet + Kollicoat [F]

[A] = Drug Esomeprazole Magnesium

[B] = Drug + Suglet

[C] = Drug + HPMC

[D] = Drug + Kollicoat

[E] = Drug + Suglet + HPMC

[F] = Drug + Suglet + Kollicoat

Table 0.2 FTIR spectrum values for Esomeprazole Magnesium

Functional group	Wave number
Sulphonyl group [a]	1077 cm^{-1}
Secondary amine C-N stretch [b]	1152 cm^{-1}
Methylene C-H band [c]	1475 cm^{-1}
Aromatic C-H out of plane band [d]	768 cm^{-1}
Alkyne C-H band [e]	634 cm^{-1}
Methoxy group [f]	2830 cm^{-1}

FORMULATION AND DEVELOPMENT OF ENTERIC COATED PELLETS CONTAINING ESOMEPRAZOLE (ECP-EMZ)

CHARACTERIZATION OF PELLETS

Particle size, flow properties, drug load, drug content and % yield was calculated for all the batches (D_1 – D_5) results obtained are shown in **Table 0.3**

Table 0.3 : results for different evaluation parameters for pellets

Evaluation parameter	Unit	D_1	D_2	D_3	D_4	D_5
Particle size	µm	710-850	710-850	710-850	710-850	710-850
Angle of repose	º	17.58	23.74	27.69	20.22	19.40
Compressibility index	-	0	0	0	0	0
Drug load	%	2.92%	6.64%	10.41%	12.2 %	13.2 %
% Yield	%	34%	42.5%	85.37%	64.44 %	66.26 %
Drug content	mg/0.5 gm pellets	14.64	33.21	52.06	61.34	66.02

0.4: Aspect ratio

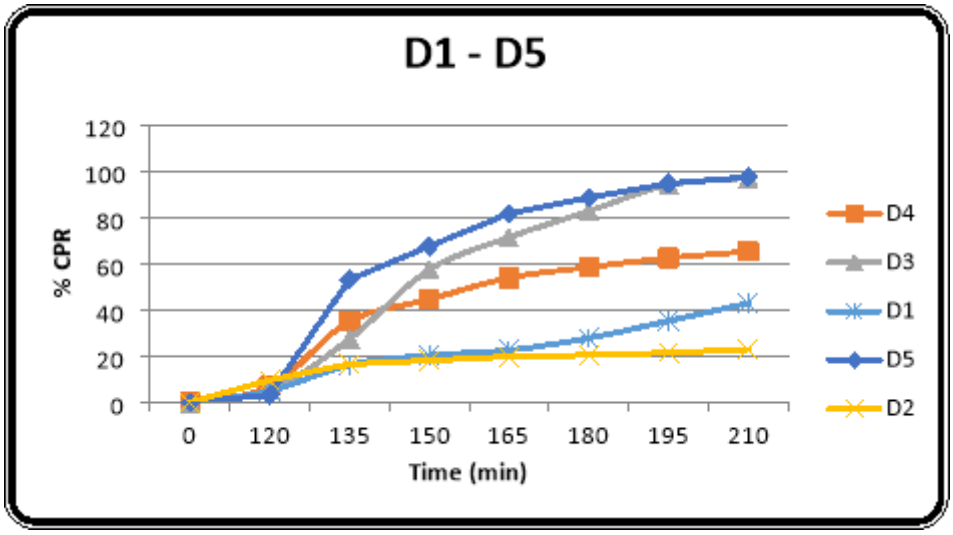
Sr. no.	d_{max}	d_{min}	d_{max} / d_{min}
1.	0.823	0.754	1.091512
2.	o.632	0.599	1.055092
3.	0.787	0.697	1.129125
4.	0.892	0.799	1.116395
5.	0.887	0.822	1.079075
6.	0.884	0.798	1.107769
7.	0.838	0.787	1.064803
8.	0.897	0.834	1.07554

9.	0.881	0.765	1.151634
10.	1.025	0.923	1.110509
11.	0.879	0.832	1.05649
12.	0.828	0.799	1.036295
13.	0.803	0.776	1.034794
14.	0.824	0.746	1.104558
15.	0.844	0.797	1.058971
16.	0.752	0.692	1.086705
17.	0.823	0.731	1.125855
18.	0.879	0.815	1.078528
19.	0.961	0.802	1.198254
20.	0.891	0.785	1.135032

Aspect ratio of pellets was found to be 1.095 that is near to 1, which showed shape of the pellets near to sphere, that shows even distribution of coating on the pellet surface has occurred. Also denotes the efficiency of the FBC in preparation of uniform sized pellets.

Drug release study

Release study was done for all the prepared formulation results are shown figure 6.12

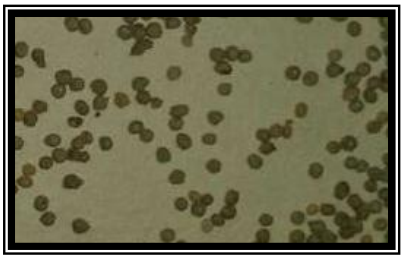


0.7: Comparative drug release study for batch D1-D5

- D_1 batch showed very poor drug load, so amount of drug in the coating solution was increased. But when the drug amount is increased without changing the polymer amount (D_2), drug release was found to be poor.
- So in the D_3 batch the amount of polymer was also increased and the results found was better drug load better release profile
- drug polymer ratio 1:1 was found to give better release with maximum drug load
- Due to hygroscopic nature of the drug there was a problem in handling of pellets so for that pellets were not withdrawn from the FBD chamber until the barrier coat have been coated, good results were obtained.
- Another thing was done is use of Kollicoat in place of HPMC E5…..it had reduced the problem of pellets getting wet
- Proper enteric coating was done using formula:
  - 30 ml of Eudragit dispersion
  - 70 ml IPA
  - 100 ml water

- When enteric coat is 8 %to the final composition we can say it is completely enteric coated.
- Comparison of all batches showed batch D_3 had good flow properties, maximum drug load and higher percentage yield as compared to other.
- Batch D_3 had percentage drug release less than 10 % up to 2 hrs and almost 85 % release in the next 1 hr i.e. desired release profile.
- In the batch D_4 and D_5 Kollicoat IR was used as coating polymer and it was found that pellets did not get wet after discharged from FBC also use of Kollicoat has improved drug release within 1 hr.
- It was found that coating with Kollicoat IR had decreased drug content as compared to coating with HPMC.
- Batch D_5 was selected for further preparation of ODTs. When compared all the relevance parameters, it was found that drug content was higher in case of D_5.as shown in table …….
- Batch D_3 and D_5 both showed almost desired release profile, but D_5 showed more closeness with the desired release profile.
- Pellets made using HPMC showed even coating by appearance, and also proper round shape pellets were formed, while in case of using Kollicoat as coating polymer a little unevenness of coating was observed

Suglets (Non Pareil Seeds)

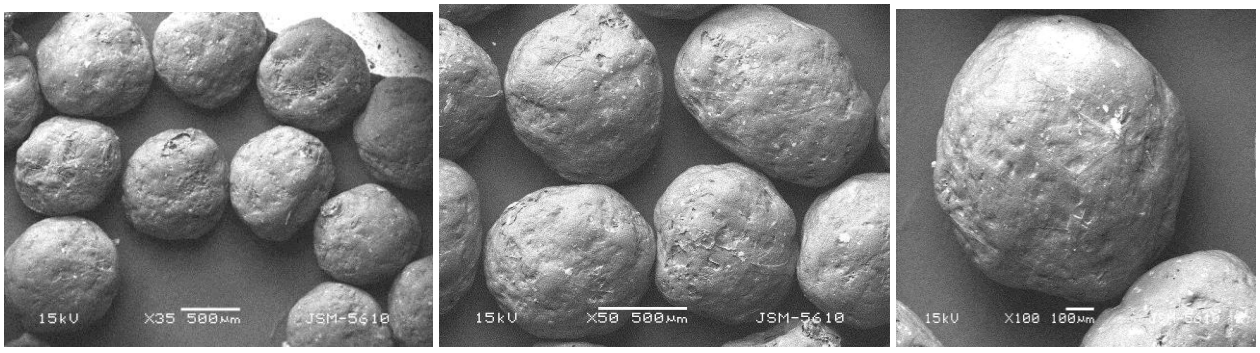


coating of drug using Kollicoat IR as coating polymer

Enteric coated pellets for batch D5

SCANNING ELECTRON MICROSCOPY OF PELLETS

SEM images for pellets



SEM results show round shape, smooth surface with even coating and also uniformity of the pellet size.

Optimization of ODTs

(Solid mixture before direct compression)

Bulk density	0.53 gm/ml
Tapped density	0.613 gm/ml
Angle of repose	31.38º
Carr's index	13.53 %

Pre compression parameters show good flow of powder mixture

Table 0.5 : Post compression evaluation parameters of tablets prepared by Direct compression method

Thickness (mm)	5.211± 0.004
Diameter (mm)	10.113±0.01
Hardness (Kg/cm^2)	3.5
Friability (%)	0.52
Disintegration time (sec)	9
Wetting time (sec)	6.5

The hardness of the formulation was 3.5 kg/cm^2 and friability was less than 1%, that indicates good mechanical resistance of tablets. Disintegration time was less than 30 sec.

OPTIMIZATION OF ODTs USING 3^2 FACTORIAL DESIGN

Table 0.6 : Pre compression evaluation parameters

Batch	Bulk density	Tapped density	Angle of repose	Carr's index
F_1	0.529	0.615	31.38	13.98
F_2	0.532	0.608	32.68	12.50
F_3	0.533	0.611	31.24	12.76
F_4	0.527	0.610	31.74	13.60
F_5	0.537	0.617	34.22	12.96
F_6	0.531	0.610	31.90	12.95
F_7	0.533	0.612	34.28	12.90
F_8	0.526	0.606	31.21	13.20
F_9	0.535	0.615	31.92	13.00

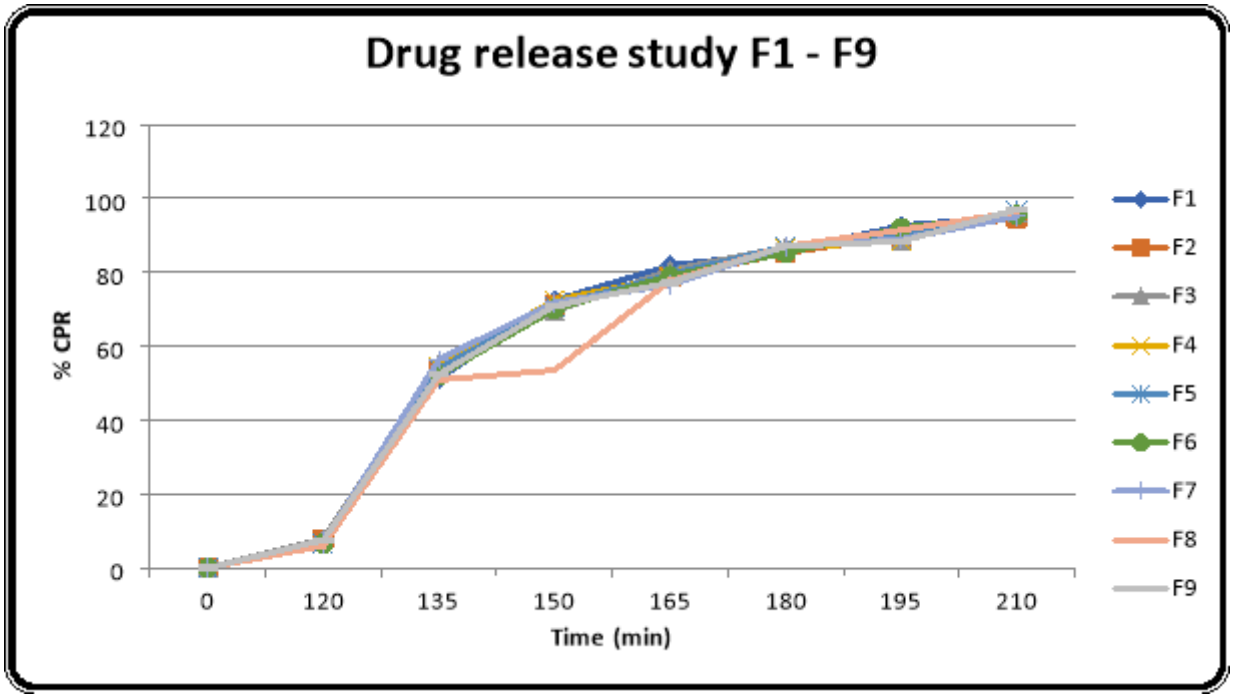
Table 0.7 : Post compression evaluation parameters of tablets

Batch code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm2)	% Friability	Disintegration time (Sec)	Wetting time (sec)
F_1	10.164±0.01	5.212±0.005	3.5	0.522	6	6.22
F_2	10.189±0.01	5.237±0.002	3.5	0.544	9	6.09
F_3	10.072±0.01	5.168±0.002	3.5	0.592	9	5.24
F_4	10.114±0.02	5.217±0.003	3.5	0.630	10	6.33
F_5	10.052±0.01	5.191±0.002	3.5	0.581	9	5.85
F_6	10.197±0.01	5.166±0.001	3.5	0.563	9	5.32
F_7	10.177±0.00	5.155±0.000	3.5	0.539	11	5.90
F_8	10.116±0.01	5.235±0.005	3.5	0.689	8	6.12
F_9	10.143±0.02	5.175±0.001	3.5	0.545	10	5.36

As the tablets were compressed from the same die, tablet diameter was found to be same for all the tablets. The friability of all the batches was less than 1% (meeting the acceptance criteria), which prevents loss of material during handling. Hardness of tablets was kept same 3.5 kg/cm^2, which was found to be under the specified limit for harness for ODTs. Disintegration time was found to be less than 30 sec for all the batches that is critical criteria for ODTs to be followed.

0.8: In vitro drug release study for factorial bathes

Time [min]	% CPR								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0	0	0	0	0
120	6.925	7.840	7.839	6.619	6.620	6.619	6.920	6.006	7.534
135	51.234	53.685	55.010	54.587	53.976	52.146	56.420	50.919	52.461
150	72.469	71.276	69.436	72.507	70.975	70.039	71.917	53.553	70.958
165	81.852	78.788	80.597	78.801	79.394	79.079	76.659	77.676	77.259
180	85.614	85.275	86.820	86.495	87.112	85.278	87.082	87.095	87.088
195	92.671	89.922	88.719	88.715	90.247	92.057	89.027	91.468	88.417
210	95.189	94.854	96.060	96.670	96.687	95.487	95.149	96.396	96.972



0.8: Comparative dissolution profiles of formulations F1 – F9

After comparing all the data resulted for release study what comes out is, there was no significant difference between the release profiles, so this study concludes that there is no direct or indirect effect of concentration of MCC and concentration of CCS on drug release.

Table 0.9 : Results for dependent variable

Batch code	Coded values		Dependent variable
	X_1	X_2	R
F_1	-1	0	9
F_2	0	0	8
F_3	1	-1	10
F_4	-1	-1	11
F_5	1	0	10
F_6	0	-1	9
F_7	1	1	9
F_8	-1	1	9
F_9	0	1	6

X_1 = Amount of CCS (mg)

X_2 = Amount of MCC (mg)

R = Disintegration time (sec)

Disintegration time for different formulations

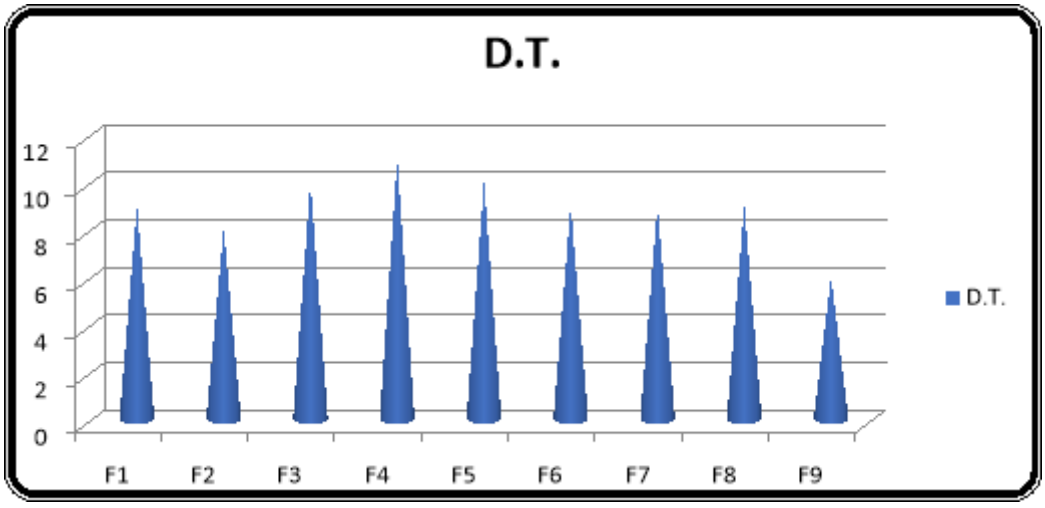


Figure 0.9: DT for formulations F_1 - F_9

From the graph it was suggested that batch F9 with conc. of ccs 15 gms and conc of MCC 175 gms showes minimum in vitro disintegration time.

ANOVA for Response Surface Reduced Quadratic Model

Response : **Disintegration time**

Table 0.10 : Analysis of variance table [Partial sum of squares – Type III]

Source	Sum of squares	Df	Mean square	F value	P –value Prob > F	
Model	14.25	4	3.56	8.14	0.0333	
A – A	0.000	1	0.000	0.000	1.0000	
B – B	6.00	1	6.00	13.71	0.0208	Significant
AB	0.25	1	0.25	0.57	0.4918	
A^2	8.00	1	8.00	18.29	0.0129	
Residual	1.75	4	0.44			
Core Total	16.00	8				

- The Model F-value of 8.14 implies the model is significant.
- There is only a 3.33% chance that a "Model F-Value" this large could occur due to noise.
- Values of "Prob > F" less than 0.0500 indicate model terms are significant.
- In this case B, A^2 are significant model terms.
- Values greater than 0.1000 indicate the model terms are not significant.
- If there are many insignificant model terms (not counting those required to support hierarchy),
- model reduction may improve model.

Table 0.11 : Summary of ANOVA results

Std. Dev.	0.66
Mean	9.00
C.V. %	7.35
PRESS	12.17
R-Squared	0.8906
Adj R-Squared	0.7813
Pred R-Squared	0.2396
Adeq Precision	8.621

- The "Pred R-Squared" of 0.2396 is not as close to the "Adj R-Squared" of 0.7813 as one might normally expect. This may indicate a large block effect or a possible problem with \ mode and/or data. Things to consider are model reduction, response tranformation, outliers, etc.
- "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 8.621 indicates an adequate signal. This model can be used to navigate the design space.

Table 0.12 : Summary of evaluation of different factors

Factor	Coefficient Estimate	Df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	7.67	1	0.38	6.61	8.73	
A – A	0.000	1	0.27	-0.75	0.75	1.00
B – B	-1.00	1	0.27	-1.75	-0.25	1.00
AB	0.25	1	0.33	-0.67	1.17	1.00
A^2	2.00	1	0.47	0.70	3.30	1.00

Full factorial design equations for quadratic models were

Final Equation in Terms of Coded Factors:

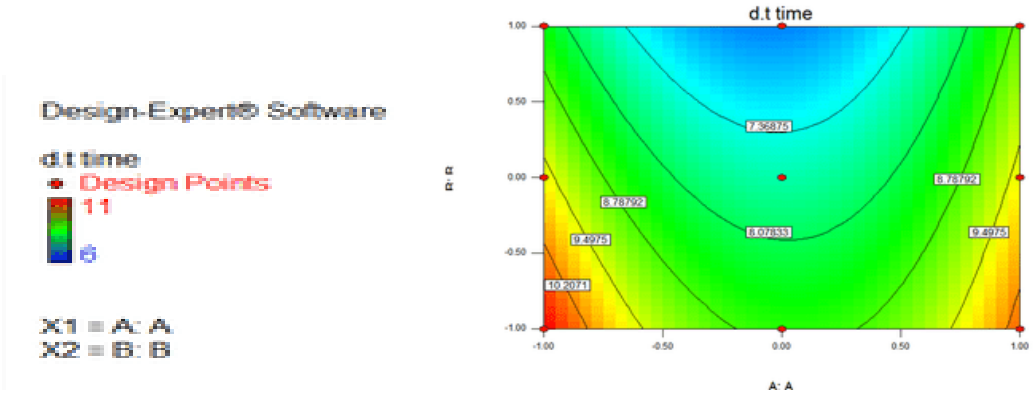
d.t time =+7.67+0.000* A-1.00* B+0.25* A * B+2.00* A^2

Final Equation in Terms of Actual Values:

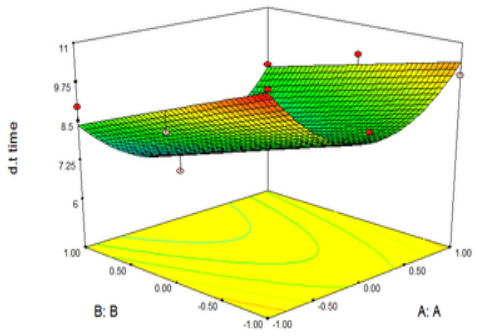
Disintegration time = 7.66667+0.000000*A-1.00000*B+0.25000*A*B+2.00000* A^2

Equation suggests that A (Conc. Of CCS), A*B and A^2 have positive effect on response i.e. Disintegration time,while B (Conc. Of MCC) has negative effect on Disintegration time.Thus increse in conc. of croscarmellose sodium will increase disintegration time. while decreasing the conc. of MCC will result in increase in disintegration time, stil, as the combination of these two have positive effect, so conc. of MCC also affect D.T. not alone, but in combination with CCS.

Effect of Independent variables on Response

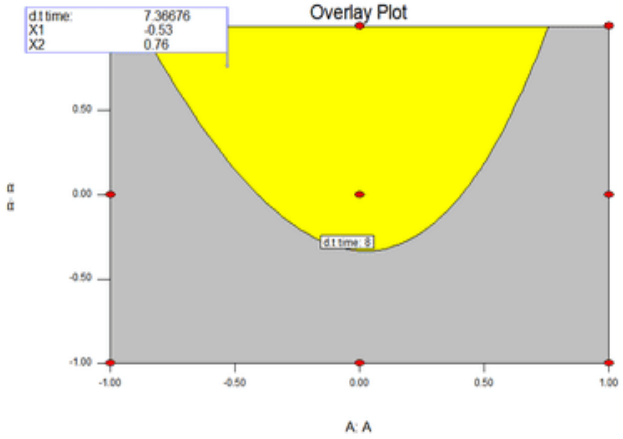


0.10: Contour plot



0.11: 3D Surface plot

Optimization



For validation of check point batch the formulation was prepared which was suggested by Over lay plot.

Table 0.13 : Composition of check point batch

In order to access the reliability of the equation that describes influence of the factors on the response one check point batch was formulated composition of check point batch was:

Factor	Name	Level	Low Level	High Level	Std. Dev.	Actual value
A	Amount of CCS	-0.53	-1.00	1.00	0.000	5.3 mg
B	Amount of MCC	0.76	-1.00	1.00	0.000	133 mg

Table 0.14 : Theoretical result derived by DOE

Response	Prediction	SE Mean	95% CI low	95% CI high	SE Pred	95% PI low	95% PI high
D.T.	7.36663	0.40	6.25	8.48	0.77	5.22	9.52

Evaluation of factorial design by check point batch

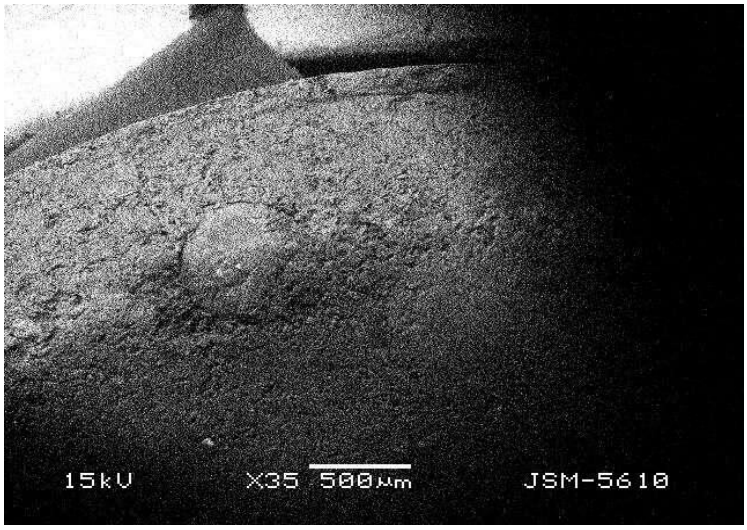
Table 0.15 : Evaluation of factorial design by check point batch

Parameters	Theoretical results	Practical results
DT	7.37 sec	8.12 sec

Value obtained practically was found to be in the limit that was resulted by DOE.

➢ SCANNING ELECTRON MICROSCOPY

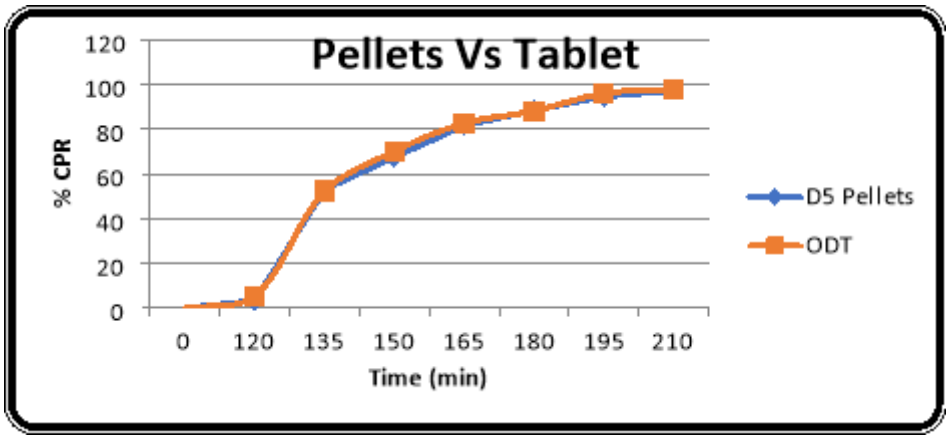
SEM analysis was performed for the optimized formulation of ODT. Images obtained were shown in figure 6.22. SEM of cross section of tablet shows that pellets remain intact even after compression. Coating was not ruptured and drug release was not affected.



0.12: SEM images for ODT

Intactness of the pellets

It was checked by applying similarity factor between dissolution profile of pellets and optimized tablet.

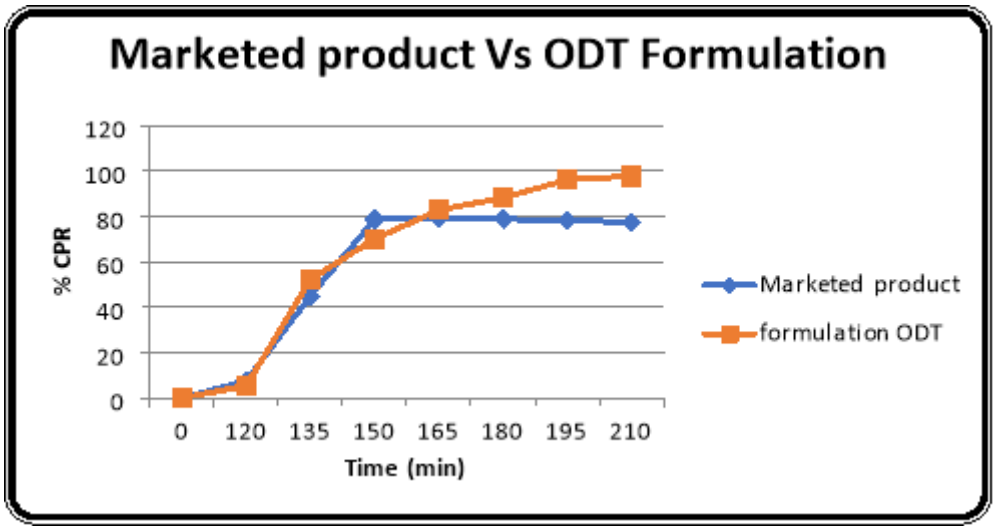


f_2 value 100 shows the two profiles are identical and f2 value of 50 or greater (50-100) ensures sameness or equivalence of the two curves and, thus, the performance of the two products.

For release profiles of tablets and pellets f_2 value was found to be 94.8297, i.e. close to 100 and f_2, so the release profiles of the tablets after compression and pellets before compression shows near to identical profiles. This proposes that pellets were intact after compression into tablet.

Comparison with marketed product

Comparison of release profile of Oral Disintegrating Tablet with Marketed product was done (**Figure0.13**)



0.13: Comparative release study of marketed product with ODT

Stability study of optimized batch

Table 0.16 : Stability study of optimized batch

Time period	In vitro disintegration time (seconds)	Hardness (kg/cm2)	Wetting time (seconds)	% Friability	Drug content
Initial	8.10	3.5	6.49	0.562	162.5 mg
After 1 month	8.13	3.5	7.02	0.544	162.3 mg

Stability condition: 40 ± 0.5°C, 75 ± 0.2% RH

Table 0.17 : comparision with marketed product

Product	%CPR up to 120 min	% CPR 120 onwards					
		135	150	165	180	195	210
Marketed product	7.625	45.01	78.739	79.11	78.86	78.11	77.60
Optimized batch	5.53	52.29	70.14	82.8	88.2	96.13	97.73

CONCLUSION

Finally it was concluded that Oral Disintegrating Tablets of enteric coated Esomeprazole pellets can be prepared using suitable superdisintegrant and pellet intactness after compression can be retained using cushioning agent like MCC. ODTs were formulated by mixing these pellets with croscarmellose sodium, MCC, Magnesium stearate, and Mannogem-EZ (Mannitol). Direct compression method was used to prepare Oral Disintegrating Tablet. Design of Experiment was applied to investigate the effect of variation in concentration of CCS and MCC. Finally Optimized batch of ODTs was prepared characterized for disintegration time and % release.

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