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Formulation, Development and Evaluation of Fast Disintegrating Thin Film of Esomeprazole Magnesium Trihydrate

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ABSTRACT

The objective of present study was to prepare and evaluate orally fast dissolving film of Esomeprazole magnesium trihydrate for the effective management of peptic ulcers to prevent excess amount of acid secretion in the stomach. Drug Esomeprazole was identified using DSC, FTIR and XRD. To improve the water solubility beta cyclodextrin complex of drug in 1:1 milimolar ratio was prepared. Solubility of drug in complex was found to be 7.67±0.52 mg/ml, represents the complex formation between drug and beta cyclodextrin. 21 batches of fast dissolving film of beta cyclodextrin complex were prepared by using different type of film forming agent, different concentration of film forming agent, different type of plasticizers, and different concentration of plasticizer agent. On evaluation, HPMC E15 and propylene glycol was optimized. Most of the films were homogeneous, transparent, colorless, flexible and easily peel out. The prepared films were subjected to characterization for weight variations, thickness, disintegration time, dissolving time, drug release pattern, % moisture loss etc. On drug release kinetic mode study, optimized fast dissolving film following Higuchi model. The scanning electron photomicrograph of the film showed smooth surface with some little pores and without any scratches or transverse striations which is an indication of uniform distribution of drug particles and fast disintegration. Films were stored at different temperature did not show any changes in the physical appearance. Clear, transparent and homogeneous films remained throughout the 90 days but at accelerated temperature conditions, some part of film was breakdown during Peeling out.

Keywords: Esomeprazole Magnesium trihydrate, Oral films, Solvent casting, Propylene glycol, Pharmacokinetics, HPMC E15.

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INTRODUCTION

Esomeprazole Magnesium trihydrate is a substituted benzimidazole; used for the treatment of NSAIDs-associated gastric ulcers, Helicobacter pylori eradication and control of pathological hypersecretory conditions.[1]It is a proton pump inhibitor which reduces acid secretion through inhibition of ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. The primary uses of Esomeprazole Magnesium trihydrate are gastroesophageal reflux disease, treatment of duodenal ulcers caused by H. pylori and treatment of gastrointestinal ulcers associated with Crohn's disease. It is s-isomer of omeprazole and it is a mixture of the S- and R- isomers.[3]It is benzimidazole derivative of H2 receptor blocker. Generally proton pump inhibitors are administered as an inactive prodrug form because these are acid suppressive drugs. These drugs will be degraded when present in the gastric fluids, so enteric-coating is done to avoid the acid degradation. When the enteric coating formulations are passing through the stomach into the proximal intestine the drug will release immediately in duodenum part of intestine by this formulation.[2] For the treatment of NSAIDs-associated peptic ulcer disease, its site of targeting is intestine[5]. Its half-life is 1-1.5 hours and has a bioavailability of 50%-90%.So, it will be degraded by the gastric enzymes when conventional dosage form reaches to the gastric fluids. This problem is avoiding by the enteric coated formulation. It is official in The Merck Index, Martindale.[1] It provides better acid control than current racemic proton pump inhibitors and has a favourable pharmacokinetic profile relative to Omeprazole.[4, 5]It is a drug that blocks excessive amount of acid secretion in the stomach. Esomeprazole magnesium is being studied in the prevention of oesophageal cancer and in the treatment of other conditions, including side effects of chemotherapy. It is a type of anti-ulcer agent. It is also called Esomeprazole and Nexium.[2, 3]

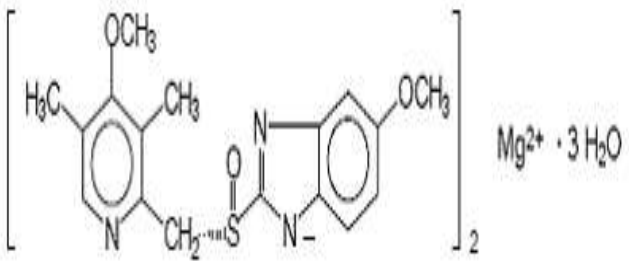

Figure 1: Structure of Drug

MATERIALS AND METHOD

Instruments and Apparatus

A double beam UV-Visible spectrophotometer, spectral band width of 1nm, wavelength accuracy

• ± 0.5nm and a pair of 1cm matched quartz cells was used to measure absorbance of the resulting solution and connected with computer loaded UV Probe software. HPLC, Electronic weighing balance ,Eppendorf tubes,Hot air oven ,Magnetic stirrer ,Cooling centrifuge, Microcentrifuge, Vaccum pump, micropipette, Dissolution apparatus, Lyophilizer ,Vortex type mixture etc. All the glassware's are calibrated before use.

Chemicals and Reagents

Esomeprazole Magnesium Trihydratewas received as a gift samples from Suven Pharmaceuticals (Vadodara, Gujrat, India).All the solvents and chemicals likeHPMC E5, E6, E15, E50, and K100M were gifted by Colorcon Asia Pvt. Ltd, Goa.PEG 200, PEG 400, Propylene Glycol were gifted by Merck, Mumbai. Betacyclodextrin are purchased by Gangwal Chemicals Pvt. Ltd. , Mumbai. Glycerol and Sodium hydroxide were purchased from Thomas Baker Pvt.Ltd., Mumbai All other ingredients used were of analytical grade.

PREFORMULATION STUDIES

Organoleptic characterization

The Organoleptic studies like general appearance like nature, color, odor etc. were performed by visual observations.

Micromeritic properties of drug

The density of a powder is often determined using a measuring cylinder. A 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.[6] By measuring both the untapped volume and the tapped volume the following can be determined:

- Pour (or Bulk) density = mass / untapped volume
- Tapped density = mass / tapped volume
- Hausner ratio = tapped density / pour density
- Carr's Index = (tapped density – bulk density) x 100 / tapped density

Angle of repose (°q):

Angle of repose was determined by measuring the height and radius

of the heap of the powder/granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the horizontal plane. Powder/granule was placed in the funnel and allowed to flow freely. With the help of scale the height and radius of the heap were measured and noted[7]. Average of triplicate readings was computed (n = 3).

Tan ø = h /r

h = height of heap of powder/granule bed.

r = radius of heap of powder/granule bed.

DRUG POLYMER INTRECTION STUDY

Fourier transform infrared spectrum interpretation (FTIR) Study

The Infra red spectroscopy of the sample was carried out to ascertain identity of the drugs. A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3-5 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments). The pellet was mounted in IR compartment and scanned between wave number 3500 – 1000cm^{-1} using a Shimadzu Model 8400 FTIR.

Differential Scanning Colorimetry (DSC)

Differential Scanning Colorimetry (DSC) Was Performed to Determine the Melting Point of Esomeprazole Magnesium trihydrate.The DSC analysis of pure drug Esomeprazole magnesium trihydrate, Physical mixture and optimized formulation were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10°C/min over a temperature range of 20°C to 200°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

HPLC ANALYSIS OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

The HPLC (Shimadzu, Kyoto, Japan) instrument was equipped with two LC-10 ATVP pumps, SPD-10AVP UV-Visible detector, Rheodyne injector with a 50 μL loop. The results were acquired and processed using Shimadzu LC-solution version 6.42 software for data acquisition and processing.

Chromatographic Conditions

Instrument	HPLC (Shimadzu, Kyoto, Japan)
Detector	SPD-10AVP UV-Visible
Software	Shimadzu LC-solution version 6.42
Column	Nucleodur C18
λmax	285 nm
Diluent	ACN
Mobile phase	Buffer: ACN (60:40)
Injection Vol.	20µl
Flow rate	1.0 ml/min

Retention time 3.4 min

PREPARATION OF FAST DISSOLVING FILMS

Preparation of 2-HP-ß-CD complex of Esomeprazole Mg trihydrate using lyophilization

Solid complex of Esomeprazole Mg trihydrate with 2-HP-ß-CD was synthesized by mixing Esomeprazole Mg trihydrate with 2-HP-ß-CD in aqueous phase (pH ~9.0) in 1:1 mili molar ratio. The resultant solutions were stirred for 24 h in an orbit shaker (150 rpm) at 37±1 ◦C. Subsequently, the solutions were lyophilized and collected as solid complex.

Evaluation of 2-HP-ß-CD complex of Esomeprazole Mg trihydrate

Percentage Yield

The prepared Complex was weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the Complex.

% Yield = (Actual weight of Complex/ Total weight of drug and 2-HP-ß-CD) x 100

Determination of Solubility

The solubility of Esomeprazole and Esomeprazole Mg trihydrate 2-HP-ß-CD complex in aqueous phase was determined by preparing the respective saturated solutions. Briefly, 20 mg of Drug was added to 1 ml simulated salivary fluid pH 6.8 and stirred for 24 h in a water Bath shaker at 37 ± 1°C. Subsequently the suspensions were centrifuged, and supernatants were filtered through a 0.22µm membrane filter (MDI, India) and analyzed in an UV/Visible spectrophotometer (Shimadzu, UV1800) at absorption maxima at 301 nm. A similar method was followed for the Esomeprazole Mg trihydrate 2-HP-ß-CD complex. All experiments were carried out in triplicate (n≥3).

Procedure: Solution of polymer was prepared by dissolving 150mg of polymer in 5ml of distilled water on magnetic stirrer with continuous stirring at 1000rpm for 30 minutes. 2-hydroxy propyl beta cyclodextrin complex equivalent to 30 mg of drug was added into polymeric solution. Plasticizer 550 mg of PEG 400, 10 mg citric acid and flavoring agent were added with continued stirring and it was continuing for additional 1hr. After stirring the mixture was allowed to de-aerate for 2 h in vacuum desiccator to remove the bubbles and finally the films were casted in glass Petri plate of area 17.50 sq cm. The films were dried at 35°C for 48 h, cut into dimension of 1 × 1 cm^2 and stored in desiccator until further use.

Preparation of fast dissolving film using different film forming agents

Table 1: Composition of Drug and different film forming agent containing fast dissolving film

S.No.	Ingredients Name	Formulation code							
		B1	B2	B3	B4	B5	B6	B7	B8
1	Esomeprazole Mg trihydrate 2-HP-ß-CD complex	Equivalent to 30 mg of drug							
2	HPMC E5(mg)	150	-	-	-	-	-	-	-
3	HPMC E6(mg)	-	150	-	-	-	-	-	-
4	HPMC E15(mg)	-	-	150	-	-	-	-	-
5	HPMC E50(mg)	-	-	-	150	-	-	-	-
6	HPMC K 100 M(mg)	-	-	-	-	150	-	-	-
7	Methyl Cellulose (mg)	-	-	-	-	-	150	-	-
8	PVP K 30 (mg)	-	-	-	-	-	-	150	-
9	Sodium alginate (mg)	-	-	-	-	-	-	-	150
10	PEG 400 (mg)	550	550	550	550	550	550	550	550
11	Citric acid (mg)	10	10	10	10	10	10	10	10
12	Grape fruit Flavor(mg)	5	5	5	5	5	5	5	5
13	Water (ml)	5	5	5	5	5	5	5	5

Effect of different Concentration of Film forming agents

Table 2: Composition of Drug and different conc. of film forming agent containing fast dissolving film

S.No.	Formulation Code	Drug 2-hydroxy propyl beta cyclodextrin complex amount (mg	Amount of HPMC E 15 (mg)	Amount of PEG 400 (mg)	Citric acid (mg)	Grape fruit flavor(mg)	Water (ml)
1	B9	Equivalent to 30mg of drug	50	550	10	5	5
2	B10		75	550	10	5	5
3	B11		100	550	10	5	5
4	B12		150	550	10	5	5
5	B13		200	550	10	5	5

Preparation of fast dissolving film using different plasticizer agents

Table 3: Composition of different plasticizer agent containing fast dissolving film

S.No.	Ingredients Name	Formulation code			
		B14	B15	B16	B17
1	Esomeprazole Mg trihydrate 2-HP-ß-CD complex	Equivalent to 30 mg of drug			
2	HPMC E15(mg)	150	150	150	150
3	PEG 400 (mg)	550		-	-
4	Propylene glycol (mg)	-	550		-
5	PEG 200(mg)	-	-	550	
6	Glycerol(mg)	-	-	-	550
7	Citric acid (mg)	10	10	10	10
8	Grape fruit flavor(mg)	5	5	5	5
9	Water (ml)	5	5	5	5

Preparation of Fast dissolving film using different concentration of Plasticizer agent

Table 4: Composition of different conc. of plasticizer agent containing fast dissolving film

S.No.	Ingredients Name	Formulation code			
		B18	**B19**	**B20**	**B21**
1	Esomeprazole Mg trihydrate 2-HP-ß-CD complex	Equivalent to 30 mg of drug			
2	HPMC E15(mg)	150			
4	Propylene glycol (mg)	250	450	550	750
7	Citric acid (mg)	10	10	10	10
8	Grape fruit flavor(mg)	5	5	5	5
9	Water (ml)	5	5	5	5

EVALUATION PARAMETERS OF FAST DISSOLVING FILM

Film Forming Capacity

It is the ability of film formers to form desired films. It is categorized according to strip forming capacity such as very poor, poor, average, good, very good, and excellent.[8]

Visual inspection & film formation capacity

The film was evaluated visually for its clarity, transparency and stickiness. If it was satisfactory, then it was taken for further evaluation. If the formed films were not satisfactory they were discarded.

Morphology study:

To study the morphology of films, electron microscopic (SEM) at definite magnification is used.[9]

Surface pH of Film

Deviation of film surface pH on either side from neutral pH may produce discomfort or irritation of the mucosal membrane. Hence attempt was made to keep surface pH as close to neutral as possible.[10] Surface pH of the film was measured using previously reported method. Equally cut strip of 1 × 1 cm^2 was placed in a petri dish and moistened with 1 ml of distilled water for 1 min. The surface pH was measured by micro probe pH electrode.[9] Test was performed in triplicate

Percentage Drug content

Drug content of all the films was determined by UV-spectrophotometric method. For this 1x1 cm^2 strip from the each film was cut and dissolved in 10ml of simulated salivary fluid (pH 6.8). The solution was filtered and absorbance was recorded at 301nm. Drug content was calculated by using standard curve of drug.

In vitro disintegration and dissolving time

In vitro disintegration test is done to find out the actual time required for disintegration of the film. It needs USP disintegration apparatus. Film strip (1 × 1 cm^2) of each batch was placed in 10 ml of simulated saliva, kept mildly agitated by swirling every 10 s. The disintegration time is the time when a film starts to break or disintegrate. The dissolving time is the time when the film

completely dissolves.[11] The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time can be vary depending on the formulation.

Weight Variation

All films were evaluated for their weight variation. Weight variation was evaluated by using electronic balance .The film (1*1 cm^2) was cut and weight of each film was taken in triplicate and the difference in weight variation of film was noted.

Folding Endurance

It is the number of times the film is folded without breaking. The evaluation of films involves determining the folding capacity of the films when subjected to continues extreme condition of folding.[12]It is determined by repeated folding of the film at the same place till it breaks.[10]

Thickness

Film thickness can be calculated by using micrometer screw gauge. It is very essential to determine the uniformity of film thickness.[13]It is directly related to the accuracy of dose in the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers**.** Three readings from all the batches were measured and mean thickness was calculated.

Percentage moisture loss

The formulated films (FDF) were weighed initially and placed in a desiccator containing anhydrous calcium chloride for three days.[14]After three days, the fast dissolving films (FDF) were taken out and weighed again. The percentage moisture loss was calculated according to the formula.

Percentage moisture loss = (initial weight- final weight/ initial weight)*100

Contact angle

The dissolution is dependent on the wetting ability of the film that can be determined by contact angle measurement. The contact angle of the formulations closely ranged between 25°–30° indicative of strongly hydrophilic film surface. If the contact angle is less than 30° the nature of the surface in contact with liquid is termed strongly hydrophilic and facilitates fast dissolution.[6,7] A drop of distilled water was placed on the surface of film using micropipette and images were instantly taken with digital camera. The contact angle was measured on both sides of the drop image and averaged.

Tensile strength:

It is the maximum stress which can be applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strips.[9]

Tensile strength = Load at breakage/ Strip thickness × Strip Width

Percent elongation:

Strain is basically the deformation of strip divided by original dimension of the sample. Normally, elongation of strip increases with the increase in plasticizer content. When stress is applied, a strip sample stretches and this is referred to as strain.

% Elongation = Increase in length/original length×100

Folding endurance:

It is the number of times the film is folded without breaking. The evaluation of films involves determining the folding capacity of the films when subjected to continue extreme condition of folding.[11]It is determined by repeated folding of the film at the same place till it breaks.

Hydration Study (water uptake/ swelling study)

The hydration and swelling behavior of the polymer is crucial for its bioadhesive nature because it is necessary to initiate the intimate contact of the film with the mucosal surface.[14]The rate and the extent of film hydration and swelling also affect the film adhesion and consequently the drug release from the film. The film sample was weighed and placed on a preweighed stainless steel wire mesh. The wire mesh was then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film was determined at regular time intervals until a constant weight was obtained. The hydration ratio of the film was calculated using following formula-

$$\text{Hydration ratio} = W_t - W_0/W_0$$

Where W_t = weight of film at time t and W_0 = weight of film at zero time.

In vitro dissolution test

Dissolution studies of films were performed by USP XXIII type I apparatus. These require 300 ml simulated salivary fluid .The temperature (37±0.5°C) and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically. The dissolution test can be difficult many times while operating with paddle apparatus due to tendency of the strip to float onto the dissolution medium.

Stability studies

The storage conditions to be selected are based upon the climatic zone in which the product is intended to be marketed or for which the product is proposed to be filed for regulatory approval.[13]Final optimized formulation (B20) was subjected to aggravated conditions of temperature and relative humidity by wrapping it in aluminium foil and packaging it in glass container. The films were kept in stability chamber, at 2-8°C, 25-30°C and 45-50°C temperaturefor 3 months. After 1, 2 and 3 months, films were tested.

RESULTS AND DISCUSSION

Organoleptic characterization

The organoleptic studies like general appearance like nature, color, odor etc. were performed by visual observations. Organoleptic properties of drug Esomeprazole magnesium trihydrate found to be as per I.P. monograph

Table 5: Organoleptic properties of drug

Drug	Test	Specification	Observation
Esomeprazole mg trihydrate	Colour	white to slightly colored crystalline powder	white to slightly colored crystalline powder
Esomeprazole mg trihydrate	Odor	odorless	odorless

Micromeritic properties of drug

The density of a powder is often determined using a measuring cylinder. It was found that drug powder was easily flowable but freely.

Table 6: Micromeritic property of Drug powder

S.No	Name of Ingredients	Bulk Density	Tapped density	Cars index	Hausner's ration	Angle of repose
1	Esomeprazole mg trihydrate	0.17±0.001	0.21±0.001	19.27±0.005	1.23±0.003	39.2±0.003

*Mean of 3 determinations ± SD

DRUG POLYMER INTRECTION STUDY

Fourier transform infrared spectrum interpretation (FTIR) Study

The Infra red spectroscopy of the sample was carried out to ascertain identity of the drugs.

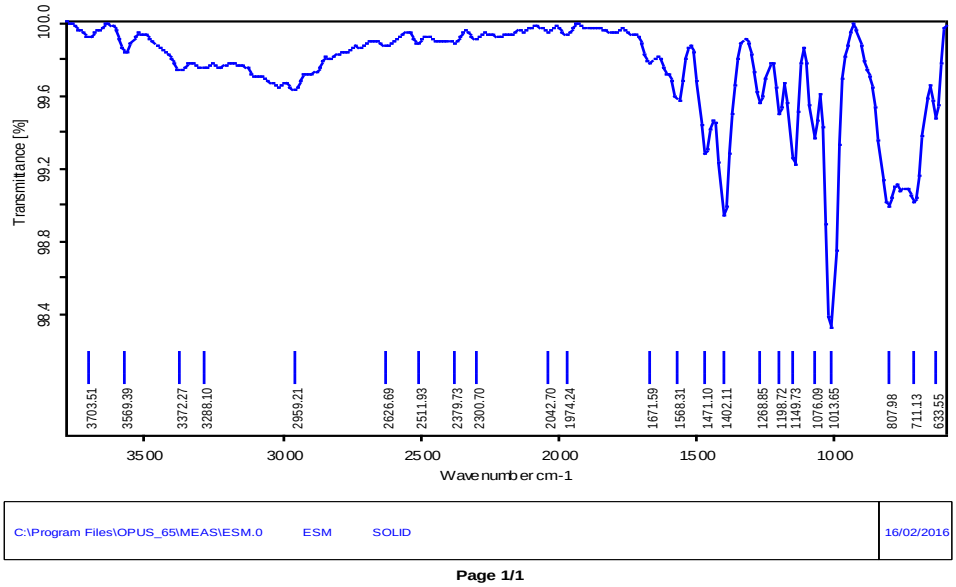

Figure 2: FTIR Spectrum of Pure Drug

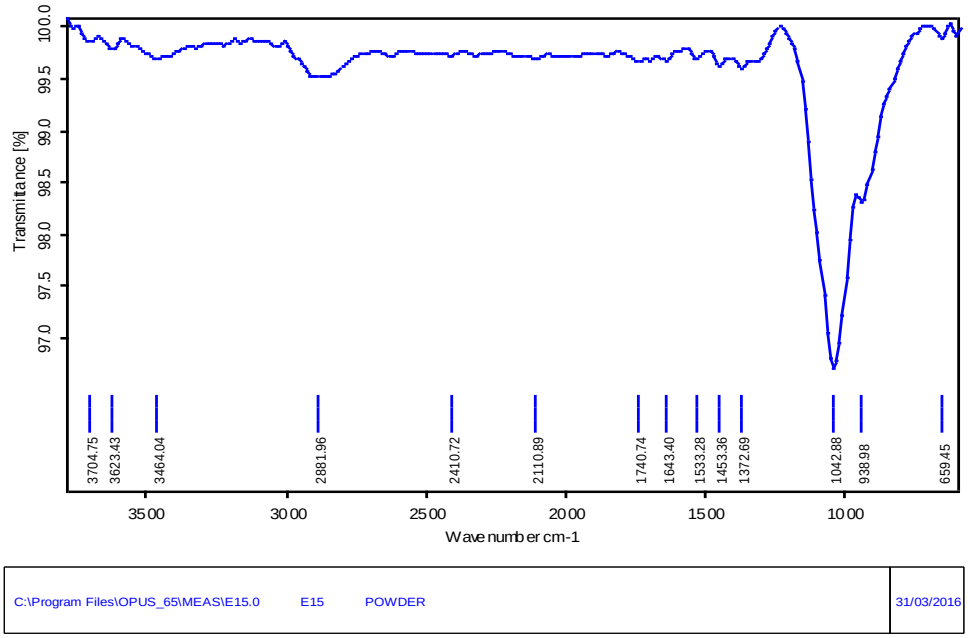

Figure 3: FTIR Spectrum of HPMC E15

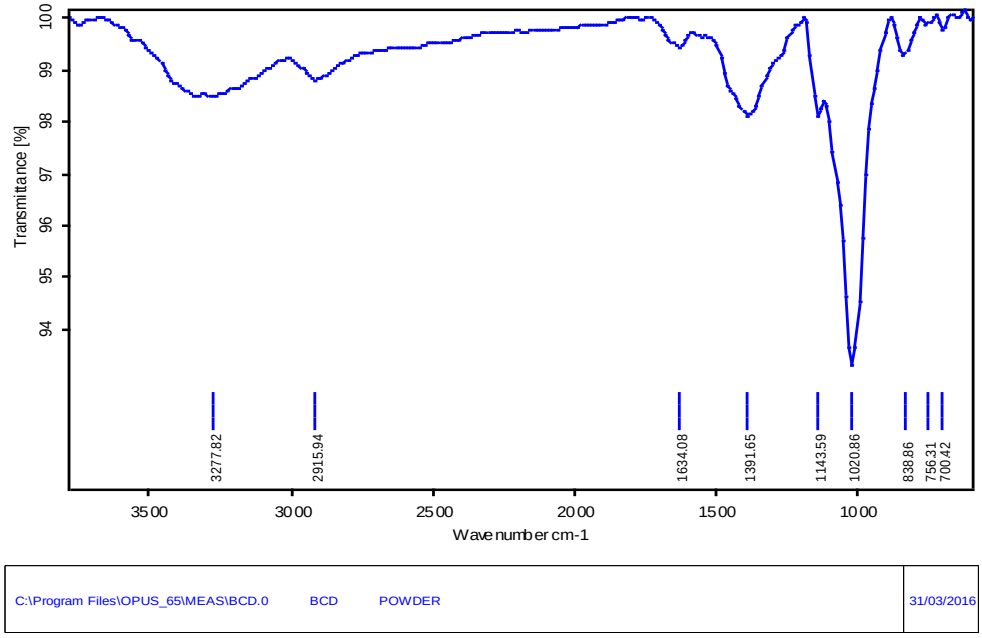

Figure 4: FTIR Spectrum of beta cyclodextrin complex of Drug

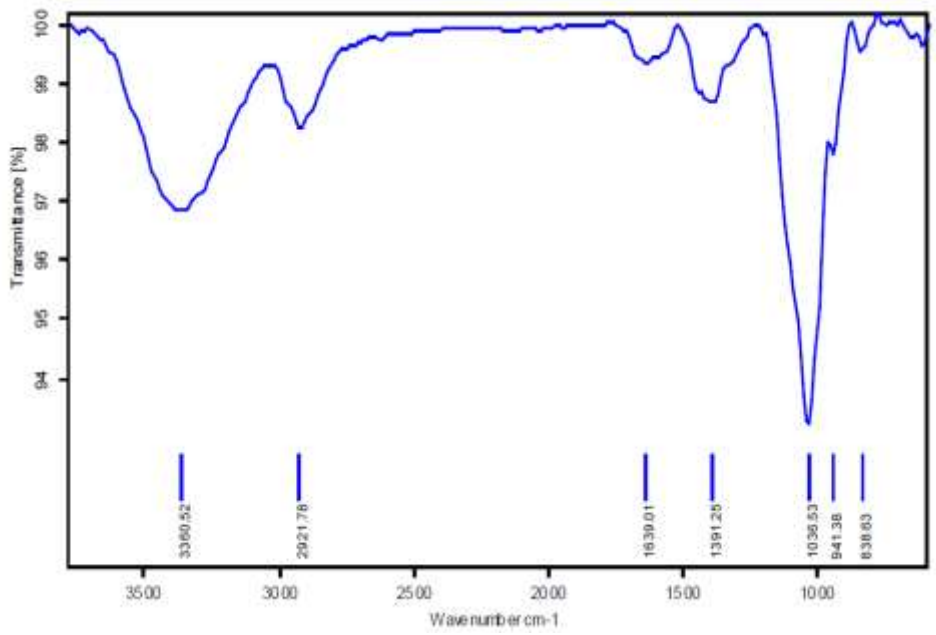

Figure 5: FTIR Spectrum of fast dissolving film of beta cyclodextrin complex of Drug

Interpretation:

FTIR spectrum of pure drug shows peak of different functional groups like 1076.09 (S=O stretching), 1198.72 (C-O stretching), 1402.11 (N-H bending), 1568.31, 3288.10 (C=N stretching). While FTIR spectrum of HPMC E 15 shows following peaks like 1042 (Stretching vibration of C-O-C group), 1372 (υ C-O-C and symmetric bending of methoxy group), 1453 Assymmetric bending vibration of methyl group in CH_3O, 3464.04 O-H stretching vibration, intermolecular H-bonding. FTIR peaks of pure drug and optimized formulation are almost all equal which indicates no interaction of the polymer with drug in its formulation.

Table 7: Interpretation of FTIR (cm^{-1})

Type of vibrations	Observed Frequencies(cm^{-1})	Reported Frequencies(cm^{-1})
C-H bending (Aromatics)	838.63	900-690
C-O stretching(Ethers)	1036.53	1300-1000
C-N stretching (Amines)	1391.25	1350-1000
N-H bending (Amines)	1639.01	1640-1550
C-H stretching (Alkanes)	2921.78	3000-2850
N-H stretching (Amines)	3360.52	3500-3100

The compatibility study for drugs and various excipients were performed by FTIR spectrophotometric analysis. It is done to examine Drug –Excipients and Drug –Polymer interaction. IR spectra of pure drug were carried out for qualitative compound identification. The peaks obtained in the spectra of each physical mixture correlates with the peaks of drug spectrum. So all ingredients are compatible with the drugs. FTIR spectrum of pure drug and optimized

formulation are almost all equal which indicates no interaction of the polymer with drug in its formulation. So all ingredients are chemically compatible with each others in film.

Differential Scanning Colorimetry (DSC)

Differential Scanning Colorimetry (DSC) Was Performed to Determine the Melting Point of Esomeprazole Magnesium trihydrate

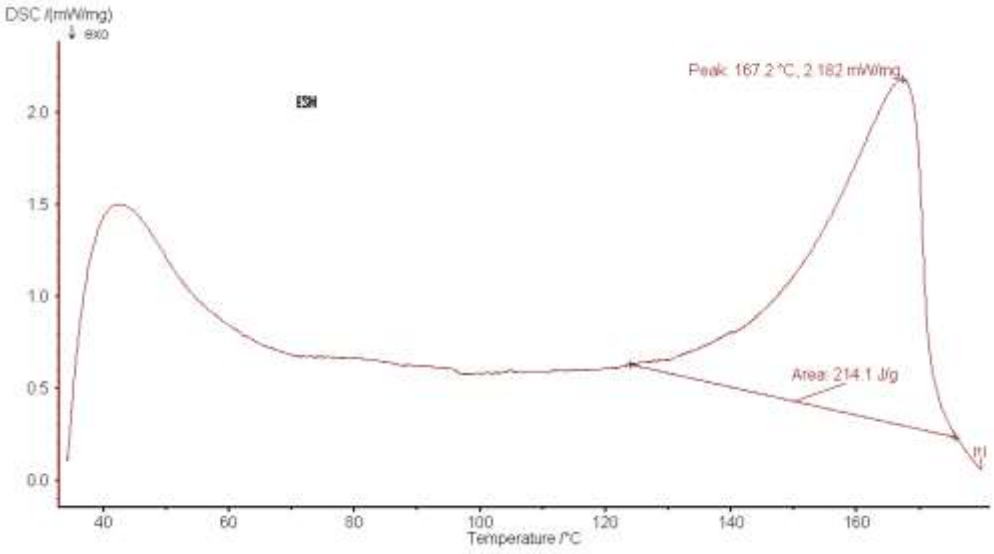

Figure 6: DSC of pure drug

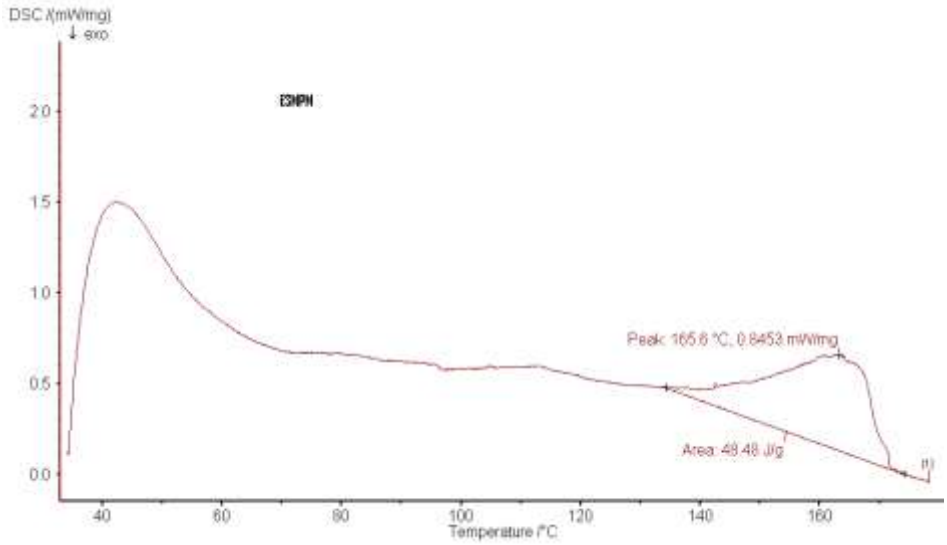

Figure 7: DSC thermogram of physical mixture

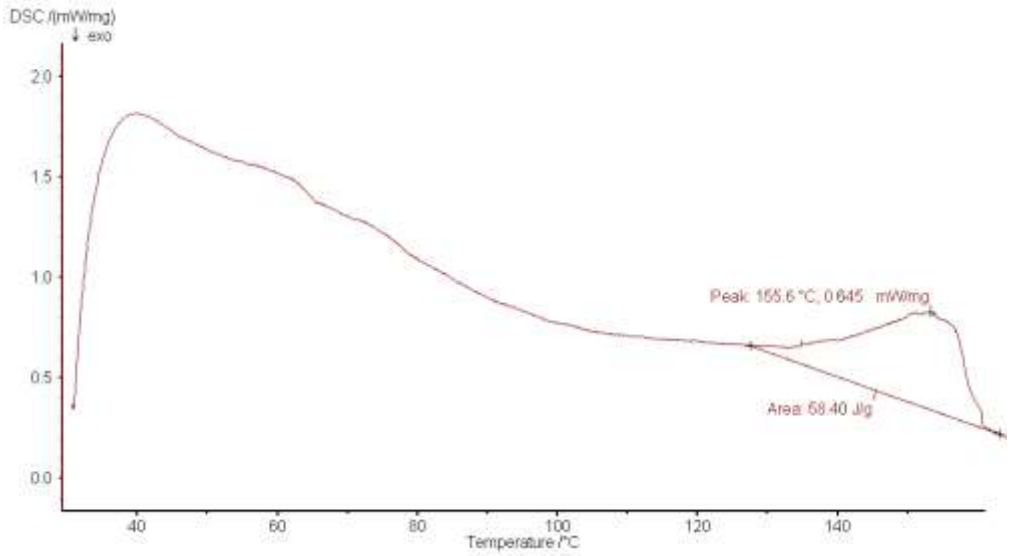

Figure 8: DSC thermogram of optimized formulation

Interpretation of DSC Data

The DSC thermograms of the pure drug exhibited a sharp exothermic peak in the range of 167.2°C (∆H=214.1J/g) corresponding to the melting point of the drug. The thermograms of Physical mixture exhibited the exothermic peaks at 165.6°C which is almost equal to pure drug. The thermogram of optimized formulation exhibit exothermic peak at 155.6°C (∆H=58.40J/g) These shifting of drug peak is due to complexation of drug with 2-Hydroxy propyl-β-cyclodextrin in optimized formulation.

From these observations it is quite obvious to conclude that the drug has not lost its properties and does not show any type of interactions with the polymers and excipients. . The appearance of a peak corresponding to the melting point of pure drug was also evident in the thermogram of the physical mixture. Optimized formulation showed their identical peaks at defined temperature range .The results revealed a negligible change in the melting point of pure drug in the presence of polymeric materials .Presence of all peaks indicates that all ingredients are compatible with drug and there is no interaction takes place between drug and other excipients used in the formulation.

HPLC Analysis of Esomeprazole Mg trihydrate

The HPLC (Shimadzu, Kyoto, Japan) instrument was equipped with two LC-10 ATVP pumps, SPD-10AVP UV-Visible detector, Rheodyne injector with a 50 μL loop. The results were acquired and processed using Shimadzu LC-solution version 6.42 software for data acquisition and processing.

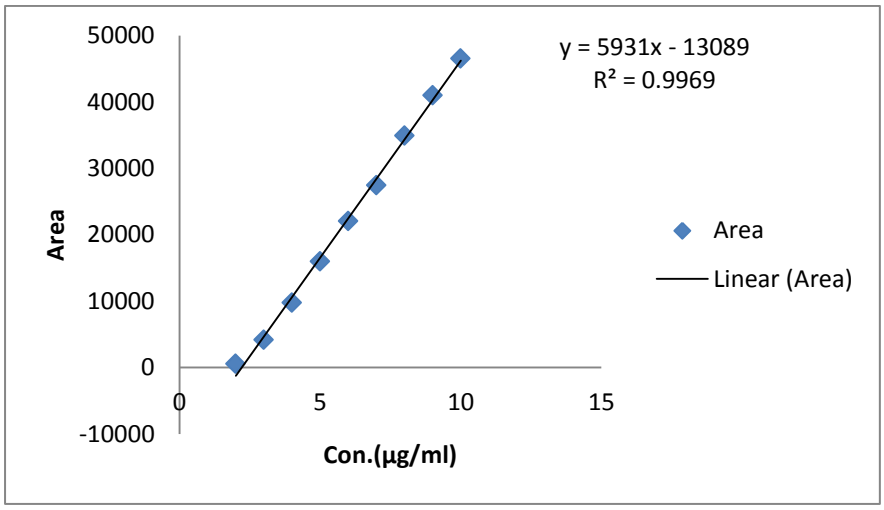

Figure 9: Standard Calibration curve of Drug

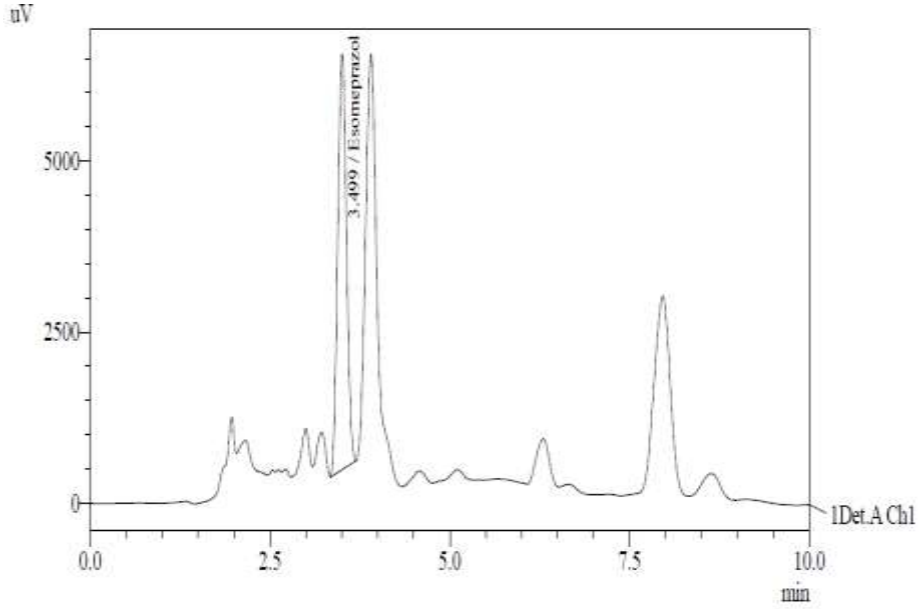

Figure 10: HPLC Chromatogram of Drug

Result:

A satisfactory separation and good peak symmetry for Esomeprazole magnesium trihydrate was obtained with a mobile phase of mixture containing Buffer: ACN (60:40), at a flow rate of 1.0 ml/min. Quantification was achieved with PDA detection at 285 nm based on peak area. Retention time: 3.4 minutes. It is a measure of time taken for a solute to pass through a chromatography column.

PREPARATION OF FAST DISSOLVING FILMS

Preparation of 2-HP-ß-CD complex of Esomeprazole Mg trihydrate using lyophilization

Solid complex of Esomeprazole Mg trihydrate with 2-HP-ß-CD was synthesized by mixing Esomeprazole Mg trihydrate with 2-HP-ß-CD in aqueous phase (pH ~9.0) in 1:1 mili molar ratio

Table 8: Evaluation parameters of 2-HP-ß-CD complex of Drug

S.No	Formulation	% yield	Solubility
1	2-HP-ß-CD complex of Esomeprazole Mg trihydrate	89.09±0.032.	7.67±0.52 mg/ml

*Mean of 3 determinations ± SD

Solubility analysis was done to ensure the effect of cycloencapsulation of Drug in 2-HP-ß-CD cavity. We observed significantly enhanced solubility of the complex of Drug with 2-HP-ß-CD (7.67±0.52 mg/ml) compared to free Drug (1.5±0.88mg/ml).

Figure 11: Image of Fast Dissolving Film by solvent-casting Method

EVALUATION PARAMETERS OF FAST DISSOLVING FILMS

Morphology study:

To study the morphology of films, electron microscopic (SEM) at definite magnification is used.[9]

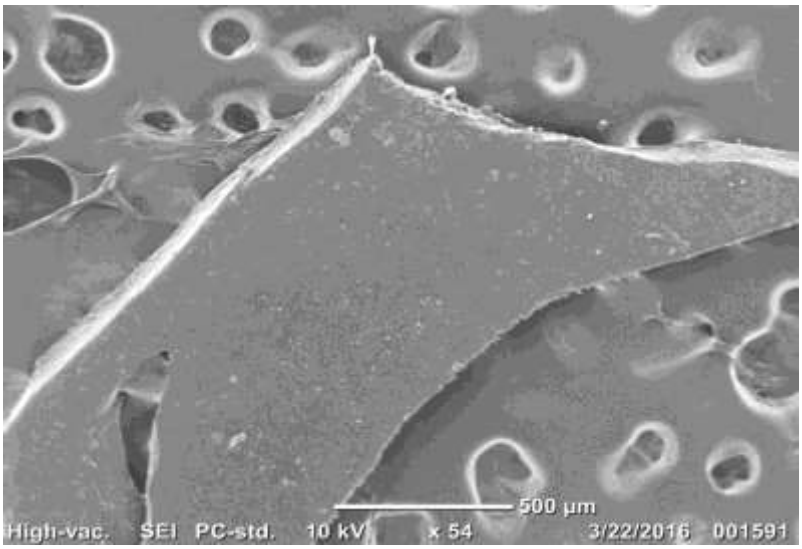

Figure 12: SEM image of optimized film formulation

The prepared film containing Esomeprazole mg trihydrate was clear and colorless. The scanning electron photomicrograph of the film showed smooth surface with some little pores and without

any scratches or transverse striations which is an indication of uniform distribution of drug particles

Visual inspection & film formation capacity

Table 9: Visual Inspection of different fast dissolving film

S.No.	Formulation Code	Visual Inspection & Film formation & Surface roughness, flexibility	Film Forming capacity
1	B18	Brittle and Fragmented easily During Peeling out	Low
2	B19	Homogeneous, transparent, colorless, both sides smooth Transparent, flexible and Easily peel out	Better
3	B20	Homogeneous, transparent, colorless, both sides smooth Transparent, flexible and Easily peel out	Better
4	B21	Film was not Dry completely it took more time for as compare to other film	Film was not dry completely.

From the table it was found that B18 and B21 formulations was not selected for further study because B18 was break down during peeling out from Petri dish and B21 was not dry completely.

Table 10: Physical Characterization of Fast Dissolving Film Formulation(Formulation B18-B21)

Formulation Code	Visual Inspection & Film formation & Surface roughness, flexibility	Surface pH	Percentage Drug Content	Disintegration time (Sec)	Dissolving time (Sec)	Weight variation (mg)
B18	Low	7.7±0.005	97.56±0.034	_	_	_
B19	Better	7.5±0.009	98.76±0.098	50±0.023	61±0.032	21.54±0.036
B20	Better	7.4±0.004	99.23±0.067	48±0.078	60±0.066	22±0.018
B21	Film was not dry completely	_	_	_	_	_

Table 11: Result of Thickness, Contact angle and Mechanical properties of Fast dissolving Film

Formulation Code	Folding Endurance	Thickness ((µm)	Percentage Moisture loss	Contact angle	Tensile strength (N/mm^2)	Percent elongation	Elastic modules
B18	-	-	-	-	-	-	-
B19	More then 5	85±0.66	1.86±0.011	28.2°±0.016	_	_	_
B20	More then 5	98±0.54	1.80.008	27.9°±0.005	2.74×10^{-4}	35.8%	3.56±0.77
B21	-	-	-	-	-	-	-

*Mean of 3 determinations ± SD

Table 14: In-vitro Disintegration time and Percentage Drug content of B20 fast dissolving film at different temperature

S.No.	Formulation code	In-vitro Disintegration time (sec.)			Percentage Drug Content		
		30 Days	60 Days	90 Days	30 Days	60 Days	90 Days
1	B20fast dissolving film at refrigerator temperature 2-8°C (45% RH)	48±0.078	49±0.045	51±0.067	99.12±0.090	98.55±0.032	97.11±0.045
2	B20fast dissolving film at 25-30°C (60% RH) temperature	48±0.078	50±0.022	50±0.078	99.09±0.012	98.43±0.056	97.90±0.034
3	B20fast dissolving film at 45-50°C (75% RH) temperature	48±0.078	49±0.065	51±0.043	98.99±0.043	98.12±0.012	97.34±0.023

*Mean of 3 determinations ± SD

From different evaluation parameters HPMC E15 gives Better Penetration Of Water , Smooth Surface, Better Contact Angel, Less Tackiness, Low Moisture Absorption, Better Drug Content, less disintegration and dissolving time as Compare To other Film Forming agents. Propylene glycol had more polarity as compare to other Plasticizers due to its higher dielectric constant. Water will penetrate more into propylene glycol containing formulation as compare to other film. High dielectric constant made propylene glycol more hydrophilic in nature. Due to high dielectric constant it has low disintegration time as well as dissolving time thus we select Propylene glycol for preparation of fast dissolving film. So, fast dissolving film (B20) containing HPMC E15 and propylene glycol can be optimized as final formulation.

In vitro dissolution test (formulation B20)

Dissolution studies of films were performed by USP XXIII type I apparatus. This requires 300 ml simulated salivary fluid .The temperature (37±0.5°C) and the rotation speed was 50 rpm.

Comparison of percentage drug release of fast dissolving film, market preparation and pure drug

Table 12: Percentage Drug release of fast dissolving film, market preparation and Pure Drug

Time(min.)	Percentage Drug release of FDF (B20)	Percentage Drug release of Pure Drug	Percentage Drug release of Market Preparation
0	0±0	0±0	0±0
0.25	10.26±0.043	1.73±0.66	1.96±0.23
0.5	22.15±0.062	5.88±0.52	6.92±0.61
1	30.11±0.011	9.23±0.89	15.23±0.38
2	49.5±0.092	18.23±0.71	28.84±0.84
3	59.53±0.56	21.92±0.6	30.80±0.96
4	73.73±0.73	22.96±0.55	33.57±0.74
5	82.61±0.33	24.92±0.26	45.11±0.33
6	94.5±0.49	32.19±0.49	51.80±0.1
8	100.26±0.26	36.80±0.32	59.88±0.09

*Mean of 3 determinations ± SD

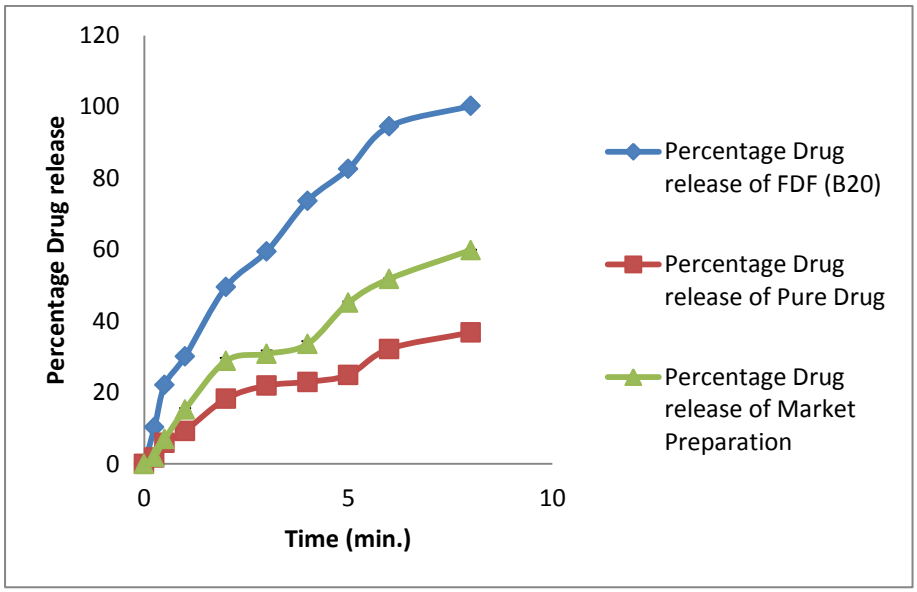

Figure 13: Comparison of in-vitro dissolution study of fast dissolving film, market preparation and pure drug

Discussion:

From the table it was found that fast dissolving film of Esomeprazole magnesium trihydrate release 100.26% drug ,Market preparation release 59.88% drug and pure drug release 36.80% in 8 minutes.So,fast dissolving film showed fast dissolution and drug release as compare to market preparation formulation and pure Drug.

Stability studies

The films were kept in stability chamber, at 2-8°C, 25-30°C and 45-50°C temperaturefor 3 months. After 1, 2 and 3 months, films were tested.

Table 13: pH study of formulation B 20 fast dissolving film at different temperature

S.No.	Formulation	Initial pH	pH after 30 days	pH after 60 days	pH after 90 days
1	B20 fast dissolving film at refrigerator temperature 2-8°C (45% RH)	7.4±0.004	7.47±0.004	7.67±0.003	7.80±0.007
2	B20 fast dissolving film at 25-30°C (65% RH) temperature	7.4±0.004	7.6±0.002	7.7±0.002	7.7±0.001
3	B 20 fast dissolving film at 45-50°C (75% RH) temperature	7.4±0.004	7.5±0.008	7.7±0.006	7.7±0.004

*Mean of 3 determinations ± SD

Films were stored at different temperature did not show any changes in the physical appearance. Clear, transparent and homogeneous films remained throughout the 90 days but at accelerated temperature conditions, some part of Film was Breakdown during Peeling out. Therefore, films were stable at room temperature and refrigerated temperature Condition.

CONCLUSION

The fast dissolving oral thin films containing Esomeprazole magnesium trihydrate were prepared for the first time. The film prepared using HPMC E15 and Propylene glycol revealed excellent uniformity and stability of drug and rapidly disintegrated in water. Plasticizer used Propylene glycol resulted inbetter films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance , flexibility etc.In SEM image, pores were seen that favours fast disintegration of Fast dissolving film. On study drug release kinetic model, formulation B20 fast dissolving film following Higuchi model .On stability study, there is no change in the appearance of film. pHand in-vitro disintegration time was slightly increases. In conclusion, significance of orally fast dissolving film includes do not require water for administration, accuracy of dosage, alternative to liquid dosage form, ideal for pediatric and geriatric patient and rapid onset of action. Due to such wide significance, this drug delivery system may leads to better patient compliance and ultimate clinical output.

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