IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
June 2018 Vol.:12, Issue:3

Formulation and Evaluation of Orodispersible Tablet of Esomeprazole

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ISSN 2349-7203
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Submission: 20 May 2018
Accepted: 27 May 2018
Published: 30 June 2018

Keywords: Esomeprazole, orodispersible tablet, direct compression, Sodium Starch Glycolate, Cross Carmellose Sodium, Chitosan.

ABSTRACT

The objective of the present work was formulation and evaluation of orodispersible tablet of Esomeprazole. Orodispersible tablets of Esomeprazole were prepared by direct compression method using croscarmellose sodium, sodium starch glycolate, and chitosan as Superdisintegrants. In this work microcrystalline cellulose and mannitol are investigated as diluents. The compatibility of a drug with excipients was studied by FTIR spectroscopy. Precompression and post-compression parameters were evaluated. It was found that increasing concentration of Superdisintegrant influences the disintegration of a tablet. The tablets disintegrated within minutes. The optimum release of drug around a period of 30 min was shown by formulation F8. And also the formulation F8 shows lower disintegration time and wetting time compared to other formulations. Formulation f8 contain croscarmellose sodium as Superdisintegrant at higher concentration. The 'n' value of optimized formulation indicated that the drug release follows anomalous Quasi -Fickian release. It was confirmed from the stability studies that the optimized formulation remained stable at 40^{o}C and 75% relative humidity.

INTRODUCTION

[1]Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms is available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a different type of drug delivery mechanisms. These classical/ modern dosage forms have some advantages and disadvantages. Therefore, the development of an ideal drug delivery system is a big challenge to the pharmacist in the present scenario. In order to get the desired effect, the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form, a thorough study of the physicochemical principles that govern a specific formulation of a drug should be subjected.

[2] Majority of the drug product is administered through oral route because it is the most convenient route with several advantages such as ease of ingestion, pain avoidance, versatility and most importantly better patient compliance. Also, the solid delivery system does not require a sterile condition for manufacture so less expensive compared to other dosage forms. This may lead to the development of the variety of oral dosage form however one of the most important is an orally disintegrating system.

[3]Nearly 35% of the general population, especially the elderly patients and children suffer from dysphasia or difficulty in swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non -co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water.

[4]These problems are overcome by the development of a novel drug delivery systems (NDDS) which enhance safety and efficacy of drug molecule and to achieve better patient compliance. One such approach is "Oral dispersible Tablet", which disintegrate or dissolve in saliva and are swallowed without water. As tablet disintegrates in the mouth, this could enhance the

clinical effect of a drug through pregastric absorption from the mouth, pharynx, and esophagus. This leads to an increase in the bioavailability by avoiding first pass liver metabolism. In similar fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of Langerhans cells makes oral mucosa tolerant to potential allergens.

[5]The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Most of the orodispersible tablet include certain superdisintegrants and taste masking agents.

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. And hence used for the treatment of various ulcers.

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8% with the optimum concentration of about 4% although in many cases 2% is sufficient. Disintegration occurs by the rapid uptake of water followed by rapid and enormous swelling. Croscarmellose sodium as a disintegrant for tablets (wet granulation and direct compression), capsules and granules at a concentration of 2 - 5%.Chitosan is a natural Superdisintegrant used for the formulation of orodispersible tablet.

The aim of the present work was to formulate and to evaluate the orodispersible tablets of an anti-ulcer drug by direct compression method using a blend of superdisintegrants to achieve a safe, rapid and effective dosage form with enhanced drug dissolution and oral bioavailability as compared to its conventional dosage forms.

MATERIALS AND METHODS:

MATERIALS:

Esomeprazole was supplied from Yarrow Chem Products, Mumbai. All other excipients and solvents used were of an analytical or pharmaceutical grade.

METHODS:

Compatibility studies using FT-IR Spectroscopy

The pure drug, drug, and polymer were prepared and scanned from 1500-800 cm-1 in FTIR spectrophotometer. The FT-IR spectrum of the obtained sample of drug and polymer were compared with the standard functional group frequencies of Esomeprazole, sodium starch glycolate, croscarmellose sodium, chitosan and microcrystalline cellulose. The compatibility between the drug, polymer was evaluated using FTIR peak matching method.

Preparation of Standard Calibration Curve Esomeprazole[6]

Accurately weighed 10mg of Esomeprazole and transferred to the 100ml volumetric flask. To this added few drops of ethanol to dissolve the drug. Then made up to100ml with phosphate buffer pH 6.8 to get a stock solution of concentration 100µg/ml. From the stock solution aliquots of 1, 2, 3, 4, 5ml of solutions were transferred to separate 10ml standard flask and made up to the volume with phosphate buffer pH6.8 to get the concentrations of 10, 20, 30, 40, 50 µg/ml respectively. The absorbance of resultant solutions was measured at 315nm by UV spectrophotometer. A graph of concentration Vs absorbance was plotted.

Preparation of orodispersible tablet of Esomeprazole by a direct compression method

Orodispersible tablet of Esomeprazole was prepared by direct compression method, using various superdisintegrants such as sodium starch glycolate, croscarmellose sodium, chitosan in different ratios and directly compressible microcrystalline cellulose as diluent and mannitol to enhance the mouthfeel.

- All the ingredients were weighed and passed through sieve no 80 separately prior to mixing
- Then the ingredients were mixed in geometrical order

- The mixed blend of excipients was compressed using a concave face round tooling on multistation tablet compression machine.

Twelve batches F1 to F12 were prepared with various proportions of super disintegrants and microcrystalline cellulose shown in table.

Table 1: Formulation of Esomeprazole orodispersible tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Esomeprazole(mg)	40	40	40	40	40	40	40	40	40	40	40	40
Sodium Starch Glycolate(mg)	5.48	11.48	17.48	23.48	-	-	-	-	-	-	-	-
Cross carmellose sodium(mg)	-	-	-	-	5.48	11.48	17.48	23.48	-	-	-	-
Chitosan (mg)	-	-	-	-	-	-	-	-	5.48	11.48	17.48	23.48
Microcrystalline cellulose(mg)	103.31	97.31	91.31	85.31	103.31	97 31	91.31	85.31	103.31	97.31	91.31	85.31
Mannitol (mg)	45.74	45.74	45.74	45.74	45.74	45.74	45.74	45.74	45.74	45.74	45.74	45.74
Talc (mg)	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65
Magnesium stearate (mg)	1.82	1.82	1.82	1.82	1.82	1.82	1.82	1.82	1.82	1.82	1.82	1.82
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of Esomeprazole orodispersible tablets

- **Precompression parameters**

1) Bulk density[7]

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk

density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per mL (g/mL) although the international unit is kilograms per cubic meter (1 g/mL = 1000 kg/m3) because the measurements are made using cylinders. It may also be expressed in grams per cubic centimeter (g/cm3). The bulking properties of a powder are dependent upon the preparation, treatment, and storage of the sample, i.e., how it was handled.

Apparent bulk density (ρ_b) was determined by pouring previously weighed blend into a graduated cylinder, then bulk volume (V_b) was noted. The apparent bulk density was calculated using the formula.

$$\rho_b = M/V_b$$

Where M – Weight of powder

2) Tapped density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing a powder sample. After observing the initial powder volume or weight, the measuring cylinder or vessel is mechanically tapped, and volume or weight readings are taken until little further volume or weight change is observed.

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated by using formula.

$$\rho_t = M/V_t$$

3) Angle of repose[8]

The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°. The morphology of the material affects the angle of repose; smooth, rounded sand grains cannot be piled as steeply as can rough, interlocking sands

An angle of repose was determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The inverse tangent of this ratio is the angle of repose. The radius of the heap(r) was measured and the angle of repose (Θ) was calculated using the formula.

$$\Theta = \tan^{-1}(h/r)$$

Table 2: Flow property based on an angle of repose

An angle of Repose (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

4) Compressibility index[9]

The Carr index or Carr's Compressibility Index is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. The Carr index is calculated by the formula

$$C = 100[(V_b - V_t)/V_b]$$

Where V_b is the volume that a given mass of powder would occupy if let settled freely, and V_t is the volume of the same mass of powder would occupy after "tapping down". It can also be expressed as,

$$C = 100[1-(\rho_b/\rho_t)]$$

Where ρ_b is the freely settled bulk density of the powder and ρ_t is the tapped density of the powder. The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder.

Table 3: Flow property based on compressibility index

% Compressibility index	Flow property
<10	Excellent
11-15	Good
16-20	Fair –aid not needed
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

5) Hausner ratio[10]

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner. The Hausner ratio is calculated by the formula.

$$H_R = \rho_t/\rho_b$$

Where ρ_b is the freely settled bulk density of the powder and $\rho_t$is the tapped density of the powder. The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it. The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. Lower Hausner ratio (<1.25) indicates better flow property than higher ones (>1.25).

- **Post-compression parameters**

1) Physical appearance

The shape of the tablet can be dimensionally described, monitored and controlled.

2) Organoleptic properties

It includes color and odor of the prepared tablet.

3) Weight variation test[11]

The tablet designed to contain a specific amount of drug in a specific amount of tablet formula. The weight of the tablet made was routinely measured to ensure that a tablet contains the proper amount of drug.

The weight variation test was carried out in order to ensure uniformity in the weight of tablets in a batch. First, the total weight of 10 tablets from each formulation is determined and the average is calculated. The individual weight of each tablet is also determined to find out the weight variation

Table 4: Weight variation specification as per USP

The average weight of tablets(mg)	Maximum percentage difference allowed
130 or less	±10
130-324	±7.5
More than 324	±5

4) Thickness[12]

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using the filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. The thickness of the tablets was measured using Vernier caliper. It is expressed in mm.

5) Hardness test[13]

A hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation, and handling before usage depends on its hardness. The hardness of the tablet indicates its tensile strength and is measured in terms of load/pressure required to crush it when placed on its edge. The hardness has the influence on disintegration and dissolution times and is such as a factor that may affect bioavailabilities

The force required to break the tablets is measured in kilograms and a crushing strength of 4kg is usually considered to be minimum for satisfactory tablets. Oral tablets normally have a

hardness of 4-10kg, however hypodermic and chewable tablets are usually much softer (3kg) and some sustained-release tablets are much harder 10-20kg.

6) Friability[14]

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. Friability of the tablet was checked by using Roche Laboratory friabilator. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm dropping the tablets at a distance of 6 inches with each revolution. A pre-weighed sample of 5 tablets was placed in a friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed, the loss in the weight of the tablet is the measure of friability and is expressed in percentage as:

% Friability = [(Initial Weight-Final Weight)/Initial Weight]*100

7) Wetting time[15]

A piece of tissue paper (10.75 × 12 mm) folded twice was placed in a petri dish (d = 6.5 cm) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was carefully placed on the surface of tissue paper and the time required for simulated saliva to reach the upper

Surface of the tablet was noted as the wetting time.

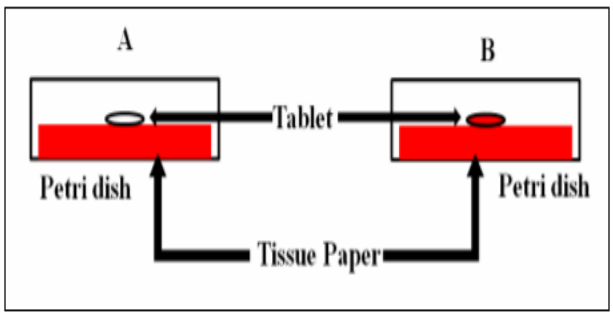


Figure 1: Wetting time measurement A)Before absorbance of water B) After absorbance of water

8) Water absorption ratio[16]

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed. Water absorption ratio, R was determined using following equation,

$$R = 100^{*} Wa\text{-}Wb/Wb$$

Where Wa = weight of tablet after water absorption Wb = weight of tablet before water absorption.

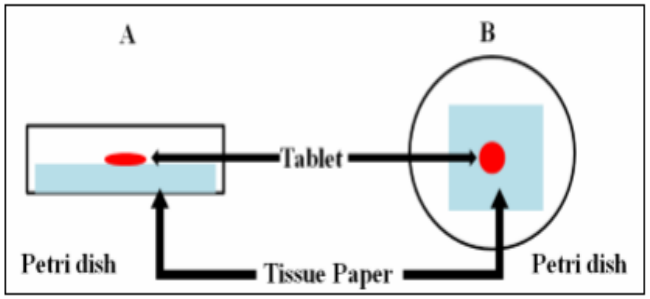


Figure 2: Water absorption ratio A) frontal view B) ventral view

9) Content uniformity test[17]

The tablets were tested for their drug content uniformity. At random 5 tablets were weighed and powdered. The powder equivalent to 10 mg of esomeprazole was transferred to 100 ml volumetric flask and added few ml of ethanol to dissolve the drug. The solution was shaken thoroughly. Then the volume is adjusted to 100ml with phosphate buffer pH 6.8. The absorbance of the solutions was measured at 315 nm. The concentration of the drug was calculated from the standard curve of esomeprazole. Then percentage drug content was determined.

10) *In-vitro* disintegration studies[18]

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH

6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus measured and recorded.

11) *In-vitro* dissolution studies[19]

➢ **Procedure for dissolution :**

The release rate of esomeprazole from orodispersible tablets was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37±0.5 °C and was maintained throughout the experiment. A sample (2ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 5, 10, 15, 20, 25 and 30min. The samples were replaced with fresh dissolution medium of the same quantity. An absorbance of these solutions was measured at 315nm using a Shimadzu UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetics of *in-vitro* drug release[20]

The results obtained from *in-vitro* release studies were attempted to be fitted into various mathematical models as follows:

1. Cumulative percent drug released Vs. Time (Zero order kinetics)

2. Log cumulative percent drug retained Vs. Time (First order kinetics)

3. Cumulative percent released Vs. A square root of Time (Higuchi model)

4. Log cumulative percent drug released Vs. Log Time (Korsmeyer-Peppas model)

In Peppas model, the value of ‘n’ characterizes the release mechanism of a drug as described in Table5

Table 5: Interpretation of diffusional release mechanism

Release exponent	Diffusion release mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non – fickian) diffusion
0.89- 1.0	Case II transport (Zero order release)
>1.0	Super case II transport

12) Stability studies[21]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and enables recommended storage conditions and shelf lives to be established. Stability studies were conducted according to ICH guidelines 40˚C ± 2˚C/ 75% ± 5% RH to test the physical and chemical stability of the developed formulations. Throughout the study, the optimized formulation of an orodispersible tablet was stored in well-closed containers. The stored formulations were evaluated for hardness, drug content, disintegration time and *in-vitro* drug release at a predetermined time interval.

RESULTS AND DISCUSSION:

Compatibility studies

FTIR spectroscopy of Esomeprazole

The FTIR spectrum of esomeprazole was shown below which complies with standard functional group frequencies

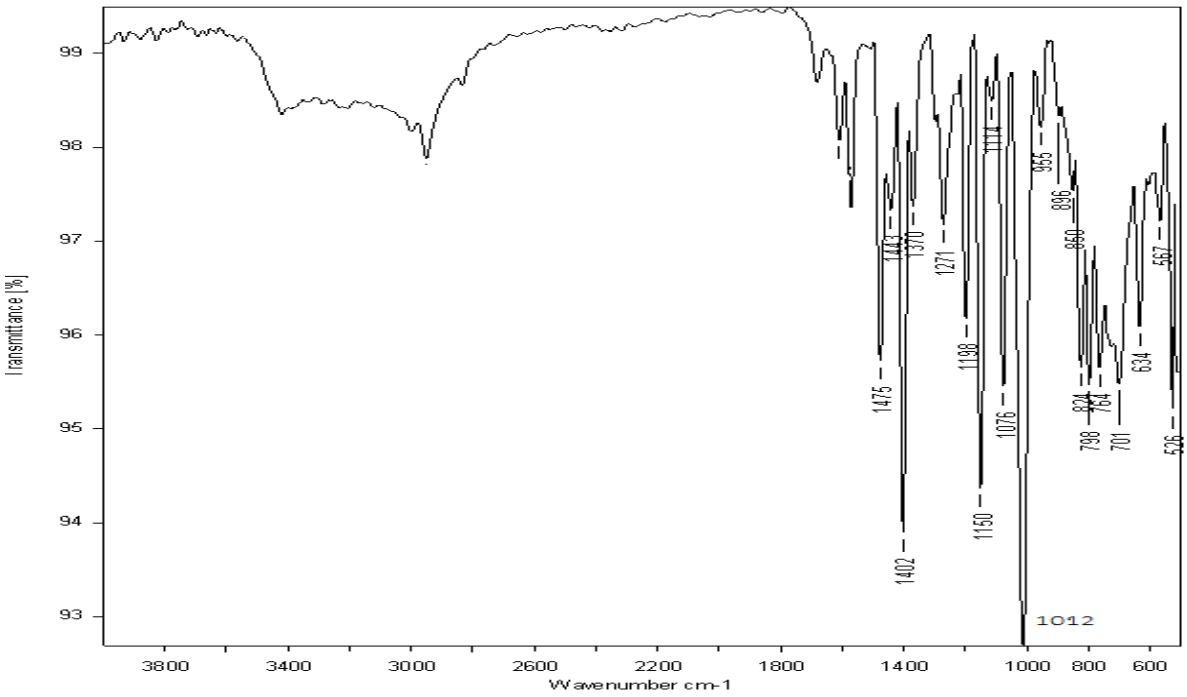


Figure 3: FTIR Spectrum of Esomeprazole

Table 6: IR frequencies of Esomeprazole

Functional group	**Characteristic wave number(cm^{-1})**	**Esomeprazole- observed wave number(cm^{-1})**
C-C stretching (in a ring)	1500-1400	1402
C-N stretching	1360-1150	1150
C-O-C stretching	1100-900	1076
S=O	1050-800	1012

The peaks analyzed in the Table indicate the most characteristic frequencies of the functional group of Esomeprazole which are C-C stretching, C-N stretching, C-O-C stretching, the presence of S=Oetc. were confirmed compared to the reported frequencies

Compatibility between drug and polymer

The FTIR spectrum of Esomeprazole with excipients are shown in figure

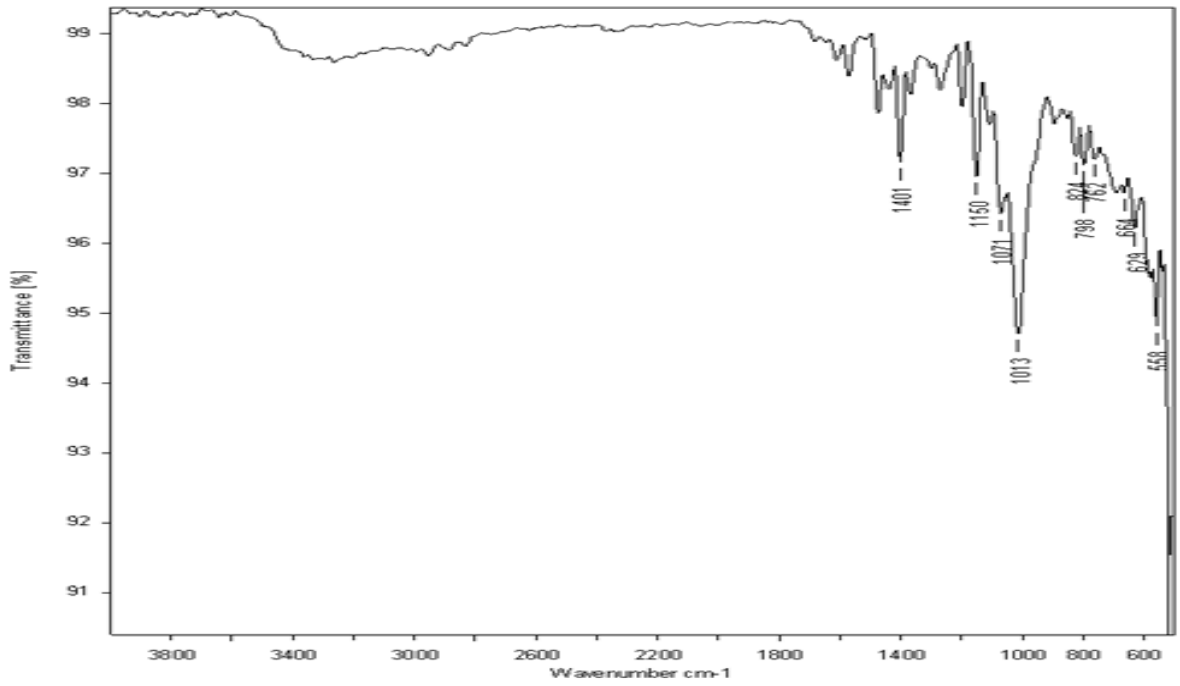


Figure 4: FTIR spectrum of the physical mixture of Esomeprazole+Croscarmellose sodium+ Microcrystalline cellulose

Table7: IR frequencies of Esomeprazole+Croscarmellose sodium+ microcrystalline cellulose

Functional group	Characteristic wave number(cm^{-1})	Esomeprazole observed wave number(cm^{-1})	Esomeprazole - excipient mixture wave number(cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1150
C-O-C stretching	1100-900	1076	1071
S=O	1050-800	1012	1013

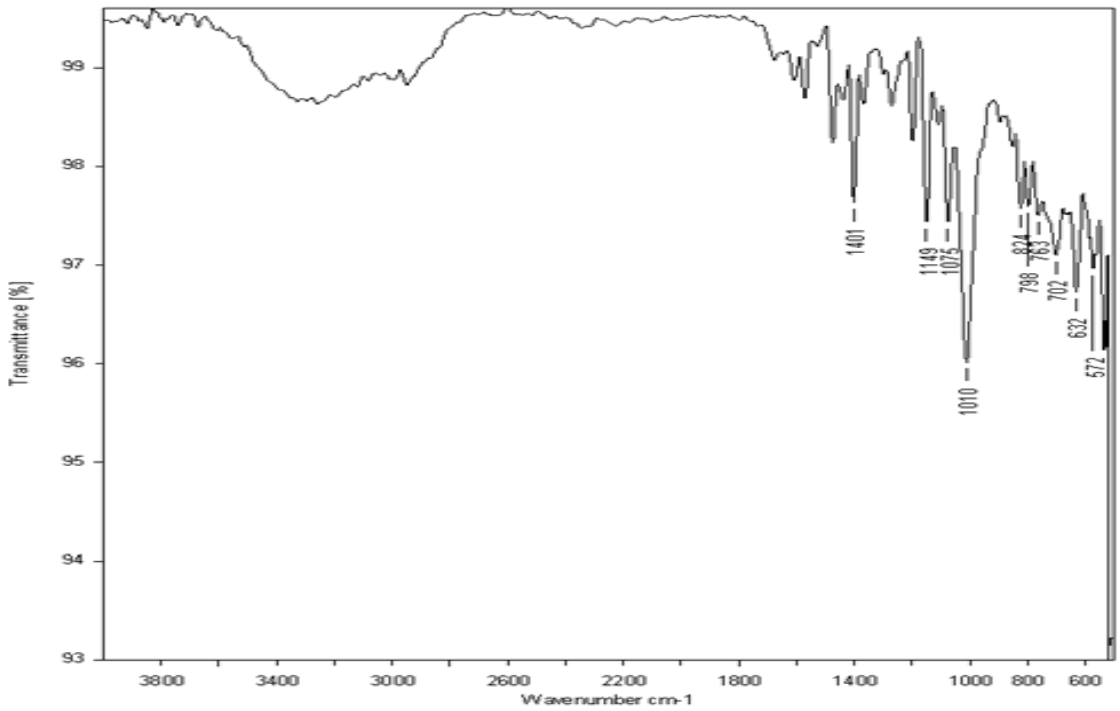


Figure 5: FTIR spectrum of the physical mixture of Esomeprazole+ Sodium starch glycollate + Microcrystalline cellulose

Table 8: IR frequencies of Esomeprazole+ Sodium starch glycollate + Microcrystalline cellulose

Functional group	Characteristic wave number (cm^{-1})	Esomeprazole observed wave number (cm^{-1})	Esomeprazole - excipient mixture wave number (cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1149
C-O-C stretching	1100-900	1076	1075
S=O	1050-800	1012	1010

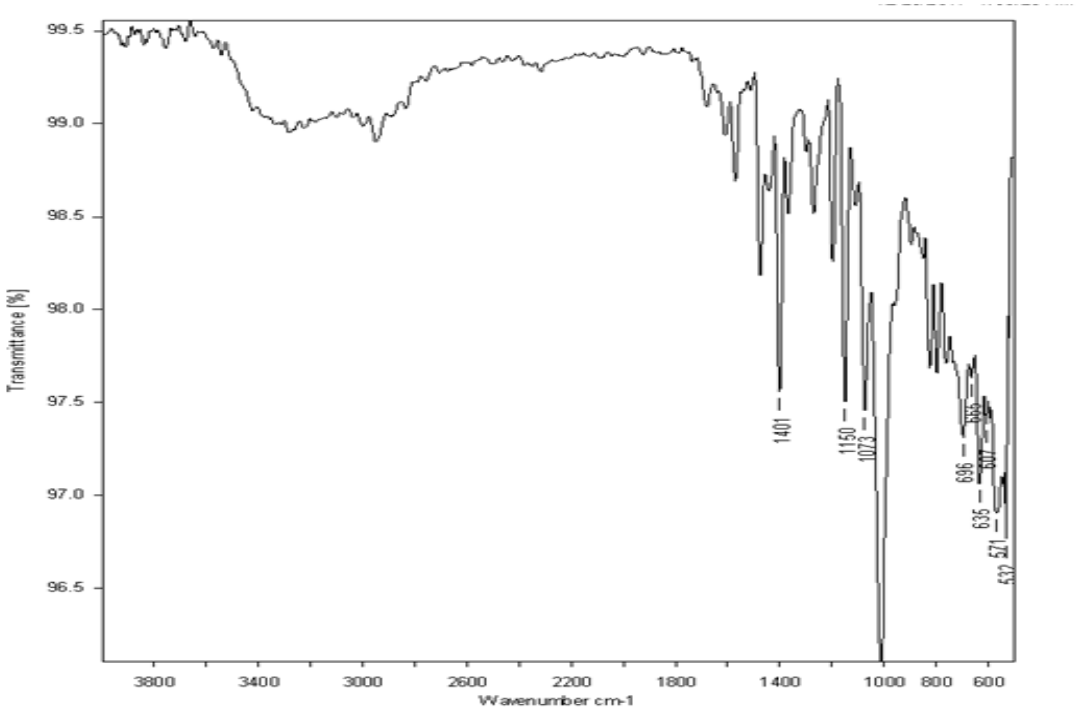


Figure 6: FTIR spectrum of the physical mixture of Esomeprazole + Chitosan + Microcrystalline cellulose

Table 9: IR frequencies Esomeprazole + Chitosan + Microcrystalline cellulose

Functional group	Characteristic wave number(cm^{-1})	Esomeprazole observed wave number(cm^{-1})	Esomeprazole -excipient mixture wave number(cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1150
C-O-C stretching	1100-900	1076	1073
S=O	1050-800	1012	1012

The compatibility between drug-polymer was carried out by using FT-IR peak matching method. All major peaks present in the spectrum of a pure drug were observed in the spectrum of the drug-polymer mixture. This suggests that the drug remains in its normal structure and hence this confirmed the absence of any chemical interaction or complexation between drug and polymers.

Preparation of standard calibration curve of Esomeprazole

The calibration curve was found to be linear in the range of 10-50 µg/ml at λmax at 315nm.

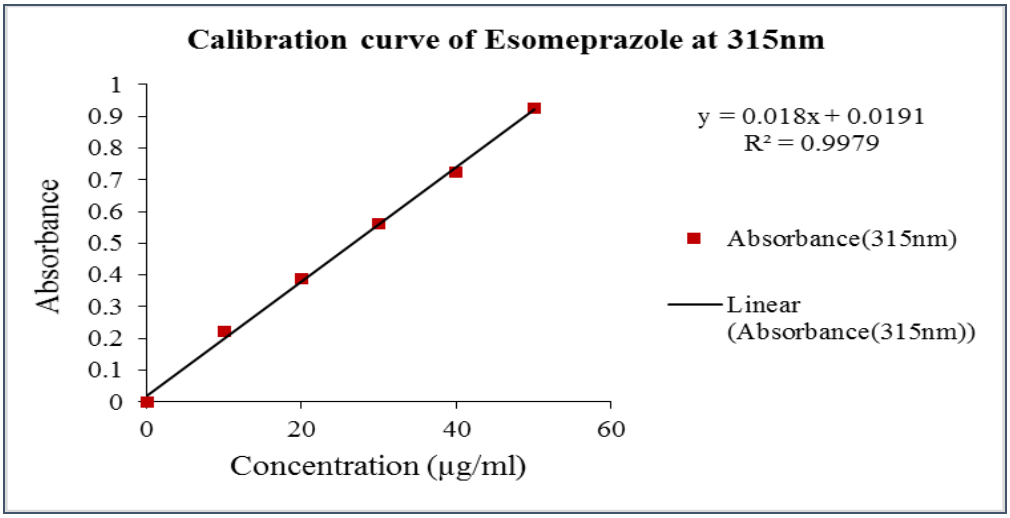


Figure 7: Standard calibration curve of Esomeprazole in phosphate buffer pH 6.8 at 315 nm

FORMULATION OF ESOMEPRAZOLE ORODISPERSIBLE TABLET

Orodispersible tablet of Esomeprazole was prepared by direct compression method, using various superdisintegrants such as Sodium starch glycolate, Croscarmellose sodium, Chitosan in different ratios and directly compressible Microcrystalline cellulose as diluent and Mannitol to enhance the mouthfeel.

- **Precompression parameters**

Table 10: Physical characteristics evaluation of powder mixture (n=3)

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	An angle of repose (°)	Compressibility index (%)	Hausner's ratio
F1	0.312±0.002	0.390±0.008	32.55±0.25	20±0.230	1.25±0.003
F2	0.297±0.018	0.368±0.010	33.72±0.28	19.23±0.115	1.23±0.002
F3	0.340±0.004	0.416±0.001	33.04±0.19	18.18±0.196	1.22±0.012
F4	0.326±0.006	0.394±0.005	33.54±0.17	17.39±0.479	1.21±0.015
F5	0.312±0.010	0.375±0.009	34.10±0.11	16.60±0.146	1.20±0.005
F6	0.310±0.011	0.387±0.002	33.85±0.29	20±0.188	1.25±0.013
F7	0.312±0.005	0.371±0.017	33.35±0.35	16±1.050	1.19±0.007
F8	0.283±0.009	0.330±0.006	34.40±0.18	14.28±0.986	1.16±0.010
F9	0.389±0.016	0.518±0.003	34.32±0.31	25±1.137	1.33±0.016
F10	0.364±0.013	0.478±0.015	34.75±0.14	23.80±0.956	1.31±0.004
F11	0.356±0.007	0.440±0.004	34.44±0.23	19.04±0.543	1.23±0.017
F12	0.318±0.019	0.418±0.013	34.46±0.36	24±0.678	1.31±0.011

- **Post-compression parameters**

Physical appearance and organoleptic properties

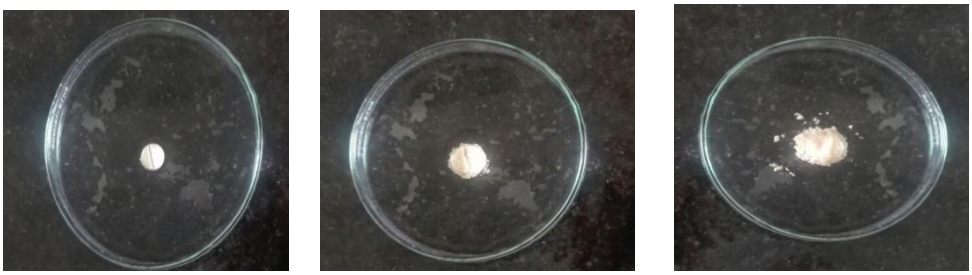
All the prepared tablet were round and standard convex in shape with off-white color

Table 11: Physicochemical evaluation of Esomeprazole orodispersible tablet (n=3)

Formulation code	Average weight (gm)	Thickness (mm)	Hardness (kg/cm^2)	%Friability	Wetting time (sec)	Water absorption ratio (%)	Content uniformity (%)	Disintegration time(sec)
F1	201±1.15	2.78±0.12	2.2±0.17	0.932±0.16	13.22±0.11	65.00±0.20	92.58±0.24	63.75±0.141
F2	204±2.05	2.57±0.24	3.2±0.15	0.866±0.28	12.85±0.15	71.42±0.40	93.94±0.11	63.00±0.163
F3	199±1.17	2.53±0.36	2.4±0.18	0.943±0.11	12.62±0.10	77.27±0.30	91.64±0.18	54.25±0.210
F4	204±1.13	2.72±0.14	1.2±0.10	0.834±0.24	12.45±0.15	80.00±0.63	94.45±0.15	38.00±0.155
F5	201±2.58	2.87±0.18	2.8±0.12	0.816±0.30	13.14±0.14	76.19±0.48	93.94±0.19	41.50±0.259
F6	204±2.31	2.93±0.39	2.6±0.19	0.910±0.29	12.64±0.17	83.33±0.32	90.80±0.16	39.25±0.168
F7	201±1.97	2.36±0.50	3.0±0.21	0.934±0.15	12.08±0.20	85.00±0.44	97.65±0.25	32.50±0.187
F8	197±2.10	2.73±0.19	2.3±0.25	0.934±0.26	10.71±0.13	90.90±0.11	98.19±0.16	24.50±0.103
F9	199±3.15	2.11±0.29	2.8±0.09	0.866±0.33	24.02±0.11	57.5±0.17	96.28±0.23	68.12±0.230
F10	207±1.48	2.54±0.64	2.4±0.28	0.919±0.17	22.7±0.16	60.00±0.21	91.97±0.38	65.25±0.298
F11	207±1.29	2.83±0.10	2.4±0.13	0.778±0.14	22.64±0.19	61.90±0.27	90.24±0.30	59.19.±0.246
F12	201±2.11	2.04±0.25	3.1±0.14	0.834±0.18	20.79±0.12	78.94±0.16	94.45±0.26	40.28±0.310

For weight variation test, ten tablets were randomly selected from each formulation and evaluated. The average weight of each formulation values are almost uniform and was within the specifications. Thus all the formulations passed the test for weight variation. The thickness value of tablet ranges from 2.04 to 2.93mm. The hardness values range from 1.2 to 3.2kg/cm^2. The friability values of tablets ranged from 0.778 to 0.943 %. All the values are below 1% indicating that the tablets of all formulations are having good friability property. Wetting time of formulations are ranged from 10.71 to 24.02sec. The water absorption ratio of the formulations ranges from 57.5 to 90.90% respectively. The content uniformity of the

prepared formulations values ranged from90.24 to 98.19%. The disintegration time of formulations values ranged from 24.50 to 68.12sec.



0 sec **6 sec** **12 sec**

18 sec **24 sec**

Figure 8: Disintegration of prepared formulation F8

***In-vitro* dissolution studies**

Table 12: Percentage cumulative drug release data for formulations F1-F4, n=3

Time (min)	F1 %CDR	F2 %CDR	F3 %CDR	F4 %CDR
0	0	0	0	0
1	31.86±0.31	32.13±0.24	40.54±0.18	31.53±0.42
2	36.25±0.15	37.08±0.16	45.05±0.13	40.54±0.56
5	41.20±0.23	50.54±0.67	58.56±0.61	59.55±0.38
10	43.94±0.46	57.68±0.55	67.57±0.52	68.56±0.17
15	47.79±0.59	70.04±0.39	76.58±0.40	73.07±0.29
20	59.33±0.11	74.99±0.48	85.59±0.23	87.90±0.45
25	79.38±0.18	82.68±0.14	90.10±0.09	91.25±0.10
30	86.52±0.25	87.90±0.10	92.35±0.27	94.60±0.21

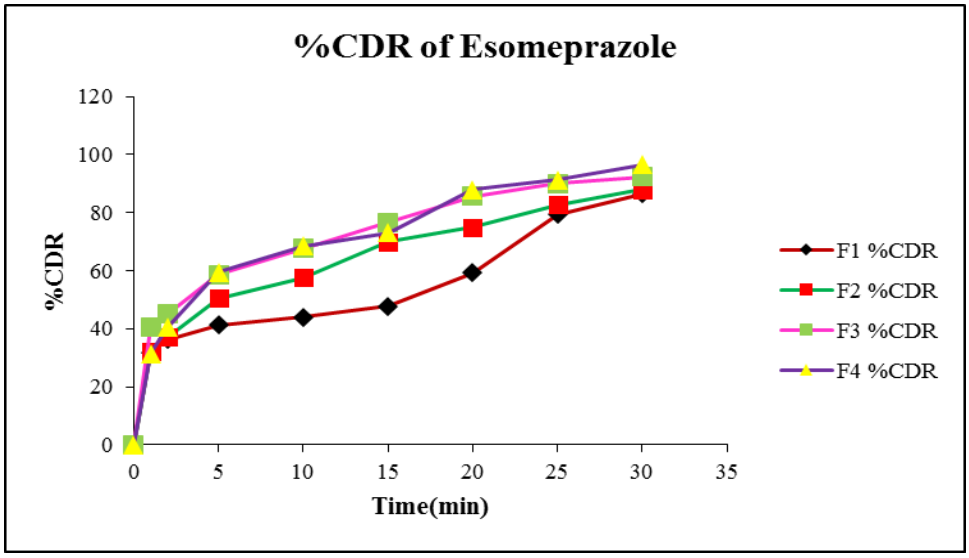


Figure 9: Percentage cumulative drug release profile of formulations F1-F4

Table 13: Percentage cumulative drug release data for formulations F5-F8, n=3

Time (min)	F5 %CDR	F6 %CDR	F7 %CDR	F8 %CDR
0	0	0	0	0
1	27.03±0.34	30.06±0.16	35.94±29	29.25±0.40
2	40.54±0.11	42.56±0.41	46.40±0.68	32.25±0.57
5	49.55±0.57	54.06±0.26	66.71±0.14	45.05±0.17
10	54.06±0.49	60.81±0.19	69.19±0.27	70.45±0.14
15	58.56±0.23	72.08±0.53	73.34±0.38	80.57±0.33
20	67.57±0.16	78.83±0.21	81.85±0.45	89.05±0.19
25	76.58±0.70	86.53±0.10	91.45±0.12	94.05±0.64
30	85.59±0.25	93.35±0.29	96.85±0.08	97.07±0.59

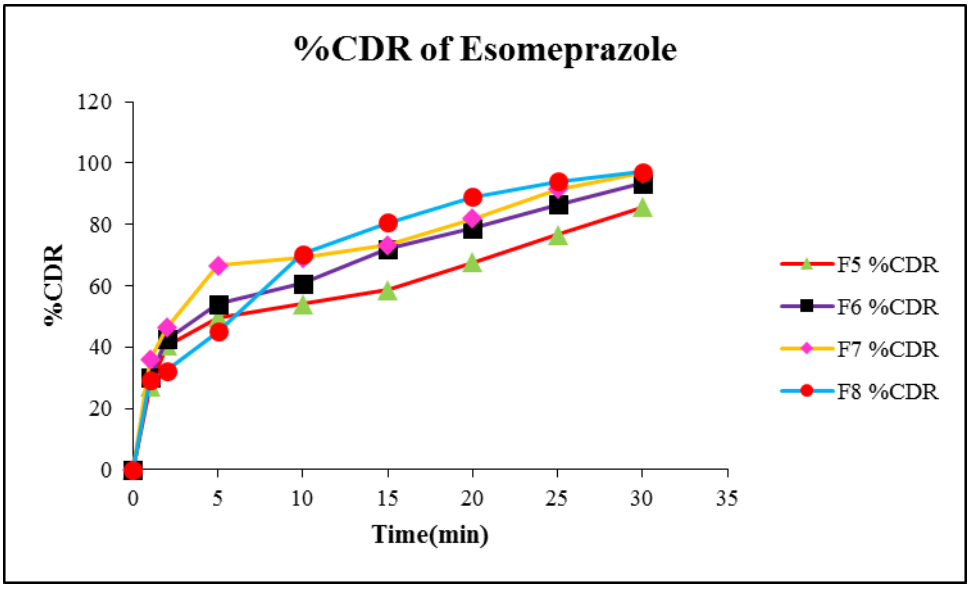


Figure 10: Percentage cumulative drug release profile of formulations F5-F8

Table 14: Percentage cumulative drug release data for formulations F9-F12, n=3

Time (min)	F9 %CDR	F10 %CDR	F11 %CDR	F12 %CDR
0	0	0	0	0
1	30.45±0.29	35.15±0.17	31.03±0.07	31.31±0.35
2	35.15±0.18	39.27±0.23	36.80±0.13	38.18±0.16
5	46.97±0.43	50.26±0.51	47.20±0.60	56.58±0.27
10	66.74±0.15	58.50±0.33	53.28±0.28	67.30±0.25
15	71.97±0.38	60.43±0.25	66.74±0.17	72.51±0.71
20	76.36±0.56	71.14±0.43	73.61±0.69	79.66±0.53
25	82.84±0.49	82.68±0.10	85.15±0.51	82.95±0.42
30	95.01±0.11	90.10±0.19	88.17±0.23	91.19±0.09

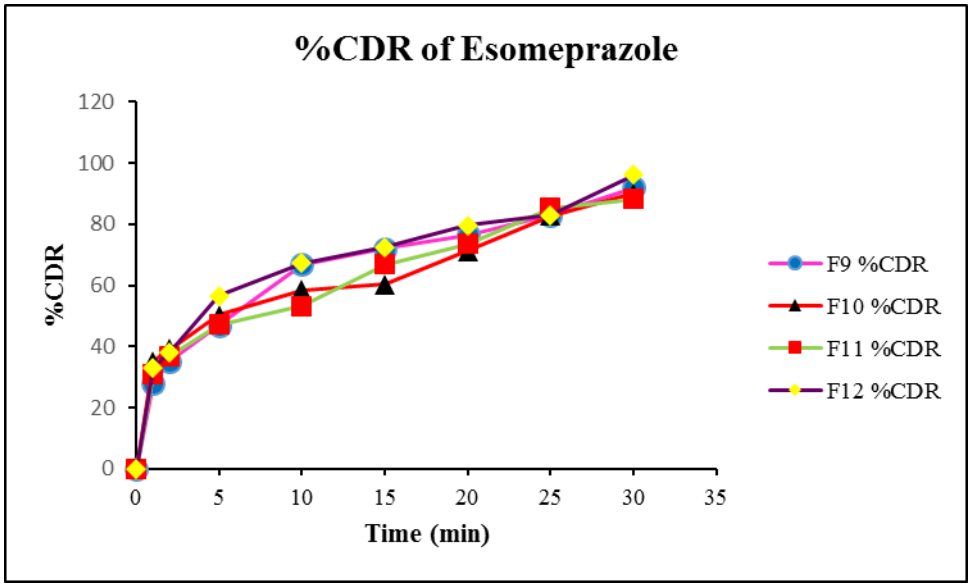


Figure 11: Percentage cumulative drug release profile of formulations F9-F12

Kinetics of *in-vitro* drug release

The *in-vitro* drug release data of all the esomeprazole orodispersible tablet formulations were subjected to the goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release.

Table 15: Kinetic study of formulations

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Peppas	
				R^2	N
F1	0.850	0.879	0.894	0.815	0.261
F2	0.824	0.971	0.959	0.991	0.298
F3	0.760	0.971	0.924	0.992	0.253
F4	0.799	0.974	0.950	0.987	0.319
F5	0.813	0.930	0.936	0.952	0.291
F6	0.821	0.962	0.957	0.985	0.308
F7	0.749	0.921	0.911	0.965	0.268
F8	0.857	0.993	0.977	0.978	0.390
F9	0.842	0.919	0.968	0.987	0.334
F10	0.821	0.931	0.933	0.957	0.264
F11	0.857	0.969	0.966	0.976	0.307
F12	0.784	0.954	0.944	0.990	0.308

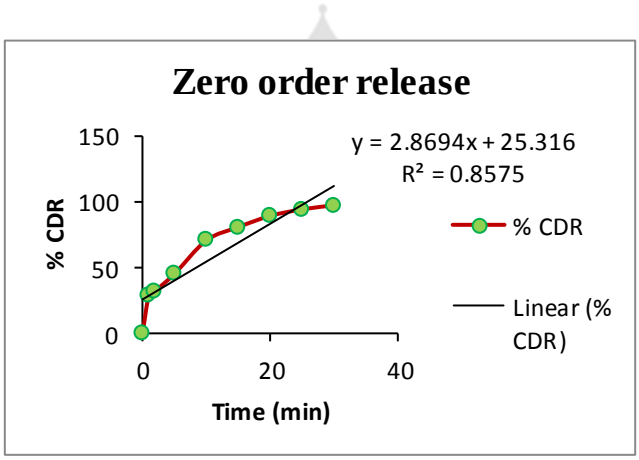


Figure 12: Zero-order release kinetics profile of optimized formulation F8

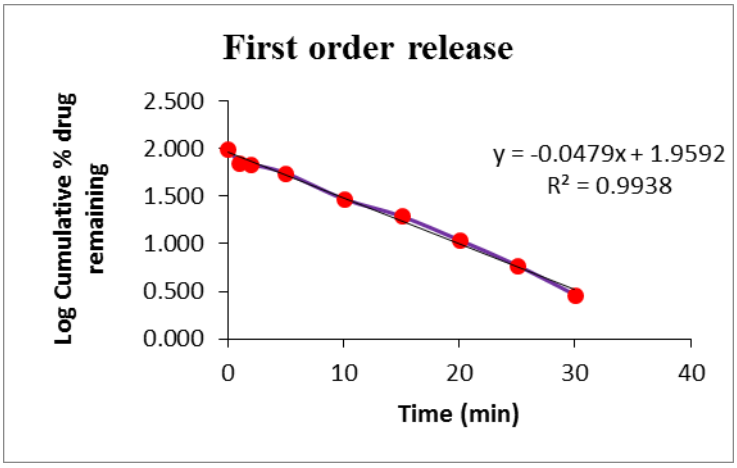


Figure 13: First order release kinetic profile of optimized formulation F8

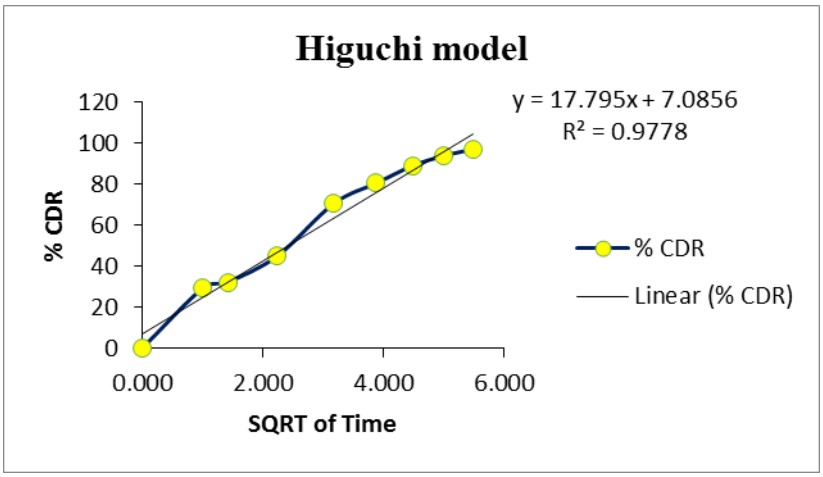


Figure 14: Higuchi release kinetics profile of optimized formulation F8

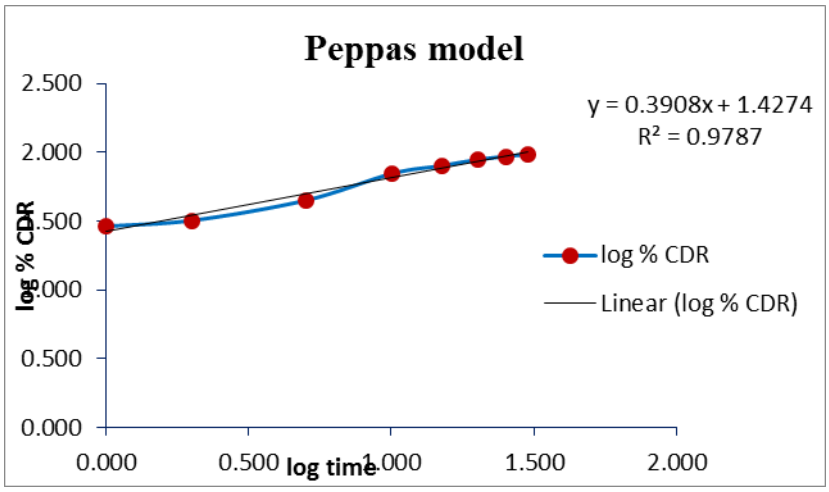


Figure 15: Peppas release kinetics profile of optimized formulation F8

From the above data, it was concluded that the formulation F8 follows first-order kinetics with R^2 value 0.993. The *in-vitro* drug release data as log % CDR versus time were fitted to Korsmeyer equation in order to understand the mechanism by which Esomeprazole was released from this formulation. Value of exponent 'n' was found to be 0.253-390. The Korsmeyer-Peppas model yields 'n' values <0.45 indicating that the diffusion mechanism from the formulation followed Quasi-Fickian diffusion.

Stability studies

Stability studies were carried out on optimized formulation F8 for a period of three months. The comparison of the parameters before and after stability studies was represented in a table

Table 16: Comparison of parameters before and after stability studies

Parameters	Before stability studies	After stability studies
Appearance	Off-white color	Off-white color
Wetting time (sec)	10.71±0.13	10.20±0.23
Water absorption ratio (%)	90.90±0.11	89.50±0.14
Disintegration time (sec)	24.50±0.103	23.90±0.05
%CDR	97.07±0.59	96.12±0.29

The results obtained from the stability studies showed that the optimized formulation F8 showed only a slight decrease in the wetting time, water absorption ratio, the disintegration time of esomeprazole orodispersible tablet at 40oC after 1 month of storage. The *in vitro* drug release also slightly decreased after the stability period. There was no change in the appearance of the formulation. From the stability studies, it was confirmed that the optimized formulation of esomeprazole remained stable at 40ºC and 75% relative humidity.

CONCLUSION

Esomeprazole orodispersible tablet was successfully prepared by direct compression method using various Superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and chitosan. Before compression, the powder blend was evaluated for precompression parameters such as bulk density, tapped density, an angle of repose, compressibility index and Hausner's ratio. All the prepared esomeprazole tablet were evaluated for physical properties, weight variation, hardness, thickness, friability, wetting time, water absorption

ratio, content uniformity, disintegration time and *in-vitro* drug release studies. Based on the evaluation data, the present study concluded that the formulation F8 which contains the highest concentration of croscarmellose sodium was found to be optimized one because it has the lowest wetting time value about 10.71sec, lowest disintegration time about 24.50 sec and promising drug release of 97.07% after 30 min when compared to other formulations. Also concluded that among three superdisintegrants sodium starch glycolate, croscarmellose sodium, chitosan; cross carmellose sodium was found to be better one. The 'n' value from Peppas model for the optimized formulation F8 indicated that the drug release follows Quasi – Fickian release. The findings of the result revealed that Esomeprazole administered in the form of orodispersible tablets will be a potential novel drug dosage form for pediatric, geriatric and also for the general population by providing faster release, better patient compliance, and reduced side effects.

ACKNOWLEDGMENT

We are extremely grateful to Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala for the facilities provided to complete this work successfully.

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