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FORMULATION AND EVALUATION OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE MICROPELLETS

A. Vivekananda[*1], CH. Ajay Babu[1], T.V. Sai Krishna[1]

[1*]Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Kotappaknda Road, Yallamanda, Narasaraopeta, Guntur, Andhra Pradesh, India.

ABSTRACT

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral administration. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. The main objective of this work is to develop a stable, pharmaceutically equivalent, robust and delayed release micro pellet formulation of Esomeprazole magnesium trihydrate, which is an orally administered benzimidazole anti-ulcer drug. The present investigation aimed to study two types of polymers hydroxypropyl methyl cellulose (HPMC), polyvinyle pyrolidine (PVP) to prepare the delayed release micropellets. All these formulations would be prepared in different percentages by wet granulation method. Evaluation of these micro pellets would be performed by post compression parameter, dissolution rate studies, and stability studies.

KEYWORDS

Micropellets, Esomeprazole magnesium trihydrate, HPMC and PVP.

Author for correspondence:

A. Vivekananda,
Department of Pharmaceutics,
Narasaraopeta Institute of Pharmaceutical Sciences, Kotappakonda Road, Yallamanda, Narasaraopeta, Guntur, Andhra Pradesh, India.

Email: vivekananda.arumalla@gmail.com.

INTRODUCTION[1,2]

Pellets are of great interest to the pharmaceutical industry for variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents.

Pellets have to meet the following requirements:

- They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

- The particle size range should be as narrow as possible. The optimum size range of pellets for pharmaceuticals use is considered to be between 600-1000 micrometers.
- The pellets should contain as much as possible of the active ingredient to keep the size of final dosage form within reasonable limits.

The most common advantages of pelletization are

- Improved appearance of the product and the core is pharmaceutically elegant.
- Pelletization offers flexibility in dosage form design and development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of irritative drugs.
- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development.
- The coating of pellets can be done with different drugs to enable a controlled release rate and modified release, delayed release of the formulations.

The present investigation aimed to study two types of polymers hydroxypropyl methyl cellulose (HPMC), polyvinyle pyrolidine (PVP) to prepare the delayed release micropellets. All these formulations would be prepared in different percentages by wet granulation method. Evaluation of these micro pellets would be performed by post compression parameter, dissolution rate studies, and stability studies. The aim of this work is to improve the dissolution rate and oral bioavailability which will further improve its biological activity.

MATERIALS AND METHODOLOGY[3]

Materials are used in the preparation of Esomeprazole magnesium trihydrate micro pellets are tabulated in Table No.1.

Process flow chart

See Figure No.1.

EVALUATION

Pre-formulation studies[5,6]

Preformulation studies like Organoleptic Properties, Flow Properties, Angle of Repose and Solubility were studied and the results are tabulated in the Table No.2.

Drug - Excipient Compatibility Studies also performed and the results are showed in the Table No.3, 4 and 5.

Procedure

a) Drug Loading

Various steps involved in the drug loading these are following,

Steps

- Base Pellets were sieved through Sieve no.30 and 40 and 33% of pellets was taken for drug loading from total batch size of 4.50kg.
- Required quantity of drug was taken and dispersed in specified ml of NaOH solution using a remi stirrer for 10 minutes.
- The above quantity of HPMC, Titanium Dioxide and Tween 80 was taken and dispersed in specified ml of purified water with a remi stirred for 10 minutes to obtain a clear solution.
- Solution of step (2) was added to solution of step (3) with stirring.
- Pellets of step (1) were loaded in to FBC bowl and coated with the following parameters accordingly

FBC Parameters

Parameter: Conditions
Inlet temp: 60 ^{0}C
Bed temp: 40 ^{0}C
Atomizing air pressure: 2 bar
Blower rpm: 800
% RH: 40%
Spray Rate: 15 ml/min

b) Barrier Coating

Barrier Coating Formula

Name of Ingredients	**Quantity (mg)**
HPMC K15	- 12 % of drug loaded pellets.
Purified water	- 12% × 16 Portion

Steps

- Required quantity of Drug loaded pellets was taken for Barrier coating.

- Required quantity of hydroxy propyl methylcellulose K15 was taken and dissolved in specified ml of purified water using remi stirrer until a clear solution was obtained.
- Pellets of step (1) were loaded in to FBC bowl and coated with the parameters accordingly.

c) Enteric Coating

Enteric Coating Formula

Name of Ingredients	**Quantity (mg)**
Acryl coat L:	- 30 D Solution, 60% of barrier coated pellets × 3.33
Talc:	- 5% of Acry coat L 30 D solution
Titanium Dioxide:	- 2%
PEG 6000:	- 6% of Acry coat L 30 D solution
Tween 80:	- 0.5% of Acry coat L 30 D solution
Sodium Hydroxide:	- 0.2% of Acry coat L 30 D solution
Purified Water:	- Equal to Acry Coat L 30 D solution.

Steps

- Specified quantity of Barrier coated pellets was taken for Enteric coating.
- Required quantity of Acry coat L 30D solution was taken and filtered it.
- Talc, Titanium Dioxide, PEG 6000 and Tween 80 was taken and dispersed in specified ml of purified water with a remi stirred for 10 minutes to obtain a clear solution.
- Solution of step (2) was added to solution of step (3) with stirring.
- Add required quantity of NaOH solution to the above solution for pH adjustment.
- Pellets of step (1) were loaded in to FBC bowl and coated with the parameters accordingly.

Characterization of the Pellets

The pellets were characterized by different tests like Bulk Density and Tapped Density, Compressibility Index, Hausner's Ratio, Friability were performed and results are showed in the Table No.6.

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$\mathbf{D_b = M/Vb}$$

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$\mathbf{D_t = M/Vt}$$

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\mathbf{\tan \theta = h/r}$$

Therefore, $\theta = \tan^{-1} h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%)=$[(D_t-D_b)X100]/D_t$

Where,

D_t is the tapped density

D_b is the bulk density

Hauser's Ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\textbf{Hausner's ratio} = D_t/D_b$$

Where,

Dt is the tapped density,

Db is the bulk density.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable (Table No.7).

$$\textbf{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

***In Vitro* Drug Release Study**

Accurately weighed a quantity of pellets equivalent to 20 mg of esomeprazole magnesium tri hydrate was transferred to six dissolution baskets having 900 ml 0.1 N HCl equilibrated to 37° C ± 0.5° C taking care to exclude air bubbles from the surface of the pellets and start the apparatus at 100 rpm for 2 hours. After 2 hours drain the medium without losing the pellets, transfer these pellets to a filter paper with identity. Fill up the dissolution bowl with 900 ml of Phosphate buffer pH 6.8 and equilibrate to 37±0.5° C. Then add the sample pellets, which have been kept in acid medium for 2 hours. Start the apparatus at 100 rpm for 45 minutes, collect 10 ml of sample from zone midway between surface of dissolution medium and top of rotating paddle, not less than 1.0 cm from the vessel wall. Centrifuge at 5000 rpm for 5 minutes of the above solution, and use clear supernatant liquid. 10 ml 0f samples (replaced) were withdrawn at predetermined time intervals. Absorbance's of the samples were measured spectrophotometrically at 280nm and 302 nm (Perkin Elmer, USA) using the dissolution medium in the reference cell. The results showed in the Table No.8.

Study Parameters

Apparatus (Paddle)	: USP Apparatus I
Medium	: pH 6.8 Phosphate buffer
Volume	: 900 ml
RPM	: 50 RPM
Temperature	: 37°C ± 0.5°C
Sampling Interval	: 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 10^{th}, 12^{th} and 24^{th} Hour.

Diluent

Dissolution medium

In vitro Dissolution Study and Kinetic Modeling also calculated and the results are tabulated in Table No.9.

RESULTS AND DISCUSSION

The present study was undertaken to formulate Esomeprazole magnesium delayed release pellets containing 20 mg of the drug. Study involves compatibility studies between drug and excipents and formulation and evaluation of pellets conducted for the optimized formulation. The effect of various type and concentration of polymers on delaying the release of esomeprazole was investigated by *in vitro* drug release characteristics. The formulations prepared with various polymers were characterized by studies such as drug content uniformity, Fourier transform infra red (FT-IR) spectroscopy and *in vitro* dissolution study. The spectra of esomeprazole delayed release formulation (selected formulation) showed a broad peak at the same place of the peak observed at the spectrum of pure drug has been observed, which indicated that there was no chemical interaction with the polymers. *In vitro* dissolution study was performed for various binary systems using 0.1N HCL as the dissolution medium. Eight formulations of esomeprazole delayed release micropellets were prepared employing the same ratio's of drug and polymers such as HPMC K15, PVPK30, PEG 6000 by using extrusion and spheronization technique (Figure No.5 and 6).

Table No.1: Formulae for Preparation of Esomeprazole Delayed Release Micro Pellets employing HPMC K15 and PVP K30

S.No	Ingredients	EDRM 1 Kg	EDRM 2 Kg	EDRM 3 Kg	EDRM 4 Kg	EDRM 5 Kg	EDRM 6 Kg	EDRM 7 Kg	EDRM 8 Kg
1	Esomeprazole	0.383	0.383	0.383	0.383	0.383	0.383	0.383	0.383
2	HPMC K15	0.191	0.230	0.230	0.230	0.230	-----	0.115	0.230
3	PVPK 30	-----	-----	-----	-----	-----	0.230	0.115	-----
4	Titanium Dioxide	0.031	0.038	0.031	0.031	0.031	0.031	0.031	0.031
5	SLS	0.008	0.008	-----	0.008	0.008	0.008	0.008	0.008
6	TWEEN 80	0.038	0.038	0.038	0.038	0.019	0.038	0.038	0.038
7	NaOH	0.046	0.046	0.046	0.038	0.046	0.046	0.046	0.046
8	Seed Pellets(30#40)	1.480	1.480	1.480	1.480	1.480	1.480	1.480	1.480
9	DM Water	4.200 LTS	4.200 LTS	4.200 LTS	4.200 LTS	4.200 LTS	4.200 LTS	4.200 LTS	4.200 LTS

Table No.2: Solubility Study

S.No	Name of Solvent	Extent of Solubility
1	Water	Insoluble
2	Acetone	Insoluble
3	Dimethylformamide	Soluble
4	Methanol	Sparingly soluble

Table No.3: Drug-Excipient Compatibility Studies at (25 ± 2^0C/60±5% RH)

S.No	Materials	Ratio (D:E)	Initial Observation	25 ± 2^0C/60±5% RH			
				Week 1	Week 2	Week 3	Week 4
1	Esomeprazole	1:00	White color powder	NC	NC	NC	NC
2	API + HPMCK15	1:05	White color powder	NC	NC	NC	NC
3	API + PVP K 30	1:05	White color powder	NC	NC	NC	NC
4	API + SLS	1:05	White color powder	NC	NC	NC	NC
5	API + TiO2	1:05	White color powder	NC	NC	NC	NC
6	API + Tween 80	1:05	White color powder	NC	NC	NC	NC
7	API + NaOH	1:05	White color powder	NC	NC	NC	NC

NC- No color change D: E- Drug +Excipient

Table No.4: Drug-Excipient Compatibility Studies (40 ± 2^0C/75±5% RH)

S.No	Materials	Ratio (D:E)	Initial Observation	25 ± 2^0C/60±5% RH			
				Week 1	Week 2	Week 3	Week 4
1	Esomeprazole	1:00	White color powder	NC	NC	NC	NC
2	API + HPMCK15	1:05	White color powder	NC	NC	NC	NC
3	API + PVP K 30	1:05	White color powder	NC	NC	NC	NC
4	API + SLS	1:05	White color powder	NC	NC	NC	NC
5	API + TiO2	1:05	White color powder	NC	NC	NC	NC
6	API + Tween 80	1:05	White color powder	NC	NC	NC	NC
7	API + NaOH	1:05	White color powder	NC	NC	NC	NC

NC- No color change D: E- Drug: Excipient

Table No.5: Drug - Excipient Compatibility Studies

S.No	Name of the Ingredients	Category	Remarks
1	HPMC K15	Binder	Compatible
2	PVP K 30	Binder	Compatible
3	Titanium Dioxide	coloring agent	Compatible

Table No.6: Bulk density, Tapped density, Hausner's ratio and Carr's index Data of Formulations

S.No	Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index
1	EDRM 1	0.923±0.26	0.989±0.21	1.07±0.25	5.47±0.31
2	EDRM II	0.937±0.29	1.0048±0.34	1.07±0.26	5.71±0.37
3	EDRM III	0.921±0.17	0.988±0.26	1.07±0.24	4.38±0.41
4	EDRM IV	0.934±0.14	0.991±0.35	1.06±0.26	4.96±0.27
5	EDRM V	0.915±0.36	0.959±0.15	1.04±0.13	5.21±0.26
6	EDRM VI	0.952±0.34	0.999±0.27	1.04±0.16	5.47±0.27
7	EDRM VII	0.947±0.39	1.028±0.26	1.08±0.21	5.39±0.19
8	EDRM VIII	0.928±0.25	0.972±0.27	1.04±0.19	5.11±0.24

Table No.7: Friability of Formulations

S.No	Formulation code	EDRM 1	EDRM 2	EDRM 3	EDRM 4	EDRM 5	EDRM 6	EDRM 7	EDRM 8
1	% Friability	0.07± 0.16	0.125±0.25	0.092±0.27	0.114±0.19	0.087±0.29	0.089±0.35	0.075±0.41	0.097±0.21

Table No.8: *In vitro* Drug Release Study of Esomeprazole Delayed Release Micropellets Employing polymers HPMC-K15, PVP K30

S.No	Sampling Time (hr)	EDRM 1	EDRM 2	EDRM 3	EDRM 4	EDRM 5	EDRM 6	EDRM 7	EDRM 8
1	1	0	0	0	0	0	0	0	0
2	2	50.36	65.36	60.16	59.78	50.12	55.60	57.10	65.33
3	3	78.75	85.69	78.77	76.60	79.76	71.15	78.43	88.67
4	4	86.41	89.35	86.09	84.88	86.93	78.04	89.88	92.18
5	5	85.63	86.18	85.23	80.45	84.40	75.12	87.19	98.65

Table No.9: Analysis of *In vitro* Dissolution Study Parameters of Formulations EDRM 1to EDRM 8

S.No	Formulation code	Zero order release		First order release		Higuchis classical diffusion	
		K_0	r	K_1	r	K_H	r
1	EDRM1	1.803	0.857	-0.045	0.915	13.822	0.967
2	EDRM2	1.694	0.784	-0.044	0.838	13.726	0.935
3	EDRM3	1.704	0.821	-0.042	0.902	13.465	0.955
4	EDRM4	1.604	0.800	-0.036	0.853	12.870	0.944
5	EDRM5	1.784	0.847	-0.043	0.890	13.751	0.961
6	EDRM6	1.493	0.803	-0.030	0.857	11.947	0.945
7	EDRM7	1.799	0.843	-0.048	0.905	13.972	0.964
8	EDRM8	1.762	0.790	-0.050	0.835	14.203	0.973

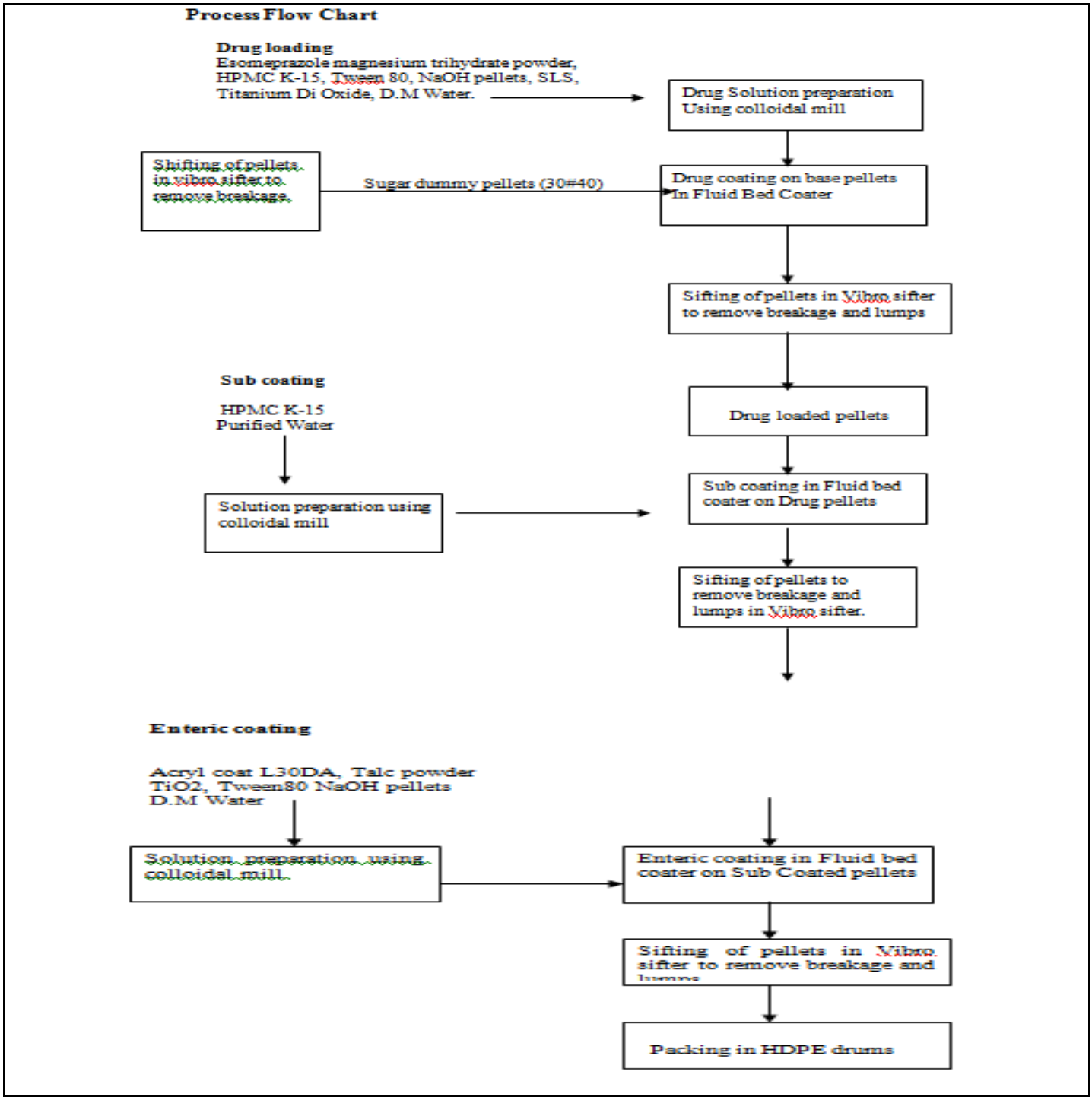

Figure No.1: Process of Flow chart

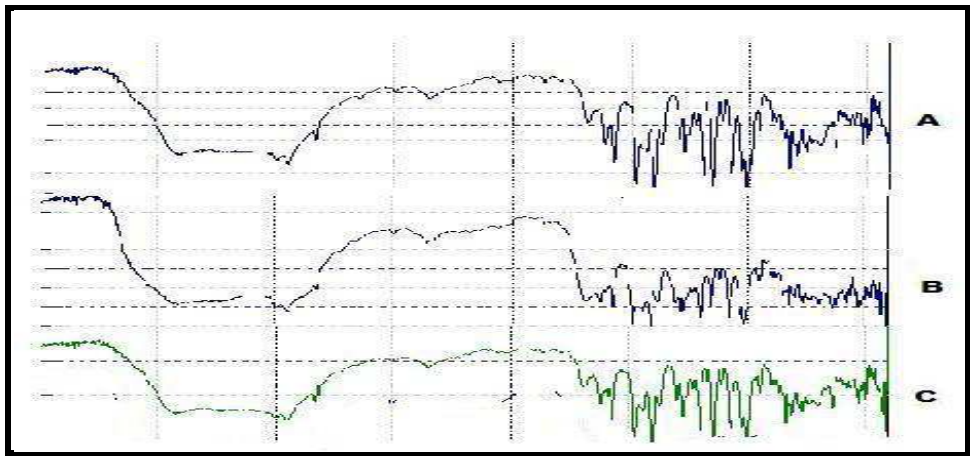

Figure No.2: FTIR Spectrum of A) Esomeprazole + B) HPMC K15 C) PVP K30

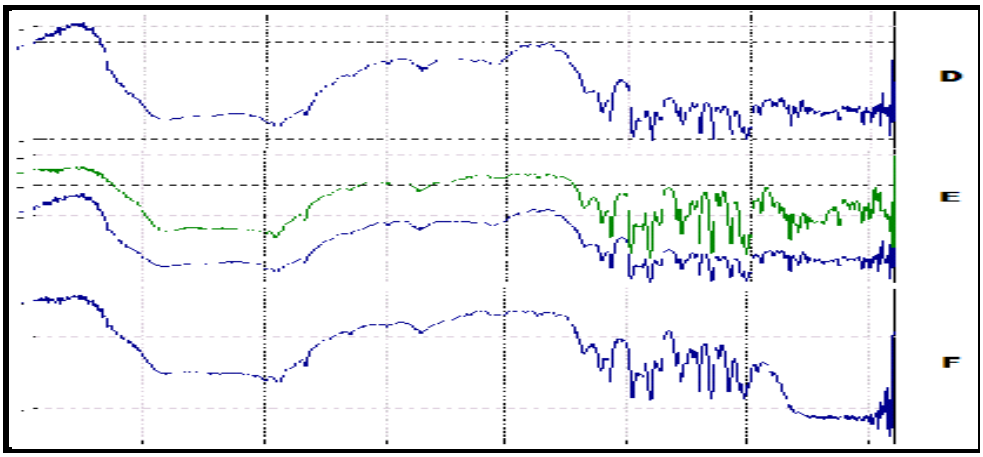

Figure No.3: FTIR Spectrum of D) Esomeprazole magnesium trihydrate+ E) PVP K30 F) TiO_2

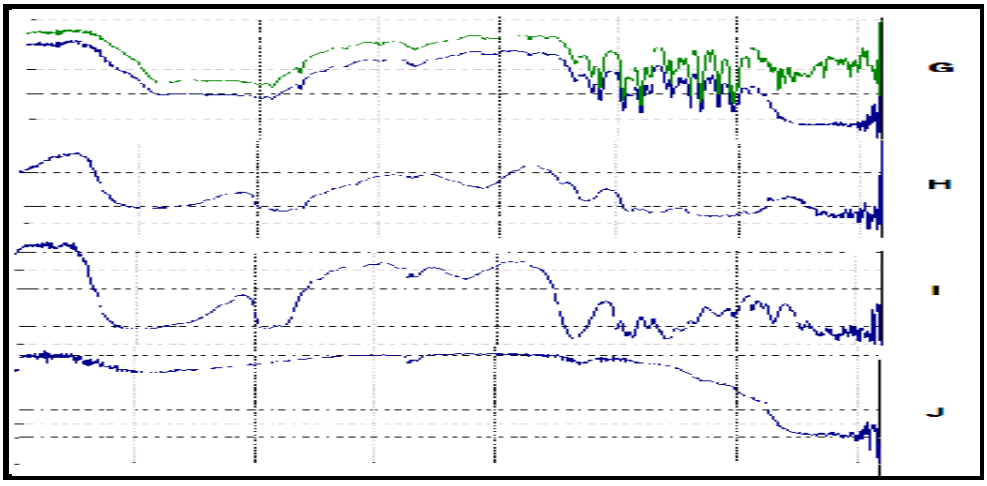

Figure No.4: FTIR Spectrum of G): Esomeprazole magnesium trihydrate + H) TiO_2 + H) HPMC K15 + I) PVP K-30+ J) TiO_2

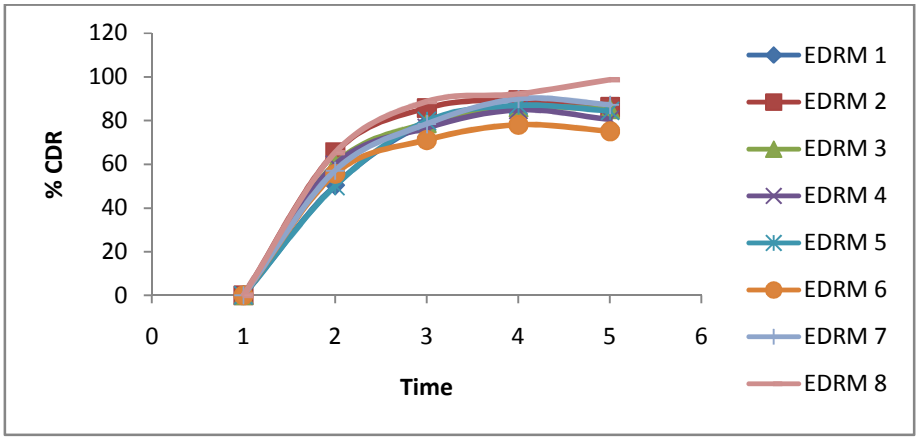

Figure No.5: *In vitro* Drug Release Study of Esomeprazole Delayed Release Micropellets Employing polymers HPMC-K15, PVP K30

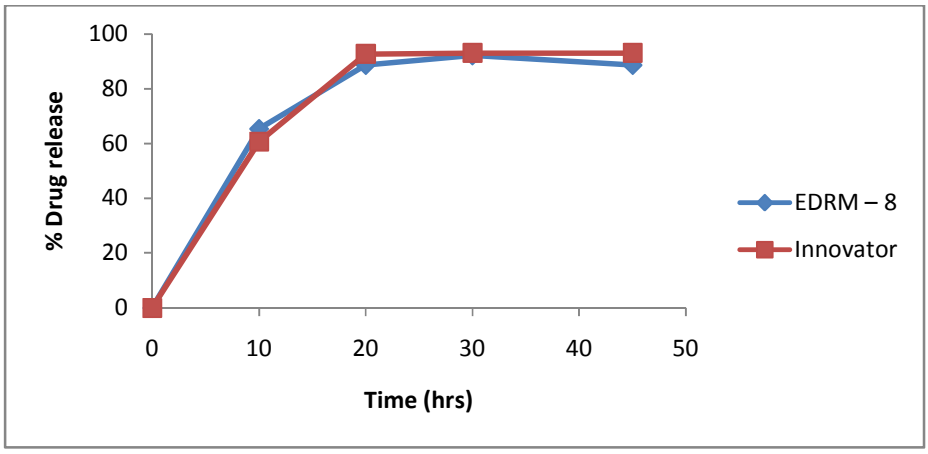

Figure No.6: Comparative Dissolution Profile of EDRM 8 with Innovator

CONCLUSION

The study was undertaken with an aim to develop delayed release micro pellets dosage form for esomeprazole magnesium trihydrate, which is a benzimidazole anti ulcer agent and is one of the most widely used drug for treating mild and severe ulcers. FT-IR spectra showed reduced absorption bands. The reduced absorption bands suggest a drug-polymer physical interaction. Since there is no total disappearance of the bands, it may be concluded that there is no chemical interaction between the drug and polymers. The approach of the present study was to make a comparative evaluation among these polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The type of polymers used imparts a conspicuous effect on release mechanism. The polymers of *in vitro* dissolution profiles indicated that all the formulations containing HPMC K15 irrespective of concentration produces better delay in the drug release when compared to the formulations containing the PVP K30 i.e (HPMC K15 > PVP K30). The formulation EDRM 8 containing HPMC K15 exhibited satisfactory release rate of the drug with 98.12% at the end of 45 mins, hence is selected as the best formulation to compare with the innovator product and it may be considered as optimized formulation. The *in vitro* dissolution data indicates that the irrespective of type of polymers HPMC K15 and PVP K3, the increase in the concentration of polymer decreases drug releases and decrease in concentration increase in the drug release. Based on the drug-excipient compatibility data and prototype formulations, the formula that

found to be giving the desired drug release pattern was considered as the optimized formulation and further studies were conducted on this formulation No. EDRM 8 to have a detailed study over that formulation. By the observations made, it can be concluded that the formulation EDRM 8 shows good similarity with release profile of Innovator (Nexium) and it was within the USP limits, and also this formulation done by FBC process which is a sophisticated method is more suitable for the preparation of this type of formulations.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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