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FORMULATION AND EVALUATION OF DELAYED RELEASE ESOMEPRAZOLE PELLETS BY SUSPENSION LAYERING OF PELLETIZATION TECHNIQUE

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Esomeprazole, Delayed release, HPMC, Meglumine

ABSTRACT

The purpose of this study was to preparedelayed release Esomeprazole pellets. These Pellets are prepared by pelletization technique. The MCC, HPMC, polysorbate 80, Methacrylic Acid polymerswere used to prepare coated pellets as seal coating drug coating sub coating and enteric coating. Pellets were evaluated for different parameters such as Assay, Acid Resistance, Drug Release and Dissolution. Based on the drug content and drug release optimized formulation of HPMC and methacrylic acid were used to prepare enteric coated pellets. The physicochemical compatibility of the drug with other excipients used in the formulations was studied by HPLC analysis. The results obtained showed no physicochemical incompatibility between the drug and other excipients used in the formulations. The prepared Capsules were evaluated for different parameters. The Capsules were also evaluated for *in vitro* drug release in 0.1N HCl for Acid stage and 6.8 pH Phosphate buffer and 7.4 pH Phosphate buffer for alkaline stage by dissolution apparatus. In order to determine the mode of release, the data was fitted into various kinetic models and the optimized formulations followed Higuchi diffusion mechanism of drug release.

INTRODUCTION

An ideal drug delivery system provides treatment for acute diseases or chronic illness to the patients for many years. Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called Immediate-release products. Other products like Modified-release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation[1,2,3].

Modified-release products fall in two categories. One is Extended-release dosage forms. Controlled and Sustained release products fall into this category. The second category is *delayed-release*[4,5].

Delayed Release Dosage Forms

1. Delayed Release Systems[6]

The design of such system involves release of drugs only at a specific site in the gastrointestinal tract.

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release system

2. Delayed Release Solid Oral Dosage Forms[7]

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

Clasification of Delayed Release Solid Oral Dosage Forms: Delayed release solid oral dosage forms are available either as single-unit (non divided formulations-tablets, capsules) or as multiple-unit (divided formulations-pellets, mini-tablets) forms.

1. Single Unit Dosage Forms[8]: The single-unit dosage forms usually refer to *diffusion controlled systems* which include *monolithic systems*, where the diffusion of a drug through a matrix is the rate-limiting step, *reservoir or multilayered matrix systems*, where the diffusion of the drug through the polymer coating or layer of the system is the rate-limiting step. However, generally, release of drugs will occur by a mixture of these two mechanisms.

2. Multiple Unit Dosage Forms[9]

Types of multiple unit dosage forms comprise

- Pellets
- Granules
- Mini tablets and mini depots (dispersed and distributed throughout the gastrointestinal tract when the capsule or tablet disintegrates)
- Micro particles (Microspheres or Microcapsules) and Nano particles
- Multiple unit tablets (divided at ingestion without loss of the depot effect, as the sub unit act as self contained depots).

PELLETS

Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration), obtained from diverse starting materials utilizing different processing techniques and conditions[10].

Pellet Growth Mechanism[11]

The most classified pelletization process involves three consecutive regions nucleation, coalescence and layering, abrasion transfer. *Nucleation* (Figure 3, A) occurs whenever a powder is wetted with liquid and presents first stage of the pellets growth. The primary particles are drawn together to form three-phase air-water-liquid nuclei and attached together by liquid bridges which are pendular in nature. Nucleation is followed by a *transition phase* with two major mechanisms, coalescence and layering. *Coalescence* (Figure 3, B) phase is characterized with formation of large-sized particles by random collision of nuclei containing slight excess of moisture. *Layering* (Figure 3, C) involves successive addition of fines and fragments on surface of nuclei. The number of nuclei remains the same, but the total mass of nuclei in the system increases due to increasing particle size as a function of time. The fragments and fine particles that are formed during the process in the stage of particle size reduction due to attrition, breakage and shatter, are picked up by large pellets. In the ball growth phase, the main mechanism affecting the slow growth of agglomeration is the *abrasion transfer* (Figure 3, D) which involves the transfer of materials from one granule formed to another without any preference in either direction.

METHODS

Pelletization Technique: Pelletization is an agglomeration process that converts

fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets [12]. The type of coating technique strongly affects the film microstructure and thus affects the release mechanism and rate from pellets coated with polymer blends [17]. There are several manufacturing techniques for production of spherical pellets

Preformulation Studies: Preformulation study is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage form.

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1. DRUG EXCIPIENTS COMPATIBILITY STUDY

Physical observation

Physical observation of sample was done every week for any color change or lumps formation and flow, the results of the physical observation were shown in Table 9. Compatibility studies by accelerated stability testing showed that there was no physical change or interaction between drug and selected excipients. Based on the physical compatibility results, IR results and the innovator product composition the above excipients were selected for formulation development**2.**

OPTIMIZATION STUDIES OF PELLETS

1. Optimization of seal coating: Seal coating was given to pellets to get enough mechanical strength to the pellets during coating process. Seal coating was done with different polymer concentration of HPMC to get % weight gain. In F1 formulation, breakage of pellets was observed during coating. In F2 and F3 formulations, breakage of pellets were not observed during coating, i.e. enough mechanical strength was observed for pellets. So optimum % of seal coating i.e., F2 formulation was finalized for further coating stages, i.e. drug coating.

2. Optimization of drug coating: Drug coating was given to F2 seal coated pellets by using suspension layering technique. Then the drug coated pellets were analyzed for the amount of drug bound over the F2 seal coated pellets. D1 and D2 showed that the amount of the drug coated was 69% and 80% respectively. By this D2 formulation was considered to be better than D1 with the same binder concentration. To improve the amount of drug to be coated on to the F2 pellets, further trails were planned with HPMC with increased binder concentration.D3 formulation showed 91% drug coating. D3 formulation was observed to be 95%, generally inclusion of overages is not recommended as per FDA. D4 formulation was found to have drug coating of 99% and process problems were not observed during coating. D5 formulation was found to have a drug coat of 98% and lumps were observed during coating process.From the above trails it was concluded that 17% HPMC was an optimized binder concentration for drug coating.

3. Optimization of sub coating: Main aim of sub coating is to protect the drug coated pellets from enteric coating and environmental conditions. In S1 and S2 formulations, yield was found to be low. Hence these formulations don't show better protection for drug coated pellets.In S3 formulation both HPMC and TEC concentrations were increased for better film formation there by better protection was obtained to drug coated pellets.

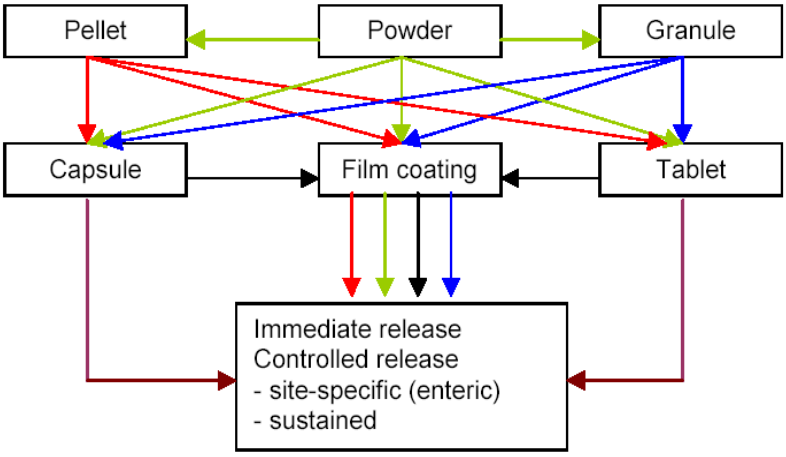


Figure 1: Relationship of pharmaceutical Delayed Release solid oral dosage forms

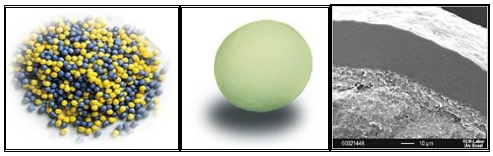


Figure 2: (a) Pellets, (b) Perfect pellet, (c) Coated pellet

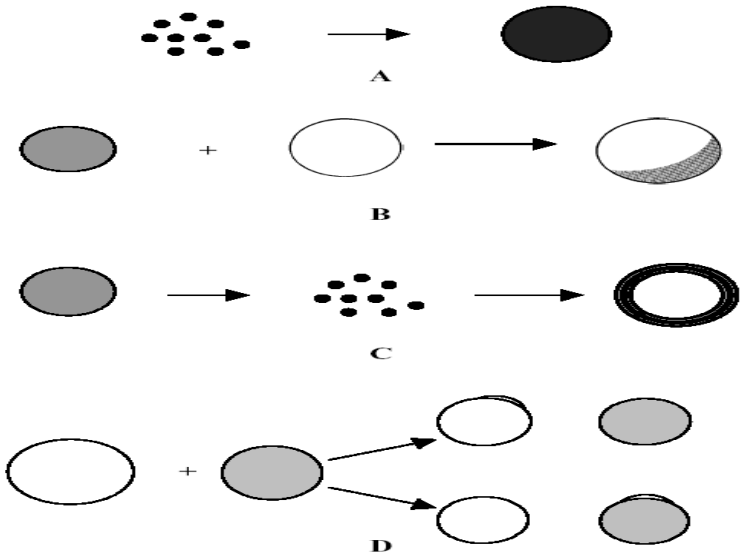


Figure 3: Pellet growth mechanisms. (A) Nucleation, (B) Coalescence, (C) layering and (D) abrasion transfer

Table no.1 List of Materials

S.no.	Material	Manufacturer
	Pellets coating	
1.	Esomeprazole magnesium dihydrate	HETERO DRUGS
2.	MCC (#60/#80) / celepher cp-203	ASAKESHI
3.	Hypromellose	THE DOW CHEMICALCOMPANY
4.	Hydroxypropyl cellulose	AQUALON
5.	Meglumine	MERCK
6.	Polyvinylpyrrolidone	BASF
7.	Methacrylic acid copolymer type C	DEGUSSA
8.	Triethyl citrate	MORFLEX
9.	Polyethylene glycol 400	CLARIANT
10.	Polysorbate 80	---
11.	Talc	LUZANAC PHARMA
12.	Purified water	HETERO DRUGS

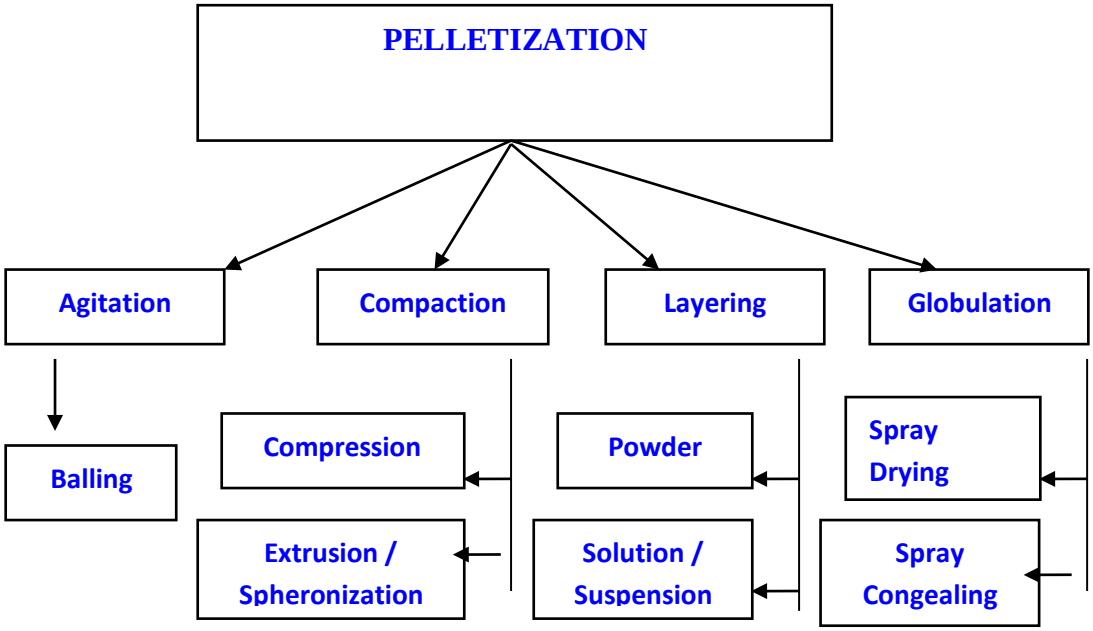


Figure 4: Different pelletization techniques

Table No.2 Drug Excipients Ratio

Batch no.	***Drug- Excipients combination***	***D:E Ratio***
1	API alone	-
2	API + MCC (#60/#80) / celepher cp-203	1:5
3	API + HPMC	1:5
4	API + Meglumine	1:5
5	API + Polyvinylpyrrolidone	1:5
6	API + Methacrylic acid copolymer type C	1:5
7	API + Triethyl citrate	1:5
8	API + Polyethylene glycol 400	1:5
9	API + Polysorbate 80	1:5
10	API + Talc	1:5

Table no. 3 SEAL COATING (Optimization)

S.No	INGREDIENTS	mg/unit		
	SEAL COATING	**F1**	***F2***	**F3**
1	MCC Pellets (celphere cp-203)	38	***38***	38
2	Hypromellose 3cps	1	***2***	3
3	Purified water	35	***35***	35
	Total	**39**	***40***	**41**
	% yield	**65**	***95***	**95**

Table no. 4. DRUG COATING (Optimization)

S. No	DRUG COATING	D1	D2	D3	*D4*	D5
1	**Seal coated pellets F2**	40	40	40	***40***	40
2	Esomeprazole magnesium dihydrate	43.5	43.5	43.5	***43.5***	43.5
3	Hypromellose 3cps	-	10	15	***17.5***	22
4	Povidone(pvp k-17)	10	-	-	-	-
5	Meglumine	2.0	2.0	2.0	***2.0***	2.0
6	Polysorbate 80	1	1	1.5	***2***	2
7	Purified water	200	200	220	***240***	240
	Total	**96.5**	**96.5**	**102.0**	**105.0**	**109.5**
	% drug coated	**69%**	**80%**	**91%**	**99%**	**98%**

Table no. 5: SUB COATING (Optimization)

S. No	SUB COATING	S1	S2	S3
1	**Drug Coated pellets D4**	105.0	105.0	105.0
2	Hydroxy propyl methyl cellulose 3cps	3	4	6
3	Triethyl citrate	-	0.4	1.0
4	Talc	1	1.5	1.5
5	Purified water	50	60	75
	Total	**109**	**110.9**	**113.5**
	% yield	**85%**	**91%**	**96%**

S.No.	ENTERIC COATING	E1	E2	E3	E4	E5	E6
1	Sub coated pellets S3	113.5	113.5	113.5	113.5	113.5	113.5
2	Methacrylic acid copolymer (Type C)	30	-	-	-	-	-
3	Methacrylic acid copolymer (Type C) 30% aqueous dispersion	-	134 (40.2)	167 (50.1)	217 (65.1)	234 (70.2)	250 (75.0)
4	Triethyl citrate	-	-	5	6.5	7	7.5

5	Polyethylene glycol 400	3	4	-	-	-	-
6	Talc	6	8	10	13	14	15
7	Polysorbate 80	0.45	0.6	0.75	0.97	1.05	1.13
8	Purified water	150	105	130	170	180	200
	Total	155.25	166.3	179.35	199.07	205.75	212.13

Table no. 6. ENTERIC COATING (Optimization)

Table no. 7. OPTIMIZED FORMULATION

S. No.	INGREDIENTS	mg/unit
I	**SEAL COATING (F2)**	
1	MCC Pellets (celphere cp-203)	38
2	Hypromellose 3cps	2
3	Purified water	35
	Total	**40**
II	**DRUG COATING (D4)**	
4	Seal coated pellets	40
5	Esomeprazole magnesium dehydrate	43.5
6	Hypromellose 3cps	17.5
7	Meglumine	2
8	Polysorbate 80	2
9	Purified water	240
10	**Total**	**105**
	Drug coated (%)	**99**
III	**SUB COATING (S3)**	
11	Drug coated pellets	105
12	Hydroxy propyl methyl cellulose	6
13	Triethyl citrate	1
14	Talc	1.5
15	Purified water	75
	Total	**113.5**
IV	**ENTERIC COATING (E5)**	
16	Sub coated pellets	113.5
17	Methacrylic acid copolymer (Type C) 30% aqueous	234(70.2)

	dispersion	
18	Triethyl citrate	7
19	Talc	14
20	Polysorbate 80	1.05
21	Purified water	180
	Total	**205.75**
	Content uniformity on 10 capsules (%)	***98.7***

Table no. 8. API Characterization

Table no. 9. Drug Excipients Compatibility Study

S. No.	TEST	SPECIFICATION	RESULT
1	Description	An off-white to cream colored crystalline hygroscopic powder	An off-white to cream colored crystalline hygroscopic powder
2	Solubility	Soluble in water and slightly soluble in methanol	Complies
3	Water Content (by Karl-Fisher)	Should be between 4.5% and 6.7%	5.2% w/w
4	LOD	by IR moisture analyzer, at 105°C	1.37 % w/w
5	Bulk density True density Haussner's Ratio Carr's/Compressibility Index (%)		0.21 gm/ml 0.27 gm/ml 1.28 22
6	Melting Point	150-155^{0}C	150^{o}C
7	Assay on Anhydrous Basis (Potentiometric)	<98% and not more than 102% w/w	99.8%w/w
8	Particle Size Analysis		µm

S. No.	Composition Details	Observations			
		Storage Condition / Duration			
		Initial	40°C/ 75%RH		
			1M	2M	3M
1	API alone	NC	NC	NC	NC
2	API + MCC (#60/#80) / celepher cp-203	NC	NC	NC	NC
3	API + HPMC, 3 Cps	NC	NC	NC	NC
4	API + HPC	NC	NC	NC	NC

5	API + Meglumine	NC	NC	NC	NC
6	API + PVP	NC	NC	NC	NC
7	API + Methacrylic acid copolymer type C	NC	NC	NC	NC
8	API + Triethyl Citrate	NC	NC	NC	NC
9	API + PEG 400	NC	NC	NC	NC
10	API + Polysorbate 80	NC	NC	NC	NC
11	API + Talc	NC	NC	NC	NC

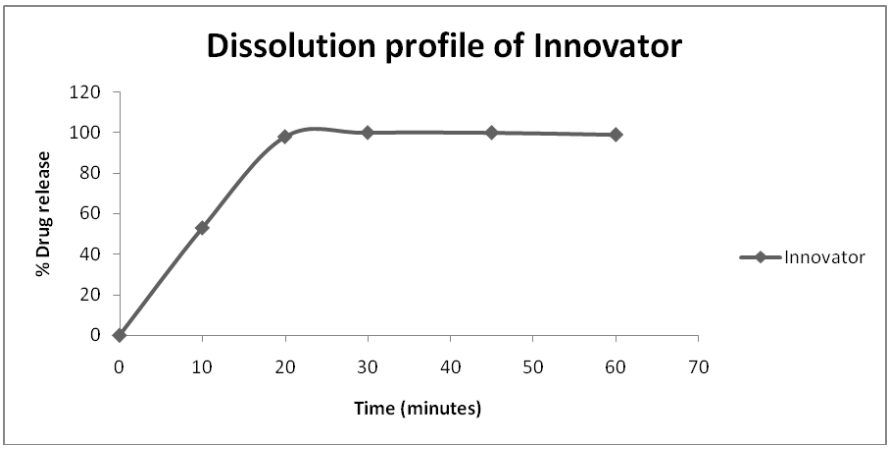


Figure 5

Table no. 10. Optimization of Drug coating (binders)

Binders Concentration (%)	**D1**	**D2**	**D3**	**D3 (10% overages)**	**D4**	**D5**
PVPK	10	-	-	-	-	-
Drug coated (%)	69	-	-	-	-	-
HPMC	-	10	15	15	17.5	22
Drug coated (%)	-	80	91	95	99	98

Table no. 11. Optimization of Enteric coating (polymers)

POLYMERS	**TRAILS**					
Methacrylic acid copolymer (type C) dry polymer	E1	-	-	-	-	-
Methacrylic acid copolymer type C polymer i.e. 30% aqueous.	-	E2	E3	E4	E5	E6

Table no. 12. Optimization of Enteric coating (% of polymers)

TRAIL	E1	E2	E3	E4	E5	E6
Enteric Coating (%)	26.8	31.7	36.7	42.9	44.8	46.4

Table no. 13. ASSAY

INNOVATOR	E1	E2	E3	E4	E5	E6
(% labelled amount of Esomeprazole)						
99.6	99.8	101.5	100.5	101.2	99.5	98.6

Table no. 14. ACID RESISTANCE

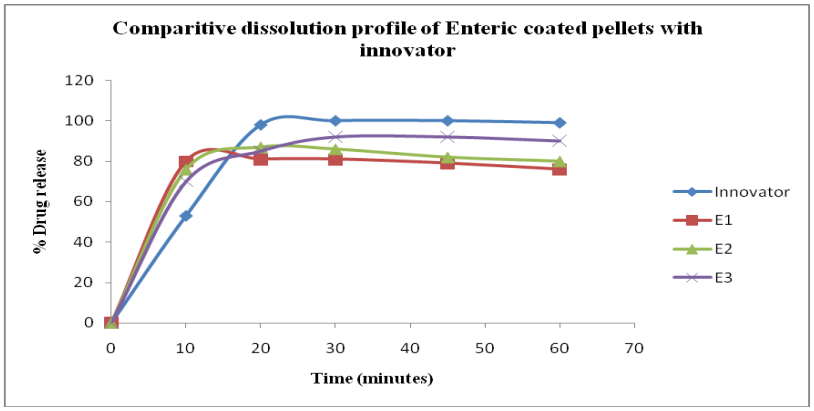
INNOVATOR	E1	E2	E3	E4	E5	E6
(% labelled amount of Esomeprazole retained in acid)						
99.3	79	80.9	87	95.2	99.6	99.8

Table no. 15. DRUG RELEASE

Time(hr)	INNOVATOR	E1	E2	E3	E4	E5	E6
	(% labelled amount of Esomeprazole released in acid)						
After 2 hrs	**0.7**	21	19.1	13	4.8	0.4	0.2

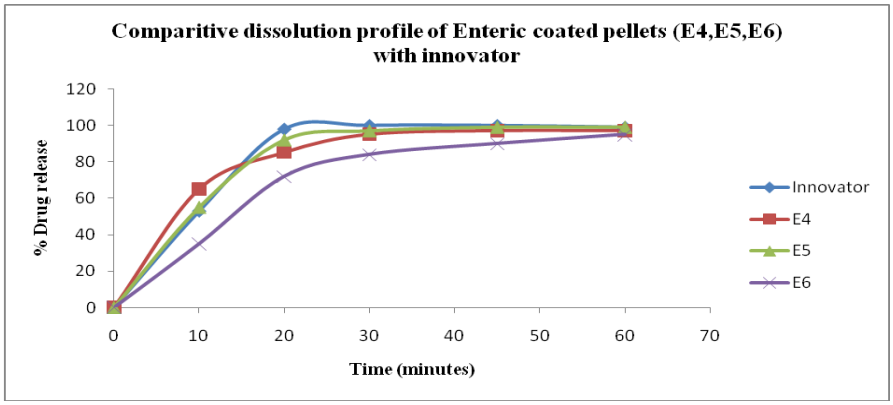
Table no. 16. Dissolution of Enteric coating (Innovator and EC Pellets)

Time(min)	Innovator	E1	E2	E3	E4	E5	E6
	(% labelled amount dissolved in buffer)						
10	**53**	80	76	70	65	55	35
20	**98**	81	86	88	90	96	85
30	**100**	81	84	92	95	97	90
45	**100**	79	82	92	92	95	95
60	**99**	76	80	90	92	95	95



In vitro dissolution profile of Enteric coated pellets (E1, E2, and E3) with Innovator

Figure 6



In vitro dissolution profile of Enteric coated pellets (E4, E5, and E6) with Innovator

Figure 7

Surface morphology study of enteric coated pellets (SEM)

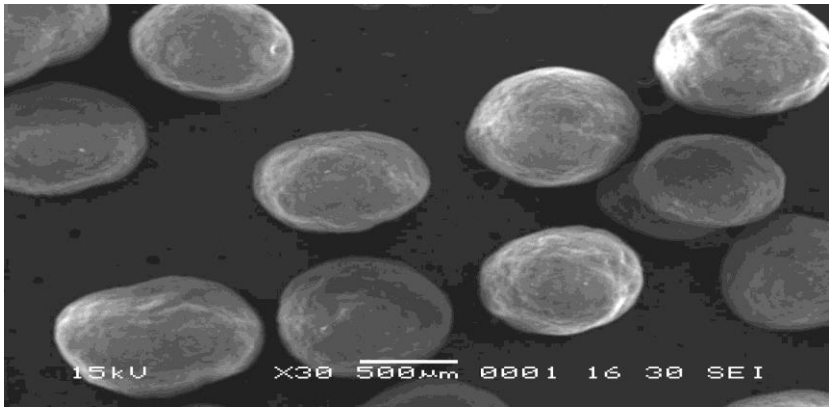


Figure 8

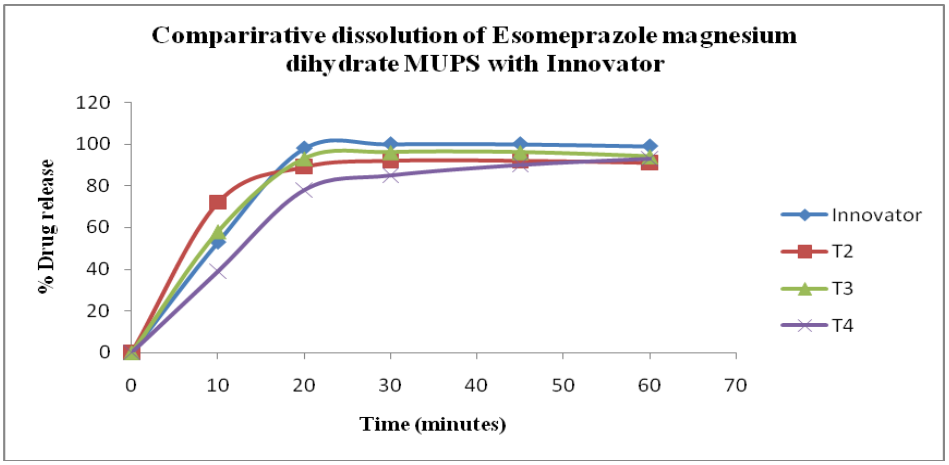
Table no. 17 Optimization and Evaluation studies of capsules

Parameters	**C1**	**C2**	**C3**	**C4**
Disintegration time (sec)	75	55	**45**	50
Content uniformity of 10 capsules (%)	89.5	90.8	**98.7**	91.6
Assay (%)	98.6	99.5	**99.2**	98.8
Acid resistance (%)	86.5	92	**96.1**	97.6
Drug Release (%)	12.1	7.5	**3.1**	1.2

Comparative *in vitro* dissolution of Innovator and capsule formulations

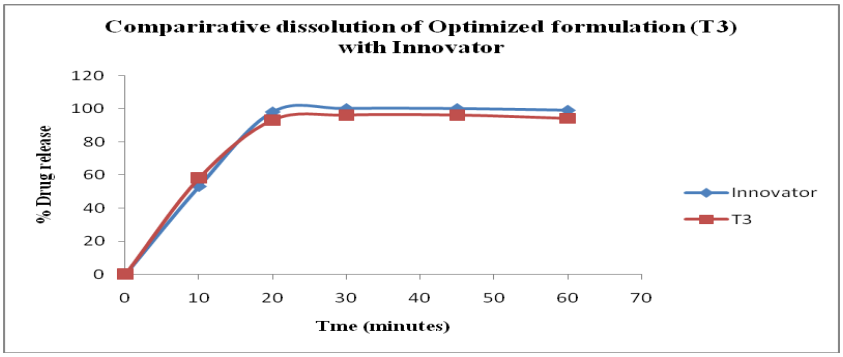
Table no. 18. Comparative *in vitro* dissolution of Innovator and capsule Formulations

Time(min)	Innovator	C1	C2	C3
	% drug release			
10	**53**	72	58	39
20	**98**	89	93	78
30	**100**	92	96	85
45	**100**	92	96	90
60	**99**	91	94	93



***In vitro* dissolution profile of formulations (T1, T2, T3) with Innovator**

Figure 9



In vitro dissolution profile of optimized formulation (C3) with Innovator

Figure 10

4. Optimization of enteric coating

According to literature review, Hydroxypropyl methyl cellulose phthalate (HPMCP) forms very harder film when compared with the Methacrylic acid copolymer (type C). So Methacrylic acid copolymer (type C) selected as enteric coating polymer. For capsules flexible film formation is needed. By type C polymer we can achieve flexible films. Optimization of enteric coating was done by comparing the parameters like assay, acid resistance and dissolution of the EC pellets with the Innovator. E1, E2, E3, E4,

E5, E6 formulations were optimized based on the following results. E1 formulation does not comply with USP limits for the % drug released in 0.1N HCl. During coating process lumps were observed, it may be due to high viscosity of the polymer. So, further trials were conducted with less viscosity grade of type C polymer i.e. 30% aqueous dispersion. E2 formulation does not comply with USP limits and Innovator for the % drug released in 0.1N HCl. Further trials were planned with increased polymer concentration. E3 formulation was found to have drug release of 13% which complies with USP limits. In buffer stage, release profile was found to be high when compared with Innovator. To retard the release profile further trials were planned with increased enteric polymer concentration. E4 formulation in buffer stage, release profile doesn't comply with Innovator. Further trials were planned with increased plasticizer concentration. E5 formulation % drug release in acid stage and release profile in buffer stage complies with Innovator. To confirm this further trial was conducted with increased polymer and plasticizer concentration. In E6 formulation %drug release was found to comply with Innovator in acid stage. But in buffer stage release was found to be decreased.

5. Optimization and evaluation studies of capsules: Evaluation tests were performed for all trials of enteric coated pellets. Then the following parameters were compared with Innovator for evaluation. C1 capsules, drug release in 0.1N HCl was found to be 12.1%; it may be due to low cushioning effect on pellets. To avoid this, cushioning effect has to be increased by increasing fill weight of capsule. Further trials were planned with increased fill weight. C2 dissolution doesn't comply with Innovator. In 10 mins dissolution was found to be high when compared with Innovator. To retard the release profile further trial C3 was planned with E5 EC pellets. C3 dissolution complies with Innovator. To confirm this formulation E6 enteric coated pellet were filled into capsules and dissolution studies were conducted, it doesn't comply with Innovator.From the above trials C3 capsules were found to be more similar with Innovator and found be optimized.

5. CONCLUTION

Optimized formulation C3 (17% w/w Hydroxy Propyl Methyl Cellulose, Methacrylic acid copolymer type C (30% aqueous dispersion), 10% TEC polymers) has successfully delayed the drug release and followed zero order drug with Higuchi release pattern. Stability studies were conducted at 40ºC / 75% RH (accelerated stability testing) for 3 months. Assay, acid resistance, dissolution release profile complies with optimized formulation (C3) and Innovator. HPLC studies combined with stability studies proved the integrity of the developed capsules. Based on the above data, it was concluded that Esomeprazole magnesium dihydrate Capsules 40mg (C3) complies with the Innovator.

6. ACKNOWLEDGEMENT

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