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DESIGN AND *IN-VITRO* CHARACTERIZATION OF DELAYED RELEASE MULTI UNIT PARTICULATES USING WURSTER TECHNOLOGY

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Abstract:

The aim of the present research was to design and characterize delayed release Multi Unit Particles (MUPS). These were produced primarily for the purpose of oral modified release dosage forms having gastro resistant and delayed-release properties. During the development of MUPS agglomeration, generations of fines and twins formation are identified as critical issues. The delayed release multiple units were prepared by layering drug suspension using Wurster technology. The prepared multi unit particulates consist of successive layers of drug layer (Esomeprazole), barrier coat and enteric coat (Eudragit L30 D55) on to inert seeds (sugar spheres #50/60). Finally the MUPS are filled into capsules (white to off white hard gelatin). The MUPS were evaluated for drug content, moisture content, particle size distribution, good flow properties and the filled capsules were evaluated for acid resistance (0.1N HCl for 2 hrs) test and In-vitro drug release (pH 6.8 phosphate buffer) and compared with the innovator product. The characterization of pellets was completed and capsules were packed into HDPE bottle (60cc with 33mm closure) and subjected to accelerated stability testing (40°C/75%RH) for six months and results were compared with initial results.

Key words: *Delayed release, multi unit particulates (MUPS), Wurster technology, Sugar spheres #50/60, Eudragit L30 D55, Q point at 30minutes NLT 75±5 %, 0.1N HCl, pH 6.8 phosphate buffer.*

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INTRODUCTION:

Recent approach that comes into existence is the one that combine the feature of both controlled release tablets and modified release capsules in one dosage form. Such system is known as MUPS technology. The delayed release systems can be used to protect the drug from degradation in the low pH environment of stomach and avoid the irritation by drug. The Esomeprazole is selected as a model drug, the drug was coated onto sugar spheres #50/60. Then further coating was followed by barrier coating was using hydrophobic agents and Enteric coating was done by using Eudragit polymer and plasticizer. In barrier coating HPC acts as binder[1-3]. The development of formulation was done by optimizing percentage (%) build up of Barrier and Enteric coating. Finally, barrier coating percentage was optimized at 55%, and enteric coating at 50%. The formulation was analyzed in 0.1N HCl up to 2hrs, the acid degradation was not exceeded 10%, and then followed by pH 6.8 phosphate buffer medium. Optimized the percentage drug release profile of Esomeprazole to be comparable with the Innovator product and evaluation of the formulation developed was found to be satisfactory [4-7].

MATERIALS AND METHODS

Materials:

Esomeprazole Magnesium Trihydrate was procured from Hetero drugs, Povidone (Kollidon 30, BASF, Germany), Polysorbate 80 (Kolliphore PS 80, BASF), Hydroxy propyl cellulose (klucel LF), Sugar Spheres (#50/60) (Colorcon), Hydroxy Propyl methyl Cellulose E5 (Dow Chemical's), Talc (Luzenac Pharma), Eudragit L30 D55 (Evonic polymers), Glyceryl Mono Stearate (BASF), Poloxamer 188 (BASF), Magnesium Oxide (Granules India), Triethyl citrate (Vertellus), Simethicone (Dow corning), methanol (Rankem chemicals), glacial acetic acid (Rankem chemicals), Acetyl Tributyl Citrate (Vertellus), Di Sodium Hydrogen Phosphate (Rankem chemicals) were used in trials.

Methods

Acid resistance

Acid resistance of Esomeprazole multi unit particulates contained capsule placed in 300 mL of 0.1N HCl medium up to 2hrs. When the test was completed, immediately discarded the medium from the vessel and collected the pellets.

Dissolution

The dissolution test carried out by USP method, the capsule containing pellets was placed in a 0.1N HCl medium followed by pH 6.8 phosphate buffer.

Assay

10 mg of omeprazole in 250 ml volumetric flask added 25 ml methanol sonicate for 15 mins, then added 50 ml of diluents and finally make up with water sonicate it up to 5 mins. Taken 5 ml of solution from above stock solution and transferred it 25 ml volumetric flask, then 2 ml of 0.25N NaOH was added and volume was made-up with diluent. Finally, 5-10 ml sample was taken and filtered through 0.45micron filter paper. The sample was Stored in a dark place.

Preformulation Studies

The pre-formulation studies of API and excipients like physical parameters evaluation like moisture content, solubility, bulk density, Drug- Excipient compatibility studies of API and excipients.

Characterization of API

Table 01: characterization of API

S. No.	Test	Result
1	Description	Cream color hygroscopic powder
2	Solubility	Complies
3	Moisture content	5.30%
4	Bulk density g/cc	0.34
5	Compressibility index %	22.7
6	Hausner's ratio	0.73

Table 02: Drug-Excipient compatibility studies

SNO	INGREDIENT NAME	RATIO	INITIAL OBSERVATION	1st WEEK	2nd WEEK	3rd WEEK	4th WEEK
1	API : Hydroxy propyl methyl cellulose	1:0.25	White to off white	NC	NC	NC	NC
2	API : Hydroxy propyl cellulose	1:0.25	White to off white	NC	NC	NC	NC
3	API : Talc	1:1	White to off white	NC	NC	NC	NC
4	API : Magnesium stearate	1:0.1	White to off white	NC	NC	NC	NC
5	API : Glyceryl mono stearate II	1:0.2	White to off white	NC	NC	NC	NC
6	API : Tween 80	1:0.01	White to off white	NC	NC	NC	NC
7	API : Eudragit L30 D55	1:0.5	White to off white	NC	NC	NC	NC
8	API : Try ethyl citrate	1:0.2	White to off white	NC	NC	NC	NC
9	API : Sugar spheres	1:1	White to off white	NC	NC	NC	NC
10	API : Magnesium oxide HA	1:0.01	White to off white	NC	NC	NC	NC
11	API: Poloxamer	1:0.1	White to off white	NC	NC	NC	NC
12	API : Povidone k 30	1:0.5	White to off white	NC	NC	NC	NC

Drug and Excipient compatibility studies

The drug and excipient compatibility studies were performed by physical method. In physical studies the drug and individual excipient, drug and all excipients and placebo was stored in 40ºC/75% RH in glass vials up to 4 weeks. The samples were observed for any colour changes in particular duration of storage.

Drug-Excipient compatibility studies (physical evaluation at 40°C/75%RH).

The following steps involved in formulation of multi unit particulates

1. Drug layering

2. Barrier coating

3. Enteric coating

1. Drug layering: The Drug dispersion was prepared based on the thickness (or) viscosity and coated onto the pellets with the assuming percentage efficiency. The problems like appearance of foam in the coating solution observed which created fines**.** It was rectified by the adding anti foaming agent for avoiding the foam during preparation of drug coating solution.

2. Barrier coating: The Barrier coating dispersion was prepared by adding different hydrophobic agents like talc, magnesium stearate. The percentage build up of coating was optimized to ensure acid resistance and desired drug release profile.

3. Enteric coating: The Enteric coating solution was prepared by adding anti tacking agent, plasticizer to the 30% Eudragit dispersion. The coating was done by maintaining low temperature. The main advantage of enteric coating is acid protection to the drug in acid media or low pH buffer media.

Process parameters: The below table explains process parameters and their importance in the process optimization and their effects on the formulation.

1. **Product Temperature**

Product temperature affects the drug-layering pattern, drug loss during layering, spray drying of coating suspension and/or twins formation. All these effects influence assay and content uniformity. The product temperature does not influence the acid resistance or dissolution.

2. Fluidization

Fluidization of sugar beads affects the pattern of flow in the coating zone and also influences the uniformity of drug layering and efficiency of the process. Therefore, both assay and content uniformity are affected. Drug layering doesn't have any impact on the acid resistance or dissolution. Hence the risk is considered to be low.

3. **Atomization/Spray rate**
Atomization pressure decides the size of globules from spray gun and spray rate will influence the volume of suspension per unit time. Globule size should be optimum since smaller size leads to spray drying and bigger globule size causes over wetting of beads and lumps formation. Spray rate should be optimum to achieve better assay and content uniformity. Too low spray rate may lead to spray drying while high spray rate may cause over wetting and lumps formation.

4. **Drying/ curing**
The drying rate of temperature was high and they easily generated fines and improper coat on to the pellets. Drying rate affects the content uniformity, dissolution and acid resistance. The curing rate defined as simply the formation of film with high integrity, smoothness and avoiding the pinholes on to the each pellet with the help of minimum film formation temperature (MFT). The literature's and polymer manufacturer recommended the curing time 90 minutes at 40-45 °C temperature.

Formulation
The below formulation table explains about drug and their excipients, percentage coating and different concentrations used in each formulation. The formulation was divided into three parts like drug layer, barrier coat and enteric coat and each coating was done based on weight gain and percentage was calculated by initial weight of loaded batch and final weight of batch.

Table 03: Formulation

Ingredient	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10
Drug layering (quantity in mg/unit)										
Sugar spheres	15	15	15	15	15	15	15	15	15	15
Esomeprazole magnesium	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Hydroxy propyl methyl cellulose	NA	6	6	6	6	6	6	6	6	6
Povidone	8	NA	NA	NA	NA	NA	NA	NA	NA	NA
Magnesium oxide	8	NA	6	6	6	6	6	NA	NA	NA
Poloxamer	3	NA	NA	NA	NA	NA	1	2	2	3
Tween 80	NA	0.6	0.6	NA	NA	NA	0.6	0.6	0.6	0.6
Simethicone	NA	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Barrier coating (quantity in mg/unit)										
Hydroxy propyl methyl cellulose	6.06	NA	NA	NA	6.46	6.46	NA	NA	NA	NA
Hydroxy propyl cellulose	NA	6.06	5.45	4.45	NA	NA	4.97	4.7	4.78	4.36
Talc	22.4	22.4	20.1	16.5	23.66	23.66	18.4	17.72	17.72	16.15
Dibutyl sebacate	0.7	NA	NA	NA	NA	NA	NA	NA	NA	NA
Magnesium stearate	1.1	1.7	1.56	1.27	1.85	1.85	1.42	1.37	1.72	1.51
Enteric coating (quantity in mg/unit)										
Eudragit	24.7	22.1	28.4	29.2	36.9	36.9	30.5	19.3	27.6	26.8
Tri ethyl citrate	2.48	2.22	2.84	2.95	3.7	3.7	3.06	NA	2.74	2.69
Acetyl tri butyl citrate	NA	NA	NA	NA	NA	NA	NA	1.92	NA	NA
Glyceryl mono stearate II	2.21	1.98	2.53	2.69	3.3	3.3	3.06	1.73	2.48	2.4

Table 04: Process parameters

Sl. No,	Parameter	Drug layering	Barrier coating	Enteric coating
1	Inlet Temperature (°C)	30-42	32-41	32-35
2	Product Temperature (°C)	28-30	28-32	22-25
3	Air inlet (CFM)	40-45	40-48	40-45
4	Spray rate (RPM)	8-10	6-8	10-12
5	Spray atomization (Bars)	1.6-1.4	1.4-1.6	1.6-1.8

Evaluation Parameters:

The following methods were done for the Evaluation of multi unit particulates like particle size distribution, bulk density, angle of repose, compressibility index, moisture content, assay, acid resistance, dissolution.

Flow properties of the Pellets

The flow properties of pellets were done by angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The below table showed results of pellets and their properties

Table 05: Flow properties of pellets

Evaluation parameter	Angle of repose	Bulk density g/cc	Tapped density g/cc	Compressibility index	Hausner's ratio
F1	23.9±0.22	0.76±0.022	0.65±0.12	13.84±0.04	0.88±0.016
F2	23.7±0.19	0.74±0.042	0.66±0.13	12.67±0.011	0.87±0.018
F3	22.5±0.10	0.75±0.021	0.66±0.24	13.36±0.041	0.86±0.092
F4	23.1±0.28	0.71±0.022	0.64±0.35	13.13±0.052	0.8±0.020
F5	22.6±0.18	0.72±0.023	0.65±0.16	12.31±0.067	0.87±0.031
F6	21.4±0.13	0.77±0.014	0.66±0.37	13.43±0.038	0.86±0.012
F7	23.1±0.17	0.76±0.035	0.65±0.21	13.83±0.018	0.87±0.053
F8	22.8±0.25	0.73±0.016	0.64±0.23	12.93±0.029	0.86±0.014
F9	23.5±0.21	0.74±0.021	0.65±0.10	12.63±0.082	0.86±0.0055
F10	22.2±0.16	0.75±0.029	0.66±0.31	12.61±0.041	0.86±0.076

Capsule filling and Evaluation

The pellets filled into capsule done by capsule filling machine. Initially, the weights were adjusted by dossier knob and locked length adjusted by locking pin. The capsules was tested in disintegration apparatus in 0.1N HCl 1000 ml at 37±0.5°C

Table 06: Capsule filling and evaluation

Batch no	Fill weight (mg)	Weight variation (%)	Locked length(mm)	DT (min)
F1	104.8 ± 1.4	0.61±0.008	14.4±0.5	8.71±0.27
F2	97.68±1.3	1.21±0.006	14.3±0.5	8.54±0.34
F3	104.68±1.5	1.35±0.007	14.4±0.5	8.61±0.31
F4	102.4±1.2	1.61±0.002	14.3±0.4	8.31±0.34
F5	106.2±2.1	0.83±0.007	14.2±0.3	8.67±0.41
F6	101.5±1.7	0.41±0.008	14.3±0.2	8.16±0.52
F7	102.7±1.6	1.23±0.004	14.1±0.7	8.24±0.36
F8	98.7±1.6	0.86±0.006	14.3±0.5	8.61±0.43
F9	105.5±1.8	0.93±0.0021	14.2±0.6	8.23±0.57
F10	106.7±1.3	1.2±0.002	14.1±0.3	8.65±0.52

RESULTS AND DISCUSSION:

Assay and Moisture content

Assay percentage of the Innovator product was 99.8±1.92, Assay percentage of F1 and F2 formulation was 98.2±1.56, 97.6±1.75 and the optimized formulation F10 showed assay percentage of 98.7±1.79 which is in limit and matches the marketed product. Moisture content of innovator product, F1and F2 formulation was 5.8±2.41, 5.8±2.41, 5.1±1.7 respectively and the moisture content of optimized formulation F10, 5.9±2.16 was comparable with the innovator product.

Table 07: Assay and Moisture content of pellets

TEST	Assay (98-102% USP)	Moisture Content NMT 8% (USP)
RLD (%)	99.8±1.92	5.8±2.41
F1	98.2±1.56	5.1±1.7
F2	97.6±1.75	6.2±1.2
F3	96.5±2.51	7.1±0.97
F4	98.3±1.62	6.7±0.94
F5	97.2±1.89	6.8±1.31
F6	99.1±1.73	7.2±0.67
F7	96.1±2.11	7.6±1.69
F8	96.9±2.31	6.5±1.24
F9	97.2±2.33	6.6±1.32
F10	98.7±1.79	5.9±2.16

Acid resistance of initial batches

The acid resistance is vital to provide protection to the pellets during gastric emptying time. The pellets were protected by enteric coating for avoiding the degradation of drug in acid media. The improvement of acid resistance was done by optimized percentage of enteric coating. Average acid resistance values of innovator product, F1, F2 is 99.07, 83.53, 85.57 and the acid resistance value of optimized formulation was 99.25 which are comparable to the innovator product or RLD (Reference Listed Drug).

Table 08: Acid Resistance of pellets

Formulation	Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	Average
RLD	98.51	99.12	98.61	99.21	99.73	99.01	99.07
F1	82.91	83.17	82.91	84.31	83.15	84.58	83.53
F2	85.91	84.62	84.26	86.27	86.93	85.14	85.57
F3	87.06	86.61	87.68	82.98	83.47	85.25	85.57
F4	88.31	88.25	87.05	89.27	89.36	89.41	88.60
F5	94.01	94.21	92.82	92.79	91.04	92.83	92.85
F6	92.17	95.23	96.51	96.57	96.92	95.28	95.38
F7	97.21	97.61	97.48	96.03	96.37	96.81	96.90
F8	98.65	98.75	99.21	99.7	97.21	97.21	98.40
F9	98.53	98.65	99.17	99.61	99.16	99.53	99.10
F10	99.62	99.67	99.28	98.89	98.91	99.51	99.25

Dissolution

The in-vitro percentage drug release of multi units contained each formulation done by dissolution method and maintained sink condition. The percent drug release of formulations F1, F2, F3, F4, F5, F6, F7, F8 F9 is 67.1±2.19, 72.5±0.98, 76.3±1.91, 88.1±2.51, 71.26±1.91, 72.9±1.09, 84.9±1.04, 89.2±1.27 94.2±2.03and the optimized formulation F10 has a maximum percentage (%) drug release of 100.1±1.91. The Q points of the formulations are not less than 75%. The optimized formulation was compared with innovator product (reference listed drug) and almost the similar drug release profile was observed.

Table 09: Percentage (%) drug release of formulations

Trials	Time(min)				
	0	**5**	**15**	**30**	**45**
F1	0	6.1±2.31	35.3±2.87	59.2±4.32	67.1±2.19
F2	0	25.4±1.91	68.2±3.47	71.4±1.95	72.5±0.98
F3	0	27.7±1.21	64.2±2.36	68.9±2.17	76.3±1.91
F4	0	30.2±2.17	82.1±1.74	84.7±1.91	88.1±2.51
F5	0	28.7±4.32	68.42±2.34	73.81±5.8	71.26±1.91
F6	0	17.2±2.01	58.8±1.08	84.6±1.21	72.9±1.09
F7	0	18.2±1.2	52.8±1.10	78.4±1.05	84.9±1.04
F8	0	11.8±0.94	47.4±1.61	72.9±1.35	89.2±1.27
F9	0	8.3±1.42	42.8±1.03	74.7±1.81	94.2±2.03
F10	0	3.2±0.92	32.1±2.61	84.7±4.81	100.1±1.91

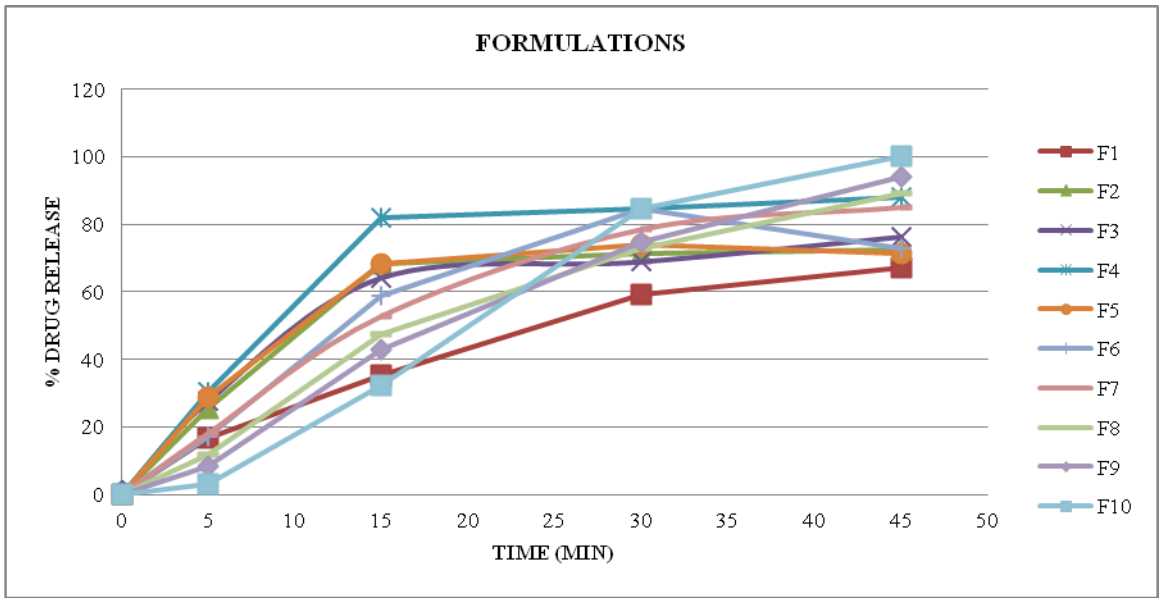

Fig.1: In-Vitro dissolution profile of all formulations

Table 10: Comparison of Innovator and Optimized formulation (% drug release)

TIME (MIN)	RLD	F10
0	0	0
5	2.9±1.19	3.2
15	26.9±3.21	32.1
30	84.7±5.71	84.7
45	101.2±2.31	100.1

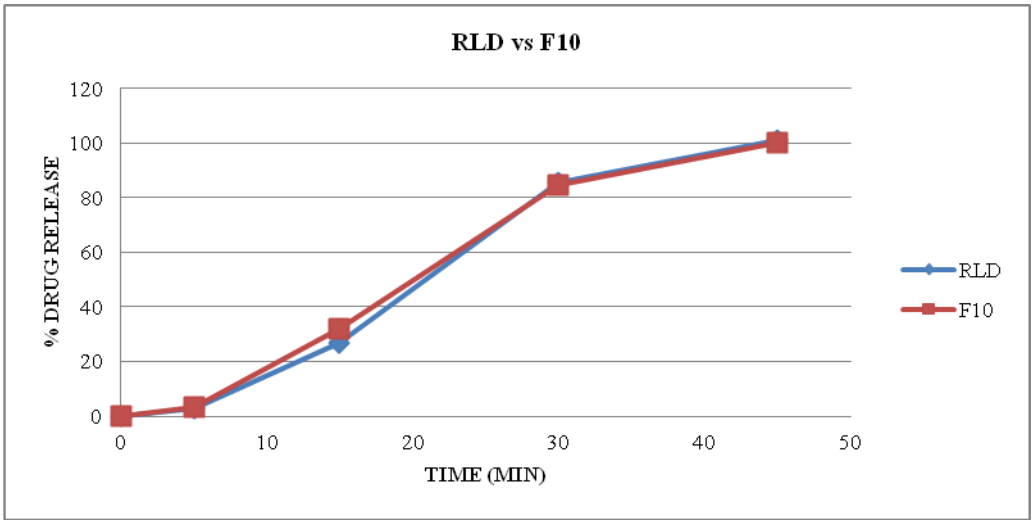

Fig. 2: In-Vitro dissolution profile of innovator and optimized formulation

Results of stability loaded batch (F10)

Assay & Moisture content

Table 11: Assay of stability batch

Trial	Condition	Duration	Assay average (%)	Moisture content Average (%)
F10	(40°C/75%RH)	1M	99.21±2.23	6.8±1.91
		2M	98.65±1.71	6.1±1.87
		3M	98.71±1.82	6.4±2.01
		6M	98.32±1.86	5.9±2.15

Acid resistance

Table 12: Acid Resistance of stability batch

Unit	RLD	F10			
	25°C/60%RH	40°C/75%RH			
	Initial	1M	2M	3M	6M
Unit -1	98.51	98.23	98.50	97.02	99.07
Unit -2	99.12	97.89	97.27	97.28	99.18
Unit -3	98.61	97.65	97.63	97.06	99.16
Unit -4	99.21	97.72	97.01	98.09	99.26
Unit -5	99.71	98.54	97.08	98.17	99.01
Unit -6	98.93	98.70	98.09	98.19	99.03

***In-vitro* Dissolution studies**

Table 13: Percentage (%) drug release of stability batch

Batch & Month	Stage	Time points (min)				
		0	5	15	30	45
		% Drug Release				
RLD	initial	0	2.9±1.19	26.9±3.21	84.7±5.71	101.2±2.31
F10	40°C/75%RH 1M	0	8.2±3.21	28.3±4.61	82.14±6.21	98.7±2.97
	40°C/75%RH 2M	0	9.1±3.71	27.8±2.13	79.51±3.41	99.52±1.02
	40°C/75%RH 3M	0	7.4±4.21	29.63±3.21	81.24±4.57	99.57±1.27
	40°C/75%RH 6M	0	4.12±1.93	32.4±3.67	81.7±5.72	99.29±1.06

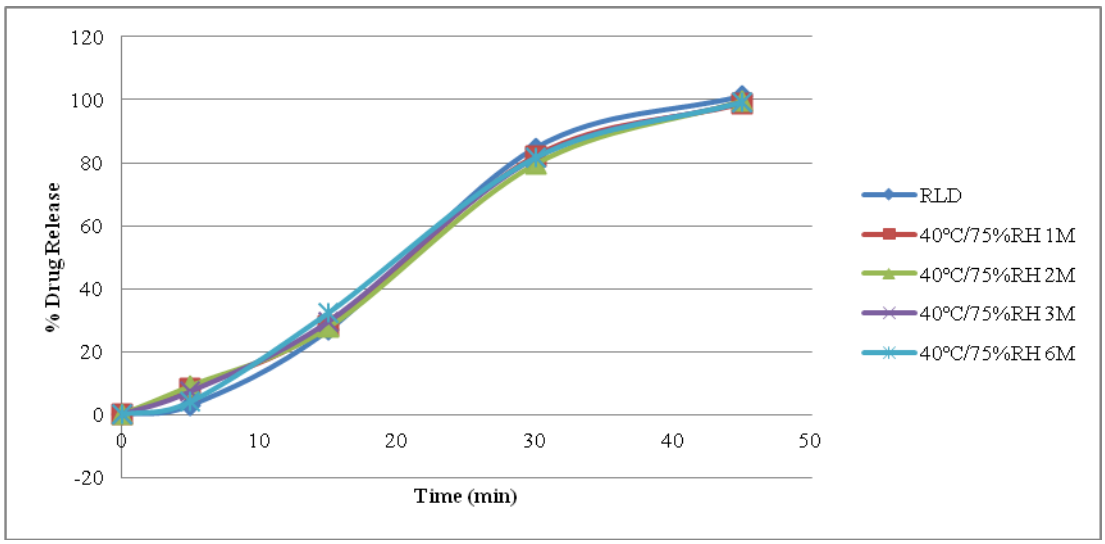

Fig.3: In-Vitro dissolution profile of innovator and stability loaded batch (F10)

CONCLUSION:

The drug Esomeprazole magnesium trihydrate was found to be suitable for the method of formulating into the multiunit particulates using the pellets as reservoir units. The release of the drug was comparable to the RLD. For the optimization of the formula various excipients and their effects on the formulation was evaluated and the optimized formula was obtained by the multiple (Drug, Barrier, Enteric) layering technique containing sugar spheres as the core were found to be suitable for formulation. All the formulations contained the DR coating in the proportion with a slight variation in their percentage w/w build up. The evaluation tests which include weight variation test fill weight, locked length, assay, dissolution, % moisture content, particle size distribution, disintegration time. All the formulations were evaluated and the formulation F10 was found to be the optimized formulation and the batch was loaded for the stability at accelerated stability condition (40 ± 2°C / 75 ±5% RH). The initial drug release was 101.1 ± 1.22 % and it was found to be 99.29 ± 1.06 % at the end of the 6th month.

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