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FORMULATION AND EVALUATION OF MODIFIED RELEASE CAPSULES OF LANSOPRASOLE

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ABSTRACT

Immediate release dosage form of Lansoprazole results rapid dissolution and rapid rise in plasma drug concentration within a short period after administration. Subsequently due to metabolism and elimination the plasma drug concentration falls below the therapeutic level. Thus require a modified release dosage form. The object of the study is to investigate controlled release property of Hypromellose pthalate by avoiding gastric release of Lansoprazole. Three coating material used in formulation Mannitol (First layer), Povidone (Second Layer) and HPMCP (Final Layer). different concentration of enteric coating, sub coating material used, and optimized the formula on basis of drug release in acid media (pH 1.2) and buffer media (pH 6.8). Drug release from capsules in acid media found 0.8 to 1.2 % and in buffer media upto 94.9 % drug released in 60 min. no impurity found in related substances test.In capsule formulation positive and encouraging results in accordance to the aim were obtained.

Keywords: Lansoprazole, HPMCP, Povidone, Mannitol.

INTRODUCTION

Solid dosage formulation and design usually involves a serious of compromises, since producing the desired properties frequently involves competing objectives. The correct selection and balance of excipients materials and processes in a solid dosage formulation, to achieve the desired response is not in practice easy to achieve. Furthermore it is essential to develop tablet formulations and processing methods which may be validated. Pellets are of a great interest to the pharmaceutical industry for a variety of reasons. Palletized products not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficiency of bioactive agents. Pellets range in size, between 0.5 to 1.5 mm,

though other sizes could be prepared, depending on the processing technique. Pharmaceutical pellets are agglomerates of fine powder particles, nearly spherical or cylindrical in shape with a narrow particle size distribution. In Order to Develop an Oral modified release Capsules of Lansoprazole, Study Focuses on controlled release property of Hypermellose pthalate by avoiding gastric release of Lansoprazole. Most PPIs absorption takes place in proximal small intestine. But PPIs are acid sensitive so a stable form should be formulated which would bypass the stomach and release the drug in small intestine.

Immediate release dosage form of Lansoprazole results rapid dissolution and rapid rise in plasma drug concentration within a short period after administration. Subsequently due to metabolism and elimination the plasma drug concentration falls below the therapeutic level. Thus require a modified release dosage form which provides intestinal release of the drug by avoiding gastric release. Looking into aforementioned characteristics, attempts have been made to develop Pellets of certain drug molecule like Lansoprazole. Selected drug candidate show most of the desirable properties for the preparation of enteric coated Pellets.

MATERIAL AND METHODS

Lansoprazole procured by Dr.Reddys lab,hydrabad, Mannitol BP, Lactose BP, Povidone BP K 30 procured by Loba chemie,cochin, Sodium hydroxy methyl Benzoate, Sodium hydroxy Propyl Benzoate, HPMCP BP (40 cps), Cetyl alcohol BP procured by S.D.Chemicals,Mumbai.

Capsules Description:

Cream colored hard gelatin capsules having LANZAP printed on both body and cap filled with white to off white spherical pellets

Standard weight – 460 mg

Label Claim – 30 mg

STANDARD FORMULA FOR PRELIMINARY TRIAL

Table No.1: Standard formula

DRUG MIXING						
Ingredients	**Batch to batch Quantity in Percentage (%)**					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Lansoprazole	8.5	8.5	8.5	8.5	8.5	8.5
Mannitol BP**	42.608	41.578	40.535	40.408	39.128	38.408
Light Magnesium carbonate BP	6.098	6.098	6.098	6.098	6.098	6.098
Lactose BP	4.634	4.634	4.634	4.634	4.634	4.634
Carmellose Calcium BP	3.049	3.049	3.049	3.049	3.049	3.049
Sucrose BP ** 25#/30#	11.585	11.585	11.585	11.585	11.585	11.585
Mannitol BP	**3.5**	**4.0**	**4.5**	**5.0**	**5.28**	**5.5**
Sucrose BP (syrup grade)	6.098	6.098	6.098	6.098	6.098	6.098
Povidone BP K 30	0.365	0.365	0.365	0.365	0.365	0.365
Sodium hydroxy methyl Benzoate	0.0067	0.0067	0.0067	0.0067	0.0067	0.0067
Sodium hydroxy Propyl Benzoate	0.00061	0.00061	0.00061	0.00061	0.00061	0.00061
Purified water @	86.60	86.60	8.660	86.60	86.60	86.60
SUB COATING						
Povidone BP (K30)	**3.40**	**3.63**	**3.84**	**4.0**	**4.2**	**4.5**
Isopropyl alcohol BP @	45.757	45.757	45.757	45.757	45.757	45.757
ENTERIC COATING						
HPMCP BP (40 cps)	**8.5**	**8.8**	**9.06**	**9.2**	**9.4**	**9.6**
Cetyl alcohol BP	1.006	1.006	1.006	1.006	1.006	1.006
TiO2 BP	0.649	0.649	0.649	0.649	0.649	0.649
Acetone BP @	74.486	74.486	74.486	74.486	74.486	74.486
Isopropyl alcohol BP @	49.657	49.657	49.657	49.657	49.657	49.657

@ Quantity non contributory in final quantity

CRITICAL PROCESS PARAMETER

Table No 2: Blending, Micronization & their Critical Parameter

S.No.	**Stages**	**Name of Parameters**	**Operation parameter**
1	Micronization	Main air Pressure	6.5 kg/cm^2
		Cyclic air pressure	5.1-5.3 kg/cm^2
2	Blending (Drug Mixing)	RPM	12
		Time	60 min

Table No.3: Process Parameter during Sub Coating

S.No.	**Name of Parameters**	**Operation parameter**
1	Inlet temp (^{O}C)	60.0-68.0
2	Exhaust Temp (^{O}C)	51.0-52.0
3	Pump RPM	20-25
4	Atomization air pressure (Kg/cm^2)	3.0
5	Pan RPM	13
6	Gun Distance From Bed (cm)	25
7	Spray rate (gm/min/gun)	150
8	Drying Time (Min)	45

Table No.4: Process Parameter during Enteric Coating

S.No.	Name of Parameters	Operation parameter
1	Inlet temp (^{O}C)	60-66
2	Exhaust Temp (^{O}C)	50-51
3	Pump RPM	35
4	Atomization air pressure (Kg/cm^2)	3.5
5	Disc RPM	10-13
6	Gun Distance From Bed (cm)	25
7	Spray rate (gm/min/gun)	110
8	Drying Time (Min)	45

Table No.5: Process Parameter during Capsule Filling

S.No.	Name of Parameters	Operation parameter
1	Speed of the machine	96 SPM

TEST AND SPECIFICATIONS

Table No.6: Test Specification of Process during various stages

S.No.	Stages	Tests	Specifications
1	Drug mixing	Content uniformity	100 ± 15 % RSD NMT 6.0 %
		Moisture content before drug coating	For information
2.	Drug Coating	Moisture content after drug coating	Desired Moisture content NMT 2.0 % w/w after drying for 12 hrs at inlet temp not exceeding 40^{o}C
		Assay	90-110 % w/w
3.	Sub Coating	Weight build up	NLT 4.0 % from the actual weight of dug coated pellets
		Content uniformity	85 %- 115 % RSD NMT 6.0 %
		Assay	NLT 7.86 % and NMT 9.13 %
4	Enteric coating	Drug Release Profile at acid stage	NMT 2.0 % at acid stage
		Drug Release Profile at Buffer stage	NLT 85 % at buffer stage
		Solvent Content	For IPA NMT 5000 ppm For acetone NMT 5000 ppm
		Related Substances	Unknown Impurity NMT 0.3 % Lansoprazole Sulphones NMT 0.5 % Total Impurities NMT 0.1 %
5	Capsule filling	Individual weight variation	Standard weight ± 6.0 %
		Drug Release Profile in acid Stage	NMT 10 % of the labeled amount of lansoprazole is dissolved in 60 min
		Drug Release Profile Buffer stage	NLT 80 % (Q) of the labeled amount of lansoprazole dissolved in 60 min
		Assay	(90 % -110 %)
		Related Substances	NMT 2.0 %
		LOD	NMT 5.0 % w/w
6	Stability Study	Drug Release in acid stage	NMT 10 % of the labeled amount of lansoprazole is dissolved in 60 min
		Drug Release in buffer stage	NLT 80 % (Q) of the labeled amount of lansoprazole dissolved in 60 min
		Assay	NLT 27.0 mg and NMT 33.0 mg
		Related Substances	NMT 2.0 %

Table No 7: Process Parameter during Drug coating

S.No.	Name of Parameters	Operation parameter
1	Pump RPM	12-65
2	Atomization air pressure (Kg/cm^2)	2.1-2.2
3	Pan RPM	36
4	Gun Distance From Bed (cm)	30-32
5	Spray rate (gm/min/gun)	130
6	Spray on time min (min)	2-3
7	Spray Off Time (min)	5

FORMULATION OF MODIFIED RELEASE CAPSULES

Micronization of active ingredient

Micronization of Lansoprazole carried out for getting desired particle size. Fluid energy mill (Malvern) is used by maintaining its cyclic pressure 5-6 kg/cm^2 and Main air pressure 6-7 $kg/cm^{2.}$results depicted in table no.8

Drug Mixing

Blend the Micronized Drug with Light magnesium carbonate, mannitol, Lactose, carmellose calcium. Blending operation carried out in Double cone Blender for 60 min at 12 rpm. In the preliminary formulation trial, content uniformity of batches F-1 to F-6 found well within the limits. Average content uniformity obtained 95 to 99 % w/w. Maximum uniformity of content of Lansoprazole achieved in Batch F-3. Individual. Results depicted in table no.9

Drug Coated Pellets

Syrup Preparation:

Sucrose Syrup prepared in steam kettle with Binder Povidone and Sodium methyl paraben & Sodium Propyl Paraben. Syrup preparation successfully done by maintaining Variables – top stirrer rpm, Paddle stirrer rpm and temperature of Kettle.

Coating:

Centrifugal coating pan used for drug coating. During coating an additional mannitol layer also applied. Ratio of Mannitol is changing in each batch to optimize the effect of outer layer Mannitol in release rate of drug. Peristaltic pump rpm, inlet temp and outlet temperatures of air were critical variable observed during coating. Ratio of Mannitol variedin Batch to optimize the effect of outer layer Mannitol in release rate of drug. Assay of content of Lansoprazole found 99.3 % w/w which is most optimum among all the batches.

Drying:

Drying of drug coated pellets is done in Tray dryer. Drying Temperature and Drying Times were important variables of Drying. Moisture content observed after 12 hrs of drying observed in batch F-3 as 0.91 % w/w which is least among all batches.resuts depicted in table no.10

Sub coated Pellets

Sub Coating solution Preparation:

Solution Prepared in stirrer. Povidone is sub coated material used with isopropyl alcohol as vehicle. Ratio of Povidone is changing in each batch to optimize the sub coating layer and monitor the influence of Drug release.

Sub Coating:

Centrifugal coater is used for Sub coating. Peristaltic pump rpm, Powder charging rpm and Disc rpm are critical variable observed during coating. Sub coated pellets having some weight build up than drug coated pellets. Ration of Povidone varied in all batches to optimize Sub coating layer. Weight build up observed from 4.1 to 4.6 % w/w.

Enteric coated Pellets

Enteric Coating solution Preparation:

Solution prepared in stirrer. Hypromellose pthalate with acetone, cetyl alcohol, and isopropyl alcohol used as vehicle. Titanium dioxide also used as opacifier in solution. Ratio of HPMCP is changing in each batch to optimize the enteric coating layer thickness and also to optimize the drug release.

Enteric Coating:

Centrifugal coater is used for Sub coating. Peristaltic pump rpm, Powder charging rpm and Disc rpm are critical variable observed during coating. Centrifugal coater is used for enteric coating. Peristaltic pump rpm, Powder charging rpm and Disc rpm are critical variable observed during coating. Enteric coated pellets evaluated for Content uniformity and Drug release profile in acid and buffer media. Average content uniformity observed 93 to 99 % w/w while best results obtained with batch F-2. Average drug release in acid media found 0.6 to 1.05 % while Drug release in buffer media observed as 84.4 to 96.8 % .Related substances and solvent content test also been carried out. Individual results depicted in tables. As Quantity of HPMCP increasing in formulation, release of drug is decreasing. Formulation batch F-3 given desired result. Drug released in buffer media from enteric coated Pellets was 96.8 % which is maximum among all other batches.

Capsule filling:

Enteric coated pellets filled in gelatin capsules by capsule filling machine. Individual weight variation of filled weight is critical parameter observed. Enteric coated pellets filled in hard gelatin capsules. Capsules evaluated for Individual fill content of capsules, Individual weight variation of capsules Found well within limits. Drug release from capsules in acid media found 0.8 to 1.2 % and in buffer media upto 94.9 % drug released in 60 min. Related substance test carried out for testing impurity after Capsules filling.

Table No.8: Micronization of Lansoprazole

Result	Particle size (µm)			
Volume under %	10 %	50 %	90 %	100 %
Size (µm)	0.48	2.66	7.41	17.62

Table No. 9: Content uniformity of Lansoprazole in Drug mix (Blend)

Limits: Content of Lansoprazole 100 ± 15 %

Sample No.	Batch to Batch Content Uniformity (in %)					
	F-1	F-2	F-3	F-4	F-5	F-6
1	98.5	101.2	104.5	99.2	91.2	95.6
2	95.8	90.6	99	98.2	90.5	94.8
3	95.6	99.8	97	99.6	99.5	96.8
4	92.5	87.3	101.2	91.2	98.2	98.9
5	96.0	100.7	98.9	98.6	91.5	99.1
6	92.1	90.5	96.5	97.5	99.2	99.5
7	89.6	103.3	98.8	101.3	96.2	98.6
8	100.1	95.2	99.5	101.5	99.1	99.1
9	94.9	95.3	96.3	100.5	99	92.8
10	90.6	91.4	100.7	103.1	91.8	99.1
Avg.	95.0	95.7	99.3	99.1	95.7	97.46

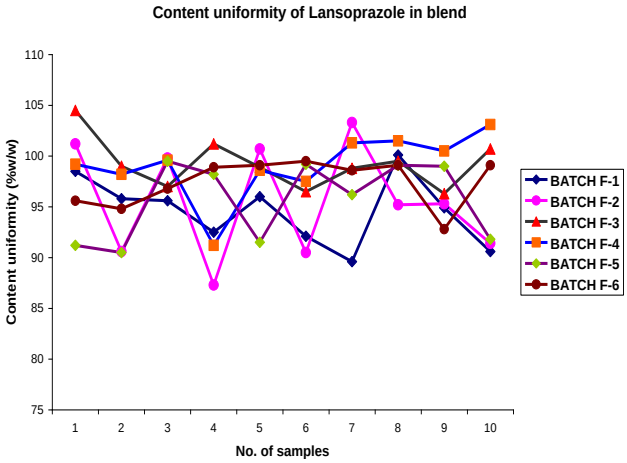


Figure No.1: Content Uniformity in Drug Mixing stage

Table No.10: Drying of Drug coated pellets

Limit: Moisture content: NMT 2.0 % w/w after 12 Hr

Parameter	Batch F -1			Batch F -2			Batch F-3		
	Drying time (hrs)			Drying time (hrs)			Drying time (hrs)		
	5	10	12	5	10	12	5	10	12
Moisture content	3.35	3.38	1.93	3.36	3.37	1.92	2.27	1.75	0.91
Parameter	**Batch F -4**			**Batch F -5**			**Batch F-6**		
	Drying time (hrs)			**Drying time (hrs)**			**Drying time(hrs)**		
	5	10	12	5	10	12	5	10	12
Moisture content	3.12	3.45	1.50	3.32	3.15	1.14	3.10	1.90	0.98

Figure No.2: Moisture Content of Drug coated Pellets during and after Drying

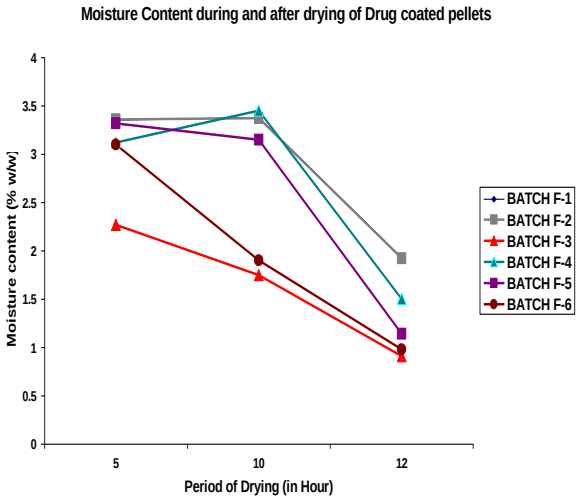


Table No.11: Assay of Drug Coated pellets

Limit: Content of Lansoprazole 90 to 110 % w/w

Sample No.	No. of Batches					
	F-1	F-2	F-3	F-4	F-5	F-6
1	96.8	97.5	102.5	97.2	98.3	99.3

Table No. 12: Weight Build up after sub coating

Limit: NLT 4.0 % from the actual weight of dug coated pellets

Batch No.	No. Of Batches					
	F-1	F-2	F-3	F-4	F-5	F-6
Actual build up	4.69 %	4.50 %	4.50 %	4.12 %	4.51 %	4.35 %

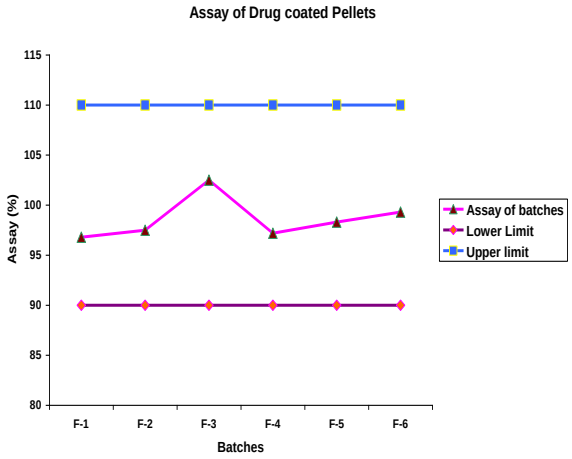


Figure No.3: Assay of Lansoprazole in Drug Coated Pellets

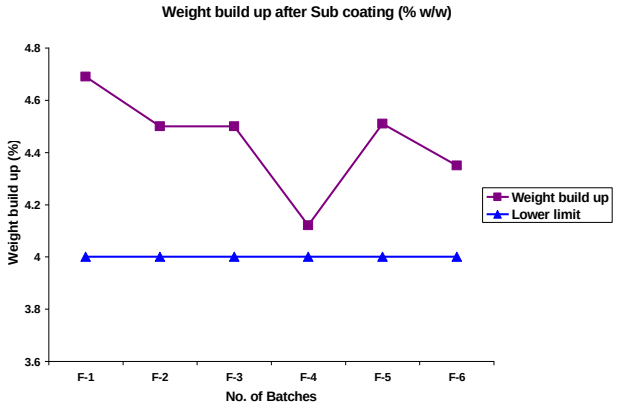


Figure No.4: Weight Build up of Sub Coating

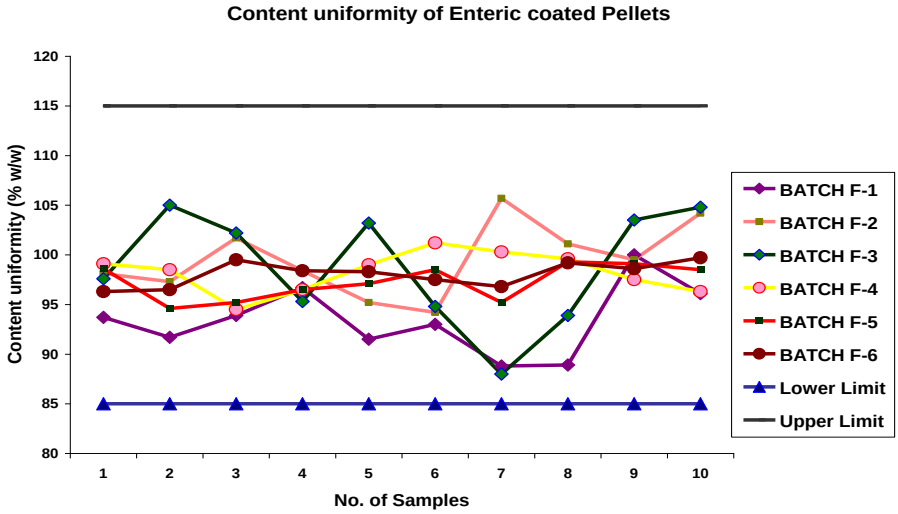


Figure No.5: Content Uniformity of Lansoprazole in Enteric coated Pellets

Table No. 13: Assay of Lansoprazole in Enteric coated pellets

Limits: Content of Drug NLT 7.86 % and NMT 9.13 % w/w

Parameter	No. of Batches					
	F-1	F-2	F-3	F-4	F-5	F-6
Assay	8.181 %	8.548 %	8.066 %	8.452 %	8.440 %	8.510 %

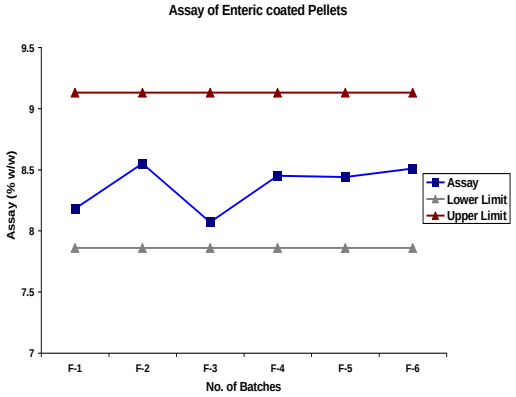


Figure No.6: Assay of Lansoprazole in Enteric coated Pellets

Table No. 14: Drug release in acid media from enteric coated Pellets

Limits: NMT 2.0 % content of drug release in acid media within 60 min

No. of samples	Content of Lansoprazole released in acid Media (in 60 min)					
	F-1	F-2	F-3	F-4	F-5	F-6
1	0.5	0.6	0.5	0.7	0.2	0.1
2	1.1	0.9	0.4	0.7	0.4	0.4
3	1.6	1.5	0.2	0.6	0.0	0.6
4	1.1	1.1	1.2	1.0	0.5	0.2
5	0.9	0.5	1.1	0.3	1.1	0.9
6	1.1	0.4	0.3	0.9	0.2	1.6
Min	0.5	0.4	0.2	0.3	0.0	0.1
Max	1.6	1.5	1.2	1.0	1.1	1.6
Avg	1.05	0.83	0.61	0.7	0.4	0.6

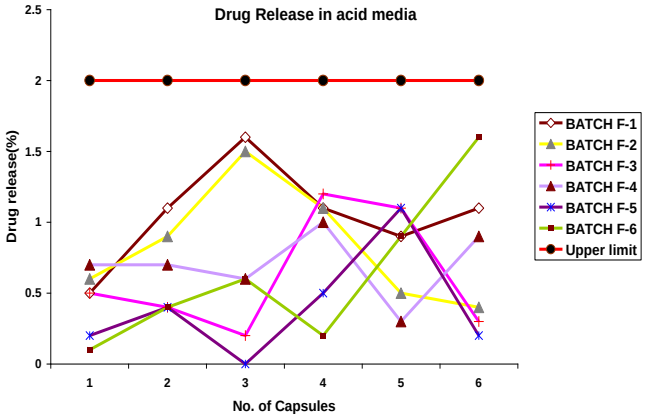


Figure No.7: Drug release profile in acid media from enteric coated Pellets

Table No. 15: Drug release profile in Buffer media from enteric coated Pellets

Limits: NLT 85 % content of drug release in Buffer Medium within 60 min

Batches	Content of Lansoprazole (%) Released in Buffer Media						
	Sampling Time (Min)						
	5	10	15	20	30	45	60
F-1	8.7	17.6	22.4	34.6	56.8	71.6	84.4
F-2	12.6	19.5	28.2	37.5	61.8	76.9	90.1
F-3	17.3	21.5	38.5	52.9	68.42	88.2	96.8
F-4	16.5	23.4	36.9	48.4	58.2	82.4	91.2
F-5	15.9	25.6	36.3	44.7	61.6	82.5	89.5
F-6	13.7	21.8	37.1	48.6	57.9	77.8	88.4

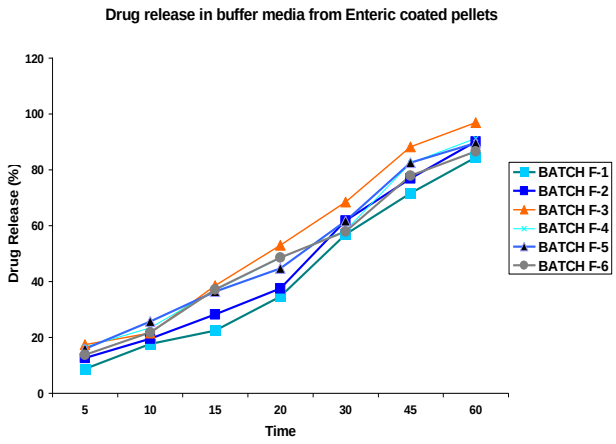


Figure No.8: Drug Release of Enteric coated Pellets in Buffer Media (pH 6.8)

Table No.16: Solvent content of Enteric Coated pellets

Limit: For IPA NMT 5000 ppm For acetone NMT 5000 ppm

Solvents	No. of Batches					
	F-1	F-2	F-3	F-4	F-5	F-6
IPA (ppm)	7.34	356.372	370.770	381.120	379.254	381.152
Acetone (ppm)	1.10	432.995	547.119	475.120	489.125	510.124

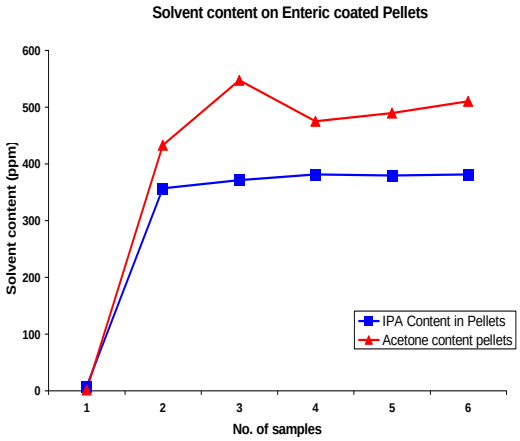


Figure No.9: Solvent Content of Enteric coated Pellets

Figure No.10: Drug release in acid media from Capsules

Limits: NMT 10 % of the labeled amount of lansoprazole is dissolved in 60 min

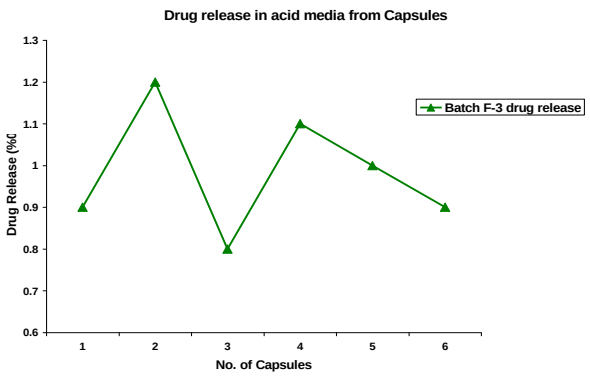
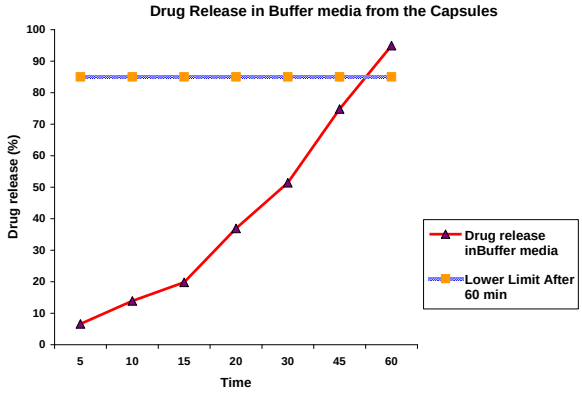


Figure No.11: Drug release in Buffer media from Capsules

Limit: NLT 80 % (Q) of the labeled amount of lansoprazole dissolved in 60 min



SUMMARY AND CONCLUSION

Formulation of modified release capsules carried out with six preliminary trials. In the preliminary formulation trial, content uniformity of batches F-1 to F-6 found well within the limits. Average content uniformity obtained 95 to 99 % w/w. Drug mix (Blend) processed in centrifugal coating pan for drug coating during coating ratio of Mannitol varied in each batch to optimize the effect of outer layer Mannitol in release rate of drug. Assay of content of Lansoprazole found 96.8 to 102.5 % w/w. Drug coated pellets dried in tray drier, moisture content observed after 12 hrs of drying observed in batch F-3 as 0.91 % w/w which is least among all batches.Sub coated pellets again coated with HPMCP, enteric coated pellets evaluated for Content uniformity and Drug release profile in acid and buffer media. Average content uniformity observed 93 to 99 % w/w while best results obtained with batch F-2.while Batch F-3 contain 98.8 %. Average drug release in acid media found 0.6 to 1.05 % while Drug release in buffer media observed as 84.4 to 96.8 % .Batch F-3 Average release of active in acid media was 0.6 % which is comparatively lowest among all formulation. Most optimization factor was Release of drug in buffer media and Batch F-3 released 96.8 % of active in 60 min of multipoint dissolution study and Batch f-3 fulfill the criteria of objective. So on basis of in process and quality control data Batch F-3 optimized and forwarded for next processing stages.

Enteric coated pellets filled in gelatin capsules by capsule filling machine. Capsules evaluated for Individual fill content of capsules, individual weight variation of capsules found well within limits. Drug release from capsules in acid media found 0.8 to 1.2 % and in buffer media upto 94.9 % drug released in 60 min. no impurity found in related substances test.In capsule formulation positive and encouraging results in accordance to the aim were obtained. Percentage of mannitol 3.5 % to 5.5 %, povidone 3.4 to 4.5 % and Enteric coating layer HPMCP 8.5 % to 9.6 % used. as percentage of coating layer increasing, drug release from enteric coated pellets in acid media (pH 1.2) is decreasing from 1.05 % to 0.4 % after 60 min of dissolution study, while in buffer media (pH 6.8) drug release is increasing Batch F-1(84.4), Batch F-2 (90.1 %), Batch F-3 (96.8 %) while release rate is decreasing Batch F-4 (91.2%), Batch F-5 (89.5%), Batch F-6 (88.4%). After filling enteric coated pellets in hard gelatin capsules drug release in acid media found 0.8 % and in buffer media it was 94.9 %.

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