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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Multiple Unit Pellet System of Dexlansoprazole

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ABSTRACT
The aim of present work was to develop extended release multiple unit pellets of Dexlansoprazole used for the treatment gastroesophageal reflux disease, by extrusion- spheronization (E/S) and solution/suspension layering (S/S) method. In the E/S, Optimization of Dexlansoprazole drug pellets were carried out with different diluents. To the optimized drug pellets, subsequent seal coating, barrier coating and enteric coating were given and formulation optimization was carried out; finally lubricated with Colloidal silicon dioxide and Talc. In the S/S method, Delayed release pellets of Dexlansoprazole were prepared by S/S on to the inert sugar spheres. Seal coating was carried out with sugar spheres and HPMC 5 cps. Optimization of drug coating was done with different weight seal coated pellets and for the concentration of binder and wetting agent. Further optimization of barrier coating and enteric coating was accomplished. Triethyl Citrate (TEC), Polyethylene Glycol 400 were selected for the plasticizer optimization. In the E/S Optimization of Drug pellets: DD5 with mannitol was optimized. Further in seal coating stage, DD5S2 and in barrier coating, DD5S2B2 was optimized. For enteric coating, DD5S2B2P3 was optimized. In the S/S: Seal coating: Core sugar spheres weight (18, 28 & 38 mg/unit) was optimized by using different HPMC weights (1, 2 & 3 mg/unit). In these 40 mg/unit (DS8) seal coated pellets were optimized. Drug loading process was evaluated by using binders, finalized the process with HPMC, 5cps -12.5 mg/unit (DS8D6). Barrier coating formulation trials were done by using binders. Barrier coating was optimized (DS8D6B5) with Hypromellose, 5cps (7mg/unit) and Sodium Lauryl Sulfate. Enteric coating was optimized (B5E6) with enteric polymer Eudragit L30D55 (234 mg/unit with 70.2 mg/unit solids) and plasticizer TEC (7 mg/unit) by evaluating acid resistance in 0.1N HCl. Dexlansoprazole Delayed Release formulation by E/S and S/S was advantageous.
Keywords: *Delayed release multiple unit pellets, Dexlansoprazole*

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INTRODUCTION

The oral route of administration of drugs is the most important method for achieving systemic effects. In the process of absorption of drug from oral route dissolution is the rate limiting step [1].

Multiparticulate drug delivery systems (like pellets, granules, etc.) provide better gastrointestinal distribution and transportation resulting in minimizing the peak plasma fluctuations and side effects related to drug which are major advantages over single unit systems. Also, these delivery systems facilitate co-administration of incompatible drugs (using coated pellets) [2-4].

Pellets are oral dosage forms which are spherical beads with a mean particle size between 0.5 to 2 mm. Pellets are pharmaceutical formulations in which the active pharmaceutical ingredient is present as a number of small discrete units, each exhibiting some desired characteristics [5].

Pellets provide flexibility of delivery system, i.e. either be filled in capsules or compressed into tablets. Other advantages include lower irritative effects due to decreased local concentration and lower the risk effect due to dose dumping [6-9]. Pellets reduce the intra- and inter-subject variability in drug concentration by reducing the gastric emptying rate and transit time [10].

Extrusion-spheronisation is one of the most common and widely accepted methods for preparation of pellets in pharmaceutical technology [11, 12]. It is a multi-step process which produces pellets of good physical strength, uniform diameter and good porosity. The main advantage of pellets prepared by extrusion-spheronization method over other methods is the ability to incorporate high levels of active

ingredient without producing excessively large particles [13, 14].
Since the *Dexlansoprazole* drug belongs to BCS class I, it is necessary to retard dissolution to ensure delayed release of drug. Dexlansoprazole is a Proton-pump inhibitor, having an elimination half-life of 1-2 hrs and its maximum daily dose is 30-40 mg/kg/day. Hence it is an ideal candidate for extended release formulation. The objective of the study is to prepare Dexlansoprazole Delayed release pellets by extrusion spheronization technology.

MATERIAL AND METHODS

Dexlansoprazole was procured from MSN Laboratories Private Limited, Provided by Sura Labs, Dilsukhnagar. Acetone, Colloidal Silicon Dioxide (Aerosil 200), Crospovidone (Kollidon-CL), Ethanol, Eudragit L30D55, Hypromellose Phthalate (HP55), Hypromellose, 3 cps, Hypromellose, 5 cps, Isopropyl Alcohol, Low-substituted Hydroxy Propyl Cellulose (LH-31), Magnesium Carbonate, Meglumine, Methylene Chloride, Poloxamer (Lutrol-188), Polyethylene Glycol 400, Polysorbate 80, Povidone (PVP K-30, 17), Sodium Lauryl Sulphate, Talc, Titanium Dioxide, Triethyl Citrate were purchased from S.D Fine chemicals, Mumbai.

METHODOLOGY:

Method A: Extrusion-Spheronization: DSP drug pellets were prepared by extrusion-spheronization and further seal coating, drug coating, barrier coating and enteric coating was done subsequently by layering technique in fluid bed processor.

Table 1: Optimization of Dexlansoprazole drug pellets by extrusion-spheronization (DD1-DD13)

Quantity→	mg/unit												
Ingredients↓	**DD1**	**DD2**	**DD3**	**DD4**	**DD5**	**DD6**	**DD7**	**DD 8**	**DD 9**	**DD 10**	**DD 11**	**DD12**	**DD13**
Dry mix													
Dexlansoprazole	43.5	43.5	43.5	43.5	**43.5**	43.5	43.5	43.5	43.5	43.5	43.5	43.5	43.5
MCC (Avicel PH 102)	75	75	70	66	**-**	16.5	33	49.5	16.5	33	49.5	16.5	-
Mannitol	-	-	-	-	**66**	49.5	33	16.5	-	-	-	-	-
Lactose Monohydrate	-	-	-	-	**-**	-	-	-	49.5	33	16.5	-	-
Glyceryl Monostearate	-	-	-	-	**-**	-	-	-	-	-	-	49.5	66
Magnesium Carbonate	30	30	30	30	**30**	30	30	30	30	30	30	30	30
Low-substituted-Hydroxy Propyl Cellulose (LH-31)	2	2	2	2	**2**	2	2	2	2	2	2	2	2
Crospovidone (Kollidon-CL)	-	-	5	5	**5**	5	5	5	5	5	5	5	5
Poloxamer (Lutrol-188)	-	-	-	4	**4**	4	4	4	4	4	4	4	4
Binder Solution													
Hypromellose, 5 cps	5	-	5	5	**5**	5	5	5	5	5	5	5	5
Povidone (PVPK-30)	-	5	-	-	**-**	-	-	-	-	-	-	-	-
Purified water**	80	80	50	50	**50**	50	50	50	50	50	50	50	50
Total weight of Pellets	155.5	155.5	155.5	155.5	**155.5**	155.5	155.5	155.5	155.5	155.5	155.5	155.5	155.5

** It will not appear in final product except in traces.

Table 2: Optimization of Dexlansoprazole Seal Coating

Quantity→	**mg/unit**		
Ingredients↓	**DD5S1**	**DD5S2**	**DD5S3**
Drug pellets	155.5	**155.5**	155.5
Hypromellose, 5 cps	2	**4**	6
Talc	1.5	**3**	4.5
Purified water**	60	**120**	180
Total weight of seal coated pellets	159	**162.5**	166
% w/w solids in solution/suspension	5.51	**5.51**	5.51
% Weight build up	2.25	**4.50**	6.75

** It will not appear in final product except in traces.

Table 3: Optimization of Dexlansoprazole Barrier Coating

Quantity→	**mg/unit**		
Ingredients↓	**DD5S2B1**	**DD5S2B2**	**DD5S2B3**
Seal coated pellets	162.5	**162.5**	162.5
Hypromellose, 5 cps	10	**12**	14
Talc	8	**9**	11
Sodium Lauryl Sulphate	1	**3**	3
Purified water**	130	**200**	240
Total weight of barrier coated pellets	181.5	**186.5**	190.5
% w/w solids in solution/suspension	12.75	**10.71**	10.45
% Weight build up	11.69	**14.77**	17.23

Table 4: Optimization of Dexlansoprazole Enteric Coating

Quantity→	**mg/unit**				
Ingredients↓	**DD5S2B2P1**	**DD5S2B2P2**	**DD5S2B2P3**	**DD5S2B2P4**	**DD5S2B2P5**
Barrier coated pellets	186.5	186.5	**186.5**	186.5	186.5
Eudragit L30D55*	60 (18)	80 (24)	**92 (27.6)**	110 (33)	120 (36)
Triethyl Citrate	2	2.4	**3**	3	3.3
Talc	2	2	**3**	3	3
Titanium Dioxide	1	1	**1**	1	1
Purified water**	150	192	**223**	260	280
Total weight	209.5	215.9	**221.1**	226.5	229.8
% w/w solids in solution/suspension	10.70	10.60	**10.75**	10.61	10.63
% Weight build up	12.33	15.76	**18.55**	21.45	23.22
Lubrication					
Enteric coated pellets	209.5	215.9	**221.1**	226.5	229.8
Colloidal Silicon Dioxide (Aerosil 200)	0.9	0.9	**0.9**	0.9	0.9
Talc	1	1	**1**	1	1
Total weight of lubricated pellets	211.4	217.8	**223**	228.4	231.7

*Contains 30% w/w solid content

** It will not appear in final product except in traces.

Method B: Solution/suspension layering

Delayed release pellets of Dexlansoprazole were prepared by solution/suspension layering on to the inert sugar spheres.

Table 5: Optimization of Dexlansoprazole (DSP) Seal coating

Quantity→	**mg/unit**								
Ingredients↓	**DS1**	**DS2**	**DS3**	**DS4**	**DS5**	**DS6**	**DS7**	**DS8**	**DS9**
Sugar spheres	18	18	18	28	28	28	38	**38**	38
Hypromellose, 5 cps	1	2	3	1	2	3	1	**2**	3
Purified water**	50	60	60	50	60	60	50	**60**	60
Weight of seal coated pellets	19	20	21	29	30	31	39	**40**	41
% w/w solids in solution/suspension	1.96	3.23	4.76	1.96	3.23	4.76	1.96	**3.23**	4.76
% weight build up	5.56	11.11	16.67	3.57	7.14	10.71	2.63	**5.26**	7.89

** It will not appear in final product except in traces.

Table 6: Optimization of DSP Drug coating with different weight seal coated pellets

Quantity→	mg/unit						
Ingredients↓	**DS2D1**	**DS5D2**	**DS8D3**	**DS8D4**	**DS8D5**	**DS8D6**	**DS8D7**
Seal coated pellets	20	30	40	40	40	**40**	40
Dexlansoprazole	43.50	43.50	43.50	43.50	43.50	**43.50**	43.50
Povidone (PVPK-17)	-	-	-	10	-	-	-
Hypromellose, 3 cps	10	10	10	-	-	-	-
Hypromellose, 5 cps	-	-	-	-	10	**12.5**	15
Meglumine	2	2	2	2-	2	**2**	2
Polysorbate 80	1	1	1	1	1	**2**	2
Isopropyl Alcohol**	100	100	100	100	150	**160**	170
Methylene Chloride**	100	100	100	100	150	**160**	170
Weight of drug loaded pellets	76.50	86.50	96.50	96.50	96.50	**100.00**	102.50
% w/w solids in solution/suspension	22.03	22.03	22.03	22.03	15.85	**15.79**	15.53
% weight build up	282.53	188.35	141.26	141.26	141.26	**150.01**	156.26

** It will not appear in final product except in traces.

Table 7: Optimization of DSP Barrier coating

Quantity→	mg/unit				
Ingredients↓	**DS8D6B1**	**DS8D6B2**	**DS8D6B3**	**DS8D6B4**	**DS8D6B5**
Drug pellets	100.00	100.00	100.00	100.00	**100.00**
Hypromellose, 3 cps	3	-	-	-	**-**
Hydroxypropyl Cellulose	-	3	-	-	**-**
Hypromellose, 5 cps	-	-	4	6	**7**
Sodium Lauryl Sulfate	-	-	0.5	1	**1**
Talc	1	1	1.5	2	**2**
Isopropyl Alcohol (70%)**	50	50	60	75	**90**
Methylene chloride (30%)**	50	50	60	75	**90**
Weight of barrier coated pellets	104.00	104.00	106.00	109.00	**110.00**
% w/w solids in solution/suspension	3.85	3.85	4.76	5.66	**5.26**
% weight build up	4.00	4.00	6.00	9.00	**10.00**

Table 8: Optimization of DSP Enteric coating (B5E1-B5E8)

Quantity→	mg/unit							
Ingredients↓	**B5E1**	**B5E2**	**B5E3**	**B5E4**	**B5E5**	**B5E6**	**B5E7**	**B5E8**
Barrier coated pellets	110.00	110.00	110.00	110.0(	110.0(	110.00	110.0(	110.0(
Eudragit L30D55*	50	-	-	167 (50.1)	200 (60)	234 (70.2)	250 (75)	234 (70.2)
Hypromellose Phthalate (HP55)	-	60	60	-	-	**-**	-	-
Triethyl Citrate	5	6	9	5.01	6	**7**	7.5	-
Polyethylene Glycol 400	-	-	-	-	-	**-**	-	7
Talc	5	6	9	5.01	9	**14**	15	14
Polysorbate 80	0.104	0.104	0.104	0.104	0.104	**0.104**	0.104	0.104
Purified water**	-	-	-	135	150	**190**	202	190
Acetone**	400	400	400	-	-	**-**	-	-
Ethanol**	190	190	190	-	-	**-**	-	-
Weight of Enteric coated pellets	170.11	182.11	188.11	170.2	185.11	**201.31**	207.61	201.31
% w/w solids in solution/suspension	9.25	10.89	11.69	19.29	20.57	**20.51**	20.57	20.51
% weight build up	54.64	65.55	71.00	54.75	68.27	**83.00**	88.73	83.00
Over Coating								
Hypromellose, 3 cps	2	2	2	2	2	**2**	2	2
Talc	1.4	1.4	1.4	1.4	1.4	**1.4**	1.4	1.4
Purified water**	35	35	35	35	35	**35**	35	35
Wt. of over coated pellets	173.51	185.51	191.51	173.6	188.51	**204.71**	211.01	204.71
% w/w solids in solution/suspension	8.85	8.85	8.85	8.85	8.85	**8.85**	8.85	8.85
% wt. build up	1.99	1.86	1.81	1.99	1.84	**1.68**	1.64	1.68

* contains 30 % w/w solids; ** It will not appear in final product except in traces.

Evaluation Parameters

Characterization of pellets and capsules

The characterization of pellets was evaluated as per USP, IP standards [7, 8]

***In vitro* drug release studies**

In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical test method in formulation development. Purpose of dissolution testing in research and development includes: obtaining a predefined target release profile, investigation of drug release mechanisms, analyzing formulation properties regarding influence of physiological factors (e.g., pH and food) on the drug release, generation of supportive data to bioequivalence studies for interpretation of *in vivo* results, validation of manufacturing processes, investigation of effects of different storage conditions and batch quality control. Sink conditions were maintained in the present dissolution studies.

Scanning Electron Microscopy (SEM) [9]

SEM of prepared coated and uncoated pellets was performed for studying pellet surface morphology.

Accelerated Stability Studies (AST)

The purpose of stability testing is to allow the establishment of recommended storage conditions, retest periods and shelf lives at ambient conditions. [10-12]. AST of the best fit formulations of the drug products were done at the end of 1^{st}, 2^{nd}, 3^{rd} months and studied for assay and drug release.

***In vivo* Studies**

Experimental Animals

Twelve healthy male rabbits weighing 1.5±0.2 kg were collected from Central Animal House. The animals were stored in large, spacious, and ventilated polyacrylic cages in well hygienic conditions at room temperature ranginging between 22±2°C with 12 hrs/12 hrs day/night cycle with standard pellet diet and water.

Study design

The experiment was carried out by parallel design as it more appropriate in case of drugs with carryover effects. Four groups, each of 3 rabbits were selected for the present study.

Group-I: Control

Group-II: Standard (Dexlansoprazole API 60 mg)

Group-III: Test (Dexlansoprazole Delayed Release Capsule 60 mg-B5E6)

Group-IV: Marketed Product (Dexilant Delayed Release Capsule 60 mg).

Instrumentation

The sample analysis was carried out by HPLC method.

Blood Samples Collection

The vein of rabbit marginal ear vein was punctured with Syringe and blood sample 300 µL was collected without anesthesia into a centrifugation tube pre-filled with 20 µL of 10 % disodium EDTA. Mixed well and centrifuged the blood at 3200 rpm for 5 min. The supernatant layer of plasma approx. 150 µL was collected. From this 50 µL of plasma sample was used for analysis. Same procedure was used for blank plasma collection as well as drug treated rabbits at time points 0, 0.25, 0.5, 1, 2, 4, 6, 12, 24 hrs. The formulation B5E6 was evaluated for pharmacokinetic parameters: Cmax, Tmax & AUC in rabbit and plotted plasma concentration vs. time graph.

RESULTS AND DISCUSSION

Dexlansoprazole Calbration curve: In pH 6.8 phosphate buffer, calibration curves were plotted.

Table 9: Calibration curve values of Dexlansoprazole at 285 nm

Concentration (µg/mL)	UV absorbance at 285 nm
0	0
2	0.102
4	0.193
6	0.282
8	0.377
10	0.485
12	0.598
14	0.698
16	0.784
18	0.895
20	0.998

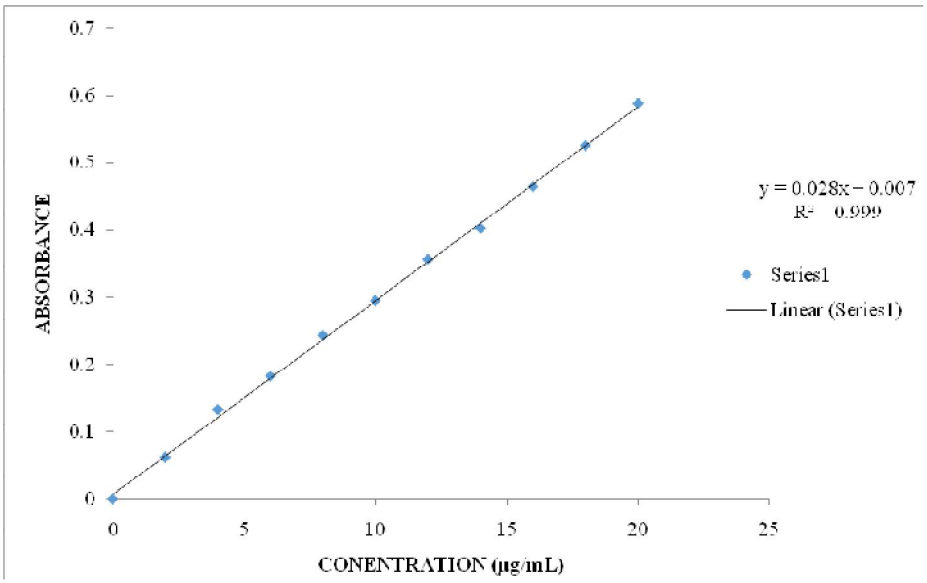

Figure 1: Calibration Curve of Dexlansoprazole

EVALUATIONPARAMETERS

Table 10: Characterization of Dexlansoprazole Delayed release pellets prepared by E/S

Formulation	%w/w DR coating	BD (g/mL)	TD (g/mL)	CI (%)	HR	%Friability	% Yield	%w/w DR coating	Average Weight	%drug content
DD5S2B2P1	13.51	0.45±0.045	0.52 ± 0.04	15.19	1.15	0.19± 0.55	95.9	12.33	287.40	96.5 ±0.82
DD5S2B2P2	18.25	0.45±0.045	0.50 ± 0.07	12.23	1.11	0.16± 0.67	98.2	15.76	293.80	98.3 ±0.59
DD5S2B2P3	20.16	0.51±0.045	0.59 ± 0.04	14.48	1.15	0.11± 0.31	96.5	18.55	299.00	97.5 ±0.13
DD5S2B2P4	26.82	0.45±0.045	0.51 ± 0.04	13.48	1.13	0.21± 0.44	97.1	21.45	304.40	98.9 ±0.25
DD5S2B2P5	18.72	0.44±0.044	0.52± 0.01	15.48	1.18	0.12± 0.53	94.5	23.22	307.70	95.2 ±0.52

Table 11: Characterization of Dexlansoprazole Delayed release pellets and pellets in capsules prepared by S/S

Formulation	%w/w DR coating	% Yield	BD (g/mL)	TD (g/mL)	CI (%)	HR	%Friability	%w/w DR coating	Average Weight	%drug content
B5E1	53.21	99.5	0.58 ± 0.04	0.66 ± 0.02	12.12	1.08	0.13± 0.13	56.82	234.51	99.5 ±0.98
B5E2	68.12	98.2	0.58 ± 0.02	0.66 ± 0.08	12.12	1.17	0.18± 0.25	69.41	246.51	97.2 ±0.65
B5E3	73.58	97.5	0.62 ± 0.04	0.67 ± 0.04	7.46	1.07	0.10± 0.94	72.39	252.51	98.9 ±0.20
B5E4	51.01	98.9	0.61 ± 0.04	0.69 ± 0.06	11.59	1.10	0.17± 0.62	59.78	234.63	98.1 ±0.39
B5E5	69.31	97.3	0.60 ± 0.03	0.69 ± 0.02	13.04	1.10	0.20± 0.47	70.82	249.51	93.9 ±0.52
B5E6	80.10	98.2	0.58 ± 0.05	0.66 ± 0.07	12.12	1.07	0.23± 0.28	85.15	265.71	99.3 ±0.19
B5E7	89.56	98.7	0.56 ± 0.05	0.65 ± 0.04	13.84	1.08	0.26± 0.12	89.36	272.01	100.2 ±0.89
B5E8	81.23	99.02	0.57 ± 0.09	0.66±0.08	13.63	1.10	0.18± 0.64	81.11	26571	98.9 ±0.71

***In vitro* Drug Release Studies**

Method A: Extrusion-spheronization:

Table 12: Dissolution Profiles of Dexlansoprazole Delayed release Capsules 60 mg prepared by Extrusion-Spheronization (DD5S2B2P1- DD5S2B2P5)

Time (hrs) ↓	% Cumulative drug release					
	Marketed product	DD5S2B2P1	DD5S2B2P2	DD5S2B2P3	DD5S2B2P4	DD5S2B2P5
0	0	0	0	0	0	0
120	5	10	5	**0.5**	6	8
130	46	68	50	**50**	41	31
140	81	70	56	**78**	68	55
150	92	82	89	**82**	74	91
165	98	85	90	**96**	98	96
180	99	90	96	**99**	100	99

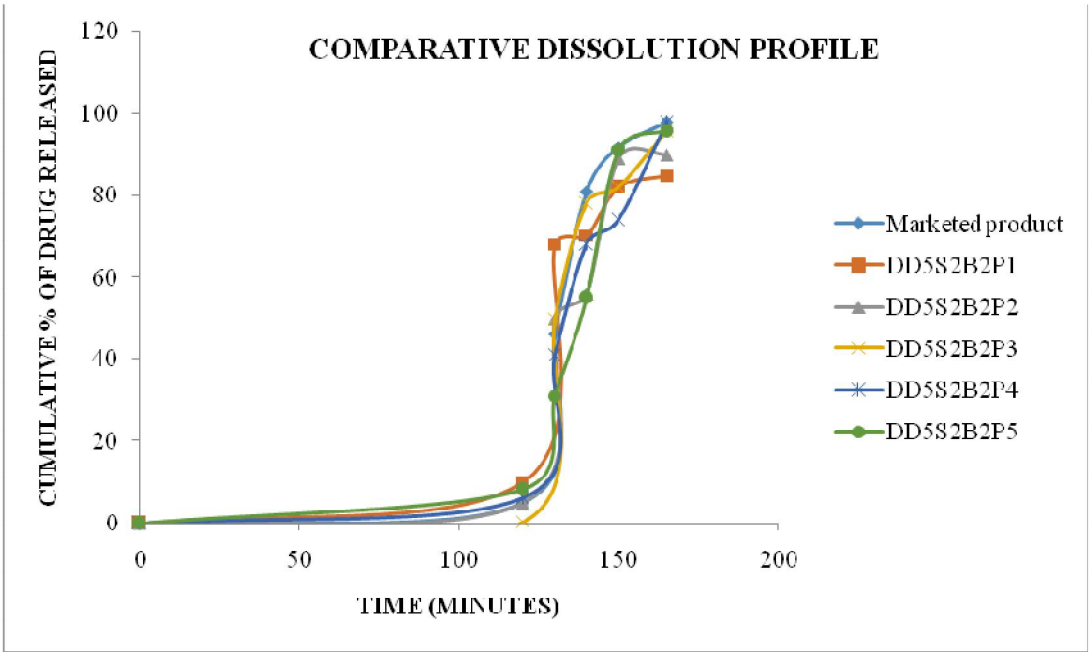

Figure 2: Comparative dissolution profile of Dexlansoprazole marketed product and DD5S2B2P1-DD5S2B2P

Optimization of Dexlansoprazole drug pellets by extrusion- spheronization (DD1-DD13): As per the literature and earlier studies conducted, microcrystalline cellulose (MCC) is considered as a golden standard for extrusion- spheronization due to its ability to absorb and retain large amounts of water. Even at high pressures the water squeezed out of the material acts as lubricant and enhances particulate flow. At high shear forces microcrystalline cellulose can be broken down into colloidal size.

In this study, other excipients mannitol, LMH, GMS were selected as an alternate aid to study the process feasibility. The yields for the trails DD1-DD13 were 98%, 97%, 95%, 97%, 97%, 95%, 97%, 99%, 85%, 89%, 92%, 88%, 86%. Pellets prepared with MCC alone, mannitol alone, combination of MCC-Mannitol, combination of MCC-GMS showed better process feasibility compared to lactose combinations. In view of better drug release, pellets prepared with mannitol (DD5) were considered optimized for further process.

Optimization of Dexlansoprazole Seal Coating (DD5S1-DD5S3): The purpose of this coating is to provide enough mechanical strength to pellets to with stand for further coating process. Binder HPMC, 5 cps concentration (2, 4, 6 mg/unit) was optimized for trails DD5S1-DD5S3 as it plays a vital role in solution preparation and coating. 4 mg/unit binder concentration was optimized based on % yield (84%, 95%, 92% respectively) and process feasibility. Optimization of Dexlansoprazole Barrier Coating (DD5S2B1-DD5S2B3): Direct interaction from enteric polymer is prevented by barrier coat and thereby the basic drug is protected. It also reduces surface roughness of the coating substrate and enhances adhesion of the enteric film on the substrate surface. Binder HPMC, 5 cps concentration (10, 12, 14 mg/unit) was optimized for trails DD5S2B1-DD5S2B3. 12 mg/unit was optimized based on process feasibility.

Optimization of Dexlansoprazole Enteric Coating (DD5S2B2P1-DD5S2B2P5): To prevent the drug

degradation and protect the drug from acidic environment of the stomach and release the drug component in the intestinal region, a delayed/ gastro- resistant coating is given with enteric coating polymers like Methacrylic acid copolymer. The polymeric backbone of an enteric polymer generally has free carboxylic acid groups and the number of carboxylic acid groups in the polymer composition influences its solubility. These polymers are insoluble in acidic juices of the stomach (pH ~3) but become de-protonated and dissolved in basic/alkaline media at nearly neutral pH values (pH>5).

In the present formulation, Eudragit L30D55 was chosen for enteric coating. The purpose of this coating is to resist the acid-labile drug in the acidic pH of the stomach. Polymer-plasticizer concentration optimization is based on acid resistance and *in vitro* drug release for the trails DD5S2B2P1-DD5S2B2P5. Lubrication of pellets was done for the free flow of pellets into capsules during filling.

Method-B: Solution/Suspension Layering

The drug release profiles of different delayed release formulations in dissolution media were shown in Figure.

Table 13: Dissolution Profiles of Dexlansoprazole DR Capsules 60 mg prepared by Solution/Suspension Layering (B5E1-B5E8)

Time (min)	% Cumulative drug release								
	Marketed Product	B5E1	B5E2	B5E3	B5E4	B5E5	B5E6	B5E7	B5E8
120	5	12	10	8	9	6	**5**	0	8
130	46	73	60	75	85	70	**46**	40	62
140	81	80	76	80	89	79	**92**	86	89
150	92	87	83	87	90	84	**96**	90	90
165	98	92	90	90	96	91	**98**	93	95
180	99	96	94	96	98	95	**98**	98	97

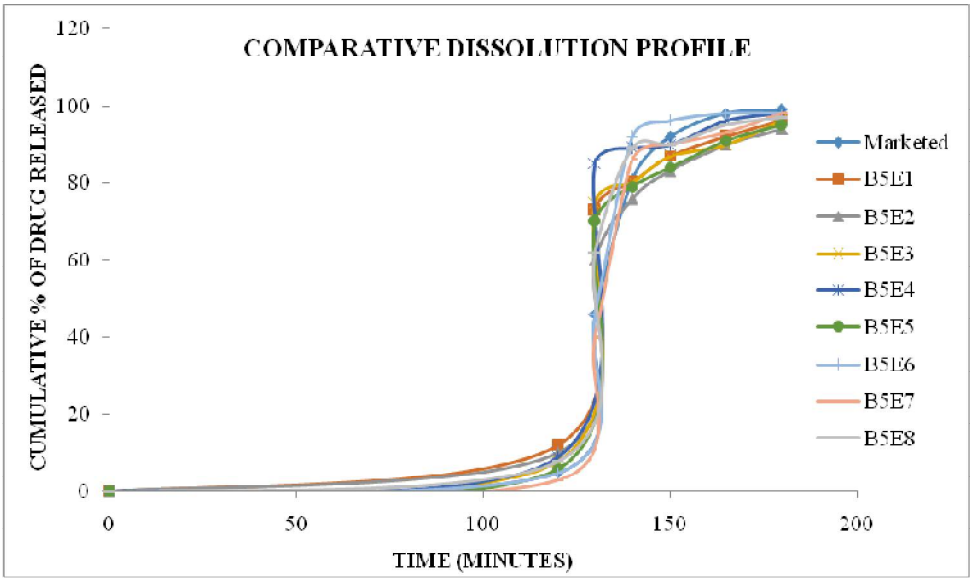

Figure 3: Comparative dissolution profile of Dexlansoprazole marketed product and B5E1- B5E8

Method B: Solution/suspension layering: Optimization of Seal coating (DS1-DS9): Sugar spheres were employed in the developmental trails because of their acceptability and accessibility in different sizes. Different binder concentrations of Hypromellose, 5 cps (1, 2, 3 mg/unit) were coated for the formulations DS1-DS9 with different weight sugar spheres (18, 28, 38 mg/unit). The trails DS2, DS5, DS8 showed good mechanical strength due to high concentration of HPMC whereas breakage of sugar spheres was observed during coating for other formulation trails. Optimization of Drug coating with different weight seal coated pellets (DS2D1, DS5D2, DS8D3) and Optimization of Drug coating for concentration of binder and wetting agents (DS8D4-DS8D7): Among DS2D1, DS5D2, DS8D3 with binder HPMC, 3 cps (10 mg/unit), DS8D3 showed better yield (74%, 79%, 83%). Hence, further optimization was carried with DS8 seal coated pellets. Povidone (PVP k-17) and HPMC, 5 cps were chosen for formulation trails DS8D4 and DS8D5, Hypromellose, 5 cps was optimized based on the % yield (89%, 95% respectively). The concentration of Hypromellose, 5 cps (12.5, 15 mg/unit) was optimized based on the % yield (97%, 94% respectively) for the formulation trails DS8D6 and DS8D7.

Optimization of Barrier Coating (DS8D6B1-DS8D6B5): Binders (3 mg/unit) - HPMC, 3 & 5 cps and HPC were chosen. Hypromellose, 5 cps was optimized based on the % yield (91%, 90%, 95%, 97%, 99% respectively). Hence DS8D6B5 was considered optimized. Both HPMC and Sodium Lauryl Sulphate were used for formation of improved film and protect the drug pellets. Optimization of Enteric coating (B5E1-B5E8): Polymers-Eudragit L30D55 and HPMCP 55; plasticizers- TEC and PEG 400 were chosen. Optimization of polymer-plasticizer concentration was based on acid resistance in 0.1N HCl for the formulation trails B5E1-B5E8.

Plasticizer concentration was optimized because the success of enteric coating efficiency mostly relies on the addition of plasticizers. The major function of the plasticizers is to improve elasticity and spreadability of the rigid and breakable polymers on the surface of the coating substrates by reducing the minimum film forming temperature of the polymers and softening the polymeric film at lower temperature.

The amount of plasticizer also influences film flexibility. Insufficient amount of plasticizer causes film blistering which could lead to a premature drug release in acidic media. However, high amount of plasticizer reduces the strength of the film and may accelerate the water/acid uptake into the cores upon storage. Over coating: To produce the characteristic gloss, enteric coated pellets of all the formulation trails from B5E1 to B5E8 were coated with the mixture of HPMC, 5 cps and Talc. After over coating, pellets of all batches were elegant.

Scanning Electron Microscopy(SEM)

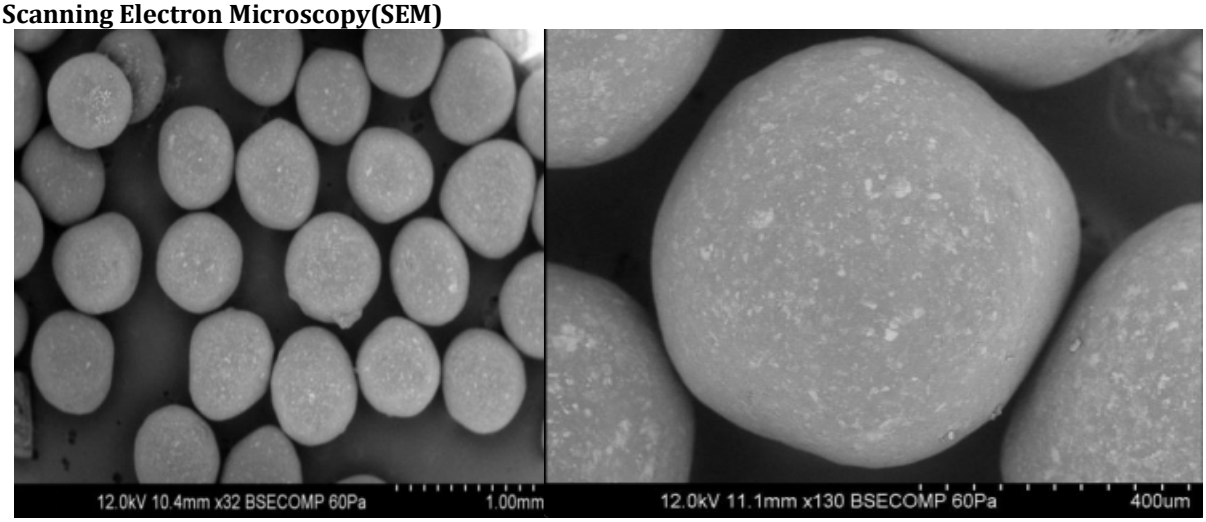

Figure 4 (a, b): SEM analysis of Dexlansoprazole DR Pellets (DD5S2B2P3) prepared by extrusion-spheronization

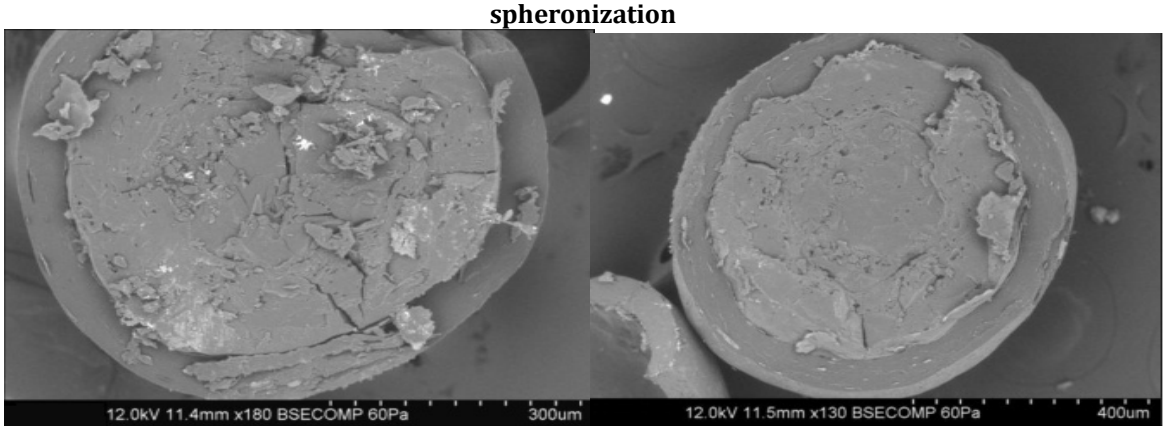

Figure 5 (a, b): Cross- section SEM analysis of Dexlansoprazole DR Pellets (B5E6) prepared by Solution/suspension layering.

Accelerated Stability Studies (AST)

Table 14: AST results of Dexlansoprazole DR Capsules 60 mg (DD5S2B2P3) prepared by Extrusion-Spheronization

Test parameter	Initial	1st month	2nd month	3rd month
Assay (% w/w)	98.5	99.1	99.4	98.8
Acid resistance (% w/w)	97.5	96.2	95.2	96.7
Acid Release (% w/w)	0.5	1.5	2.6	2.9
Dissolution Profile (cumulative % drug release)				
120 mins	0.5	1.7	2.2	2.5
130 mins	46	51	52	50
140 mins	81	80	82	84
150 mins	91	94	95	96
165 mins	97	95	96	94
180 mins	98	99	98	97

Table 15: AST results of Dexlansoprazole DR Capsules 60 mg (B5E6) prepared by Solution/suspension layering

Test parameter	Initial	1st month	2nd month	3rd month
Assay (% w/w)	99.9	99.2	100	98.1
Acid resistance (% w/w)	98.6	97.0	99.1	97.8
Acid Release (% w/w)	1.2	2.5	0.6	1.5
Dissolution Profile (cumulative % drug release)				
120 mins	1.5	2.4	0.4	1.3
130 mins	47	51	50	48
140 mins	92	91	90	89
150 mins	100	98	99	97
165 mins	99	97	98	98
180 mins	97	98	97	96

***In vivo* Studies**

The selected drug formulation Dexlansoprazole DR Capsules 60 mg (B5E6) was evaluated for its pharmacokinetics in animal model rabbit.

Table 16: Estimation of Pharmacokinetics parameters in rabbit

Time (hrs)	Mean Concentration (ng/mL)		
	Standard (Dexlansoprazole)	Test product	Marketed product
0.00	0.00	0.00	0.00
0.25	83.5	60.8	33.5
0.50	160.7	106.9	65.4
1.00	80.9	200.9	160.7
2.00	67.0	209.2	126.3
4.00	36.9	173.2	80.2
6.00	22.0	152.4	60.2
12.00	9.41	130.4	30.9
24.00	5.97	84.50	17.35
Cmax (ng/mL)	160.7	209.15	160.65
Tmax (hrs)	0.5	2.0	1.0
AUC (0-24) (ng.h/mL)	524.26	3156.24	1126.22
AUC (0-∞) (ng.h/mL)	571.11	8854.89	1381.22

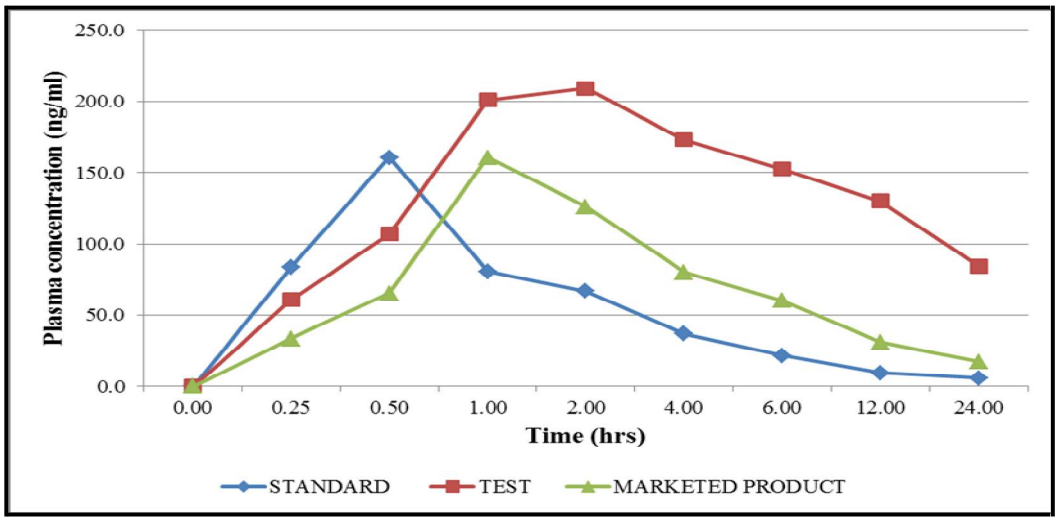

Figure 6: Comparative graph of Plasma Concentration Vs Time

Method-A: Extrusion-Spheronization: Acid stage dissolution is important for acid labile Dexlansoprazole. The % drug release criteria should be less than 10.0% w/w. Hence, enteric coating weight buildups were optimized based on drug release in acid media.

Different formulations (DD5S2B2P1 to DD5S2B2P5) were coated with %w/w build ups 12.33%, 15.76%, 18.55%, 21.45% and 23.33% respectively. The results of acid release comply with the proposed limits for these formulation trials. Among the trails, DD5S2B2P1 showed higher release and DD5S2B2P3, DD5S2B2P4, DD5S2B2P5 showed lesser release in acid media.

Further buffer stage dissolution was evaluated for all the formulations. DD5S2B2P1 & DD5S2B2P2 formulations showed higher dissolution at 10 minutes whereas DD5S2B2P4, DD5S2B2P5 showed lower dissolution at 10 minutes time point when compared with the marketed product. Formulation DD5S2B2P3 dissolution profile complies with marketed product at all the time points.

Based on these observations, DD5S2B2P3 was considered as optimized with 18.55% w/w enteric coating for extrusion- spheronization process of Dexlansoprazole DR Capsules.

Method B: Solution/Suspension Layering:

In the present formulations, Eudragit L30D55 and HPMCP were chosen as gastro-resistant polymers. HPMC and Talc was used for over coating. For all formulations, dissolution in acid stage & buffer stage was evaluated.

In B5E1 formulation, dry polymer was used. Dissolution in acid stage was found to be 8% which is on higher side and in buffer stage at 10 minutes drug release was found to be high when compared with marketed product.

Further trials B5E2 & B5E3 were planned with Hypromellose phthalate (HP55), Triethyl citrate (6 mg/unit & 9 mg/unit respectively) and evaluated for acid stage & buffer stage. Dissolution in acid stage i.e. acid release was found to be 5% & 6% respectively. Dissolution in buffer stage at 10 minutes was found to be high when compared with marketed product.

Formulations B5E4, B5E5, B5E6, B5E7 & B5E8 were formulated with the selected polymer (Eudagit L30D55) at different enteric coating weight buildup and evaluated for dissolution (acid stage & buffer stage).

Among all, B5E6 formulation results were comparable with marketed product.

The plasma concentration of Dexlansoprazole Delayed Release Capsules and Time was plotted and pharmacokinetic parameters- Cmax, Tmax, AUC were calculated. The Cmax was 160.7, 209.15, 160.65 ng/mL; Tmax was 0.50, 2.00, 1.00 hrs; AUC (0-24) was 524.26, 3156.24, 1126.22 ng.h/mL; AUC (0-∞) was 571.11, 8854.89, 1381.22ng.h/mL for Standard, Test product, Marketed product.

CONCLUSION

Dexlansoprazole is composed of a racemic mixture of the R- and S-enantiomers. and PPI is employed in curing GI acid associated ailments. This drug degrades in the stomach environment (acid pH), and leads inefficacious in healing. Formulating delayed release pellets using enteric polymer avoids drug degradation by bypassing the acidic pH of the stomach thereby prevent the drug from being destroyed/ inactivated by gastric juices and releases in a discrete portion(s) of the GIT at a period after administering orally instead of releasing immediately.

Seal coating on to inert sugar spheres with Hypromellose gives better mechanical strength to withstand for further coatings. In drug coating, Hypromellose was found to have efficient binding of drug compared Hydroxypropyl Cellulose and Povidone with respect to % yield and drug content. Barrier coating given with Hypromellose and Sodium Lauryl Sulphate combination offered better protection to the drug from acidic enteric polymer.

Enteric-polymer coating by Eudragit L30D55 offered good resistance in acidic media with the given weight buildup. In enteric coating, plasticizing agent imparts a foremost role in film development and disposition. Amongst Triethyl Citrate and Polyethylene Glycol 400, Triethyl Citrate was noticed to be beneficial and capable in formation of film effectively.

In vivo studies conducted for the selected formulation (B5E6) also showed delay in drug release. Hence, it was concluded as best fit and stable formulation of Dexlansoprazole delayed release multiparticulate capsules prepared by solution/suspension layering technique. Furthermore, the study also concluded extrusion/spheronization can be selected as a substantial method for formulating medium dose drugs.

The plasma concentration of Dexlansoprazole Delayed Release Capsules and Time was plotted and pharmacokinetic parameters- Cmax, Tmax, AUC were calculated. The Cmax was 160.7, 209.15, 160.65 ng/mL; Tmax was 0.50, 2.00, 1.00 hrs; AUC (0-24) was 524.26, 3156.24, 1126.22 ng.h/mL; AUC (0-∞) was 571.11, 8854.89, 1381.22ng.h/mL for Standard, Test product, Marketed product.

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