FORMULATION AND EVALUATION OF MULTIPLE UNIT PELLET SYSTEM OF BISOPROLOL

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ABSTRACT

The aim of present work was to develop immediate release multiple unit pellets of Bisoprolol, is an Beta blocker, used for the treatment of the high blood pressure by extrusion- spheronization (E/S) and solution/suspension layering (S/S) method. In the Extrusion-Spheronization, Immediate release drug pellets of Bisoprolol were prepared by extrusion and spheronization process in the diluent ratios of 1:3 and 3:1 respectively. Formulation of Bisoprolol drug pellets were carried out by optimizing different diluents and concentrations (Lactose Monohydrate (LMH)/MCC/Mannitol/Starch). CCS (3 mg/unit), Crospovidone (Plasdone XL-10) (3 mg/unit) and Sodium Starch Glycolate (SSG) (3 mg/unit) were selected for optimization of disintegrants. L-HPC (LH-31) (3 mg/unit) was used as a spheronizing aid. HPMC was used as binder. Polysorbate 80 and Sodium lauryl sulphate (SLS) (0.01 mg/unit) were selected for optimization of wetting agent. Lubrication was carried out with colloidal silicon dioxide (0.25 mg/unit) and magnesium stearate (0.3 mg/unit). All the prepared pellets of different formulations were filled in desired size capsules, analyzed for drug content and dissolution.

In the extrusion- spheronization (E/S) Optimization of IR pellets: Bisoprolol drug pellets were prepared by using different diluents (MCC, LMH, Mannitol and Starch) in the ratio of 1:3 and

3:1. The pellets formulated with combination of MCC: Mannitol in the ratio of 1:3 (B8) results complies with the marketed product.

In Solution/Suspension Layering: Core pellets were prepared by extrusion and spheronization using MCC, Mannitol and LMH as a diluents. CCS was used as disintegrant. LHPC (LH-31) was used as a spheronizing aid. Drug suspension was prepared by using HPMC, 5 cps as a binder and SLS as wetting agent. Drug coating was carried out on core pellets by using different HPMC concentrations (1-3 mg/unit) of drug suspension and finally lubricated with colloidal silicon dioxide and magnesium stearate. All the prepared pellets of different formulations were filled in desired size capsules, analyzed for drug content and dissolution.

In Solution/Suspension Layering: Core pellets were prepared by using different diluents (MCC, Mannitol and LMH) by using extrusion-spheronization process. The combination of MCC and Mannitol (1:3) core pellets formulation was optimized based on the %yield and process feasibility. Optimized core pellets were coated with Bisoprolol drug solution by using HPMC, 5cps as binder with 2 mg/unit. Drug pellets were lubricated with colloidal silicone dioxide and magnesium stearate for better flow during capsule filling. Dissolution profile of optimized formulation (F2) complies with marketed product.

Formulating low dose, high soluble, BCS class I drug- Bisoprolol Immediate release multiple unit pellets formulation by extrusion-spheronization and solution/suspension layering was also advantageous.

Keywords: Immediate release multiple unit pellets, Pelletization, Bisoprolol

INTRODUCTION:

Most drugs require multiple daily dosing to achieve desired blood concentration to produce therapeutic activity. To overcome these types of problems, sustained release and controlled release delivery systems have got a considerable attention in pharmaceutical industries[1]. Pelletization is one of the most promising techniques for the multi particulate drug delivery systems[2]. Pellets are of about 0.2-2.0 mm mean particle diameter, small, free flowing, spherical/ semi spherical agglomerates attained from assorted starting ingredients of fine

powder(s)/granule(s) of bulk drug(s) and/or excipient(s) employing different pelletization techniques[3]. Multiparticulate drug delivery systems are the utmost accepted and widely used dosage form as they offer so many benefits over unit dosage forms like improved bioavailability because of increased surface area, reduced inter subject variation and transportation and reduced chances of dose dumping[2]. The interest in pellets as dosage forms (filled into hard gelatine capsules or compressed into disintegrating tablets) has been increasing continuously[4].

Bisoprolol is Beta blocker that has been used for the treatment of high blood pressure.was employed as a model drug[5]. Bisoprolol is a perfect candidate drug for the preparation of a immediate-release dosage form, because it can prevent strokes, heart attacks, and kidney problems.. Therefore, a better formulation of Bisoprolol involves immediate release that offers more stable plasma profiles and thus reduces any adverse effects[6]. The objective of this study was to establish a novel, simple, and flexible method of preparing immediate-release pellets. In this study, 2 methods employed for formulate the Bisoprolol IR Capsules, Extrusion-Spheronization (E/S) and solution/suspension layering (S/S) was tried to optimize the best fit process for Bisoprolol low dose drug and study the impact of process on the final dosage form.

MATERIALS

Bisoprolol (BSP), Microcrystalline Cellulose (Avicel PH 102), Lactose Monohydrate (Pharmatose 200M), Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), Hypromellose (HPMC) 5 cps, Mannitol, Starch 1500, Polysorbate 80, Sodium Lauryl Sulphate (SLS), Colloidal Silicon Dioxide, Magnesium stearate provided from Sura Labs, Dilsukhnagar.

METHODOLOGY

Preparation of Immediate release pellets of Bisoprolol:

Method A: Extrusion-Spheronization

Immediate release drug pellets of BSP were prepared by extrusion spheronization, one specialized method of particle agglomeration to produce spherical or near-spherical particles,

with different diluents and ratios.

Figure: Process flow chart for BSP IR pellets by E/S

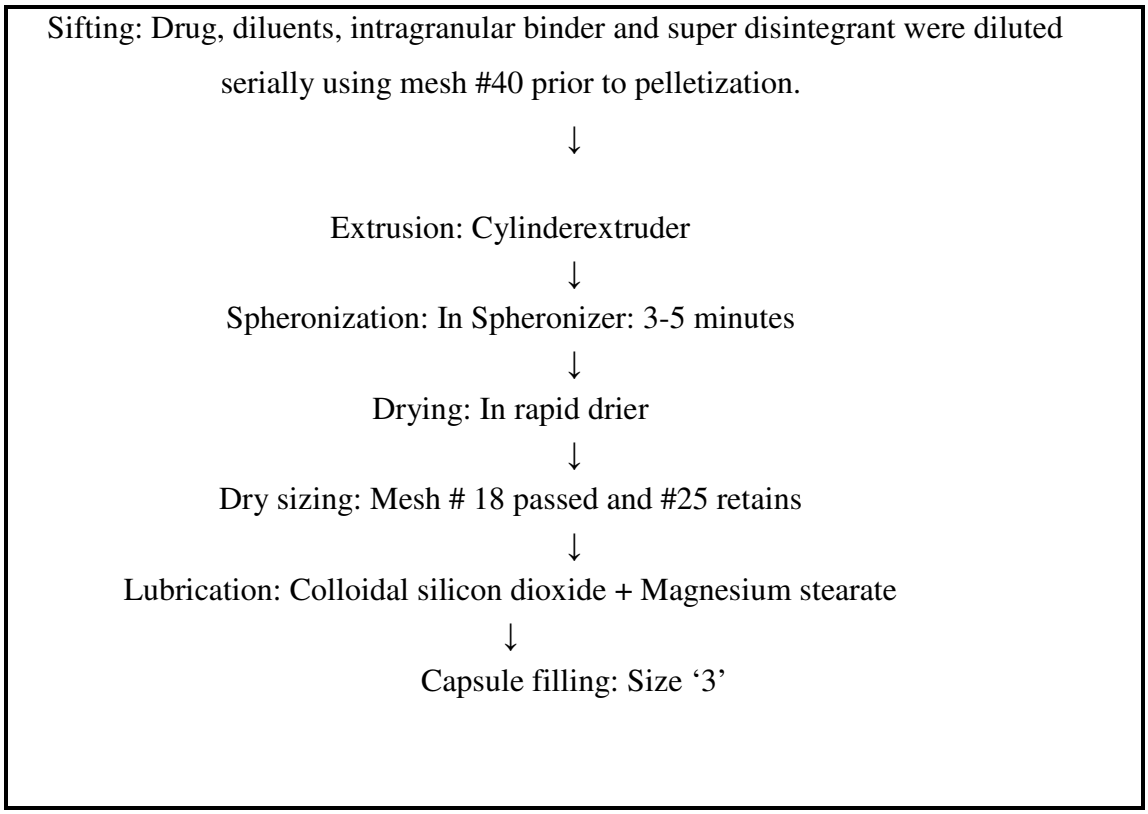

Table: Optimization of BSP IR pellets with different diluents by extrusion-spheronization (B1-B16)

Quantity→	**mg/unit**															
Ingredients↓	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	**B16**
Intragranular																
Bisoprolol	5.45	5.45	5.45	5.45	5.45	5.45	5.45	**5.45**	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45
Lactose Monohydrate	42	42	42	14	14	14	-	**-**	-	-	-	-	-	-	-	-
MCC (Avicel PH101)	14	-	-	42	-	-	14	**14**	42	42	-	-	14	14	14	14
Starch 1500	-	14	-	-	42	-	42	**-**	14	-	42	14	-	-	-	-
Mannitol	-		14	-		42	-	**42**	-	14	14	42	42	42	42	42
Croscarmellose Sodium (Ac-Di-Sol)	3	3	3	3	3	3	3	**3**	3	3	3	3	-	-	3	3
Sodium Starch Glycolate	-	-	-	-	-	-	-	**-**	-	-	-	-	3	-	-	-
Crospovidone (Plasdone XL-10)	-	-	-	-	-	-	-	**-**	-	-	-	-	-	3	-	-
L-HPC (LH31)	3	3	3	3	3	3	3	**3**	3	3	3	3	3	3	3	3
Hypromellose, 5 cps	1	1	1	1	1	1	1	**1**	1	1	1	1	1	1	1	1
Wt. of dry mix	68.45	68.45	68.45	68.45	68.45	68.45	68.45	**68.45**	68.45	68.45	68.45	68.45	68.45	68.45	68.45	68.45
Binder solution																
Hypromellose, 5 cps	2	2	2	2	2	2	2	**2**	2	2	2	2	2	2	2	2
Polysorbate 80	-	-	-	-	-	-	-	**-**	-	-	-	-	-	-	0.01	-
Sodium lauryl sulphate	-	-	-	-	-	-	-	**-**	-	-	-	-	-	-	-	0.01
Purified water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Wt. of beads	70.45	70.45	70.45	70.45	70.45	70.45	70.45	**70.45**	70.45	70.45	70.45	70.45	70.45	70.45	70.46	70.46
Lubrication																
Colloidal Silicon Dioxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	**0.25**	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium Stearate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	**0.3**	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total Wt. of beads	71	71	71	71	71	71	71	**71**	71	71	71	71	71	71	71.01	71.01

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

Method B: Solution/ suspension Layering

Core pellets were prepared by extrusion-spheronization and immediate release drug pellets of BSP were prepared by solution/suspension layering on to the prepared inert cores.

Figure 4.6: Process flow chart for BSP IR pellets by S/S

Sifting: Diluents, intragranular binder and super disintegrant were diluted serially using mesh #40 prior to pelletization.

↓

Granulation

Dry mixing: In rapid mixer granulator for 10 min.

Wet massing: Binder addition-2 min.

Kneading: 1 minute

↓

Extrusion: Cylinderextruder

↓

Spheronization: In Spheronizer: 3-5 minutes

↓

Drying: In rapid drier

↓

Dry sizing: Mesh # 18 passed and #25 retains

↓

3. Methanol + BSP

↓∞

Clear Solution

4. (2) + (3)

↓∞ (10 min)

Clear Solution

↓

Drug coating & Drying

↓

Sifting: Mesh # 18 passed and #25 retains

↓

Lubrication:

Colloidal silicon dioxide + Magnesium stearate

↓

Capsule filling: Size ‘3’

Table: Optimization of BSP IR Pellets by layering (F1-F12)

Quantity→	**mg/unit**											
Ingredients↓	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Dry mix												
MCC (Avicel PH101)	14	**14**	14	14	14	14	42	42	42	42	42	42
Mannitol	42	**42**	42	42	42	42	-	-	-	-	-	-
Lactose monohydrate (Pharrmatose 200M)	-	**-**	-	-	-	-	14	14	14	14	14	14
Croscarmellose sodium (Ac-Di-Sol)	3	**3**	3	3	3	3	3	3	3	3	3	3
L-HPC (LH31)	3	**3**	3	3	3	3	3	3	3	3	3	3
Hypromellose, 5 cps	1	**1**	1	1	1	1	1	1	1	1	1	1
Weight of dry mix	63	**63**	63	63	63	63	63	63	63	63	63	63
Binder solution												
HPMC,5 cps	2	**2**	2	2	2	2	2	2	2	2	2	2
Purified water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of beads	65	**65**	65	65	65	65	65	65	65	65	65	65
Drug Layering												
Bisoprolol	5.45	**5.45**	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45
HPMC, 5 cps	1	**2**	3	1	2	3	2	2	2	2	2	2
Sodium lauryl sulphate	-	**-**	-	0.5	0.5	0.5	-	-	-	0.5	0.5	0.5
Methanol**	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water**	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of beads	71.45	**72.45**	73.45	71.95	72.95	73.95	71.45	72.45	73.45	71.95	72.95	73.95
Lubrication												
Colloidal Silicon Dioxide	0.25	**0.25**	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	0.3	**0.3**	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total weight of beads	72	**73**	74	72.5	73.5	74.5	72	73	74	72.5	73.5	74.5

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

Method B: Solution/ suspension Layering

Core pellets were prepared by extrusion-spheronization and immediate release drug pellets of BSP were prepared by solution/suspension layering on to the prepared inertcores.

Figure: Process flow chart for BSP IR pellets by S/S

Sifting: Diluents, intragranular binder and super disintegrant were diluted serially using mesh #40 prior to pelletization.

↓

Granulation

Dry mixing: In rapid mixer granulator for 10 min.

Wet massing: Binder addition-2 min.

Kneading: 1 minute

↓

Extrusion: Cylinderextruder

↓

Spheronization: In Spheronizer: 3-5 minutes

↓

Drying: In rapid drier

↓

Dry sizing: Mesh # 18 passed and #25 retains

↓

3. Methanol + BSP

↓∞

Clear Solution

4. (2) + (3)

↓∞ (10 min)

Clear Solution

↓

Drug coating & Drying

↓

Sifting: Mesh # 18 passed and #25 retains

↓

Lubrication: Colloidal silicon dioxide + Magnesium stearate

↓

Capsule filling: Size ‘3’

Table: Optimization of BSP IR Pellets by layering (F1-F12)

Quantity→	**mg/unit**											
Ingredients↓	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Dry mix												
MCC (Avicel PH101)	14	**14**	14	14	14	14	42	42	42	42	42	42
Mannitol	42	**42**	42	42	42	42	-	-	-	-	-	-
Lactose monohydrate (Pharrmatose 200M)	-	**-**	-	-	-	-	14	14	14	14	14	14
Croscarmellose sodium (Ac-Di-Sol)	3	**3**	3	3	3	3	3	3	3	3	3	3
L-HPC (LH31)	3	**3**	3	3	3	3	3	3	3	3	3	3
Hypromellose, 5 cps	1	**1**	1	1	1	1	1	1	1	1	1	1
Weight of dry mix	63	**63**	63	63	63	63	63	63	63	63	63	63
Binder solution												
HPMC,5 cps	2	**2**	2	2	2	2	2	2	2	2	2	2
Purified water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of beads	65	**65**	65	65	65	65	65	65	65	65	65	65
Drug Layering												
Bisoprolol	5.45	**5.45**	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45	5.45
HPMC, 5 cps	1	**2**	3	1	2	3	1	2	3	1	2	3
Sodium lauryl sulphate	-	**-**	-	0.5	0.5	0.5	-	-	-	0.5	0.5	0.5
Methanol**	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water**	q.s	**q.s**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of beads	71.45	**72.45**	73.45	71.95	72.95	73.95	71.45	72.45	73.45	71.95	72.95	73.95
Lubrication												
Colloidal Silicon Dioxide	0.25	**0.25**	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	0.3	**0.3**	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total weight of beads	72	**73**	74	72.5	73.5	74.5	72	73	74	72.5	73.5	74.5

** 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 1st, 2nd, 3rd months and studied for assay and drug release.

RESULTS AND DISCUSSION

Bisoprolol Calibration Curve

Table: Calibration curve values of Bisoprolol

Concentration (µg/mL)	Absorbance at 226 nm

0	0
10	0.112
20	0.244
30	0.412
40	0.595
50	0.783
60	0.925

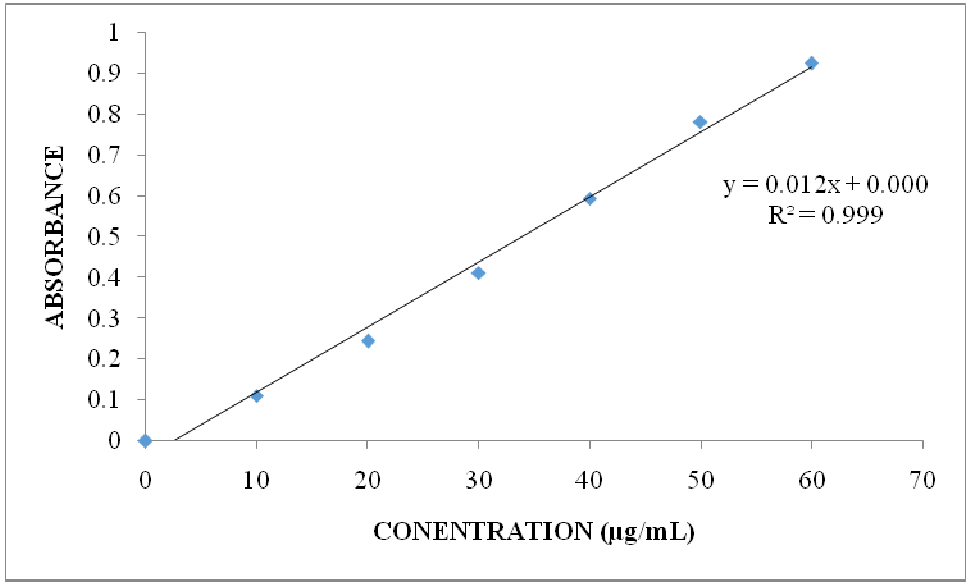

Figure: Calibration Curve of Bisoprolol

Characterization of pellets

Table: Characterization of Bisoprolol IR pellets prepared by E/S

Formulation	% Yield	BD (g/mL)	TD (g/mL)	CI (%)	HR	%Friability	Average weight	% drug content
B1	93.1	0.301±0.07	0.350±0.05	14.1	1.16	0.23± 015	119	98.6 ±0.59
B2	94.8	0.306±0.09	0.341±0.09	11.7	1.11	0.27± 0.71	119	96.9 ±0.20
B3	95.6	0.304±0.09	0.361±0.11	15.5	1.18	0.18± 0.61	119	97.3 ±0.36
B4	96.1	0.314±0.12	0.351±0.08	10.2	1.11	0.29± 0.49	119	98.6 ±0.74
B5	94.3	0.308±0.14	0.350±0.09	12.3	1.13	0.31± 0.13	119	99.2 ±0.52
B6	96.4	0.304±0.08	0.351±0.08	13.3	1.15	0.12± 0.32	119	98.7 ±0.98
B7	94.5	0.318±0.09	0.361±0.13	11.9	1.13	0.17± 0.09	119	97.6 ±0.21
B8	93.9	0.304±0.12	0.343±0.09	11.3	1.12	0.19± 0.14	119	99.0 ±0.59
B9	95.6	0.312±0.15	0.360±0.11	13.8	1.16	0.16± 0.15	119	96.5 ±0.12
B10	93.5	0.3051±0.17	0.354±0.16	13.5	1.15	0.21± 0.41	119	97.2 ±0.39
B11	93.3	0.310±0.13	0.352±0.04	11.9	1.13	0.25± 0.55	119	99.3 ±0.87
B12	95.6	0.301±0.11	0.347±0.07	13.2	1.15	0.32± 0.17	119	99.1 ±0.99
B13	94.2	0.312±0.12	0.354±0.01	11.86	1.13	0.41± 0.11	119	96.7 ±0.12
B14	95.2	0.314±0.21	0.358±0.12	12.29	1.14	0.27± 0.13	119	99.4 ±0.78
B15	96.3	0.315±0.13	0.362±0.12	12.98	1.14	0.31± 0.21	119.01	98.6 ±0.24
B16	96.8	0.314±0.11	0.360±0.14	12.77	1.14	0.21± 0.19	119.01	98.1 ±0.99

Table: Characterization of BS IR pellets prepared by S/S

Formulation	% Yield	BD (g/mL)	TD (g/mL)	CI (%)	Hauser ratio	%Friability	Average Weight	% drug content
F1	98.1	0.449±0.05	0.518±0.06	13.32	1.15	0.16± 0.63	120	98.5 ±0.36
F2	96.9	0.405±0.05	0.468±0.06	13.46	1.15	0.52± 0.20	121	96.2 ±0.24
F3	95.2	0.409±0.04	0.478±0.07	14.43	1.16	0.36± 0.27	122	98.5 ±0.29
F4	98.1	0.469±0.04	0.525±0.08	10.66	1.11	0.42± 0.52	120.5	98.3 ±0.36
F5	99.7	0.45±0.08	0.548±0.02	17.88	1.21	0.10± 0.99	121.5	99.2 ±0.75
F6	99.3	0.471±0.04	0.569±0.02	17.22	1.20	0.28± 0.15	122.5	98.1 ±0.34

F7	97.2	0.459±0.02	0.57±0.02	19.47	1.24	0.32± 0.42	120	98.2 ±0.82
F8	98.0	0.458±0.01	0.54±0.011	15.18	1.17	0.14± 0.78	121	96.5 ±0.22
F9	95.9	0.446±0.05	0.539±0.09	17.25	1.20	0.28± 0.24	122	99.2 ±0.19
F10	97.9	0.461±0.08	0.539±0.09	14.47	1.16	0.34± 0.16	120.5	99.0 ±0.42
F11	99.5	0.405±0.06	0.501±0.04	19	1.23	0.49± 0.32	121.5	97.5 ±0.36
F12	98.3	0.418±0.01	0.505±0.02	17.22	1.20	0.51± 0.78	122.5	96.5 ±0.72

Bisoprolol

The percent drug release in dissolution media should be NLT 75% in 30 minutes.

Method-A: Extrusion-Spheronization: The drug release profiles of different immediate release formulations in dissolution media were shown in Figure

Table: Dissolution Profiles of Bisoprolol IR Capsules 5 mg prepared by Extrusion-Spheronization (B1-B8)

Time (min)	**% Cumulative drug release**															
	Marketed Product	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	**B16**
10	87	50	40	77	41	39	75	35	**80**	40	64	32	47	63	73	53	55
15	90	67	63	90	65	61	96	55	**92**	64	76	62	68	80	81	70	70
20	93	90	80	97	71	76	99	70	**97**	85	90	78	89	93	90	83	80
30	96	95	90	99	90	81	99	87	**99**	98	94	90	94	98	98	91	95
45	98	99	97	100	99	98	100	94	**100**	100	99	95	99	99	99	96	98
60	99	100	100	101	100	100	100	100	**100**	100	100	99	100	99	100	99	101

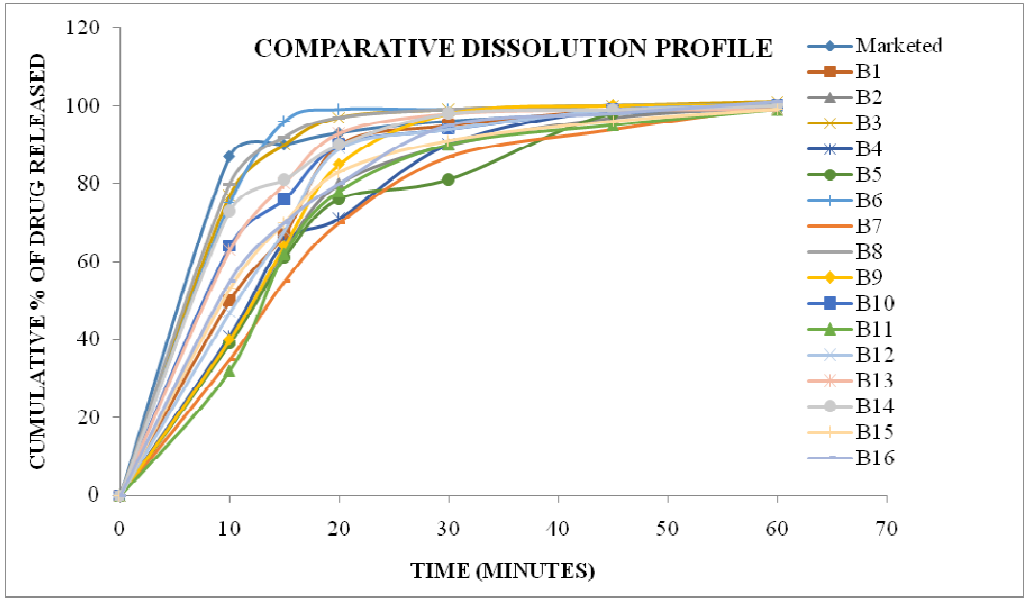

Figure: Comparative dissolution profile of BSP marketed product & B1-B16

Method-B: Solution/Suspension Layering

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

Table: Dissolution Profiles of Bisoprolol IR Capsules 5 mg prepared by Solution/Suspension Layering (F1-F6)

Time (min)	**% Cumulative drug release**												
	Marketed product	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	87	93	**85**	74	95	91	70	60	50	40	71	58	10
15	90	97	**93**	80	98	95	89	79	69	65	86	85	81
20	93	98	**98**	92	99	99	95	85	73	78	90	94	89
30	96	99	**99**	98	100	100	98	90	80	89	95	99	95
45	98	100	**100**	100	100	100	99	99	97	96	99	100	99
60	99	100	**100**	100	100	101	100	100	99	100	100	101	100

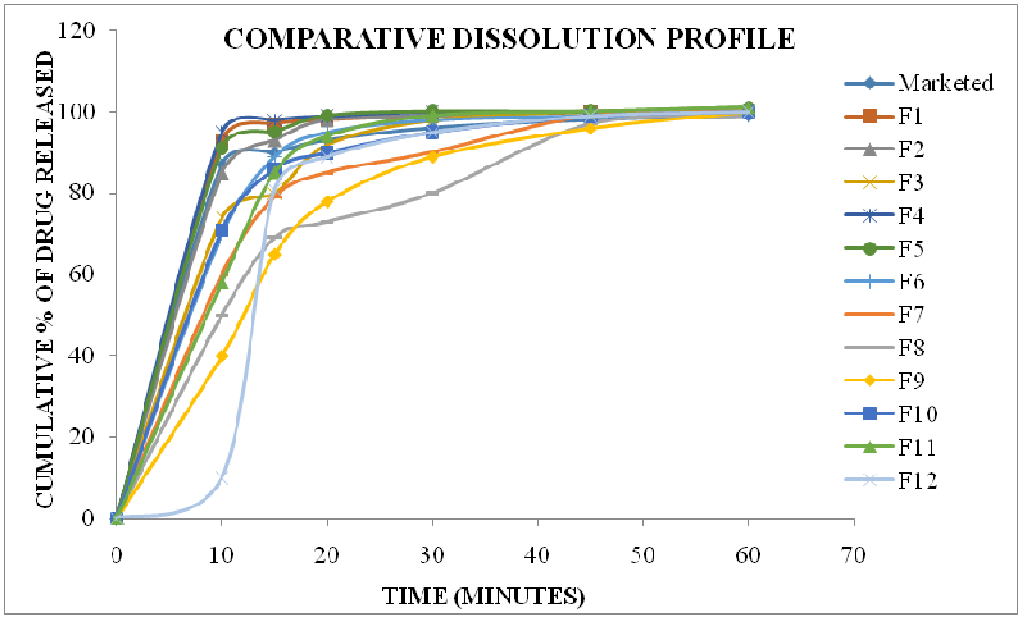

Figure: Comparative dissolution profile of BSP marketed product & F1-F12

Scanning Electron Microscopy (SEM)

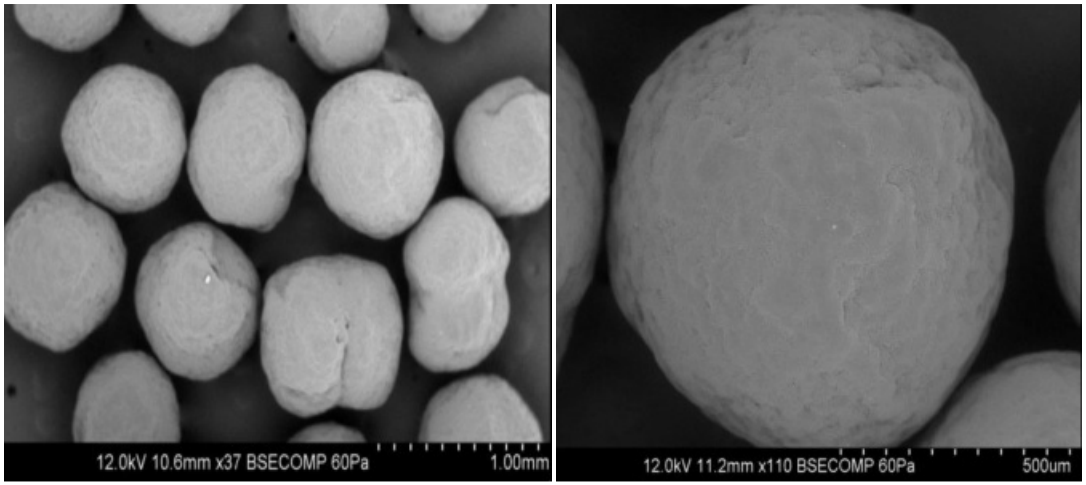

Figure: SEM analysis of Bisoprolol IR Pellets prepared by extrusion-spheronization and solution/suspension layering (a) B8 (b) F2

Accelerated Stability Studies(AST)

Table: AST results of Bisoprolol (BS) IR Capsules 5 mg (B8) prepared by Extrusion-Spheronization

Test parameter	**Initial**	**1st month**	**2nd month**	**3rd month**
Assay (% w/w)	99.6	98.5	99.2	98.3
Dissolution Profile (cumulative % drug release)				
10 mins	77	78	78	80

15 mins	90	89	87	90
20 mins	96	95	93	95
30 mins	99	99	99	98
45mins	100	99	100	99
60 mins	100	100	100	100

Table: AST results of Bisoprolol (BS) IR Capsules 5 mg (F2) prepared by Solution/suspension layering

Test parameter	**Initial**	**1st month**	**2nd month**	**3rd month**
Assay	99.8	99.1	98.9	99.5
Dissolution Profile (cumulative % drug release)				
10 mins	81	78	80	82
15 mins	90	91	91	90
20 mins	96	98	99	98
30 mins	98	99	99	100
45mins	100	99	100	100
60 mins	100	100	100	100

Conclusion:

Formulating immediate release pellets is cost-effective and thereby broadening market exclusivity with better revenue. These dosage forms also help in aiming underserved and undertreated patients.

The IR dosage forms have the ability to provide advantages of liquid medication in the form of solid preparation. They disintegrate rapidly and get dissolved to release the medicaments. When an IR product is directed to patients, the drug concentration in blood raises swiftly, peaks promptly after administration and thereby achieves therapeutic effect rapidly.

The results and observations of the conducted trails suggested that solubility can be improved by using water soluble excipients like Mannitol, Hypromellolse for a low soluble drug, Bisoprolol formulated into pelletized dosage form by pelletization techniques: extrusion-spheronization and solution/suspension layering[13]

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