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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF MULTI UNIT PARTICULATES AS RESERVOIR SYSTEMS USING HYDROPHOBIC POLYMERS

Dr. M. Sunitha Reddy*, Md. Ameeroddin[1], Muhammad S. Fazal Ul Huq[2] and Dr. V. Venkateswarlu[3]

[1, 2]Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana, India.

[3]managing Director, Neuheit Pharma Technologies Pvt Ltd, Hyderabad, Telangana, India.

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***Corresponding Author**
Dr. M Sunitha Reddy
Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana, India.

ABSTRACT

The aim of the present study is to formulate and optimize a suitable composition of Multi Unit Particulates (MUPs) as reservoir systems using hydrophobic polymers and achieve the pH independent drug release. Various drugs belonging to BCS Class – I and II have been scrutinized and Propranolol.HCl was found to be suitable for the study based on its availability. In the current study, the pellets are formulated as the reservoir units. The objective of formulating the reservoir systems is to increase the mean residence time of the dosage form in GIT and to enhance the bioavailability of the drugs. The Multi MUPs of Propranolol.HCl have been prepared using different hydrophobic polymers like PVA (KOLLICOAT®), Ethyl Cellulose (ETHOCEL STANDARD PREMIUM) (10cps, 20cps, and 100cps) in varied proportions. The initial evaluations prioritized the use of a pore former and so HPMC (HYPROMELLOSE 6cps) and PEG 400 were used. Multiple layering techniques were found preferable to the single layering technique with an enhanced and reproducible drug release profiles with that of RLD (Inderal® LA). The suitable composition of the polymer, plasticizer and pore former were optimized. The formulated MUPs have been subjected to evaluation tests which include Fill weight determination, Weight variation, Locked length analysis, Disintegration Time, Assay, Dissolution, Uniformity of dosage units, Related substances, Residual solvents, Water content and Alcohol dose dumping studies.

From the evaluation studies it was found that formulation (F6) (by multiple layering technique) consisting of Ethyl cellulose 20cps, Dibutyl sebacate, PEG® 400 in 70:10:20 ratios (w/w) was optimum. The in – vitro dissolution studies showed a drug release of 98.5 ± 1.8%. Results of Accelerated stability studies showed that formulation was stable and does not alter the drug release.

KEYWORDS: Multi Unit Particulates (MUPs), reservoir systems, hydrophobic polymers, controlled release, multiple layering technique, evaluations.

INTRODUCTION[1 – 9]

The modified-release products provide either delayed release or extended release of drug. Most delayed-release products are enteric coated tablets or capsules designed to pass through the stomach unaltered, later to release their medication within the intestinal tract. Enteric coatings are used either to protect a substance from destruction by gastric fluids or to reduce stomach distress caused by irritating drugs. Extended-release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.[1]

Extended-release tablets and capsules are commonly intended only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. The extended-release products provide an immediate release of drug that produces the desired therapeutic effect, followed by the controlled release which maintains the Minimum effective concentration and the effects (Fig. 1). The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.[1]

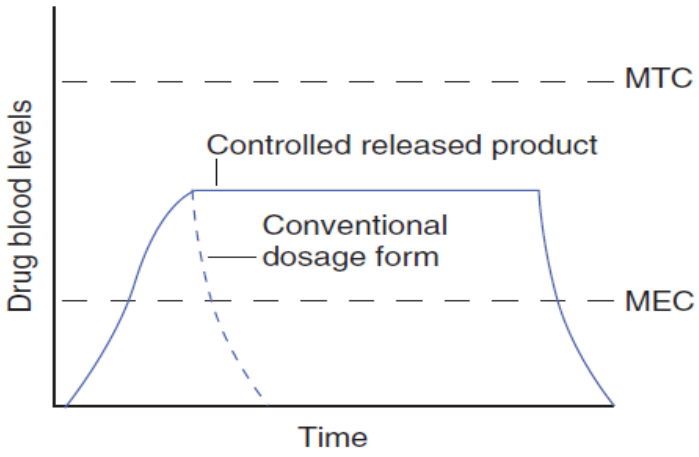


Fig 1 Hypothetical blood drug levels of a typical conventional solid dosage form and a controlled release form.

When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose (Fig 2). However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub-therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient.

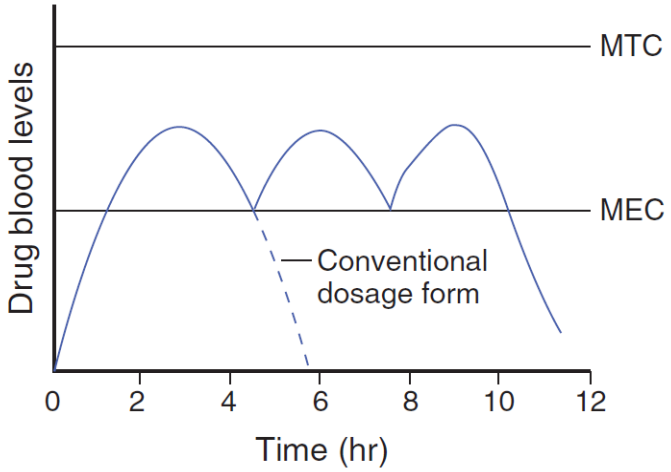


Fig 2 Hypothetical blood drug levels of a typical conventional solid dosage form and a multiple action product.

Modified release dosage forms[1]

In recent years, *modified release* has come into general use to describe dosage forms having drug release features based on time, course, and/ or location that are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms.

Extended release[1]

The U.S. Food and Drug Administration (FDA) defines an extended-release dosage form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate-release dosage form.

Delayed release[1]

A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

Repeat action[1]

Repeat-action forms usually contain two single doses of medication, one for immediate release and the second for delayed release. Two-layer tablets, for example, may be prepared with one layer of drug for immediate release with the second layer designed to release drug later as either a second dose or in an extended-release manner.

Targeted release[1]

Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, tissue, or site for absorption or for drug action.

Reservoir coated systems [4, 5, 6, 7]

A reservoir coated system consists of a drug layered core surrounded by a polymer. The major advantages of this system rely in the fact that very high drug loadings can be used and variable drug release profiles can be obtained, by just varying the type of polymeric membrane.

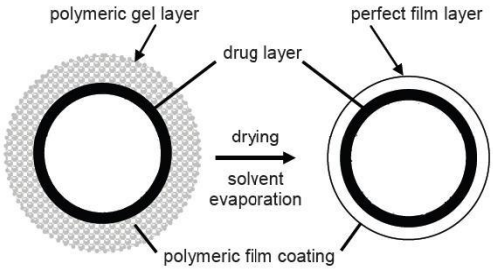


Fig 3: Schematic presentation of the film forming mechanism from organic polymer solution (Muschert, 2008)

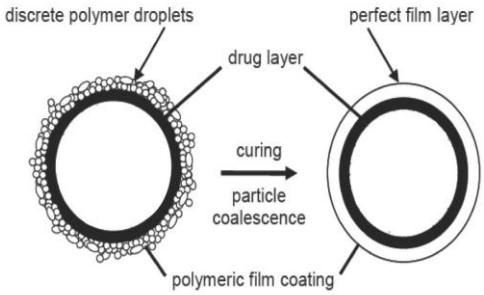


Fig 4: Schematic presentation of the film forming mechanism from aqueous polymer dispersions (Muschert, 2008)

Formulation parameters [7, 8, 9]

Polymers[7, 8, 9]

The chief component in the functional coating process is the polymer which is layered onto the drug layered pellets. The main objective is to achieve a pH independent drug release. Many hydrophobic polymers have been used individually which include ethyl cellulose (10cP, 20cP, 100cP), and PVA.

Pore formers [7, 8, 9]

The other additives that are used in the functional coating include the plasticizers, pore formers etc., which are preferably water soluble. The rationale of including the pore former is to create the pores in the functional coating layer resulting in the penetration of water. The number of pores remains more or less constant throughout the transit time.

Plasticizers [7, 8, 9]

The rationale of including the plasticizer is to promote the uniform layering of the polymer layer on the pellets. The plasticizer layer squeezes out when gets into contact with water

resulting in the enhanced drug release. Mostly the concentrations of the plasticizer will be less compared to the polymer concentration.

Drug release mechanisms [7, 8, 9]

The mechanism of controlling drug release from reservoir coated pellets is often a complex process and it depends on coating type and thickness, drug type, and core type. One of the mechanisms is diffusion through the continuous polymer film surrounding the drug loaded core. Firstly, water penetrates through the coating until reaches the pellet core. Afterwards, drug is dissolved and released. The drug is released due to the concentration gradient inside the pellet (c_i) versus outside the pellet. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick's law of diffusion).

$$\frac{dM}{dt} = D_m \cdot A \cdot K \cdot \frac{c_i}{d}$$

D_m is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase – polymeric phase), and d denotes the thickness of the film coating.

Another mechanism controlling drug release from coated pellets is due to osmotic effects. For this mechanism to occur an osmotic active core should be surrounded by semi-permeable membrane and a difference in osmotic pressure between the inner and outer side of the membrane. Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of the sugar core and the drug. Upon water uptake, drug is pushed out via pores in the coating. Drug release can be described as follows.

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l}$$

Where dV/dt denotes the water flow, A the membrane surface area, l the membrane thickness, θ the permeability of the polymeric membrane, and $\Delta\pi$ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure).

Parameters consequence fluidized bed coating process[7, 8, 9]

1. Feed particle dimension
2. Spray gun parameters

3. Coating solution
4. Coating thinness and consistency
5. Particle circulation
6. Temperature and wetness distributions
7. Spray velocity

Characterization of pellets [7, 8, 9]

A. Particle size distribution
B. Surface area
C. Density
D. Hardness and friability
E. Porosity
F. Tensile strength

MATERIALS AND METHODS

Sl. No	CHEMICAL NAME	CATEGORY	SUPPLIER
1	Propranolol. HCl I.P.	API	Pharma Trans pvt Ltd
2	Microcrystalline cellulose 175 (CELLETS® 175)	Core material	Ludwigshafen, Germany
3	PEG 400 (KOLLISOLV® PEG 400)	Pore former	BASF
4	Ethyl cellulose 100 cps (ETHOCEL STANDARD 100 PREMIUM)	Hydrophobic polymer	DOW chemicals
5	Ethyl cellulose 20 cps (ETHOCEL STANDARD 20 PREMIUM)	Hydrophobic polymer	DOW chemicals
6	Ethyl cellulose 10 cps (ETHOCEL STANDARD 10 PREMIUM)	Hydrophobic polymer	DOW chemicals
7	Hydroxy propyl methyl cellulose E5 (HYPROMELLOSE E5V)	Binder	DOW chemicals
8	Dibutyl sebacate	Plasticizer	Vertellus
9	Isopropyl alcohol	Solvent	Merck
10	Polyvinyl acetate	Polymer	BASF
10	Ethyl cellulose 10 cps (ETHOCEL STANDARD 10 PREMIUM)	Hydrophobic polymer	Colorcon chemicals Pvt Ltd
11	Hydrochloric acid	Reagent	Rankem Chemicals
12	Sodium chloride	Reagent	Rankem Chemicals
13	Cellets ® 175	Core	Rankem Chemicals
14	Hydroxy propyl methyl cellulose E6 (HYPROMELLOSE E6V)	Binder & Pore former	DOW chemicals

15	Monobasic potassium phosphate	Reagent	Rankem Chemicals
16	Acetonitrile	Solvent	Rankem Chemicals
17	Methanol	Solvent	Merck

Assay

Buffer: 6.8 mg/mL of monobasic potassium phosphate. Pass the solution through a filter of 0.5µm or finer pore size before use.

Mobile phase: Acetonitrile and Buffer (7:13)

Diluent: Acetonitrile and water (7:13)

Standard stock solution: 200 µg/mL of Propranolol Hydrochloride in methanol

Sample stock solution: Transfer the contents of Capsules (NLT 10) to a suitable volumetric flask. Add methanol (60% of the volume of the flask), and swirl by mechanical means for 2 h. Allow to stand for 16 h, then sonicate for 30 min, and swirl for 30 min. Dilute with methanol to volume, and centrifuge a portion of the solution.

Chromatographic system

Mode: LC

Detector: UV 220 nm

Column: 4mm × 15cm; 5µm

Packing: L1

Flow rate: 2 mL/min

Injection size: 20 µL

Relative Standard Deviation: NMT 2%

Calculate the percentage of $C_{16}H_{21}NO_2 \cdot HCl$ in each Capsule taken.

$$\textbf{Result} = \frac{ru}{rs} \; x \; \frac{Cs}{Cu} \; x \; 100$$

r_u = peak response from the Sample solution

r_s = peak response from the Standard solution

C_s = concentration of Propranolol Hydrochloride in the Standard solution (µg/mL)

C_u = nominal concentration of propranolol hydrochloride in the Sample solution (µg/mL)

Acceptance criteria: 90.0%–110.0%

DISSOLUTION

pH 1.2 buffer solution: Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, and dilute with water to 1 L.

pH 6.8 buffer solution: 21.72 mg/mL of anhydrous dibasic sodium phosphate and 4.94 mg/mL of citric acid monohydrate in water.

Media: pH 1.2 HCl buffer followed by 6.8 pH phosphate buffer Dosage Forms, using 900 mL of pH 1.2 buffer solution during the Acid stage, and conduct the test for 1.5 h. For the Buffer stage, use 900 mL of pH 6.8 buffer solution, conduct the test for 2.5 h (this is the 4h time point: 1.5 h in Acid stage plus 2.5 h in Buffer stage), conduct the test for the additional time points, always considering T1 = 1.5 h.

Apparatus 1: 100 rpm

Times: 1.5, 4, 8, 14, and 24 h

Standard solution: Propranolol Hydrochloride at a known concentration in water.

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with medium, if necessary.

Spectrometric conditions

Mode: UV

Analytical wavelength: Maximum absorbance at 320 nm, with respect to a baseline drawn from 355 nm through 340 nm.

Uniformity of dosage units

Procedure for content uniformity

Standard solution: 40 µg/mL of Propranolol Hydrochloride in methanol.

Sample stock solution: Transfer the contents of 1 Capsule to a suitable volumetric flask. Add methanol (70% of the volume of the flask), swirl occasionally for 30 min, sonicate for 1 min, and then swirl occasionally for an additional 30 min. Dilute with methanol to volume, and centrifuge a portion of the solution. Use the clear supernatant for preparing the Sample solution.

Sample solution: Equivalent to 40 µg/mL in methanol from Sample stock solution

Spectrometric conditions

Mode: UV

Analytical wavelength: 290 nm

Cell: 1 cm

Blank: Methanol

Calculate the percentage of $C_{16}H_{21}NO_2 \cdot HCl$ in the Capsule taken.

RESULT = $(A_u/A_s) \times (C_s/C_u) \times 100$

A_u = absorbance of the Sample solution

A_s = absorbance of the Standard solution

C_s = concentration of Propranolol Hydrochloride in the Standard solution (µg/mL)

C_u = concentration of the Sample solution (µg/mL)

In-vitro drug release study

The in-vitro dissolution studies of capsules were carried out using USP-Type I dissolution test apparatus (DS1800 Lab India) in 500mL buffer of pH 1.2 at 37±0.5^{o}C with 100rpm rotating speed. Samples were withdrawn at 1.5, 4, 8, 14, and 24 hours time intervals and filtered through 0.45µ filter. An equal volume of dissolution medium was replenished after every sampling to maintain constant volume. Samples were analyzed using UV-Spectrophotometer at 320 nm. The concentration of drug was calculated from calibration curve. Amount of drug released was calculated from concentration and absorbance.

Table 1: Specifications for the dissolution of Propranolol.HCl.

Sl. No.	Time (in hours)	Amount dissolved (in %)
1	1.5	NMT 30
2	4	35 – 60
3	8	55 – 80
4	14	70 – 95
5	24	81 – 110

Process parameters

Table 2: Process parameters

Sl. No.	Parameter	Seal coating	Drug layering -1	Extended release – 1	Drug layering -2	Extended release – 2
1	Inlet temperature (°C)	32 – 40	33 – 48	32 – 40	33 – 48	32 – 40
2	Product temperature (°C)	28 – 30	29 – 31	28 – 30	29 – 31	28 – 30
3	Air inlet (CFM)	45 – 50	50 – 55	45 – 50	50 – 55	45 – 50
4	Spray rate (g/min)	1 – 10	1 – 13	1 – 10	1 – 13	1 – 10
5	Spray atomization (bar)	1.2 – 1.6	1.2 – 1.4	1.2 – 1.6	1.2 – 1.4	1.2 – 1.6

RESULTS AND DISCUSSION

STANDARD CURE OF PROPRANOLOL HCL IN PH 1.2 ACID BUFFER

Table 3: Standard curve of Propranolol in pH 1.2 acid buffer.

Conc. (ppm)	Absorbance
9.6	0.077
36	0.249
48	0.321
90	0.623
120	0.832
150	1.05

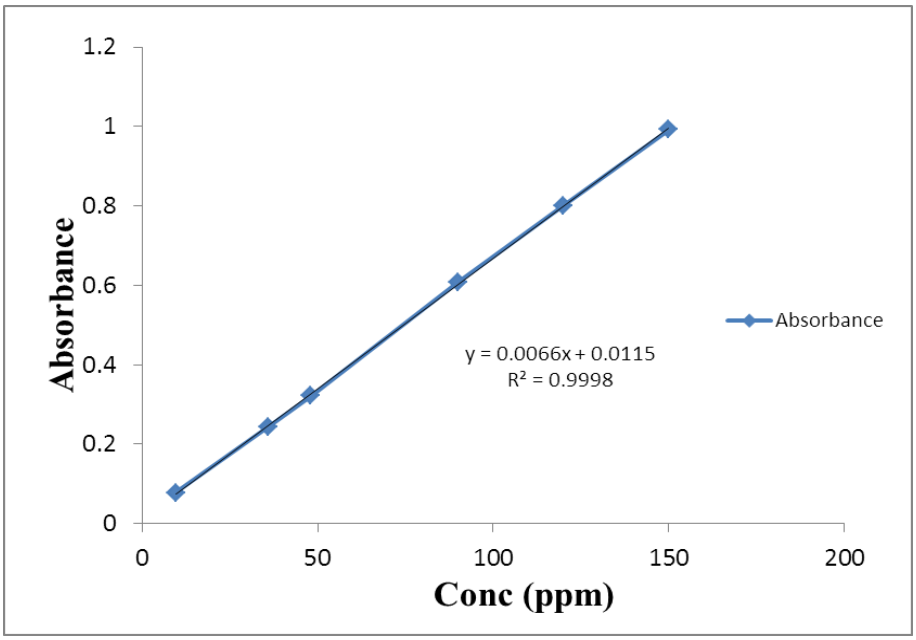
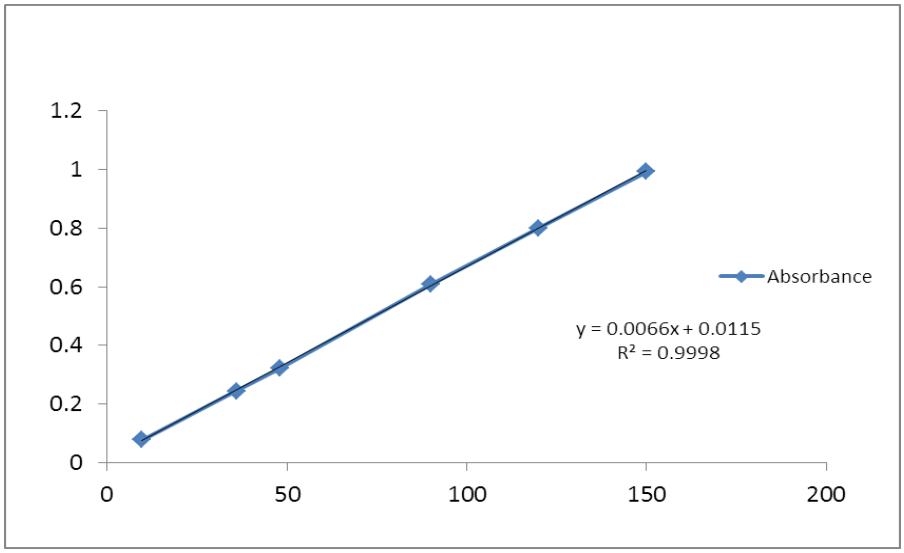


Table 4: Standard curve of Propranolol in pH 6.8 phosphate buffer.

Conc. (ppm)	Absorbance
9.6	0.078
36	0.244
48	0.322
90	0.608
120	0.801
150	0.993



Single Layering Technique with Ethyl Cellulose

Table 7: Qualitative and quantitative formula.

S. No	Ingredients	Quantity/unit (mg)				
	Formulation No	**Trial 1 (20% w/w)**	**Trial 2A (20% w/w)**	**Trial 2B (20% w/w)**	**Trial 3 (15% w/w)**	**Trial 4 (10% w/w)**
I	**Drug layering**					
1	MCC Spheres (#20-#25)	80	80	80	80	80
2	Propranolol HCl	160.00	160.00	160.00	160.00	160.00
3	Hypromellose 6cps	3.00	3.00	3.00	3.00	3.00
II	**Extended release coating**					
1	Ethyl Cellulose 10Cps	38.9	34.0	38.8	17.0	17.0
2	Dibutyl sebacate	9.7	4.9	4.9	2.4	2.4
3	PEG 400	-	9.7	4.9	4.9	-
4	HPMC E6	-	-	-	-	4.9
5	IPA	q.s.				
6	Water					

Flow properties

Table 8: Evaluation of flow

Sl. No.	Evaluation parameter	T3A	T3B
1	Angle of repose	17.5^0	17.8^0
2	Bulk Density	0.72 g/cc	0.72 g/cc
3	Tapped Density	0.81 g/cc	0.82 g/cc
4	Compressibility index	11.11	12.20
5	Hausner's ratio	1.13	1.14

Properties of pellets.

These pellets are filled into the clear transparent size – 2 hard gelatin capsules and the data is as follows.

Table 9: Evaluation of filled capsules.

Batch No	Fill weight (mg)	Wt. variation (%)	Locked length (mm)	DT (min)
T3A	268 ± 1.2	1.32 ± 0.008	16.3± 0.1	10.2 ± 1.12
T3B	**267 ± 1.5**	**1.66 ± 0.009**	**16.3 ± 0.1**	**10.5 ± 2.15**

Table 10: Drug excipient compatibility studies (RS)

Drug – Excipient Compatibility studies				40°C/75% RH open			25°C/60% RH open		
Sl. No	**Impurity**	**Limits**	**initial**	**7 days**	**15 days**	**30 days**	**7 days**	**15 days**	**30 days**
1	(2*RS*)-3-(naphthalen-1-yloxy)propane-1,2-diol (diol derivative),	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
2	1,1′-[(1-methylethyl) imino] bis [3-(naphthalen-1-yloxy) propan-2-ol] (tertiary amine derivative),	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
3	1,3-bis(naphthalen-1-yloxy)propan-2-ol (bis-ether derivative).	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
4	Individual maximum unknown	-	0.013	0.015	0.004	0.011	0.044	0.006	0.017
5	Total Unknown impurities	NMT 0.2%	0.02	0.01	0.02	0.02	0.04	0.01	0.02
6	Total impurities	NMT 0.8%	0.02	0.01	0.02	0.02	0.03	0.01	0.03
7	Assay	95-105	NA	NA	NA	NA	NA	NA	NA

Inference

The drug - excipient compatibility data did not reveal any significant change at accelerated conditions (40°C/75% RH) and long term conditions (25°C/60% RH) for 7, 15, and 30 days. These pellets were charged for the stability at accelerated conditions (40 ± 2^0C / 75 ± 5% RH). The results drawn after one month are as follows.

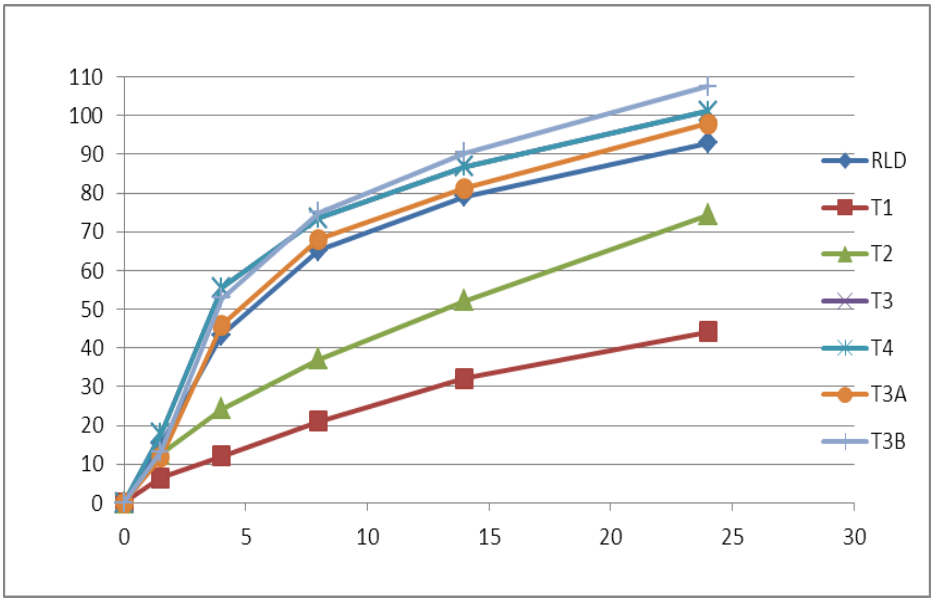


Table 11 Stability results of Invitro dissolution studies.

Stage	Batch & Month	Time points (Hr)					
		0	**1.5**	**4**	**8**	**14**	**24**
Initial	RLD	0.0	15.3 ± 0.85	43.4 ± 1.10	65.2 ± 1.02	79.1 ± 1.58	93 ± 0.85
Initial	T3A	0.0	11.8 ± 1.24	46 ± 0.57	68.1 ± 3.28	81.2 ± 0.75	97.9 ± 1.45
(40°C/75% RH)	T3A / 1 month	0.0	29.2 ± 0.58	65.1 ± 1.54	81.8 ± 2.17	94.7 ± 0.83	102.1 ± 1.48
Initial	T3B	0.0	13.2 ± 3.28	52.9 ± 0.56	75 ± 3.27	90.4 ± 2.17	107.5 ± 2.24
(40°C/75% RH)	T3B / 1 month	0.0	28.6 ± 3.31	62.1 ± 1.14	81.0 ± 3.20	94.9 ± 3.28	100.2 ± 3.28

REPORT

It was clear that the stability of the batches is failed as the release profile is exceeding the upper boundaries. Hence it is concluded that the single layering technique is not suitable for the formulation of MUPs as reservoir systems.

MULTIPLE LAYERING TECHNIQUE WITH ETHYL CELLULOSE (10cPs, 20cPs, 100cPs)

Procedure of formulation

Seal coating of the pellets with the seal coating solution

⇒

Drug layering – 1 of the seal coated pellets with the aqueous solution of Propranolol.HCl and HPMC E5 (Hypromellose E5)

⇓

Extended release – 1 coating of the drug layered pellets with the solution comprising of ethyl cellulose, PEG 400 & DBS in the ratio of 70:20:10% w/w in a mixture of IPA: H_20 in the ratio of 70:30 w/w

⇐

Drug layering – 2 of the seal coated pellets with the aqueous solution of Propranolol.HCl and HPMC E5 (Hypromellose E5)

⇓

Extended release – 2 coating of the drug layered pellets with the solution comprising of ethyl cellulose, PEG 400 & DBS in the ratio of 70:20:10% w/w in a mixture of IPA: H_20 in the ratio of 70:30 w/w

⇒

Curing of the sample at 45°C for 2 hours

The formulations F1 contains ER-1: ER - 2 in the ratio of 12:7.5 % w/w containing EC 10cPs

The formulations F2 contains ER-1: ER - 2 in the ratio of 16:7.5 % w/w containing EC 20cPs

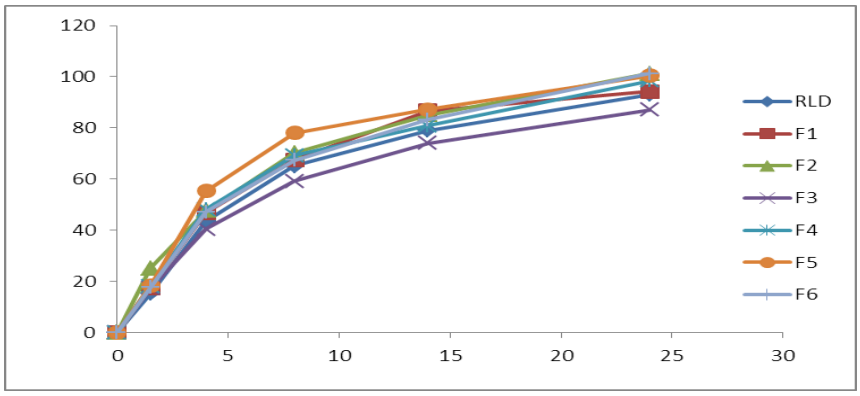
The formulations F3 contains ER-1: ER - 2 in the ratio of 12:5 % w/w containing EC 20cPs

The formulations F4 contains ER-1: ER - 2 in the ratio of 8:7.5 % w/w containing EC 20cPs

The formulations F5 contains ER-1: ER - 2 in the ratio of 12:7.5 % w/w containing EC 20cPs

The formulations F6 contains ER-1: ER - 2 in the ratio of 8:5 % w/w containing EC 20cPs

Invitro drug release studies



Flow properties

Table 12 Evaluation of flow properties of pellets.

Sl. No.	Evaluation parameter	RLD	F1	F4	F6
1	Angle of repose	18.2°	17.5°	17.8°	17.8°
2	Bulk Density	0.73 g/cc	0.72 g/cc	0.72 g/cc	0.72 g/cc
3	Tapped Density	0.81 g/cc	0.82 g/cc	0.82 g/cc	0.81 g/cc
4	Compressibility index	12.41	12.21	12.20	11.10
5	Hausner's ratio	1.15	1.14	1.14	1.13

Table 13 Evaluation of filled capsules.

Batch No	Fill weight (mg)	Wt. variation (%)	Locked length (mm)	DT (min)
RLD	268 ± 1.2	0.78 ± 0.010	16.8± 0.1	10.8 ± 0.45
F1	221 ± 1.2	1.32 ± 0.008	16.8± 0.1	10.2 ± 0.32
F4	217 ± 1.5	1.66 ± 0.009	16.8± 0.1	10.5 ± 0.40
F6	211 ± 1.2	1.32 ± 0.009	16.8± 0.1	10.3 ± 0.45

Table 14 Assay results of stability studies.

Trials	Stage	Avg (%)
RLD	Initial	100.3 ± 0.20
F1	Initial	102.3 ± 0.24
	1 Month (40°C/75% RH)	98.1 ± 1.01
	2 Months (40°C/75% RH)	97.4 ± 1.14
	3 Months (40°C/75% RH)	96.9 ± 0.75
F4	Initial	100.2 ± 0.21
	1 Month (40°C/75% RH)	98.6 ± 0.98
	2 Months (40°C/75% RH)	97.5 ± 0.20
	3 Months (40°C/75% RH)	96.8 ± 2.00
F6	Initial	102.3 ± 1.02
	1 Month (40°C/75% RH)	99.1 ± 1.51
	2 Months (40°C/75% RH)	98.4 ± 2.01
	3 Months (40°C/75% RH)	98.1 ± 0.21

LOSS ON DRYING

Table 15 LOD results of stability studies.

Trials	Stage	Avg (%)
RLD	Initial	0.75
F1	Initial	0.72
	1 Month (40°C/75% RH)	0.70
	2 Months (40°C/75% RH)	0.70
	3 Months (40°C/75% RH)	0.68
F4	Initial	0.74
	1 Month (40°C/75% RH)	0.71
	2 Months (40°C/75% RH)	0.68
	3 Months (40°C/75% RH)	0.64
F6	Initial	0.70
	1 Month (40°C/75% RH)	0.68
	2 Months (40°C/75% RH)	0.66
	3 Months (40°C/75% RH)	0.65

INVITRO DISSOLUTION STUDIES

Table 16 Stability results of Invitro dissolution studies.

Stage	Batch & Month	Time points (Hr)					
		0	**1.5**	**4**	**8**	**14**	**24**
Initial	RLD	0.0	15.3 ± 0.85	43.4 ± 1.10	65.2 ± 1.02	79.1 ± 1.58	93 ± 0.85
Initial	F10A	0.0	17.4 ± 0.85	38.5 ± 0.85	59.1 ± 1.58	70.4 ± 1.02	89.5 ± 1.02
(40°C/75% RH)	F1 / 1 month	0.0	21.2 ± 0.85	55.1 ± 1.10	68.8 ± 0.52	84.7 ± 0.45	102.1 ± 1.11
(40°C/75% RH)	F1 / 2 months	0.0	22.5 ± 1.02	56.1 ± 0.85	69.8 ± 1.10	85.2 ± 0.85	102.5 ± 1.02
(40°C/75% RH)	F1 / 3 months	0.0	23.1 ± 0.85	58.2 ± 1.02	69.5 ± 1.10	85.4 ± 1.10	102.8 ± 0.85
Initial	F4	0.0	17.8 ± 1.58	47.2 ± 1.02	68.1 ± 0.85	80.7 ± 1.02	97.1 ± 0.85
(40°C/75% RH)	F4 / 1 month	0.0	18.2 ± 1.02	49.1 ± 1.17	67.8 ± 1.45	81.5 ± 1.10	98.4 ± 0.84
(40°C/75% RH)	F4 / 2 months	0.0	18.8 ± 0.85	54.1 ± 1.02	68.1 ± 1.17	83.0 ± 1.02	99.5 ± 1.17

(40°C/75% RH)	F4 / 3 months	0.0	21.1 ± 1.17	55.8 ± 1.00	69.2 ± 1.02	84.1 ± 0.85	99.7 ± 1.10
Initial	F6	0	17.5 ± 1.02	47.1 ± 1.10	67.4 ± 0.85	83.2 ± 1.45	101.3 ± 1.36
(40°C/75% RH)	F6 / 1 month	0.0	18.6 ± 0.85	48.2 ± 1.10	67.7 ± 1.45	83.4 ± 1.00	100.2 ± 1.02
(40°C/75% RH)	F6 / 2 months	0.0	21.0 ± 1.02	51.3 ± 0.45	68.9 ± 0.85	83.7 ± 1.02	100.5 ± 1.10
(40°C/75% RH)	F6 / 3 months	0.0	23.1 ± 1.02	55.8 ± 0.85	69.8 ± 2.01	84.5 ± 1.00	102.7 ± 0.85

7.1.4 ALCOHOL DOSE DUMPING STUDIES

Stability results of Alcohol dose dumping studies of 3rd month samples

Table 17 Drug release in 0.1 N HCl

	Reference	**Test**		
	0.1 N HCl			
Time in min	**INDERAL LA**	**F10A**	**F13A**	**F15A**
0	0	0	0	0
15	3.2	1.2	1.3	1.1
30	7.3	6.8	6.6	6.9
45	10.8	10.7	11.3	10.4
60	14.0	14.6	13.9	14.8
75	16.9	18.9	17.4	19.1
90	19.9	21.2	18.9	22.2
105	22.3	24.7	21.1	24.9
120	25.4	28.2	24.8	27.2

Table 18 Drug release in 0.1 N HCl + 5% v/v alcohol.

	Reference	**Test**		
	0.1 N HCl + 5% v/v alcohol			
Time in min	**INDERAL LA**	**F10A**	**F13A**	**F15A**
0	0	0	0	0
15	2.5	2.2	1.3	1.1
30	6.4	5.1	6.6	6.9
45	9.4	11.2	11.3	10.4
60	12.5	15.3	13.9	14.8
75	15.9	19.5	17.4	19.1
90	19.3	21.1	18.9	22.2
105	21.7	23.8	21.1	24.9
120	24.5	26.4	24.8	27.2

Table 19 Drug release in 0.1 N HCl + 20% v/v alcohol

	Reference	Test		
	0.1 N HCl + 20% v/v alcohol			
Time in min	INDERAL LA	F10A	F13A	F15A
0	0	0	0	0
15	5.3	5.2	5.4	5.4
30	10.9	8.6	9.1	8.8
45	17.9	15.3	15.7	15.3
60	24.3	19.7	19.2	19.4
75	30.7	24.3	26.1	25.4
90	36.3	27.1	29.4	28.5
105	41.2	29.3	32.3	31.5
120	45.9	34.6	38.6	37.1

Table 20 Drug release in 0.1 N HCl + 40% v/v alcohol.

	Reference	Test		
	0.1 N HCl + 40% v/v alcohol			
Time in min	INDERAL LA	F10A	F13A	F15A
0	0	0	0	0
15	28.1	2.5	2.2	3.1
30	54.2	21.5	26.6	27.2
45	73.8	52.9	54.1	49.1
60	86.6	74.1	73.9	64.8
75	95.8	78.2	75.4	69.1
90	100.0	79.1	76.8	74.2
105	103.0	79.8	77.2	76.9
120	102.9	80.5	78.3	77.5

Table: 21 Results of the kinetic studies of the formulations

KINETIC MODEL	r^2 values			
	RLD	F6	F4	F1
ZERO ORDER	0.8340	0.9674	0.9321	0.9218
FIRST ORDER	0.2554	0.2704	0.2672	0.2611
SECOND ORDER	0.2145	0.2145	0.2145	0.2145
THIRD ORDER	0.2145	0.2145	0.2145	0.2145
KORSMEYER - PEPPAS	0.9984	0.9994	0.9992	0.9987
HICKSON CROWEL	0.9635	0.9913	0.9792	0.9422
HIGUCHI	0.9906	0.9915	0.9900	0.9904

SUMMARY AND CONCLUSION

The drug Propranolol.HCl 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 has been increased than the RLD and that was within the limits.

For the optimization of the formula various excipients and their effects on the formulation has been evaluated and the optimized formula was obtained by the double layering technique. The single layering technique containing sugar spheres and MCC spheres as the core were found not suitable for formulation. Use of ethyl cellulose in the single layering technique did not prove to be satisfactory. When Kollocoat was used it was also found not satisfactory as the release rate of the drug from the pellets is unpredictable.

The optimized formulation contained the subsequent layering of the drug in the ratio of 80:20 and the extended release coating was done after every drug layering process with a percentage weight build up of 12%w/w and 7.5% w/w (F13) ; 8%w/w and 5% w/w of extended release – 1 and extended release – 2 coating respectively. The incorporation of the plasticizer (in all the formulations except in S1) put up a marked elevation in the drug release. The same effect was seen when the pore former concentration was increased. The suitable proportion of the plasticizer to pore former ratio has been found to be 1:2.

The extended release coating solution composition of the optimized formulation is ethyl cellulose 20cps : dibutyl sebacate : poly ethylene glycol 400 was 70:10:20 respectively. All the formulations contained the ER 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, related substances, assay, dissolution, % moisture content, particle size distribution, disintegration time as per USP.

All the formulations were evaluated and the formulations F1, F4, F6 were found to be the optimized formulations and these batches were loaded for the stability at accelerated stability conditions (40 ± 2^{o}C / 75 ±5% RH) and they all passed the evaluations. From the stability results the formulation F7 was concluded to be the optimized formula. The stability samples were found to be containing the related substances in slightly higher concentrations than the initial formulations and were found to be within the stipulated limits. The drug release of initial samples was 101.3 ± 1.22 % and it was found to be 102.8 ± 1.14 % with the stability samples of the 3rd month.

The formulations being the modified release dosage forms were tested for the alcohol dose dumping studies. It was found that the percentage of drug release was found to be less than the RLD at any given time point. It could be therefore concluded that the formulation has passed the alcohol dose dumping studies. The same is observed with the stability samples at the end of 1st, 2nd and 3rd month.

The formulation (F7) showed better release profile than the RLD with a similarity factor of 76.05 and differential factor of 7; the r^2 value of the cumulative drug release of the RLD and the formulations was 0.94 – 0.99. The results of the evaluations of the formulations proved that the double layering technique was best suitable for formulation of pellets as reservoir units. Hence it was concluded the formulation had a greater similarity with the RLD with a better release and could be used for formulating the reservoir systems.

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