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FORMULATION DEVELOPMENT AND EVALUATION OF MODIFIED RELEASE ANTISPASMODIC PELLETS

B. S. Venkateswaralu*[1], B. Jaykar[1], N.K.K. Sreedharan[1], Palanisamy.P[1], T.V. Narayana[2]

[1]Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Missions University Salem, Tamil Nadu

[2]Department of Pharmaceutics, Vikas Institute of Pharmaceutical Sciences, Rajamundhry (A.P.)

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***Correspondence for Author**
Dr. B.S. Venkateswaralu
Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy Vinayaka Missions University Salem, Tamil Nadu.

ABSTRACT

Antispasmodic agents are used in the treatment of Irritable bowel syndrome (IBS). The formulation of antispasmodic agent in pellet, is to improve its oral bioavailability and possibility to restrict its absorption at colon, pellets were prepared by drug layering technique in three trails (T1 – T3), and further Four formulations (F1 – F4) were prepared with varying concentration polymers such as Eudragit S100, Eudragit L100 D55, Eudragit NE 30 D with suitable plasticizer. These formulations were subjected to various evaluation parameters like microscopic evaluation, flow properties, particle size distribution, assay and In-vitro drug release. In vitro release of the Formulation F4 was to optimized formulation, it posses to similarity factory with in Innovator products.

KEYWORDS: IBS, Eudragit S100, Eudragit NE 30 D, Eudragit L100D 55, plasticizer.

INTRODUCTION

The controlled release drug delivery systems provide a therapeutic release of drug to the proper site in the body to achieve and maintain the desired drug concentration. An ideal dosage regimen in therapy of any disease is the one which immediately attains the desired therapeutic concentration of the drug in plasma or at the site of action and maintains it constant for the entire duration of treatment. This is usually achieved by repeated administration of a drug in a suitable amount (dose) and at a particular frequency.[1-2]

An alternative approach to maintain the desired therapeutic plasma concentrations constantly for the entire duration of treatment is the design and use of controlled release dosage forms. Controlled release drug delivery systems are those dosage formulations designed to release an active ingredient at rates predesigned, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible. Pellets may be manufactured by using different methods. The methods used for pelletization are essentially the same as the granulation methods. The most widely used processes are extrusion and spheronization, solution or suspension layering, and powder layering. Other processes with limited application in the development of pharmaceutical palletized products include globulation, balling, and compression.[3]

The aim and objective of the present study was to develop modified release pellets in form of capsule. Pellets with a coating for modified release have a lower risk of dose dumping than coated tablets. To develop modified release capsules of 24 hours release for to reduce the dosing frequency when compared with the tablet for treating irritable bowel syndrome.

MATERIALS AND METHODS

Materials: Antispasmodic drug was received as a gift sample from Caplin Point Research Laboratory. Micro crystalline cellulose 101, Hypromellose 6 cps, Povidone K-30, Purified Talc, Purified Talc, Eudragit L30 D 55, Eudragit NE 30 D and Eudragit S 100 gifted by FMC Bio-polymer (India).[4-5]

Determination of λmax of pure drug: The λmax of pure drug is carried out by UV absorption spectrum by finding the maximum absorption and that absorption λmax is the wavelength of the pure drug. (Fig.No:1)

Standard Curve of Drug substance in pH 6.8 phosphate Buffer

100 mg of drug substance was dissolved in 100 ml calibrated volumetric flask and completing to volume with pH 6.8 phosphate Buffer. From this 10ml pipette out in 100 ml calibrated volumetric flask and dilution was made with pH 6.8phosphate Buffer. From this solution 2 ml, 4ml, 6ml, 8ml…up to 10ml was pipetted out in different 10 ml volumetric

flask and this was finally diluted with pH 6.8phosphate Buffer to 10ml. The absorbance was noted λ_{max} at 264nm in UV spectrophotometer.

Standard curve of drug substance was determined by plotting absorbance V/s concentration at 264 nm, and it follows the Beer's law. The R^2 value found to be 0.997. . (Fig.No: 2)

Drug–Excipient Compatibility Study[6]

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added. Drug: Excipient compatibility studies carried out with the selected excipients.

Sample preparation: Binary mixtures of the drug and excipients are prepared by placing the accurately weighed amount of the drug and excipients in polybag and mixed till homogenous mixture is achieved. Then, these mixtures are filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals. These samples are charged at 40°C/75% RH conditions.

Sample analysis: All vials will be inspected for the appearance, color and odour and will be recorded. The samples removed from 40°C/75% RH will be analyzed as per the Schedule.

Selection of Excipient: Based on the results of the Drug-Excipient Compatibility studies, excipients used in the formulation were selected.

Preformulation Studies[7-8]

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

Hence, the following preformulation studies were performed on the obtained sample of drug.

I. Organoleptic characters
II. Physical properties such as (1,2,3,4,5 & 6 table. No: 5)

1. Bulk Density (Db)
2. Tapped Density (Dt)

3. Angle of Repose (θ)
4. Hausner ratio
5. Carr's index (or) % compressibility
6. Hausner ratio

The results are shown in Table. no: 5

Drug Layering: The drug layering was done in three Trails (T1, T2 & T3)

Table No 1: Formulation trials T1 – T3 quantity are in mg/tablet.

S.No	Ingredients	Percentage quantity		
		T1	T2	T3
1	MCC Pellets	8.16	7.91	7.91
2	Drug Substance	81.63	79.13	78.02
3	Micro crystalline cellulose 101	8.16	7.91	8.59
4	Hypromellose 6 cps	0.82	3.86	---
5	Povidone K-30	---	---	4.19
6	Purified Talc	0.82	0.79	0.86
7	Colloidal silicon dioxide	0.41	0.40	0.43
8	Isopropyl alcohol	Q.S	Q.S	Q.S
9	Purified water	Q.S	Q.S	Q.S
	TOTAL	**100.00**	**100.00**	**100.00**

MR Coating: The drug layered pellets of **Trial3** was coated with 4 trials (F1, F2, F3 & F4) with various concentration polymers.

Table No 2: Formulation trials F1 – F4

S.No	Ingredients	Percentage quantity			
		F1	F2	F3	F4
1	Drug layered pellets	86.57	86.93	85.91	84.63
2	Eudragit L30 D 55	3.53	2.94	---	---
3	Eudragit NE 30 D	5.30	4.66	9.48	---
4	Eudragit S 100	---	---	---	10.58
8	Triethyl citrate	0.88	0.86	0.95	1.06
9	Purified Talc	0.88	1.86	0.95	1.06
11	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S
12	Purified water	Q.S	Q.S	Q.S	Q.S
	LUBRICATION				
13	Colloidal silicon dioxide	0.71	0.69	0.68	0.67
14	Purified Talc	2.12	2.06	2.04	2.01
	TOTAL	**100.0**	**100.0**	**100.0**	**100.0**

Evaluation of Pellets[9-12]

Pellets were evaluated for physical characteristics like bulk density, tapped density, compressibility index, Hausner's ratio Table No. 6-11.

A. Particle Size Distribution

PSD was performed by sieve analysis method. The sieves are stacked one over the other in descending order of the mesh size. Weigh the individual empty sieve and place an accurately weighed quantity (about 10 capsules) in the sieve top. Cover the sieve at the top with the lid provided, and place a receiver at the bottom to collect the sample after sieving. Fix and fasten the sieves set up into the sieve shaker and set time at 10min, set the sieving speed rate at power 10 switch on the sieve shaker. After the specified time take the sieves and weigh individual sieve with sample and the sample weight was calculated table No: 6.

B. Weight variation

The uniformity of dosage units may be demonstrated by determining weight variation and/or content uniformity. The weight variation method is as follows. Ten capsules are individually weighed and the contents removed. The emptied capsules are individually weighed and the net weight of the contents calculated by subtraction. From the results of an assay performed as directed in the individual monograph, the content of active ingredient in each of the capsules is determined table No: 6.

C. Content uniformity

The amount of active ingredient determined by assay is within the range of 5% to 115% of the label claim for 9 of 10 dosage units assayed with no unit outside the range of 70% to 125% of label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes and all the capsules are within the range of BP table No: 6

D. Moisture permeation test

The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules.

The degree and rate of moisture penetration is determined by packing the dosage unit together with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating

desiccating absorption of moisture) and comparing the pre and post weight of the packaged unit table No: 6

E. Microbial examination

The test is carried out based on European Pharmacopoeia by using Pour plate method. Prepare medium for at least 2 Petri dishes for each level of dilution. Incubate the plates containing medium at 30 - 35ºC for 3 – 5 days and calculate the number of colonies. Take arithmetic mean for culture medium of the counts and calculate the number of CFU (colony forming unit) per gram or per Milliliter of product table No: 6

F. Dissolution test

For capsules place 900ml of dissolution medium in each vessel and allow the medium to equilibrate to a temperature of 37 ± 0.5ºC .place one capsules in each of the basket and operate the apparatus at 100 rpm for specific time. With draw 10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through 0.45microns membrane filter and discard first few ml of the filtrate. Dissolution study was carried out in pH 6.8 buffer for 1,2,4,6,8,10,12,14,16,18,20,22 & 24 hours by HPLC method table No: 7

Stability studies[13-14]

It is very essential that any product developed in the formulation department should be stable. The regulatory agencies in different countries try to ensure that the stability studies are carried out on the product. The formulation is subjected to accelerated stability conditions (40^0C±2^0C/75% RH ±5%). The effects of temperature and time on the physical and chemical characteristics of the tablet were evaluated for assessing the stability of the formulated tablets. The results indicate that there wasn't any significant change in hardness & % drug content. There is a significant weight gain and increased wetting time. Disintegration and in vitro drug release was found to be increased a little more at 40^0C temperature. No significant change was observed in drug content table. No:8

The international Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements.

Table. No: 3: ICH guidelines for stability study

Study	Storage condition	Time period
Long term	$25^0C\pm2^0C/60\%RH\pm5RH$ (or) $30^0C\pm2^0C/65\%RH\pm5\%RH$	12 month
Intermediate	$30^0C\pm2^0C/65\%RH\pm5\%RH$	6 month
Accelerated	$40^0C\pm2^0C/75\%RH\pm5\%RH$	6month

RESULT AND DISCUSSION

Determination of $\lambda_{max\ of}$ Drug substance by UV spectrum

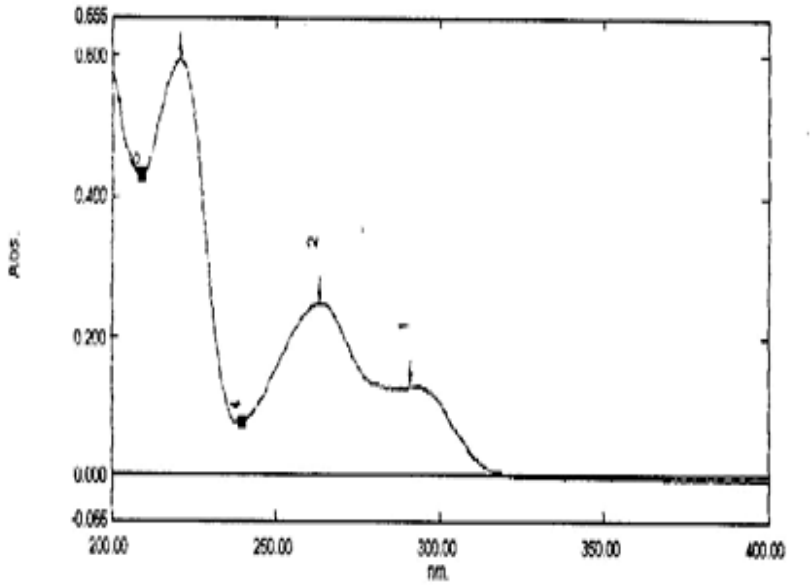

Figure No 14 : UV Spectrum of Drug substance

The λ_{max} of Drug substance is determined by UV spectrum, the graph indicates that the maximum absorbance is observed at 264nm and it is the λ_{max} of drug substance.

Table No 4: Standard curve values of Drug substance

S.No	Concentration µg/ml	Absorbance at 264nm
1	2	0.06
2	4	0.132
3	6	0.212
4	8	0.268
5	10	0.327

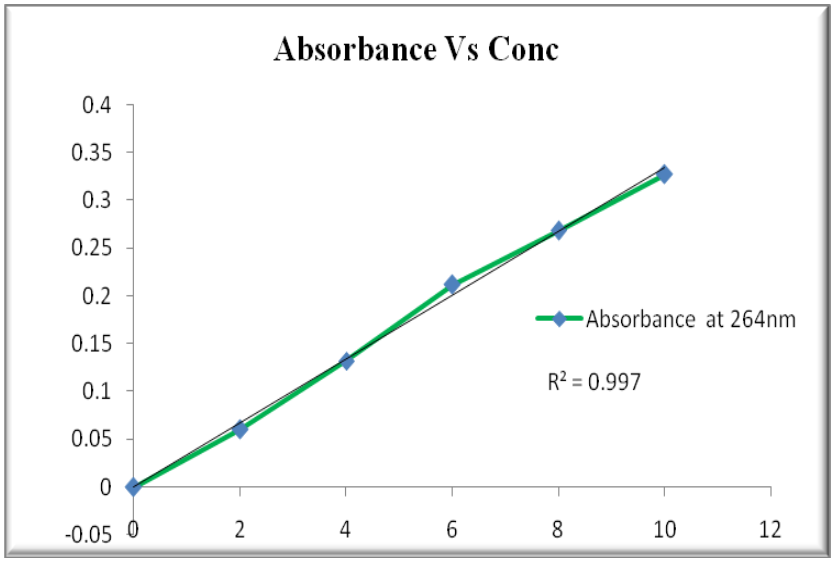

Figure No 2: Standard Curve of Drug substance

Drug: Excipient compatibility study: All the excipients which were taken for Drug: excipients compatibility study were compatible with the drug substance. Based on the study results and Innovator product composition the following inactive excipients were selected for formulation of the product.

Evaluation of Formulation Trials

Table No 5 : Flow Properties for Formulations F1 - F4

S.NO	PARAMETERS	F1	F2	F3	F4
1	Bulk density (g/ml)	0.588	0.597	0.596	0.596
2	Tapped density (g/ml)	0.635	0.635	0.643	0.643
3	Carr's Index (%)	7.353	5.970	7.353	7.353
4	Hausner's Ratio	1.079	1.063	1.079	1.079

Table No 6 : Particle size distribution, Moisture content values, Weight variation, Content uniformity and Microbial test for Formulations of F1 - F4

S.N*o	Parameter	Cumulative% Retained of RLD*	Cumulative % Retained of Formulations			
			F1	F2	F3	F4
1	Sieve No#14	2.09	-	-	-	-
2	Sieve No#16	22.18	5.86	0.02	0.02	1.22
3	Sieve No#18	49.37	61.44	7.2	72	91.38
4	Sieve No#20	68.2	84.12	93.41	91.61	99.29
5	Sieve No#25	-	93.45	96.8	95.2	100
6	Sieve No#30	89.96	96.38	99.94	98.34	100
7	Sieve No#40	99.58	100	100	100	100
8	Bowl	100	100	100	100	100
9	Moisture content		1.56%	1.67%	1.58%	1.54%

10	Weight variation		1.82%	1.65%	1.35%	1.16%
11	Content uniformity (200mg)		200.50	200.25	201.1	200.50
12	TAMC (Total Aerobic Mould count)	NMT (1000 CFU/gm)	110	105	120	90
13	TYMC (Total Yeast Mould count)	≤ 100	12	10	10	10
14	E.Coli	NIL	NIL	NIL	NIL	NIL
15	Salmonella	NIL	NIL	NIL	NIL	NIL

Comparative Dissolution Profile of Various Formulations Vs Innovator Product

Table No 7: Comparative dissolution profile

Time in Hours	Innovator product	F1	F2	F3	F4
0	0	0	0	0	0
1	21	65	62	72	25
2	41	70	68	78	41
3	55	76	72	81	50
4	64	84	78	86	61
6	76	89	81	89	68
8	83	92	91	92	72
10	87	98	96	96	76
12	91	98	96	101	86
14	93	101	101	101	91
16	94	101	101	102	92
20	94	101	101	102	94
24	94	101	101	102	96
Dissimilarity	**F1**	**34.43**	**28.34**	**39.11**	**9.84**
Similarity	**F2**	**31.09**	**33.94**	**27.68**	**57.13**

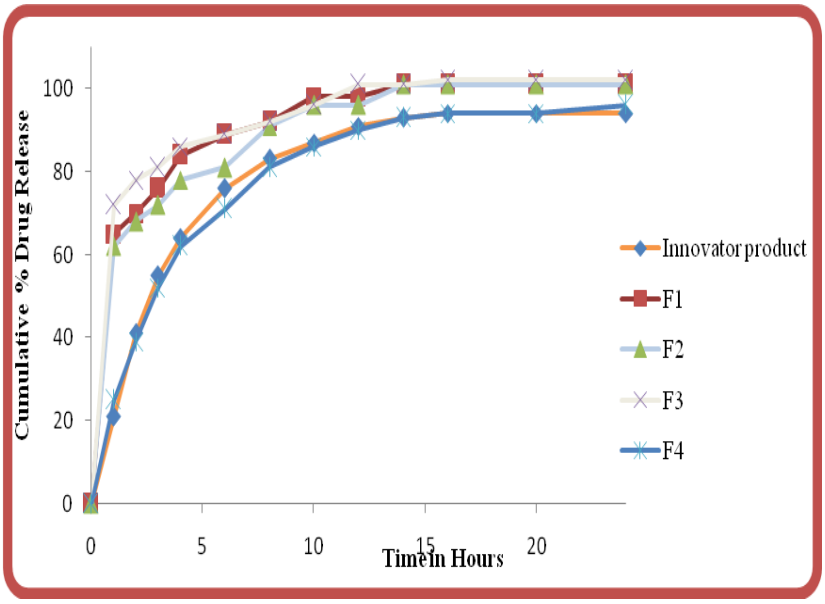

Figure No 3: Comparative dissolution profile Innovator product Vs F4

Stability study: The final batches were packed in PVC Alu-blisters & loaded in the stability chambers at accelerated (40°C/75% RH) up to 3 months and at stress condition.

Table No 8: Stability Studies

Test Name	TIME POINT	Initial				40°C/75% RH											
						1st month				2nd month				3rd month			
	Hours	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Max**	**Avg**	**RSD**
Dissolution by HPLC (%w/w)	1	21	27	**24**	8.4	27	33	**30**	7.9	24	29	**26**	6.7	21	25	**23**	5.8
	2	43	46	**45**	3.1	43	50	**47**	6.6	39	45	**41**	4.8	32	41	**36**	8.8
	4	61	64	**63**	1.7	57	64	**60**	5.0	50	58	**53**	5.7	48	56	**51**	5.3
	8	75	79	**77**	1.8	69	77	**73**	4.5	62	71	**66**	4.5	62	70	**65**	4.1
	12	83	87	**85**	1.8	77	85	**81**	3.9	70	78	**73**	3.7	70	78	**73**	3.8
	16	88	91	**89**	1.7	81	89	**85**	3.7	76	83	**79**	3.2	78	86	**82**	3.5
	20	89	94	**91**	2.1	84	90	**88**	2.6	83	87	**85**	1.8	84	92	**88**	3.1
	24	90	97	**93**	2.7	86	92	**90**	2.9	87	91	**88**	1.7	88	96	**91**	3.4
Related Substances by HPLC(%w/w) - (Proposed specification)																	
Known impurity I	NMT 0.20	0.02				0.02				0.01				0.02			
Known impurity II	NMT 0.20	0.01				0.01				0.01				0.01			
unknown impurity	NMT 0.20	0.09				0.09				0.08				0.08			
Total impurities	NMT 1.5	0.17				0.17				0.18				0.18			
Water by KF (% w/w)	NMT 7.0	1.50				1.54				1.96				1.52			
Assay by HPLC %w/w	NLT 90.0 and NMT 110.0	100.8				101.3				100.5				100.7%			

SUMMARY AND CONCLUSION

The Dissertation work entitled, "Formulation Development and evaluation of Modified Release Antispasmodic Pellets" was carried out for the optimization of the formulation to meet the quality standards with regard to API, excipients, manufacturing process and finished product.

Drug-excipient compatibility studies were carried out for 3 months and the results showed that there was no physical and chemical change in the API. This indicated that, the drug was compatible with the formulation aspects. Hence MCC 101, Povidone K30, Purified Talc, Colloidal silicon dioxide, Eudragit S 100, L100 D55, NE 30 D were selected as excipients for the lab scale development.

In-vitro parameter for the prepared pellets carried out such as particle size distribution by sieve analysis, content uniformity, and weight variation test as per pharmacopoeial specification. Moisture permeation test as per USP pharmacopoeial and microbial examination carried out pour plate method. The result indicated the particles distribution evenly for all the formulations. Content uniformity, weight variation test within the pharmacopoeial specification moisture content was within the limits 1.54 to 1.67%. The microbial examination reviewed the formulations aspects from E.Coli and Salmonella type organism and TAMC & TYMC are within limit less then 1000 CFU/Grams and less than 100 CFU/Grams.

The Prototype formulations were developed (F1 to F4), and the F4 formulation was optimized, the dissolution profile of the optimized batch F4 was similar to the Innovator product.

The F4 formulation was taken for stability studies as per the ICH Guidelines, F-4 batch were packed in PVC Blisters charged at 40ºC ± 2 / 75 ± 5 %RH for the period of three months. The results were found satisfactory and it complies with the specifications.

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