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FORMULATION AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF DESVENLAFAXINE SUCCINATE

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ABSTRACT

The objective of this investigation was to prepare extended release of Desvenlafaxine succinate and to carryout in-vitro dissolution studies to demonstrate sustained action of designed dosage form. The design of dosage form was performed by choosing hydrophilic hydroxypropyl methyl cellulose (HPMC K4M), Carbopol (Acrypol 974), Microcrystalline cellulose (MCC) polymers as matrix builders and Polyvinyl pyrolidone (Kollidon K30) as granulating polymer. Granules were prepared by mixing thoroughly HPMC K4M, Carbopol (Acrypol 974P) and Microcrystalline cellulose with the drug and then by kneading with granulating solution of Polyvinyl pyrrolidone with Isopropyl alcohol & air dried. Optimized formulation of 100 mg Desvenlafaxine was formed by using 33.78 % HPMC K4M, 3% Microcrystalline cellulose, 15% of Carbopol (Acrypol 974) and 5% ratio of Kollidon K30 as binder .The network formed by HPMC, MCC and Carbopol (Acrypol 974) in the granules when compacted by compressing it into a Tablet exhibited 24 hours extended drug release in vitro.

KEYWORDS: Desvenlafaxine Succinate SR Matrix Tablet, DVS, HPMC K4M, Carbopol, Extended release.

INTRODUCTION

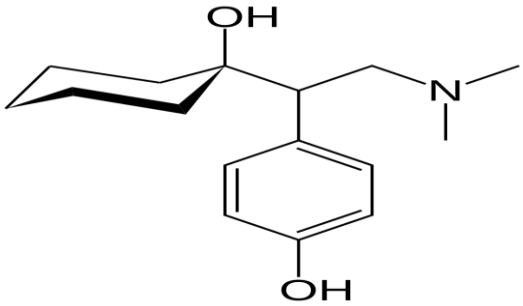

Fig.1. Desvenlafaxine chemical structure.

Desvenlafaxine 4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl]phenol Fast release drug generally causes toxicity if not formulated as extended release dosage form. Developing oral-sustained release formulations for highly water soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. In the present study, a sustained release dosage form of Desvenlafaxine (DVS) has been developed that enables less frequent administering of drug [1-3]. Though among various formulation approaches, in controlling the release of water soluble drugs, the development of sustained release tablets has a advantage of lessening the chance of dose dumping and patient compliance for taking tablets orally is much lesser than for parentral and other routes of administrations. Tablets are prepared by compressing granules of Desvenlafaxine which were prepared by appropriate combination of HPMC, Carbopol, Microcystalline cellulose and Kollidon K30 was chosen to form the granules of extend duration of drug release. Desvenlafaxine (o-desmethyl venlafaxine) is an active metabolite of Venlafaxine. Inhibits the neuronal reuptake of norepinephrine, serotonin and to a lesser extent dopamine but have no monoamine oxidase inhibitory activity and low affinity for brain muscaranic, cholinergic, histaminergic or alpha adrenergic receptors [4]. The solubility of Desvenlafaxine is highly dependent on pH; the significant pH dependency of solubility percents challenges the development of controlled release formulations of Desvenlafaxine for obtaining consistent dissolution profiles [5,6]. The objectives of this work were: 1) to evaluate the physical characters of prepared tablets 2) to elucidate the effect of polymer composition and the release kinetics.

MATERIALS AND METHODS

Formulation Different batches:

Table 1

Sr No.	Ingredients	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tab	F6 mg/tab	F7 mg/tab	F8 mg/tab
	DRY MIX								
1	DVS	152.00	152.00	152.00	152.00	152.00	152.00	152.00	152.00
2	MCCP	50.00	50.00	30.00	10.00	10.00	10.00	10.00	20.00
3	HPMC K4M	90.00	100.00	110.00	125.00	140.000	160.00	150.00	150.00
4	Acrypol 974P	50.00	40.00	50.00	55.00	40.000	20.00	30.00	20.00
	BINDER								
5	PVP K-30	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
6	IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	LUBRICATION								
7	Talc	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
8	Mg. Stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
	TOTAL	370.000	370.000	370.000	370.000	370.000	370.000	370.000	370.000

Materials Used

Table 2

Sr. No.	Ingredients	Manufacturer/Supplier
1	DVS	Ami lifesciences Pvt Ltd
2	MCCP	(Avicel) FMC Biopolymers India Ltd.
3	HPMC K4M	(Novocoat K4M), Novo Exicipients Pvt Ltd.
4	Carbopol 974	Acrypol 974P Corel Pharmachem.
5	PVP K-30	Kollidon K-30 BASF India Ltd

Method of Granulation

Formulations (F1, F2, F3, F4, F5, F6, F7 and F8) were prepared according to the Table 1. Desvenlafaxine succinate monohydrate, Methocel K4M, Carbopol, Microcystalline cellulose were mixed uniformly in polybag and granulated with non aqueous solution of Kollidon K30 in Isopropyl alcohol followed by tray drying at 60˚C, the dried granules passed through #30 mesh and finally blend with purified talc and magnesium stearate in appropriate quantities and compressed with 10.2 mm round standard concave punches.

Characterisation of Granules

Bulk density

Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as weight of granules divided by bulk volume (Appearant volume without tapping)

$$\text{Bulk density} = \frac{\text{Weight}}{\text{Bulk volume}}$$

Tapped density

Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as weight of granules divided by tapped volume (Appearant volume after tapping : 100 tapings)

$$\text{Tapped density} = \frac{\text{Weight}}{\text{Tapped volume}}$$

Housner's Ratio

Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as tap density divided by bulk density.

$$\text{Housner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's Index/Compressibility Index

Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as tap density divided by bulk density.

$$\text{Compressibility Index} = \frac{\text{Tapped density - Bulk densiry}}{\text{Tapped density}} \times 100$$

Angle of Repose

$$\text{Angle of Repose} = \text{Tan}^{-1}\frac{\text{Height of heap}}{\text{Radius}}$$

Drug Content

Drug Content of tablet is determined HPLC method (Waters Acuity H class) using Inertsil ODS 3V 150 mm x 4.6 mm, 5µ coloumn using wavelength 225 nm (mentioned bellow.)

COMPRESSION

Characterisation of Compressed Tablets

Physical Characterization of Tablets

Formulated tablets were subjected to different physical characterization studies.

Uniformity of weight

The weight variation was determined on 20 tablets using an electronic balance (Electolab, India).

Diameter

Ten tablets were taken and their thickness was recorded by a digital Vernier calliper.

Thickness

Ten tablets were taken and their thickness was recorded by a digital Vernier calliper.

Hardness

Tablet hardness was determined for a minimum of six tablets using a vertically mounted Pfizer type hardness tester (Veego, India).

Friability

Friability was calculated as the percentage weight loss of 20 tablets using a Roche type friabilator (Electrolab India) for 4 min at 25 rpm.

Chemical Characterization of Tablets

Drug Content of Tablets or Assay

About 20 tablets were finely powdered, powdered sample equivalent to 50 mg of Desvenlafaxine was accurately weighed and transferred to a 100 mL volumetric flask, 50 ml distilled water was added, sonicated for 30 minutes. Final volume was made with distilled water. Further, diluted 5 ml of above solution to 25 ml with mobile phase. Standard solutions were prepared in same manner. The drug content of the formulated tablets was estimated using HPLC system (Waters Acuity H Class), using Inertsil ODS 3V 150 mm x 4.6 mm x 5µm chromatographic column. and detection wavelength 225 nm.

Content uniformity

10 good tablets were triturated individually and sample transferred to 10 different 200 mL volumetric flasks as 1 tablet to each, initially 100 mL of distilled water was added to the volumetric flask and allowed to sonicate for 30 min to ensure complete solubility of the drug. The supernatant liquid was filtered through a 0.2 µm membrane filter. Further, diluted 5 ml of above solution to 25 ml with mobile phase. Standard solutions were prepared in same manner. The drug content of the formulated tablets was estimated using HPLC system (Waters Acuity H class) at wavelength of 225 nm. It was ascertained that none of the ingredients used in the matrix formulations interfered with the assay of drug (DVS).

In-vitro Dissolution Study

The in vitro dissolution studies were performed by USP type I (Basket) dissolution apparatus at 100 rpm. The dissolution medium consisted of 0.9% Normal saline and the medium was maintained at 37˚C ± 0.5˚C. An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of fresh medium at same temperature. The withdrawal sample was filtered through 0.22 µm filter paper. Next, its drug content was determined by HPLC (Waters Acuity H class). The release studies were conducted in triplicate. Mean percent cumulative drug release was plotted against time of release.

RESULTS AND DISCUSSION

In the present study, granules were prepared initially using various compositions (Table 1) of matrix forming polymers (HPMC, Carbopol and Microcrystalline cellulose) with the help of granulating agent i.e. Polyvinyl pyrrolidone was used as Binder. Tablets were tested to check dissolution period up to 100% cumulative drug release. Tablets with code no F4 exhibited extended drug release up to 24 hr (Table 6). Rate of drug release was significant when combination of HPMC and Carbopol as a Matrix builder. Suitable combination of HPMC K4M with Carbopol and Microcrystalline gave the effect of hydrophilic polymer leading to controlled and extended release of drug (Table 6, F4). It seems the pores formed by Microcrystalline cellulose (were filled by hydrophilic polymer making a well balanced matrix. Enhancement of permeability by using MCC and retardation of permeation by matrix formed by HPMC K4M and Carbopol (Acypol 974P) caused controlled and extended release of drug. Physical characteristics of these granules were recorded and tabulated in Table 3. Physical characteristics of these tablets were recorded and tabulated in Table 4. This indicated combined effect of diffusion and erosion mechanism on the release of drug. (Table 6 F4).

Characterisation of Granules

Table 3

Formulation Code	Bulk Density	Tapped Density	Hausner's ratio	Carr's Index	Angle of repose (θ)	Drug Content
F1	0.434±0.04	0.584±0.04	25.69±0.04	0.74	29.24°	99.27±0.04
F2	0.424±0.03	0.574±0.03	26.13±0.03	0.73	29.34°	99.87±0.04
F3	0.431±0.03	0.581±0.03	25.82±0.03	0.76	30.51°	99.57±0.04
F4	0.436±0.02	0.576±0.02	24.31±0.02	0.75	29.17°	99.13±0.04
F5	0.429±0.04	0.579±0.04	25.91±0.04	0.74	30.19°	98.89±0.04
F6	0.433±0.04	0.583±0.04	25.73±0.04	0.74	29.24°	99.23±0.04
F7	0.432±0.04	0.582±0.04	25.77±0.04	0.74	29.14°	99.88±0.04
F8	0.427±0.04	0.577±0.04	25.99±0.04	0.74	29.11°	98.26±0.04

Characterisation of Compressed Tablets

Physical Characterization of Tablets

Table 4

Formulation Code	Uniformity of weight	Diameter	Thickness	Hardness	Friability
F1	370±0.92	10.2±0.04	4.3±0.06	6.8±0.2	0.12 %
F2	370±0.84	10.2±0.06	4.3±0.07	8.2±0.4	0.13 %
F3	370±1.04	10.2±0.07	4.3±0.08	6.2±0.6	Nil
F4	370±1.06	10.2±0.06	4.3±0.07	6.8±0.6	0.17 %
F5	370±1.12	10.2±0.05	4.3±0.08	7.8±0.8	0.16 %
F6	370±1.21	10.2±0.04	4.3±0.08	7.6±0.8	0.18 %
F7	370±0.86	10.2±0.03	4.3±0.07	6.8±0.6	0.19 %
F8	370±0.99	10.2±0.03	4.3±0.06	7.4±0.8	0.15 %

Chemical Characterization of Tablets

Table 5

Formulation Code	Drug Content (ASSAY)	Content Uniformity		
		Min.	Max.	Avg.
F1	99.27±0.74	98.57	101.02	99.55
F2	99.87±0.78	98.32	100.18	99.47
F3	99.57±0.84	98.25	100.13	99.32
F4	99.13±0.82	98.17	100.17	99.58
F5	98.89±0.91	98.16	100.24	99.23
F6	99.23±0.87	98.27	100.31	99.43
F7	99.88±0.78	98.32	100.58	99.31
F8	98.26±0.88	98.15	100.20	99.16

In-vitro Dissolution Study

Table 6

Time In Hours	F1	F2	F3	F4	F5	F6	F7	F8
	%	%	%	%	%	%	%	%
1	15±0.22	21±0.25	20±0.36	14±0.11	10±0.22	9±0.74	10±0.51	10±0.24
2	26±0.34	34±0.36	38±0.22	23±0.21	15±0.24	13±0.21	14±0.22	15±0.21
4	36±0.21	44±0.34	45±0.23	38±0.34	21±0.17	19±0.31	18±0.32	21±0.31
8	59±0.33	65±0.43	69±0.31	58±0.51	26±0.24	26±0.35	24±0.27	29±0.43
12	80±0.51	89±0.32	91±0.26	69±0.43	31±0.56	30±0.41	32±0.38	36±0.37
16	93±0.31	96±0.54	98±0.31	73±0.42	41±0.37	42±0.51	45±0.41	49±0.39
20	--	--	--	89±0.39	53±0.31	53±0.34	54±0.37	66±0.21
24	--	--	--	94±0.25	62±0.47	63±0.36	62±0.29	75±0.41

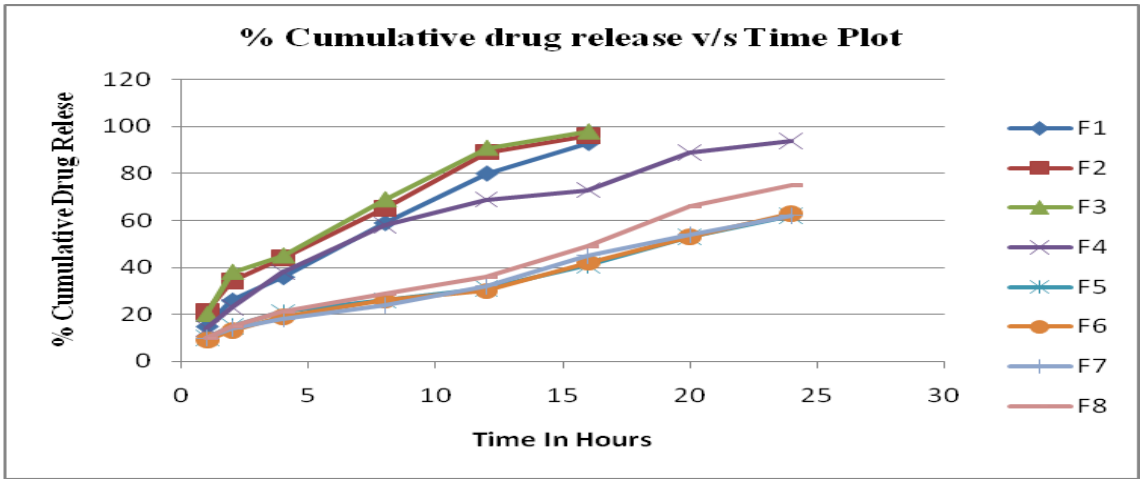

Fig. 2. % Cumulative Drug Release.

CONCLUSION

A new sustained release tablet formulation F4 of Desvenlafaxine succinate has been developed and evaluated for its in vitro drug release. Extended release tablets were found to be an effective technique for a highly water-soluble drug Desvenlafaxine succinate monohydrate. Bioavailability studies should be done to assess the usefulness of this formulation in comparison with existing market products (PRISTQ) of extended release Desvenlafaxine succinate.

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