



FORMULATION AND EVALUATION OF DESVENLAFAXINE SUCCINATE MICROCAPSULES

**N. Santhi Priya^{1*}, P. Siva Krishna², P. Srinivasa Babu¹, D. Amani¹, K. Sree Pujitha¹, K. Tejasri¹,
Ch. Vinay Babu¹ and T. Seshu Reddy¹**

¹Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.

²Department of Pharmaceutical Analysis, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.



*Corresponding Author: N. Santhi Priya

Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.

Article Received on 22/10/2023

Article Revised on 12/11/2023

Article Accepted on 01/12/2023

ABSTRACT

Desvenlafaxine succinate (DSV) is a water soluble anti-depressant drug, which is rapidly absorbed after oral administration exaggerating its side effects. The current work is aimed to prepare controllable release DSV matrix to reduce DSV side effects related to its initial burst. Sustained release microcapsules of Desvenlafaxine Succinate were prepared by ionotropic gelation method. Microcapsule system is one of the novel drug delivery system found applications in many areas of science and technology. This microcapsules to overcome the drug-related adverse effects like gastric irritation, improve its bioavailability. Total ten formulation batches (F1-F10) were formulated using sodium alginate alone and combination with sod.CMC, Carbopol 934, Guargum and HPMC K100 polymers as drug release modifiers in various properties and investigated for physicochemical properties and drug release potential. All investigated properties showed satisfactory results. Increase in the concentration of polymers dispersions increased size distribution, flow properties and mean diameter of the microcapsules. The drug entrapment efficiency obtained in the range 70% to 94.03%. In-vitro study drug release in batch F9 and F10 showed faster release than F5, F6, F7 and F8. The mechanism of drug release from Microcapsules was found to be following Case-II transport. From the study it was concluded that controlled release Desvenlafaxine Succinate Microcapsules can be developed successfully by using ionotropic gelation technique.

KEYWORDS: Desvenlafaxine Succinate, Microcapsules, Ionotropic gelation technique, Sustained release, Sodium alginate.

INTRODUCTION

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic cholinergic, H1-histaminergic, or α 1-adrenergic receptors in vitro. PRISTIQ also lacked monoamine oxidase (MAO) inhibitory activity.

Desvenlafaxine succinate is an antidepressant of the serotonin-nor epinephrine reuptake inhibitor class. Desvenlafaxine is a synthetic form of the isolated major active metabolite of venlafaxine, and is categorized as a serotonin or epinephrine reuptake inhibitor (SNRI). It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse.

Non-clinical studies have shown that desvenlafaxine succinate is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI). The clinical

efficacy of desvenlafaxine succinate is thought to be related to the potentiation of these neurotransmitters in the central nervous system. moclobemide, phenelzine, procarbazine, rasagiline, selegiline, tranylcypromine) during treatment with his medication. Most MAO inhibitors should also not be taken for two weeks before treatment with this medication.

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarini cholinergic, H1-histaminergic, or α 1-adrenergic receptors in vitro. PRISTIQ also lacked monoamine oxidase (MAO) inhibitory activity.

The objectives of sustained/controlled release drug delivery include two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ

or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue.

MATERIALS AND METHODS

Materials

Desvenlafaxine Succinate was a gift sample from Optimus pharma pvt. Limited (Hyderabad, India). Sodium alginate, was kindly provided by Merck labs (Mumbai, India), Hydroxy Propyl Methyl Cellulose(HPMC), Mylan Lab(Hyderabad, India), Sodium Carboxy Methyl Cellulose(sodium CMC),Guar gum, Carbopol 934, was a gift sample from Polychem (Mumbai, India).

METHODS

Preparation of sustained release microcapsule

Microcapsules were prepared by ionotropic-gelation method. Sodium alginate and other polymers were dissolved in purified water to form a homogenous polymer solution. The active substance, Desvenlafaxine is added to polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion is then added manually drop wise into CaCl₂(10% w/v) solution through a syringe with needle. The added droplets are mixed into the CaCl₂ solution for 15 min to complete the curing reaction s and to produce spherical rigid microcapsule. The microcapsules are collected by decantation, and the product thus separated, washed repeatedly with a water and dried at 45°C for 12 hours.

Formulation design of microcapsules

Formulation	DVS (mg)	Sodium Alginate(mg)	Calcium Chloride (%)	Carbopol 934(mg)	Guargum (mg)	HPMC K100 (mg)	Sodium CMC(mg)	Water (ml)
F1	-	250	10	-	-	-	250	q.s
F2	-	250	10	250	-	-	-	q.s
F3	-	250	10	-	-	250	-	q.s
F4	-	250	10	-	250	-	-	q.s
F5	250	250	10	-	-	-	250	q.s
F6	250	250	10	-	-	-	500	q.s
F7	250	250	10	-	250	-	-	q.s
F8	250	250	10	-	500	-	-	q.s
F9	250	250	10	250	-	-	-	q.s
F10	250	250	10	500	-	-	-	q.s

Evaluation parameters for microcapsules

1. Measurement of Micromeritic Properties of Microcapsules

Granulometric study

The particle size has very significant effect on the release profile of microcapsules. Granulometric study was conducted to determine the particle size distribution pattern. For this study sieve analysis was carried out on mechanical sieve shaker, using different size meshes (#12, #16, #22, #30). The size distribution of Microcapsules is reported in table no.

Flow property

The flow properties were investigated by measuring the angle of repose of microcapsules using fixed-base cone method. The microcapsules were carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The height (h) and radius(r) of the cone funnel was measured. The angle of repose (θ) was given by the following formula,

$$\text{Angle of repose } (\theta) = \tan^{-1} h/r$$

Bulk density

The bulk density was measured in a 10ml graduated measuring cylinder to measure packability of the microcapsules.

Bulk density was determined by the following formula,

$$\text{Bulk density} = \text{Sample weight} / \text{Sample volume}$$

Tapped Density

The tapped density was determined by tapping method, in which the cylinder containing known amount (M) of microcapsules was subjected to a fixed number of taps (approximately 100) until the bed of microcapsules had reached the minimum. The final volume after tapping 'Vo' was recorded and the tapped density was calculated by the following equation,

$$\text{Tapped density (Pp)} = M/V_o$$

Particle size analysis

The particle size determination of microcapsules was carried out using optical microscopy along with a stage micrometer having an accuracy of 0.01 mm. A suspension of microcapsules in liquid paraffin was prepared in a beaker and then one drop of this was dropped on a clean glass slide and covered with a cover slip. The average sizes of 100 microcapsules were determined for each formulation using the calibration factor.

The average particle size of the microcapsules was determined by using Edmondson's equation

$$D_{\text{mean}} = \Sigma nd / \Sigma n$$

Where, n = Number of microcapsules checked; d = Mean size range

Surface study

The surface morphological details of the microcapsules were determined by using a Scanning electron microscope (SEM).

All samples were randomly examined for their surface properties by using scanning electron microscopy. The microcapsules were placed on one side of an adhesive stub and the stub was then coated with conductive gold-palladium with sputter coater attached to the instrument.

Swelling properties: Swellability of the microcapsules was determined by allowing the microcapsules to swell in the phosphate buffer pH 6.8. 100 mg of accurately weighed microcapsules were immersed in little excess of phosphate buffer pH 6.8 for 24 hours and washed thoroughly with deionised water and blotted with filter paper to remove excess surface liquid. The % swelling was arrived at using the following formula.

$$\text{Degree of Swelling} = \frac{W_s - W_o}{W_o}$$

Where, W_o is the weight of microcapsules before swelling and W_s is the weight of microcapsules after swelling.

Drug Entrapment Efficiency

DVS microcapsules were dissolved in 10 mL of phosphate buffer (pH 6.8) under occasional shaking for 2-3 hrs. The resultant solution was filtered through

0.46 μ m filter paper and after suitable dilution, the amount of O-DVS present in the formulation was determined using a UV Visible spectrophotometer at 225nm.

Drug incorporation efficiency can be given by the following formula,

$$\text{Drug incorporation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

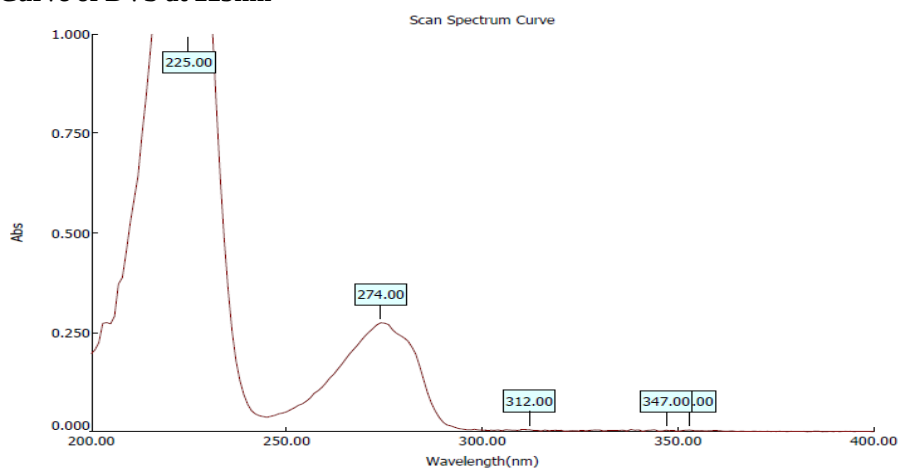
The results of DEE (Drug Entrapment Efficiency) are reported in table no.

In vitro drug dissolution studies

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 $37^\circ\text{C} \pm 0.5^\circ\text{C}$. 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 μ m 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

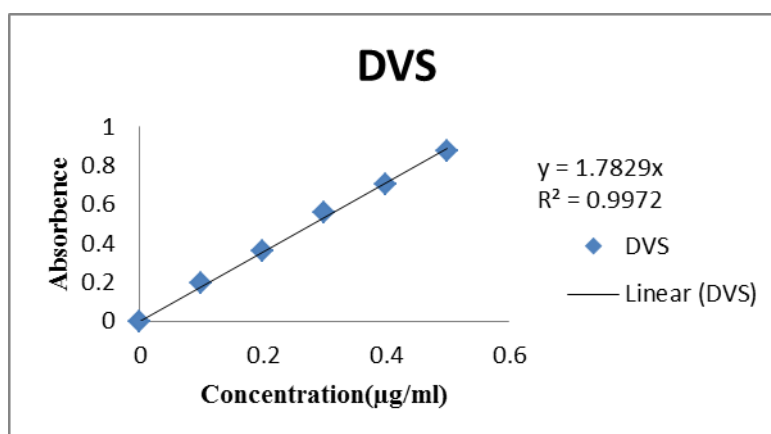
Scan Spectrum Curve of DVS at 225nm



scanned spectrum of DVS

Calibration curve for Desvenlafaxine Succinate

Sr.No.	Concentration ($\mu\text{g/ml}$)	Absorbance at 225nm
0	0	0
1	0.2	0.198
2	0.4	0.364
3	0.6	0.562
4	0.8	0.701
5	1	0.878



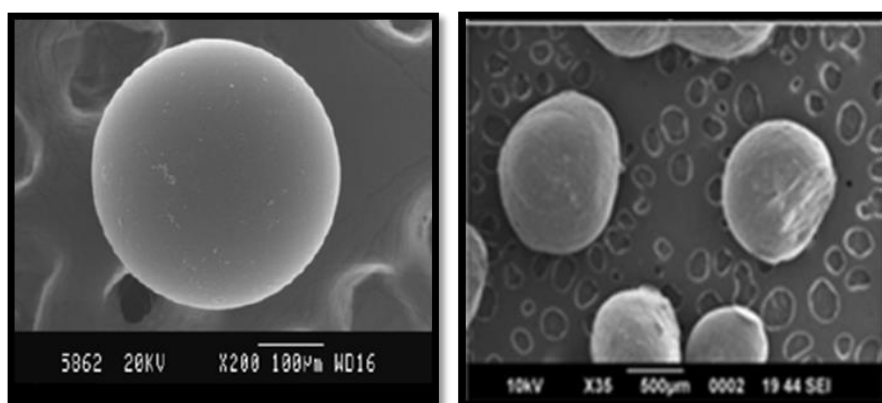
Standard Calibration Curve of DVS

Table No.: Percentage of weight remained on various sieve sizes.

Formulations	#12(1.68mm) 1190-1680µm	#16(1.19mm) 840-1190µm	#20(0.84mm) 590-840µm	#30(0.59mm) 297-590µm
F1	3.42	8.54	80.54	3.62
F2	4.17	20.85	66.40	4.54
F3	5.79	26.15	65.64	4.14
F4	6.98	35.37	55.84	2.58
F5	5.68	39.94	53.42	1.54
F6	8.67	45.65	45.48	1.05
F7	7.32	49.32	48.85	1.87
F8	6.48	37.32	43.25	2.58
F9	4.55	42.48	54.22	2.01
F10	9.58	35.55	47.55	4.18

Table No. Micromeritic Properties of Microcapsules.

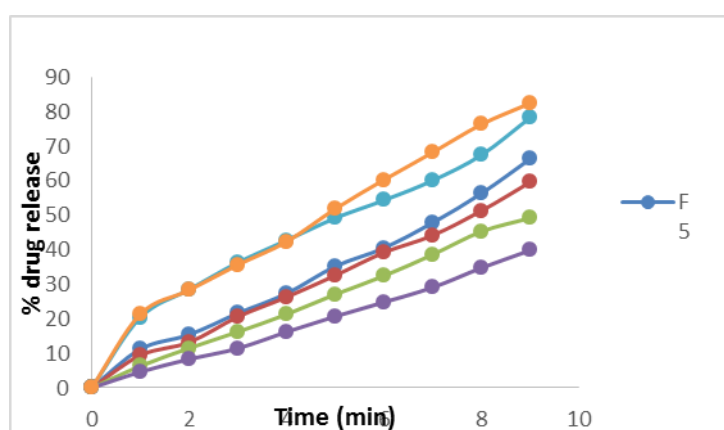
Formulations	Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Mean Diameter (µm)
F1	31°.23'	0.437	0.652	729.12
F2	30°.13'	0.624	0.747	825.41
F3	27°.43'	0.742	0.845	745.15
F4	29°.36'	0.754	0.800	865.14
F5	21°.43'	0.748	0.815	745.47
F6	26°.12'	0.654	0.822	882.31
F7	25°.34'	0.547	0.821	741.25
F8	28°.33'	0.478	0.844	665.28
F9	24°.45'	0.784	0.754	621.54
F10	29°.37'	0.785	0.878	743.85



Scanning Electron Microscopy of Desvenlafaxine Succinate microcapsule

Table No. *In vitro* drug release studies of DVS microcapsules.

Sl.no	Time (h)	% Drug release					
		F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0
2	1	11.23	9.45	6.34	4.65	20.42	21.34
3	2	15.42	13.23	11.52	8.32	28.49	28.32
4	3	21.62	20.60	16.24	11.46	36.32	35.67
5	4	27.35	26.32	21.32	16.24	42.76	42.36
6	5	35.21	32.59	27.11	20.72	49.20	51.89
7	6	40.56	39.24	32.46	24.83	54.37	60.29
8	7	47.87	44.21	38.64	29.12	60.11	68.24
9	8	56.35	51.32	45.32	34.78	67.49	76.36
10	9	66.39	59.64	49.24	39.88	78.32	82.47



In-vitro drug release studies of DVS Microcapsules (F5-F10)

Kinetics results of Formulation F5 - F10: Model fitting data of the release profile for DVS using four different Models (r-values).

Formulation	Regression values (r ²)			
	Zero order	First order	Higuchi	Peppas
F5	0.991	0.563	0.888	0.888
F6	0.996	0.539	0.888	0.888
F7	0.998	0.642	0.888	0.888
F8	0.995	0.796	0.888	0.888
F9	0.913	0.167	0.888	0.888
F10	0.950	0.217	0.888	0.888

The values of coefficient of correlation were calculated and were found to be more linear for zero order release as compared to first order. It was concluded that release of drug from the optimized formulations F5 - F10 followed zero order kinetics.

CONCLUSION

A new sustained release microcapsule formulation F8 Desvenlafaxine succinate has been developed and evaluated for its *in vitro* drug release. Sustained release microcapsules were found to be an effective technique for a highly water-soluble Desvenlafaxine succinate.

The mechanism of drug release from DVS microcapsules exhibited zero order kinetics and the release of the drug from the microcapsules was found to be following case II transport.

Our study has suggested that microencapsulation by ionotropic gelation technique is inexpensive compared with other techniques and also advantages to prevent the drug related adverse effects of conventional dosage forms and maintain the sustain drug release over an extended period of time.

ACKNOWLEDGEMENT

The author wish to thank to Optimus pharma pvt. limited, Hyderabad to providing gift sample of Desvenlafaxine succinate also thankful to Vignan pharmacy college, Vadlamudi to provide necessary facilities to carryout research work.

REFERENCES

1. Bhusnure Omprakash G, Kawale Prasad, Gholve Sachine B, and Giram Padmaja S., Formulation and In-Vitro Evaluation of Sustained Release Matrix

- Tablet of Desvenlafaxine Succinate by Interpolyelectrolyte Complex (IPEC) Formation Technique, Research Journal of Pharmaceutical, Biological and Chemical Sciences, ISSN: 0975-8585.
2. Gajanan Jalindar Chavan, Sachin Dhondiram Patil¹, Atul Pandurang Kumbhar¹, Nikhil Prabhakar Patil¹, Swapnali Roshan Charya¹, Rohit Bhaskar Kadam¹, Formulation and Evaluation of Extended release Matrix Tablets of Desvenlafaxine Succinate, World Journal of Pharmaceutical Research, 3(7): 377-385. ISSN 2277 – 7105.
 3. Elgindy, Nazik; Elnoby, Ayman; M. El-Gowelli, Hanan; Samy, Wael., A Multi-layered Particulate System for Desvenlafaxine Succinate Oral Customized Release.
 4. Mansing G. Patil, Saurabh Kumar Banerjee, C.G. Bonde and Gurmeet S. Chhabra., UV Spectrometric Method Development for The Determination of Desvenlafaxine Succinate Tablet Formulation, Bulletin of Pharmaceutical Research, 2011; 1(1): 40-3.
 5. Shashidhar Reddy Dodda¹, Prakash Rao Boggrapu., Development and in Vitro-in Vivo Evaluation of Controlled Release Matrix Tablets of Desvenlafaxine, Pharmacology & Pharmacy, 2012; 3: 15-19.
 6. Aravind Vitthalrao Bendre, Amol Ambadas Tagalpallewar, Akash. Panjabrao Patil, Priyanka Ganapati Khapekar., Formulation, Optimization and Evaluation of Desvenlafaxine Extended Release Tablet, Journal of Pharmacy Research, 2012; 5(4): 1825-1826.
 7. Ansel C.H., Poppovich N.G., Pharmaceutical dosage forms and drug delivery systems, 6th Ed., B.I. Waverly Pvt.Ltd., New Delhi, 1995; 213.
 8. Gupta P.K., Robinson J.R., Chapter 6. Oral controlled release system, In; Kydonieus, A., (Ed), Treatise on controlled drug delivery, Marcel Dekker Inc., New York, 1992; 256.
 9. Meshali MM and Gabr KE. Effect of Interpolyelectrolyte complex formation of chitosan with pectin or acacia on the release behaviour of chlorpromazine HCl. International Journal of Pharmaceutics, 1993; 89(3): 177-181.
 10. Charged starch nanoparticles prepared by polyelectrolyte complex formation, Chemija, 2012; 23(4): 328–335.
 11. Jeong Hwan Kim, Thiruganesh Ramasamy, Tuan Hiep Tran, Ju Yeon Choi, Hyuk Jun Cho, Chul.
 12. Maria Teresa, Sidney H Kennedy. Desvenlafaxine in the treatment of major depressive disorder Neuropsychiatr Dis Treat, 2009; 5: 127–136.