Formulation Development and Evaluation of Desvenlafaxine Microspheres

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ABSTRACT:

The aim of the present study was to formulate and evaluate sustained-release microspheres of Desvenlafaxine for the management and treatment of depression. Sustained release microspheres of Desvenlafaxine were prepared by solvent evaporation technique by using natural polymers such as chitosan and sodium alginates. Further, the sustained-release microspheres were evaluated for flow characteristics, entrapment efficiency,percentage yield, particle size analysis, zeta potential analysis, scanning electron microscopy, *in-vitro* drug release, and kinetics of drug release.*In-vitro*, drug release studies were carried out in a phosphate buffer solution (pH7.4).Theprepared microspheres show good encapsulation efficiency and the particle size of the microspheres ranges from 34.6µm to 60.6 µm. The IR spectrum revealed that there was no interaction between the drug and the polymer.Micromeritics studies showed good flow properties and maximum entrapment efficiency was found to be 82.87% from the chitosan F4 DSV microsphere. Among the microsphere batches, F4 of chitosan was observed as an optimized batch.The in-vitro drug release of the F4 formulation prepared by using chitosan was found to be 94.60%, which sustained the action of the drug for 24 hours and its stability study indicates that these microspheres were stable at selected temperature and humidity while storage for 60 days without any significant changes in drug release characteristics. The sustained-release microspheres were formulated successfully and results clearly stated that Desvenlafaxine microspheres were safe and effective drug delivery over an extended period, which can increase bioavailability,patient compliance, and decrease dosing frequency.

KEYWORDS: Desvenlafaxine, Chitosan, Sodium alginate, Solvent evaporation, Sustained release microspheres.

INTRODUCTION:

The goal of any drug delivery system is to provide and maintain the therapeutic concentration of the drug at the target biological site. The oral route is the most common route for drug administration. It is the most preferred route due to the ease of administration. The term "novel drug delivery system" refers to a modified drug delivery system that increases drug potency, controls drug release,and sustained the therapeutic effect of the drug,which

provides greater safety, and delivers a drug to the target site, such as a particular tissue or organ. Conventional drug delivery systems have some drawbacks, including the higher dose of a drug required, lower efficacy, toxicity, and undesirable side effects. Microspheres as new drug delivery systems were developed to overcome problems associated with conventional drug deliverysystems[1].

Depression is a common mental disorder that presents with a depressedmood, loss of interest or pleasure,feelings of guilt or low self-worth, disturbed sleep, and loss of appetite. Depression is a mood disorder that causes a persistent feeling of sadness also called a major depressive disorder or clinical depression, it affects how you feel, think,behave and can leads to a variety of emotional and physical problems. According to a WHO current report, depression is one of the leading causes of disability affecting more than 350 million people worldwide.Depression is a condition in which a patient needs continuous medication for that oral sustained release microspheres of Desvenlafaxine were prepared which releasethe drug for a longer period of time and provide effective concentration of drug to treat depression[2].

Desvenlafaxine (O-desmethylvenlafaxine) is the main active metabolite of the third-generation antidepressant agent venlafaxine. Desvenlafaxine has good efficacy equivalent to venlafaxine and fewerside effects. Desvenlafaxine was approved by the Food and Drug Administration (FDA)in 2008 for use in the treatment of major depressive disorder[3]. Desvenlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) and in depressionacts by binds to receptors present in the brain that are associated with release ofcertain neurotransmitters such as serotonin, norepinephrine, and increasing the release of these neurotransmitters from synaptic vesicles. Desvenlafaxine is also used in the treatment of anxiety, menopause vasomotor symptoms and neuropathic pain. It is BCS class I drug with short half-life and low oral bioavailability. Desvenlafaxine is rapidly and completely absorbed by the oral route. DES soluble in water, and DMSO, and it has a melting point between 127 to 135 °C. Desvenlafaxinemetabolized by thecytochrome P450 3A4 enzyme via N-demethylation with 30% protein binding[4].

Microspheres are small, spherical particles with a diameter 1µm to 1000 µm. They are spherical, free-flowing particles consisting ofproteins or synthetic polymers which are biodegradable in nature. Microencapsulationtechnology allows protection of drug from environment, stabilization of drug substances, elimination of incompatibilities, or masking the unpleasant taste of the drug. Hence, they play an important role in drug delivery systems to improvethe bioavailability of conventional drugs and minimize their side effects[5].

Thereare 2 types of microspheres.Microcapsules are those in which drug substance is surrounded by a distinct capsule wall made up of either natural or synthetic polymer by the microencapsulation process.Micromatrices is a system in which drug substance is uniformly distributed throughout the matrix. Both natural and synthetic polymers were used for preparation of microspheres.The choice of polymer is an important stepin the development of controlled-release dosage forms as it acts as a drug carrier.Chitosan is a polysaccharide made up of natural polymers of glucosamine and N-acetylglucosamine. Chitosanisused in the formulation of novel drug delivery systems to achieve controlled or sustained drug delivery as it is biodegradable and biocompatiblein nature. Chitosan has been widely investigated as a drug carrier for various possible routes as it has good biological properties, such as non-toxicity, biocompatibility, and biodegradability[6].Sodium alginate is a naturally occurring polymer found in brown algae, was alsoused for controlled or sustained drug delivery systems. The safety of alginate was widely known, and it has a protective effect on the viability of gastrointestinal mucous membranes.The simple definition of sustained release is “Any drug or dosage form,any treatment which prolongs the therapeutic activity of a drug for longer period of time”. The main objective is to

ensure that the drug is uniformly distributed throughout the body at predetermined route within the specified period after oral administration or injection of the drug[7].

The goal of this studywas to prepare a desvenlafaxine microsphere using natural polymers such as chitosan and sodium alginate to prolong drug release and determine the effect of different polymerconcentrationson the prepared desvenlafaxine microsphere's flow properties, shape, surface characteristics, and release pattern.

MATERIALS AND METHODS:

Materials:

Desvenlafaxine was obtained as a gift sample from Lupin Limited Verna- Goa. Chitosan, Sodium alginate, Ethanol, Dichloromethane, Liquid paraffin, n-hexane, and all other chemicals, reagents, and solvents used in the study were of the highest analytical grades.

Methods:

Desvenlafaxine microspheres were prepared by solvent evaporation method. Here, required amount of polymer eitherchitosan or sodium alginate was dissolved into 10 ml mixture of ethanol and dichloromethane in a ratio of 1:1[8].Then, required amount of drug desvenlafaxine was addedto the polymer solution by stirring with a magnetic stirrer.The resultant solution was poured into 50 ml liquid paraffin containing 0.5% span 80 drop by drop with constant stirring in beaker. This process was repeated for 5 hrs until all of the ethanol and dichloromethane solvent was completely evaporated and fine droplets were formed from dispersed polymers.The resulting microsphereswerefiltered through Whatman's filter paper. The residue was washed 4 to 5 times with n-hexane. Microspheres were dried at 60^0Cfor 24 hours. The composition of the Microsphere is given in table4 [9].

Optimization:

The Central Composite Design was used for the optimization of polymer- stabilizer ratiofor desvenlafaxine microspheres. In this design, 2 factors were evaluated at 2 levels. Both the amount of the stabilizer, span 80, and the amount of the polymer, chitosan or sodium alginate, were selected as independent variables. Each factorwas studied at 2 levels -1 and +1 levels. Tables no. 1 and 2 give the levels of independent variables used[10].

Factorial Design by design expert software:

Central Composite Design for chitosan:

2 = levels like Low (-1), High (+1)

2 = Factors like independent variables and responses.

The independent variables in this design are: X_1 = concentration of chitosan

X_2 = concentration of span 80

The responses in this design are Y_1= Drug release,

Y_2= Entrapment efficacy

Central Composite design for sodium alginate:

2 = levels like Low (-1), High(+1)

2 = Factors like independent variables and responses.

The independent variables in this design are: X_1 = concentration of sodium alginate

X_2 = concentration of span 80

The responses in this design are Y_1= Drug release,

Y_2= Entrapment efficacy

Table1: Table for batch design

Levels	Low (-1)	High (+1)

Chitosan (%)	1	3
Span 80(%)	0.5	1
Sodium alginate (%)	1	2

Table2: Formulation batches of chitosan as per CCD factorial Design

Sr.No.	Factor 1	Factor 2
Formulation batches	**Chitosan**	**Span 80**
1	0	0
2	-1	-1
3	1	-1
4	1.2	0
5	-1	0
6	0	1.2
7	-1	1
8	0	0
9	0	0

Table 3: Formulation batches of sodium alginate as per CCD factorial Design

Sr.No	Factor 1	Factor 2
Batches	**Sodium Alginate**	**Span 80**
1	0	0
2	0	-1
3	1	-1
4	-1	0
5	0	0
6	1.2	0
7	-1	1
8	0	1.2
9	0	0

Formulation development of Desvenlafaxine microspheres:

Various batches of microsphere formulation F1 to F9 for the drug Desvenlafaxinewere developed, and indicated in following Table 4.

Table 4. Formulation batches of desvenlafaxine microspheres.

Sr. no.	Desvenlafaxine (mg)	Polymers Coded values		Span 80 Coded Values		Liquid paraffin (ml)	Dichloro-methane (ml)	Ethanol (ml)	n-Hexane
		CH	SA	CH	SA				
F1	75	0	0	0	0	50	5	5	QS
F2	75	-1	0	-1	-1	50	5	5	QS
F3	75	1	1	-1	-1	50	5	5	QS
F4	75	1.2	-1	0	0	50	5	5	QS
F5	75	-1	0	0	0	50	5	5	QS
F6	75	0	1.2	1.2	0	50	5	5	QS
F7	75	-1	-1	1	1	50	5	5	QS
F8	75	0	0	0	1.2	50	5	5	QS
F9	75	0	0	0	0	50	5	5	QS

SA= Sodium alginate microspheres, CH= Chitosan microspheres

Evaluation of the microsphere formulation:

The prepared microspheres were evaluated by the following parameters:

Preformulation:

The preformulationstudy was carried out to check drug-polymer compatibility. It was done using FTIR, and DSC. Also, a calibration curve was plotted and the UV spectrum was checked. Desvenlafaxine FTIR spectra

were measured both alone and in combination with chitosan, sodium alginate, and a physical mixture of desvenlafaxine**.**

Percentage yield:

The yield of microspheres was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug[11].

$$\% \text{ Yield} = \text{Total weight of microspheres obtained} / \text{Total weight of drug} + \text{polymer} * 100$$

Particle size:

The particle size of desvenlafaxine microsphereswas measured byoptical microscopy using a stage micrometer[12].

Flow properties:

The prepared microspheres were characterized by theirmicrometricproperties such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose[13].

Bulk density:

For the determination ofbulk density of the microsphere, weighed quantities of microsphere were introduced intograduated measuring cylinder and were tapped mechanically or either manually until a constant volume was obtained. The bulk density of microspheres depends on particle size and shape.The bulk density was calculated by using the following formula,

$$\text{Bulk density} = \text{Mass ofmicrospheres} / \text{Volume ofMicrospheres}$$

Tapped density:

Tapped density is the volume of powder determined by tapping using a measuring cylinder containing weighted amount of sample. The measuring cylinder containing a known mass of microspheres were tapped for a fixed time, and the minimum volume occupied in cylinder was measured.The tapped density was calculated by using the following formula.

$$\text{Tapped density} = \text{Mass of microspheres} / \text{Volume of microspheres after tapping}$$

Compressibility Index:

It is onemethod for determining flow properties and also called as % consolidation index. It is indirectly related to the relative flow rate, cohesiveness and particle size. This is an important property in uniform weight. It is calculated using the following equation,

$$\% \text{ Compressibility index} = \text{Tapped density} - \text{Bulk density} / \text{Tapped density} * 100$$

Hausner ratio:

A similar index like percentage compressibility index has been defined by Hausner ratio. Values less than 1.25 indicate good flow; whereas greater than 1.25 indicate poor flow. Hausner ratio was calculated by formula,

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density}$$

The angle of Repose:

The angle of repose of each microsphere was determined by glass funnel method. Powder was weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that

the tip of the funnel just touched the apex of the heap. The diameter of the powder cone formed was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, θ = angle of repose

H = height of pile and

R = radius of the powder cone.

The angle of repose less than 30^0 shows good flow property.

Entrapment efficiency:

The entrapment efficiency of the microsphere was evaluated by determining the percent drug entrapment.The drug content of drug loaded microsphere was determined by dispersing10 mg ofmicrospheres in 10 ml of phosphate buffer solution (pH 7.4) followedby agitation with a magnetic stirrer for around 24 hrs to extract the drug and dissolved completely. The above solution was filtered using Whatman filter paper, then pipette out 1 ml of the filtrate into a volumetric flask and diluted up to 10 ml. Drug concentration in the PBS of pH 7.4 was recorded by taking the absorbance of the above solution using UV spectrophotometry at 225 nm, and the percentage of drug entrapment was calculated. The amount of drug loaded and entrapped in the microsphere was calculated by the following formula[14].

$$\%\ \text{Drug entrapment} = \text{Amount of drug actually present}/\text{Theoretical drug loaded} * 100$$

In vitro drug release study:

A USP paddle apparatus was used to study invitro drug release from the microsphere for formulation batches (F1 to F9). In the present study, drug release was studied using a USP dissolution apparatus type 2 at 50-100 RPM with 900 ml of phosphate buffer 7.4 as dissolution medium maintained at 37 ± 0.5^{o}C. 5 ml of sample were withdrawn at specific time intervals and analysed spectrophotometrically at 225nm using a UV spectrophotometer. Each time, the volume was replaced with an equal volume of freshlyprepared dissolution medium to maintain the sink condition. The cumulative% drug release was calculated and a graph of % cumulative drug release vs. time was plotted[15].

Kinetic of Drug Release:

In vitro dissolution has been recognized as an important element in drug development. To determine the mechanism for the drug release and release rate kinetics of the formulated dosage form, the data obtained from dissolution studies was fitted into zero order,first order, Higuchi, Korsmeyerpeppas, and Hixon Crowellmodels. In this by comparing the r- values obtained, the best-fit model was selected[16].

Scanning electron Microscopy:

The scanning electron microscopy was used to observe the surface morphology of the prepared microspheres (Nova Nano SEM NPEP303). The surface of a sample was scanned bythe high electron beam in scanning electron microscopy, the beam of electron interacts with particles present onthe surface of the microsphere and it wasrepresented as topographic images of the sample. The microsphere sample was placed on an aluminum stub by a tiny layer of gold plating. Then, a microsphere sample was scanned to provide topographical photographs of the sample[17].

Zeta Potential:

The charge present on the surface of desvenlafaxine-loaded microspheres was determined by Zeta potential analyser (Zetasizer).Zeta potential test of desvenlafaxine microspherewas carried out by dispersing the sample in a particular solvent.The above dispersion was placed in a zeta cell and analysed using zetasizer[18].

Stability Studies:

Stability of a drug has been defined as the ability of a dosage form, in a specific container, to remain within its physical, chemical, and therapeutic specifications. Adrug formulation is said to be stable if it fulfils the following criteria:

i. It should contain at least 90% of its active component.
ii. It should not show discoloration or precipitation.
iii. It should not develop irritation or toxicity.

The stability study of microsphere was carried out at various temperatures and relative humidity levels as per ICH Q1 A guidelines. The duration of the study and the storage conditions were carried out as per the International Conference on Harmonization guidelines (ICH):

Long-term testing: 25°C ± 2°C / 60% RH ± 5% for 12 months.

Accelerated testing: 40°C ± 2°C / 75% RH ± 5% for 6 months[19].

RESULT AND DISCUSSION:

The present study had been successful attempt to formulate Desvenlafaxine sustained release microspheres to improvethe release of the drug.From the experimental results it can be concluded that the different polymers were used for screening amongst them the microsphere prepared by chitosan and sodium alginate shows good sphericity and particle size. The preformulation studies were conducted to determine the compatibility of the drug and polymer by FTIR spectroscopy. The results of FTIR study revealed that there was no physical or chemical interaction between drug and polymer. As per the results of DSC study, the melting pointofDesvenlafaxinewas found to be withinacceptable range. For the formulation biocompatible polymer Chitosan and sodium alginate were chosen in amounts varying proportion with the drug.Solvent evaporation method was used to prepare microsphere by using ethanol and dichloromethane as solvent to dissolve the drug and polymer.

Preformulation studies:

This study involved the calibration curve of the drug using a concentration range of 2–10 µg/ml. R^2value was found to be 0.9993. Also, the evaluation of the compatibility of the drug with the different polymers of the formulation was conducted. λ_{max} of Desvenlafaxine was found to be 225nm in Phosphate Buffer 7.4 pH by UV spectrophotometer.

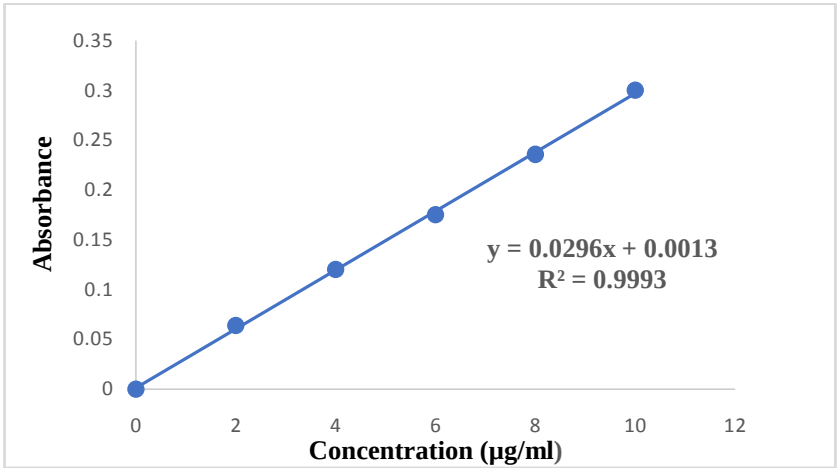

Figure 1: Standard Calibration curve of Desvenlafaxine in pH 7.4

Excipient Compatibility studies:

The Drug-Excipient compatibility studies were conducted using FTIR instrumentto examine drug compatibility both alone and in combination with polymers and physical mixture. It was observed that the characteristics drugs peak was seen in the physical blend as well as in the formulation. It was concluded that the drug is biocompatible with polymers. From DSC spectra melting point of Desvenlafaxine was found to be 122.66-128.83^{0}C at -362.78 mJ heat.

Table 5: FTIR Spectrum data of Desvenlafaxine

Sr. No.	Wave Number(cm^{-1})	Functional Groups
1.	3479	-OH group
2.	2962	-CH, Ar
3.	1627	C=C, Ar
4.	1249	C-C Aliphatic

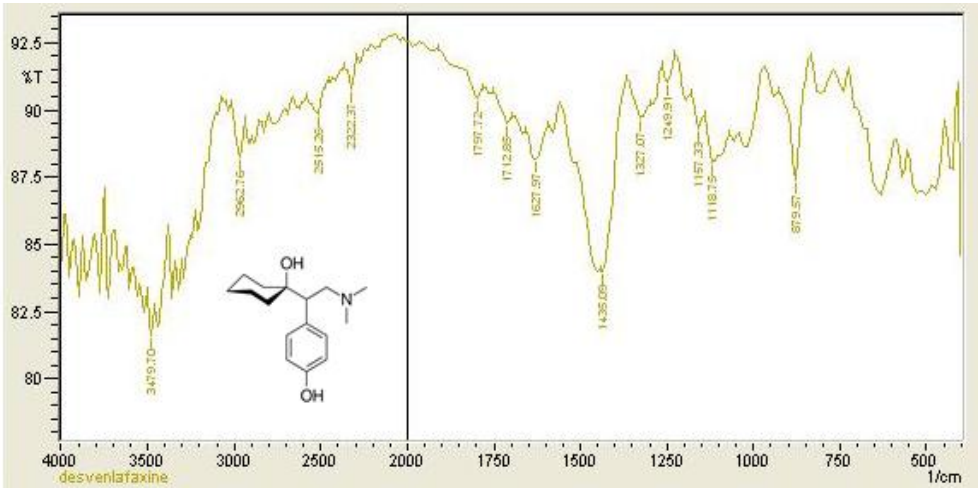

Figure 2: FTIR Spectra of Desvenlafaxine

Table 6: FTIR Spectrum data of Desvenlafaxine + Chitosan

Sr. No.	Wave Number(cm^{-1})	Functional Group Assigned
1.	3371	-OH group
2.	3263,3032	-NH group
3.	2931	-CH, Ar
4.	1597	C=C, Ar
5.	1226	C-C Aliphatic
6.	1141	C-O-C group

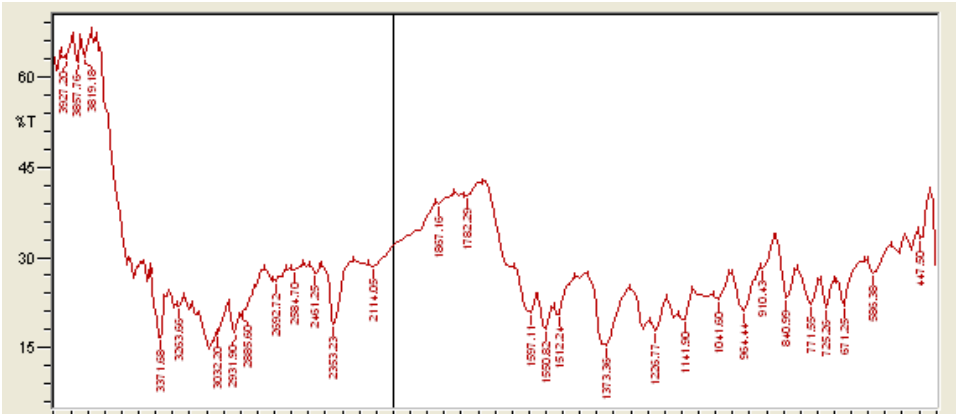

Figure3: FTIR Spectra of Desvenlafaxine + Chitosan

Table 7: FTIR Spectrum data of Desvenlafaxine + Sodium alginate

Sr. No.	Wave Number(cm^{-1})	Functional Group Assigned
1.	3479	-OH group
2.	2924	-CH, Ar
3.	1674	C=O group
4.	1580	C=C, Ar
5.	1265	C-C Aliphatic
6.	1141	C-O-C group

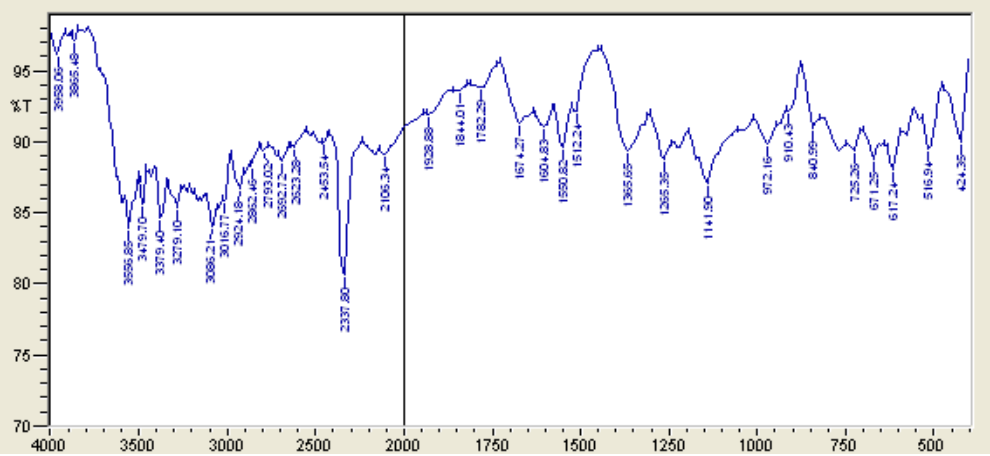

Figure 4: FTIR Spectra of Desvenlafaxine + Sodium Alginate

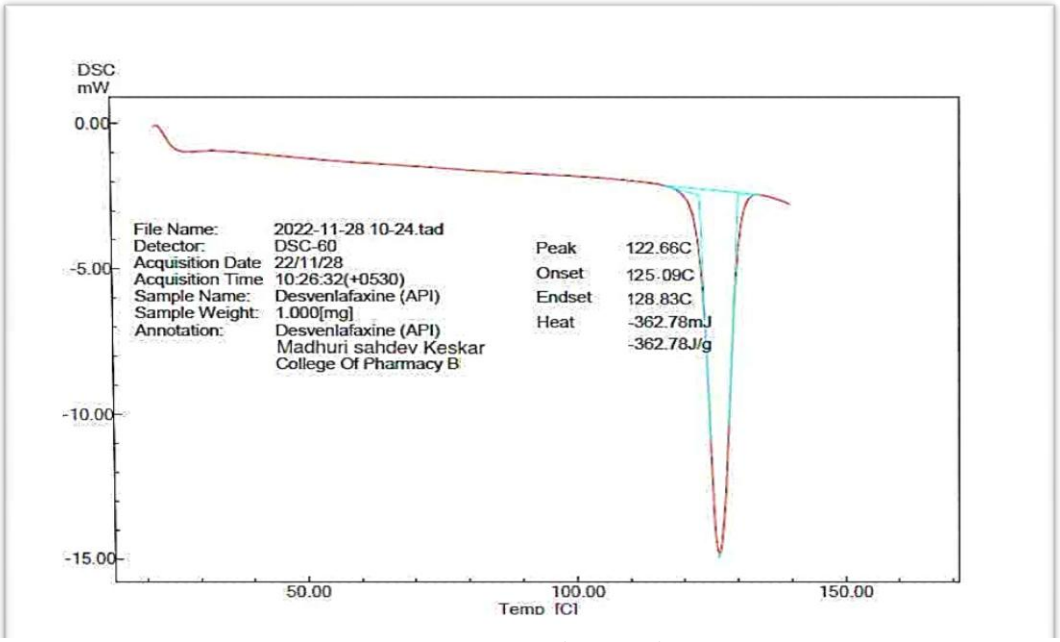

Figure 5: DSC Spectra of Desvenlafaxine.

Table8. Flow properties of Desvenlafaxine microspheres by chitosan.

Batches	The angle of Repose (^{o}) ±S. D	Bulk density (g/cm^3) ±S. D	Tapped density (g/cm^3) ±S. D	Carr's Index (%) ±S. D	Hausner's Ratio ±S. D
F1	24.38±0.018	0.425±0.002	0.474±0.001	10.33±0.013	1.11±0.011
F2	24.40±0.020	0.422±0.007	0.469±0.004	10.02±0.052	1.11±0.042
F3	28.52±0.010	0.538±0.003	0.643±0.009	16.32±0.076	1.19±0.089
F4	28.58±0.030	0.542±0.001	0.646±0.002	16.09±0.011	1.19±0.016
F5	24.34±0.017	0.423±0.002	0.473±0.002	10.57±0.024	1.11±0.061
F6	26.50±0.018	0.432±0.006	0.483±0.003	12.42±0.039	1.11±0.065
F7	26.52±0.015	0.424±0.005	0.474±0.001	10.54±0.068	1.11±0.063
F8	24.28±0.017	0.424±0.001	0.474±0.004	10.54±0.092	1.11±0.060
F9	24.38±0.012	0.420±0.007	0.484±0.005	13.22±0.051	1.15±0.059

Table 9: Flow properties of Desvenlafaxine microspheres by sodium alginate

Batches	The angle of Repose (^{o}) ±S. D	Bulk density (g/cm^3) ±S. D	Tapped density (g/cm^3) ±S. D	Carr's Index (%) ±S. D	Hausner's Ratio ±S. D
F1	24.54±0.012	0.400±0.001	0.483±0.007	17.18±0.023	1.2±0.022
F2	26.24±0.032	0.340±0.002	0.478±0.004	28.0±0.012	1.4±0.019
F3	26.80±0.021	0.320±0.005	0.400±0.003	20±0.015	1.2±0.056
F4	28.00±0.050	0.350±0.002	0.420±0.001	16±0.006	1.1±0.010
F5	28.20±0.023	0.361±0.003	0.430±0.002	16±0.016	1.1±0.011
F6	26.33±0.011	0.370±0.004	0.450±0.005	17±0.032	1.2±0.024
F7	26.20±0.032	0.310±0.001	0.322±0.003	19±0.021	1.0±0.054
F8	26.10±0.022	0.352±0.002	0.434±0.006	18±0.010	1.2±0.010
F9	28.20±0.032	0.380±0.004	0.440±0.002	13.22±0.087	1.1±0.021

Table 10: % yield and entrapment efficiency of Desvenlafaxine microspheres.

Sr.no	Formulations of Desvenlafaxine Microspheres	Entrapment efficiency (%) ±S.D		Percentage Yield (%) ±S.D	
		Chitosan microspheres	Sodium alginate microspheres	Chitosan microspheres	Sodium alginate microspheres
1.	F1	72.66± 0.11	68.50±0.12	68.44 ± 0.368	64.66±0.464
2.	F2	43.87±0.09	68.51±0.15	66±0.716	66.1±0.432
3.	F3	78.20±0.05	78.87±0.07	80±0.554	88±0.431
4.	F4	82.87±0.01	29.45±0.05	98±0.134	53±0.460
5.	F5	29.45±0.17	70.66±0.07	52±0.378	69±0.500
6.	F6	73.60±0.29	80.29±0.19	71±0.324	82±0.480
7.	F7	44.10±0.16	45.70±18	60±0.452	70±0.330
8.	F8	74.03±0.07	68.29±0.12	72±0.420	74±0.821
9.	F9	74.20±0.12	68.29±0.06	70±0.810	64±0.756

Particle size analysis:

The particle size of chitosan microspheres was found to be in the range 35.33±0.43μm to 46.33±0.10 μm, and for sodiumalginate microspheres was in the range 34.6±0.87 μm to 60.6±0.23 μm.

Table 11: The particle size of Chitosan and sodium alginate microspheres

Sr. No	Batches of Desvenlafaxine microspheres	Mean Particle size (μm) ±S. D	
		Chitosan microspheres	Sodium alginate microspheres
1.	F1	44.66±0.30	43.33±0.12
2.	F2	43.66±0.34	42±0.45
3.	F3	57±0.70	57.6±0.32
4.	F4	46.33±0.10	41.66±0.43
5.	F5	36±0.034	42.33±0.54
6.	F6	43.66±0.78	60.6±0.23
7.	F7	35.33±0.43	34.6±0.87
8.	F8	38±0.87	39.3±0.23
9.	F9	40.66±0.65	41.33±0.16

In-vitro release study:

The following figuredisplays the in-vitro drug release data for the formulations F1 to F9. From all batches,the F4 batch of chitosanmicrospheres showed 94.60% drug release in 24 hours due to their high polymer ratio hence, it was selected as an optimized batch.

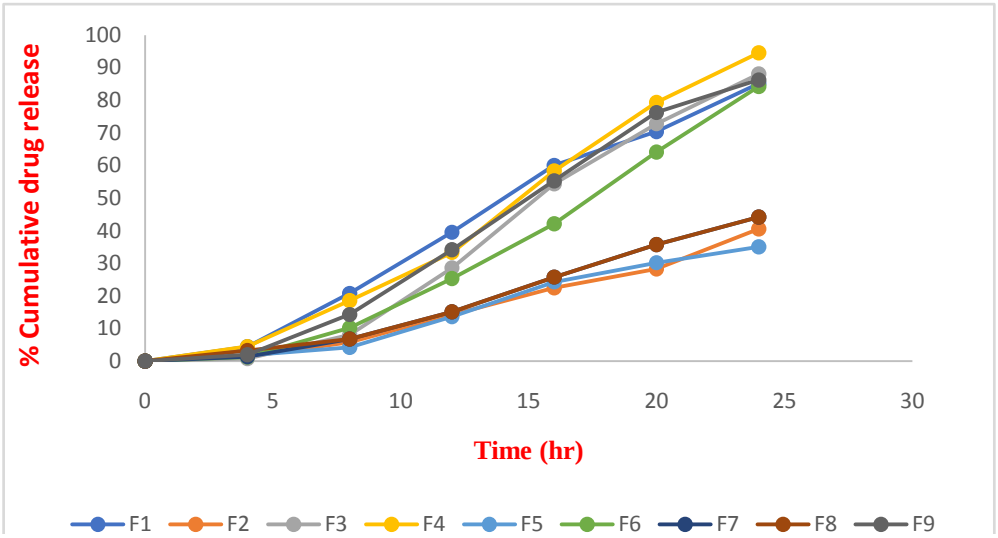

Figure 6: The plot of time Vs % Cumulative Drug Release Desvenlafaxine microspheres prepared by chitosan polymer Batches F1, F2, F3, F4, F5, F6 up to F9.

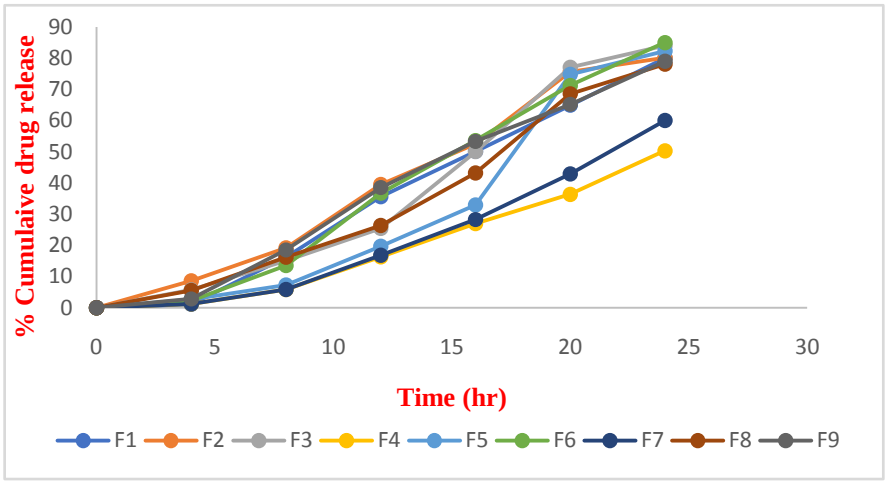

Figure 7: The plot of time Vs % Cumulative Drug Release Desvenlafaxine microspheres prepared by sodium alginate polymer Batches F1, F2, F3, F4, F5, F6 upto F9.

Kinetic of Drug Release:

The kinetic release rate profile of the prepared formulations F1 to F9 was determined by the curve fitting method, which provides information of both the rate of release and the mechanism of drug release. Based on the highest regression value, the invitro dissolution data were compared to one another for the model (r). The formulations F1, F4,and F8 of chitosan and F5, F6, and F8 of sodium alginatefollowed the Korsmeyer Peppas model. Higuchi Model suitable forF2, F3, F4, F5, F6, and F7 of chitosan, and F1, F4, and F9 of sodium alginatefollowed the Hixson Crowell model, and the Higuchi model suitable for F2, F3, F7 of sodium alginate according to the fitting of the release rate data to the various models.

Table 12: Model Fitting Profile of Desvenlafaxine microspheres F1-F9.

Sr.no	Mathematical Models (Kinetics)									
	Zero-order		First order		Higuchi model		Korsmeyer Peppas		Hixson Crowell	
	CM	SAM	CM	SAM	CM	SAM	CM	SAM	CM	SAM
	R	R	R	R	R	R	R	R	R	R
F1	0.9810	0.9810	0.9527	0.9333	0.9187	0.9039	0.991	0.9637	0.9817	0.9833
F2	0.9600	0.9159	0.9626	0.988	0.8769	0.9902	0.944	0.9573	0.9682	0.9018
F3	0.9346	0.964	0.8684	0.9543	0.8094	0.9830	0.9327	0.8473	0.9537	0.964
F4	0.969	0.9450	0.8572	0.924	0.8662	0.8367	0.993	0.8976	0.9537	0.964
F5	0.9254	0.814	0.8839	0.715	0.8030	0.6673	0.9315	0.9369	0.9418	0.8682
F6	0.9480	0.9700	0.8594	0.9333	0.8262	0.8906	0.9448	0.9869	0.9484	0.9792
F7	0.9450	0.9450	0.9369	0.9234	0.8445	0.9464	0.9309	0.8108	0.9587	0.892
F8	0.8381	0.9387	0.7377	0.8609	0.6897	0.8258	0.9577	0.9743	0.8854	0.9568
F9	0.9700	0.9700	0.9162	0.9679	0.881	0.9195	0.9548	0.9397	0.9736	0.985

DVS= Desvenlafaxine, CM=Chitosan microspheres, SAM= Sodium alginate microspheres

Scanning Electron Microscopy:

The SEM analysis was carried out foroptimized F4 batch of desvenlafaxine-loaded microspheres prepared by chitosan. The scanning electron micrograph of the microspheres shows that some microspheres were spherical and ellipsoidal in shape with a rough outer surface.

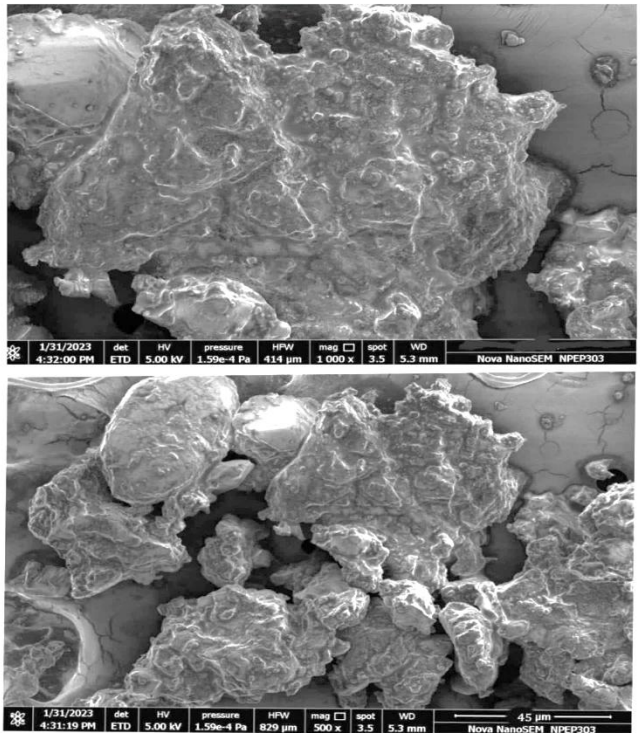

Figure 8. Scanning Electron Microscopy of Chitosan F4 Batch of DesvenlafaxineMicrospheres.

Zeta potential measurement:

The zeta potential ofan optimized formulation of chitosan F4 microspheres was found to be -16.92 mV, which indicates that the microspheres have high negative surface charge.Thisdenotes higher stability because the negative charge revealed that the formulation would be stable for longer period of time. Therefore,the F4 batch of chitosan DVS microspheres exhibit sustained release action for a longer period.

Table 13:Zeta potential of F4 Chitosan DVS microspheres

Brookhaven Instruments

Summary Statistics Report

Type	Start Date/Time	Sample ID	Zeta Potential (mV)	Mobility (µ/s)/(V/cm)	RMS Residual
PALS	13-01-2023 16:54:22	DES venla faxine - 1	-15.15	-1.18	2.1869e-02
PALS	13-01-2023 16:55:00	DES venla faxine - 2	-19.80	-1.55	4.2786e-02
PALS	13-01-2023 16:55:38	DES venla faxine - 3	-15.80	-1.23	2.7511e-02
		Mean:	-16.92	-1.32	3.0722e-02
		Std Err:	1.45	0.11	6.2478e-03
		Std Dev:	2.51	0.20	1.0821e-02

Sample		Results	
Type:	PALS	Zeta Potential (mV):	-19.80
Sample ID:	DES venla faxine - 2	Analysis Type:	Smoluchowski
Operator ID:	Unknown Operator	Mobility (µ/s)/(V/cm):	-1.55
SOP ID:	College Of Pharmacy Bhor		
Start Date/Time:	13-01-2023 16:55:00		
Notes:			

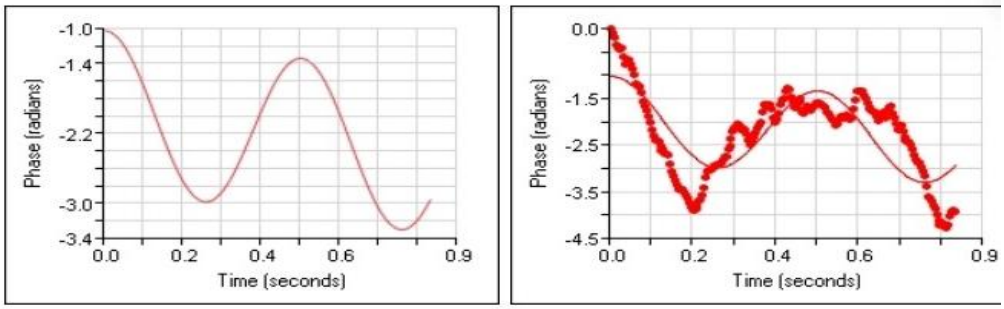

Figure 9: Zeta potential Spectra (1) of F4 Chitosan DSV microspheres.

Brookhaven Instruments

Basic PALS Report

Sample		Results	
Type:	PALS	Zeta Potential (mV):	-15.15
Sample ID:	DES venla faxine - 1	Analysis Type:	Smoluchowski
Operator ID:	Unknown Operator	Mobility (µ/s)/(V/cm):	-1.18
SOP ID:	College Of Pharmacy Bhor		
Start Date/Time:	13-01-2023 16:54:22		
Notes:			

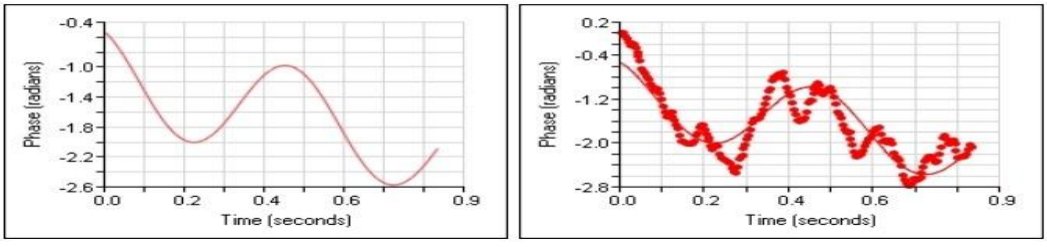

Figure 10: Zeta potential Spectra (2) of F4 Chitosan DSV microspheres.

Stability study:

The stability studies of optimum formulation were carried out and the results state that there is no change in drug release and entrapment efficiency was observed over a period of 60 days. No significant change was observed at 40 ±2ºC, 75% RH hence formulation F4 prepared with chitosan was found to be stable for 2 months.

Table 14: Stability study of Optimized Formulation

Stability (40 ±2ºC)	Percentage yield (%)	Entrapment Efficiency (%)	Invitro drug release (%)
Initial	98	82.87	94.60
15 days	97.95	82.83	94.58
30 days	97.84	82.80	94.57
45 days	97.79	82.79	94.55
60 days	97.50	82.72	94.53

CONCLUSION:

Microspheres are one of the novel drug delivery systems and they are prepared to obtain prolonged or controlled drug delivery, improve bioavailability or stability, and target drugs specific sites. Microspheres also provide advantages like limiting fluctuation in plasma drug concentration, reducing side effects, decreasing the dosing frequency, and improving patient compliance. Microspheres of Desvenlafaxine were prepared according to CCD factorial design using the solvent evaporation method by selecting the concentration of chitosan,sodium alginate, and span 80 as independent variables. Increasing polymer concentration leads to a more sustained release effect. The prepared formulation was evaluated for its percentage yield, micromeritic properties, particle size, drug entrapment, and invitro drug release studies. Almost all formulations showed acceptable results. Microspheres of different sizes and improved drug entrapment efficiency would be obtained by varying the drug-to-polymer ratio. The formulation showed good flow properties. It is concluded that formulated desvenlafaxine microspheres prolonged drug release for 24 hours as per in vitro drug release and drug entrapment studies.According to the results of the zeta potential,the prepared microsphere does not form aggregates and is non-sticky in nature. The negative the zeta potential value, the stronger the repulsive force between the particles will sustain the action of the drug for a longer period. The F4 formulation of chitosan may be the potential candidate for safe and effective over an extended period with reduced dosing frequency.

CONFLICT OF INTEREST:

None

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REFERENCES:

1. R. R. Bhagwat. Novel Drug Delivery Systems: An Overview R.R. Bhagwat and I.S. Vaidhya Department of Quality Assurance, Dr. L.H. Hiranandani College of Pharmacy, C.H.M. College Campus, Opp. Rly Stn., Ulhasnagar- 421003, Maharashtra, India," vol. 4, no. 3, pp. 970–982, 2013.

2. Tong GF, Qin N, Sun LW. Development and evaluation of Desvenlafaxine-loaded PLGA-chitosan nanoparticles for brain delivery. *Saudi Pharm J*. 2017;25(6):844-851. doi:10.1016/j.jsps.2016.12.003

3. Bhusnure Omprkash G, Prasad K, Gholve Sachine B, Giram Padmaja S. Formulation and in-vitro

evaluation of sustained release matrix tablet of desvenlafaxine succinate by interpolyelectrolyte complex (IPEC) formation technique. *Res J Pharm Biol Chem Sci*. 2016;7(2):108-112.

4. Samy W, Elnoby A, El-Gowelli HM, Elgindy N. Hybrid polymeric matrices for oral modified release of Desvenlafaxine succinate tablets. *Saudi Pharm J*. 2017;25(5):676-687. doi:10.1016/j.jsps.2016.10.005

5. Samirkumar P, Chand T, Maulik T. Formulation Development and Evaluation of Microspheres Containing Duloxetine Hydrochloride. 2013;4(2):568-572.

6. Abdul I, Tadwee K, Shahi S, Thube M, Ankit S. Review on Microspheres. 2011;1:24-33.

7. KAKKAR V, WANI SUD, GAUTAM SP, QADRIE ZL. Role of Microspheres in Novel Drug Delivery Systems: Preparation Methods and Applications. *Int J Curr Pharm Res*. 2020;12(3):10-15. doi:10.22159/ijcpr.2020v12i3.38326

8. Sabarinathan. R, Formulation, and Evaluation of Sustained Release Microspheres of Venlafaxine Hydrochloride, Master thesis Adhiparasakthi College of Pharmacy., M.G.R. Medical University Chennai; 2012.

9. Panpaliya D V., Sahare AY, Lanje P, Dhoke P. Formulation Development and Evaluation of Sustained Release Microsphere of Levetiracetam. *Int J Pharm Sci Rev Res*. 2021;71(2):165-173. doi:10.47583/ijpsrr.2021.v71i02.026

10. Bhavsar MD, Tiwari SB, Amiji MM. Formulation optimization for the nanoparticles-in-microsphere hybrid oral delivery system using factorial design. *J Control Release*. 2006;110(2):422-430. doi:10.1016/j.jconrel.2005.11.001

11. Mokale V, Naik J, Wagh P, Khairnar G. Venlafaxine HCl Microspheres. 2014;13(1):83-91.

12. Prabu SL, Shirwaikar A. Formulation and evaluation sustained release microspheres of rosin containing aceclofenac. 2014;(January 2009).

13. Iswariya VT, Sahithi TVVS, Maheswari A, Madhu K, Maryswarnalatha K. Formulation and Evaluation of Atenolol Microspheres. 2022;16(05):1218-1221.

14. Bindu madhavi B, Zulkar M, B Nain Kamal, Kusum. and David Banji. Formulation and Evaluation of Venlafaxine HCl Microspheres, Hygeia Journal for Drugs and Medicines, 2011, 64-70.

15. Phutane P, Shidhaye S, Lotlikar V, Ghule A, Sutar S, Kadam V. In vitro Evaluation of Novel Sustained Release Microspheres of Glipizide Prepared by the Emulsion Solvent Diffusion-Evaporation Method. *J Young Pharm*. 2(1):35-41. doi:10.4103/0975-1483.62210

16. Parmar GR. FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF. 2014;(April).

17. Mitra A, Dey B. Chitosan Microspheres in Novel Drug Delivery Systems. 2011;(July). doi:10.4103/0250-474X.95607

18. Dwivedi R.K. Development of Novel Formulation for Intranasal Delivery Containing Antidepressant Agent. Saudi Journal of Medical and Pharmaceutical Sciences., vol. 4929, no. 8, pp. 358–367, 2021, doi 10.36348/sjmps.2021.v07i08.003.

19. F Z, R R, K S. a Review on Stability Testing Guidelines of Pharmaceutical Products. *Asian J Pharm Clin Res*. 2020;(October):3-9. doi:10.22159/ajpcr.2020.v13i10.38848