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International Journal of Chemistry and Pharmaceutical Sciences

2013, Vol.1 (2): 94-107

ISSN 2321-3132

Research Article

Pharma Research Library

Design and Evaluation of Extended release Multiunit Particulate System for Novel class-I Antidepressant Drug

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ABSTRACT

Pellets have long been employed to improve the bioavailability of drugs undergoing significant first pass hepatic metabolism. Venlafaxine hcl is an antidepressant drug. It has very strong side effect of vomiting in the IR dosage form, so it is necessary to developed its SR dosage form to avoiding this side effect. Chances of dose dumping were very negligible in the MUPS drug delivery system. It was under goes extensive first pass metabolism resulting in an oral bioavailability of 45 % and it shows variable absorption from GIT. Multiunit particulate oral drug delivery system offers several advantages such as rapid absorption, reducing peak plasma fluctuation and ease of administration and termination of therapy. Hence in the present work pellets of venlafaxine hcl were prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolog period of time. Extended released pellets containing venlafaxine hcl was prepared using an extrusion-spheronization technique. Amount of Microcrystalline cellulose (Avicel pH101, Hypromellose 15 cps and Eudragit NE 30D were taken as the formulation variables for optimizing to keep round shape of pellets and percentage release of drug. The pellets were evaluated for Physical characterization, Assay, Sizing, SEM, In-vitro drug release and Binder's concentration tends to very effective pellets shape and size. Percentage release of drug tended to very non-linear with polymer type and percentage of coating on the pellets. The formulation with 0.45% HPMC, 65.94% MCC and 13% Eudragit NE 30D coating was consider as a best product with respect to perfect size and shaped pellets and In-vitro drug release study.

Key words: Extended Release Capsule, venlafaxine hcl, Eudragit NE 30D, Avicel 101, HPMC 15CPS, Mcc, Talc, Aerosil

Introduction

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration[1]. Implants of small, sterilecylinders formed by compression from medicated masses are also defined as pellets in pharmacy[2]. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements.

1. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 µm.
3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Theory of Pellet Formation and Growth[3]

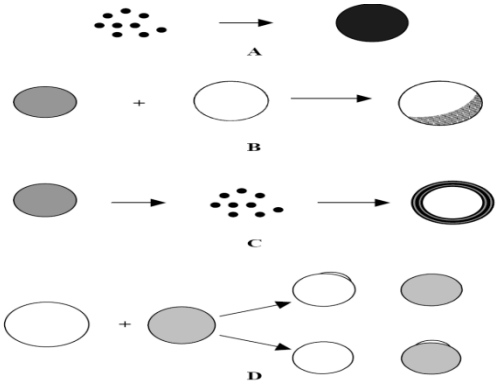


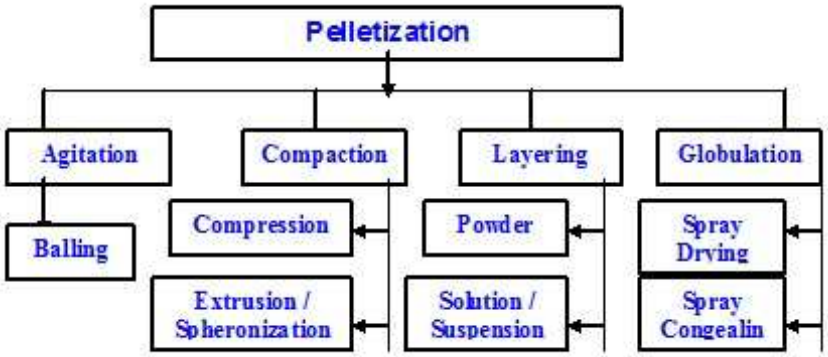
Figure.No.1 Pellet growth mechanisms. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer[4]

Desirable Properties of Pellets:[5&6]

Methods of preparing pellets[7]**:**

Compaction and drug layering are the most widely used pelletisation techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletisation has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale. Following of the mainly techniques used for the pelletization.

Different Pelletization Techniques[8]:



This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of Venlafaxine HCL, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulation which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of Venlafaxine HCL comprising a therapeutically effective amount of Venlafaxine HCL, microcrystalline cellulose, and optionally, HPMC coated with a mixture of ethyl cellulose and HPMC[9].

Material and Methods

Materials for component selection
Venlafaxine hcl pure drug was a gift sample from Torrent pharmaceutical limited, Ahmadabad (Gujarat, India). HPMC was gift sample from Leon chemicals, Bangalore, India and HPMC 15CPS, EUDRAGIT NE 30D, MCC were gift samples from S.D. Fine Chem. Ltd, Mumbai, India. All other chemicals were of analytical grade.

Preformulation Study
Estimation of Venlafaxine:
Preparation of standard & sample solution:
1. Preparation of stock solution
An accurately weighed 10 mg. Drug was dissolved and diluted to 100 ml with purified water to produce 100 µg/ml
2. Preparation of sample solution
Different dilution of stock solution with purified water were made to obtain solution having concentration 10,20,30,40,50 µg/ml. Absorbance was measured at 227 nm for this solutions against purified water as blank

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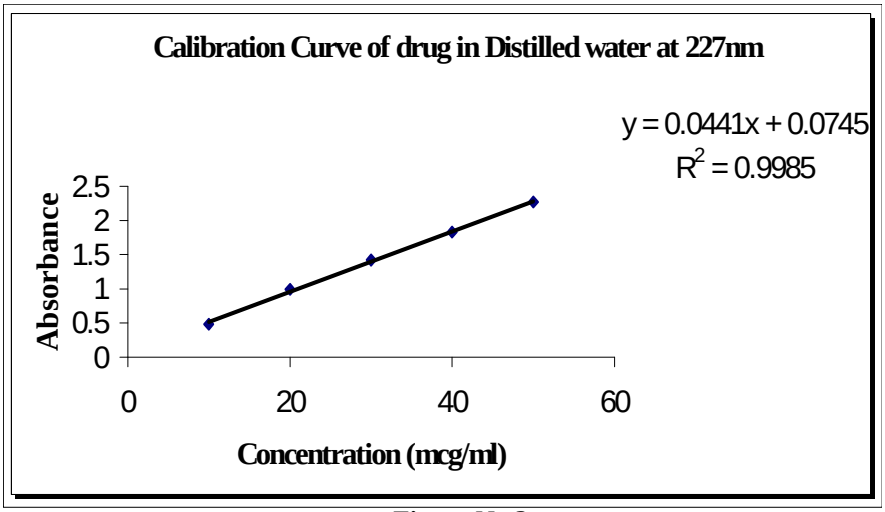


Figure.No.2

Calibration curve of drug in purified water has been shown below. The concentration and absorbance data has been shown in table. It can be seen from calibration curve of the drug that the relation between concentration and absorbance is linear (R^2=0.9985)

Drug-Excipients interaction study using differential scanning calorimetry:
A differential scanning calorimeter was used for thermal analysis of drug and mixture of drug and excipients. The drug and excipients were passed through the sieve no. 60 and mixed in ratio as shown in table no.15 the drug alone and mixture of drug and excipients was weighed directly in the pierced DSC aluminum pan (Aluminum Standard 40 ul) and scanned at the temperature range of 50-300 °c and at heating rate of 10 °c/min. and nitrogen purging rate 50 ml/min. the thermogram obtained were observed for any interaction.

Figure No.3DSC THERMOGRAPH OF API

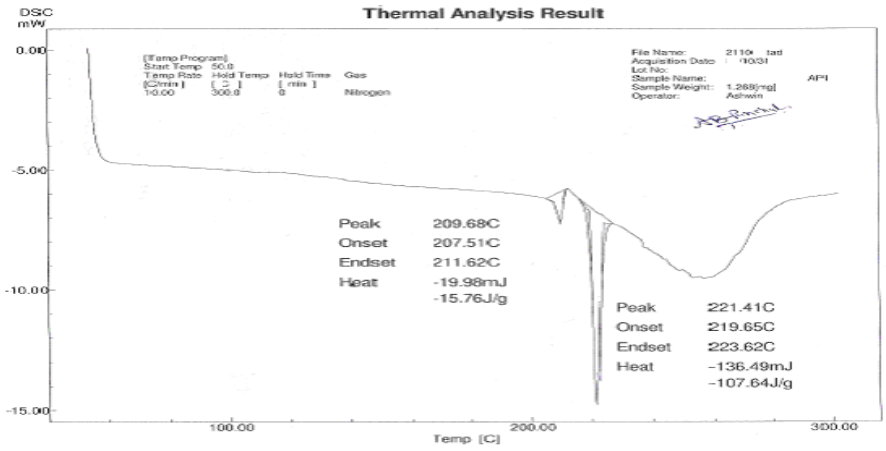


Figure No.4 DSC THERMOGRAPH OF API + MCC

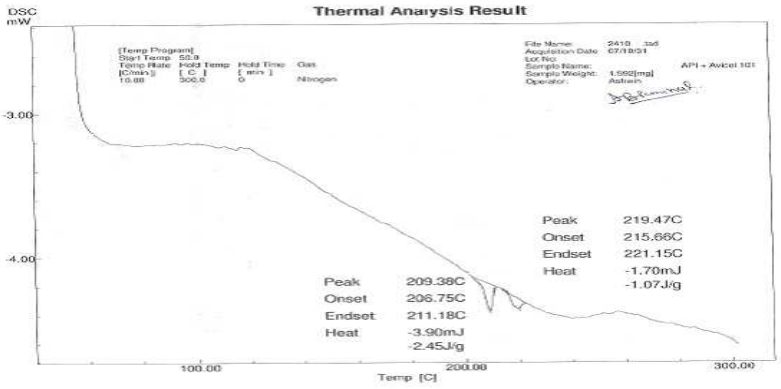


Figure No.5 DSC THERMOGRAPH OF API + HPMC 15CPS

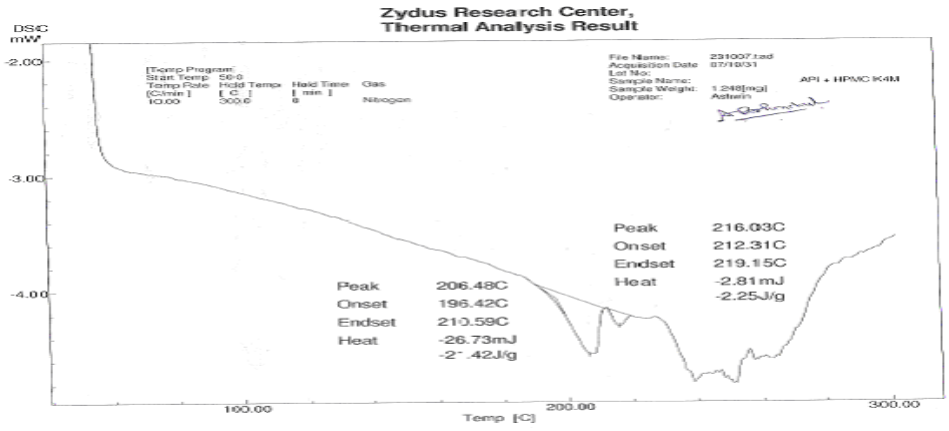


Figure No.6 DSC THERMOGRAPH OF API + TALC

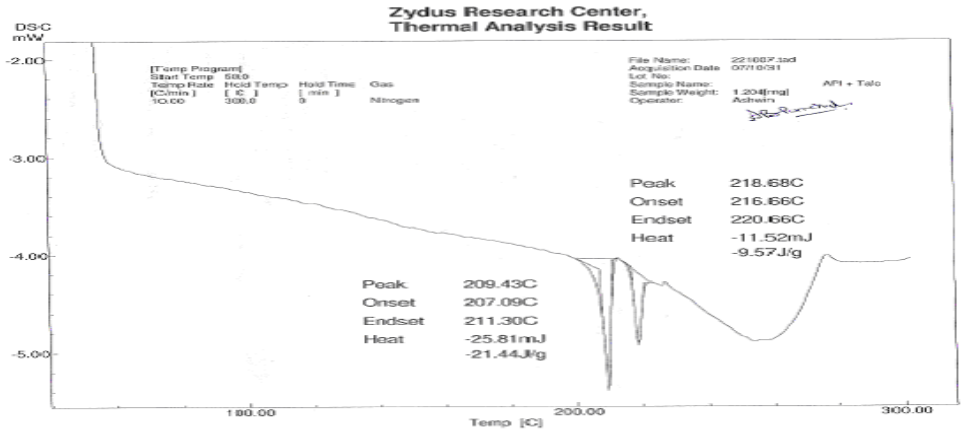
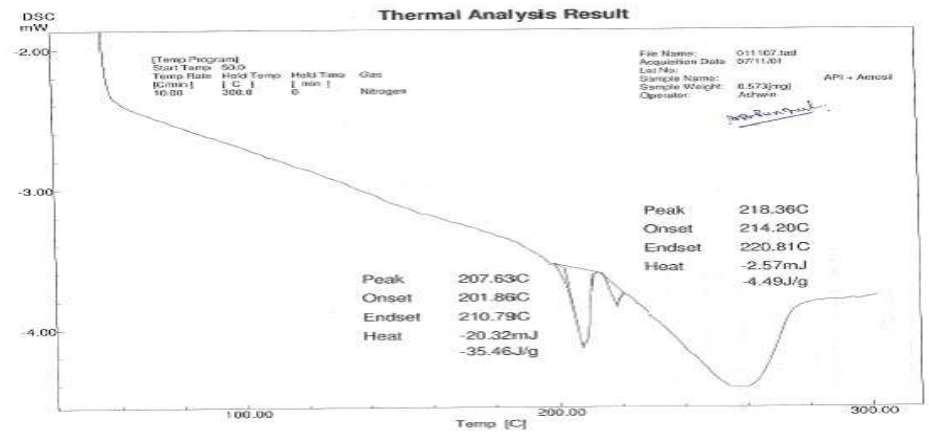


Figure No.7 DSC THERMOGRAPH OF API + AERO



Interpretation of DSC Thermogram of Drug and Mixture of Drug and EXCIPIENTS:

Table No.1

Combination	Onset (°c)	End set (°c)	Peak (°c)	Integral (mj)
API	219.65	223.62	221.41	-136.49
API + MCC (Avicel pH 101)	215.66	221.15	219.47	-1.70
API + HPMC	212.31	219.15	216.03	-2.81
API + Talc	216.66	220.66	218.68	-11.52
API + Aerosil 200	214.20	210.79	207.63	-20.32

The thermal behavior of the pure drug and the combination of drug and excipients is compared:
The DSC trace of API showed a sharp endothermic peak at 221.41°c. In the DSC trace of the mixture of API and excipients, the sharp endothermic peak observed neared to 221.41°c, in the majority of case. Melting endotherm of the drug was well preserved with a slight change in terms of broadening of peak or shifting towards the lower

temperature. Thus these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipients, which lowers the purity of each component in the mixture and may not necessarily indicating potential incompatibility.

Precompression Parameters of developed formulation[10,13]

1. Organoleptic characteristics[10]
2. Solubility of drug[10]
3. Sieve analysis[10]
4. Bulk density[10,13]
5. Tapped density[10,13]
6. Carr's index[10,12]
7. Haussner's ratio[10,11]
8. Compatibility study[12]

Table No.2

Parameter	Results				
	API	**MCC (Avicel pH 101)**	**HPMC (15cps)**	**TALC**	**AEROSIL**
Loss on Drying (%w/w)	0.3%	5.0%	5-7%	6.5%	2.5%
Bulk Density (gm/cm^3)	0.211	0.32%	0.341%	0.277%	0.035%
Tapped Density (gm/cm^3)	0.300	0.45%	0.557%	0.534%	0.05%
Compressibility Index	29.41%	28.88%	38.77%	48.12%	30%
Hauser's Ratio	1.417	1.40	1.63	1.92	1.42
Particle size	57.41µm	20-200µm	10-300µm	44-74µm	7-16nm

Drug Excipients Compatibility Study[14]:
Protocol for drug-excipients compatibility:

Table.No.3

Combination	Determined Ratio
API alone	
Drug + HPMC	1:1
Drug + Talc	1:5
Drug + Avicel pH 101	1:5
Drug + Eudragit NE 30D	1:2
Drug + Aerosil	1:1

Preparation of drug containing pellets:

Extended release pellets of venlafaxine hcl were prepared by wet granulation technique using Microcrystalline Cellulose pH 101 were passed through the 30# sieve and dry blended in rapid mixer granulator till uniform mixing obtained. Hydroxypropyl methylcellulose was passed through 30# sieve and dissolved in a sufficient quantity of purified water using continuous stirring with mechanical stirrer, till thick transparent paste was obtained. Now dry blend was granulated using previously made solution and add extra water if necessary.

Above wet mass was transfer in to extruder of 1 mm screened sized die. Start extruder at 50 rpm and collect road shape pellets.
Now above extruded product was transfer in to sheronizer and start it on 800 rpm, continuous observed it and collects it after perfect round shape was obtained. It would be taken time for Aprroximately 10 min. These pellets were added in to mechanical sifter for the size separation through 12-24# sieve. Sprinkle extra talc for reducing clumping formation or reduce the static charges between pellets.

Preparation of Coating Solution:
First of all, Talc and Aerosil was sifted through 40# sieve. Mixed both excipients and homogenize using water in homogenizer till very fine particles in solution were obtained. Now collect it from homogenizer and mixed with Eudragit NE 30D polymer using mechanical stirrer for the continuous stirring, which help to prevent settlement of talc at the bottom of the mixing tank.
Above solution was sifted through the 100# sieve, and used for the coating on the previously prepared pellets.

Polymer coating on drug containing pellets:
Transfer the previously prepared drug pellets into a Fluidised Bed Coater and set the parameters as per mentioned below. Now coating was started for targeted build up in pellet weigh.

Figure No.8 Coating of Core Pellets

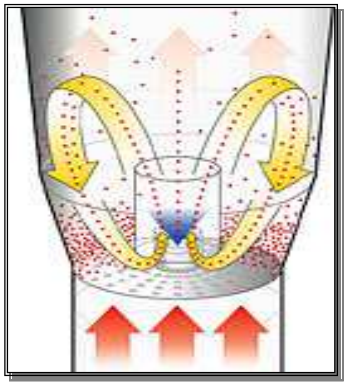


Figure No.9 Bottom Spray Fluidised Bed Coater

Curing on the pellets:
At 60ºC for 2 hrs curing was done on the pellets after polymer coating.
Capsule filling:
Capsule filling was done by laboratory scale capsule filling machine or by manually method.

Figure No.10 Capsule Filling Machine

Composition Of Formulation of Trial Series For Core Pellets:

Table No.4

INGREDIENTS	BATCH NO.								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	60	40	45	30	30	60	50	45	40
Methocel K4M		0.6							
HPMC 15 cps			0.3	0.8	0.5	0.3	0.35	0.4	0.45
RanQ pH 101		59.4							
Avicel pH 101	40						49.65	54.6	59.55
Avicel pH 102			54.7	69.2					
Avicel pH 301					69.5				
Avicel pH 200						39.7			
P. Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

**** Quantities of excipients were taken in %**

Conclusion:
As per the above-obtained data it may be concluded that Avicel pH101 is the most suitable MCC grade, hence pellets prepared using F9 formula was best round pellet. So all the trials were taken on the basis of formula F9.Total weight of pellets was 432.258.

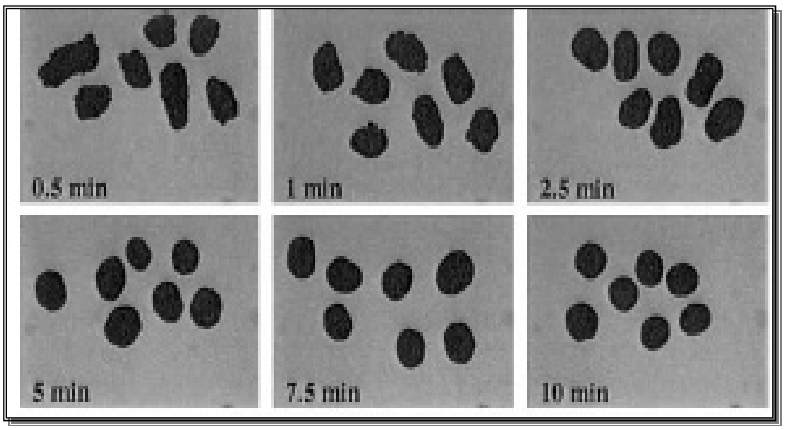
Composition of formulation of trial series for obtaining extended drug release from pellets:

Table No.5

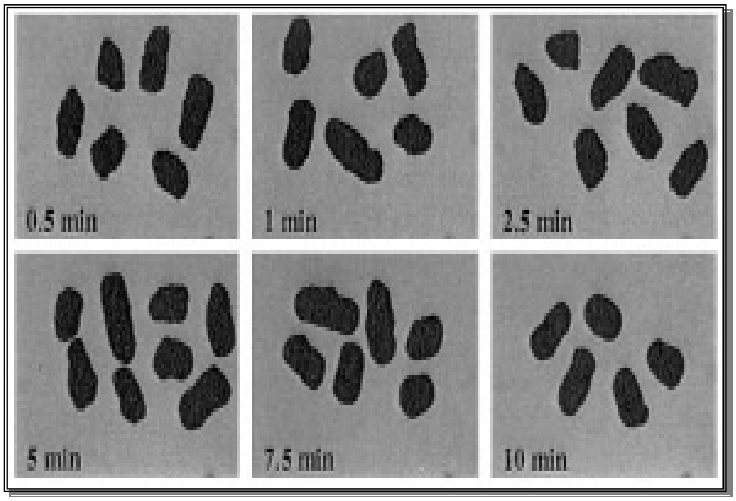
INGREDIENTS	F9								
	A	B	C	D	E	F	G	H	I
Ethyl cellulose 7 cps	2.5%	5.0%	------	------	------	------	------	------	------
Hypromellose 6 cps	2.5%	----	5.0%	------	------	------	------	------	------
Eudragit RL30D	------	----	------	5.0%	------	------	------	------	------
Eudragit RS30D	------	----	------	------	10.0%	------	------	------	------
Eudragit NE30D**	------	----	------	------	-------	5.0%	8.0%	15.0%	13.0%

***Talc and Aerosil were added in the coating solution with the polymer dispersion.**
Weights of coated pellets are 488.45 mg.

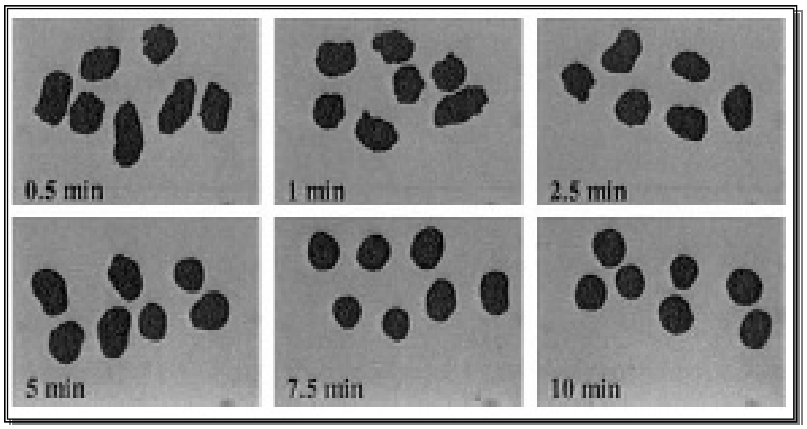
Optimization of formulation:
Spheroidal forms at various spheronization process in different grades of microcrystalline cellulose:



I. AVICEL pH 101 Figure No.11



II. AVICEL pH 301 Figure No.12



III. AVICEL pH 200 Figure No.13

ASSAY:

Calculate quantity in mg of drug per net content of pellet by using following formula

$$\text{Drug Content} = \frac{ATi}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{200}{WTi} \times \frac{P}{100} \times \frac{277.40}{313.87} \times \text{Net content for respective strength}$$

Where,

ATi = Peak area of sample injection of the respective strength
AS = Peak are of standard injection
WS = Weight of working standard taken in mg
WTi = Weight of sample taken in mg (i = 1&2)
P = Percentage purity of working standard (on as is basis)
277.40 = Molecular weight of Drug
313.87 = Molecular weight of drug with salt

$$\text{Assay} = \frac{\text{Drug content (practically)}}{\text{Drug content (Theoretically)]}} \times 100$$

Results and Discussions

For Uncoated Pellets

Pellets were tested as above method for the drug content in pellets, which were shown ***99.83%*** in the final formulation.

For Coated Pellets

Pellets were tested as above method for the drug content in the coated pellets, which were shown ***99.82%*** in the final formulation.

In-vitro drug dissolution profile:

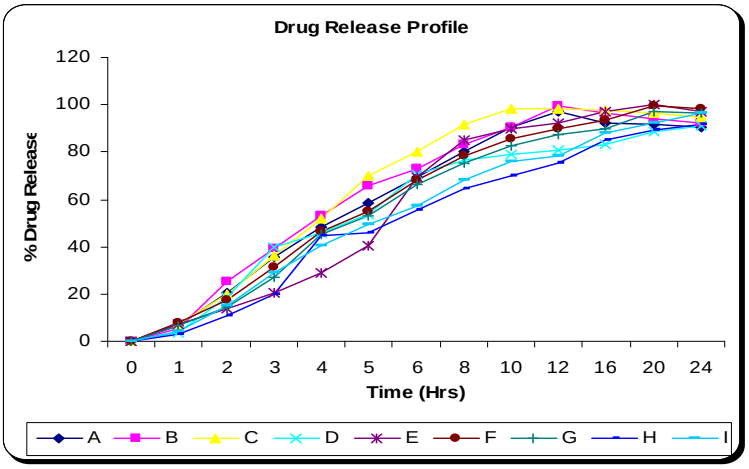
Table. No.6

TIME (hrs.)	% Drug Release From F9								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
1	6.8	5.4	7.0	3.7	7.4	8.1	6.5	3.2	4.2
2	20.3	25.5	19.6	18.4	13.9	17.3	14.7	11.0	15.0
3	35.7	39.4	35.9	40.1	20.6	31.4	27.4	20.0	29.1
4	48.4	52.8	51.6	45.7	29.0	46.7	45.1	44.4	40.7
5	58.4	65.6	69.7	53.6	40.7	54.6	53.0	45.6	49.6
6	69.2	72.8	80.0	70.8	69.2	68.4	66.1	55.2	57.1
8	80.4	83.2	91.8	76.5	85.1	78.3	75.4	64.8	68.3
10	90.7	90.6	**98.4**	78.7	89.6	85.4	82.7	70.2	75.8
12	**97.1**	**99.2**	98.1	80.9	92.4	89.9	87.2	75.1	78.5
16	92.1	96.7	97.5	83.4	97.1	93.5	90.0	85.0	88.1
20	91.5	94.3	96.7	88.4	**99.8**	**99.4**	**97.0**	89.3	92.1
24	90.5	92.2	94.9	**91.0**	97.1	98.2	96.7	**91.7**	**96.7**

Above results are averages of the 6 samples.

Graphical presentation of %Drug dissolution versus Time (hrs.):

Figure No.14



9.6 Evaluation of Capsule:

9.6.1 Description:

White to off-white pellets filled in size "0" hard gelatin capsules with dark orange colored cap printed with "ZA-37" in black ink & white body printed with "150 mg" in black ink. The capsule should be free of all physical defects. Filled weight in the capsule shell was 525.54 mg.

Assay:

Table No.7

Sr. No.	Sample	No. of Injections
1	Mobile phase	1
2	Standard preparation	5
3	Sample preparation	1

Capsules were tested as above method for the drug content in capsules, which were shown ***99.83%*** in the final formulation.

In-Vitro Drug Dissolution Profile:

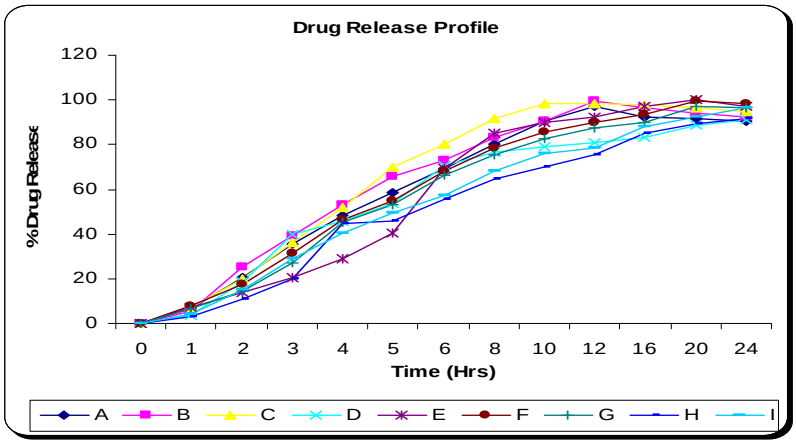
Table No. 8

TIME (hrs.)	% DRUG RELEASE FROM F9								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
1	6.8	5.4	7.0	3.7	7.4	8.1	6.5	3.2	4.2
2	20.3	25.5	19.6	18.4	13.9	17.3	14.7	11.0	15.0
3	35.7	39.4	35.9	40.1	20.6	31.4	27.4	20.0	29.1
4	48.4	52.8	51.6	45.7	29.0	46.7	45.1	44.4	40.7
5	58.4	65.6	69.7	53.6	40.7	54.6	53.0	45.6	49.6
6	69.2	72.8	80.0	70.8	69.2	68.4	66.1	55.2	57.1
8	80.4	83.2	91.8	76.5	85.1	78.3	75.4	64.8	68.3
10	90.7	90.6	**98.4**	78.7	89.6	85.4	82.7	70.2	75.8
12	**97.1**	**99.2**	98.1	80.9	92.4	89.9	87.2	75.1	78.5
16	92.1	96.7	97.5	83.4	97.1	93.5	90.0	85.0	88.1
20	91.5	94.3	96.7	88.4	**99.8**	**99.4**	**97.0**	89.3	92.1
24	90.5	92.2	94.9	**91.0**	97.1	98.2	96.7	**91.7**	**96.7**

****Above results are averages of the 6 samples**.

Graphical presentation of %Drug dissolution versus Time (hrs.):

Figure No.15



Drug Release Models:

Table.No.9

Formulation	Drug Release Models				
	First order	Baker & Lonsdale	Hixson & Crowell's	Zero order	Higuchi
A	0.7987	0.8219	-0.7323	0.9374	0.9720
B	0.7875	0.8154	-0.7040	0.9301	0.9710
C	0.7619	0.8051	-0.7039	0.9143	0.9579
D	0.8261	0.9537	-0.7183	0.9466	0.9715
E	0.8500	0.9359	-0.8058	0.9564	0.9648
F	0.8661	0.9757	-0.7894	0.9723	0.9914
G	0.8688	0.9799	-0.7869	0.9829	0.9913
H	0.8971	0.9938	-0.7926	0.9813	0.9924
I	**0.9045**	**0.9976**	**-0.8005**	**0.9872**	**0.9982**

From above result it may be concluded that final formulation follows Higuchi's square root model.

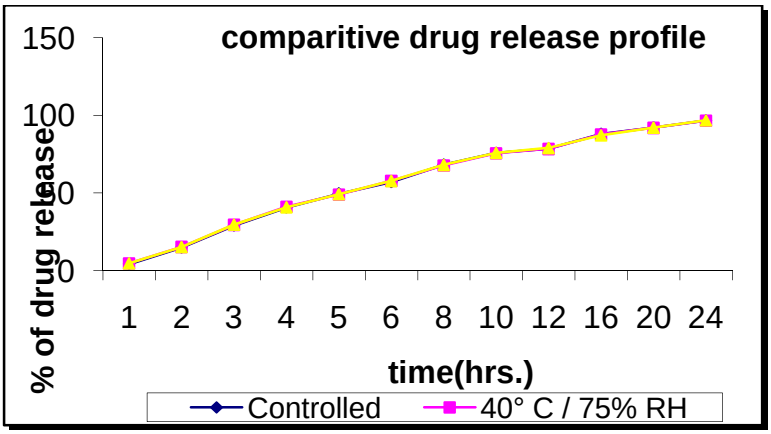
Stability Study:
Dissolution profile of stability batch:

Table No.10

Time (hrs.)	% Drug Release		
	Controlled	40° C / 75% RH	60° C / 85% RH
1	4.2	4.7	4.8
2	15.0	15.3	15.3
3	29.1	29.5	29.7
4	40.7	41.1	40.9
5	49.6	49.0	49.3
6	57.1	57.8	57.8
8	68.3	67.7	68.1
10	75.8	75.6	75.9
12	78.5	78.4	79.0
16	88.1	87.8	87.2
20	92.1	92.0	92.1
24	**96.7**	**96.6**	**96.8**

Graphical presentation of %Drug dissolution of stability batch:

Figure No.16



From the above result obtained it may be concluded that there was not any significant changes observed in the formulation after keep it in stability condition.

Summary and Conclusion

Venlafaxine hcl is an anti-depressant drug. It is under goes extensive first pass metabolism resulting in an oral bioavailability of 45 % and it shows variable absorption from GIT. MUPS oral drug delivery system offers several advantages such as rapid absorption, reducing peak plasma fluctuation and ease of administration and termination of therapy. Hence in the present work pellets of venlafaxine hclwere prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolog period of time. In the present work, the drug containing pellets were prepared by wet granulation technique, coating with Eudragit NE 30 D and then filled in hard gelatin capsule shell.

The Extended released pellets containing venlafaxine hcl was prepared using an extrusion-spheronization technique. Amount of Microcrystalline cellulose (Avicel pH101, Hypromellose 15 cps and Eudragit NE 30D were taken as the formulation variables for optimizing to keep round shape of pellets and percentage release of drug. The pellets were evaluated for Physical characterization, Assay, Sizing, Aspect ratio, density, SEM, In-vitro drug release and Binder's concentration tends to very effective pellets shape and size. Percentage release of drug tended to very non-linear with polymer type and percentage of coating on the pellets.

The formulation with 0.45% HPMC, 65.94% MCC and 13% Eudragit NE 30D coating was consider as a best product with respect to perfect size and shaped pellets and In-vitro drug release study. Multiunit particulate drug delivery system gives unique release pattern, which was seen in F9I formula. This product was further subjected to stability study, the results of which indicated no significant change with respect to Shape, color, surface and in vitro drug release.

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