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Formulation and Evaluation of Floating Microcapsules of Zolpidem Tartarate

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Abstract: *The hydro dynamically balanced modified release dosage form of ZOPLIDEM TARTARATE was targeted to be developed using a unique microcapsules platform..Microcapsules were formulated using Ethyl cellulose 7 cps as the controlled release polymer, HPMC 5 cps as the pore former and DCM and IPA as solvents for the drug and polymers. Water with 1% Tween 80 was used as the continuous phase. The formulation was optimized by using statistically designed 2^3 Design of experiments. The particle size, particle yield, drug content, entrapment efficiency, buoyancy studies and in vitro dissolution profile were the measurable parameters.The formulation showed that the particle size distribution, batch yield, drug content, entrapment efficiency, buoyancy studies were not the dependent variable. There were no significant differences in any of the above parameters in all the 8 experimental runs. However, in case of the in-vitro dissolution studies, the rate and extent of the release profile was strongly dependent on the drug and polymer ratio as well as on the pore forming concentration.[1,2]. A design space was defined within which an optimum formulation could be successfully achieved with the in- vitro release profile matching to the Target product profile.[3]*

Keywords: *Zolpidem tartarate, Floating microcapsules, HPMC, Ethyl cellulose, DOE*

I. Introduction

- The aim is to prepare gastro intestinal floating drug delivery system microcapsules using Zolpidem[ZT] as a model drug.[5]
- The aim of the system is to get the in vitro dissolution profile similar to Ambien CR tablets .
- The concept selected for the current project is by formulating microcapsules.
- The design is to have formulate ethyl cellulose (EC) based microcapsules of ZT which will float on the GI content over a period of 4 to 6 hours.
- The release profile shall be controlled by varying the concentration of EC and poreformer HPMC in the microcapsules.

Zolpidem was proven as effective as benzodiazepine in the management of short-term insomnia. Zolpidem is effective in reducing the time to sleep onset and increasing total sleep time. The hypnotic effects of Zolpidem have been reported primarily in the first 3 hours post-dose which can lead to sub therapeutic effects on sleep maintenance in the later portion of the night for some patients. In an effort to expand the coverage of sleep complaints and overcome the lack of efficacy in sleep maintenance. The microcapsules were designed to control release of drug and thus maintains a plasma concentration for a longer duration of time.[4,5]

Immediate release dosage forms of zolpidem provide a burst of drug substance shortly after ingestion, to induce rapid onset of sleep. Whereas such dosage forms address the latency to sleep problem, unless the drug substance has a long half life, in order to maintain effective blood plasma concentration levels over an extended period of time, patients experiencing short sleep duration or frequent nocturnal awakening events will need to take further dosage forms during the night to maintain sleep.[15]

The optimization shall be done using the Design Optimization and Experimentation that is DOE concept.A batch of the optimized formulation shall be scaled up and subjected to 3 months accelerated stability study. Factorial experimental designs investigate the effects of many different factors by varying them simultaneously instead of changing only one factor at a time. Factorial designs allow estimation of the sensitivity to each factor and also to the combined effect of two or more factors.[31]. By applying DOE for the optimization of formulation variables, the critical concentration of the variables can be known, with which the best formulation can be fabricated.DOE pro XL software was used for the present study.

II. Materials And Methods

Materials- Table-1

Sr.No	Drug/ Excipient/ Polymer/ Solvent	Manufacturer
1.	Zolpidem tartarate	Emco Industries, Hyderabad
2.	Hydroxy propyl methyl cellulose (HPMC 5cps	S. D. Fine Chemicals
3.	Ethyl cellulose 7cps	S. D. Fine Chemicals
4.	Dichloromethane	S. D. Fine Chemicals.
5.	Isopropyl alcohol	S. D. Fine Chemicals.
6.	Tween 80	Laboratory Grade
7.	Hydrochloric acid	Laboratory Grade
8.	Sulphuric acid	Laboratory Grade

Zolpidem Tartarate Powder
Colour: White fine powder

Melting point determination: The melting point of the obtained drug sample was found to be 196°C which is the reported range of 196°C -197°C.It complies with the USP standards thus indicating the purity of the drug soluble.

Solubility analysis: ZOPLIDEM TARTARATE sample was found to be soluble in water, 0.1 N Hcl, very slightly soluble in ethanol, practically insoluble in acetone.

Compatibility studies.-
Fourier Transformation Infra-red (FTIR) analysis: Infra-red spectroscopy analysis was performed by Fourier Transform Infrared Spectrophotometer.

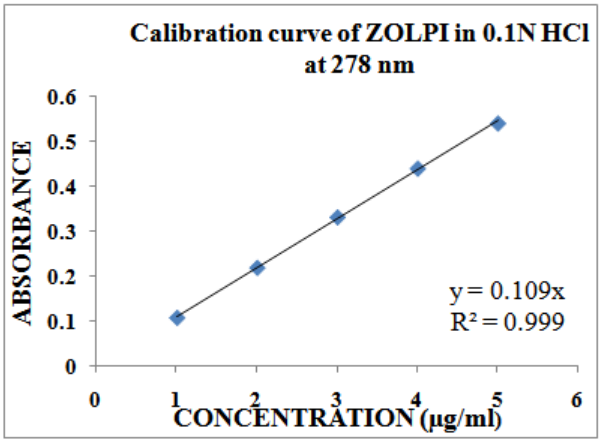
Differential scanning calorimetry (DSC): DSC was performed in order to assess the thermotropic properties and thermal behavior.

TABLE-2Spectral analysis:

S.No	Concentration	Absorbance
1	1	0.107
2	2	0.219
3	3	0.332
4	4	0.441
5	5	0.542

Determination of λmax of ZOPLIDEM TARTARATE by using 0.1N HCL. The absorption maximum of ZOPLIDEM TARTARATE in 0.1 N HCL was found to be 278 nm.

Figure1 :Calibration curve of ZOPLIDEM TARTARATE in 0.1N HCL



3.1 Experimental Design And Process Of Optimization

A full 2^3 factorial design was introduced to optimize the formulation of Zolpidem loaded EC+ HPMC microcapsules using the solvent evaporation technique (Table).
Entrapment efficiency was considered as a measurable parameter for this study.

Doe Approach

Experimentation

A design matrix comprising of 8 experimental runs was constructed using DOE Pro XL Software to investigate the effect of factors .

- Zolpidem concentration as (A),
- EC concentration as (B),
- HPMC concentration as (C)

-on the response variable i.e. % entrapment efficiency .

Experimental Design and Process Optimization

A full 2^3 factorial design was introduced to optimize the formulation of ZOLPI loaded EC+ HPMC microcapsules using the solvent evaporation technique .
A design matrix comprising of 8 experimental runs was constructed using DOE Pro XL Software to investigate the effect of 3 factors .

- ZOLPI concentration as (A),
- EC concentration as (B),
- HPMC concentration as (C)

on the response variable i.e. % Drug released at 1 hour (D1) and % Drug release at 8 hours (D8) were considered as measurable parameters.

Volume of solvent (50 ml), ratio of IPA and DCM (1:1) , volume of aqueous phase (500 ml) concentration of Tween (2.5ml), stirring speed (500 rpm) and temperature (ambient) were kept constant.

TABLE-3 **Formulation chart**

Formulation	Zolpidem tartarate	Ethyl cellulose 7cps	HPMC 5cps
F1	L	L	L
F2	L	L	H
F3	L	H	L
F4	L	H	H
F5	H	L	L
F6	H	L	H
F7	H	H	L
F8	H	H	H

TABLE-4 . Design of Experiment

S.No.	Ingredients	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
		F1	F2	F3	F4	F5	F6	F7	F8
1	Zolpidem	250	250	250	250	1000	1000	1000	1000
2	Ethyl cellulose 7cps	250	250	1000	1000	250	250	1000	1000
3	HPMC 5cps	2	20	2	20	2	20	2	20
4	Isopropyl alcohol (IPA) (ml)	25	25	25	25	25	25	25	25
5	Dichloromethane (DCM) (ml)	25	25	25	25	25	25	25	25
6	Tween 80 (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Water (ml)	500	500	500	500	500	500	500	500

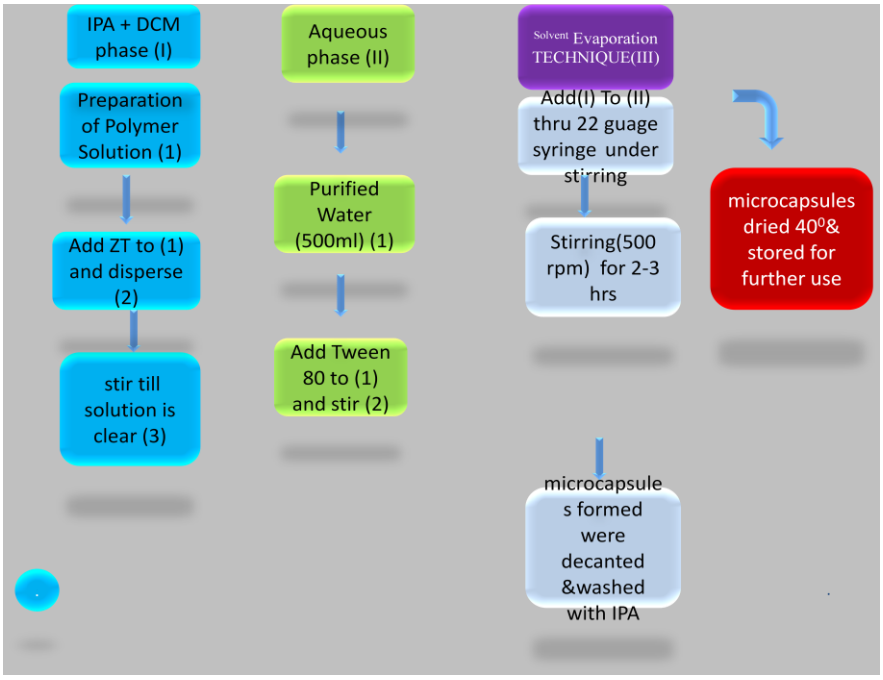


FIGURE-2 Method of Preparation of Microcapsules

- **Percentage yield**

Percentage yield of different formulations,F1-F8,were calculated

3.2characterization Of Microcapsules

- **Particle size analysis**
  Particle size distribution of microcapsules was determined by optical microscope fitted with an ocular micrometer
- **Shape and surface morphology**
  Surface morphology and internal cross sectional structure of the floating microcapsules were investigated with scanning electron microscope.
- **Drug loading & entrapment efficiency:**

In vitro Buoyancy Studies:

The duration of floatation for all the batches of microcapsules was evaluated as follows:

- Quantity of microcapsules equivalent to 12.5 mg of Zolpidem Tartarate was accurately weighed out for each batch.
- This amount was added to a 500 ml glass beaker containing 250 ml of 0.1N HCl (medium). A three blade remi stirrer was fitted into the medium.
- The mediuim was stirred at 50 rpm for a period of 12 hours
- The behaviour of the microcapsules was observed at 2, 4, 8 and 12 hours interval and the visual observations were noted.

- **In-vitro Dissolution Studies**
- The Design space for the Zolpidem Tartarate, EC and HPMC is defined by DOE by feeding data of entrapment efficiency.
- In order to confirm the design space, 3 formulations [F optima 1, 2,3] within the space were fabricated at a larger scale and evaluted for dissolution profile.
- **Stability Studies**

III. Results & Discussion

A total of 8 formulations of Zolpidem Tartarate floating microcapsules were formulated by solvent evaporation technique using DOE approach, which was already discussed in the previous chapter. The formulations were subjected to evaluation parameters like particle size, surface morphology, drug entrapment efficiency, In-vitro drug release studies.

4.1 Preformulation Studies- Identification Of Pure Drug

4.2 FT-IR Spectroscopy- The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Zolpidem Tartarate. The spectra of the drug and the cross linked microcapsules were shown in the figures 8.1,8.2 respectively

.

4.3 Melting Point Determination-The melting point of the obtained drug sample was found to be 196^0C which is the reported range of 195 to 197^0C.It complies with the USP standards thus indicating the purity of the drug sample.

4.4 Solubility Analysis-Zolpidem Tartarate sample was found to be soluble in water (18.8 mg/ml), 2-propanol and ethanol, sparingly soluble in acetone. Soluble in 0.1N NaOH .

4.5.Compatibility studies-From the FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristics peaks of Zolpidem Tartarate were present in the combination spectra thus indicating the compatibility of the drug with the polymer used.

The IR spectrum of the Zolpidem Tartrate shows the peaks at following values which are characteristic of the drug.

3380 cm-1	-O-H stretching,
1646 cm-1	- C=O stretching for carbonyl,
2900 cm-1	aliphatic C-H stretching

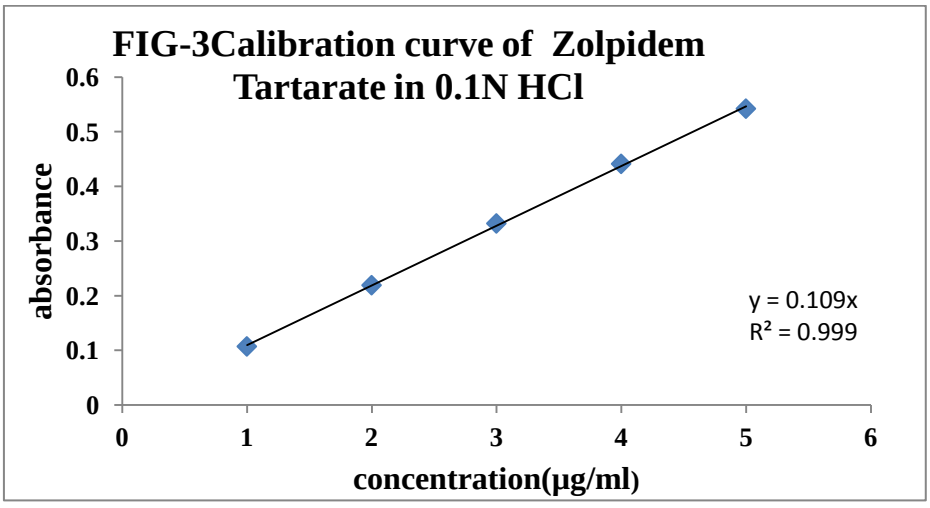
Differential Scanning Calorimetry(Dsc) Study -Differential scanning calorimetry (DSC) studies of drug-polymer mixtures were performed using a Toledo DSC (Mettler Star SW 9.20) to determine the drug excipient compatibility study.Thermograms of pure Zolpidem Tartrate showed sharp endothermic peak at 196 °C. Similar peaks were obtained in the prepared drug-polymer mixtures. This clearly indicates the nil drug polymer interaction.

4.6 Standard Calibration Curve of Zolpidem Tartarate in Buffers (pH 1.2):

Standard calibrated values of Zolpidem Tartarate in 0.1N HCl were tabulated as follows. They were at different concentrations ranging from 1-5µg/ml in acidic buffer (pH 1.2). The curves of respective values are also presented below.

S.NO	CONCENTRATION	ABSORBANCE
1	1	0.107
2	2	0.219
3	3	0.332
4	4	0.441
5	5	0.542

TABLE-5: Calibration values of Zolpidem Tartarate in 0.1N HCl.



4.7 Percentage yield

Percentage yield of different formulations,F1-F8,were calculated and the yield was found to be above 45%.The results are tabulated in the Table 8.2.the results indicate that the solvent evaporation technique gives excellent yield of the floating microcapsule.

Formulation	Percentage Yield(%w/w)
F1	54.82
F2	59.45
F3	77.92
F4	80.23
F5	46.87
F6	48.57
F7	65.97
F8	68.97

TABLE-6: Percentage Yield of Formulation

4.8. Discussion:

The yield of microcapsules seems to depend on the concentration of polymer in the preparation. For formulation F3 , F4, F7 and F8, where the EC concentration is 1000 mg, the yields are > 60%.
For formulations with low EC concetration, the yields are in the range of 45 to 55%.

9. Characterization Of Microcapsules

4.9.Particle size analysis

Particle size distribution of microcapsules was determined by optical microscope fitted with an ocular micrometer and stage micrometer.the particle sizes of the microcapsules were found in the range of(65-525µm) for 8formulations(DOE).The particle size of the formulations were shown in the table

FORMULATION	MEAN PARTICLE SIZE(D90) (µm)
LLL	355.86
LLH	344.86
HLL	278.98
LHH	330.77
HLL	357.29
HLH	288.86
HHL	386.55
HHH	289.26

TABLE-7: Mean Particle Size of the Microcapsules of the Formulations.

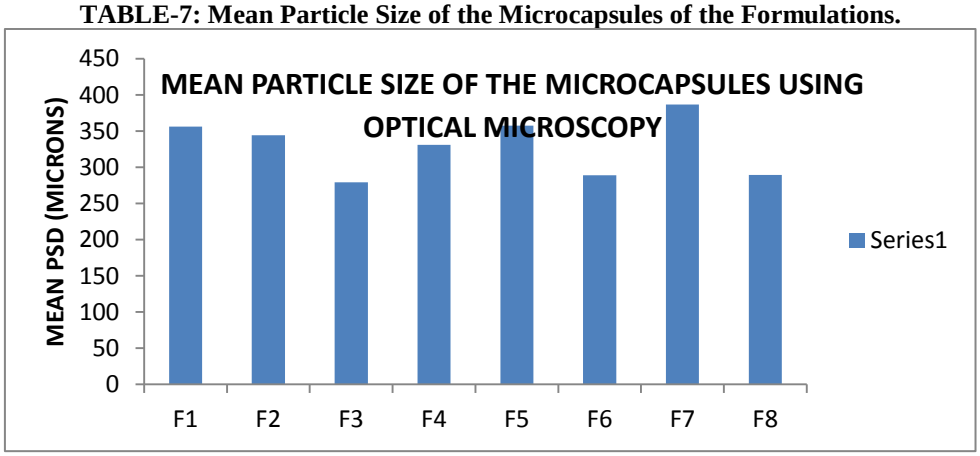


Figure 4 : Mean Particle Size of the Microcapsules of the Formulations

IV. Discussion

For all formulations, the microcapsules are in the average particle size range of 250 to 375 µm. The particle size distribution is independent of the formulation and is dependent more on the process follows.

5.1Shape and surface morphology Surface morphology and internal cross sectional structure of the floating microcapsules were investigated with scanning electron microscope.SEM photomicrographs of the blank microcapsules, optimized formulation were shown in the figures. The microcapsules were smooth, spherical and discrete particles. Very less particulate matter of the drug were seen on the surface of the microcapsules indicating uniform distribution of the drug in the polymer

Figure 5: SEM of Blank

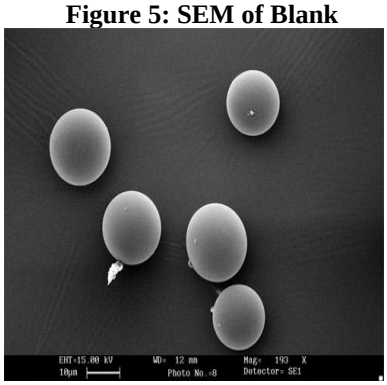
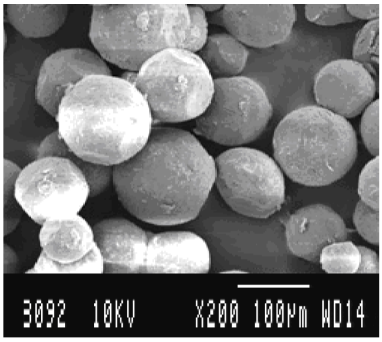


Figure 6: SEM of Foptima 1



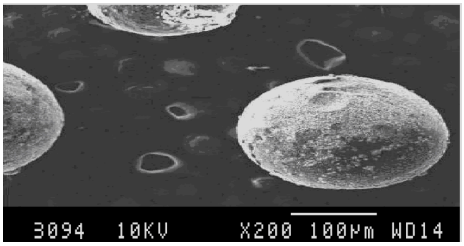


Fig 7: SEM of F optima2

5.2.Discussion:

The SEM images show spherical microcapsules with a rough and porous surface. The microcapsules for the scale up batch (Fig) shows that the microcapsules obtained for the scale up batch are reproducible in surface characteristics.

TABLE-8 Drug loading & entrapment efficiency: .

FORMULATION	ENTRAPMENT EFFICIENCY
F1	67.39
F2	70.58
F3	94.00
F4	84.61
F5	74.97
F6	72.41
F7	89.27
F8	91.70

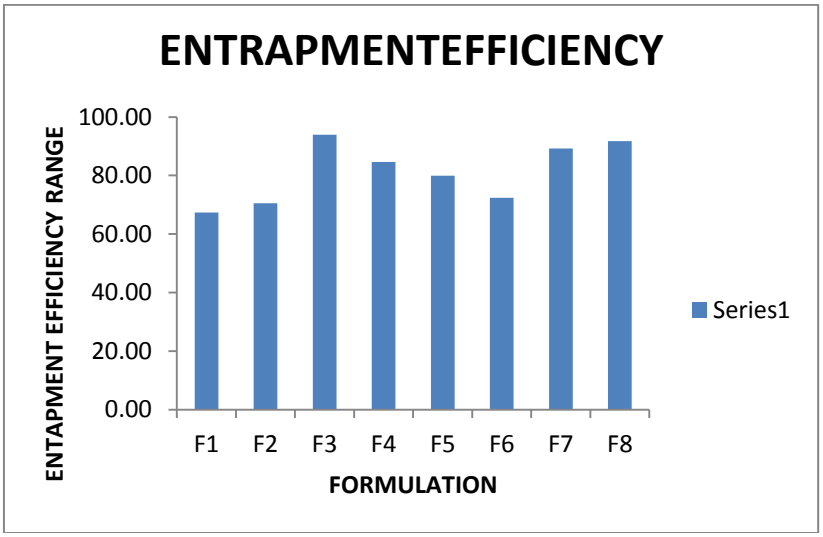


Figure 8: Entrapment Efficiency

Discussion: The drug entrapment efficiency is dependent on the level of EC in the formula. For formulations with EC is 1000 mg, the entrappment efficiency is > 80%. For formulations with EC levels at 250 mg, the efficiency is around 6o to 75%

5.3 In Vitro Buoyancy Studies: The duration of floatation for all the batches of microcapsules was evaluated as follows: -Quantity of microcapsules equivalent to 12.5 mg of Zolpidem Tartarate was accurately weighed out for each batch.This amount was added to a 500 ml glass beaker containing 250 ml of 0.1N HCl (medium). A three blade remi stirrer was fitted into the medium.The medium was stirred at 50 rpm for a period of 12 hours.

S. No.	Formulation No.	Time (Hours)				
		0	2	4	8	12
1	F1	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
2	F2	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
3	F3	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
4	F4	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
5	F5	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface
6	F6	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface
7	F7	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
8	F8	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface

Table-9: In Vitro Buoyancy Studies

5.4. In-vitro Dissolution Studies:

In vitro release study of Zolpidem Tartarate floating microcapsules were performed in the following pH media (pH 1.2) at $37^0C \pm 0.5^0C$.

- In vitro dissolution testing was conducted on microcapsules equivalent to 12.5mg of ZOLPIDEM TARTARATE.
- Microcapsules were filled in hard gelatin capsules shells
- USP Type I apparatus was used
- Media 900 ml 0.1N HCl
- RPM: 50 rpm
- Time points: 0. 0.5, 1, 2, 4 and 8 hours
- Estimation by UV spectrophotometry.

The *in vitro* release profile of Zolpidem Tartarate Floating microcapsules was shown below-

TIME		DISSOLUTION PROFILE FOR ZOLPIDEM TARTARATE FLOATING MICROCAPSULES						
	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	6.35	9.23	1.87	3.23	35.87	44.32	4.32	7.54
1	11.87	18.45	3.69	7.89	72.61	89.45	7.29	15.88
2	24.79	42.67	10.44	18.44	88.45	90.76	18.35	33.49
4	45.32	75.34	35.68	43.87	90.26	98.12	38.44	67.7
8	85.29	94.35	65.43	72.64	98.23	98.5	82.48	90.58

Table -10: Dissolution Profile at pH 1.2

Discussion: The drug release rate and extent is dependent of the ratio of the drug and ethyl cellulose as well as the pore former concentration.

For formulations with Drug to polymer ratio 1:1 (F1, F2, F7, F8), the release is dependent on concentration of HPMC (faster release for higher HPMC levels)

For formulations with drug to polymer ratio 1:4, F3 and F4 the release is very slow (< 70% in 8 hours)

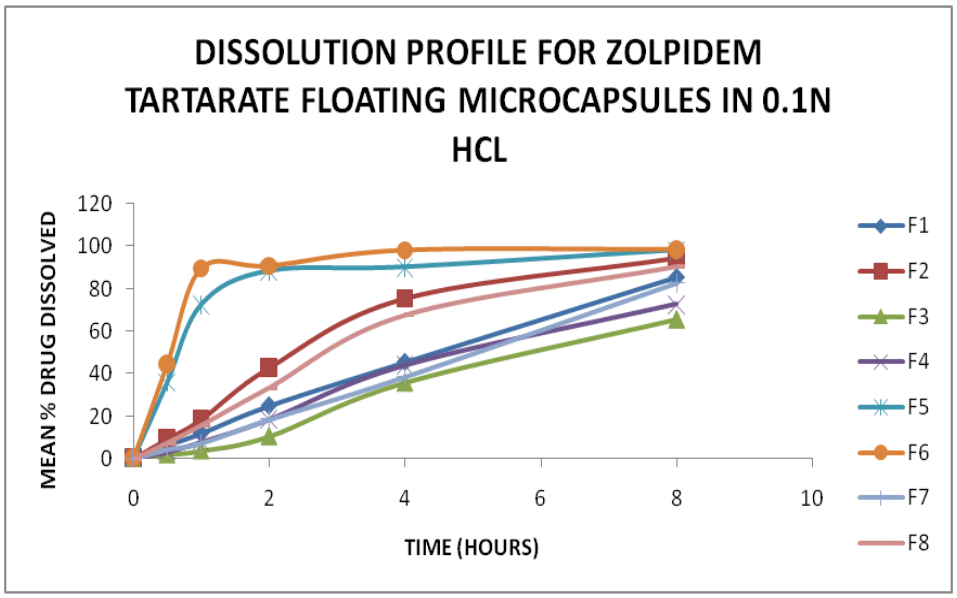


Figure-9 Dissolution Profile For Zolpidem Tatarate Floating Microcapsules In 0.1n Hcl

For formulations with drug to polymer ratio 4:1, F5 and F6 the release is very fast (> 80% in 2 hours)

Discussion:

- The drug release rate and extent is dependent of the ratio of the drug and ethyl cellulose as well as the pore former concentration.
- For formulations with Drug to polymer ratio 1:1 (F1, F2, F7, F8), the release is dependent on concentration of HPMC (faster release for higher HPMC levels)
- For formulations with drug to polymer ratio 1:4, F3 and F4 the release is very slow (< 70% in 8 hours)
- For formulations with drug to polymer ratio 4:1, F5 and F6 the release is very fast (> 80% in 2 hours)

5.5 Release kinetics

Formulation	R^2				Peppas N
	Zero	First	Higuchi	Peppas	
F1	0.9981	0.9646	0.9272	0.9991	0.943
F2	0.9080	0.9964	0.9524	0.9659	0.874
F3	0.9867	0.9800	0.8689	0.9885	1.353
F4	0.9876	0.9918	0.9165	0.9915	1.146
F5	0.5225	0.9057	0.7911	0.7384	0.322
F6	0.4127	0.7461	0.6958	0.6188	0.244
F7	0.9981	0.9491	0.8834	0.9949	1.091
F8	0.9420	0.9946	0.9491	0.9803	0.927

Table -11 :Release rate of Zolpidem Tartarate from formulations (F1 to F8)

In order to understand the mechanism of drug release from the microcapsules, the in vitro drug release data were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874 to 1.353 for the formulations F1 TO F4 and F7 TO F8.. Based on these values we can say that formulations exhibited super case ii transport. The release exponents formulations F6 & F5 was found to be 0.244 & 0.322 Based on these values we can say that formulations exhibited anomalous diffusion mechanism (non fickian transport).

The formulations F1 & F3 showed higher r values for Korsmeyer and Peppas release plot indicating that the drug release from these formulations exhibited anomalous diffusion mechanism. Also the remaining formulations showed higher r values for .first order plot indicating that the drug release followed first order kinetics and also the drug release from the microcapsules were by both diffusion and erosion .

Discussion: The release of Zolpidem Tartarate at 1 hour and 8 hours time points were taken as the measurable parameters for running the DOE experiments. The 1 hour time point indicates the rate of release and the 8 hours time point is a measure the extent of release. The following are the observations from the DOE software output:
(1) For both 1 hour and 8 hours, there is a strong positive interaction between the drug to EC ratio and the rate and extrent of drug release..
(2) HPMC 5 cps which is added as the pore former, does not show either positive or negative impact on drug release. However, for formulations having HPMC in higher concentrations, the drug release is more complete (at higher EC level) than formulations having low level of HPMC
(3) The design space for the Zolpidem Tartarate, EC and HPMC is defined as per Table .
(4) In order to confirm the design space, 3 formulations within the space were fabricated at a larger scale and evaluted for dissolution profile.
(5) These formulations were subjected to accelerated stability studies after filling into hard gelatin capsules shells.

V. Doe Charts:

The DOE charts were obtained by feeding the entrapment efficiency data in to the DOE Pro XL software and the design space values were calculated using residual analysis.Y-hat contour plots,Y-hat surface plots,Y- hat interaction plots were plotted for independent variables that is Zolpidem Tartarate,Ethyl cellulose and HPMC, . The charts reveal that there is strong positive interaction between Zolpidem Tartarate and EC and HPMC.

By considering the below observations an optimized formula was designed, formulated and evaluated. The Y-Contour plots specify the design space within which each formulation component can be varied without compromising on the entrapment efficiencies. The design space values are tabulated in Table.

TABLE-12: Design Space Range for entrappment efficiency > 77% for Zolpidem Tartarate

S.No	Indgredients (mg/unit)	Lower Limit	Higher Limit
1	ZOLPIDEM TARTARATE	50	70
2	Ethyl Cellulose 7cps	145	150
3	HPMC 6 cps	0.4	2.0

S.no	Formulation No.	Formulation Ingredients	Mg/unit
1	**Foptima 1**	**Zolpidem Tartarate**	**50**
		EC	**145**
		HPMC	**0.4**
2	**Foptima 2**	**Zolpidem Tartarate**	**60**
		EC	**147**
		HPMC	**1.0**
3	**Foptima 3**	**Zolpidem Tartarate**	**70**
		EC	**150**
		HPMC	**2**
4		**Tween 80 (ml)**	**100**
5		**IPA (ml)**	**500**
6		**DCM (ml)**	**500**
7		**Water (ml)**	**5000**

Based on the values given in the above table an F optimum formulation was fabricated and evaluated for entrapment efficiency.Formulation composition and
Entrapment efficiency achieved are given in **Table13-FORMULATION CHART**

TABLE 14: Composition and Entrapment efficiency of Optimised Formulation

CHARCTERISTICS	F OPTIMA-1	F OPTIMA-2	F-OPTIMA-3
YIELD(%w/w/	74.82	79.45	77.92
ASSAY(mg Zolpidem Tartarate/100mg)	25.357	24.734	28.799
ENTRAPMENT EFFICIENCY	87.39	88.58	78.00
AVG.PARTICLE SIZE DISTRIBUTION (D90 ,MICRONS)	355.86	344.25	278.98

Discussion: The process used for the initial batches, is reproducible and scalable. The results for yield assay, entrapment efficiency and particle size distribution are reproducible. This indicates that the selected solvent evaopration techinque is suitable for formulation of floating microcapsules

TIME	Foptima1	Foptima2	Foptima3
0	0	0	0
0.5	6.35	9.23	7.54
1	11.87	18.45	15.88
2	24.79	28.67	33.49
4	65.32	75.34	67.7
8	85.29	94.35	90.58

Table15 Dissolution Profile For Optimized Formulations

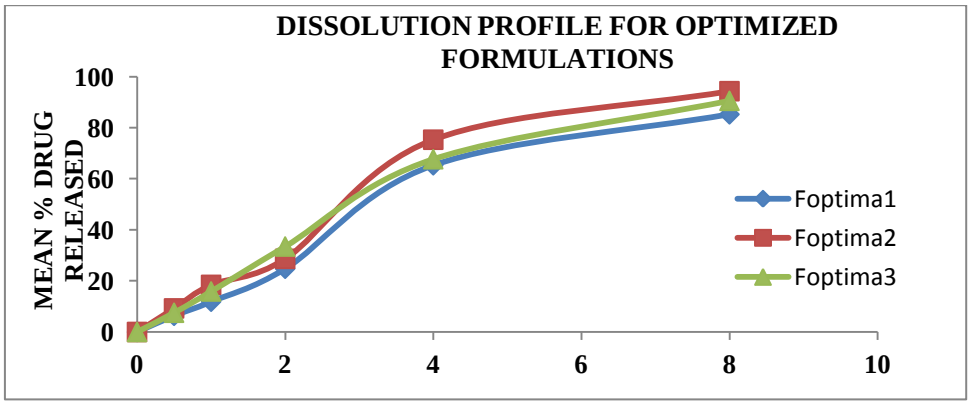


Figure10: Dissolution profile for optimized formulation of Zolpidem Tartarate microcapsules

VI. Discussion

The dissolution profile for all three formulations fabricated within the design space are showing Matching values. This indicates that any formulation fabricated within the design space will give a product having dissolution profile in a very narrow range of acceptability.

Formulation	R^2				Peppas N
	Zero	First	Higuchi	Peppas	
F-optima1	0.9377	0.9843	0.9195	0.9797	0.996
F-optima2	0.9241	0.9846	0.9281	0.9746	0.874
F-optima3	0.9420	0.9946	0.9491	0.9803	0.927

Table 16: Release rate of Zolpidem Tartarate from optimized formulations

In order to understand the mechanism of drug release from the microcapsules, the in vitro drug release data of the optimized formulations were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874, 0.996 and 0.927. Based on these values we can say that formulations exhibited super case II transport

All the optimized formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from microcapsules were by both diffusion and erosion.

VII. Accelerated Stability Studies For Zolpidem Tartarate Floating Microcapsules:

Three batches of optimized formulations were fabricated as per the table below:

S.no	Formulation No.	Formula Ingredients	Mg/unit	g/500 units
1	Foptima 1	Zolpidem Tartarate	50	25
		EC	145	72.5
		HPMC	0.2	0.1
2	Foptima 2	Zolpidem Tartarate	60	30
		EC	147	73.5
		HPMC	1.0	0.5
3	Foptima 3	Zolpidem Tartarate	70	35
		EC	150	75
		HPMC	2	1.0
		Tween 80 (ml)		100
		IPA (ml)		500
		DCM (ml)		500
		Water (ml)		5000

TABLE-17:Formulation chart of F optima 1,2,3

The batches were fabricated by the process described in Materials and Methods. The process was reproducible at this scale.

These batches were evaluated for assay, % entrapment efficiency , flow properties and in vitro dissolution profile in 0.1N HCl. The results of the physical properties, assay an d% entrapment efficiency are given in Table. The invitro dissolution profile for these 3 batches is given in Table.

The microcapsules were filled in size '1' hard gelatin capsules shells, packed in 90 cc HDPE container and subjected to accelerated stability studies at 40◦C/75% RH stability conditions. Samples were withdrawn at 1M, 2M and 3M intervals and evaluated for assay and in vitro dissolution testing. The results are given in Table-26

Tests	Specifications	F optima1			F optima2			Foptima3		
		1M	2M	3M	1M	2M	3M	1M	2M	3M
Description	White to off white microcapsules filled in transperant size '1' capsules shells	Complies	Comp Lies	Complies	Complies	Comp Lies	Comp lies	Complies	Comp Lies	Comp Lies
Assay (mg/100mg)	between 20 to 35 mg/100 mg	25.40	24.98	25.00	24.77	24.89	24.64	28.79	27.68	27.54
Targeted Dissolution profile										
0	0	0	0	0	0	0	0	0	0	0
0.5	NMT 10%	6.00	5.99	6.28	8,76	8.57	8.01	7.54	7.00	7.04
1.0	10 – 20%	10.97	10.00	11.43	15,88	13.09	15.54	17.28	16.43	15.98
2.0	15 – 40%	24.78	23.51	27.84	25.32	27.12	28.25	34.08	32.15	35.04
4.0	55 – 75%	63,37	60.43	65.33	70.66	73.07	71.17	72.91	70.69	71.45
8.0	NLT80% (Q)	87.98	87.09	88.96	90.42	93.22	95,24	92.83	89.09	93.65

Table-18: Stability Studies Of F Optima 1,2,3

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9 .Summary & Conclusion: In order to understand the mechanism of drug release from the microcapsules, the *in vitro* drug release data of the optimized formulations were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874, 0.996 and 0.927. Based on these values we can say that formulations exhibited super case II transport.All the optimized formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from microcapsules were by both diffusion and erosion.

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