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FORMULATION, OPTIMIZATION, AND EVALUATION OF ASENAPINE MICROSPHERES USING SOLVENT EVAPORATION

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Abstract

The objective of the present study was formulation and evaluation of Asenapine microspheres by using solvent evaporation technique. Asenapine is loaded with ethyl cellulose & HPMC 15 microspheres and it was prepared by solvent evaporation method. Asenapine used in the treatment of psychotric patients. The results of FTIR indicated the stable character of Asenapine microspheres loaded with ethyl cellulose, HPMC K15M there is no incompatability between drug & polymers. The Morphological characters of Asenapine microspheres is carried out by SEM. From the results it seem that formulation AM 8 was found to be the excellent Morphological properties, % yield of microsphere of best formulation was found to be AM 8 (86.92%), Entrapment efficiency of best formulation was found to be (75.6 %) , Drug loading efficiency of best formulation was found to be (88.1 %), Swelling index best formulation was found to be (1.3 sec), Particle size of best formulation was found to be (102 µm), Drug content determination of best formulation was found to be (97.4) and *in vitro* drug release was fitted with various Release kinetic studies of a sustained manner with constant fashion over extended period of time for 45 Mints. It was observed that concentration of Ethyl cellulose affected all the evaluation parameter significantly. Hence the prepared microspheres of Asenapine may prove to be potential candidate for safe and effective sustained drug delivery.

Keywords: *Asenapine, Microspheres, Invitro dissolution studies, swelling index.*

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INTRODUCTION

The term "microsphere" refers to spherical particles with dimensions ranging from 1 µm to 1000 µm that include a core component. The synthetic polymer-containing microspheres have distinctive powders that flow freely. They have a particle size of less than 200 micrometers and are biodegradable. Due to their incapacity to limit and localize the system to the gastrointestinal tract, the majority of medications administered orally have conventional dosage formulations that have short-term limits. It is a beneficial procedure that allows the drug delivery system to come into close contact with the absorbing membrane 2. It can be accomplished by creating bioadhesive microspheres by combining the bioadhesion properties with microspheres [1]. These microspheres have a number of benefits, including improved medication bioavailability and efficient absorption because to their high surface to volume ratio, considerably closer interaction with the mucous layer, and precise drug targeting to the absorption site. For oral controlled or sustained release

drug administration systems, the relativity will be brief to overcome the GI time and enhance localization. Oral medication delivery is greatly improved by the polymers that cling to the mucin epithelial surface. The technique of microencapsulation involves applying thin coatings on tiny solid particles or liquid and dispersion droplets [2]. The range of particle sizes spans few tenths of a micron to 5000 microns. The internal phase diffuses through the capsule wall, or the contents of the capsules are held within the wall until they are released to shatter, crush, melt, dissolve, rupture, or remove the shell. The first study focuses on the creation of pharmaceutical microencapsulation techniques. Microspheres are widely used in controlled drug delivery systems, both oral and parenteral. They needed a polymer that served as both a core material and a carrier. It is created for the formulation of microspheres among the many techniques. A non-ionic, inert, hydrophobic, non-biodegradable, biocompatible polymer with low toxicity is ethyl cellulose. It is one of the most researched techniques for encasing medicinal compounds for controlled release [3]. The polymer HPMC is swellable and non-ionic. In controlled drug delivery systems, hydrophilic polymer gel matrix technologies are frequently utilized. Because of their adaptability, it is employed to achieve both cost effectiveness and a desired medication release profile.

ADVANTAGES:

1. If the medicine is changed, it is a dependable way to deliver it to the target site with specificity and to keep the desired concentration at the location of interest without causing side effects.
2. The solid biodegradable microspheres may have an impact on the drug's regulated release across the particle matrix.
3. Microspheres have drawn a lot of attention for their ability to direct anticancer medications to the tumor in addition to providing sustained drug release.
4. It has been discovered that the size, surface charge, and surface hydrophilicity of microspheres play a significant role in dictating the fate of particles in vivo [4].

Disadvantages of microspheres:

1. A number of factors, including meals and the rate of transit through the stomach, affect the controlled release microspheres' release rate.
2. The release rate varies from one dose to the next.
3. Toxicity may result from the drug being lost from the controlled release microspheres.
4. Do not chew or crush the microspheres [5].

MATERIAL AND METHODS

Asenapine gifted from Hetero drug limited. Ethyl cellulose, HPLMCK15M, Ethanol was procurer from Rohm Gmbh & CoKG, Germany.

Methodology

Compatibility studies

IR studies : In the preparation of drug and polymer may interact with each other, It leads to the instability of drug preformulation studies regarding the drug and polymer interaction.They are very critical in appropriate polymer. FTIR Spectroscopy was employed to ascertain the compatibility between Asenapine, ethyl cellulose and HPMC K15M polymer [6].

Morphology Of The Particles:

Scanning Electron Microscopy: Scanning Electron Microscopy is a technique. It is very useful in a scetaing the overall shape and morphology of the Microspheres. The morphology and surface appearance of both coated microspheres and Ethyl cellulose& HPMCK15M microspheres were found by Scanning Electron Microscopy [7]. The particles were freeze dried, and coated with gold palladium to achieve a film of 20nm thickness (Sputter coater, Balzers SCD 004,

Liechtenstein) and observed microscopically (SEM, JSM-6400, Tokyo, Japan).

Procedure of Asenapine Microspheres: The Asenapine microspheres were obtained by the solvent Evaporation method by using distilled water as an external phase. The internal phase consists of a good solvent ethanol including Asenapine with concentration of polymers like HPMCK15M and Ethyl cellulose. The drug and polymers were co-dissolved in an organic solvent mixture with polymers with different ratio. The drug solution was slowly injected via syringe in to the external water phase under agitating. The system was stirred at 800 rpm continuously for about one hour. The droplets gradually solidified & formed microspheres. The system was filtered to separate the microspheres from the preparation system. The resultant product was washed with distilled water and dried [8]. The whole process was carried out at room temperature. The ratio of drug and polymers were showed in table 01.

TABLE 01: FORMULATIONS OFASENAPINE MICROSPHERES

Sl.No	Ingredients	AM1	AM 2	AM 3	AM 4	AM 5	AM6	AM 7	AM 8
1	Asenapine (gms)	1.0	1.4	0.6	1.8	2.1	2.4	2.8	2.6
2	Ethyl Cellulose (gms)	1.0	1.4	1.1	1.6	2.0	2.4	2.1	2.2
3	HPMC K15 M (gms)	0.5	0.6	0.5	0.9	1.4	1.1	0.6	1.0
4	Ethanol	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
5	Distilled water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

EVALUATION OF MICROSPHERES

Percentage production yield (PY)

$$PY\ (\%) = \frac{\text{Practical mass of microspheres}}{\text{Theoretical mass}} \times 100$$

Each formulation was carried out in triplicate and the PY (%) was calculated [9].

Entrapment efficiency: The Microspheres was prepared by Solvent Evaporation technique. It was centrifuged at 14,000 rpm for 40 min at 10°C. The amount of Asenapine is encapsulated into the Ethyl cellulose and HPMCK15M. It was the difference between the total amounts that are used to prepare the Microspheres and the amount was found in the supernatant [10]. The amount of free Asenapine in the supernatant was analyzed by UV-spectrophotometer at 260 nm. It is calculated by the following equation

$$\%EE = \left(\frac{M_{\text{Initial drug}} - M_{\text{Free drug}}}{M_{\text{Initial drug}}} \right) X100$$

Where

"$M_{\text{Initial drug}}$" is the mass of initial drug used for the assay

"$M_{\text{Free drug}}$" is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

Drug loading efficiency: Drug loading efficiency was removed and the remaining sediments (precipitations) were washed by distilled water. It is dispersed in a mixture of chloroform: acetone (2.5:2.5, v/v) in a 10 ml volumetric flask. It is used to ensure the complete extraction of drug from Microspheres, then it was sonicated for 30 min.The volume was made-up to 10 ml with chloroform [11]. The resulting solution was centrifuged at 14,000 rpm at 10°C for 30 min and supernatants were obtained and analyzed in triplicate for the loaded drug by UV spectrophotometer at 260 nm.

Particle size determination: The Particle size of Microspheres was determined by using an optical microscopy method. Approximately 100 microspheres

were counted for particle size. The distribution of particle size was measured by suspending in water [12].

Equilibrium swelling studies of microspheres: A preweighed amount of microspheres was placed in Phosphate buffer (pH7.4). It is allowed to swell at a constant weight. The microspheres were removed and blotted with filter paper, and their changes in weight were measured. The degree of swelling (a) was calculated by the following formula [13].

$$\alpha = wg - wo / wo$$

Where

Wo is the initial weight of the microspheres and

Wg is the weight of the microspheres at equilibrium swelling in the medium.

Drug content determination: 50mg of Asenapine microspheres was crushed and suspended in water to extract the drug from the microspheres. After 24 h, the filtrate was assayed spectrophotometrically at 260 nm for drug content against water as blank [14].

***In-vitro* drug release studies:** *In-vitro* drug release studies were carried out by using USP XXIV dissolution apparatus type II, with 500 ml of dissolution medium.It is maintained at 37±0.5 °C for 45 Mits, at 50 rpm, and pH 7.4 ± 0.2 phosphate buffer as dissolution medium. Results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi model)
3. Cumulative percent drug remaining versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyer's peppas model)

DATA ANALYSIS: To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained and it was fitted in to Zero order, First order, Higuchi matrix and Korsmeyer and Peppas model. Comparing the r-values are obtained, the best-fit model was selected [15-20].

Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that does not disaggregate and the drug will be released slowly, assuming that the area does not change and no equilibrium conditions are obtained. It can be represented by the following equation

$$Q_t = Q_o + K_o t$$

Where

Q_t = amount of drug dissolved in time t,

Q_o = initial amount of drug in the solution

K_o = zero order release constant.

First order kinetics: To study the first order release rate kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + K_1 t / 2.303$$

Where

Q_t is the amount of drug released in time t,

Q_o is the initial amount of drug in the solution,

K_1 is the first order release constant.

Higuchi model: This model is developed by several theoretical models. To study the release of water-soluble and low soluble drugs. They are incorporated in to semisolids and or solid matrices, the equation is

$$Q_t = K_H \cdot t^{1/2}$$

Where

Q_t= Amount of drug released in time t,

K_H = Higuchi dissolution constant.

Korsmeyer and Peppas release model:

To study this model the release rate data are fitted to the following equation

$$M_t / M_\infty = K.t^n$$

Where

M_t / M_∞ is the fraction of drug release,

K is the release constant, t is the release time

n is the Diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

RESULTS AND DISCUSSION

Compatability studies

IR studies

The IR spectrum of the pure Asenapine sample is recorded by FTIR. This is compared with standard functional group frequencies of Asenapine as shown in Table 03. The FTIR spectrum of formulation shown in Figure 02.

COMPARISON OF FT-IR SPECTRA OF ASENAPINE AND POLYMERS

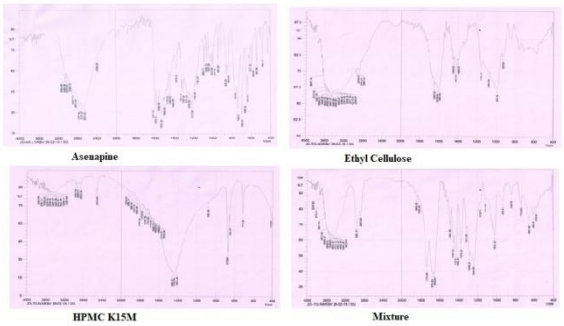


Figure 02: FT-IR Spectra of Asenapine pure drug

Table 03: FT-IR Interpretation data for Drug and Mixture

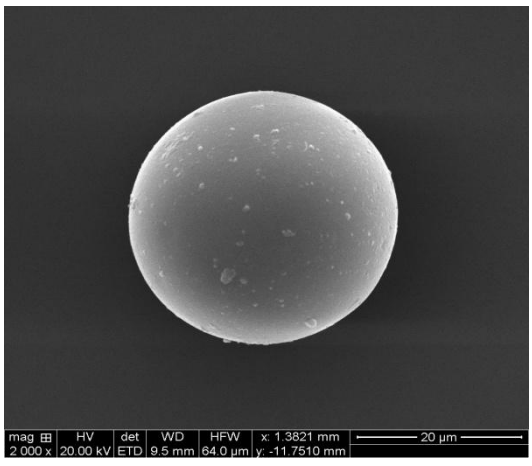
IR absorption bands (cm-1)		Functional group
Observed peak	Characteristic peak	
ASENAPINE		
3064,	3300-2500,	C-H stretch
1533	1550-1475	N-O asymmetric stretch
1307	1335-1250	C-N stretch
1245	1300-1000	C-O stretch
997,941	1000-650	C-H bend
858,761	850-550	C-CL bend
ETHYL CELLULOSE		
3612	3640-3610	O-H stretch
2970,2941	3000-2850	C-H stretch
1596	1650-1580	N-H bend
991	1000-650	C-H bend
929	950-910	O-H bend
HPMCK15M		
3481,3641,3444	3500-3200	O-H stretch
2925	3000-2850	C-H stretch
1747	1760-1690	C=O stretch
1081	1320-1000	C-N stretch
873,856	1000-650	C-H bend
MIXTURE		
3612,3483,346o	3500-3200	O-H stretch
1733	1760-1665	C=O stretch
1670	1680-1640	C=C stretch
844,734	850-550	C-CL stretch

MORPHOLOGY OF THE PARTICLES:

The following methods are used to determine the particle size, size distribution, and morphology of Asenapine microspheres.

Scanning Electron Microscopy: Morphology and structure of Microspheres were determined by using scanning electron microscopy and photomicrographs were taken at suitable magnifications. The photographs of the optimized formulation are taken by Scanning electron microscopy are shown in the Figure 04.

SHAPE AND SURFACE MORPHOLOGY



Figures 04: SEM Samples of Best formulations

EVALUATION OF ASENAPINE MICROSPHERES

Percentage Yield: The production yield of microspheres of Asenapine using HPMCK15M & Ethyl cellulose results as shown in Table 05

Encapsulation efficiency

Drug entrapment efficiency (%EE): Percentage entrapment efficiency of AM1 – 90.6%, AM2 – 68.0%, AM3 – 86.5%, AM4 – 65.8%, AM5 – 74.2%, AM6 – 61.3%, AM7 – 87.9%, AM8 – 75.6%.The AM 8 shows the good formulation & high efficiency. Results as shown in Table 05

Entrapment Loading (%EL)

Percentage entrapment loading of AM1 – 87.3%, AM2 – 78.5%, AM3 – 80.6%, AM4 – 52.4%, AM5 – 61.1%, AM6 – 79.2%, AM7 – 85.3%, AM8 – 88.1%.The AM 8 shows the good formulation & high efficiency. Results as shown in Table 05.

Particle size

The Particle size distribution of Microspheres represented by

M1 (248 µm), AM2 (152 µm), AM3 (182 µm), AM4 (147 µm), AM5 (346 µm), AM6 (205 µm), AM7 (298 µm), and AM8 (102 µm). values as shown in given Table 05.

Equilibrium swelling studies of microspheres.

A preweighed amount (100 a constant weight. The microspheres were removed and blotted with filter paper, and their mg) of microspheres was placed in Phosphate buffer (pH7.4) and allowed to swell to changes in weight were measured results as shown in Table 05.

Percentage drug content Determination:

Drug content distribution of Microspheres represented it indicated that drug content isAM1 (66.2%), AM2 (70.1%), AM3 (89.6%), AM4 (90.2%), AM5 (74.6%), AM6 (84.5%), AM7 (87.9%), and AM8 (97.4%), as shown in given Table 05.

Table 05: Characterization of Asenapine microspheres

Formu lation code	% yield (%)	Drug Content	Entrapment Efficiency (%)	Drug Loading capacity (%)	Particle sie(µm)	Swellability Studies (Sec)
AM1	74.12	66.2	90.6	87.3	248	0.7 Sec
AM 2	84.76	70.1	68.0	78.5	152	0.6 Sec
AM 3	54.05	89.6	86.5	80.6	182	0.5 Sec
AM 4	69.48	90.2	65.8	52.4	147	0.7 Sec
AM 5	79.36	74.6	74.2	61.1	346	0.8 Sec
AM 6	82.03	84.5	6.13	79.2	205	0.6 Sec
AM 7	79.68	87.9	87.9	85.3	298	0.7 Sec
AM 8	86.92	97.4	75.6	88.1	102	1.3 Sec

***In vitro* dissolution Studies:**

For understanding the mechanism of drug release rate kinetics of the drug from dosage forms, the *invitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Korsmeyer Peppas model. The values are complied in Table 6 & Figure 7. The % drug release with data to various kinetic models for different microspheres formulations is presented in figure 8 to 11 Figure 12 & 13.

Table 06: In *Vitro* dissolution Studies of Asenapine Microspheres

Sl.no	Time	% of Drug release							
		AM1	AM2	AM3	AM4	AM5	AM6	AM7	AM8
1	5	6.72	3.18	9.12	7.85	10.74	6.28	5.34	10.34
2	10	10.84	7.12	19.48	12.58	29.10	11.16	14.34	20.42
3	15	21.30	10.68	31.82	24.90	39.68	23.40	33.24	38.36
4	20	43.92	21.80	44.98	39.70	43.52	34.20	36.34	48.14
5	2	51.	35.	59.6	43.	57.4	46.6	45.	50.

	5	90	70	8	48	2	2	24	27
6	30	65.78	47.40	61.24	55.70	67.42	58.98	60.23	69.14
7	35	77.42	55.10	75.12	69.02	79.80	61.30	72.23	75.26
8	40	81.26	62.82	81.36	75.28	83.02	71.46	74.24	83.12
9	45	89.02	70.60	90.48	88.20	89.64	86.92	89.34	92.12

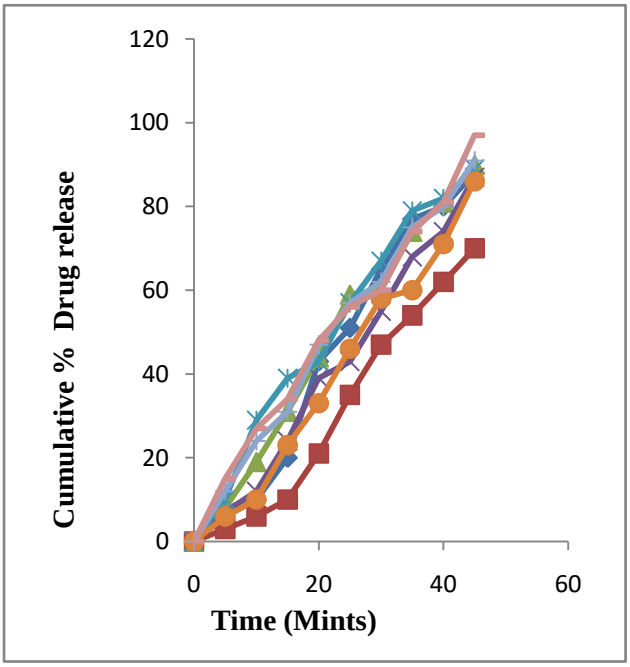


Figure 07: *In vitro* dissolution studies of Asenapine microspheres

RELEASE ORDER KINETICS OF ASENAPINE MICROSPHERES:

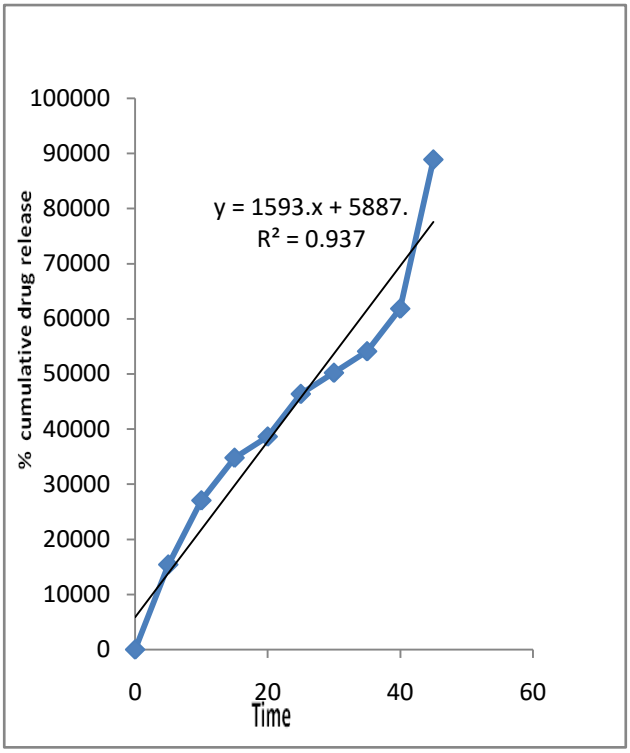


Figure 08: ZM 8 of *In vitro* dissolution studies of zero order kinetics

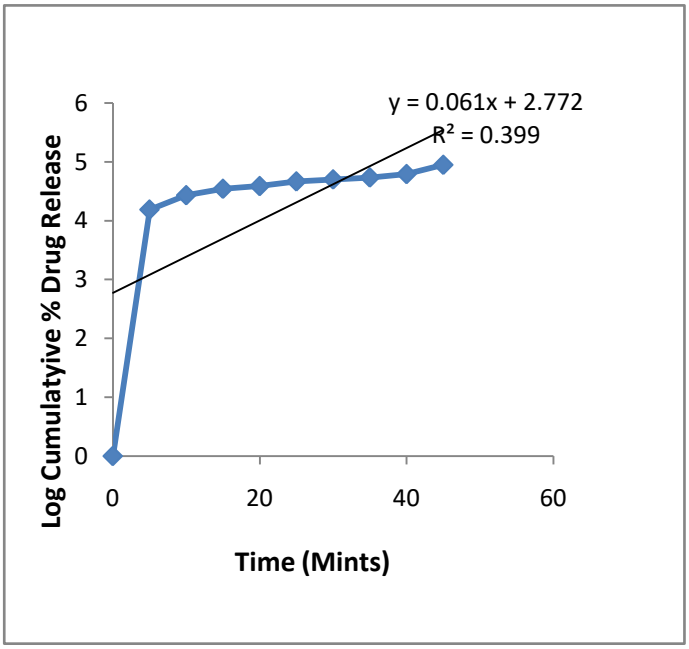


Figure 09: AM 8 of *In vitro* dissolution studies of first order kinetics

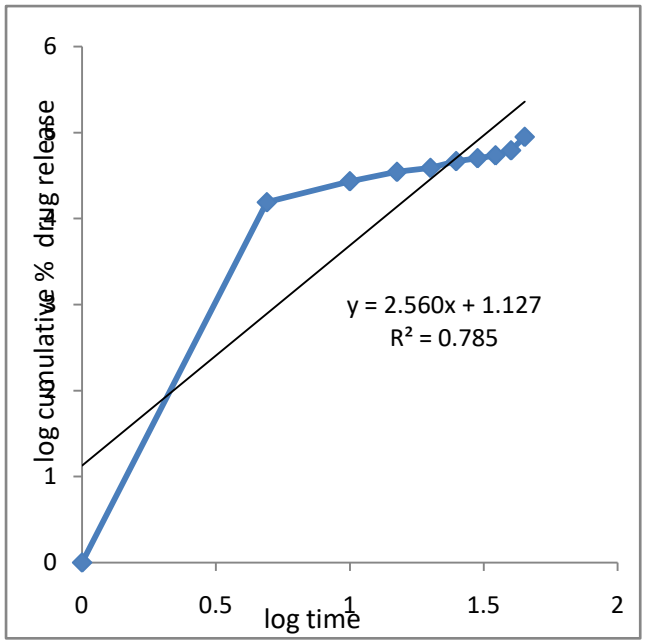


Figure 10: AM 8 of *In vitro* dissolution studies of korsmeyer peppas

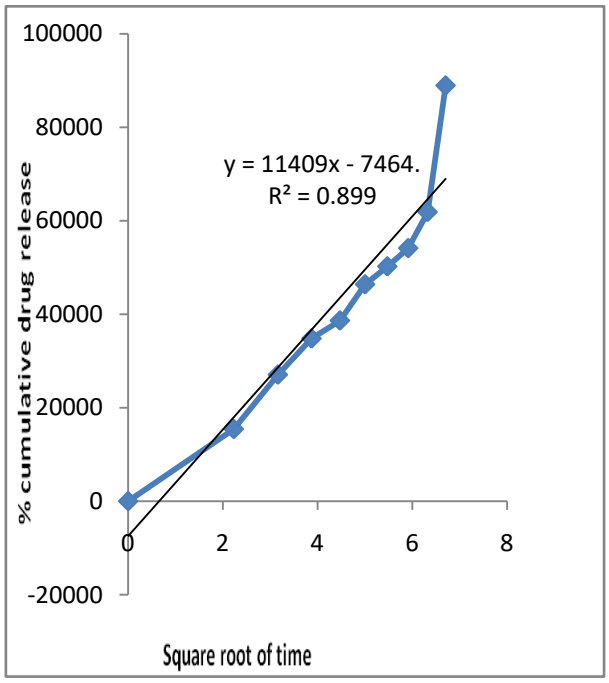


Figure 11: AM 8 of *In vitro* dissolution studies of Higuchi

Table 12: Release kinetics of Asenapine Microspheres of all formulation AM1 to AM5

Model	AM1		AM 2		AM 3		AM 4		AM 5	
	R^2	m	R^2	m	R^2	M	R^2	M	R^2	M
Zero order	0.655	69.4	0.939	1123	0.007	15.93	0.202	72.88	0.928	1414
First order	0.494	0.061	0.540	0.067	0.257	0.038	0.352	0.044	0.438	0.062
Higuchi's Matrix	0.516	4508	0.767	7420	0.023	212.0	0.189	515.5	0.803	9618

Korsmeyer-Peppar	0.835	2.354	0.884	2.545	0.572	1.709	0.663	1.813	0.806	2.517

Table 13: Release kinetics of Asenapine Microspheres of formulation AM6 - AM8

Model	AM1		AM 2		AM 3		AM 4		AM 5	
	R2	m	R2	m	R2	M	R2	M	R2	M
Zero order	0.655	69.4	0.939	1123	0.007	15.93	0.202	72.88	0.928	1414
First order	0.494	0.061	0.540	0.067	0.257	0.038	0.352	0.044	0.438	0.062
Higuchi's Matrix	0.516	4508	0.767	7420	0.023	212.0	0.189	515.5	0.803	9618
Korsmeyer-Peppar	0.835	2.354	0.884	2.545	0.572	1.709	0.663	1.813	0.806	2.517

CONCLUSION

The purpose of present work was to develop microspheres of Asenapine for sustained drug delivery system. From the results it seem that formulation AM 8 was found to be the excellent Morphological properties, % yield of microsphere of best formulation was found to be AM 8 (86.92%), Entrapment efficiency of best formulation was found to be (75.6 %) , Drug loading efficiency of best formulation was found to be (88.1 %), Swelling index best formulation was found to be (1.3 sec), Particle size of best formulation was found to be (102 µm), Drug content determination of best formulation was found to be (97.4) and *in vitro* drug release was fitted with various Release kinetic studies of a sustained manner with constant fashion over extended period of time for 45 Mints. It was observed that concentration of Ethyl cellulose affected all the evaluation parameter significantly. Hence the prepared microspheres of Asenapine may prove to be potential candidate for safe and effective sustained drug delivery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Not Applicable.

ETHICAL STATEMENT

No human or animal studies were performed.

AUTHOR CONTRIBUTION

Both Authors contributed equally.

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