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Research Article

Formulation and Evaluation of Capsules of Asenapine Maleate Loaded Chitosan Nanoparticles

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Abstract

Asenapine Maleate is an antipsychotic drug which has poor bioavailability due to its insolubility in water and belongs to biopharmaceutics Classification-IV. The aim of this study is to enhance the bioavailability of Asenapine Maleate by the preparation of Nanoparticles using ionic gelation method. In present work different formulations were prepared by using different ratios of polymer, Tween 80 (stabilizer) and sodium tri polyphosphate (cross linking agent). Prepared Nanoparticle was evaluated for its Particle Size, zeta potential, scanning electron microscopy, Percentage practical yield, Drug Entrapment Efficiency, and *in-vitro* drug release studies. NPs formulation was subsequently loaded into hard gelatin capsules that were evaluated for preformulation studies, *in-vitro* dissolution and pharmacokinetic behavior. The optimized CSNPs was found with particle size of 41.1 nm, zeta potential -9.9 Mv, percentage practical yield was 97.5%. Entrapment efficiency (%EE) of 65.7%, scanning electron microscopy irregular shape. The *in-vitro* release profile was found to be 92.5% sustained up to 510 minutes. Thus, incorporation of Asenapine maleate into CSNPs results in enhanced bioavailability when compared to pure drug.

Keywords: Asenapine Maleate; Schizophrenia; Ionic Gelation; Nanoparticle; *In Vitro* Drug Release

Abbreviations

Cs: Chitosan; Stpp: Sodium Tri Polyphosphate; NP: Nanoparticles; LBD: Loose Bulk Density; TBD: Tapped Bulk Density; CsNP: Chitosan Nanoparticles

Introduction

Chitosan is a natural polymer has mucoadhesive properties because of its positive charges at neutral Ph, which enable an ionic interaction with the negative charges of sialic acid residues on the mucus [1]. Mucoadhesive polymer and can increase the residence time at the site of absorption and has favorable controlled drug-release abilities [2].

Chitosan nanoparticles are a drug carrier with wide development potential and have the advantage of slow/controlled drug release, which improves drug solubility and stability, enhances efficacy, and reduces toxicity. Because of their small size, they are capable of passing through biological barriers *in-vivo* (such as the blood-brain barrier) and delivering drugs to the lesion site to enhance efficacy. modified nanoparticles also have other properties such as improved drug targeting. Under the action of enzymes *in vivo*, biodegradable nanoparticles can produce water and carbon dioxide without adverse effects and have thus become the focus of increasing research [3].

Schizophrenia is serious mental disorder which is characterized by psychotic symptoms such as hallucinations and delusions, disorganized thought and behavior, and impairments in cognitive functions such as attention, learning, memory and executive functioning. Arpi Minassian., *et al.* [4] worldwide, schizophrenia affects approximately 0.5% to 1.5% of the population, and the annual incidence rate averages between 0.5 and 5.0 per 10,000 people. The most typical age for the onset of schizophrenia is the late teens and early 20s; however, cases of onset at age 5 or 6 have also been reported. There is no gender difference in this disorder and both men and women with the disorder are equally affected; however, individuals with an early age of onset (18 - 25 years old), are most often men who have more signs of structural brain abnormalities and more prominent negative symptoms [5]. with high risk of suicidality with frequently reported model rate of suicide rate being approximately 10%.

Among many antipsychotics available, no single medication is effective for all patients with schizophrenia. Moreover, available treatment options have found to be ineffective in treating negative and cognitive symptoms of the disease. The Severity of this mental illness is needed to be considered and is of great importance because 20 - 45% of patients show unsatisfactory response to antipsychotic medications leading to increased patient noncompliance [6].

Asenapine maleate (ASPM), a novel antipsychotic agent marketed in the form of sublingual tablets, was recently being approved by us food and drug administration in august 2009 (Usfda., *et al.* 2009). ASPM belongs to di-benzooxe pino pyrrole class of atypical antipsychotics and is intended for treatment of schizophrenia and bipolar i disorder for acute manic or mixed episodes (Tga., *et al.* 2011). Asenapine (ASP) undergoes extensive first pass metabolism, with oral bioavailability only 2% but sublingually increase up to 35% and $t_{1/2}$ is 24 hours. Also, dose of ASP is just 5 to 10 mg and it has no odor. The molecular weight of ASP is just 285.76. Presently ASP is available only in the form of sublingual tablet in the market. But, sublingual administration has less amount of drug penetration through mucosa because of no mucoadhesive property and less residence time that show poor patient compliance. To overcome the drawback associated with extensive metabolism and hence, to increase the bioavailability of Asenapine maleate has chosen for nanoparticles [5].

Incorporation of drugs in nanoparticles is another approach that offers opportunities for the modulation of both solubility and permeability of the drug. Since the unique properties of these nanocarriers would be imparted to the entrapped drugs, these systems could be used to improve the oral bioavailability of class ii and iv drugs. The incorporation of the poorly soluble drugs into these Nano-sized particles means the reduction of drug particle size down to the submicron level which could significantly increase the solubility and dissolution rate and thus improve the oral bioavailability. In addition to the reduction in particle size, having the drug dispersed in the nanoparticles is another way of enhancing the effective surface area available for dissolution. Moreover, the dissolution properties of the polymers used to construct nanoparticles could govern the specific site of drug release and thus make it more available for absorption which in turn could increase the oral bioavailability (Alberto Berardi., *et al.* 2004).

Materials and Methods

Method: Ionic Gelation Method

Chitosan was dissolved in aqueous solution of acetic acid (3%) in 100 ml of distilled water. Under magnetic stirring at room temperature, tween 80 was add above solution and 10 ml of (w/v) S.TPP aqueous solution was added dropwise using syringe needle into 100 ml chitosan solution containing 20 mg of Asenapine maleate. The stirring was continued for about 2.30 hrs. The resultant nanoparticles suspensions were centrifuged at 12000 × g for 15 minutes using C24 centrifuge. Samples were washed with water and dried. The formation of the particles was a result of the interaction between the negative groups of the TPP and the positively charged amino groups of chitosan (ionic gelation) [7].

Preparation of Drug Loaded Nanoparticles

S. No	Formulation	Asenapine Maleate (mg)	Chitosan (mg)	Tween 80 (ml)	Acetic acid (%)	S.Tpp (%)	Methanol	Water (ml)
1	F1	20	100	0.1	3	6	q.s	100
2	F2	20	150	0.2	3	6	q.s	100
3	F3	20	200	0.3	3	6	q.s	100
4	F4	20	250	0.4	3	6	q.s	100
5	F5	20	300	0.5	3	6	q.s	100
6	F6	20	350	0.6	3	6	q.s	100
7	F7	20	400	0.7	3	6	q.s	100
8	F8	20	450	0.8	3	6	q.s	100
9	F9	20	500	0.9	3	6	q.s	100
10	F10	20	550	01	3	7	q.s	100
11	F11	20	600	02	3	8	q.s	100
12	F12	20	650	03	3	9	q.s	100

Table 1: Formulation of Asenapine maleate loaded chitosan nanoparticles.

Physico - Chemical Characterization of Nanoparticles

Solubility studies

Solubility of the drug is predicted by dissolving 100 mg of the drug in proportions of 1 ml, 10 ml, 20 ml, 30 ml and 100 ml of the proposed solvents like, ethanol, methanol, chloroform, water. So according to the dilution or dissolving property the solubility was predicted by measuring the absorbance by using UV spectrophotometric method [8].

Melting point

A capillary tube was taken, and it was filled with the drug was placed in a melting point viewer and degree at which the drug gets melted down was considered as the melting point of the drug [8].

Fourier transform infra-red spectroscopy (FT-IR) analysis

The FT-IR spectra of pure neomycin, chitosan and their mixture were recorded using Shimadzu IR spectrophotometer, Model 840, Japan, to check drug polymer interaction and stability of drug.

Standard curve of Asenapine maleate

100 mg of drug was dissolved in 100 ml of 7.4 phosphate buffer the concentration of the above solution was 1000 µg/ml and it is noted as stock 1. From the above stock solution 1.1 ml of the sample was taken and makeup to the 10 ml in the volumetric flask and the concentration of the above solution was found to be 100 µg/ml and it is noted as the stock 2. From the above stock solution 2.1 ml of the sample was taken and makeup to the 10 ml in the volumetric flask and the concentration of the above solution was found to be 10 µg/ml and it is noted as the stock 3 from this series of the sample was taken such a 2 ml, 4 ml, 6 ml, 8 ml,10 ml and make it up to the 10 ml and the concentration of the above sample was found to be 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml. And the absorbance of the samples was check through the UV-spectroscopy in triplicate [8].

Surface morphology study

Scanning electron microscopy (SEM) of drug loaded chitosan Nanoparticle was performed to examine the surface morphology. The nanoparticles were mounted on metal stubs and the stub was then coated with conductive gold with sputter coater attached to the instrument. The photographs were taken using a Jeol scanning electron microscope under magnification of 7500 - 20000 × [9].

Zeta potential

The Zeta-potential and particle size of drug loaded nanoparticles was measured by Zeta sizer (Malvern Zetasizer 3000HS, UK). To determine the zeta potential and particle size nanoparticles samples were diluted with water (0.1 ml) and placed in electrophoretic cell where an electrical field of 15.2 V/cm was applied. Each sample was analyzed in triplicate [10].

Evaluation of Nanoparticles

Percentage Practical yield

Dried nanoparticles were collected and weighed to determine practical yield (PY) from the following equation [11].

$$Percentage\ Practical\ yield\ (\%) = \frac{nanoparticle\ weight}{theoretical\ mass\ (polymer + drug + s.tpp)} \times 100$$

Drug entrapment efficiency

Drug entrapment efficiency was determined by centrifugation method. The nanoparticles suspension was centrifuged at 12000 rpm for 15 minutes at 25˚C to separate the free drug in the supernatant. Concentration of Asenapine maleate in the supernatant was determined by using UV-visible spectrophotometer at 262 nm after suitable dilution. The drug entrapment efficiency (% EE) was determined using the relationship in equation [12].

$$EE\ (\%) = \frac{experimental\ drug\ content}{theoretical\ drug\ content} \times 100$$

Evaluation of *In-vitro* drug release

In-vitro dissolution study on drug loaded nanoparticles and pure Asenapine maleate (10 mg) were carried out using dissolution test apparatus in pH 7.4 buffer solution at 37 ± 0.5°C with 75 rpm rotating speed. Samples of 5 ml were withdrawn at regular time interval of 30 minutes, 1, 1.30, 2, 2.30, 3, 3.30, 4, 4.30, 5, 5.30, 6, 6.30, 7, 7.30, 8, 8.30 hrs. An equal volume of respective dissolution medium was added to maintain the sink condition. Drug content from sample was analyzed using UV-spectrophotometer (Shimadzu UV-1700) at 262 nm. All measurements were done in triplicate from three independent samples [13].

Characterization of Optimized Nanoparticles

Angle of repose

The angle of repose of solid nanoparticle was determined by funnel method. Accurately weighed sample was taken in a funnel. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of Solid powder. The powders were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured, and angle of repose calculated using the following equation [14].

$$Angle\ of\ respose\ (\theta) = Tan^{-1}\frac{h}{r}$$

Bulk density and tapped density

Both loose bulk density and tapped bulk density were determined. A quantity of 1.48g of Solid nanoparticle was introduced into a 10 ml measuring cylinder. Initial volume was observed, and the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula [14].

$$Bulk\ density = \frac{Weight\ of\ dry\ powder\ (g)}{Bulk\ volume\ (cc)}$$

$$Tapped\ density = \frac{Weight\ of\ dry\ powder\ (g)}{Tapped\ volume\ (cc)}$$

Hausner Ratio

A similar index like compressibility index has been defined by Hausner. It can be calculated by formula [14].

$$Hausner\ ratio = \frac{Tapped\ density}{Bluk\ density}$$

Filling of Asenapine maleate nanoparticle in capsule

Hard gelatine capsules size 4 filled with either the optimized Asenapine maleate NPs were prepared. The dried NPs was mixed with 2% magnesium stearate and 2% talc in a clean jar. Proper mixing was achieved by following the geometric dilution method. The NPs, was tumbled after each addition of the diluents. Finally, the capsules were filled manually, in which 10 mg of Asenapine maleate was loaded into each unit [15].

Evaluations of optimized nanoparticles loaded Capsules

Weight variation

10 capsules are weighed individually. Average weight is calculated. The individual weights are compared with the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation in shows in below table and none deviates by more than 7% [16].

$$weight\ variation = \frac{Average\ weight - intial\ weight}{Average\ weight} \times 100$$

Disintegration

One Capsule is placed in each tube which are then suspended in the beakers to move up and down for 15 minutes by using timer and capsules pass the test if no residue of drug or fragments remain on No. 10 mesh screen of tubes [17].

In-Vitro Drug Release for The Prepared Capsule

In-vitro dissolution study on solid nanoparticles (equivalent to 10 mg) filled in capsules and plain Asenapine maleate (10 mg) were carried out using dissolution test apparatus in pH 7.4 buffer solution at 37 ± 0.5°C with 75 rpm rotating speed. Samples of 5 ml were withdrawn at regular time interval of 30 minutes, 1, 1.30, 2, 2.30, 3, 3.30, 4, 4.30, 5, 5.30, 6, 6.30, 7, 7.30, 8, 8.30 hrs.

An equal volume of respective dissolution medium was added to maintain the sink condition. Drug content from sample was analyzed using UV-spectrophotometer (Shimadzu UV-1700) at 262 nm. All measurements were done in triplicate from three independent samples [13].

Kinetics Studies

(Theoretical calculation from % Cumulative drug release): To study the release kinetics, data obtained from *in-vitro* release were plotted in various kinetic models.

Zero order equation

The graph was plotted as % drug released versus time in days. C = Ko t Where, K0= Zero order rate constant in concentration/time; T= Time in days. The graph would yield a straight line with a slope equal to K0 and intercept the origin of the axis.

First order equation

The graph was plotted as log cumulative % drug remaining versus time in days.

Log C= log C0-Kt/2.303. Where, C0= Initial concentration of drug; K= First order constant; t= Time.

Higuchi kinetics

The graph was plotted as cumulative % drug released versus square root of time. Q = Kt½. Where, K= Constant reflecting design variable of system; t= Time in days Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release.

Hixson Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson Crowell rate equation. The graph was plotted by cube root of % drug remaining versus time in days. QO 1/3 - Qt 1/3 = KHC x t, Where, Qt= Amount of drug released in time t; QO= Initial amount of drug; KHC= Rate constant for Hixson Crowell equation.

Korsmeyer- Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released versus time. Mt /Mα= Ktn and log Mt /Mα= log K + n log t. Where Mt / Mα= fraction of drug released at time t; T= release time; K= Kinetic constant (incorporating structural and geometric characteristics of preparation); n= diffusional exponent indicative of the mechanism drug release. If n value is 0.5 or less, the release mechanism follows "Fickian diffusion" and higher values of $0.5 < n < 1$ for mass transfer follow a non- fickian model (anomalous transport). The drug release follows zero-order drug release and case II transport if the n value is 1. For the values of n higher than 1, the mechanism of drug release is regarded as super case II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known, or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative percentage of drug released versus log time [18].

Results and Discussion

Melting Point

A capillary tube was taken, and it was filled with the drug was placed in a melting point viewer and degree at which the drug gets melted down was considered as the melting point of the drug.

Solubility Study

Solubility of Asenapine maleate in different solvent was done, insoluble in water and freely soluble in methanol. 100 mg of drug was dissolved in 10 ml of methanol.

Standard Curve of Asenapine Maleate

S. No	Concentrations (µg/ml)	Absorbance (n = 3)
1	2	0.112667 ± 0.012897
2	4	0.248667 ± 0.006110
3	6	0.396667 ± 0.010214
4	8	0.5165032± 0.00347
5	10	0.686333 ± 0.013204

Table 2: Standard curve of Asenapine maleate.

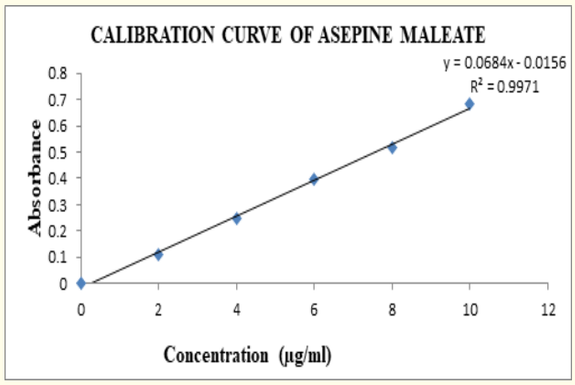

Figure 1: Standard Calibration curve of Asenapine maleate.

The calibration curve of asenapine maleate was performed in 7.4 Phosphate buffer and it showed regression value of 0.998.

Compatibility studies by FTIR

FTIR spectra of the Asenapine maleate, chitosan and physical mixture performed using FTIR spectrometer are as follows.

Figure 2: FTIR Spectrum of Asenapine maleate.

Figure 3: FTIR spectrum chitosan.

Figure 4: FTIR spectrum of Asenapine maleate and chitosan.

S. No	Observed range cm^{-1}			Characteristic peak	Functional group
	Asenapine malate	Chitosan	Physical mixture		
1.	3182	3073	3196	3000-3700	OH
2.	1699	1649	1651	1600-1700	C-C
3.	1349	1323	1348	1300-1500	C-H
4	1039	1076	1088	1000-1400	CF
5	798	875	769	700-900	N-H

Table 3: Drug - excipients interaction studies by FTIR.

From the peak analysis of Asenapine maleate and chitosan mixture, it was clearly identified that all the characteristic functional groups of Asenapine maleate and mixture being concluded that there was no incompatibility of Asenapine maleate with the polymer chitosan.

Particle size

Figure 5: Particle size of drug loaded nanoparticles.

Figure 6: Particle size of blank nanoparticles.

Zeta potential

Figure 7: Zeta potential of drug loaded nanoparticles.

Figure 8: Zeta potential of blank nanoparticles.

Scanning electron microscope

The prepared nanoparticles surface morphology was performed by using Scanning Electron Microscopy (SEM). The SEM images of the blank chitosan and drug loaded nanoparticles are shown in figure 9 and 10.

From the results, it was observed that the particle size of drug changes by ionic gelation technique. This may be due to face specific adsorption of stabilizing agent alters the growth rate of the crystal faces where adsorption takes place and thus changes the morphology of the nanoparticles. Where morphology of analyzed nanoparticles are flat and irregular and smooth clusters in appearance.

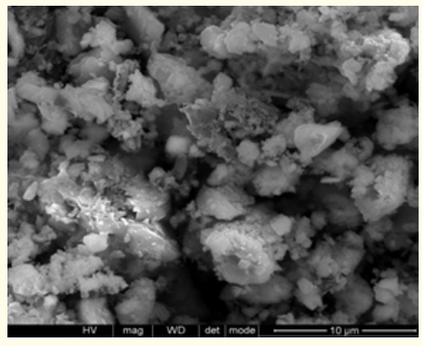

Figure 9: SEM images of drug loaded nanoparticles.

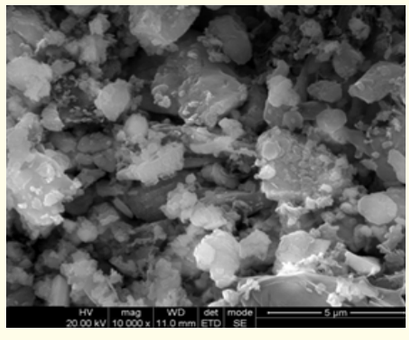

Figure 10: SEM images of blank nanoparticles.

Percentage yield

S. No	Formulations	Percentage yield
1	F1	80.6 ± 0.012%
2	F2	84.7 ± 0.023%
3	F3	97.50 ± 0.611%
4	F4	80.12 ± 0.021%
5	F5	82.36 ± 0.021%
6	F6	85.36 ± 0.062%
7	F7	88.18 ± 0.058%
8	F8	89.24 ± 0.054%
9	F9	90.51 ± 0.0123%
10	F10	92.45 ± 0.032%
11	F11	94.10 ± 0.014%
12	F12	95.98 ± 0.019%

Table 4: Percentage yield of various formulations.

When different formulations were prepared with a varying ratio of drug, polymer, cross linking agent and stabilizing agent, there was no much difference in the percentage yield of the product. All the twelve formulations showed good percentage yield between 80.17% to 97.44%. But among all, F3 formulation showed highest percentage yield i.e. 97.44%

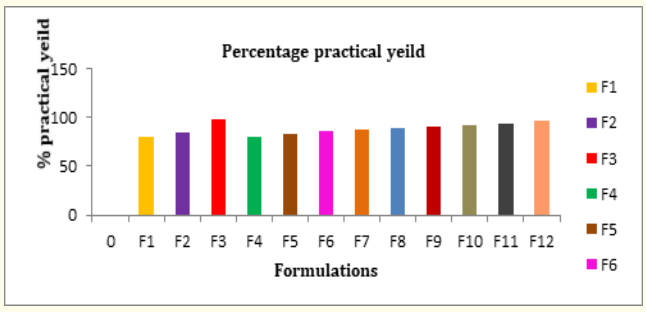

Figure 11: Percentage practical yeild.

Drug entrapment efficiency

S.no	Formulations	% Drug entrapment efficiency
1	F1	20.91 ± 0.05%
2	F2	43.0 ± 0.021%
3	F3	65.7 ± 0.267%
4	F4	53.41 ± 0.011%
5	F5	29.51 ± 0.031%
6	F6	34.75 ± 00189%
7	F7	59.30 ± 0.081%
8	F8	39.9 ± 0.032%
9	F9	49.3 ± 0.016%
10	F10	51.6 ± 0.021%
11	F11	59.5 ± 0.032%
12	F12	39.8 ± 0.031%

Table 5: Drug entrapment efficiencies of various formulations.

The average percentage drug entrapment efficiency of the twelve formulations ranges from 20.91% to 65.70%. Where the formulation F3 showed a maximum drug entrapment of 65.70%.

Figure 12: % Drug entrapment efficiency.

Drug Release Studies

Figure 13: Percentage drug release.

S.no	Time (min)	Percentage drug release (% Drug Release)					
		F1	F2	F3	F4	F5	F6
1.	30	12.9	14.3	15.0	16.1	19.0	17.7
2.	60	13.6	19.7	15.6	18.5	21.1	21.1
3.	90	17.0	22.5	21.1	21.1	24.5	25.9
4.	120	19.0	27.2	25.9	33.4	26.5	27.9
5.	150	21.8	30.6	27.2	36.1	29.3	30.6
6.	180	25.9	32.0	33.4	40.9	32.7	34.7
7.	210	29.3	33.4	34.7	42.9	32.7	38.8
8.	240	33.4	34.0	39.5	46.3	34.7	41.5
9.	270	34.7	34.7	44.2	48.3	39.5	45.6
10.	300	45.6	34.7	49.2	53.1	40.2	47.0
11.	330	45.6	35.4	50.4	55.9	46.3	51.2
12.	360	48.4	35.4	57.7	61.3	47.0	56.1
13.	390	53.1	48.4	64.6	63.4	53.1	60.0
14.	420	53.8	51.1	70.8	67.5	56.5	63..4
15.	450	60.0	54.5	78.2	70.9	59.2	67.3
16.	480	65.4	62.0	84.6	71.6	65.7	69.9
17.	510	68.8	70.2	92.5	72.0	71.3	73.2

Drug release studies of various formulations F1-F6

S.no	Time (min)	Percentage drug release (% Drug Release)					
		F7	F8	F9	F10	F11	F12
1.	30	15.0	11.5	13.6	13.0	5.4	6.1
2.	60	17.7	12.9	18.4	15.3	7.5	8.1
3.	90	19.0	15.9	19.7	19.0	7.5	12.4
4.	120	26.5	18.3	21.8	21.1	16.4	14.3
5.	150	29.7	22.5	26.5	28.6	21.1	20.3
6.	180	34.6	28.3	32.7	34.7	25.6	24.5
7.	210	37.7	34.7	34.7	38.3	32.7	30.0
8.	240	42.9	39.5	37.5	43.4	33.4	35.4
9.	270	45.7	47.7	41.5	47.0	34.7	40.2
10.	300	47.7	49.0	43.3	53.8	38.8	44.3
11.	330	51.1	51.1	47.7	55.9	42.9	47.7
12.	360	56.5	54.4	50.4	58.0	47.7	49.7
13.	390	62.0	58.2	58.6	60.6	52.5	55.9
14.	420	66.1	63.7	63.4	63.4	55.9	57.9
15.	450	70.9	68.4	67.5	66.1	66.1	63.4
16.	480	75.5	70.2	72.2	69.6	72.6	72.2
17.	510	80.4	74.3	81.1	74.0	79.5	76.5

Drug release studies of various formulations F7-F12

Table 6: Drug release studies of various formulations F1-F12.

When twelve formulations were carried for the *in-vitro* drug release studies, all the formulations showed good release profile where formulations F3 and F9 showed maximum release of drug with in 8 - 9 hrs.

Comparision of drug release profile with drug loaded nanoparticles, pure drug and Nanoparticles loaded capsule

The optimized nanoparticle formulation showed higher percentage drug release of 92.30% at 510 minutes when compared to pure drug, and nanoparticles loaded capsules showed drug release 80.20%.

Figure 14: Drug release studies of optimized formulations, pure drug and nanoparticles loaded capsule.

S. No	Time (min)	Percentage Drug Release		Nanoparticles loaded capsules
		Pure drug	Nanoparticle optimized (F3) Formulation	
1	30	7.1 ± 0.048	15.0 ± 0.045	12.3 ± 0.043
2	60	9.4 ± 0.048	15.6 ± 0.048	13.4 ± 0.035
3	90	12.5 ± 0.048	21.1 ± 0.038	18.2 ± 0.048
4	120	16.3 ± 0.043	25.9 ± 0.038	21.5 ± 0.045
5	150	19.2 ± 0.094	27.2 ± 0.032	26.2 ± 0.645
6	180	22.1 ± 0.082	33.4 ± 0.085	30.3 ± 0.064
7	210	24.5 ± 0.083	34.7 ± 0.042	32.4 ± 0.099
8	240	27.3 ± 0.044	39.5 ± 0.034	35.8 ± 0.053
9	270	30.1 ± 0.048	44.2 ± 0.04	43.4 ± 0.075
10	300	32.4 ± 0.082	49.2 ± 0.093	46.1 ± 0.073
11	330	36.4 ± 0.042	50.4 ± 0.083	49.2 ± 0.012
12	360	39.2 ± 0.024	57.7 ± 0.095	54.0 ± 0.042
13	390	42.1 ± 0.045	64.6 ± 0.942	59.4 ± 0.034
14	420	44.9 ± 0.025	70.8 ± 0.084	64.5 ± 0.012
15	450	50.4 ± 0.044	78.2 ± 0.082	70.7 ± 0.013
16	480	57.2 ± 0.024	84.6 ± 0.035	75.4 ± 0.012
17	510	60.3 ± 0.084	92.5 ± 0.028	80.2 ± 0.041

Table 7: Drug release studies of optimized formulations, pure drug and capsule.

Pre-formulation studies for drug loaded nanoparticles

Formulations	Parameters		
	Angle of repose (ɵ)	Bulk density (g/ml)	Tapped density (g/ml)
F3	26.56 ± 0.12	0.74 ± 0.08	0.87 ± 0.08

Table 8: Angle of repose, bulk density and tapped density of nanoparticulate capsules.

Evaluation of drug loaded nanoparticles capsules

Weight variation

S.no	Weight of empty Capsule (mg)	Weight of filled capsules (mg)	Net weight (mg)	% Weight variation
1	0.03	0.179	0.209	1.64
2	0.031	0.181	0.212	0.54
3	0.031	0.183	0.214	-0.54
4	0.032	0.183	0.215	-0.54
5	0.034	0.182	0.213	-000
6	0.032	0.181	0.213	0.54
7	0.035	0.184	0.219	-0.56
8	0.031	0.181	0.212	0.54
9	0.032	0.181	0.213	0.54
10	0.037	0.82	0.820	-000
Average:	=0.31	=0.182		=0.21%

Table 9: Weight variations of nanoparticles loaded capsules

Weight variations of nanoparticles loaded capsules was found to be within the limit as per IP.

Disintegration Time

Disintegration of nanoparticle filled capsules was found to be 4.5 minutes.

Drug release kinetics

Formulation	Zero order plot	First order plot	Higuchi plot	Peppas plot	Hixon-Crowell
Capsule	0.947	0.964	0.971	0.848	0.959

Table 10: Drug release kinetic (r-values) of nanoparticles loaded capsule.

Conclusions

Asenapine maleate was successfully encapsulated into chitosan nanoparticles by ionic gelation method. Various formulations of Asenapine maleate loaded chitosan nanoparticles were developed using various Stabilizing agents to polymer ratio. The prepared formulations were evaluated for drug entrapment efficiency formulation f3 registered highest entrapment of 65.7% and practical yield of 97.5% The incompatibility studies between the drug and polymer was evaluated using FTIR spectrophotometry. There was no significance difference in the IR spectra of pure drug & excipients. Zeta potential F3 formulation was found to be-9.9 mV, Particle size found to be 41.1 nm and scanning electron microscopy have discrete irregular shape. The *in-vitro* drug release of formulation F3 is found to be 92.5% over 510 minutes in controlled manner hence the present study was a successful attempt to formulate and extend the drug release of asenapine maleate by nanoparticulate system.

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