Effect Of Natural And Synthetic Polymers On The Controlled Release Of Nevirapine Mucoadhesive Microspheres

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Abstract

Background: Short-half-life drugs must be dosed often since they are quickly excreted from the circulation and readily absorbed from the GIT. In order to gradually release the medication into the GIT and sustain a constant drug concentration in the blood for a longer length of time, oral controlled-release formulations have been developed.

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Aim: The current study aim is to create an oral controlled release dosage form that not only delays drug delivery but also delays the passage of the dosage forms through the stomach and small intestine, allowing for the complete release of the drug over the chosen time.

Method: In the current study, natural and synthetic polymers were used in various ratios to prepare and assess a microparticles drug delivery system for Nevirapine. The study includes 12 different Nevirapine microsphere formulations that were prepared using the ionotropic gelation technique

Results: The results revealed that entrapment efficiency depends on the drug-to-polymer ratio. According to the particle size study, all formulations produced particles with sizes between 705.21, and 935.45 µm, which is appropriate for oral administration of the formulation. The formulation F8 was selected as the best one out of the twelve formulations because it had a good drug release profile in 12 hours (98.74%) and good entrapment efficiency (90.48%), when HPC and sodium alginate were combined (1:2).

Conclusion: Formulation F8, which showed higher entrapment efficiency and provides the desired drug release rate. The F8 formulation was the best and optimized of all the remaining formulations.

Keywords: Controlled Release Drug Delivery System, Drug Entrapment Efficiency, Hydroxy Propyl Cellulose, Micro particulate Drug Delivery System

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1. Introduction

Most researchers agree that the micro particle delivery method is a safe and effective way to deliver medication to specific target sites while maintaining the desired concentration in the area of interest. [1] A microcapsule is a sphere-shaped particle with a diameter of between 50 nm and 2 mm and a core material inside. In the strictest sense, microspheres are spherical empty particles.[2] On the other hand, microcapsules and microspheres are frequently used interchangeably. In addition, certain similar terms are used, such as "micro beads" and "beads," which are used interchangeably.

For rigid morphology, spheres and spherical particles are used.[1-3]

Microspheres are naturally biodegradable free-flowing powders made up of natural or synthetic polymers that have a particle size of less than 200 micrometres. The controlled release of drugs is possible with solid biodegradable microspheres, including a drug disseminated or dissolved throughout the particle matrix.[4-6]

Nevirapine, an antiviral drug used to treat HIV/AIDS and viral infections, is categorised as BCS class II, due to its poor water solubility and has low and variable oral bioavailability.[7] A peptidomimetic inhibitor called Nevirapine blocks the HIV-1 and HIV-2 proteases. Because of its short biological half-life (3-5 hours), low bioavailability (65%), limited therapeutic index, and predominant stomach absorption, Nevirapine must be released in a controlled manner.[8] Because of these drawbacks, mucoadhesive microspheres were developed to increase dosage form retention in the GI tract, allowing for full utilization of Nevirapine efficacy while lowering dose frequency and enhancing bioavailability.[9] These results suggest that mucoadhesive microspheres appear to be a required choice for administering Nevirapine to treat HIV patients.

The distinctive feature of this study is the use of mucoadhesive polymers to combine the benefits of particulate systems (microspheres) with mucoadhesive drug delivery systems.

2. Materials and Method

2.1 Materials

Nevirapine was received from Aurobindo Pharma Ltd., in Hyderabad, as a gift sample. We bought Ethyl cellulose, Hydroxypropyl cellulose, and Hydroxypropyl methylcellulose K100 from Oxford Laboratory in Mumbai. Sodium alginate was received from S.D. Fine Chem. Ltd., Mumbai, as a gift sample. All additional compounds were of analytical grade.

2.2 Preparation of microparticles

Ionotropic external gelation approach was used to prepare the Nevirapine mucoadhesive microspheres[10,11]. Nevirapine and mucoadhesive polymers were each passed through #80 separately. In order to create a homogeneous polymer solution, the weighed amount of Nevirapine was added to filtered water that already included the mucoadhesive polymers. The mixture was then carefully stirred at 400 rpm. To get rid of any air bubbles, the resultant dispersion was sonicated for 30 minutes. For the creation of mucoadhesive microspheres, the dispersion was extruded dropwise into an aqueous aluminium sulphate solution (10%) from a height of about 5 cm while being agitated at 400 rpm. To complete the curing process and create spherical, hard Nevirapine mucoadhesive microspheres, the additional droplets were kept in the aluminium sulphate solution for 30 minutes[12]. Then, Whatman filter paper was used to filter the fluid containing the Nevirapine microspheres that had developed. It took 12 hours for the mucoadhesive microspheres to dry out at 45 °C. Table1 listed the composition of various formulations of Nevirapine microspheres.

Table 1: Preparation of Nevirapine Mucoadhesive microspheres

Formulation	Ratio of Polymer	Drug: Polymer
F1	0.25:0.25 (SA:EC)	1:0.5
F2	0.5:0.5 (SA:EC)	1:1
F3	0.75:0.75 (SA:EC)	1:1.5
F4	1:1 (SA:EC)	1:2
F5	0.25:0.25 (SA: HPC)	1:0.5
F6	0.5:0.5 (SA: HPC)	1:1
F7	0.75:0.75 (SA: HPC)	1:1.5
F8	1:1 (SA: HPC)	1:2
F9	0.25:0.25 (SA: HPMC K100)	1:0.5
F10	0.5:0.5 (SA: HPMC K100)	1:1
F11	0.75:0.75 (SA: HPMC K100)	1:1.5
F12	1:1(SA: HPMC K100)	1:2

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SA-Sodium Alginate; EC- Ethyl cellulose; HPC-Hydroxy Propyl cellulose; HPMC-Hydroxy Propyl methyl cellulose

Preparation of a drug standard curve using a pH 7.4 phosphate buffer

Aliquots of stock solution (100 g/ml) corresponding to 5–25 µg (5,10,15,20, and 25 ml) were pipetted out into a series of 100 ml volumetric flasks and phosphate buffer pH 7.4 was used to make the volume up to 100 ml. Using a UV-visible double beam spectrophotometer, the absorbance of these solutions was measured against a phosphate buffer pH 7.4 as a blank at 313 nm[13].

2.3 Evaluation of Micro particles

2.3.1 % Yield

The weight of the dried finished product in relation to the starting total weight of the Nevirapine and polymer used to prepare the Nevirapine mucoadhesive microspheres[14] was used to calculate the percentage yield of Nevirapine microspheres of various batches.

2.3.2 Particle Size

The Nevirapine mucoadhesive microspheres' particle size and size distribution were determined using the sieve analysis technique[15]. The Nevirapine mucoadhesive microspheres were sieved for 10 minutes using conventional sieves with nominal mesh openings of 1.4 mm, 1.2 mm, 1.0 mm, 0.85 mm, and 0.71 mm, and the mean particle size was calculated.

2.3.3 Microspheres Morphology

The Nevirapine mucoadhesive microspheres' surface morphology and shape were examined using scanning electron microscopy. (JEOL JSM-5200). The microsphere sample was attached to an aluminium stub and coated with platinum particles using a sputtering process in an environment of argon.[16]

2.3.4 Micromeritics Properties

Microspheres that had been precisely weighed were gently put into a graduated cylinder at the 10 ml mark using a glass funnel, initial volume was noted. Bulk density and tapped density were noted using tapping method using measuring cylinder (of 10 ml)[17].

Angle of repose of prepared microspheres (n=3) was determined by fixed funnel standing method. On a sheet of paper held flat, the granules were allowed to flow down a funnel opening to collect in a pile. The following formulae were used to compute the angle of repose (θ), Hausner's ratio (H), and Carr's index (percent C) to analyse the flow characteristics of microspheres.

$$\theta = \mathrm{Tan}^{-1}h/r \qquad \text{Equation 1}$$

$$H = Dt/Db \qquad \text{Equation 2}$$

$$\%\ C = Dt\text{-}Db/Dt \times 100 \qquad \text{Equation 3}$$

Where h is the pile's height and r its radius. where Db is the bulk density and Dt is the tap density, respectively[17,18].

2.3.5 Drug Entrapment Efficiency

The amount of Nevirapine entrapped was estimated by method of extraction of drug present in mucoadhesive microsphere. The dried Nevirapine mucoadhesive microspheres (100 mg) were taken and extracted in 100 ml of 0.1N HCl for 24 hours in rotary shaker. The solution was filtered through a 0.45 µm filter and the concentration of Nevirapine present in filtrate determined spectrophotometrically at 284 nm (LABINDIA UV-3092 PC) against 0.1 N HCl as a blank[19].

2.3.6 FTIR

The optimal formulation and pure drug was scanned utilising the KBr disc technique, using the Fourier transform infrared spectroscopy (FTIR) spectra. The samples were examined in the range of wave numbers 4000 to 400 cm^{-1} [20]

2.3.7 Mucoadhesive test

Nevirapine microspheres' mucoadhesive property was assessed using the wash-off method, an in vitro adhesion testing technique. The freshly excised piece of the goat intestinal mucosa was mounted on the glass slide with cotton thread. Each prepared glass slide was covered with about 100 microspheres before the support was instantly hang from the arm of the USP disintegration machine. The intestinal mucosa was given a steady, regular up and down movement in the test fluid (0.1N HCL buffer) at 37±0.5°C when the test device was operating. The equipment was stopped every 60 minutes to eight hours, and the number of Nevirapine microspheres remained adhered to the intestinal mucosa was counted and the percentage of mucoadhesion was measured[21].

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2.3.9 In vitro dissolution

Using a dissolution test paddle type at 37±0.5°C and a rotating speed of 50 rpm, the release of Nevirapine from the mucoadhesive microspheres was investigated in 0.1N HCl buffer pH 1.2 as the medium. In each test, a sample of mucoadhesive microspheres corresponding to 100 mg of Nevirapine was employed. Hourly for 12 hours, 5 ml aliquots were removed from the dissolving device using a 0.45 filter and replaced with an equal volume of new dissolution liquid. Utilizing a UV spectrophotometer, the samples' Nevirapine

content was determined at 284nm. [22] (LABINDIA UV-3092 PC).

2.3.10 Release kinetic studies

By fitting the dissolution data into different kinetic models, such as zero order, first order, regression analysis of the aforementioned plots was used to obtain the korsemeyer peppas, Higuchi's model, and Coefficient of Correlation (r) values for the liner curves. The rate and the mechanism of Nevirapine release from the prepared mucoadhesive microspheres were then examined. [23].

2.3.11 Thermal Analysis (DSC)

With the use of a Shimadzu DSC 60, differential scanning calorimetry (DSC) was used to examine any potential interactions between the medicine Nevirapine and mucoadhesive polymers. Five milligrams samples were precisely weighed into aluminium pans and then sealed. DSC tests were carried out in nitrogen atmospheres over a temperature range of 40-300 °C at a heating rate of 10 °C/min.[24-25].

2.3.12 X-Ray Diffraction study (XRD)

An X-ray diffractometer was used to measure the crystallinities of pure drug and Nevirapine loaded mucoadhesive microspheres. XRD studies were performed on the prepared samples by exposing them to Cuk α1 radiation (40 kV, 30 mA) and the scanning rate was 5° /min over a range of 4-90° and with an interval of 0.1[25-27].

2.3.13 Stability study

Nevirapine stability studies were completed in accordance with ICH (International Conference on Harmonization) standards. The best mucoadhesive microsphere formulation (F8) was kept for 90 days at 4 °C/ambient, 25 °C/60 %, and 40 °C/75 % RH in closed bottles. The samples (F8) were evaluated for mucoadhesion % and entrapment efficiency every month for up to three months. [28-30].

3. Results and Discussion

3.1 Standard Graph of Nevirapine

The concentration in µg/ml on the X-axis and the absorbance on the Y-axis were used to plot the calibration curve. represented in figure 1

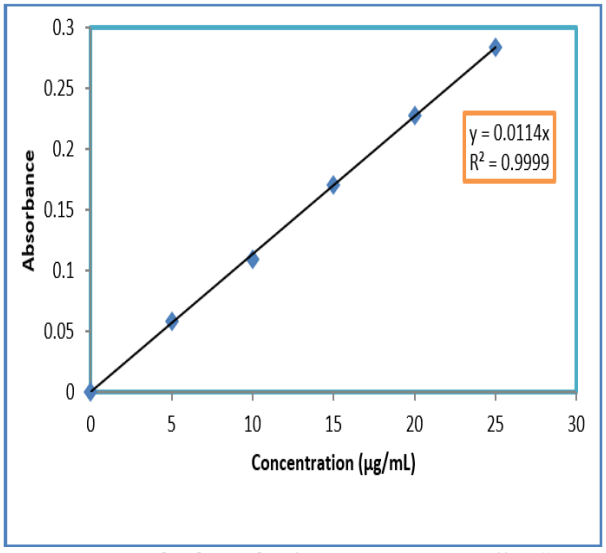


Figure 1: Standard graph of Nevirapine 7.4 Buffer (λmax at 313 nm)

3.2 Percentage yield

The percentage yields of Nevirapine microspheres generated by the ionotropic gelation technique were found to be between 84.33 % to 94.28 % as indicated in table 3. It was discovered that the manufacturing yield of the microspheres made using HPMC K100 was higher than that of the grades HPC and EC.

3.3 Particle size

According to table 3, the Nevirapine microspheres' average particle size varied from 705.21±2.00 to 935.45±2.07 µm The high viscosity of the mucoadhesive polymer solution may be the cause of the considerable rise in mean particle size with increasing mucoadhesive polymer concentration.

3.4 Entrapment Efficiency

According to table 3, the range of the entrapment efficiency in terms of a percentage was 64.52 to 96.42%. The Nevirapine microspheres made with HPMC K100 had a better entrapment efficiency than those made with HPC and EC grades. This could be explained by the fact that HPMC K100 has a larger molecular weight than HPC and EC grades. An increase in the molecular weight of the polymer enhances the entrapment efficiency of the mucoadhesive microspheres by creating a more complete matrix network.

Table 2: Physicochemical properties of Nevirapine Mucoadhesive microspheres

Formulation code	% yield [a]	Entrapment Efficiency [a]	Particle size [µm][a]
F1	84.33	64.52±0.75	705.21±2.00
F2	88.15	73.27±1.11	723.33±2.42
F3	90.80	78.42±1.62	749.38±1.25
F4	91.08	86.66±1.67	785.80±2.61
F5	86.46	72.72±0.75	774.58±1.70
F6	89.84	80.06±1.00	816.49±1.10
F7	90.04	85.45±1.54	863.13±2.54
F8	93.38	90.48±1.67	901.08±1.91
F9	88.12	92.87±0.79	920.58±1.91
F10	90.38	94.88±1.00	925.52±2.21
F11	92.58	95.52±1.18	930.92±2.09
F12	94.28	96.42±1.67	935.45±2.07

[a] Mean ± SD, n = 3.

3.5 Micromeritics properties

The micrometric characteristics of each formulation of Nevirapine microspheres were assessed. Results are shown in table 4. Angle of repose of all microspheres batch varied from 22.72 to 30.61. Compressibility index varies from 9.76 % to 14.08 %. Hausner's ratio varies from 1.10 to 1.16. Here all these formulations results revealed excellent (F1, F2, and F5) and good flow property and compressibility.

Table 3: Micromeritics properties of Nevirapine Mucoadhesive microspheres

Formulation code	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (θ)[a]	Compressibility Index (%) [a]	Hausner's Ratio [a]	Flow Property
F1	0.493	0.543	22.72	09.76	1.10	Excellent
F2	0.529	0.587	24.40	10.66	1.11	Excellent
F3	0.529	0.587	25.73	11.42	1.11	Good
F4	0.529	0.587	27.49	11.86	1.11	Good
F5	0.529	0.587	23.45	10.53	1.11	Excellent
F6	0.497	0.550	24.92	12.04	1.13	Good
F7	0.522	0.597	27.80	12.70	1.14	Good
F8	0.538	0.626	28.79	13.89	1.16	Good
F9	0.478	0.543	25.17	10.97	1.12	Good
F10	0.478	0.543	26.85	11.77	1.12	Good
F11	0.522	0.597	28.79	12.78	1.14	Good
F12	0.538	0.626	30.61	14.08	1.16	Good

[a] Mean ± SD, n = 3

3.6 FTIR Studies:

There was no significant difference in the pattern of peaks between the IR spectra of the pure drug sample of Nevirapine and those of Nevirapine-loaded microspheres, in figure.2. Hence there was no interaction seen in between Nevirapine and Mucoadhesive polymers.

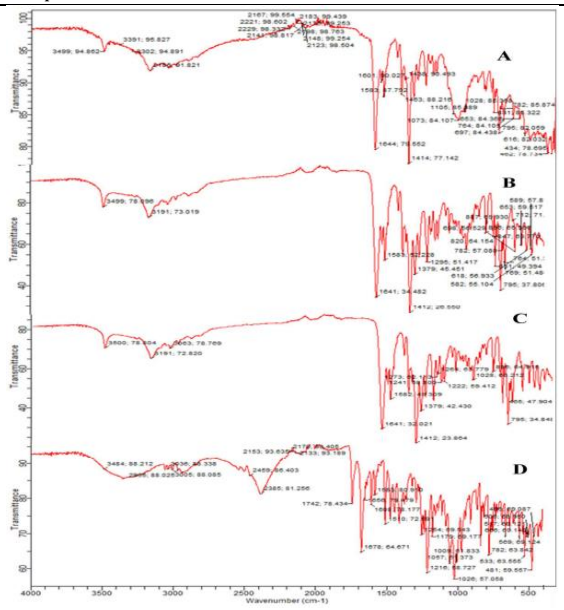
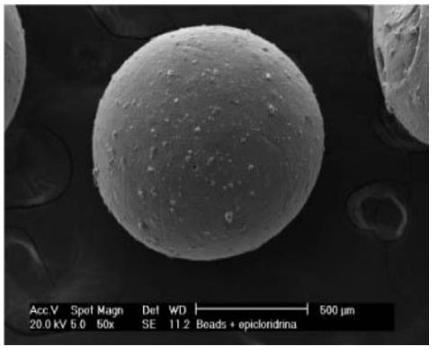


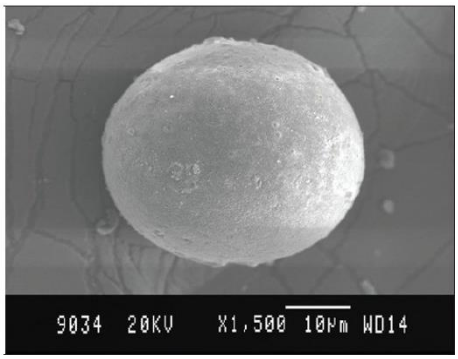
Figure 2: FTIR spectra of, (A): Pure Nevirapine; (B): Formulation containing SA+EC (C): Formulation containing SA+HPMC K100M; (D): Formulation containing SA+HPC

3.7 SEM

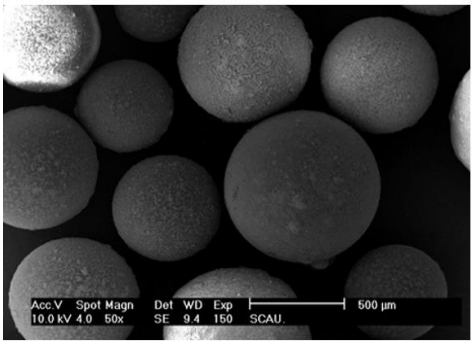
Scanning electron microscopy was used to analyse the morphology of the best formulation F8 mucoadhesive microspheres (SEM). The Nevirapine microspheres were seen in the SEM images to be distinct, spherical, and to have the rough surface morphology seen in figure 3.



a. 50X



b. 100X



c. 150X

Figure 3: SEM images of optimised formulation

3.8 Mucoadhesive test

Table 4 displays the results of all Nevirapine microsphere formulations' in vitro mucoadhesion testing. The percentage of mucoadhesion in Nevirapine formulations rises along with the concentration of mucoadhesive polymers. The larger molecular weight of HPMC K100 than HPC and EC based microspheres may be the cause of the increased mucoadhesion of HPMC K100 based mucoadhesive microspheres. The Robinson et al. research backs up our finding.[19] The pH of the in-vitro wash off medium affects the polymers' solubility, hydration, and mucoadhesiveness. The findings of the in-vitro wash-off test showed that the mucoadhesive characteristics of the Nevirapine microspheres had fairly good Mucoadhesive properties.

Table 4: Results of in vitro wash off test

ZF. Code	1st Hour[a]	2nd Hour[a]	4th Houra	6th Hour[a]	8th Hour[a]
F1	96±1.52	86±2.08	55±0.57	34±1.15	05±0.57
F2	97±1.15	88±1.52	62±0.57	40±1.00	14±1.15
F3	98±1.00	94±1.52	68±1.15	48±1.52	24±1.73
F4	100	99±1.15	72±1.00	56±0.57	36±1.52
F5	100	90±0.57	74±1.52	57±0.57	38±1.15
F6	100	98±0.57	82±1.00	64±1.15	46±1.52
F7	100	99±1.53	83±1.00	67±1.15	48±0.57
F8	100	99±0.57	87±1.15	70±1.52	50±0.57
F9	100	100±0.55	88±1.15	73±1.00	55±1.55
F10	100	100±0.57	90±0.57	74±1.00	62±1.52
F11	100	100	93±0.57	80±1.00	64±1.53
F12	100	100	95±0.57	82±1.52	70±1.00

[a]Mean ± SD, n = 3

3.9 *In vitro* Drug Release:

The in vitro Nevirapine release profile for all batches was shown in figure 4. These mucoadhesive microspheres released drugs slowly and under regulated conditions, depending on the nature and quantity of mucoadhesive polymers used[22] [23]. When the amount of mucoadhesive polymer increased, it was observed that the release of Nevirapine decreased. This might be explained by the microspheres expanding more after being hydrated and having more mucoadhesive polymer in them, which lengthens the diffusion channel and delays medication release. Out of all the formulations, F8 was selected as the best formulation because it had an excellent drug release profile in 12 hours (98.74%) and contained sodium alginate and HPC (1:2). As a result, F8 is regarded as the best microsphere formulation and a promising for controlled release.

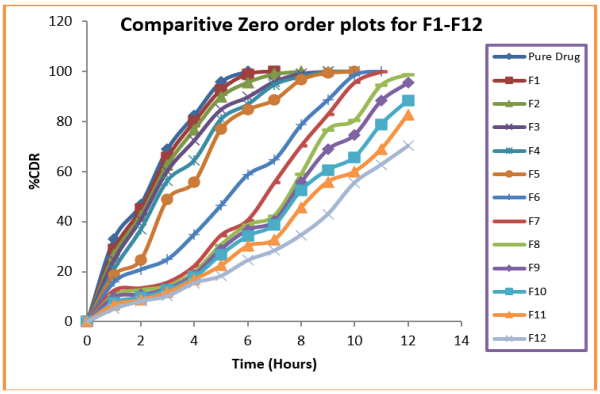


Figure 4: Comparative Zero order plots for Pure drug and F1-F12 formulations

3.10 Release Kinetics

Table 5 displays the drug release kinetic data for the mucoadhesive microspheres of Nevirapine with regression values ranging from 0.920 to 0.996, all of the microsphere formulations (F1 to F12) adhered to the Korsmeyer-Peppas model and zero-order release kinetics. The Nevirapine release mechanism was followed by case-II transport (Zero order Release) and super case-II transport, according to Korsmeyer-Peppas plots, where the 'n' value ranged from 1.035 to 1.476.

Table 5: Release kinetic parameter of Nevirapine from Mucoadhesive microspheres

F. Code	Zero order	First Order	Higuchi	Korsmeyer peppas	n-value	Release Mechanism
F1	0.967	0.955	0.989	0.920	1.394	Super case-II transport
F2	0.956	0.958	0.988	0.926	1.402	
F3	0.951	0.916	0.989	0.925	1.388	
F4	0.951	0.886	0.984	0.935	1.415	
F5	0.967	0.860	0.963	0.966	1.476	
F6	0.955	0.712	0.951	0.983	1.237	
F7	0.982	0.659	0.903	0.989	1.163	
F8	0.982	0.652	0.928	0.988	1.095	Case-II transport
F9	0.984	0.647	0.924	0.991	1.104	Super case-II transport
F10	0.987	0.643	0.923	0.994	1.147	
F11	0.983	0.633	0.935	0.996	1.075	Case-II transport
F12	0.978	0.622	0.943	0.995	1.035	

3.11Thermal Analysis (DSC)

Figure 5 illustrates the study of the thermal behaviour of manufactured Nevirapine microspheres in relation to thermos grams of both pure Nevirapine and drug-loaded microspheres. The melting point of Nevirapine, 245.6 °C, was clearly visible on the thermogram of the pure substance. The microspheres containing Nevirapine with HPC (1:2) F8 may easily be identified by their distinctive peak (240.9 °C) Nevirapine and the mucoadhesive polymers utilised to create the microspheres were compatible with one another.

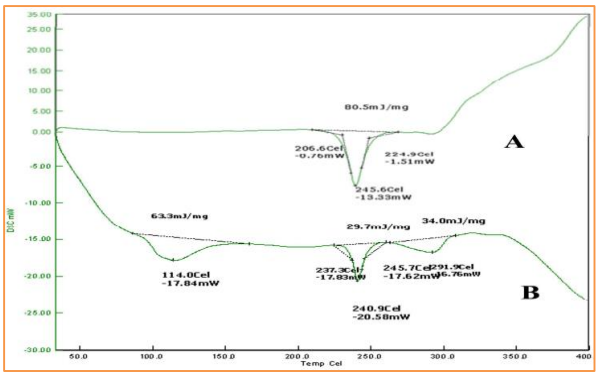


Figure 5: DSC thermogram A. Pure Nevirapine; B. Optimized formulation F8

3.12 X-Ray Diffraction study (XRD)

For the purpose of determining the crystallinity of Nevirapine in the mucoadhesive microspheres, the X-ray diffraction spectra of Nevirapine and Nevirapine loaded microspheres (F8) were recorded. Nevirapine X-ray diffractogram revealed high peaks at 6000, which are shown in figure 6 as a typical crystalline form. However, mucoadhesive microspheres loaded with Nevirapine displayed peaks at low intensities (3000), indicating that some Nevirapine had been converted to an amorphous state.

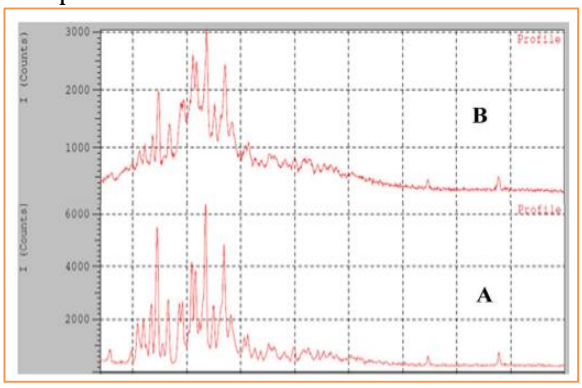


Figure 6: XRD spectra of A. Pure Nevirapine B. Optimized formulation F8

3.13 Stability data

The optimized F8 formulation were tested for stability by being stored for three months at 4 °C/Ambient, 25±2°C/60±5% RH, 40±2°C/75±5 % RH for 3 months. According to table 6, the optimized formulation (F8) exhibits negligible variation in percentage entrapment efficiency and percentage mucoadhesion. Therefore, it can be claimed that the HPC-prepared Nevirapine mucoadhesive microspheres are stable.

Table 6: Percentage entrapment efficiency and mucoadhesion of the F8 formulation

Condition	Day	% Entrapment Efficiency[a]	% Mucoadhesion[a]
4 °C/Ambient	0	96.42±1.67	70.12±1.16
	30	96.38±1.53	69.24±1.45
	60	96.24±1.17	68.48±1.37
	90	95.89±1.12	67.54±1.35
25±2°C/60±5 % RH	0	96.42±1.67	70.12±±1.16
	30	96.24±1.35	68.28±1.35
	60	95.92±1.72	67.54±1.12
	90	95.74±1.21	66.45±1.35
40±2°C/75±5 % RH	0	96.42±1.67	70.12±1.12
	30	96.12±1.28	67.32±1.18
	60	95.78±1.12	66.24±1.35
	90	95.64±1.72	65.45±1.45

[a] Mean ±SD, n = 3.

4. Conclusion

In order to increase the drug's bioavailability, the current study has effectively developed a mucoadhesive system for oral delivery of Nevirapine. Ionotropic method used successfully to create natural polymer combined with synthetic polymer containing mucoadhesive microspheres of Nevirapine. The current procedure was quick, easy, and does not require the use of dangerous chemical solvent. The IR and DSC spectra showed that there was no interaction between polymers and Nevirapine, indicating that they are compatible, according to the experimental data. Nevirapine loaded mucoadhesive microspheres produced good Micromeritics parameters. According to the particle size study, all formulations produced particles with a size between 705.21 and 935.45 m, which is appropriate for oral administration of the formulation. The formulation F8 was selected as the optimized one out of the other formulations because it had a good drug release profile in 12 hours (98.74%) and high entrapment efficiency (90.48%) when HPC and

sodium alginate were combined (1:2). As the plot of the Pappas model was discovered to be zero order drug release, the drug release was erosion regulated. The SEM analysis of the F8 microspheres revealed that the formulation was abrasive and spherical with a nice surface shape. The type and concentration of mucoadhesive polymers in the polymer matrix affecting Nevirapine drug release rate. Thus, the findings show the possibility for using sodium alginate in combination with both natural and synthetic polymers to create microspheres that transport Nevirapine mucoadhesive and remain at the absorption site for an extended period of time. To improve patient compliance and providing regulated release, the produced mucoadhesive microspheres of Nevirapine will enhance therapeutic efficacy and overcome the limitations of traditional treatment.

5. Acknowledgement

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6. Ethical Approval

The study did not require ethics committee approval or patient informed consent because it did not focus on any clinical parameters and did not utilize any humans or animals for the processing of work.

7. Conflicts Of Interest

No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

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Abbreviation

Gastrointestinal Tract (GIT), Sodium Alginate (SA), Ethyl Cellulose (EC), Hydroxy Propyl Cellulose (HPC), Hydroxy Propyl Methyl Cellulose (HPMC), Controlled Release Drug Delivery System (CRDDS), Drug Entrapment Efficiency (DEE), Micro particulate Drug Delivery System (MPDS), Human Immunodeficiency Viruses (HIV), Acquired Immune Deficiency Syndrome (AIDS), Fourier Transforms Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), International Conference on Harmonization (ICH), and Scanning Electron Microscopy (SEM).

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