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Original Article

Formulation and Evaluation of Eudragit L- 100 based Nanoparticles of Senna for Treatment of Constipation

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ABSTRACT

Background: The pharmaceutical industries are keen in development of new herbal bioactive molecules with an improved effect and less toxicity in order to replace synthetic drugs. Constipation is the most prevalent medical concerns. It's estimated that one in five adults worldwide suffers from constipation. Hence, the demand of herbal laxatives is increasing worldwide. The purpose of this research work was to develop Senna nanoparticles with the help of Eudragit L100 an enteric coating polymer to provide site specific activity and to prevent degradation of Senna in acidic environment. **Materials and Methods:** Senna loaded nanoparticles were prepared by using emulsion solvent evaporation method. Different formulation has been formulated with varying concentration of Eudragit L-100 and constant aqueous and organic phase ratio (1:9). Drug and polymer compatibility study was analysed by FTIR. The prepared formulation was characterized by melting point, particle size, zeta potential, polydispersity index, vesical morphology and *in-vitro* drug release. **Results:** All the formulation batches shows particle size between 380.61 - 1061.71nm. The zeta of optimized batch (F5) was found to be -23.75mV. Entrapment efficiency of the entire prepared formulation batch in between 3.16±0.31-55.18±0.35%. The *in-vitro* drug release shows maximum drug release i.e. 61.03% in 8 hrs which shows that release of drug prolonged and site specific due to use of enteric coated polymer Eudragit L100. **Conclusion:** The developed Senna loaded nanoparticles can provide site specific drug delivery. The polymer used in Senna Nanoparticles formulations shows efficient and targeted drug release as well as reduction in dose, dosing frequency and side effects.

Keywords: Nanotechnology, Sodium lauryl sulphate, Tinnevelly.

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INTRODUCTION

Constipation is one of the most common complaints reported by many individuals. It's estimated that one in every five adults worldwide suffers from constipation. Hence, the demand for the use of laxatives is increasing worldwide. Constipation may be a condition during which bowel evacuations occur infrequently or during which the faeces are hard and small, or where passage of faeces causes difficulty or pain. A laxative is the drug used to stimulate or increase the frequency of bowel evacuation.[1] Herbal medicines have been used to treat a wide range of diseases and ailments since ancient times. Senna is listed in several pharmacopoeias and is also listed as a medicinal plant in the World Health Organization's monograph. Senna is the most commonly used laxative world-wide.

Senna is a well-known medication that is used to treat constipation in both Ayurveda and allopathic therapy. The presence of sennosides A and B in Senna and its formulations gives it a laxative effect.[2] Senna, also known as Tinnevelly Senna, belongs to the Leguminoseae family and mostly affects the large intestine.[3-5] The glycosides and anthraquinone are absorbed from the intestine and released into the colon, where they stimulate and augment the peristaltic motions of the colon by local action. As a result, water absorption is reduced, resulting in bulkier and softer faecal matter. This indicates that they act in the intestine and have no impact on the stomach.[6-8] With the use of enteric coating, we can direct the sennosides to the intestine.[9] Many conventional dosage forms are available for the treatment of constipation, like tablets, capsules, etc. But these conventional dosage forms have been reported to have several side effects, like the degradation of drugs in the stomach. So, there is a need to formulate a novel drug delivery system for such a drug. For example, liposomes, nanoparticles, and microemulsion matrices structure carbon nanotubes.

Nanoparticles are subionized colloidal structures consisting of synthesised or semi-synthesised polymers. The size of a nanoparticle is in the range of 10–1000 nm. A drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle matrix. There are two types of nanoparticles, i.e., Nanosphere and Nanocapsule. A nanosphere is the matrix system in which the drug is physically and uniformly distributed, and a nanocapsule is a drug-contained system surrounded by a distinct polymer membrane.[10]

The Nanoparticulate drug delivery system offers several advantages, like targeted delivery of drugs to specific sites to minimise toxicity. It also helps to achieve a maximum therapeutic response with minimal side effects. Nanoparticles can be administered by parenteral, nasal, and ocular routes. By enhancing aqueous solubility, nanoparticles also improve bioavailability by increasing drug resistance time in the body. Nanoparticles gives Sustained and controlled release effect as well as improved fluctuation in therapeutic ranges.[11-12] With the help of the enteric coating polymer Eudragit L100, we can provide site-specific action of Senna to the intestine. Hence, in the present study, an attempt was made to formulate a novel drug delivery system, i.e., nanoparticles loaded with Senna for reducing side effects and providing site-specific activity.

MATERIALS AND METHODS

Material

Senna extract was gifted by Bhoomi Nutraceuticals Benglure. Eudragit L100, sodium lauryl sulphate and methanol were purchased from modern science Nashik. Other chemicals used were of analytical grade.

Method of Preparation of Nanoparticles

Preformulation study of Senna and polymer

Preformulation parameters are checked for Senna and Eudragit and they were characterised by organoleptic properties, solubility, melting point and compatibility studies by using FTIR techniques.

Organoleptic properties

The drug samples of Senna were studied for appearance, colour, and odour by using a visual method. The drug sample was evaluated for colour and texture.[13]

Solubility study

The solubility of a drug is determined by the shake flask method. The drug was dissolved in (water, methanol, and Dimethylsulphoxide) 10 ml of solvent. Then the solution was stirred for 24 hr with the magnetic stirrer at 37°C and allow it to equilibrate. After 24 hr, the sample was removed, filtered, and analysed with a UV spectrophotometer.[14-15] (Shimadzu UV-2600)

Melting point

The melting point of Senna was determined by placing a small amount of the substance in a sealed capillary tube with one end closed, a thermometer attached with a rubber band, and the tube immersed in the Thieles tube. As a result of the heating, the temperature ranges at which the sample melts can be detected. The freezing point of the sample is the point at which melting is noticed, and so the temperature remains constant while heating.[16-17]

UV-visible spectroscopy

Preparation of calibration curve by U.V Visible spectrophotometric method

Determination of λ_{max} in methanol

Senna's UV spectrum was obtained using a UV Shimadzu2600 in Japan. The accurately weighed 10 mg Senna was dissolved in a sufficient amount of methanol and the volume was increased to 10 ml. stock solution was diluted to get a 100 ug/ml concentration. The 1 ml of aliquot was withdrawn and the volume was made up to 10 ml by using methanol to obtain a 10 ug/ml concentration. The resultant solutions were scanned from 200 to 400 nm. The spectrum was recorded to get a reading of the maximum wavelength.

Construction Beer Lamberts plot in methanol

The stock solution of 100ug/ml was prepared in methanol. This stock solution was used to prepare different dilutions in the range of 2–20g/ml. A UV visible spectrophotometer was used to measure the absorbance of the resulting solutions at 276nm.[18]

Drug-excipient Compatibility Studies

A compatibility analysis was conducted in order to ensure that the drug and excipients utilised in the formulation did not interact. The vial was filled with the drug and physical mixture of the drug: polymer (1:1) and sealed. The sealed vials were stored in a desiccator for 45 days at a particular temperature. After a month, the mixture was analysed using FTIR. FTIR was used to determine preliminary compatibility (Shimadzu: IR Affinity-1S). The FTIR spectrum was taken at a wavelength of 4500 cm^{-1}. Using a typical KBr sample, infrared spectra of pure drugs and physical mixtures of drugs with polymers were produced.[19]

FTIR Analysis

The drug's dry sample was combined with KBr in a ratio of 1:99. The material was triturated before being placed in a sample holder and compacted at 15 tonnes per minute using a motorised pellet press. The pellets were then scanned with an FTIR spectrophotometer (Shimadzu; IR Affinity-1S) throughout frequency ranges of 4000 to 400 cm^{-1}, and the spectra were compared to the typical ranges of functional groups.

Emulsion solvent evaporation method

There are several methods of preparation of nanoparticles, but the emulsion solvent evaporation method offers several advantages, like it requires only mild conditions such as ambient temperature and constant stirring. Thus, a stable emulsion can be found without compromising the activity of the drug. It also gained most attention because of its ease of use and scale up and lower residual solvent potential as compared to other methods.

The Preparation of nanoparticles was done by the emulsion solvent evaporation method. The formulation batches are shown in Table 1. In which the organic phase and aqueous phase were mixed with a ratio of (1:9) The organic phase is Senna, methanol and Eudragit L100. The aqueous phase is sodium lauryl sulphate in water. Then the O/W emulsion was prepared by adding the organic phase into the aqueous phase. Then this emulsion was homogenised (GLH-850) for 1 hr at 6000 RPM. After that, the solvent was removed from it by a Rotary evaporator. (SCI100-S 5L), then the obtained nanoparticles were detected by laser light scattering.[20]

Characterization

Determination of percentage yield

The yield of nanoparticles was measured with concern to drug and polymer weight. After the preparation of nanoparticles, they are collected, dried and weighed over electronic balance and percentage yield was calculated by formula.[21]

$$\text{Percentage yield} = \frac{\text{Weight of Nanoparticles}}{\text{Weight of polymers} + \text{Weight of drug}} \times 100$$

Determination of drug entrapment efficiency

Weighed 10 mg samples of drug-loaded nanoparticles and then dissolved in 10 ml of methanol under sonication for 1 hr. The sample have centrifuged at a high speed of 9000 rpm for 30 min and the supernatant liquid was analysed for non-bound drug in UV spectrophotometer at 276 nm.[22] The % EE was determined using the below equation.

$$\%\ \text{Entrapment efficiency} = \frac{\text{Total drug loaded} - \text{unentrapped drug}}{\text{Total drug loaded}} \times 100$$

Particle size, polydispersity index, zeta potential measurement

1 ml of nanoparticle suspension was diluted with 10 ml double distilled water and then zeta potential, polydispersity index and mean particle size were determined by a dynamic light scattering particle size analyser Malvern zetasizer. (Malvern instrument Ltd) all sample were measured at 25± 0.5°C.[23]

Scanning electron microscopy

A scanning electron microscopy (SEM) was use to examine the morphology of vesicles. A drop of nanoparticle dispersion was dropped onto a carbon coated grid to form a thin film, which was then negatively stained with 1% phosphotungstic acid before drying. a drop of staining

Table 1: Formulation Batches for Nanoparticle Preparation.

Sl. No	Formulation code	Organic phase			Aqueous phase	
		Drug (mg) Senna extract	Polymer (mg) Eudragit L100	Solvent (ml) Methanol	Distilled water (ml)	Sodium lauryl sulphate(mg)
1	F1	150	100	10	90	80
2	F2	150	110	10	90	80
3	F3	150	120	10	90	80
4	F4	150	130	10	90	100
5	F5	150	140	10	90	100
6	F6	150	150	10	90	100

solution was applied to the filter paper. The grid was allowed to air dry before the sample was examined.[24]

In-vitro drug release study

In-vitro drug release study of nanoparticles were done in USP apparatus II. Sample were placed in the dialysis bag. In order to simulate pH changes along with Gastrointestinal tract dissolution medium with 0.1 N HCl and phosphate buffer 6.8 were used. Firstly 0.1 N HCl used for 2 hrs which was then replaced by fresh phosphate buffer 6.8 at 37± 0.5°C and 100 rpm up to 8 hrs. At each time interval 5 ml of sample was collected and analysed by spectrophotometrically.[25]

RESULTS

Preformulation study

Organoleptic properties

The organoleptic characteristics of the drug sample were examined, and they revealed that it was brown in colour and hygroscopic in nature.

Solubility research

The drug Senna was found to be practically insoluble in water. Solubility of Senna was found to be 1.8 mg/ml in methanol and 1.5 mg/ml in Dimethylsulphoxide. Results of solubility are mentioned in Table 2.

Melting point

The melting point of sennosides in Senna extract is found to be 220-225°C, which is found to be nearly to standard melting point range. This indicates the samples obtained were of pure quality.

UV-visible spectroscopy

The determination of the λ_{max} of Senna in methanol

The UV spectrum of Senna extract solution in methanol exhibits a wavelength of absorbance maximum of 265 nm. This is close to the reported value. However, keeping in mind the probable concentrations likely to be encountered while carrying out *in vitro* drug release studies and considering the predicted theoretical max was decided as 265nm. The spectrum of Senna is shown in Figure 1.

Construction of Beer lamberts plot in methanol

The calibration curve (Figure 2) was found to be linear in the concentration range of 2 to 20 ug/ml (Table 3), with a coefficient of regression of R^2 = 0.9802 and a slope of y = 0.0018x+ 0.0013 in methanol.

FTIR analysis

The FTIR analysis of pure Senna and Senna loaded nanoparticles was done and FTIR spectra of pure Senna were reported at wave numbers 3452.58, 2920.23, 1741.52, 1649.14, 1564.27, 630.72 cm^{-1}. Also, FTIR spectra of Senna-loaded nanoparticles were reported at wave numbers 3469.94, 2920.23, 2852.72, 1707, 1552.70, and 630.72 cm^{-1}.

Table 2: Solubility of Senna extract in different solvent.

Solvent	Solubility mg/ml	Inference
Water	-	insoluble
Methanol	1.8 mg/ml	Soluble
DMSO	1.5mg/ml	Soluble

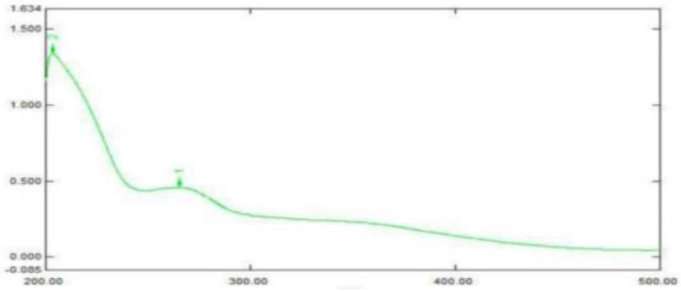

Figure 1: UV –visible spectrum of Senna in methanol.

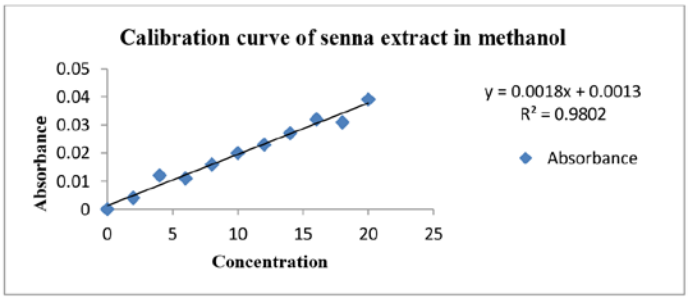

Figure 2: Calibration curve of senna extract in methanol.

In these FTIR spectra of Senna, a characteristic peak at wave number 630.72 cm^{-1} indicates the presence of a benzene derivative. The peak at 1564.27 cm^{-1} indicates a presence of C=C stretching of the aromatic ring. Also peak at 1741.52, which indicates the C=O stretch functional group of carboxylic acid. The presence of peak at 1649.14 cm^{-1} indicates the C=O stretching. Two peaks observed at 2920.23 cm^{-1} and 3452.58 cm^{-1} indicate the presence of an O-H stretching functional group. In these spectra of Senna loaded nanoparticles, the same peaks are observed at wave number 3469.94, which indicates the presence of O-H stretching. The peak at 1707 cm^{-1} reveals the presence of C=O stretching. Also, the peak at 1552 cm^{-1} and 630.72 cm^{-1} indicates the presence of C=C stretch and benzene derivatives, respectively. The absorption band shown by Senna and Senna nanoparticles shows all the characteristics of groups

Table 3: **Absorbance of Senna extract in methanol.**

Sl. No	Concentration in (ppm)	Absorbance(nm)
1	2	0.004
2	4	0.011
3	6	0.013
4	8	0.016
5	10	0.020
6	12	0.023
7	14	0.027
8	16	0.031
9	18	0.033
10	20	0.039

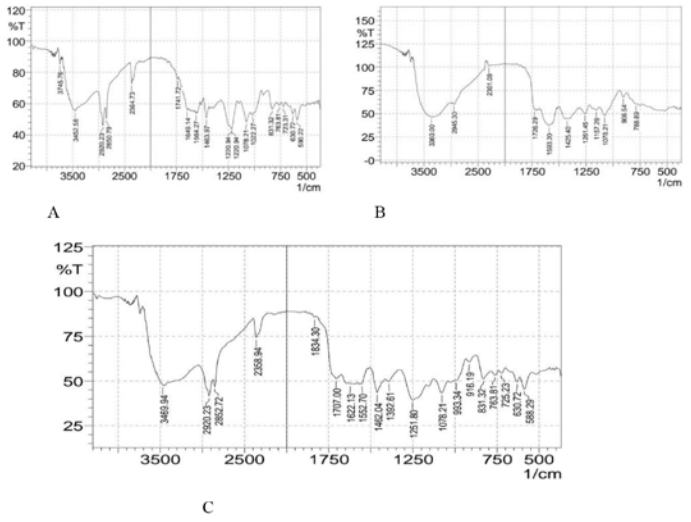

Figure 3: A. FTIR spectra of Senna B. FTIR spectra of Senna and eudragit l 100 C.

present in their molecular structure. The presence of an absorption band corresponding to the functional groups present in the structure of Senna confirmed the identification and purity of the purchased Senna extract sample. Results are shown in Figure 3.

FTIR spectra of Senna nanoparticles

Characterization

Evaluation of prepared nanoparticles of Senna was carried out for percentage yield, entrapment efficiency, particle size, and scanning electron microscopy study.

Percentage yield

As shown in the Table 4 the percentage yield of nanoparticles ranged from 58 to 85.12%. The optimised batch was found to be F5 on the basis of percentage yield. The percentage yield of the optimised batch was found to be 85.12%.

Entrapment efficiency

After preparing nanoparticles dispersion, the unentrapped drug is separated by the centrifugation and the drug that remains entrapped in nanoparticles is determined by a spectrophotometric method. Entrapment efficiency of nanoparticles was found in the range of 3.16±0.31 to 55.18±0.35%. The entrapment efficiency of the optimised

Table 4: **Percentage yield of Nanoparticles.**

Batch number	Percentage yield (%)
F1	58
F2	84.63
F3	80
F4	83.15
F5	85.12
F6	73

Table 5: **Entrapment efficiency in Nanoparticles.**

Batch code	Absorbance at 265nm	Unentrapped drug (%)	%Entrapment in nanoparticles
F1	0.163	90.01	39.95±0.14
F2	0.174	95.75	36.15±0.41
F3	0.262	145.2	3.16±0.31
F4	0.219	121.12	19.22±0.39
F5	0.124	67.23	55.18±0.35
F6	0.206	113.53	24.29±0.33

Table 6: **Polydispersity Index, Particle size and zeta potential.**

Batch code	Polydispersity index	Particle size(nm)	Zeta potential
F1	0.375	1032.82	-24.27
F2	0.410	1061.71	-21.66
F3	0.395	995.27	-20.63
F4	0.344	428.18	-22.34
F5	0.350	380.61	-23.75
F6	0.319	984.21	-25.13

batch (F5) was found to be 55.18±0.35%. Entrapment efficiency increased with increasing polymer concentration and it was also reported that with increasing polymer concentration, the EE also increased as there were more chances of drug entrapment. Entrapment efficiency of all formulation batches as listed in Table 5.

Particle size, polydispersity index, zeta potential measurement

The particle size of nanoparticles varies with the polymer concentration used. One from each batch is subjected to particle size determination, depending upon the percentage drug entrapment efficiency. There were significant differences in particle size. A graphical representation of the particle size and zeta potential determination is given in Figure 4 and Figure 5 respectively. The particle size, polydispersity index, and zeta potential are determined for all formulation batches listed in the Table 6 The average particle size of the optimised batch (F5) was found to be 380.61 nm. The polydispersity index was 0.350. The zeta potential of the optimised batch was -23.75mV.

Scanning electron microscopy

The SEM technique is used to study the microscopic behaviour of drug-nanoparticle compositions. The SEM image shown in Figure 6 revealed the highly porous structure of the Senna loaded nanoparticles formulation batch (F5). The porous texture of nanoparticles facilitates the infiltration of a drug into the interpenetrating network of nanoparticles.

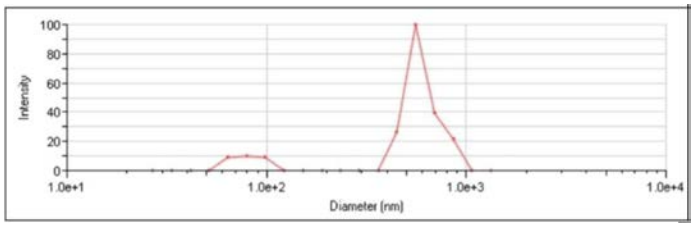

Figure 4: Particle size distribution of optimized batch.

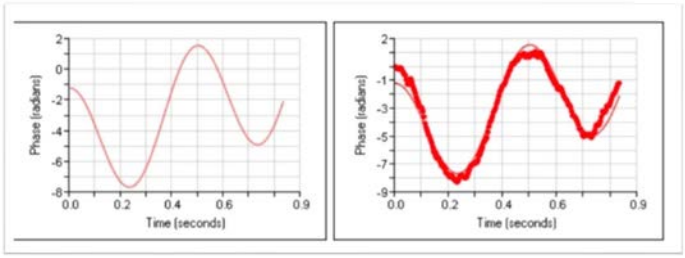

Figure 5: Zeta potential of optimized batch.

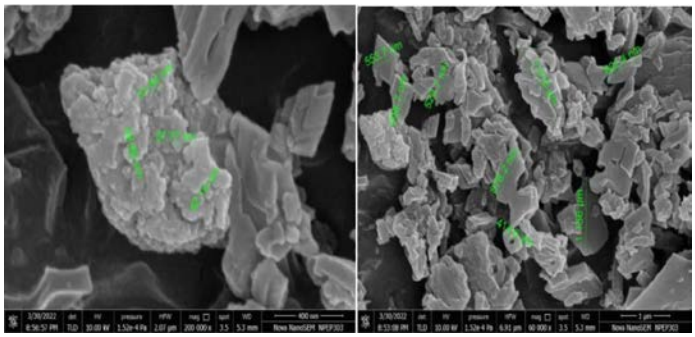

Figure 6: SEM of nanoparticles of optimized batch.

In-vitro drug released study

The *in-vitro* Senna release from nanoparticles was determined by using a dissolution test apparatus (USP II). The minimum drug release was observed after 2 hr in 0.1N HCl, and the maximum drug release was observed after 2 hr in phosphate buffer. Within 8 hr, the Senna released from the optimised batch (F5) was found to be 61.03%. The F5 formulation batch shows the highest drug released and hence is considered an optimised formulation batch. The comparative drug release is shown in Figure 7 and Table 7.

DISCUSSION

The Eudragit L 100-based Senna-loaded Nanoparticles were prepared by the emulsion solvent evaporation method. The organic phase is composed of Senna, methanol and Eudragit L100. The aqueous phase is sodium lauryl sulphate in water. Then the O/W emulsion was prepared by adding the organic phase into the aqueous phase. Then this emulsion was homogenised (GLH-850) for 1 hr at 600 RPM. After that, the solvent was removed from it by a rotary evaporator. (SCI100-S 5L), then the obtained nanoparticles were detected by laser light scattering. Formulation batches are shown in Table 1. With an increase in polymer concentration, the entrapment efficiency increases. The optimised formulation batch (f5) shows the highest entrapment efficiency and percentage yield. The entrapment capacity of the Eudragit L100 plays an important role in the formation of nanoparticles.[26] The FTIR spectra of

Table 7: *In-vitro* drug Release profile of senna nanoparticles.

Sl. No	Time(hrs.)	Cumulative percentage drug release(%)					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	2.6	1.4	2.67	4.62	2.3	3.2
3	2	8.9	8.98	9.45	7.34	3.2	9.75
4	3	19.54	23.88	20.12	23.89	28.01	26.23
5	4	21.08	15.74	30.46	28.65	40.45	33.67
6	5	24.87	27.17	40.05	31.42	45.8	36.76
7	6	27.65	28.26	41.67	34.78	51.49	38.88
8	7	29.45	31.09	43.17	37.94	60.25	41.85
9	8	34.24	36.01	48.23	41.9	61.03	45.9

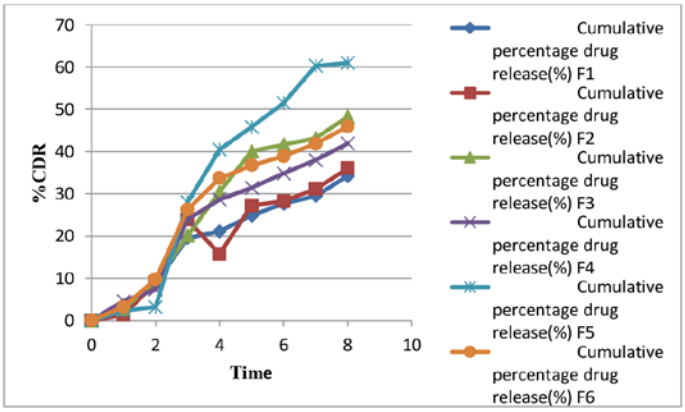

Figure 7: % Cumulative drug release profile.

the pure drug Senna is compatible with the formulation elements shown in Figure 3. The particle size of the optimised batch (f5) was found to be 380.61 nm, which is in the standard range of nanoparticles. The zeta potential of the optimised batch was found to be -23.75mV, which was considered quite sufficient for keeping the particles well separated from each other as a result of electric repulsion. The SEM technique is used to study the microscopic behaviour of drug-nanoparticle compositions. The SEM image shown in Figure 6 revealed the highly porous structure of the Senna loaded nanoparticles formulation batch (f5). The release of a drug in the first 2 hrs was minimal in 0.1N HCL as the drug was enteric coated with Eudragit L100. The Senna released from the optimised batch was found to be 61.03% in the next 6 hrs in phosphate buffer pH 6.8.[27] The *in vitro* drug release study confirmed the release of Senna for a prolonged time. Hence, from this overall study, we can conclude that Senna loaded nanoparticle formulations were successfully developed and useful for site-specific laxative effects.

CONCLUSION

From all the observations and results obtained, it can be concluded that the prepared formulation batches show satisfactory organoleptic properties. A characterization of the drug and excipient was performed and no immeasurable peaks were observed in FT-IR analysis, so characterization confirmed that there was no interaction between the drug and polymers. All results were compared to the standard, which concluded that the drug and excipient were of pure and standard quality. The particle size of the nanoparticles is 380.61nm. The zeta potential of the optimised batch (F5) was found to be -23.75, which reveals good

stability of formulation. Eudragit L-100's enteric coating protects Senna from degradation in the gastrointestinal tract, and it can be immediately dissolved in intestinal pH 6.8 without releasing Senna into the stomach, providing site-specific activity in the intestine for constipation treatment. This is one of the key advantages of nanoparticles over traditional drug delivery. The *in-vitro* drug release study confirmed the release of Senna for a prolonged period of time. Finally, from this overall study, we concluded that Senna nanoparticle formulation can be successfully used for site-specific activity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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