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"PREPARATION, CHARACTERIZATION AND OPTIMIZATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM CONTAINING ANTIASTHMATIC DRUG"

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ABSTRACT

Self-nanoemulsifying Drug Delivery system (SNEDDS) is isotropic mixture of natural or synthetic oil, surfactants and co-surfactants. The present work is to prepare, characterize and optimization of Self nano emulsifying drug delivery system containing Anti-asthmatic drug. The SNEDDS of Montelukast sodium is prepared by probe Sonication method using span 60 as surfactant, Eudragit RL 100 and Eudragit RSPO as components and PVA as Co-surfactant. They are characterized for FTIR studies, SEM study, particles size analysis and drug entrapment efficiency and they are evaluated for visual assessment, self emulsification time, Robustness to dilution, *in-vitro* dissolution studies and stability studies. The FTIR spectra's of SNEDDS are compatible with each other without any drug polymer interaction The prepared nanoparticles are smooth in surface and showing spherical in shape. The average particle size of the nanoparticles was found in the range of 315 nm to 513 nm. The drug encapsulation efficiency (DEE) of the SNEDDS was found in the range of 77.58% to 93.26%. By the visualization study all the formulations are found to be Grade III. Self emulsification time is found to be within 1 minute. Phase separation or no precipitation indicating the stability of nano emulsion. The *in-vitro* drug release data of all the formulations were found to be controlled release over a period of 24 hr. The short time stability study of optimized formulations has done and subjected to drug encapsulation efficiency and in-vitro drug release studies, where results shown that there is no significant change in the formulation.

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INTRODUCTION

Solid oral dosage form covers highest market due to their easy administration and greater stability. There has been a consistent increase in number of new chemical entities (NCE) which possess poor aqueous solubility belonging to BCS Class II drug, low solubility and high membrane permeability presents a major challenge to modern drug delivery system.[1]

SNEDDS

The Self Nanoemulsifying Drug Delivery System (SNEDDS) is a Novel Drug Delivery System for Enhancement of water solubility of poorly water soluble drugs. Self-nanoemulsifying Drug Delivery system (SNEDDS) is isotropic mixture of natural or synthetic oil, surfactants and co-surfactants that have a unique ability of forming fine oil-in-water (O/W) nano-emulsions under mild Agitation followed aqueous media.

The Self Nanoemulsifying Drug Delivery System is also known as Nanoemulsion, Miniemulsion, ultrafine emulsion, Submicron emulsion. [2] The present work is to prepare, characterize and optimization of self nano emulsifying drug delivery system containing Antiasthmatic drug.

Bronchial asthma is a kind of chronic airway disease that affects patients worldwide. According to the report of the World Health Organization, the number of patients with bronchial asthma is up to 30 million in China and 15 million in India. Glucocorticoid therapy is the most common therapeutic regimen for acute bronchial asthma, so Montelukast is a kind of antagonist of cysteinyl leukotriene (Cys-LT) receptor that can regulate the leukotriene pathway, which is clinically used in the acute and long-term treatment of asthma and widely applied in the treatment of asthma.[3] Montelukast is a cysteinyl leukotriene receptor antagonist that has been found to be effective both in the treatment of allergic rhinitis and asthma.[4] It shows plasma or biological half life 2.5 hrs, thereby decreasing bioavailability up to 34%. [5] SNEDDS will helps to enhance the bioavailability of Montelukast also to overcome the adverse effects of drug we selected as targeted self-nano emulsifying drug delivery system for treatment of Asthma. Hence, the present work is to prepare, characterize and optimization of self nano emulsifying drug delivery system containing Antiasthmatic drug by Sonication method using surfactant, co-surfactant and synthetic as well as natural components.

MATERIALS AND METHODS

Montelukast sodium was gifted sample from Optrix lab Pvt Ltd, Bhuvanagiri. Span 60, Eudragit RL 100 were purchased from Yarrow chemicals. Polyvinyl alcohol (PVA) were purchased from Fisher Scientifics. Iso Propyl alcohol, NAOH were purchased from SD Fine chemicals Ltd, and all other chemicals and reagents used were of analytical grade.

Estimation of drug

For the estimation of drug (montelukast), Spectrophotometric method was used by using Phosphate buffer pH 7.4. Scanning range: 200 to 400 nm and Absorption Maxima of Montelukast Sodium was found to be: 287 nm.

PREPARATION OF SNEDDS BY SONICATION METHOD

Solution of surfactant SPAN 60/ Eudragit RL 100 / Eudragit RSPO in Iso propyl alcohol was mixed with Co-surfactant polyvinyl alcohol by using controlled flow rate syringe pump 3ml/min rate. During this mixing the aqueous phase was sonicated using a probe sonicator set at 10 KHz of energy output (Labman Pro-500) to produce oil in water type of emulsion. Place this preparation for magnetic stirrer at 1000 rpm until the organic phase is to evaporate. The obtained nanoparticles were recovered by centrifugation (Remi PR 24) at 10,000 rpm for 15-20 min and washed thrice with distilled water. The washing water was removed by a further centrifugation and nanoparticles weredried.

Table No: 01. Formulation table of SNEDDS by Sonication Technique.

Formulation Code	Montelukast sodium (mg)	Eudragit RL 100 (w/v) (gm)	Eudragit RSPO (gm)	Isopropyl alcohol (ml)	Span 60 (w/v) (mg)	Polyvinyl alcohol (PVA)(%)
MS1	10	0.5	-	30	100	0.5
MS2	10	1	-	30	150	0.5
MS3	10	1.5	-	30	200	0.5
MS4	10	-	0.5	30	100	0.5
MS5	10	-	1	30	150	0.5
MS6	10	-	1.5	30	200	0.5
MS7	10	1	1	30	200	0.5

Characterization of SNEDDS

FTIR Study:

FTIR spectra of pure drugs, physical mixture of SPAN 60 and Eudragit RL 100, Eudragit RSPO and drug loaded Nanoparticles were recorded on a BRUKER IR Spectrophotometer and scanned in the spectral region between 4000 cm^{-1} and 600 cm^{-1}.

Surface morphology:

The surface morphology is most commonly measured by Scanning Electron microscopy. The surface morphology has been studied by using JEOL JSMT -330A Scanning electron microscopy (SEM).

Particle size

The particle size and distribution is measured by HORIBA Scientific SZ-100 by Wet technique. The average particle sizes of the individual batch of self nano emulsifying Nanoparticles were reported.

Zeta potential:

The Zeta potential of a self nano emulsifying Nanoparticles is commonly used to characterize the surface charge property of Nanoparticles. Zeta potential is measured by HORIBA Scientific SZ-100.

Evaluation parameters of SNEDDS:

Visual observation:

The formulation were diluted and made to stand for 24 hours at 37° C. They were observed for phase separation and turbidity.

Self-emulsification time:

1ml of formulations was added to 100 ml of distilled water at 37° C being agitated at 100 rpm. The time required for the formation of a milky emulsion was noted**.**

Robustness to dilution:

The formulations were diluted to 10 ml, 50 ml, and 100 ml were observed over a period of 24 hours for phase separation or signs of precipitation.

In-Vitro drug release study:

In-vitro drug release studies were performed in USP Type II dissolution apparatus at rotation speed of 50 rpm. The prepared Nanoparticles were immersed in 900ml of phosphate buffer solution in a vessel, and temperature was maintained at 37±0.20°C. Required quantity 5ml of the medium was withdrawn at specific time periods and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn samples were analyzed using UV spectrophotometer (SHIMADZU 1700).

Short term Stability studies:

The Prepared SNEDDS were packed in screw capped HDPE bottles and were stored at 40± 20 C and 75 % RH for 45 days. After storage for 45 days, the products were tested for drug entrapment efficiency and drug release study as per the ICH guidelines.

RESULTS AND DISCUSSION:

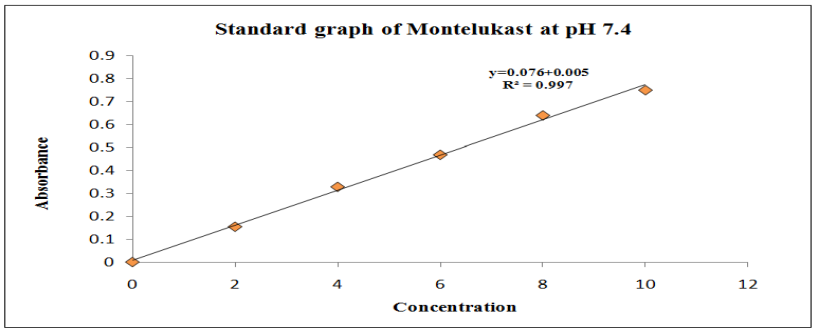


Figure 02: Caliberation curve of Montelukast Sodium.

Results of R^2 value of standard graph of drug not more than 0.99 i.e. it obeys beer's law.

Drug-polymer interaction study by FT-IR spectrophotometer:

The IR spectra shows peak at 3426 cm^{-1} due to presence of Hydroxyl group (OH). The peak at 2850 cm^{-1} due to presence of C-H group , the peak at 1729 cm^{-1} due to presence of C=O group, the peak at 1567 cm^{-1} due to presence of C=N group. The peak at 1464 cm^{-1} due to presence of C=C group and peak at 1167 is because of presence of C-S-C group. These similar peaks are obtained in IR spectra of pure drug (Montelukast) and MS7 formulation. It indicates that there is no interaction between drug and polymer used for the preparation of SNEDDS and the results are shown in Figure no 03.

FTIR spectra of Montelukast Sodium **FTIR spectra of Formulation MS7**

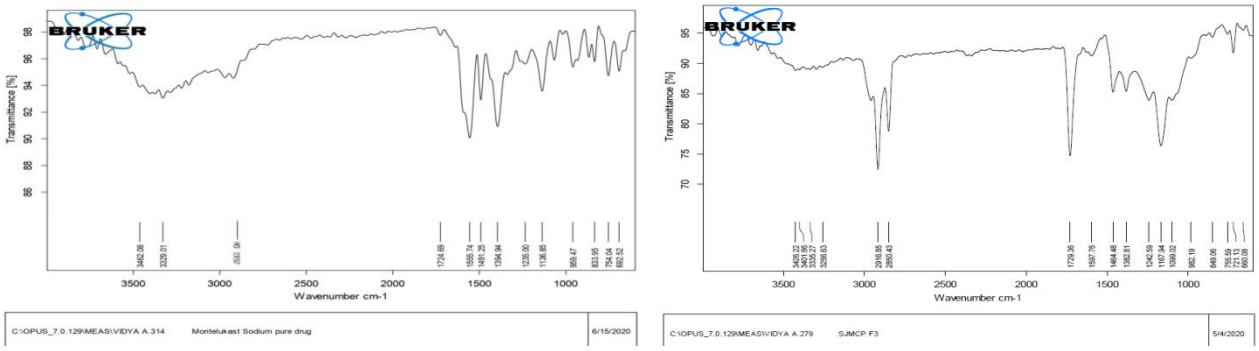


Figure No: 03 IR spectrum of Montelukast and formulation MS7.

Surface Morphology:

The surface morphology of the prepared SNEDDS was characterized by SEM studies. Figure no 04 show the SEM images of polymeric nanoparticles containing the drug Montelukast Sodium.

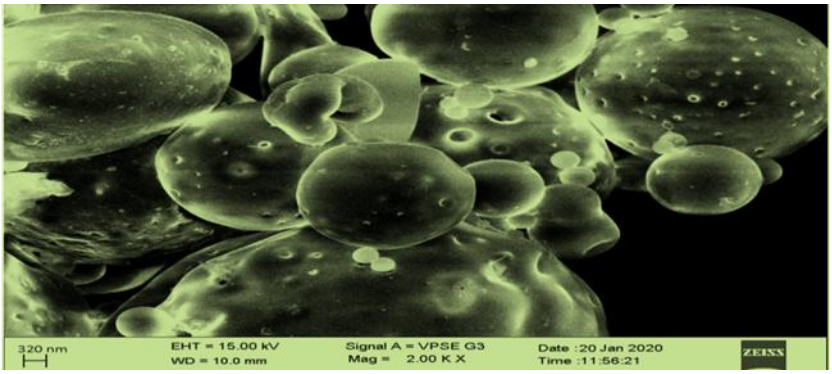
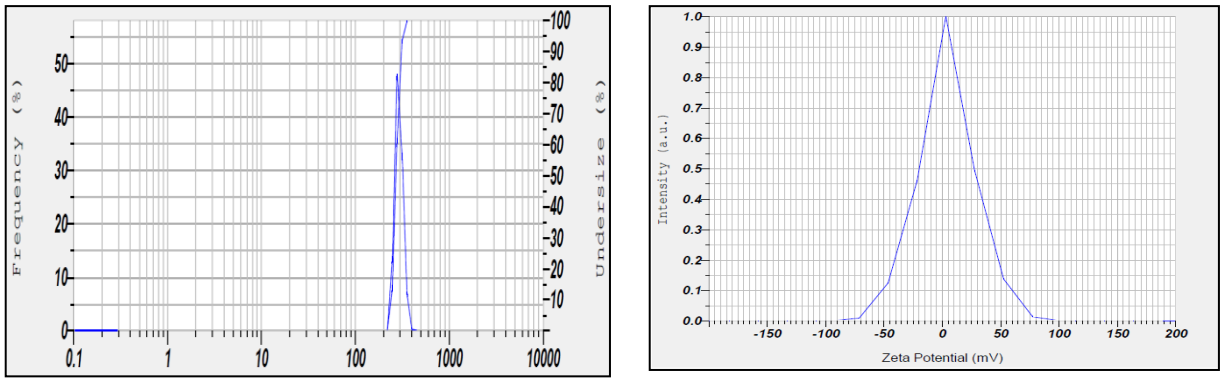


Figure No 04: SEM image of MS7.

Table No: 02 Particle size and drug entrapment efficiency analysis of SNEDDS.

Sl. No	Formulation code	Particle size analysis (nm)	Drug EE (%)
01	MS1	513	77.58
02	MS2	454	78.50
03	MS3	402	80.26
04	MS4	449	86.5
05	MS5	356	89.26
06	MS6	460	90.57
07	MS7	315	92.38



Particle Size distribution of MS7. **Zeta potential (mV) of MS7.**

Figure No 05: Particle Size and Zeta Potential.

Visual assessment

In self nano-emulsion formulations only MS2, MS4, MS5, MS6 and MS7 were clear. The rest of the formulations showed precipitation.

Table No: 03 Visual assessment of MS_1-MS_7.

Sl. No	Formulations	Visibility Grade	Precipitation
01	MS1	IV	YES
02	MS2	IV	NO
03	MS3	III	YES
04	MS4	III	NO
05	MS5	III	NO
06	MS6	III	NO
07	MS7	III	NO

Self emulsification time

1ml of formulations was added to 100ml of distilled water at 37° C being agitated at 100 rpm. The time required for the formation of a milky emulsion was noted for MS2, MS4, MS5, MS6 and MS7 were 58 sec, 53 sec, 51 sec, 49 & 48 sec.

***In-vitro* Drug release Study:**

Table No: 04 *In - vitro* drug release of SNEDDS Formulation from MS1 to MS7.

Time (hr)	% Drug Release $\bar{X}$± SD						
	MS1	MS2	MS3	MS4	MS5	MS6	MS7
0	0	0	0	0	0	0	0
0.5	3.81±0.015	4.25±0.018	3.25±0.025	4.12±0.014	4.16±0.014	5.42±0.035	3.48±0.047
1	7.45±0.021	7.85±0.013	8.16±0.024	12.45±0.016	9.51±0.034	10.16±0.029	9.91±0.014
1.5	13.48±0.35	15.85±0.021	12.25±0.051	16.86±0.023	14.45±0.026	15.42±0.038	11.64±0.025
2	20.47±0.51	22.85±0.035	17.48±0.014	24.32±0.026	23.48±0.021	26.14±0.017	24.45±0.087
3	28.64±0.68	32.86±0.016	22.78±0.064	37.21±0.034	38.42±0.013	35.46±0.015	36.56±0.091
4	35.21±0.042	38.50±0.028	36. 12±0.047	44.23±0.021	40.16±0.026	45.96±0.014	40.89±0.032
5	45.87±0.062	43.85±0.087	41.24±0.078	48.26±0.013	46.28±0.038	51.48±0.029	48.98±0.021
6	51.26±0.072	57.85±0.038	48.84±0.047	56.28±0.014	55.89±0.034	61.87±0.026	54.56±0.017
7	58.50±0.021	63.54±0.078	59.42±0.014	65.62±0.025	68.14±0.011	68.12±0.034	60.48±0.027
8	63.45±0.035	71.75±0.026	64.14±0.033	69.65±0.024	71.63±0.027	70.85±0.031	66.89±0.087
9	68.98±0.063	72.05±0.084	69.54±0.018	70.14±0.031	73.65±0.018	75.65±0.028	70.46±0.024
10	72.45±0.019	73.52±0.018	70.42±0.047	74.25±0.027	75.89±0.026	78.85±0.017	77.65±0.078
11	74.26±0.023	75.15±0.084	71.54±0.087	78.65±0.027	81.56±0.039	82.25±0.018	86.45±0.026
12	76.45±0.054	76.24±0.051	74.24±0.048	80.24±0.09	85.69±0.026	86.24±0.039	87.98±0.087
18	77.85±0.061	77.49±0.027	80.42±0.074	82.25±0.028	87.56±0.013	87.2±0.024	91.01±0.026
24	78.58±0.031	79.68±0.034	82.42±0.015	83.65±0.031	88.95±0.028	88.27±0.014	92.78±0.018

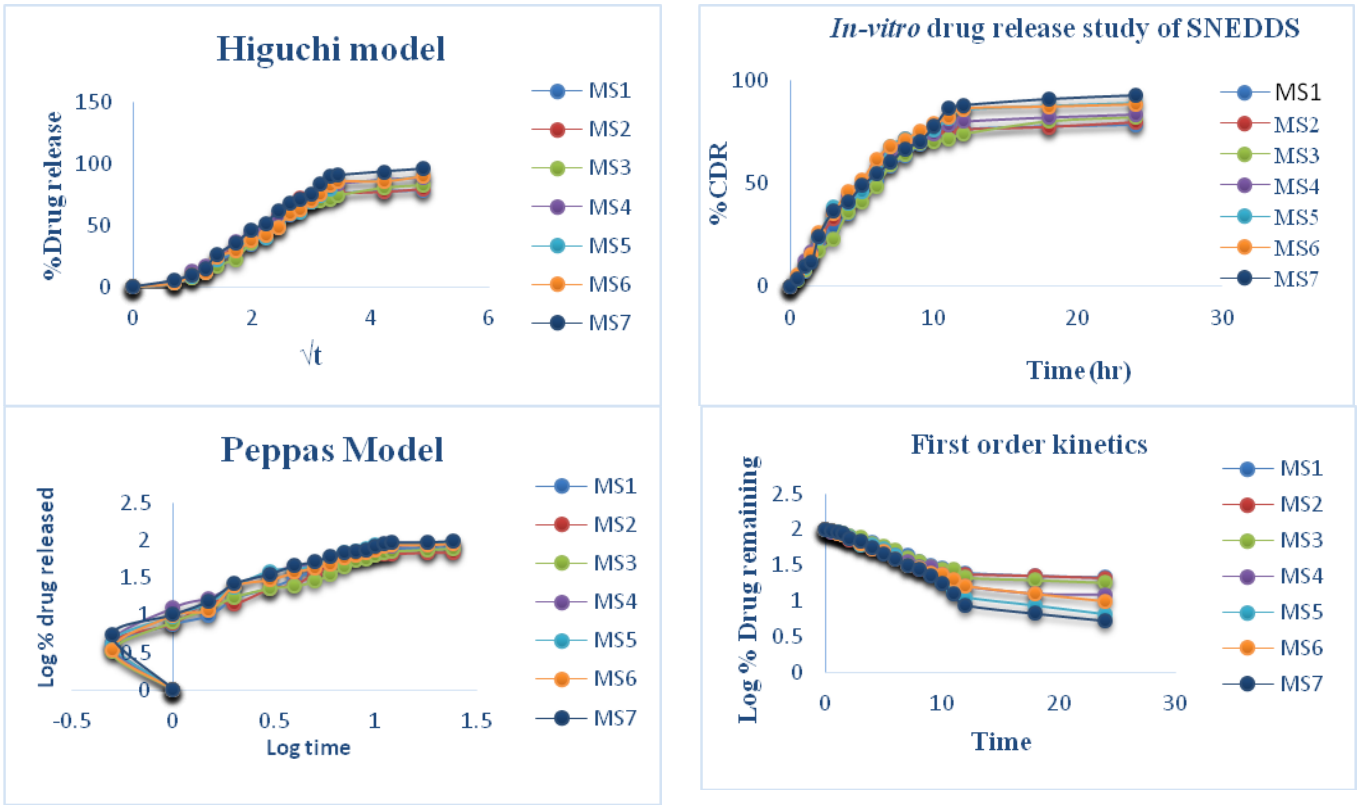


Figure No: 06 *In-Vitro* Drug Release Study of Montelukast from MS1 to MS7 SNEDDS.

Stability study:

After storage for 45 days the products were tested for drug release rate as per the methods described earlier. The results are given in below Table no 04.

Table No: 04 Stability Study of MS_7.

Formulation	Percentage of drug release	
	Before stability test	After stability test
MS7	90.01	89.15

CONCLUSION

From the results it can be concluded that biocompatible and cost-effective polymer like Eudragit RL 100 and Eudragit RSPO can be used to formulate an efficient self nano emulsifying drug delivery system formulation with good percentage entrapment efficiency and practical yield. The particle size analysis indicated that the nanoparticles were in the size range of 315-513nm, and showed good flow properties. The nanoparticles were smooth, as shown by the scanning electron microscopic studies. *In-vitro* drug release showed that release from the SNEDDS successfully retarded for over 24h. The formulations were found to be stable in short term stability studies. Pharmacokinetic studies indicate that the *In-vitro* drug release of the formulations fitted Peppas model the mechanism follows non-Fickian drug release. Here we have selected MS_7 as an optimized formulation which shown good morphological features, drug entrapment efficiency and Maximum drug release. By considering the results obtained from *in-vitro* and stability studies, it can be suggested that there is further scope for the *in-vivo* and the pharmacokinetic study.

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LIST OF ABBREVATIONS

ABBREVATION	DEFINITION
SNEDDS	Self Nano Emulsifying Drug Delivery System
PVA	Polyvinyl Alcohol
FTIR	Forier Transform Infra-Red Spectra
SEM	Scanning Electron Microscopy
DEE	Drug Encapsulation Efficiency

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