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SOLID SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF PROCHLORPERAZINE MALEATE USING ANHYDROUS LACTOSE AS ADSORBENT

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ABSTRACT
Self-micro emulsifying drug delivery system is one of the promising drug delivery systems among the other lipid-based drug delivery systems. These are mainly used for the delivery of poorly water soluble drugs which are known to show less oral bioavailability. These are commonly dispensed in the form of liquids but due to some of the disadvantages these are solidified and thus either compressed as tablets or filled in the capsules for dispensing. The present study involves the solidification of the liquid self-micro emulsifying drug delivery system of prochlorperazine maleate by adsorption technique using anhydrous lactose as adsorbent. The prepared S-SMEDDS showed the percentage drug content 93.78 ±4.1463 %, and SEM showed that the formulation had microparticles without aggregation. The *in-vitro* dissolution profile of the drug from the S-SMEDDS (OF1SAL) was 91.11± 0.09 % in 60 minutes which was more than the pure drug and L-SMEDDS. Accelerated stability studies was performed at 40^0C ± 2^0 C and 75% ± 5% RH and found to be satisfactory. Thus, it can be concluded that a lipid-based drug delivery system in the solid form can be successfully developed with the potential of enhancing the solubility, dissolution, and oral absorption of the drug.

KEYWORDS: S-SMEDDS, adsorbents, stability, self-emulsification.

INTRODUCTION
Oral route considered to be a most suitable route for the administration of the drugs as it is patient convenient, easy administration etc. The BCS class 2 and class 4 drugs which shows poor water solubility makes it difficult for oral administration due to their lipoidal nature. Various techniques have been employed to increase their solubility thus increasing their oral bioavailability. Lipid containing formulations such as emulsions, lipid solutions and many other formulation strategies have been developed which acts as carrier for the poorly water-soluble drugs. Conventional emulsions show difficulty in manufacturing, stability, and storage. Thus, a novel approach has been developed such as self-emulsifying drug delivery system (SEDDS), self-micro emulsifying drug delivery system (SMEDDS), self-nano emulsifying drug delivery system (SNEDDS) etc. These are isotropic mixtures of drug, oils, and surfactants, usually with one or more hydrophilic co-surfactants which is followed by dilution with aqueous media, results in fine (oil in water) emulsion instantaneously, upon mild agitation.[1]

These are usually prepared in the form of liquid dosage forms which are then dispensed in the form of solutions or filled in the capsules. But these dosage forms show some problems, and thus they are converted into solid forms by using different methods. The liquid or semisolid forms prepared are solidified either adsorption techniques, hot melt extrusion, spray drying, and melt granulation etc. Adsorption on to the solid carriers is one of the easiest methods employed since they provide good uniformity for the final preparation. Solid carriers such as silica, talcum, lactose, and magnesium oxide etc. are mixed with the L-SMEDDS, which are then dried and then dispensed in the form of tablets or capsules.[2]

Prochlorperazine maleate is a phenothiazine derivative which is mainly used as antiemetic for the treatment of emesis and nausea caused by chemotherapeutic agents. This drug show low oral bioavailability 12-15%, showing low solubility, thus acting as a suitable candidate for the development into SMEDDS [3].

Present study mainly focuses on increasing the solubility of prochlorperazine maleate by converting them on to solid self-micro emulsifying drug delivery system.

MATERIALS AND METHODS
Materials
Prochlorperazine maleate was obtained as a gift sample from Yarrow chem products, Mumbai, India. Excipients

such as Isopropyl myristate(oil), Tween 80(surfactant), PEG 400(co-surfactant) and anhydrous lactose(carrier) were purchased from Loba chemie, Mumbai, India. All the other chemicals were reagent grade.

Methods

Preparation of L-SMEDDS[4]

Based on the solubility study of Prochlorperazine maleate in different oils, surfactants, and co-surfactants and construction of pseudo ternary phase diagram, the liquid self-micro emulsifying drug delivery system was developed and further they were evaluated.

Initially, Prochlorperazine maleate was dissolved in the PEG 400 at 60^0 C maintain the temperature throughout the formulation. Isopropyl myristate was the added, and cooled to room temperature. Then the formulation was mixed with the Tween 80 further the mixture was sonicated to get clear solution. the formulation was equilibrated at room temperature for 48 hrs and observed for any separation of turbidity by visual observation. Further, this formulation was stored in suitable container until it is used.

Preparation of solid-SMEDDS[5]

The solidification of L-SMEDDS by using different adsorbents such as Colloidal silicon dioxide, Magnesium oxide, Micro crystalline cellulose and anhydrous lactose were studied.

The above-mentioned adsorbents were added to the L-SMEDDS at different ratios and stirred evenly so that the adsorbents get thoroughly mixed. The slight wetness of the formulation indicates the saturation of the adsorbent and further they were dried to get solidified liquid self-micro emulsifying drug delivery system(S-SMEDDS).

The optimized formulation was selected based on the self-micro emulsifying time and visual appearance after the dilution with water.

1ml of the formulations with different adsorbents were added to the 100ml of the distilled water at 37^0 C and stirred for 10mins on a magnetic stirrer. Based on the self-emulsification the final formulation was selected.

EVALUATION OF S-SMEDDS

FTIR Studies[6]

The compatibility between the drug and excipients were studied by using the Fourier transform infra-red spectroscopy. The drug was dissolved in the selected adsorbent and equilibrated for 72 hours. The pure drug, physical mixture and the formulation was scanned between 400-4000 cm^{-1} . The spectrum obtained was compared with the reported values of the pure drug.

Micromeritics studies[7]

Angle of repose

The angle of repose of S-SMEDDS was determined by using funnel method. The formulation was taken in a funnel and attached to the stand. The tip of the funnel was fixed near the apex of the heap of the powder. The powder was allowed to fall on the plain surface. The radius of the cone (r) and the height of the powder(h) pile was measured and the angle of repose(θ) was calculated using the following formula: $\tan \theta = h/r$.

Bulk density

The S-SMEDDS was taken in a measuring cylinder and the initial volume was recorded. The cylinder was tapped continuously and the change in the volume was recorded. Readings were taken in triplicate. The loose bulk density (LBD) and tapped bulk density (TBD) was calculated using the following equations:

LBD = weight of the powder/ volume of the packing

TBD = weight of the powder/ tapped volume of the packing

Carr's compressibility index

The compressibility of the powder blend was determined by using the following equation:

Carr's compressibility index = [(TBD – LBD) / TBD] * 100

Drug content estimation[8]

S-SMEDDS containing 5mg of drug equivalent to pure drug was suitably diluted with the methanol. Further this was centrifuged at 3000rpm for 15min. The supernatant solution was suitably diluted with the solvent and analyzed by UV-Visible spectrophotometer.

Morphological analysis by scanning electron microscopy[9]

The S-SMEDDS was fixed on a glass slide and the morphological characterization was studied by using scanning electron microscopy. The surface structure of the formulation was reported.

Differential scanning colorimetry analysis[10]

Approximately 5mg of the pure drug and the formulation was kept on an aluminum plate and heated from 30^0 C to 300^0 C. The DSC thermograms of these samples were recorded.

In-vitro drug dissolution study of S-SMEDDS[11]

The *in-vitro* performance of the formulation was studied by using standard-USP dissolution apparatus by using 0.1 N hydrochloric acid as a dissolution medium. The formulation equivalent to 5mg of the pure drug was added into the capsules and placed in the apparatus at 50rpm and at 37 ± 5^0 C. the aliquots of the samples was withdrawn at different interval of time. Percentage cumulative drug release was calculated by measuring the absorbance of the sample at lambda max of the drug.

Stability studies[12]

The stability of the formulation was studied according to international conference of harmonization (ICH). The physical appearance, % drug content, speed of emulsification and % drug release was measured at 40 ± 2^0 C, 75 ± 5 % RH for 6months.

RESULTS AND DISCUSSIONS

The adsorption technique was employed to convert the L-SMEDDS into S-SMEDDS. Different adsorbents such as colloidal silicon dioxide, microcrystalline cellulose, magnesium oxide and anhydrous lactose were added to L-SMEDDS (Table 1). Based on the self-emulsification time and clarity of the preparation final adsorbent was selected (Fig 1).

Table 1: Comparison study of different adsorbents with the formulation

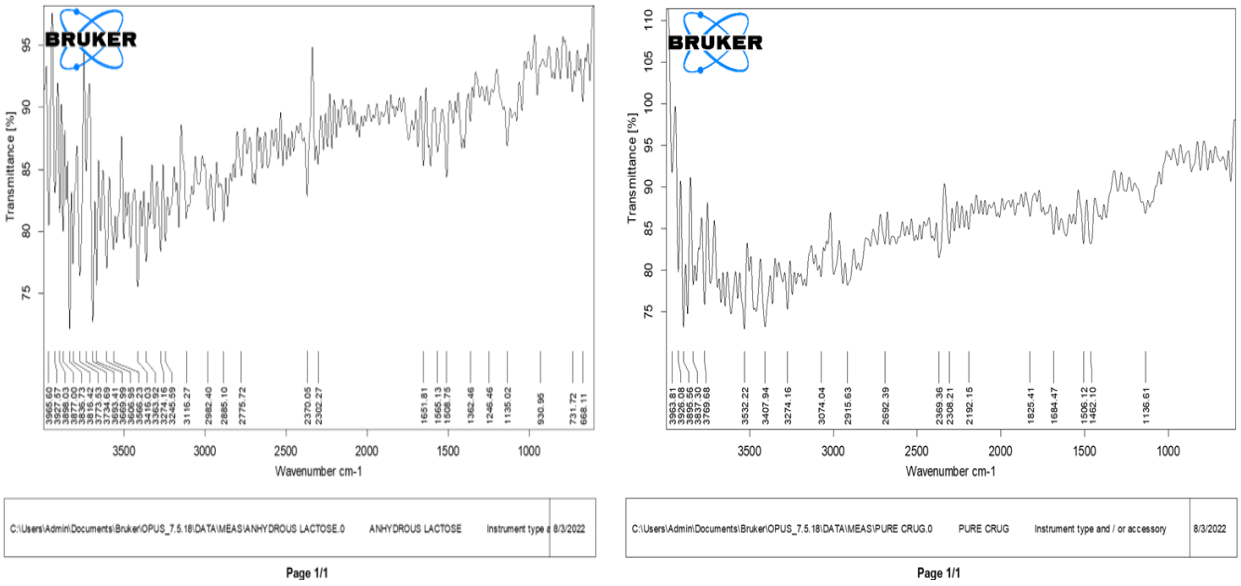
Formulation code	Adsorbents	Self emulsification time (seconds)	Clarity
OF1SCD	Colloidal silicon dioxide	175	Cloudy white appearance
OF1SMC	MCC	95	Clear and transparent
OF1SMG	MgO	90	Clear and transparent
OF1SAL	Anhydrous lactose	45	Clear and transparent

Fig. 1: L-SMEDDS with different adsorbents; colloidal silicon dioxide (OF1SCD), magnesium oxide (OF1SMG), MCC (OF1SMC) and anhydrous lactose (OF1SAL).

Among all the adsorbents used, anhydrous lactose showed self-emulsification within 45 seconds resulted in clear, transparent solution upon dilution. Thus, the L-SMEDDS was converted in to free-flowing solid powder by using anhydrous lactose as adsorbent.

FTIR studies

The FTIR spectrum of pure drug, anhydrous lactose and formulation were reported and showed that there are no interactions between the drug and excipients as there is no change in the spectrum. This indicated that the method used for the formulation does not the affect the stability of the formulation.



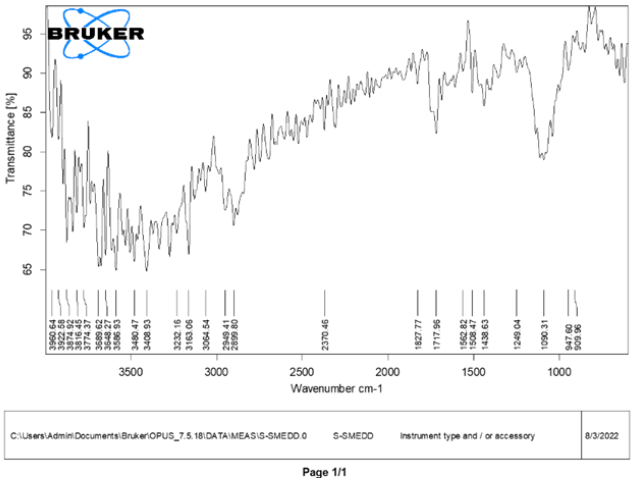


Fig. 2: FTIR spectra of Prochlorperazine maleate, Anhydrous lactose and formulation S-SMEDDS (OF1SAL).

Micromeritics studies

The micromeritic studies of the prepared formulation was carried out and shown below.

Table 2: Micromeritic study of the prepared S-SMEDDS of Prochlorperazine maleate (OF1SAL)

Micromeritic evaluation parameters	Observation*	Inference
Angle of repose	$28^0 \pm 0.04$	Shows good flow property
Loose Bulk density	0.3725±0.012 g/ml	Powders are loosely packed
Tapped bulk density	0.4004±0.035 g/ml	Powders are loosely packed
Compressibility/ Carr's index	6.968 ± 0.05 %	Shows excellent compressibility
Hausner's ratio	1.074	Shows excellent flow property

(*Data represented as mean ± standard deviation and n=3)

Drug content estimation

The percent drug content of the S-SMEDDS formulation (OF1SAL) was found to be 93.78 ±4.1463 %. They showed the drug uniformly distributed in the formulation.

Morphological analysis

SEM analysis of S-SMEDDS (OF1SAL) were performed. Fig. 3 showed that these images showed particles were loose without much aggregations.

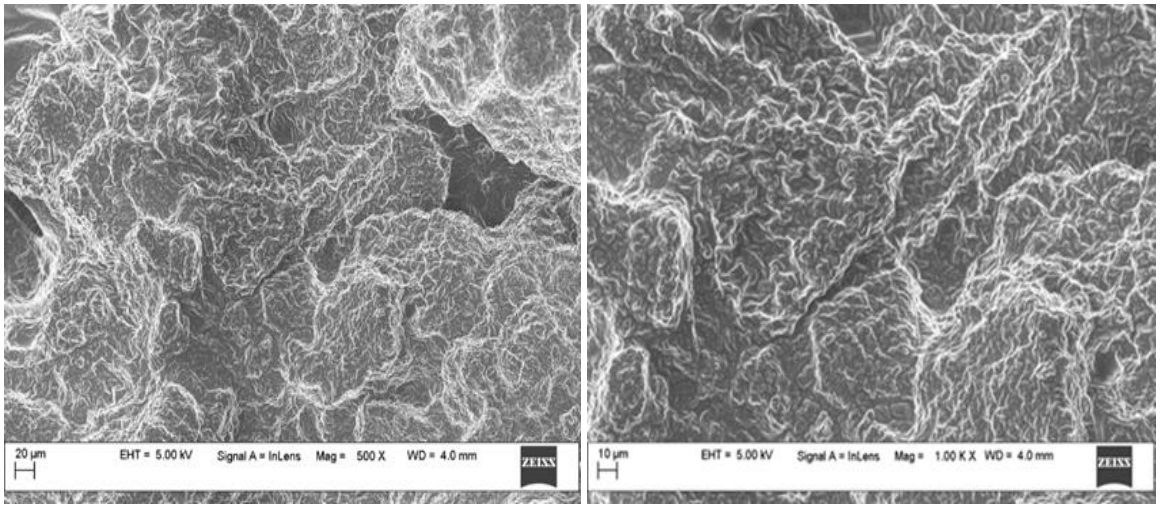


Fig. 3: SEM photographs of formulation S-SMEDDS(OF1SAL) at 500 magnification and at 1000 magnification.

Differential scanning colorimetry analysis

DSC analysis of Prochlorperazine maleate showed sharp endothermic peaks at about 205.21°C, corresponding to their melting point 209°C. It noticed that there was a shift in the melting point from 205° to 233.42°. This further contributes to the high aqueous solubility of the formulation and increased dissolution rate.

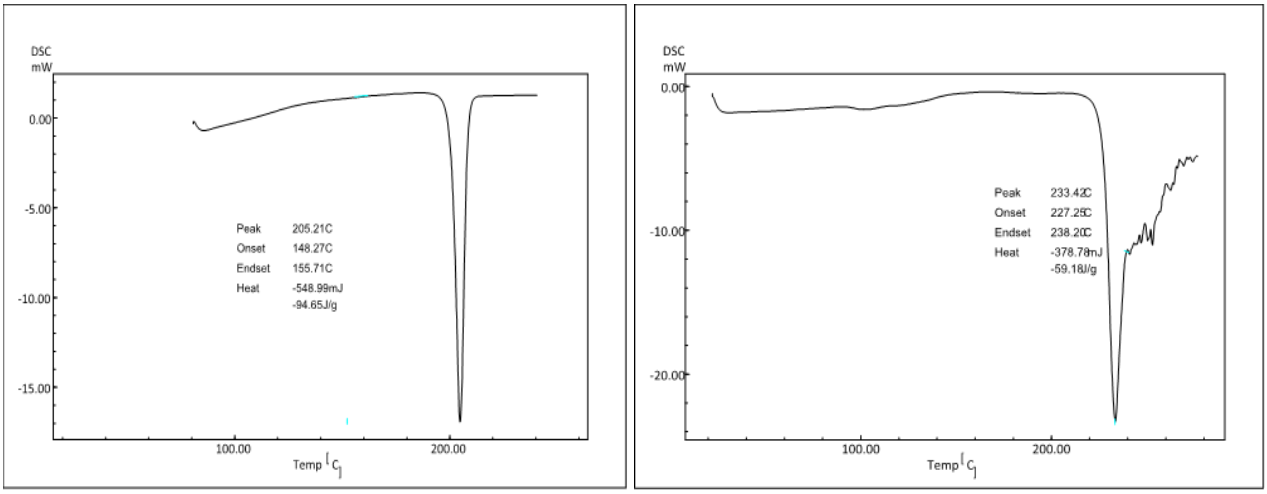


Fig. 4: DSC spectra of pure Prochlorperazine maleate and S-SMEDDS (OF1SAL).

***In-vitro* drug dissolution study of S-SMEDDS**

The % cumulative drug release from the selected S-SMEDDS (OF1SAL) formulation was found to be 91.11±0.09%, which was 2 times higher when compared to that of the pure drug and was superior to that of the L-SMEDDS (OF1).

Table 3: Comparison of Percentage cumulative drug release (%CDR) from pure drug, optimized L-SMEDDS(OF1) formulation, and S-SMEDDS(OF1SAL)

Time in minutes	%CDR from pure drug*	%CDR from L-SMEDDS*	%CDR from S-SMEDDS*
0	0 ± 0.00	0 ± 0.00	0 ± 0.00
5	10.08 ± 0.38	43.09±0.99	56.89±0.19
10	11.81 ± 0.26	44.62±0.87	61.92±0.27
15	13.97 ± 0.23	46.46±0.92	67.9 ±0.80
20	15.23 ± 0.72	49.48±0.36	69.89 ±0.06
25	20.83 ± 0.20	52.45±0.28	72.33±0.88
30	23.29 ± 0.84	56.88±0.32	74.90±0.35
35	28.12 ± 0.57	60.84±0.19	79.48±0.85
40	34.87 ± 0.18	66.78±0.21	82.21±0.13
45	37.13 ± 0.13	68.29±0.32	86.23±0.03
50	39.67 ± 0.51	71.92±0.32	88.02±0.98
55	42.02 ± 0.13	74.02±0.71	90.81±0.54
60	49.46 ± 0.92	79.12±0.11	91.11±0.09

(*Data represented as mean ± standard deviation and n=3)

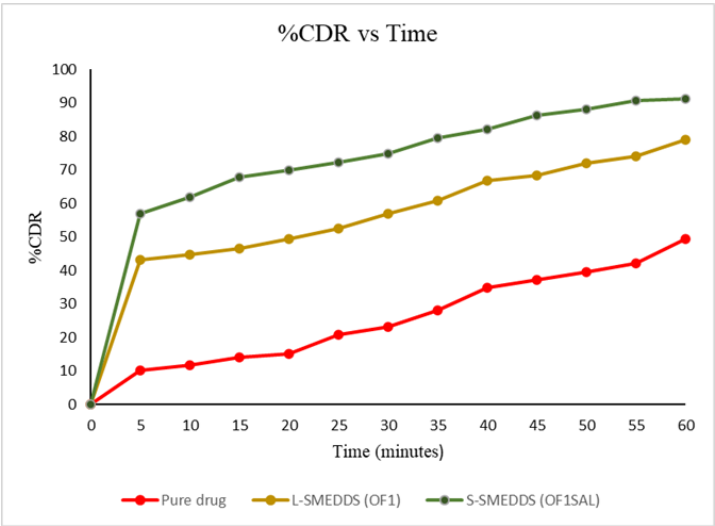


Fig. 4: % Cumulative drug release of pure drug, liquid formulation (OF1) and S-SMEDDS (OF1SAL)

Accelerated stability studies

From the stability study, it was found that the evaluated formulation showed there was no influence of variety of environment factors such as temperature, humidity, and light, and during storage conditions or shelf life of drug in Table 4. The data showed that there were no significant changes in visual appearance, speed of emulsification, % drug content and *in-vitro* drug release after 60 mins.

Table 4: Observations made at $40^0 \pm 2\ ^0C$/ 75 ± 5 % RH of S-SMEDDS (OF1SAL).

Time	Physical appearance upon dilution	Speed of emulsification (seconds)*	Drug content (%)*	% Drug release after 60 min (%) *
0	Clear, transparent appearance	45 ± 0.00145	92±0.044	88±0.009
30 days	Clear, transparent appearance	57± 0.002	92±0.012	87±0.0034
90 days	milky white appearance	68±0.00013	90±0.0001	85±0.0001

(*Data represented as mean ± standard deviation and n=3)

CONCLUSION

The present study demonstrates the novel approach of treating the emesis caused by chemotherapeutic agents in the form of solid-self micro emulsifying drug delivery system than the conventional dosage form. The prepared Prochlorperazine maleate S-SMEDDS (OF1SAL) were uniform and homogeneous. The drug content of OF1SAL was 93.78 ±4.1463 %. The percentage cumulative drug release from OF1SAL after 60min was found to be 91.11%, Prepared formulation (OF1SAL) did not show much difference in drug content and %CDR hence it is proved that prepared formulation was found to be stable. Hence it is concluded that above formulation can be more effective than conventional tablets used in treatment of emesis.

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