Original Article

Development and Evaluation of a System for Colonic Delivery of Budesonide

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ABSTRACT

In the present study an attempt has been made to address low solubility issue and colonic delivery of Budesonide by developing enteric coated capsule containing Budesonide in a nano emulsifying drug delivery system. Herein, the formulated liquid SNEDDS was transformed to a solid form by spray draying method. Subsequently, it was filled into capsules coated with pH sensitive polymer, Eudragit S- 100 along with band sealing. However, the drug solubility is an important parameter which was determined in different oils, surfactants and co-surfactants. Ternary phase diagrams were constructed to obtain maximum nano-emulsion area. SNEDDS containing Capmule ®MCM L8 as oil, Tween-80 as surfactant and polyethylene glycol 400 as co-surfactant were formulated to get maximum nano-emulsion in the phase diagram. *In vitro* drug release of the optimized SNEDDS (particle size 116.32 nm) revealed enhanced drug release in colonic pH as compared to pure drug. The developed SNEDDS of budesonide also demonstrated better activity against ulcerative colitis as evidenced by the gradually diminishing morphological damages in the histopathological studies in the TNBS induced ulcerative colitis in rats. Thus, SNEDDS enhanced the solubility of Budesonide while the enteric coating provides its colonic release.

Key words: SNEDDS, Colonic Release, Budesonide, Solubility, *In vitro*, *In-vivo*, Ulcerative Colitis.

INTRODUCTION

Budesonide (BUD) is a locally acting corticosteroid with high affinity for glucocorticoid receptors. It offers several therapeutic advantages such as negligible oral bioavailability, rapid clearance and no formation of active metabolites and hence is preferred over old steroids such as hydrocortisone, prednisolone and dexamethasone for the localized treatment of inflammatory bowel diseases.[1] However, budesonide has poor solubility and bioavailability, a property which limits its dissolution and therapeutic potential. Nevertheless, the solubility of BUD needs much improvement and a formulation for effective drug targeting. Moreover, the Self nano-emulsifying drug delivery system (SNEDDS) is composed of with a peculiar isotropic mixture of lipids and surface coating emulsion. These systems with drugs particles size less than 100 nm appear optically clear and thermodynamically stable. Amongst the various lipid-based systems, SNEDDS accelerates and improves the permeability rate of drug through biological membrane. SNEDDS spread readily *in vivo* and motility of the stomach and the intestine causes self-emulsification.[2] Rapid emulsion formation helps to keep the drug in soluble form whereas the high surface area provided by the small droplets enables more efficient drug transport through the membrane leading to improved oral bioavailability.[3,4] Thus a SNEDDS containing BUD would enhance its solubility and permeability into the tissue and cells at the site of inflammation.

There are different local and systemic drug delivery system treatments useful in colonic disease like ulcerative colitis, crohn's disease but the challenge the oral drug delivery systems face is to reache up to colon without

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releasing it into stomach and small intestine. Hence, this study was mainly focused to increase the effectiveness of BUD through the concept of an oral enteric coated capsule containing its solid SNEDDS. For colonic delivery of BUD, many approaches such as preparation of BUD loaded microspheres coated with guar gum, microencapsulated cellulosic cores, solid dispersion in dextran, pH and time dependent polymeric nanoparticles and eudragit coated pellets etc. are available. These reported dosage forms have been formulated with the aim of only targeting drug BUD to colon to enhance its anti-inflammatory activity. The anti-inflammatory activity of BUD is a function of its solubility too. Nevertheless, the solubility of BUD is low and this issue also has to be dealt. The current investigation deserves merit as it addresses both the issues of solubility enhancement and colon targeting by SNEDDS formulation and enteric coating respectively. The formulation of SNEDDS contains Capmule MCM L8, Tween–80 and polyethylene glycol as oil, surfactant and co-surfactant respectively. Subsequently the emulsion form of SNEDDS was spray dried and filled into capsules with coating of pH sensitive polymer of Eudragit S-100 to achieve colonic targeting. The colon targeted SNEDDS were evaluated for pharmacokinetics and pharmacodynamics parameters.[5-8]

MATERIALS AND METHODS

Materials

Budesonide was procured from Lupin pharmaceutical, Inc, Pune, Maharashtra, India. Oils that is Capmule® L8, Cremophor® EL, Captex® 300, Captex® 355, Maisine™ were purchased from Abitec Ingredient company. Polyetlylene glycol-400, Tween-80 and Tween-20 were received from Loba Chemie Pvt. Ltd, Mumbai. Co-surfactants like Plurol Oleique® and Labrafil M 1944 CS were purchased from Gattefosse, France through Colorcon Asia Ltd, Mumbai. For All others reagents used were of pharmaceutical and analytical grade.

METHODS

SNEDDS Components

SNEDDS was composed of three main components such as oil, surfactant and co-surfactant. Maximum solubility of BUD in each of these components was determined by weighing 40 mg drug in 1 ml of different components such as Capmul® MCM L8, Captex®300, Captex® 355, Maisine™, Labrafil® M 1944 CS and emulsifiers like Tween-80, tween-20, Cremophor® EL, polyethylene glycol-400, Propylene glycol and plurol Olieque ® in a 5-10 ml vial. This mixture was stirred for 15 min on magnetic stirrer and further in orbital shaker for 72 h at 37^{0}C, followed by centrifugation for 15m at 3000 rpm. 1ml of supernatant obtained was diluted with methanol to make up 10 ml and its absorption measured by UV Spectroscopy at 247 nm.[3-9]

Diagrammatic Study

Pseudo ternary phase diagram was built up by water titration method to obtain concentration ranges of oils and S-Mix (a mixture of both Surfactant and co-surfactant). S-mix was prepared in different ratios of 1:1, 1:2, 1:3, 2:1, & 3:1 (w/w) of surfactant and co-surfactant respectively. An appropriate fixed ratio of S-mix was selected and then it was combined with oil in different ratios of oil-S-Mix such as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (w/w) respectively. As per water titration method, oil and S-mix were taken in above mentioned ratios in pre-weighted vials and slowly water drops were added in to this liquid mixture with the help of burette until clear bluish liquid is seen then stopped adding water. This indicated formulation of a nano emulsion by further adding 2-3 water drops in it, the mixture become opaque. CHEMIX School software was used for construction of ternary phase diagram.

SNEDDS Formulation

The results obtained from solubility study and ternary phase diagram were used to select concentration of Capmul® MCM L8, Tween® 80, polyethylene glycol-400 for the preparation of nano emulsion formulation. The BUD loaded SNEDDS were prepared by dissolving accurately weighed drug (budesonide-6mg) properly in S-mix and oil. The mixture was homogenized the formulation at 40-50^{0}C, cooled to 25-30^{0}C and stored at same temperature.

Evaluation of Liquid SNEDDS

Microscopic Examination

Microscopic study exhibits certain unique characteristics regarding, whether any changes has taken places or not during its storage at normal condition (at 30^{0}C); like homogeneity, color, transparency and phase separation.

Percent Transmission Measurement

Transmission study data revealed stability of the formulation; higher is the percent transmission more stable is the formulation. The formulation (100mg) was diluted into 100 ml of distilled water, 0.1 N HCl and pH 7.4 phosphate buffer solutions. Percent transmission was measured by UV spectrophotometer at 628nm in triplicate.[10]

Self-emulsification Time Analysis

Self-emulsification time of SNEDDS was estimated by type II USP dissolution apparatus. The formulation (500 mg) was added drop wise into 500 ml distilled water maintained at 37±0.5^{0}C and at 50 rpm. Emulsification time was assessed visually.[11]

Determination of Cloud Point

Cloud point measurement is an essential parameter to form a stable nano emulsion. In this method its determination was done by addition of distilled water to formulation in 1:250 ratio in a water bath at 60^{0}C. The time required for solution to become opaque and cloudy was noted as the cloud point.

Particle Size Measurement and Polydispersity Index

Nanophox particle size analyzer instrument was used to measure particle size and polydispersity index of liquid SNEDDS.

Dilution Factor

Robustness of dilution test was performed by diluting SNEDDS to 10, 100 and 1000 times with dissolution media like 0.1 N HCl, pH 6.8 and pH 7.4 phosphate buffer solution. These dilutions were kept for 12 hr and observed for turbidity or phase separation.

Drug stability

Temperature Stability

SNEDDS of BUD was kept under ambient room temperature (20-25^0) for 3 months and observed for changes in physical stability. The stored samples were evaluated every 4 weeks for appearance, color, drug content and percent transmission.

Centrifugation Stability

The liquid SNEDDS preparation was subjected to centrifugation (5000 rpm for 30 m) for observing the changes in homogeneity of nano emulsion. In this method 100 mg formulation was diluted with 100 ml distilled water and then centrifuged.

Spray Drying of Liquid SNEDDS

It was felt necessary to convert liquid SNEDDS into its most stable solid SNEDDS form. The liquid SNEDDS formulation was added into a solid carrier (Aerosil) previously dissolved in ethanol and stirred for 20 m at 250 rpm. This liquid was subjected to spray drying. Hard gelatin capsules of size 00 were used to fills dry powder and stored at 15 to 25^0 till further use.[12]

Characterization of Solid SNEDDS

DSC Study

The differential scanning calorimeter (DSC 823 Mettler Toledo, Japan) was used to study thermogram of pure drug and prepared solid SNEDDS. A closed pierced aluminum pan was used to heat sample (near about 2-5 mg) at temperature from 30^0 to 180^{0}C. Heating rate and nitrogen flow rate were maintained at 5^0/m and 50ml/m respectively to obtain the thermogram.

XRD Analysis

The powder X-Ray diffractometer was used to studied crystalline nature of pure drug and solid SNEDDS.

Surface Morphological Determination

Scanning electron microscopy (JSM-6360A, JEOL, Japan) was used to determined surface morphological characteristics like shape and texture of particles. The samples were coated by platinum which was placed on aluminum stub and then this coated sample was observed under scanning electron microscope.

Drug Content Determination

The solid SNEDDS sample (10 mg) was dissolved in 10ml methanol and stirred by vortex mixing followed by membrane filtration technique using 0.45 μm filter. The concentration of drug was estimated by UV visible spectroscopy using methanol as solvent at 247 nm.

pH Sensitive Polymer Coating Solution

A polymeric coating solution of Eudragit S-100 was used for coating capsules filled with solid SNEDDS. The coating solution constituted of Eudragit S-100 (15 g), talc (3 g) and triethyl citrate (3 g) in isopropyl alcohol (280 g).

The Eudragit S-100 coated capsule was further given a band seal. Band sealing solution consisted of gelatin type-B (1200 g), Polysobate 80 (10 g), purified water (4800 g) and colorant (q.s).

In vitro Study

The release pattern of drug from pH sensitive polymer coated capsules was evaluated by using type II USP dissolution test apparatus (parameters was set at 50rpm and 37^{0}C). Drug release from solid SNEDDS and pure drug (Budesonide) was checked by using 900 ml dissolution media of pH 1.1 (0.1 N HCl), pH 6.8 and pH 7.4 (phosphate buffer). Drug released study was performed in 0.1 N HCl for 1h, pH 6.8 for 3h and in pH 7.4 for further time till complete release. About 5 ml sample was withdrawn and replaced with fresh media. Then

concentration of each sample was determined using UV spectrophotometer at 247 nm.

In vivo Evaluation of Budesonide Loaded SNEDDS in Colitis

Animal ethics approved protocol referred number is (MCP/IAEC/61/2012).

Treatment Groups

According to weight of rats they were grouped into three, each group consisting of 3 animals. Group I (normal control group) received 0.5 ml oral saline daily. Group II (colitis control group) received TNBS (Trinitrobenzenesulphonic acid in ethanolic solution) and Group III received BUD loaded SNEDDS formulation. Ulceration was induced by TNBS and after 24h of induction, rectal administration of solid SNEDDS (reconstituted) was given daily to the rats up to 7 days.[13]

Induction of Ulcerative Colitis

Colonic ulcer was produced in anesthetic rat by using 20mg TNBS dissolved in 0.5ml (40%v/v) ethanol. Intra colonic ulcer was produced by administration of TNBS solution which was introduced with the help of infant feeding tube (25cm long) rectally. Rats were held upside-down with the help of tail for 1–2 m to minimize outflow of the dose and were then returned to their cages until recovery. The above mentioned method was used for control group also by giving normal saline solution. After the 3 days treatment of TNBS, treatment group and normal group rats were sacrificed at 4th day. Ulcer induced colons were analyzed histopathologically.

Histopathological Determination

Thin sections of epithelium tissues of colon (6μm) were stained with conventional method using staining agent (hematooxylin and eosin). Then interpretation of slides was done after microscopic examination.

RESULT AND DISCUSSION

Formulation and Development of SNEDDS

Solubility Study

The components such as oils, surfactant and co-surfactant, in which the drug has maximum solubility were identified in this study. The importance of this study was to improve drug loading efficiency and reduce final volume of SNEDDS formulation.[14] The oils investigated were capable of solubilising remarkable amounts of BUD. As seen in Table 1, from selected oils, Capmul® MCM L-8 could significantly solubilise in higher amount of BUD (38.28 ± 0.02 mg/ml). Hence, it was selected as ideal oil for SNEDDS formulation.

Surfactants are amphiphilic in nature and due to their high HLB and hydrophilicity most hydrophobic drugs are solubilized readily. Non-ionic surfactants were preferred for formation of SNEDDS due to less toxicity and due to effectiveness at all pH effectiveness. Also, surfactants of HLB 12-18 were chosen to form stable o/w nano emulsion. Among all the surfactants tested, Tween 80 had maximum solubilization potential for BUD and was selected as the surfactant for formation of SNEDDS.

Co-surfactants help to reduce the concentration of surfactants which are otherwise harmful in maximum amount. They also provide flexibility to interfacial film to attain the required curvature to form nano emulsion. The co-surfactants screened included PEG 400, propylene glycol and Plurol Olieque®. BUD showed maximum solubility in PEG-400 and hence it was used for formation of SNEDDS.

Construction of Ternary Phase Diagram

The final ratio of selected components was playing an essential role in stability of formulation. By constructing ternary phase diagram components ratio (oil:surfactant: co-surfactant) was optimized. The ratio of oils and S-mix were taken as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. The ratio of surfactant:co-surfactant to obtain SNEDDS (designated as S-Mix) studied were as 1:1, 2:1, 3:1, 1:2, 1:3 (data not shown). It was found that S-mix:oil ratio of 3:7 showed excellent stability. Hence, this ratio was finalized to further check effect of different S-mix combinations. All the components in different combination are listed in Table 2. If nano-emulsion region was obtained then it is mentioned as NE and if nano-emulsion region was not obtained then it is mentioned as NO.

In Figure 1 ternary phase diagram, colored region shows formation of nano emulsion region. A mixture of surfactant: co-surfactant i.e S-mix of Tween 80: Polyethylene glycol-400 in the ratio of 1:1 along with Capmule® MCM L8 oil in the ratio of 3:7 showed maximum nano emulsion area than others and hence were selected as the final composition of the BUD SNEDDS.

Preparation of drug loaded SNEDDS

BUD loaded SNEDDS were prepared in varying compositions to study the effect of drug loading on the performance of the oils, S-Mix and their ratios selected

Table 1: Solubility of Budesonide in different oils, surfactant and co-sufactant components

Oils	Solubility (mg/ml)	Surfactant	Solubility (mg/ml)	Co-surfactant	Solubility (mg/ml)
Capmule® MCM L8	38.23±0.04	Cremophor® EL	14.47±0.10	Plurol olieque®	32.80±0.11
Labrafil® M 1944 CS	22.85±0.09	Tween 80	38.46±0.17	PEG-400	33.95±0.12
Captex®355	16.85±0.06	Tween 20	19.39±0.07		
Captex® 300	25.33±0.06				
Maisine ™	13.39±0.08				

± Standard deviation

Table 2: Observations for nano emulsion region in the constructed ternary phase diagrams

Oil	Surfactants	Co-surfactants	S-mix Ratio	Oil to S-mix ratio	Nano-emulsion region (NE) or None
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	1:9	NE
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	2:8	NE
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	3:7	NE
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	4:6	NE
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	5:5	NE
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	6:4	None
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	7:3	None
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	8:2	None
Capmule MCM L8	Tween 80	Polyethylene glycol-400	1:1	9:1	None

Table 3: Composition of formulations

Formulation code	Amount of Capmule® MCM L8 oil (mg)	Amount of Tween 80: Polyethylene glycol-400 (surfactant:cosurfactant) (mg)	Amount of Budesonide drug (mg)
F1	100	900	06
F2	200	800	06
F3	300	700	06
F4	400	600	06
F5	500	500	06

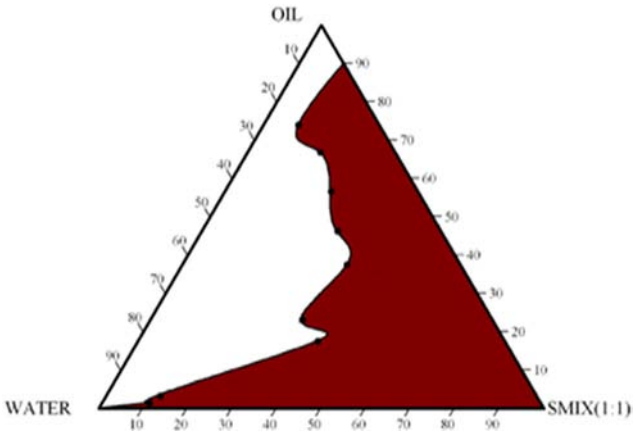

Figure 1 (a):Ternary phase diagram of a mixture of surfactant:co-surfactant in different ratio with oil. (Colored region indicated nanoemulsion areas) 1 (a):Pseudo-ternary phase diagram of Smix 1:1 ratio

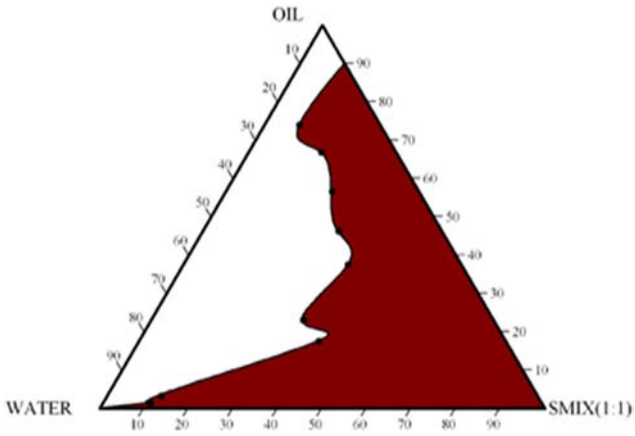

Figure 1 (b): 1 (b): Pseudo-ternary phase diagram of Smix 1:2 ratio

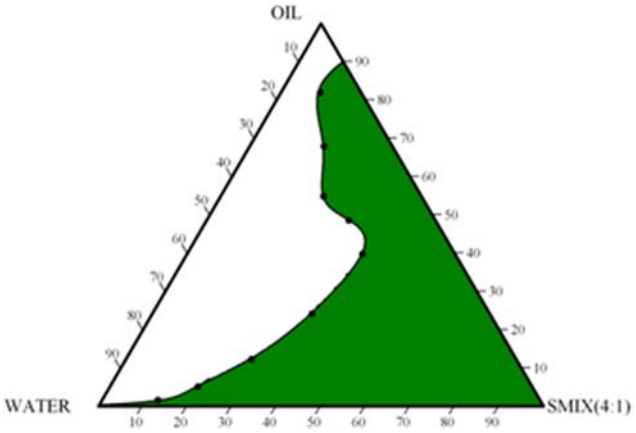

Figure 1 (c): Pseudo-ternary phase diagram of Smix 1:3 ratio.

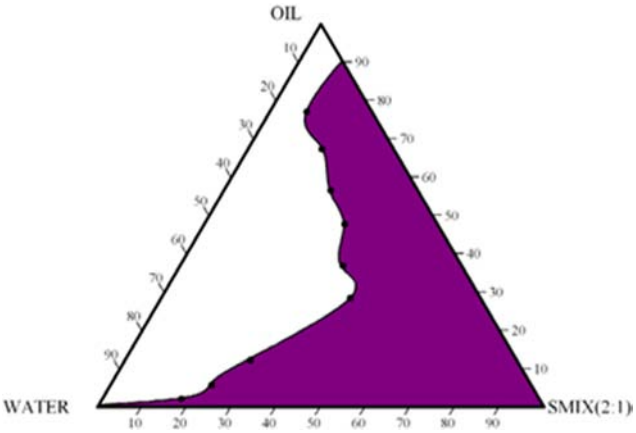

Figure 1 (d) : Pseudo-ternary phase diagram of Smix 2:1ratio.

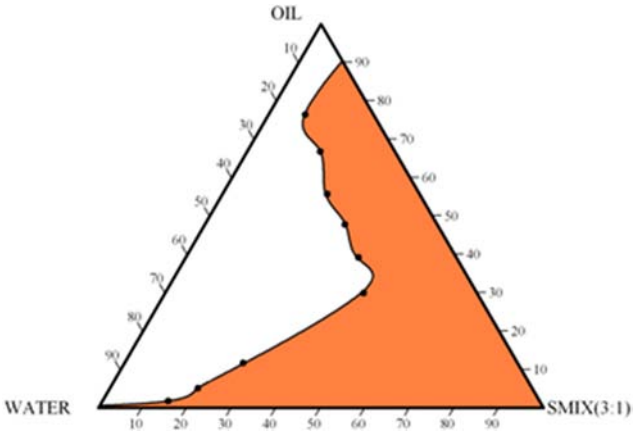

Figure 1 (e) : Pseudo-ternary phase diagram of Smix 3:1 ratio.

in the preceding section. The compositions of formulations F1 to F5 is given in Table 3.

Characterization of Liquid SNEDDS

Macroscopic Evaluation

After storing the liquid SNEDDS at 30^0C ± 2^0C for 3 months, no phase separation had occurred and formulation was seen to be clear and homogeneous.

Transmission Test

The percent transmittance of each formulation after dilution with 0.1 N HCl, pH 6.8 and 7.4 phosphate buffer was checked with the help of UV-spectrophotometer at 628 nm (Figure 2). A higher concentrations of oil in formulation produced low percent transmission and slightly cloudy dispersions were obtained. When concentration of surfactant was increased it resulted in a proportionate increase in percent transmission and produced a clear solution. The percent transmittance of formulations, F1-F5 (composition as in Table 3) was above 95% in all media tested indicating that the droplet size was in nanometer range and a transparent nanoemulsion was formed. The maximum percent transmission had shown optically clear nano emulsion formulation.

Robustness Test

The liquid SNEDDS were diluted with dissolution media (0.1 N HCl, pH 6.8 and 7.4 phosphate buffer) except F4 and F5; remaining formulations did not show any phase separation, precipitation and cloudiness in 24h. SNEDDS formulations were exposed to different media in an attempt to mimic the *in vivo* condit4ion. Each SNEDDS formulation except F4 & F5, on dilutions with distilled water, 0.1 N HCl, and phosphate buffer pH 6.8, phosphate buffer pH 7.4 did not show signs of precipitation, cloudiness or separation after 24 h. Slightly turbidity observed in F4 and F5 formulation may have been due to the higher percentage of oil.

Self-emulsification Analysis

Need of this analysis was to find efficiency of nano emulsion formulation. On gentle agitation, the time required to self emulsification of SNEDDS was found to be 2m and all the batches showed emulsification time of not more than 2 m.

Cloud Point Measurement

Most of the hydrophilic surfactant showed turbidity above certain temperature that is known as cloud point. As the temperature increased, phase separation appears and drug absorption gets affected due to dehydration of ingredients of formulation. Hence, to avoid this, the formulation must be stabilized to above 37^0C (above normal body temperature). It was found that all formulation showed cloud point above 60^0C.[16]

Droplet Size Determination

The average globule size of micro emulsion formed by F1-F3 was between 90 -94 nm (Table 4). The small droplet size is probably a result of more surfactant content relative to that of oil present on oil-water interface.

Polydispersity index for F1-F3 was found to be 0.069 to 0.128 indicating uniformity of droplet size.[17]

Optimized Batch

F3 batch was finalized on the basis of highest percent transmittance, higher amount of S-mix, lower mean droplet size and polydispersity index. Optimized components are shown in Table 5. Its droplet size distribution is shown in Figure 3.

Stability

Although, the stability studies directly co-relates with shelf life of the formulation it is also an important to study temperature stability by subjecting optimized batch to variant stress conditions like temperature (at 37-40^0) and centrifugation (at 5000 rpm for 30 m). The formulation F3 did not show evidence of phase separation or flocculation or precipitation at 37-40^0 temperature.

Evaluation of Solid SNEDDS

The stability of solid formulation is more as compared to liquid formulation reported by Mishra *et al*., 2009.[18] Hence, with the help of spray drier machine, liquid SNEDDS was converted into its solid form. The BUD loaded solid SMEDDs was characterized for the following study:

DSC Study

If the drug showed sharp endothermic peak, then it was in its crystalline form. Here, pure Budesonide DSC thermogram showed endothermic peak at 234.3^0 and there was no drug peak found in the solid SNEDDS of budesonide, indicating loss of crystallinity of drug. The SNEDDS showed no sharp peaks indicating BUD was in molecularly dissolved state in optimized formulation.

Powder X-ray Diffraction

A further confirmation that drug is in structurally dissolved state was carried out by X-ray powder diffractograms. X-ray powder diffractogram for pure drug and solid SNEDDS is shown in Figure 4 The BUD displayed a peak of reduced crystallinity in SNEDDS.

Scanning Electron Microscopy

The scanning electron micrograph of solid SNEDDS shown in Figure 5 indicated that the powder particles had smooth surface and were spherical in shape.

Drug Content in Solid SNEDDS

The optimized batch (F3) contained 6 mg drug out of total weight of 190 mg of capsule contents.

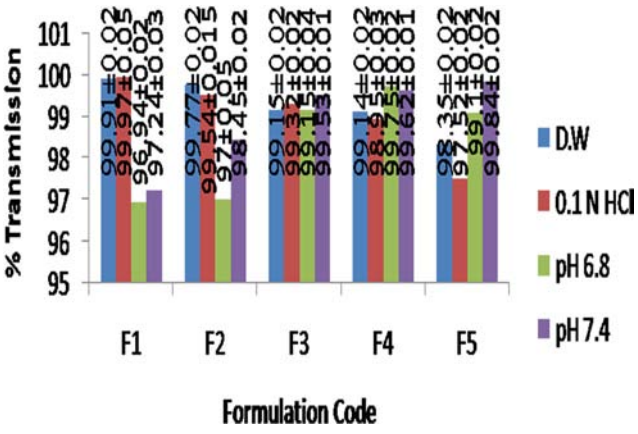

Figure 2: Percent transmission test at 628 nm in distilled water, 0.1 N HCl, phosphate buffer 6.8, phosphate buffer 7.4.

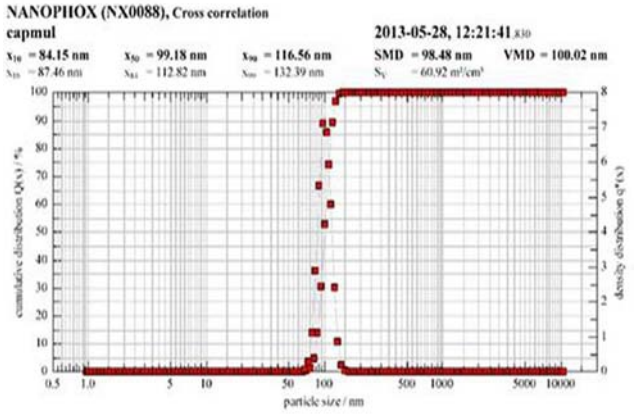

Figure 3: Droplet size distribution of Formulation code F3. The average droplet size of optimized formulation was found to be 116.52 nm.

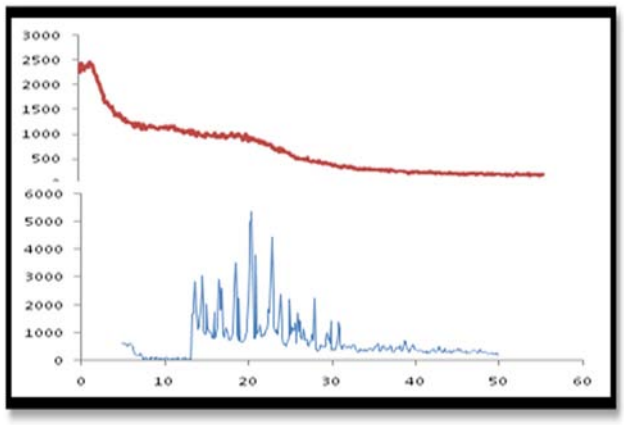

Figure-4 :X-ray powder diffract gram a) pure Budesonide and b) formulation F3 (solid SNEDDS)

Transmission Test

A transmittance of more than 97 % in all the media tested indicated formation of nano emulsion with approximate particle size 100 nm.

Table 4: Globule size and polydispersity index		
Formulation Code	**Globule size (nm) Mean ± S.D**	**Polydispersity index Mean ± S.D**
F1	93.10±0.05	0.069±0.001
F2	93.54±0.045	0.023±0.001
F3	93.84±0.056	0.128±0.001

S.D- Standard deviation

Table 5: Optimized composition of SNEDDS	
Ingredient	**Quantity (mg)**
Capmul MCM C8	300
S-mix	700
Drug	06
Total	1006

S-mix-Surfactant-cosufactant mixture, SNEDDS-Self-nanoemulsifying drug delivery system

Table 6: Drug release kinetics for formulations				
Formulation	**Best fit model**	**N**	**k**	**R**
F3	peppas	0.3907	0.0690	0.6472
Pure drug	peppas	0.3338	0.0632	0.5949

F_3-Formulation code

Mean Particle Size Determination

The reconstituted solid SNEDDS and liquid SNEDDS were evaluated for its particle size and polydispersity index and it was found to be 116.52 ± 0.75, 0.289 ± 0.0026 & 98.48 ± 0.77, 0.326 ± 0.0035 respectively. Since, Aerosil was used as adsorbent in spray dryer this has resulted in the slight increase in particle size.

Flow Properties

The bulk density (0.160 ± 0.0084 g/ml) and tapped density (0.183 ± 0.058 g/ml) indicated that the prepared solid SNEDDS had higher bulk volume. The Carr's compressibility index was 12.56 ± 0.040 % while the Hausner's ratio was less than 1.25.

Drug Release Study

Firstly the solid SNEDDS formulation filled into capsules then coating solution of pH sensitive polymer Eudragit S-100 sprayed on capsules with the help of spray gun in pan coater. These coated capsules remained intact in dissolution media used 0.1 N HCl of pH 1.1 and phosphate buffer solution of pH 6.8. As soon as the capsule comes in a contact with pH 7.4 phosphate buffer, capsules began to dissolve to give immediate and complete release of BUD in 1 h. As seen in Figure 6, a significantly higher amount of BUD (more than 95 %) was released at 6 h from the solid SNEDDS than pure form of drug (57 %). Self nano emulsifying drug delivery system highly contributed to enhanced solubility

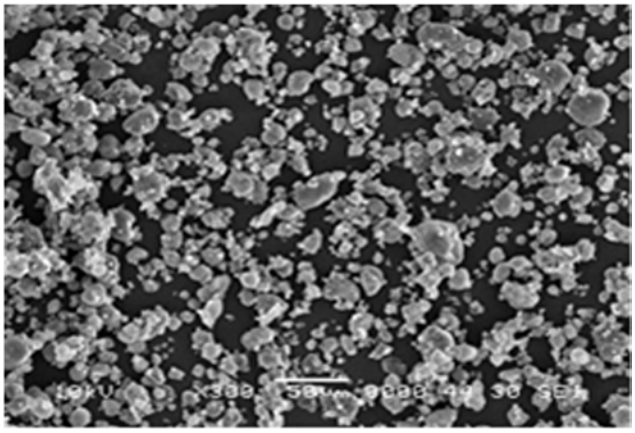

Figure 5 : SEM of solid SNEDDS of optimized formulation (F3).

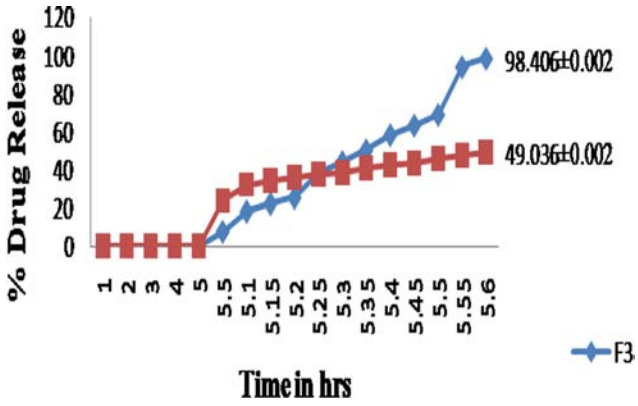

Figure 6 : *In vitro* drug release studies in pH 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4

of drug. Also, the 'n' value in all the cases was within 0.5 which meant that it followed Fickian diffusion (Table 6).

Stability Study

Solid SNEDDS on dilution did not show precipitation of drug and percent transmission was near 99 % that indicated formation of nanoemulsion having globule size less than 100 nm. No change was observed in globule size of solid SNEDDS. Thus, solid SNEDDS of BUD was physically and chemically stable. Results showed that there was no significant drug loss during the stability test periods.

In vivo Study

The histopathological sections of colon receiving different treatments are shown in Figure 7. The histopathological sections of normal colon (Figure 7-I) did not show any damage in microscopic examination (arrow-Mucosal and sub-mucosal layer). As seen in (Figure 7-II), histopathological section of severely damaged colon by TNBS, showed ulceration to mucosa and sub-mucosa layer of epithelium tissue (arrow). Figure 7-III showed tissue damages induced by administration of TNBS were diminished by after seven days treatment of SNEDDS formulation.

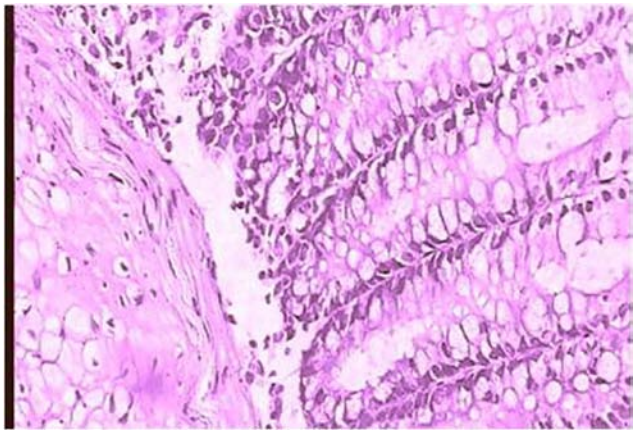

Figure 7 (a) : Representative histological appearance of rat colonic mucosa I-normal control (mucosal layer)

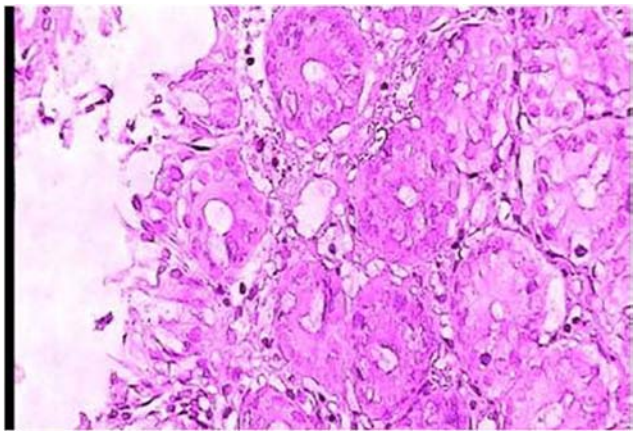

Figure 7 (d) : Representative histological appearance of rat colonic mucosa II- colitis control (submucosal layers).

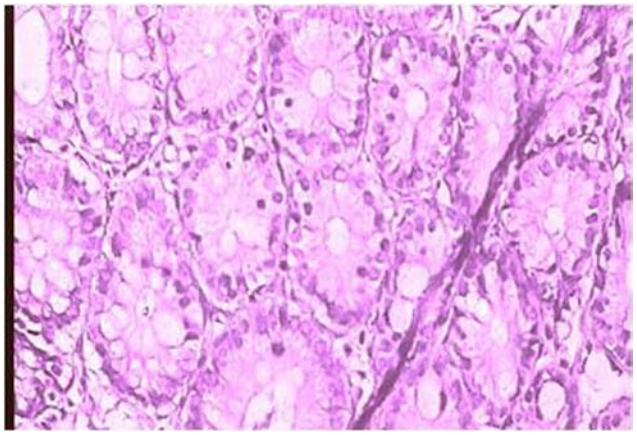

Figure 7 (b): Representative histological appearance of rat colonic mucosa I- normal control (submucosal layers).

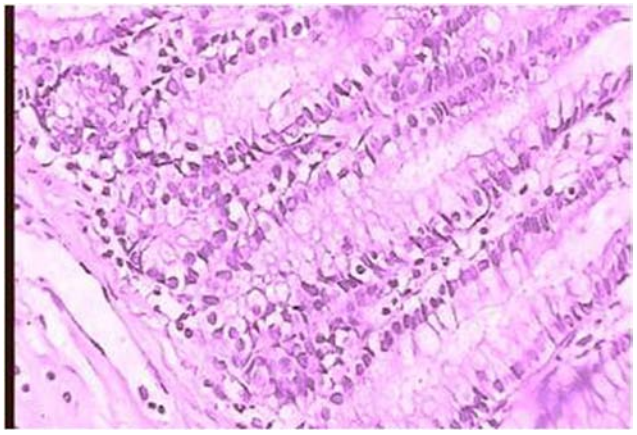

Figure 7 (e): Representative histological appearance of rat colonic mucosa III- budesonide enteric coated capsules (300 µg/kg/day) (mucosal layers).

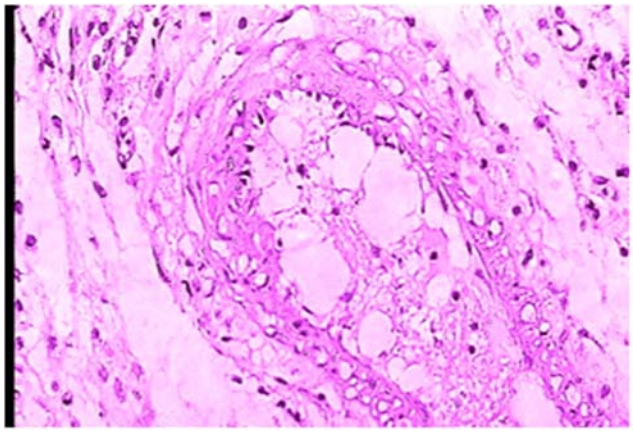

Figure 7 (c) : Representative histological appearance of rat colonic mucosa II- colitis control (mucosal layer).

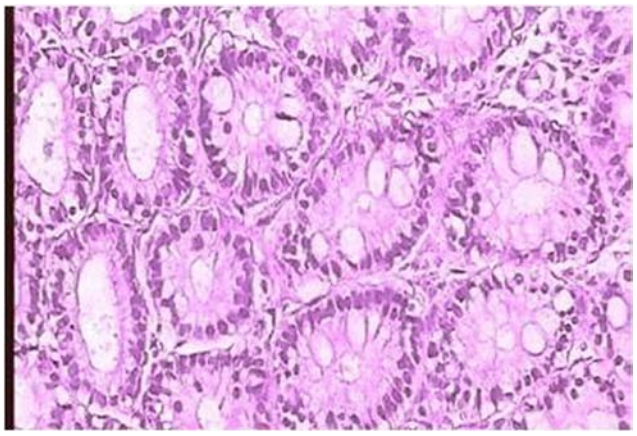

Figure 7 (f) : Representative histological appearance of rat colonic mucosa III- budesonide enteric coated capsules (300 µg/kg/day) (submucosal layer).

The histopathological study thus revealed that SNEDDS formulation demonstrated anti-inflammatory activity of BUD and thereby has potential in inflammatory bowel disease.

CONCLUSION

The SNEDDS of Budesonide were found to enhance the aqueous solubility. The SNEDDS was successfully targeted to the colon via encapsulating in a capsule coated by a pH dependent polymer. *In vitro* dissolution test studies demonstrated high release of drug from the formulated SNEDDS. *In-vivo* study concluded enhanced anti-inflammatory efficacy of budesonide loaded in SNEDDS. Thus, SNEDDS loaded with budesonide may prove better formulation for treatment of Ulcerative colitis. The present study has brought out the potential of enteric coated SNEDDS formulation in ulcerative colitis. Extensive clinical studies will further substantiate the merit of this novel formulation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATION USED

SNEDDS: Self-nanoemulsifying Drug Delivery System; **BUD:** Budesonide; **S-Mix:** Mixture of surfactant and Co-surfactant; **W/W:** Weight by weight; **V/V:** Volume by volume; **nm:** Nanometer; **ml:** Milliliters; **HLB:** Hydrophilic lipophilic balance; **XRD:** X-Ray diffractometer; **DSC:** Differential scanning calorimeter; **TNBS:** Trinitrobenzenesulphonic acid; **NE:** Nanoemulsion area; **NO:** Not Obtained; **F1-F5:** Formulation code.

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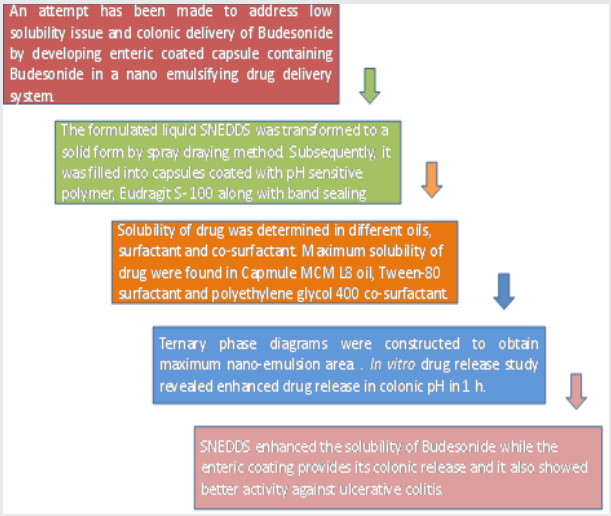
PICTORIAL ABSTRACT



SUMMARY

- The Self-nanoemulsifying Drug Delivery System was developed for colonic delivery of budesonide drug as novel technique to efficiently improve drug solubility and enhance bioavailability.
- The drug Solubility is an important parameter which was determined in different oils, surfactants and co-surfactants. Ternary phase diagrams were constructed to obtain maximum nano-emulsion area. SNEDDS containing Capmule ®MCM L8 as oil, Tween-80 as surfactant and polyethylene glycol 400 as co-surfactant were formulated to get maximum nano-emulsion in the phase diagram
- The formulated liquid SNEDDS was transformed to a solid form by spray draying method. Subsequently, it was filled into capsules coated with pH sensitive polymer, Eudragit S- 100 along with band sealing.
- The prepared formulations were characterized for physicochemical parameters and *In vitro* drug release study. The optimized SNEDDS (particle size 116.32nm) revealed enhanced drug release in colonic pH as compared to pure drug.
- The developed SNEDDS of budesonide also demonstrated better activity against ulcerative colitis as evidenced by the gradually diminishing morphological damages in the histopathological studies in the TNBS induced ulcerative colitis in rats. Thus, SNEDDS enhanced the solubility of Budesonide while the enteric coating provides its colonic release.

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