

Formulation, Optimization and Evaluation of Ticagrelor Loaded Self Microemulsifying Chewable Tablets

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ABSTRACT

Ticagrelor is a new generation Adenosine diphosphate receptor inhibitor drug which is highly lipophilic having poor aqueous solubility used in the treatment of Acute Coronary Syndrome and prevention of Thrombotic events like Stroke and Heart Attack. An approach has been made to develop Chewable tablets of drug loaded on Self-microemulsifying drug delivery systems (SMEDDS), screen suitable adsorbent for solidification of formulated SMEDDS and to study the effect of superdisintegrants in chewable tablets.

Methods: On basis of Pseudoternary diagrams constructed for selected oil, surfactant and cosurfactant, SMEDDS formulation was formulated using Capmul MCM EP oil with surfactant (Cremophor RH 40) and co-surfactant (PEG 400) which was solidified using selected adsorbent. Chewable tablets were compressed by direct compression method using superdisintegrants. **Results:** IR Studies and DSC studies revealed compatibility and stability of drug in formulation. Compression blend containing Solidified SMEDDS possessed good flow and compressibility. Chewable tablets compressed using Soy Polysaccharides as super disintegrant showed least wetting and disintegration time, drug release of 97.68% within 30 min. Short term stability studies revealed no significant change in physical and chemical properties. **Conclusion:** These results suggest that the Ticagrelor loaded self microemulsifying chewable tablets can be a promising oral drug delivery system to improve the solubility and dissolution profile of Ticagrelor.

Key words: Ticagrelor, SMEDDS, Adsorbents, Chewable tablets, Acute coronary syndrome.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in the disease category around the world. According to WHO, it is estimated that 17.9 million people succumb to CVD each year.¹ According to the Global Burden of Disease study, India has an age-standardized CVD fatality rate of 272 per 100,000 people, which is higher than the world average of 235 per 100,000 people.² Coronary artery disease and Acute coronary syndrome (ACS) are examples of CVDs that damage the heart and arteries. ACS has a greater risk of morbidity and mortality than other illnesses which is been treated with medications that prevent ischemia and angina by limiting the extent of the infarct (the area of the myocardium that is

affected), as well that prevent clot formation due to aggregation of cellular blood components.^{3,4}

Self-Micro emulsifying drug delivery systems (SMEDDS) approach has gained potential as a viable method to enhance solubility, permeability and there by improve bioavailability of poorly soluble drugs.⁵ SMEDDS are isotropic combinations of natural or synthetic oils, surfactants, and cosurfactants that have the distinctive capacity to create fine oil-in-water (o/w) microemulsions with modest agitation followed by dilution in aqueous media.^{6,7} The employment of two or more oil soluble emulsifiers and water soluble surfactant is commonly used to reduce interfacial tension,

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which is the main driving force for microemulsion generation.⁸ To address handling, storage and stability issues there is a need for conversion of liquid SMEDDS to solid SMEDDS which can be accomplished by adsorption onto solid carriers.⁹ The adsorbents can adsorb up to 70% w/w of their weight when they are loaded with liquid SEDDS /SMEDDS.¹⁰

Ticagrelor is a new generation ADP (Adenosine diphosphate) receptor inhibitor drug, used in the treatment of ACS which acts by preventing clot formation due to aggregation of platelets. It belongs to Biopharmaceutical Class IV with very low aqueous solubility of approximately 3.5mg/L and moderate intrinsic permeability characteristics which poses a challenge to formulate an optimal oral solid dosage form with desired bioavailability.⁴ Conventional dose of Ticagrelor have a drawback of slow inhibition of platelet aggregation due to its low solubility and oral bioavailability leading to its slow onset of action.¹¹ In order to address these issues Ticagrelor was formulated using approaches like solid dispersion,^{12,13} sublingual tablets,¹⁴ and Film coated tablets.¹⁵ The drug has been administered orally at 90 mg dose twice a day for a year, followed with 60 mg doses twice a day, due to which patient experience dysphagia.¹⁶

With the objective to enhance drug solubility and thereby oral bioavailability an attempt has been made to develop Chewable tablets of Ticagrelor using formulated SMEDDS. For solidification of liquid SMEDDS adsorbents were screened. Effect of super disintegrants on drug release in chewable tablet formulation was also investigated.

MATERIALS AND METHODS

Materials

Ticagrelor and Virgin coconut oil was purchased from Sigma Aldrich, Mumbai. Capryol PGMC(propylene glycol monocaprylate, type I), Mysine 35-1, Labrafil M 2125 C (linoleoyl macrogol-6 glycerides), Labrasol (caprylocaproyl macrogol-8 glycerides), Lauroglycol FCC (propylene glycol monolaurate, type I), Transcutol P (diethylene glycol monoethyl), Transcutol HP (Diethylene glycol monoethyl ether) were gifted from Gattefosse India Pvt. Ltd. Capmul MCME P (glycerylcaprylate/caprate), Capmul MCM C8 (Glyceryl Monocaprylate), Capmul PG-8 EP (Propylene Glycol Monocaprylate), Acconon MC8-2 EP (Caprylocaproyl Macrogolglycerides EP), Captex 170 EP (CocoylCaprylocaprate EP), Captex 200 P (Propylene Glycol Dicaprylocaprate EP) were gifted by IMCD India private limited, Mumbai. Natural

Vitamin E oil was gifted by Matrix Fine Science Pvt.Ltd. Aurangabad. Kolliphor EL and Kollisolv MCT-70 was gifted by BASF India Limited, Navi Mumbai India. Castor oil, Oleic acid, and Propylene glycol were procured from LobaChemiePvt. Ltd. Mumbai. Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil), Tween 80 (Polyoxyethylene sorbitan monooleate) were purchased from HiMedia Laboratories Pvt. Ltd. Nashik. Tween 20, Tween 60, Isopropyl Alcohol, Methyl Alcohol were procured from S D Fine-Chem Limited. Mumbai, India. Spherolac 100 (sieved lactose monohydrate USP) and Sorbolac 400 (milled lactose monohydrate USP) was gifted by Signet excipients Pvt. Ltd. Mumbai. Vivasol GF LM (Croscarmellose Sodium), Emcosoy STS IP (soy polysaccharides), Vivapharm PVP K30 (Polyvinyl pyrrolidone) and Prosolv ODT G2(orally disintegrating tablet matrix) were gifted by Rettenmaier India PVT. LTD. A member of the JRS group. Pharmatose 200M (Lactose Monohydrate) was purchased from Lepid life sciences (P) Limited, Alwar, Rajasthan. MICCEL-101 (Microcrystalline Cellulose 101) and MICCEL-112 (Microcrystalline Cellulose 112) were gifted by Ankit pulps and boards PVT. LTD Mumbai, India. All the chemicals used were Pharmaceutical and analytical grades.

Methods

Formulation of Self Emulsifying Drug Delivery systems(SMEED)

Screening of oil, surfactant and co-surfactant based on solubility studies

The saturation solubility of drug was determined by solubilising drug in various oils (Capryol PGMC, Virgin Coconut oil, Natural Vitamin E Oil, Maisine 35 – 1, Labrafil M-2125 CS, Castor Oil, Oleic acid, Labrafac PG, Isopropyl Myristate, Kollisolv MCT-70, Capmul MCM EP, Capmul PG 8,Captex 200p, Captex 170p, Capmul MCM C8 and Acconon MC8 – 2), surfactants (Kolliphor EL, Cremophor RH 40, Labrasol, Brij 35 30% w/v, Tween 20, Tween 60, Tween 80) and co-surfactants (PEG 400, Propylene glycol, Lauroglycol FCC, PEG 600, PEG 200, Transcutol P and Transcutol HP). An excess amount of drug was dissolved in 1ml of oil, surfactant and co-surfactant respectively. The mixture was stirred continuously for 24 hr at room temperature on a magnetic stirrer. After equilibrium was attained the mixture was centrifuged at 15000 rpm for 15 to 20 min. The supernatant layer was filtered through the PTFE syringe filter by using 0.45µm filter disk. The filtered solution was diluted with Isopropyl

alcohol and absorbance was measured at 221 nm using UV Spectrophotometer.¹⁷⁻²⁰

Construction of pseudoternary phase diagram

Based on solubility studies of Ticagrelor in oil, surfactant and co-surfactant, the excipient mixture of oil, surfactant and Co-surfactant were selected. The pseudoternary phase diagram of oil (Capmul MCM Ep) surfactant (Cremophor RH 40) and Co-surfactant (Polyethylene glycol 400) were constructed using aqueous titration method. Surfactant and co-surfactant were mixed in different volume of ratios (1:1, 1:2, 2:1, 1:3 and 3:1). For each phase diagram, oil was mixed with selected S_{mix} (oil: S_{mix}) in different volume ratios from 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 respectively in glass vials. The obtained mixture was then subjected to titration wherein distilled water was added dropwise, vigorously stirring the mixture on magnetic stirrer until the mixture turned turbid. For each phase diagram visual observation were reported. These values were used to determine the microemulsion region correlated with the selected value of oil and S_{mix} ratio and Degree of Emulsification was evaluated.²¹⁻²⁵

Preparation of SMEDDS

With reference to the constructed pseudoternary phase diagram, the mixture having higher microemulsion region was selected for SMEDDS formulation. The composition of microemulsion formulation was Capmul MCM EP as an oil phase (5%), Cremophor RH 40 as surfactant (63.2%) and Polyethylene glycol 400 as co-surfactant (31.6%) and 90mg of drug. An accurately weighed amount of drug was dissolved in the measured volume of oil with continuous stirring on magnetic stirrer. Surfactant was mixed with co-surfactant in another beaker to give S_{mix} (2:1). The oil phase was added into the S_{mix} with constant stirring until the drug was completely dissolved. The mixture was stored at room temperature for further use. The composition of microemulsion formulation was Capmul MCM EP as an oil phase (5%), Cremophor RH 40 as surfactant (63.2%) and Polyethylene glycol 400 as co-surfactant (31.6%) and 90mg of drug.

Characterization of SMEDDS

Determination of Droplet size and viscosity

Formulation mixture of about 0.5 ml of was diluted with 20 ml of milli pore water and stirred gently at 100 rpm using magnetic stirrer. The Droplet size of the solution and polydispersity index were analysed using Nanotrack.^{26,27} Viscosity of the microemulsion

formulation was determined using Brookfield Programmable DV-II I + Rheometer.^{28,29}

Drug content

1 ml of microemulsion formulation was dissolved in 100 ml of Isopropyl alcohol. Aliquot of 1 ml was further serially diluted to get absorbance within beer's range of drug. The drug content of microemulsion formulation was determined using UV Spectrophotometer at 221 nm.³⁰

Percent Transmittance

The microemulsion of about 0.1 ml was dissolved in 10 ml of Millipore water. The percent transmittance of the resulting microemulsion was determined at 221 nm using UV Spectrophotometer.³¹

Solidification of Liquid SMEDDS

Silica based and Non-silica based adsorbents were screened. Selection of adsorbent was based on flow properties, droplet size and % drug loading. Ticagrelor loaded SMEDDS formulation (TCG-SM) was prepared by adding drug (90 mg) to prepared SMEDDS (300 mg). Adsorbent was then added, blended to obtain solidified nongreasy product (Sol-TCG-SM), passed through #20 mesh and stored at room temperature in a closed vessel.

Bulk Characterization of Solidified SMEDDS

Flow properties of Ticagrelor loaded SMEDDS-adsorbent mixture was evaluated by determining its bulk density, tapped density, angle of repose, hausner's ratio and carr's index.³²

Particle size of Ticagrelor loaded SMEDDS

0.5 gm of formulation mixture was diluted with 20 ml of milli pore water and stirred gently at 100 rpm using magnetic stirrer. The particle size of the solution and polydispersity index was analysed using Nanotrack.²⁷

Drug Content

Primary stock solution was prepared by dissolving 1 g of solidified SMEDDS-adsorbent mixture containing 90 mg of Ticagrelor in 100 ml of Isopropyl alcohol. Aliquot of 1 ml sample was withdrawn from the above solution and diluted to 10 ml with Isopropyl alcohol. Further, 1 ml sample of aliquot was diluted with 10ml of Isopropyl alcohol. Then the drug content was determined using UV Spectrophotometer at 221 nm using Isopropyl alcohol as blank.³³

Formulation of Chewable Tablets loaded with SMEDDS

Compression blend for compression of Ticagrelor loaded Self microemulsifying chewable tablets was prepared by lubricating the solidified SMEDDS with

Magnesium stearate and talc to improve the flow property. Super disintegrant was added to blend and tablets compressed by direct compression method using 15 mm punch, single punch tableting machine (Rimek Mini Press-I Ahmedabad, India.). Composition of formulations is tabulated in Table 1.

Evaluation of Chewable tablets

Thickness and diameter test

Thickness and diameter of 10 tablets from each batch was measured respectively using Vernier calliper. Dimensions (mm) were measured in triplicate.^{34,35}

Hardness test

Hardness of tablet was determined using Monsanto hardness tester. Hardness was expressed in kg/cm², measured in Triplicate.^{34,35}

Weight variation test

Randomly 20 tablets from each batch were selected and weighed individually. Average weight and percent deviation of each tablet was calculated. A limit for percentage deviation is $\pm 5\%$ for tablets weighing 250 mg and $\pm 10\%$ for 300 mg tablets.

Friability test

Friability was determined using Roche Friabilator. Randomly 5 tablets were selected and placed in drum and rotated for 100 revolutions at 25 rpm, tablets were

removed and dusted. Percentage friability of tablets was calculated by noting the difference in initial weight of tablet (W1) and final weight of tablet (W2).

Drug Content

Five tablets were randomly selected, weighted, crushed and powder equivalent to one was dissolved in 10 ml of isopropyl alcohol which was diluted to 100 ml using pH buffer 1.2. 1 ml of stock solution was further diluted to 100 ml with 1.2 pH buffer. Absorbance was measured at λ_{\max} 221 nm using UV- spectrophotometer.^{34,35}

Wetting time

A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petri dish (ID = 6.5 cm) containing 6 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of tablet was measured using a stopwatch. Three trials for each batch was recorded, the standard deviation was determined.^{36,37}

Disintegration studies

Disintegration apparatus (LabtronicsLT-74) containing a basket rack assembly with six open glass tubes with a wire mesh #10 on lower side was used for the test. In each tube one tablet is placed over which a plastic stud is placed to avoid overflow of tablet during test. The basket is raised and lowered in the medium of 900 ml of pH 6.8 phosphate buffer which is maintained at $37 \pm 2^\circ\text{C}$. Time required for complete passage of tablet fragments through the sieve #10 was considered as the disintegration time of the tablet.^{38,39}

In-vitro dissolution studies

In-vitro dissolution studies were performed using USP Dissolution Test Apparatus Type –II (paddle method) in four different dissolution media pH buffer 1.2, 4.5, 6.8 and distilled water respectively. The tablet was placed in 900 ml of respective buffers, at regular intervals of time 5 ml of sample was withdrawn, replaced with fresh sample maintained under sink condition. 1ml was above aliquot was filtered, diluted to 10 ml with respective buffer and absorbance measured at λ_{\max} 221 nm using UV-spectrophotometer.^{39,40}

Short term stability studies

Stability studies were performed for optimised tablets at room temperature and accelerated temperatures. Tablets were placed in amber coloured tightly plugged bottles and stored at $25 \pm 2^\circ\text{C}$ and 60 % RH and $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 30 days. At regular time interval tablets were collected and analysed for its hardness,

Table 1: Formulation design of Ticagrelor loaded self microemulsifying chewable tablets.

Ingredients (mg)	Formulation code			
	F1	F2	F3	F4
Ticagrelor	90	90	90	90
Capmul MCM EP	15	15	15	15
Cremophor RH 40	190	190	190	190
PEG 400	95	95	95	95
Microcrystalline Cellulose 102	200	200	200	200
Microcrystalline Cellulose 112	100	100	100	100
Soy Polysaccharides	5	-	-	-
Crospovidone	-	5	-	-
Croscarmellose Sodium	-	-	5	-
Prosolv ODT G2	-	-	-	95
Mannitol	85	85	85	-
Magnesium stearate	5	5	5	5
Talc	5	5	5	5
Aspartame	5	5	5	-
Vanillin	5	5	5	5

mg: milligrams

disintegration time, drug content and *in-vitro* drug release.⁴¹

RESULTS AND DISCUSSION

Formulation of Self Emulsifying Drug Delivery systems (SMEED)

Screening of oil, surfactant, and co-surfactant based on solubility studies

Solubility studies of drug in various oils, surfactant and cosolvent showed maximum solubility in Capmul MCM oil (116.82 mg/ml), Cremophor RH 40 surfactant (119.652 mg/ml) and Polyethylene glycol 400 solvent (117.92 mg/ml). Selection of components in formulation of SMEDDS is critical. Oils solubilize hydrophobic drugs and can improve the lipophilicity of drug, surfactants lower the surface energy and allow oil to disperse into small droplet size in the aqueous phase and cosurfactants aid in increasing drug solubility by forming micelles in the aqueous phase preventing precipitation of drug. The solubility of Ticagrelor in above solvents was shown in Figure 1.

Construction of Pseudoternary phase diagram

The concentrations of oil, surfactant, and co-surfactant for formulation of SMEDDS was selected by construction of pseudo-ternary phase diagram using water titration method in the absence of drug. A large microemulsion region was formed by combining Capmul MCM oil with Cremophor RH 40, and PEG 400 in a 2:1 ratio compared to other S Mix ratios. Pseudoternary diagrams for each mixture was constructed using Grapher software, shown in the Figure 2. Mixture of Oil and S_{mix} were emulsification-graded from Clear to slight bluish solution to gel formation upon mixing with the water, shown in Table 2.

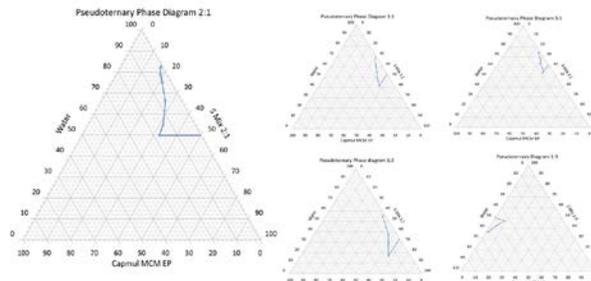


Figure 2: Pseudoternary diagram of SMEDDS mixture.

Table 2: Emulsification grade of SMEDDS mixture: SMix 2:1 ratio.

Capmul MCM EP (ml)	Cremophor RH 40 (ml)	PEG 400 (ml)	Water added (ml)	Grade
0.05	0.6332	0.3166	3.8	A
0.1	0.600	0.300	3.1	A
0.15	0.566	0.2833	3.0	A
0.2	0.533	0.266	2.0	B
0.25	0.5	0.25	1.6	C
0.3	0.466	0.233	1.2	C
0.35	0.433	0.2166	1	C
0.4	0.4	0.2	0.6	C
0.45	0.366	0.1833	0.2	C
0.50	0.33	0.166	0.2	D
0.55	0.300	0.15	0.2	D
0.60	0.266	0.133	0.1	D
0.65	0.233	0.116	0.1	E
0.70	0.2	0.1	0.1	E
0.75	0.166	0.0833	0.1	E
0.80	0.133	0.066	0.1	E
0.85	0.1	0.05	0.1	E
0.90	0.033	0.033	0.1	E

Grade A - Clear to slight bluish solution
 Grade B - Slight clear to bluish solution
 Grade C - Almost white precipitation
 Grade D - White precipitation to complete turbid solution
 Grade E - Gel

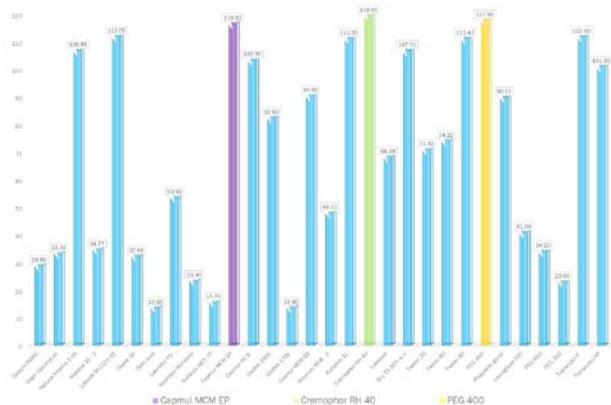


Figure 1: Solubility of Ticagrelor in various oils, surfactants and co-surfactants.

Preparation of Ticagrelor loaded SMEDDS

The ideal mixture ratio for the formulation based on the Pseudoternary diagram and Emulsification grade evaluation was of 5 % Capmul MCM EP, 63.2 % Cremophor RH 40, and 31.6% of PEG 400. Drug is readily soluble in the above mixture which of found to be 128.6 ± 2.00273.

Characterization of SMEDDS

Droplet size and Viscosity of SMEDDS

The droplet size of microemulsion was found to be 54.0333 ± 3.852 nm exhibiting viable range limit of Self microemulsifying drug delivery system, shown in Table 3. Small droplet size provides a large surface area for rapid dissolution, absorption of the drug and increases the drug's permeability through the intestinal membrane. The viscosity of formulation was found to decrease upon dilution with distilled water indicating increased absorption of Ticagrelor loaded SMEDDS, shown in Table 4. For increased absorption of drug in stomach the SMEDDS formulation should exhibit lower viscosity when diluted with gastric contents compared to undiluted SMEDDS.

Percent Transmittance of SMEDDS

The percentage transmittance of Ticagrelor loaded SMEDDS formulation was found to be 98.7167 ± 0.235 indicating the formulation is clear, transparent, free from precipitation and hence stable, shown in the Table 4.

Preparation of solidified Ticagrelor-loaded self-microemulsifying drug delivery formulation

From the various Silica and Non-silica-based adsorbents screened it was found that Microcrystalline cellulose 102 and Microcrystalline cellulose 112 (2:1 ratio) readily solidified Ticagrelor loaded liquid SMEDDS. Solidified SMEDDS was evaluated for micromeritic properties; Bulk density was found to be in the range of 0.345 ± 0.018 to 0.764 ± 0.021 g/ml., The tapped density of the mixtures was found to be in the range of 0.415 ± 0.011 to 0.977 ± 0.028 g/ml, The Hausner's ratio

of mixtures was found to be in range of 1.145 ± 0.039 to 1.38 ± 0.008 respectively. Angle of repose was found to be in range of $23.18^\circ \pm 1.12$ and $42.09^\circ \pm 0.11$ respectively, Results tabulated in Table 5,6. The values indicated that the solidified SMEED possessed good flow and compressibility.

Evaluation of Ticagrelor loaded SMEDDS – Adsorbent Mixture

Determination of droplet size of Ticagrelor loaded SMEDDS

The droplet size of solidified SMEDDS was observed to be in the range of 74.12 ± 1.4 – 133.8 ± 3.2 nm. with no aggregation. As a result, the solidified SMEDDS would be sufficiently desorbed from the adsorbent and hence into the media. Results shown in Table 6.

Determination of Ticagrelor content in solidified Ticagrelor loaded SMEDDS

Drug content in solidified Ticagrelor loaded SMEDDS-Adsorbent mixture was found to be 84.6 to 99.7 percent, indicating that TCG-SM was efficiently adsorbed to the adsorbent, shown in Table 6.

Formulation and evaluation of Ticagrelor loaded self microemulsifying chewable tablets

Chewable tablets of solidified Ticagrelor loaded SMEDDS was formulated using super disintegrants and tablet excipients. Compression blend possessed good flow properties and compressibility. Results shown in Table 7. Compressed chewable tablets were evaluated post compression; tablets were found to be of uniform weight, size, and thickness with good mechanical strength. Results tabulated in Table 8. Drug content was found to be in range of 97.09 ± 0.9 to 98.5 ± 0.2 %, formulations showed quick wetting, due to ability to swell and capacity of absorb water. Tablets formulated using Soy polysaccharides and mannitol as diluent disintegrated rapidly within 2 min. Hence, batches of formulated chewable tablets satisfied the criteria of chewable tablets as specified by FDA. Results are shown in Table 9.

The *in-vitro* dissolution studies of formulated chewable tablets and marketed conventional tablet was performed in pH buffer 1.2, 4.5, 6.8 and distilled water respectively. The cumulative drug release of all formulations in above dissolution media varies from 85.12 ± 0.33 % to 97.68 ± 0.71 %. Formulation F1 showed maximum cumulative drug release of about 97.68 ± 0.71 % and conventional tablet showed cumulative drug release of about 67.3 ± 0.33 %. It can thus be concluded that, drug release increases with addition of super disintegrants and

Table 3: Droplet size, PDI and % Transmittance of SMEDDS Mixture SMix 2:1 Ratio.

Trials	Mean size in nm	PDI	%Transmittance
1	52.9	0.789	98.25
2	48	0.522	99.14
3	61.2	0.819	98.9
Avg	54.0333 ± 3.852	0.71 ± 0.0944	98.7167 ± 0.235

PDI: Poly Dispersibility Index

Data are expressed as Mean \pm S.D. (n=3)

Table 4: Viscosity of SMEDDS mixture: SMix 2:1 ratio upon dilution with distilled water.

Sample	Viscosity in cP
Drug + SMEDDS Mixture	503.1
Drug + SMEDDS Mixture Diluted up to 10 times in Distilled water	5
Drug + SMEDDS Mixture Diluted up to 100 times in Distilled water	3.2

cP = Centipoise

Table 5: Evaluation of physical parameters and flow properties of Ticagrelor loaded SMEDDS – adsorbent mixture.

Sample	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Angle of Repose (°)	Hausner Ratio	Carr's Index
Non-Silica Based Adsorbents					
Pharmatose 200M	0.764±0.021	0.977±0.028	42.1± 2.8	1.278±1.2	23.84±0.32
MICCEL-102	0.382±0.018	0.512±0.026	41.2±1.1	1.340±0.098	25.39±1.8
MICCEL 112	0.393±0.023	0.540±0.021	42.9±1.43	1.374±0.061	27.22±1.2
MICCEL 102-112 (2:1)	0.378±0.012	0.523±0.028	40.1±2.1	1.38±0.008	27.72±2.1
Sorbolac – 400 (M.L)	0.362±0.032	0.621±0.019	38.1±1.8	1.715±0.0052	41.7±1.0
Spherolac – 100 (S.L)	0.721±0.048	0.890±0.032	41.6±2.3	1.234±0.042	18.9±2.4
Silica Based Adsorbents					
Aerosil 200	0.412±0.068	0.472±0.016	23.1±1.12	1.145±0.039	12.711±1.6
Calcium Silicate	0.345±0.018	0.415±0.011	31.8±1.82	1.20±0.052	16.86±1.2

Data are expressed as Mean ±S.D. (n=3)

Table 6: Droplet size and drug content of Ticagrelor loaded SMEDDS adsorbent mixture.

Sample	Droplet Size (nm)	Drug content (%)
Non-Silica Based Adsorbents		
Pharmatose 200M	133.8±3.2	93.4±1.3
MICCEL-102	125.24±2.1	95.1±0.98
MICCEL 112	129.32±1.7	94.2±1.8
MICCEL 102-112 (2:1)	124.45±1.2	97.9±0.8
Sorbolac – 400 (M.L)	89.43±1.9	90.1±0.6
Spherolac – 100 (S.L)	130.6±2.4	92.8±2.3
Silica Based Adsorbents		
Aerosil 200	74.12±1.4	94±1.2
Calcium Silicate	133.48±2.8	84.6±1.6

Data are expressed as Mean ±S.D. (n=3)

Table 7: Evaluation of pre compression parameters of Ticagrelor loaded self microemulsifying chewable tablets.

Formulation Code	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Angle of Repose (°)	Hausner Ratio	Carr's Index
F1	0.63 ± 0.018	0.73 ± 0.025	35.2 ± 0.55	1.18 ± 0.062	13.79
F2	0.63 ± 0.037	0.72 ± 0.024	35.3 ± 0.76	1.14 ± 0.037	12.32
F3	0.61 ± 0.010	0.69 ± 0.023	34.1 ± 1.04	1.19 ± 0.070	12.84
F4	0.64 ± 0.020	0.72 ± 0.025	30.4 ± 0.22	1.11 ± 0.004	10.69

Data are expressed as Mean ±S.D. (n=3)

Table 8: Evaluation of post compression parameters of Ticagrelor loaded self microemulsifying chewable tablets.

Formulation code	Hardness(kg/cm ²)	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.4 ± 0.05	3.9 ± 0.05	0.5 ± 0.04	801.3 ± 1.23	98.17 ± 0.60
F2	3.3 ± 0.23	3.8 ± 0.05	0.5 ± 0.05	800.5 ± 1.56	97.77 ± 0.35
F3	3.8 ± 0.25	3.8 ± 0.05	0.5 ± 0.01	801.2 ± 0.46	98.78 ± 0.60
F4	2.8 ± 0.05	3.8 ± 0.05	0.6 ± 0.01	806.0 ± 0.76	98.18 ± 0.00

Data are expressed as Mean ±S.D. (n=3)

Table 9: Post compression evaluation of Ticagrelor loaded self microemulsifying chewable tablets.

Formulation Code	Wetting Time in sec	Disintegration Time in sec
F1	44	67 ± 2
F2	47	79 ± 4
F3	54	70 ± 2
F4	39	69 ± 1

sec: seconds

Average data is expressed are of triplicate (n=3)

formulated chewable tablets exhibit higher cumulative drug release compared to conventional tablet. An *in-vitro* drug release result has been depicted in Figure 3.

Stability studies

The optimized chewable tablet formulation F1 subjected to short term stability studies was found to be stable since no significant change in physical and *in vitro* drug performance characteristics as shown in Table 10.

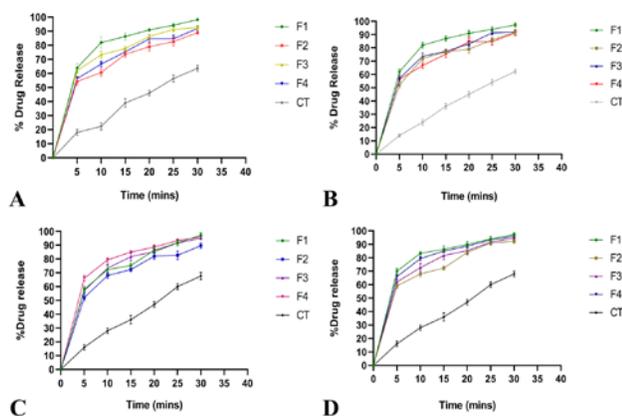


Figure 3: *In vitro* dissolution studies using A: pH – 6.8 buffer, B: pH – 1.2 buffer, C: pH – 4.5 buffer and D: distilled water respectively.

Table 10: Short time stability studies of F1 formulation.

Temperature	Days	Drug Content (%)	Hardness in Kg/cm ²	Disintegration Time in sec	Drug Release %
25°C	15	98.78 ± 0.35	3.81 ± 0.05	68.26 ± 1.41	97.97 ± 0.35
	30	98.58 ± 0.34	3.85 ± 0.01	72.03 ± 0.73	97.376 ± 0.21
40°C /75% RH	15	97.97 ± 0.35	3.88 ± 0.01	74.30 ± 0.81	97.31 ± 0.19
	30	97.77 ± 0.34	4.06 ± 0.11	77.30 ± 0.95	97.16 ± 0.14

Data are expressed as Mean ± S.D. (n=3)

CONCLUSION

A successful attempt has been made to develop Ticagrelor loaded self-microemulsifying chewable tablets for the treatment of acute coronary syndrome. Ticagrelor loaded SMEDDS was formulated based on solubility studies in SMEDDS mixture and constructed pseudoternary phase diagram. Ticagrelor loaded SMEDDS consisting of 5 % of Capmul MCM EP, 63.2 % of Cremophor RH 40, and 31.6% of PEG 400 was solidified using adsorbent Microcrystalline cellulose which was further compressed with addition of Soy Polysaccharides as super disintegrant. Formulated chewable tablets of SMEDDS showed high drug release in comparison to conventional marketed tablet. Short time stability studies indicated formulation to be stable on storage. These results suggest that the Ticagrelor loaded self microemulsifying chewable tablets can be promising as oral drug delivery system, to improve the solubility and dissolution profile of Ticagrelor.

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CONFLICT OF INTEREST

The authors declare that they have no any conflict of interests.

ABBREVIATIONS

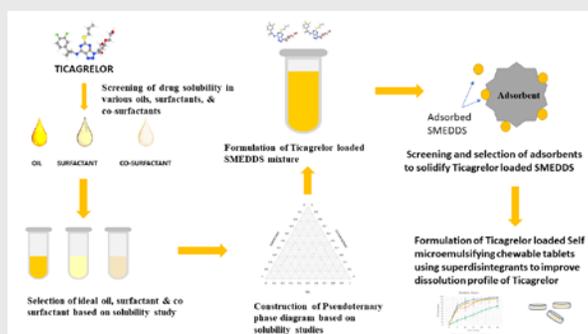
BCS: Biopharmaceutical Classification System; **SMEDDS:** Self Micro Emulsifying Drug Delivery System; **PDI:** Polydispersity Index; **ACS:** Acute Coronary Syndrome.

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PICTORIAL ABSTRACT



SUMMARY

- Ticagrelor loaded self microemulsifying chewable tablets were successfully produced by using direct compression method
- Preformulation study to determine drug-excipient compatibility was carried out by FTIR and DSC, which revealed that, the drug sample was pure and the excipients used were compatible with Ticagrelor.
- Solubility studies of Ticagrelor in various oils, surfactants and co surfactants was carried out and it was found to be Ticagrelor was highly soluble in Capmul MCM oil (116.82 mg/ml), Cremophor RH 40 surfactant (119.652 mg/ml) and Polyethylene glycol 400 co surfactant (117.92 mg/ml).
- Based on the Pseudoternary diagram and Emulsification grade evaluation the SMEDDS Mixture consisting of 5 % of Capmul MCM EP, 63.2 % of Cremophor RH 40, and 31.6% of PEG 400 is considered as ideal mixture ratio for the formulation.
- Ticagrelor loaded SMEDDS formulation is evaluated for droplet size, %transmittance, and viscosity. Obtained results were within the limit required for SMEDDS system
- Ticagrelor loaded SMEDDS was solidified using silica and non-silica based adsorbents, the mixture of TCG-SMEDDS with Microcrystalline cellulose 102 and Microcrystalline cellulose 112 (2:1) ratio exhibited better drug release compared to other adsorbent mixture.
- Ticagrelor loaded self microemulsifying chewable tablets were prepared by direct compression method. Four formulations were prepared, each containing different super disintegrants and formulation F4 contained PROSOLV ODT G2 a functional excipient matrix was also prepared.
- Before chewable tablets prepared the granules were subjected for pre compression evaluation and they possessed good flow properties
- Ticagrelor loaded self microemulsifying chewable tablets were then subjected for post compression evaluation for hardness, friability, weight variation, drug content and results were in within the limit.
- The percentage cumulative drug release from the F1 formulation containing Soy Polysaccharides as super disintegrant was found to be 97.68 %, which was highest among all the formulations. Thus, this formulation was considered as optimized formulation which resulted in better Disintegration time (67 sec), wetting time (44 sec), and had better stability.
- F1 formulation was subjected for short time stability study for 30 days as per ICH guidelines in normal and accelerated conditions. The results showed no significant changes in characteristics of formulated Chewable tablets. It may be concluded that, formulation was found to be safe and retains its original characteristics on storage.

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