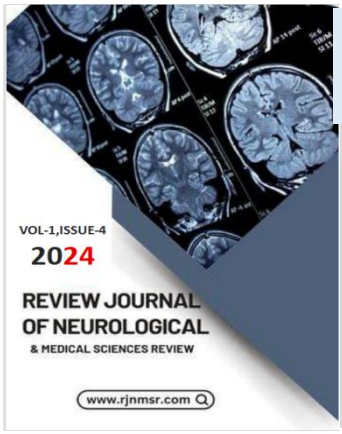

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Formulation Development And Enhancement Solubility Of Poorly Water Soluble Drug Montelukast By Solid Self-Emulsifying Drugs Delivery Systems (SEDDSs)

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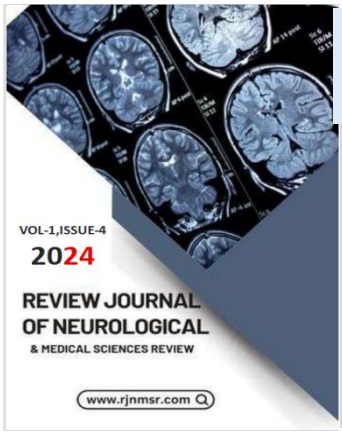
Abstract

Self-emulsifying drug-delivery systems (SEDDSs) are designed to enhance the oral bioavailability of montelukast which is a poorly water-soluble drug. This study aimed at formulating and characterization of SEDDS-based tablets for montelukast using



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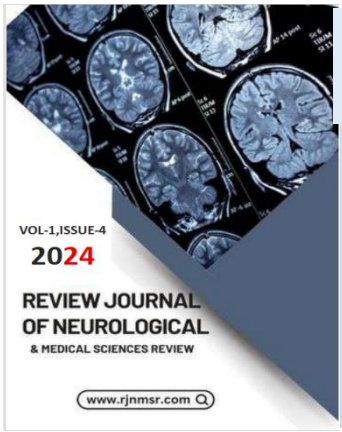
Oleic acid as solvent, Tween 20 as a surfactant and PEG 400 as a co surfactant because they exhibited maximum solubility for montelukast. Based on solubility studies liquids SEDDS were produced by using different ratios of oil, surfactant and co surfactant. The formulated liquid SEDDS were adsorbed on aerosil 200 and all the formulations were subsequently compressed to produce tablets. The tablets produced by SEDDS were tested for different quality control parameters at pre and post compression levels. The tablets produced were physically in good shape and free of any evidence of physical abnormalities. The results of all pre compression and post compression tests were all within limits and according to USP guidelines. The results of different quality control tests evaluated the possibility of formulating SEDDS tablets of montelukast. Thus by formulating SEDDS tablets will eliminate the problem of poor absorption of lipophilic and enhances the bioavailability of class II BCS drugs.

Keywords: Montelukast; self emulsyfiying drug delivery system; oleic acid, Tween 20; PEG 40.

Introduction

Oral route is most widely used method for drug administration. It is easy and convenient method for drug administration. Oral drugs are mostly used to treat chronic illness & offers high degree of patient's acceptance compared to intravenous route. Many patients preferred oral route on intravenous route as IV route of drug administration is painful and can cause site infection, thrombosis and phlebitis [1]. Compare to other routes of drug delivery, oral administration is economical. But in spite of all above advantages of oral route administration there is also a disadvantage of decrease water solubility. Most of the newly discovered medicine compounds have poor water solubility and poor water solubility of drug means poor oral absorption [2]. The drugs having low water solubility when administered will not be dissolved in GIT and due to incomplete released from dosage form, drug will not be properly absorbed into the blood. This all will ultimately result in low clinical response [3]. Many new techniques are developed to improve the solubility of drugs, some techniques are reduction of drug particle size, salt formation, drug nanonization, lipid base formulation and solid dispersion etc. These techniques are used to make medications that aren't very water soluble more soluble, which will boost their oral bioavailability [4]. However these techniques are associated with stability as well as manufacturing difficulties.

Drug substances that have lipid based in the formulation are easily absorbed through oral route. Using lipid as base in drug formulation can improve the dissolution of drug in gastrointestinal tract and so its systemic bioavailability. Lipid based formulation are designed to stimulates enzymes and bile acid secretions. Lipid based drug delivery system (LBDDS) consist of various formulations in form of oil solution, emulsion, self-emulsifying drug delivery system, micelles and SMEDDS/SNEDDS [5]. Formulating poor soluble drugs as SMEDDS will improve solubility of lipophilic drugs. SMEDDS has many advantages over emulsion as it can be used for long term because of its thermodynamic stability and can be stored for larger duration. The sizes of globules in coarse and micro emulsion are different. The size in coarse



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emulsion is in range of 2-10 micrometer and in case of micro emulsion, it is in between 20-100 nanometer. The smaller the globules size, the surface area will be large and when the surface area is larger, it will make the absorption better and so will be the bioavailability.

SEDDS (self-emulsifying drug delivery system) or SEOF (self-emulsifying oil formulations) consists of blend of hydrophobic drugs, surfactants and oils (synthetic or natural), forming isotropic mixture. It also may contain co-solvent or co-surfactants. SEDDS spontaneously form fine emulsion of oil in water (o/w) with aqueous phase upon gently agitation. A fine emulsion forms as result of gentle agitation in the stomach and intestine are of two types, it may be nano or micro emulsion. After oral administration, in human gastrointestinal tract, gastric fluid and gastric movement aid in formation of emulsion. SEDDS formulation has advantages of reducing the drug dose and has the ability to increase drug loading capacity. SEDDS formulation has the ability to be stable in GIT tract for long period of time. As compared to other dosage form, manufacturing drug through SEDDS is easy. Because of poor water solubility, hydrophobic drugs have not the reasonable blood time profile to produce its desire response. So they can be formulated through SEDDS to enhance their solubility. Optimized SEDDS formulations of lipophilic drugs may improve the rate and extent of systemic absorption, and also the blood-time profile [6, 7]. SEDDS are classified into two types based on the size of the oil droplet or globule: SMEDDS and SNEDDS. When globule size is in range from 50 to 100nm, it is SNEDDS and when it is in range from 100 to 300 it is called SMEDDS. Because of their higher solubility, these SEDDS incorporate more drugs and provide a larger surface area for drug substance transport across the intestinal membrane. As result absorption of poor water soluble drug is increase and so the bioavailability [8].

Montelukast belongs to Class II of BCS (biopharmaceutical classification system) having low solubility. Montelukast is leukotriene receptor antagonist and is approved by FDA to be used in asthma, for seasonal allergic rhinitis. Montelukast is used in bronchospasm during exercise. It block leukotriene receptors and lower the inflammation and cause relaxation of smooth muscles [9]. BCS class II drug's oral bioavailability mainly depends upon its rate of dissolution from the solid dosage form. Different strategies have been employed to enhance the dissolution rate and subsequent bioavailability. The present study was designed for the formulation development of montelukast SEDDS with improved dissolution profile and bioavailability.

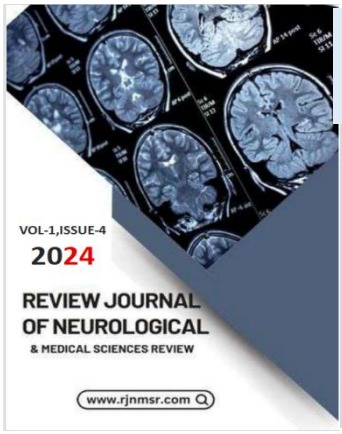
Material And Methods

Instruments

Analytical balance Ohaus USA, Tablet hardness tester Curio, Friabilator Curio (Model: FB2020), Disintegration apparatus Dawn (Model: DT08), Dissolution (Model: DIS/6B), Glass wares (local manufactured)), UV/Visible spectrophotometer (Model: CE CECIL USA).

Materials and Reagents

The drug montelukast (Maithri Laboratories, India) was provided by MKB Pharma Peshawar. Other excipients both synthetic and natural were purchased locally for



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formulating montelukast solid SEDDS. These materials includes castor oil, capric/caprylic triglycerides, sesame oil, coriander oil, clove oil, cinnamon oil, oleic acid, sunflower oil, crodomol oil, and cod liver oil (Molkerei Meggle, Germany).The surfactants tested in the formulation were polysorbate 80, polysorbate 60, polysorbate 40, polysorbate 20 (FMC International, Ireland)were purchased locally. Co-surfactants used were polyethylene glycol 600, polyethylene glycol 400, polyethylene glycol 200, and Propylene glycol (PG) (Coin Powder International Taiwan) were also purchased from the local market. For the development of tablet micro crystalline cellulose PH-101, aerosil-200, starch maize, magnesium stearate, cross carmellose sodium (Coin Powder International, Taiwan) were purchased locally and used as such. All the solvents and reagents used were of analytical grade, while the purified water was obtained using Milli-Q (Millipore, Milford, MA, USA).

Methodology

Solubility Study/Selection of Oil Phase

Solubility study is the first and foremost step in the development of formulation of SEDDS. Solubility studies were carried out for montelukast in different oils, co-surfactants & surfactants. 5ml from oil surfactant and co-surfactant were taken and excess quantity of montelukast was added to it. The mixture was shaken in sonicater for 25-30 minutes at 37°C. When saturation of drug does not occur, more drug was added to achieve saturation level. When saturation was achieved the excess can be removed by centrifugation and after centrifugation they were analyzed for the solubility [2].

Liquid SEDDS Formualtions

Solubility studies help in selection of best oil, surfactant and co-surfactant with correct composition. For developing liquid self-emulsifying drug delivery systems, five different formulations were developed. Each formulation consists of various proportions of surfactant, co-surfactant ratio and oil while montelukast was maintained in same concentration in each formulation as shown in table 1. To a mixture of oil and surfactant/co surfactant, a constant quantity of drug was added and mixed with the help of high speed homogenizer for 10 minutes.

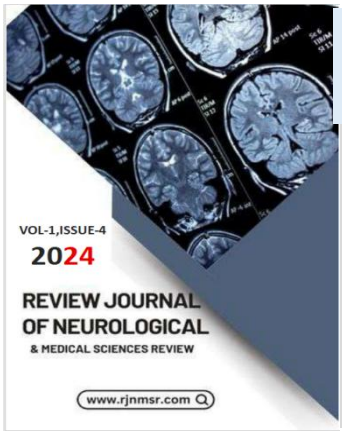
Table 1. Composition of liquid montelukast SEDDS having constant concentration (10mg) of montelukast in all formulations.

Formulations	Oleic acid (%)	Tween 80/PEG 400 (1:1) (%)
F1	10	90
F2	20	80
F3	30	70
F4	40	60
F5	50	50

Evaluation of Liquid SEDDS

Time of Self-Emulsification

Self-emulsification time is the time in which SEDDS formulation spontaneously form emulsion. Emulsification time must be less than 25 or 30 seconds for spontaneous emulsion. Self-emulsification time was calculated by adding 2 ml of each liquid



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SEDDS formulation in 0.1N of HCl and making it up to 100 ml volume. All formulations were diluted in same manner with 0.1 N HCl and their affinities for spontaneous emulsification were checked. They were classified as clear, cloudy, translucent, stable or unstable on basis of appearance [12]

Phase Separation Study

Phase separation study was performed via centrifugation test. Centrifugation tests were performed to evaluate phase separation of the emulsion. Centrifugation of the developed formulations was determined at 3000 *g* for 8 min and phase separation was checked.

Percentage Transmission

Percentage transmittance was used to find transparency degree and homogeneity of formulations. This is a special test which was performed to determine the degree of transparency and homogeneity of Montelukast liquid self-emulsifying drug delivery systems. Test was done by taking 1 ml from montelukast loaded SEDDS formulationand was diluted with distilled water at 37 C which was then examined by measuring the percentage of liquid SEDDS transparency using a UV spectrophotometer [11].

$$Assay\ \% = absorption\ of\ sample\ absorption\ of\ standard \times weight\ of\ standard\ weight\ of\ sample \times 100$$

Stability Test

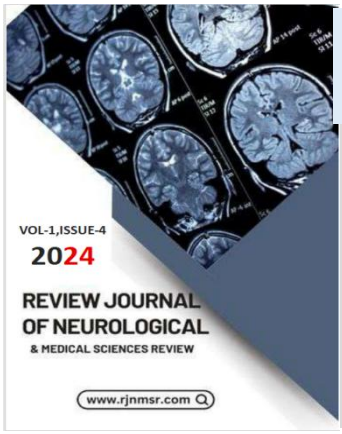
Stability of liquid SEDDS formulation of montelukast was evaluated. In stability test SEDDS formulation of montelukast was diluted with distilled water and was placed in both at room and freezing temperature which was then checked for precipitation of drug and also checked for phase separation [13].

Solidifying Liquid SEDDS and Tablet Formulation

These liquid lipid base formulations of montelukast was then converted into solid SEDDS by adsorption of liquid formulation onto a solid carrier called aerosil 200. S-SEDDS preparations were mixed with other excipients for 30 min in a laboratory scale double-cone mixer at 25 rpm. The blended powder was then compressed by a ZP-21 rotary compression machine having round shaped concave punches. The target weight of the compressed tablets was set at 350 mg/tablet, and around 500 tablets were compressed from each formulation.

Precompression Evaluation

The montelukast liquid self-emulsifying drug delivery system was converted into a solid self-emulsifying drug delivery system by adsorbing the liquid formulation onto a solid carrier. Adsorbent used should be selected on basis of its compatibility with other excipients. Adsorbent used for solidification of formulation was aerosil 200 which convert the liquid formulation into free flowing powder. Aerosil was used to provide large surface area. The powder of the optimized formulation was assessed for various parameters like Carr's index, Hausner's ratio, bulk and tapped densityprior to compression into tablets [14].



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Post Compression Evaluation

SEDDS formulation powder was compressed into tablets. Then compressed tablets were evaluated for different quality control parameters and the results were compared with marketed product of montelukast. Physical characteristics, weight, hardness, friability, disintegration, and drug release behavior of SSEDDS of montelukast was compared with marketed products of montelukast. The following characteristics of montelukast-loaded SEDDS tablets were evaluated.

Weight uniformity

The tablet's weight should be in range and uniform. If there is any weight variation, that weights of the tablets should be in weight variation acceptable limits. To determine weight of the tablets or to know about weight variation, 20 tablets should be taken from the batch randomly and should be weight individually with the help of digital balance. The average weight of the tablets was determined. The following formula was used to calculate percentage weight variation [13].

Weight variation = Average weight - individual weight / Average weight

Thickness

By randomly selecting ten tablets from the batch, the thickness of the tablets was determined. Thickness was determined with help of Pharama test hardness tester. Thickness of tablets was observed in millimeter [15].

Hardness

Ten tablets were chosen at random and their hardness was determined using a Pharma test hardness tester. Hardness was recorded in Newtons [15].

Friability

Friability is the measure if the tendency of the tablets to undergo easy breakage. Friability of the tablets was determining using Pharma test fribilator. Friability test is used to determine powder loss during friability. To find out the friability, tablets of weight which was equal to 6.5g were taken. This weight was considered as revolutions at 25 RPM. After completion of the process, tablets were removed from friability test apparatus. The tablets were weighted again which gave us weight two (W2). To determine powder loss the following formula was used [16].

Friability = W1 – W2 / W1 x 100

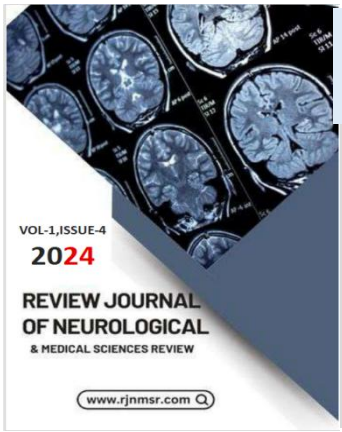
Disintegration Time

The test for disintegration of the SEDDS tablets was carried out by using a disintegration test apparatus.

Randomly six tablets were chosen and put in the Pharma test disintegration apparatus; the disintegration times in minutes were recorded [15].

Dissolution Rate

The dissolution apparatus was used to study the dissolution of montelukast SEDDS tablets. In this study, a formulated SEDDS tablet of montelukast was subjected to dissolution testing using a dissolution apparatus USP type II (Paddle method). The specified amount of sample was taken after 15,30,45 and 60 minutes, filtered and the concentration of drug released was measured using UV spectrophotometer at a wavelength of 284 nm [13].



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Results And Discussion

Solubility Study

The high solubility of selected drug in the oil phase is very important parameter in formulating stable SEDDS formulations. In the current study, the main ingredients of SEDDSs formulations were oil, surfactant/co surfactant, which were selected on the basis of drug solubility because solubility directly affects drug loading [17]. Solubility of montelukast was determined in different oils, surfactants and co surfactants as shown in table 2. Among these, better results were obtained at Oleic acid, Tween 20 and PEG 400. Besides the high drug solubility in oil as a basic requirement, the presence of surfactant in SEDDS formulation plays a very critical role by reducing the surface tension between aqueous and oily phase thus stabilizing the dispersed droplets in emulsion and enhances the miscibility process of oily phase of the formulation with GIT fluid [17]. All the three components i.e Oleic acid, Tween 20 and PEG 400 were selected have shown to solubilize maximum amount of montelukast. Thus the above three components were selected for the formulation development of montelukast on SEDDS technique.

Table 2. Solubility of montelukast in different oils, surfactants and co surfactants

S.No.	Oils	Solubility(mg/ml) Mean ± SD	Surfactant	Solubility in mg / ml (mean ±SD)
1.	Cinnamon oil	18.00±0.006	Tween 20	33.80±0.016
2.	Cod liver oil	20.85±0.010	Tween 40	24.62±0.010
3.	Oleic acid	59.45±0.016	Tween 60	29.81±0.02
4.	Sunflower oil	28.20±0.07	Tween 80	22.13±0.02
5.	Crodomol oil	19.93±0.01	**Co-Surfactants**	69.30±0.02
6.		34.65±0.017		90.20±0.006
7.	Capric/caprylic	47.44±0.0105	PEG 200	81.78±0.001
8.	Clove oil	36.97±0.0190	PEG 400	88.15±0.03
9.	Coriander oil	48.31±0.085	PEG 600	
10.	Sesame oil	13.12±0.016	Propylene	

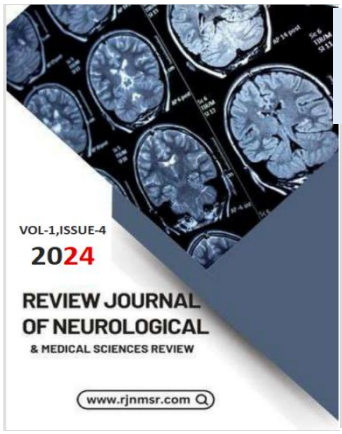
Formulation of Liquid SEDDS

Several SEDDS formulations were developed using different percentages of the selected oil, keeping the concentration of drug constant in all formulations (Table 1). All the ingredients in each formulation were mixed to form emulsion. All the formulations were combined and agitated for 24 hours at 25 °C in a sonicator to ensure complete solubilization.

Liquid SEDDS Evaluation

Time of Self-Emulsification

Self emulsification time test was carried out to determine the self-emulsifying properties of the desired formulations. According to literature [18] the desired SEDDS formulations should have the ability to disperse rapidly when conditioned to aqueous dilution with gentle stirring. This rapid dispersion is due to surfactant



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present in the SEDDS formulations which lowers the interfacial tension between oils and aqueous phases.

Table 3. Time required for emulsification of various liquid SEDDS formulations

S. No.	Formulations	Self-emulsification time (seconds)
1.	F1	20
2.	F2	23
3.	F3	2
4.	F4	
5.	F5	28

Table 3 revealed self emulsification time of all formulations. Among all the formulations, formulation (F1), have least emulsification time. The primary cause was that F1 have high percentage of the surfactant and co-surfactant, both of which are necessary for the creation of a stable emulsion. All other Formulations F2, F3, F4, and F5 were self-emulsified in less than 30 seconds as shown in table 3.

Phase Separation Study

Phase separation study of desired formulations was evaluated based on centrifugation tests. Phase separation was not observed in any formulation and all formulations were stable after centrifugation at 3000 *g* for 8 min. There was no evidence of phase separation, indicating their kinetic stability.

Percentage Transmittance

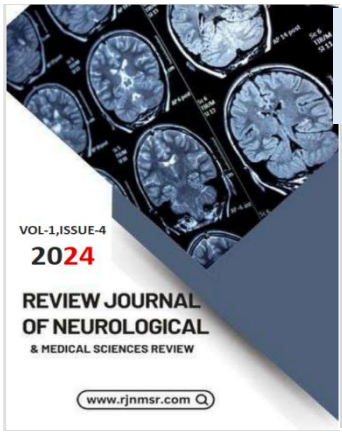
To determine degree of transparency and homogeneity of various formulations of liquid SEDDS of montelukast, a special test was performed called percentage transmittance test. A UV spectrophotometer was used to calculate the liquid SEDDS's percentage transparency. If percentage transmittance of formulation is over 90%, then formulations have a transparent nature. All Formulations produced clear micro emulsion. The transparency of the formulation improves as surfactant and co-surfactant concentrations grow. Percentage transparency of all formulations was above 90% as shown in table 4.

Table .4. Formulation Percentage Transparency of Liquid SEDDS

S. No.	Formulations	% transparency (Mean ±SD)
1.	Formulation (F1)	98.87±0.10
2.	Formulation (F2)	98.52±0.24
3.	Formulation (F3)	97.25±0.08
4.	Formulation (F4)	92.77±0.17
5.	Formulation (F5)	91.25±0.08

Stability Study

The desired SEDDS formulations should be stable under different temperature conditions. It's also desirable that upon dilution the formulation produced should not lose the spontaneous emulsification property. Therefore, the stability assessment in different temperature conditions was carried out for all formulations. It was noticed that F1, F2 and F3 survived the thermodynamic stability tests and no sign of



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phase separation was observed while F4 and F5 have phase separation after 24 hours, thus these two preparations will not be processed further.

Precompression Evaluation

The optimized liquid SEDDS formulations of montelukast were converted into solid self-emulsifying drug delivery systems via adsorption of liquid formulation onto solid carrier. Selection of absorbent was on the basis of its compatibility with other excipients. Adsorbent used for solidification of formulation was aerosil 200 which convert the liquid formulation into free flowing powder. Aerosil 200 was used to provide large surface area. Before compressing into tablets, the powder of the improved formulation was examined for a number of rheological properties and better flow was noticed for all three formulations (table 5). Bulk density and tapped density, Hausner's ratio & Carr's index were calculated for the optimized formulations indicated better flow of the desired powder which is due to granulating effect of the oil phase. The proper flow of powder is required for effective tablet compression. If powder has flow issue that is if powder is poor in flow, then there will be problem in compression of tablets, weight of the tablets will not be uniform and there will be weight variation in the compressed tablets.

Table .5. Pre-Compression Evaluation Montelukast SEDDS Powder

	Montelukast SEDDS powder parameters			
Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)
F1	0.490±1.5	0.646±0.098	1.33±3.2	15.8±1.3
F2	0.465±2.4	0.619±0.34	1.34±2.3	18.9±2.4
F3	0.581±0.12	0.722±1.14	1.25±2.5	14.4±0.023

Post Compression Evaluation

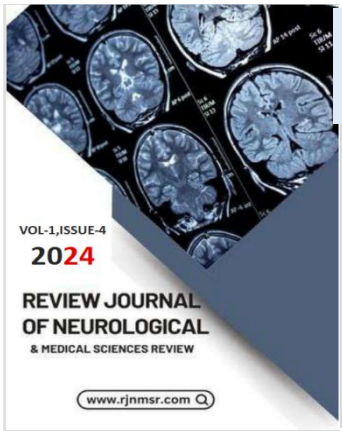
Direct compression method of tablet manufacturing was selected to compress the optimized solid SEDDS formulation into tablets. Different quality control tests including weight variation, friability, rate of disintegration, hardness, and thickness. These tests were conducted fir all three formulations. The results are presented in table 6 below.

Weigh Variation Test

Weigh variation test was carried out for tablets of all three batches according to USP guidelines. Thickness of tablets selected randomly was also well within the limit as indicated in table 5. The results of these two tests indicated uniform blending and flow of the powder mixture produced by SEDDS technology.

Hardness And Friability Test

Hardness and friability tests were used to determine the mechanical strength of tablets (table 6). These are important tests carried out to determine that whether the tablets bear the physical stress during handling, transportation etc or not. As indicated from the table 6 the hardness range was 25–31 N for all tablets The mechanical or crushing strength of all the formulations developed was in the range of 25–31 N. According to literature [17] high oil content contribute to lower crushing strength. For example formulation 3 having a higher quantity of the oil with low crushing strength as shown in table 5 while F1 and F2 have relatively low oil



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contents in their formulations exhibiting comparatively high crushing strength. Friability test was also carried out according to the USP specifications, and the results in table 6 indicated that all the formulations complied with the pharmacopeial specifications. The weight loss before and after the tests was determined and in all the cases was less than 1%. Not a single table broke during the test so the test was considered pass according to USP guidelines.

Disintegration Time

Disintegration test is another important test to determine whether the desired tablet disintegrate within the prescribed time. The test was performed on randomly selected six tablets of each developed formulation. As indicated from the table 6, all the formulations showed disintegration time within the official limits of USP (≤15 min). SEDDS formulations are thought to have higher disintegration time because it have oil which is hydrophobic in nature however the formulation contained disintegrating agent which facilitates disintegration which is also augmented by the presence of surfactant in the formulation. Surfactants worked by increasing water penetration of the tablets and decreasing surface tension, thus resulting in high disintegration of tablets [17].

Table .6. Post-Compression Characterization Of Montelukast Sedds Tablets

Parameters	Values (Mean ±SD)		
	F1	F2	F3
Average weight in mg151.1±2.4	3.35150.6±1.06		152.02±1.8
Thickness in mm Hardness±2.6		3.37±1.07	3.32±.008
in Newton Friability %	30.9±1.8	30.4±1.09	28.2±0.005
Disintegration time in0.98±1.2%		0.95±1.06	0.97±0.008
minutes	12±0.03	10±0.005	8.3±1.6

Dissolution Test

In vitro release of montelukast from the tablets of all three developed formulations was tested as per USP monograph. According to the USP, the drug release from montelukast tablets should not be less than 75% after 45 min. In this study, drug release was determined for 15,30, 45 and after 60 minutes to determine the time for 100% drug release. The dissolution rate of the marketed product of montelukast (name not mention here) was also checked and used as control for comparison with our developed formulations. Figure 3 indicated quick and over 85% drug release was observed within 30 min from all the developed formulations. The release profile of all developed formulations and control product (marketed montelukast) was evaluated based on four different time points. Results in figure 2 indicated that all developed formulations had higher release profile of drug at all four tested points. Thus SEDDS formulations developed with montelukast exhibited higher drug release profile than the conventional tablets of montelukast, suggesting that self-emulsification technique significantly increased thedissolution rate of poorly water-soluble drugs. Thus SEDDS technology can be used for type II BCS drugs having

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solubility and dissolution problems to produce drugs that having high solubility, dissolution and bioavailability profiles.

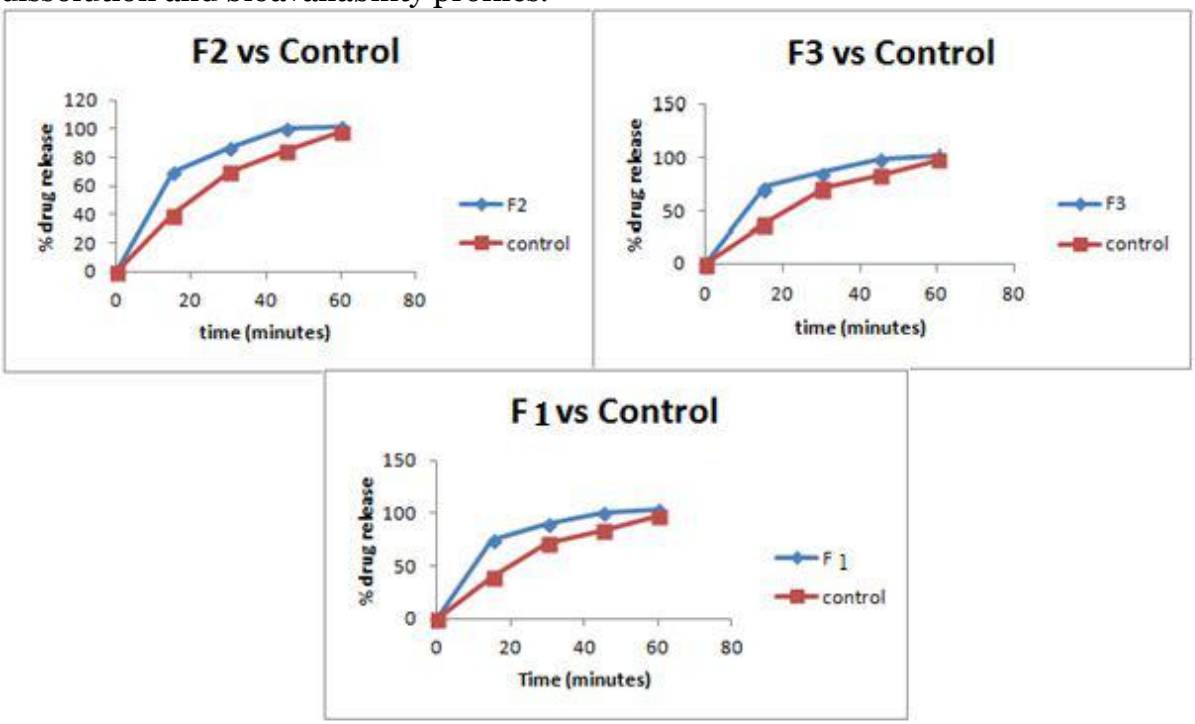

Fig.2. In Vitro Dissolution Profile Of Montelukast From Optimized Ssedds Formulations And Marketed Product (Control)

Conclusion

Liquid SEDDS for montelukast with oleic acid as oily phase, Tween 20 as surfactant and PEG 400 as co-surfactant were successfully developed. Based on the, phase separation test, emulsification time, percentage transmittance thermodynamic stability test, three optimal compositions of L-SEDDS of montelukast were selected. The optimized liquid montelukast SEDDS were finally successfully compressed to S-SEDDS having better post compression quality control parameters than the marketed product. In short, by using commonly available excipients and compression machinery, SEDDS tablets with better dissolution rates can be prepared by direct compression. Enhanced dissolution rate, along with drug presence in emulsion form, will improve the bioavailability of poorly water soluble drug montelukast.

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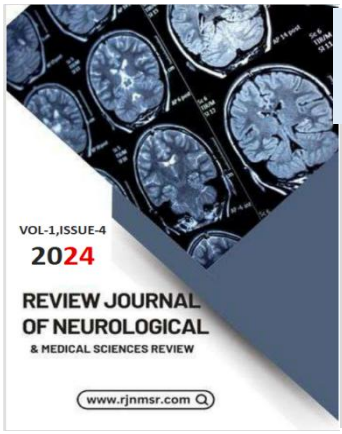

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