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Formulation, Optimization and Evaluation of Self Emulsifying Drug Delivery System of Diclofenac Sodium Tablets

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ABSTRACT

Various strategies have been widely investigated to enhance the solubility of poorly soluble drugs. These strategies increase the clinical efficacy when the drug is administered orally. Around 40% of novel chemical entities show evidence of poor aqueous solubility and their bioavailability becomes low. Thus to overcome this problem new technologies are applied. This new technologies improve the solubility of those drugs whose water solubility is poor. This new technology is known as SEDDS. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. It can be orally administered in soft or hard gelatin capsules. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation.

Keywords: Isotropic Mixture, SEDDS, Oils, Surfactants, Solvents, Co-solvents

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INTRODUCTION

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Those drugs which are poorly water soluble, they having slow absorption of drug and have low bioavailability. The improvement of drug solubility is one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are various approaches to enhance the solubility of drug which are poorly water-soluble. The selections of solubility enhancement techniques are done on the basis of properties of dosage forms, nature of drugs and nature of excipients.

The drug having low dissolution and poor water solubility in aqueous gastrointestinal fluids often causes insufficient bioavailability.

Various strategies have been widely investigated to enhance the solubility of poorly soluble drugs. These strategies increase the clinical efficacy when the drug is administered orally.

Around 40% of novel chemical entities show evidence of poor aqueous solubility and their bioavailability becomes low. The bioavailability of hydrophobic drug can be improve by Self-emulsifying drug delivery systems (SEDDS).

This is the new technology to improve the solubility of those drugs whose water solubility is poor. SEDDS have lipid formulation and its size ranges from100nm (SEDDs) to less than 50nm.

SMEDDs are the mixture of surfactant, co-surfactant and oils. While formulation their ratio should be kept in correct order and can be emulsified in aqueous media by gently stirring method[1-7]

MATERIALS AND METHOD

Diclofenac sodium was obtained as gift sample from Bio Chemical & Synthetic Product Ltd, Hyderabad India. Glycerine, PEG-6000, Span-80, Span-20, Tween-80, Tween-20, Soyabean oil, Oleic acid, Lactose, PVPK-30, Crosscarmellose sodium (CCS), were purchase from Central drug house, New Delhi. The reagents and chemicals which are used in the formulation are analytical grade.

DRUG RELATED STUDIES[8]

Melting point determination

Melting point of drug was found to be 284°C, which is well within the range of literature specifications, 284-286°C indicating the identity and purity of drug sample as diclofenac sodium.

FTIR of Diclofenac Sodium

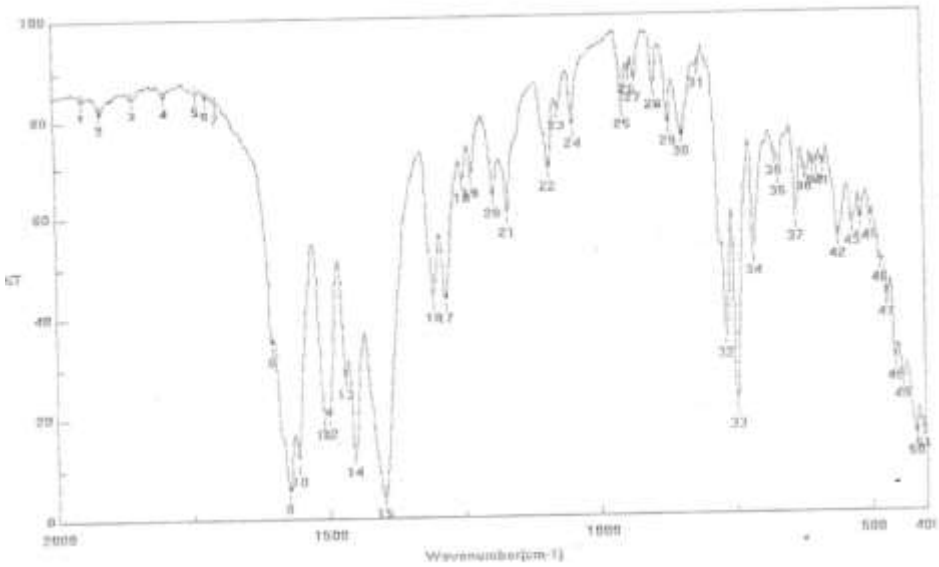

Figure 1: FTIR of Diclofenac Sodium

PREPARATION AND CHARACTERIZATION OF GRANULES

The SEDDS of diclofenac sodium can be prepared by melting the surfactant mixture of tween-80 or tween-20 in co-solvents like PEG-6000 or span-80 or span-20 by using oil like soyaben oil or oleic acid .During melting the temperature should be 70°C. The molten blend was prepared by using china dish. By using different ratio of ingredients, several formulations were prepared as shown in table 2. Then the prepared blend is mixed with the drug until a creamy dispersion was produced. Finally the blended excipients (CCS, Lactose, and PVPK-30) were mixed physically in different proportions. Creamy dispersion was then mixed thoroughly until a suitable mass was obtained. Then this mass was semi-dry after semi dry it was screening and then sends for full dry. After complete dry it was lubricated and then compressed as tablet.

Table 1 Rheological properties of granules

Granules	Bulk density(gm/cm^3) ± S.D	Tapped density(gm/cm^3) ± S.D	Angle of repose(degree) ± S.D	Carr's compressibility index (%)±S.D	Hausner's ratio±S.D
F1	0.729±0.134	0.863±0.78	31.331±0.16	12.570±0.25	1.070±0.19
F2	0.730±0.32	0.842±0.23	30.377±0.25	13.410±0.23	1.080±0.22
F3	0.742±0.62	0.859±0.21	31.877±0.10	14.347±0.19	1.115±0.54
F4	0.754±0.12	0.857±0.36	26.505±0.19	11.482±0.69	1.142±0.35
F5	0.737±0.19	0.867±0.32	32.133±0.01	11.704±0.13	1.172±0.65
F6	0.746±0.39	0.856±0.23	31.437±0.21	12.218±0.29	1.237±0.27
F7	0.748±0.21	0.854±0.35	29.427±0.64	13.476±0.67	1.154±0.23
F8	0.745±0.45	0.863±0.67	26.346±0.35	12.062±0.45	1.144±0.012

Angle of repose

The angle of repose was calculated for each granule by static funnel method. The values determined for F1, F2, F3, F4, F5, F6, F7 and F8 ranges between 26.346±0.35 to 32.133±0.01^{o}. The values for angle of repose exhibited by formulation showed good flowability. In formulation of SEDDS the oil, surfactants, co-surfactants, solvents and co-solvents are used thus its ratio should be limited manner otherwise the flowability slightly decreases.

Bulk density and tapped density

Bulk density of F1, F2, F3, F4, F5, F6, F7 and F8 was found 0.729 ±0.134 to 0.748 ± 0.21 g/cm^3 respectively and the trapped density of the formulation ranges from 0.842 ± 0.23 to 0.867 ±0.32 g/cm^3 respectively.

The bulk density of powder is always less than the tapped density of its component because the powder contains inter-particle pores or voids. This statement reveals where as a powder can only possess a single tapped density it can have many different densities, depending on the way in which the particles are packed and bed. However, a bulk density value does not necessarily imply a closed packed low porosity bed as bulk is directly proportional to tappeddensity[8].

Hausner's ratio

Hausner's ratio is another means of defining the flow properties of prepared F1, F2, F3, F4, F5, F6, F7 and F8 formulation which was in the range of 1.142±0.35 to 1.237±0.27 clearly indicate that the values are less than 1.25, this represents that the granules have good flow property.

Carr's compressibility index

The compressibility index of the powder is a direct measure of the potential of arch or bridge strength and stability. The determination value for Carr's compressibility index of the above formulation were found in the range of 11.482 ±0.69 to 14.347 ±0.19 % were found in the range which suggest that all the prepared granules are having good compression property .

PREPARATION AND CHARECTERISATION OF SEDDS TABLETS

The SEDDS tablets were prepared by single rotator machine or by double rotator machine. The lubricated granules were weighted properly. The die cavity filled up completely with granules and is compressed with the maximum force of compression on a punch tablet machine[9].Prepared tablet formulations were coded as F1-F8 and stored in desiccators till further use.

Composition

The drug and excipients which were used in the preparation of SEDDS tablets are given in Table 2 The composition of the drug and the excipients have been designed using CCS and Lactose as same concentration where as PVPK-30 is used in different concentrations have been prepared and subjected for various pharmacotechnical evaluations.[10]

Table 2 Formulation composition of SEDDS

Formulation Code	Drug	Tween-80	Tween-20	PEG-6000(5%)	Glycerine	Span-80	Span-20	Soyaben oil	Olic acid	Lactose	PVPK-3	CCS
F1	4	6.53	-	5.24	-	7.24	-	-	2.35	16	2.42	16
F2	4	6.53	-	-	5.24	7.24	-	-	-	16	2.42	16
F3	4	-	7.25	5.24	-	-	7.21	-	2.35	16	2.42	16
F4	4	-	7.25	-	5.24	-	7.21	2.50	-	16	2.42	16
F5	4	6.53	-	5.24	-	7.24	-	2.50	2.35	16	2.42	16
F6	4	6.53	-	-	-	7.24	-	2.50	2.35	16	2.42	16
F7	4	-	7.25	5.24	5.24	-	7.21	2.50	-	16	2.42	16
F8	4	-	7.25	-	-	-	7.21	-	2.35	18	2.42	18

All polymer's are in (%W/W)

Lubricating Agent

Table 2 Lubricating agent and their concentration

S.No.	Components	F1	F2	F3	F4	F5	F6	F7	F8
1.	Talcum (%w/w)	4	4	4	4	4	4	4	4
2.	Mg.Stearate (%w/w)	2	2	2	2	2	2	2	2

The lubricating agent (Talcum and Mg.Stearate) should be used during the lubrication time according to 4% and 2% w/w after drying the granules.

EVALUATION OF PREPARED SEDDS TABLETS[11]

Hardness and friability

The hardness of the tablet affects the release pattern of the drug from the formulation. Thus, SEDDS tablets must attain a sufficient strength in order to maintain the good release pattern of the formulation. Therefore, the hardness of prepared tablets was determined. The mean values of hardness of SEDDS tablets were in the range of 5.13±0.115 to 6.85±0.100 kg/cm^2 (Table 3). The hardness of tablets increase by increasing the concentration of PVPK-30 which was attributed to binder property .All tablets showed hardness of more than 5 Kg/cm^2 that reflects, the tablets were able to handling the pass the friability test. All the prepared tablet exhibited friability less than 1 % (Table 3) which meets the pharmacopeia standard limit, indicating that the formulation were mechanically stable.

Weight variation test

The amount of drug incorporated within the system is equivalent to the dose that is to produce the optimum therapeutic effect. Any variation in the dose size i.e. to increment in that amount leads to inefficient or toxic therapy. Weight variation of solid dosage form is checked point by which one can reduce the possibilities of above problems. None of the individual tablet weight found deviate more than 2.5% from average weight as per limit and none deviated more than twice of that percentage. It result that all the tablet batches passed the weight variation test.

Thickness

Thickness of prepared tablets was determined by using Vernier Calliper and the value of thickness ranges between 5.09±0.064 to 5.28±0.021 mm. From the testing report of tablet it was found that the thickness exhibited by prepared SEDDS tablets did not cross the limit .this shows the efficiency of equipment and the process.

Drug content determination

The prepared tablet formulations were evaluated for their percentage drug content. The formulation passed the drug content test as the drug content was well within the range 95.33±0.66 to 99.67±0.64 (Table 3),suggest that a uniformity in mixing of drug with other excipients has been carried out before compression of SEDDS tablets.

Table 3: Comparative data for evaluation of various properties of SEDDS tablets

Formulation Code	Weight variation (mg)±SD	Thickness (mm) ±SD	Hardness (kg/cm^2) ±SD	Friability (%)	Drug content (%)±SD
F1	398±1.15	5.22±0.030	6.09±0.200	0.46±0.32	95.66±2.41
F2	401±0.71	5.28±0.021	5.13±0.115	0.35±0.25	97.36±3.46
F3	394±1.46	5.25±0.030	6.25±0.103	0.69±0.62	98.43±1.25
F4	395±0.86	5.09±0.064	6.15±0.123	0.36±0.71	96.62±0.95
F5	389±0.46	5.17±0.030	5.33±0.115	0.63±0.09	95.76±1.61
F6	401±2.10	5.18±0.041	6.40±0.115	0.44±0.03	95.33±0.66
F7	400±0.17	5.18±0.050	5.64±0.110	0.21±0.07	98.96±1.61
F8	397±0.66	5.24±0.052	6.85±0.100	0.12±0.12	99.67±0.64

IN VITRO DRUG RELEASE AND RELEASE KINETICS[12-15]

The release profile of formulation (F1-F8) along with in house developed SEDDS displayed in %CDR profile. The formulation F1 and F2 released 94.750±0.65 and 87.345±0.23 of drug within 120 min and achieve zero order kinetics indicated by their least regression coefficient values (r^2<0.999). However the formulation F3,F4,F5, F6, and F8 showed release of drug up to 120 minutes but Formulation,F8 best modulated zero order release kinetics up to 110 minutes with maximum regression coefficient value of r^2=0.9996; was optimized and compared for % CDR and release kinetics.

The comparative profile of in house developed SEDDS Tablets with optimized formulation (F8) showed that the in –house developed SEDDS tablet released its major part of drug within 110 minutes.

Table 4*In vitro* drug release data of SEDDS tablets in 0.1 N HCl buffer pH 1.2

Time	% cumulative drug release							
(min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	8.2	8.9	9	7.8	6.785	5.265	6.123	5.092
20	18.64	21.51	20.88	15.2	12.456	10.365	11.513	18.972
30	37.521	29.63	25.37	26.5	24.147	15.369	18.612	37.87
40	42.241	33.95	32.22	37.5	33.369	27.852	23.643	43.741
50	53.108	37.22	36	44.3	41.258	33.126	29.355	51.819
60	59.669	46.25	40.79	50.23	47.536	39.264	36.954	58.821
70	69.186	62.74	43.84	55.256	54.985	44.235	43.769	65.785
80	73.157	71.04	47.84	60.235	59.95	50.214	50.286	74.362
90	79.762	78.24	53.71	66.523	63.985	57.921	56.147	82.643
100	83.263	80.523	58.07	69.256	68.265	62.983	65.077	86.913
110	92.231	84.954	72.29	72.152	71.236	69.954	72.954	99.966
120	94.750	87.345	81.72	76.123	75.256	75.278	98.942	

Table 5 Mathematical modeling and drug release kinetics of SEDDS tablets

Formulation Code	Zero Order(r^2)	Higuchi(r^2)	First Order($r^{2)}$	Peppas "n" value
F1	0.9759±0.032	0.9623±0.021	0.5989±0.026	0.46±0.02
F2	0.9778±0.021	0.9762±0.001	0.5761±0.065	0.78±0.04
F3	0.9221±0.035	0.9932±0.008	0.6243±0.042	0.52±0.02
F4	0.9598±0.025	0.9901±0.010	0.6101±0.035	0.56±0.008
F5	0.9452±0.002	0.9854±0.015	0.6473±0.027	0.61±0.02
F6	0.9861±0.002	0.9695±0.018	0.71043±0.013	0.87±0.04
F7	0.9696±0.003	0.9701±0.042	0.7142±0.019	0.94±0.05
F8	0.9961±0.065	0.9501±0.034	0.7442±0.029	0.87±0.04

***n= 3

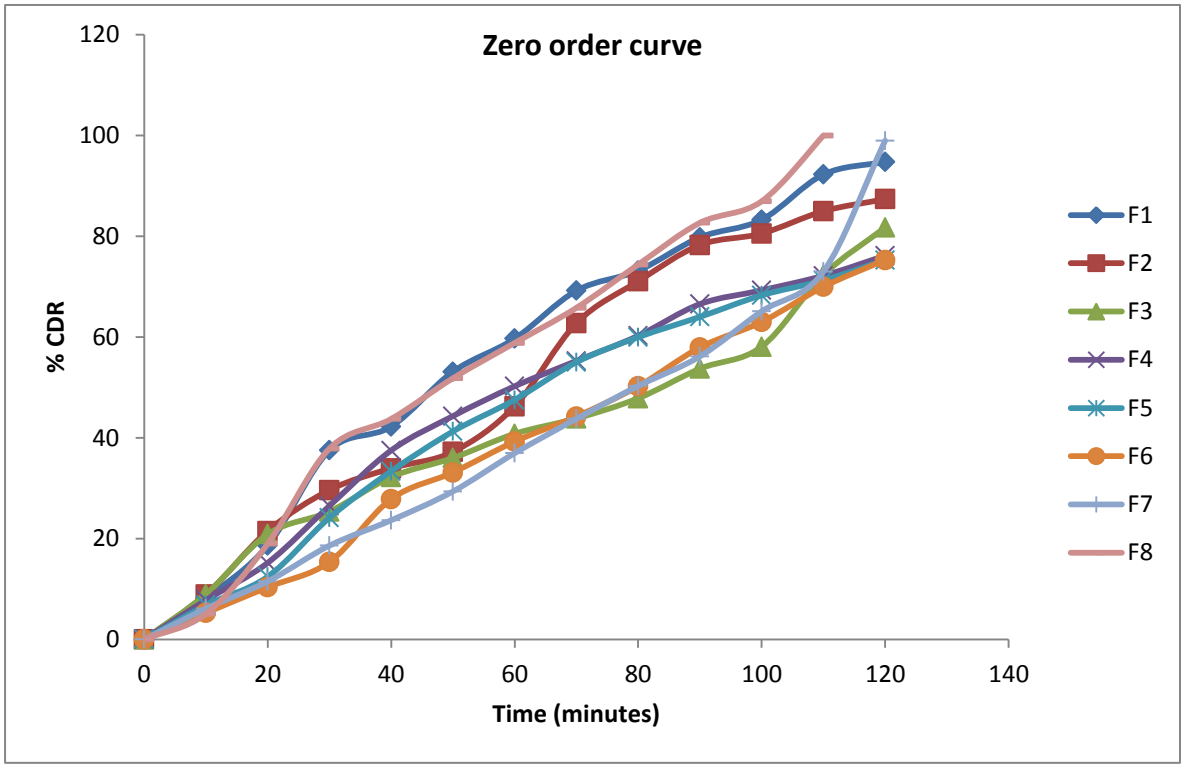

Figure 2: Zero order curve profile of prepared formulations

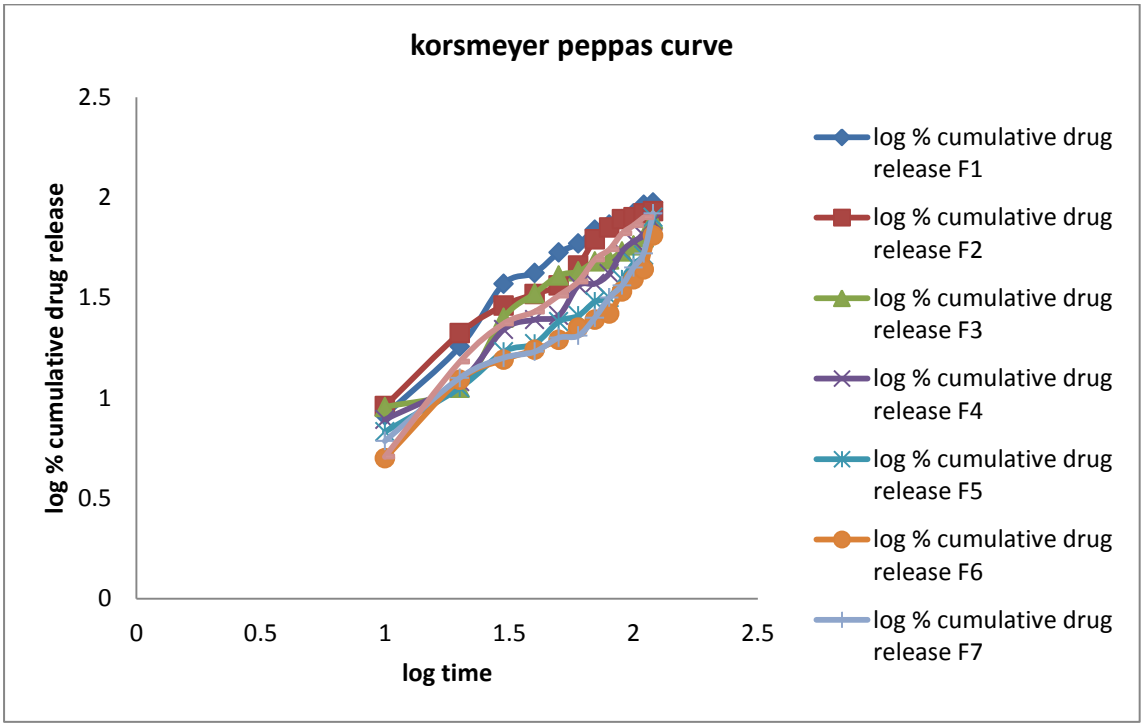

Figure 3:Korsmeyerpeppas curve profile of prepared formulations

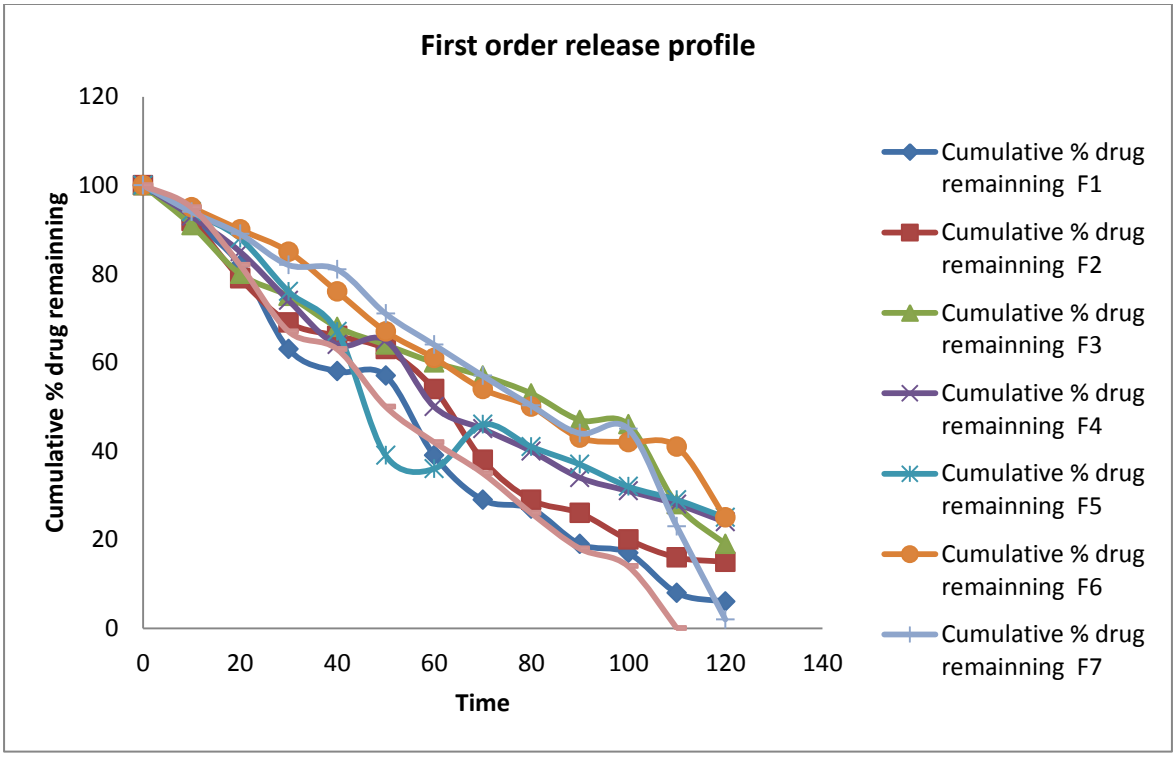

Figure 4:First order release profile of prepared formulations

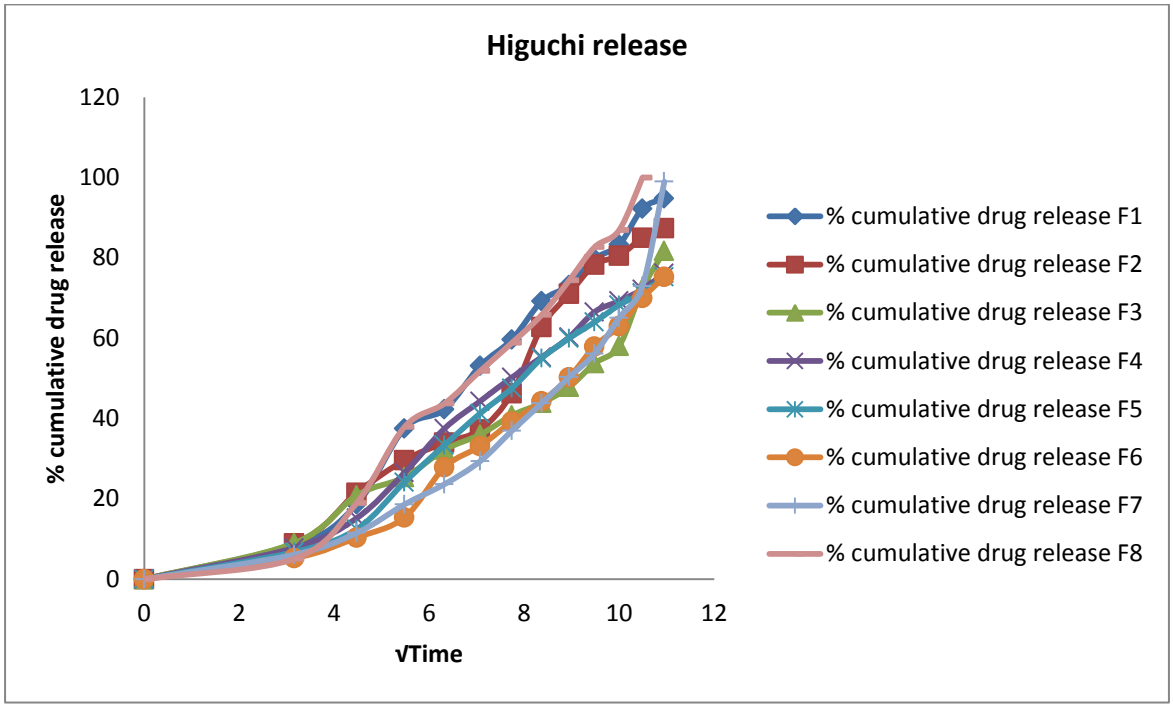

Figure 5:Higuchi release profile of prepared formulations

OPTIMIZATION OF SEDDS TABLETS

On the basis of the release kinetic the formulation F8 was found as the optimized formulationbecause it provide us the planned release kinetics *i.e.* zero order release with correlation coefficient (r^2=0.9961) in the pattern of controlled release study. The % cumulative drug release of the formulation F8 was found 99.66 in 110 minutes and thus it increases the absorption percentage of therapeutic agent.

CONCLUSION

Self-emulsifying drug delivery systems is a successful approach for the formulation of drug which having poor aqueous solubility. The hydrophobic drugs delivery by oral routes can be made possible by SEDDSs, which can improve the dissolution and oral bioavailability of drug. SEDDS shows novel applications in drug delivery in future and solve problems associated with the delivery of those drugs which have the poorly solubility. Numerous studies have confirmed that SEDDS improved solubility, dissolution, absorption and bioavailability of those drugs that's having the poor water-solubility.

While comparing liquid SEDDS to S-SEDDS, It is observed that S-SEDDS are superior in-[11]

i) Production cost

ii) Improving stability

iii) Simplifying industrial manufacture and

iv) Improving patient compliance.

Most importantly, SEDDS are very easy to develop various solid dosage forms for oral administration and for parenteral administration. It is found that the irritation through GI is avoided and controlled/sustained release or controlled release drug is achieved. There is still a long way to go, before more solid SE dosage form appear on the market.

Because there exist some fields of SEDDS about human bioavailability and their correlation of in vivo/in vitro.[12]

For example physical aging phenomenon associated with glyceride is pointing out to which attention should be paid. Oxidation of vegetable oil, and interaction between drugs and excipients In case of SEDDS development the selection of suitable excipients is most important. Thus, above aspects shows that major future aspects were found in the direction of SEDDS. For proper development of SEDDS the major thoughts most be require.The formulation F8 was found superior than the prepared other formulation thus formulation F8 was selected as the best formulation of SEDDS tablet.

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