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Study of Variables to Optimize the Formula of Diclofenac Sodium as a Self-Emulsifying Drug Delivery System

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Abstract

Some drug molecules having bioavailability problem even after a good solubility profile. This problem may be due to their branched and bulky molecular structure or due to their good affinity with skin's layers parts. That bioavailability problem may be overcome by forming a self-emulsifying drug delivery formulation. Molecules of Diclofenac Sodium though possess a good water solubility but present a below level oral bioavailability because drug food interaction and below level bioavailability because drug protein (present in skin layers). In this study Diclofenac Sodium molecules, surfactant and oil were firstly form a system in which drug having good solubility (optimized) so as it interacts and leave as well with solvent system. Granulation was done with granulating agents and converted the granules after proper lubrication. Drug release study was done and formulation code STD8 shows a good release profile in zero order release with correlation coefficient (r2=0.9961) in the pattern of controlled release study. The % cumulative drug release of the formulation SDT8 was found 99.66 in 110 minutes and thus it increases the absorption percentage of therapeutic agent. There is no indication of any type of keratolysis in applied area of cadaver skin part observe in SEM analysis. This indicates that increased penetration flux of model drug was not due to any rupture in penetration barrier but only due to support opening of channels.

Keywords: Diclofenac, STD8, NSAID, SEDDS.

Introduction

The class-II category drug molecule, which belong to having the low solubility and high permeability category, are a suitable candidate for SEDDS type formulation. A drug molecule like diclofenac sodium is suitable drug candidate for the formulation of SEDDS. The drugs that's having high permeability but the solubility is low are the write drug candidate for SEDDS formulation; diclofenac sodium belongs to class-II drug in BCS. By applying SEDDS method the solubility of diclofenac sodium can be increased. Diclofenac sodium belongs to NSAID.

The bioavailability of the formulation can be increased by increasing the drug solubility and minimizing the gastric irritation. Also, by using gelling agent we can

formulate the sustained release formulation. In SEDDS formulation the lipid matrix interacts with water used, and forming a fine (o/w) Oil in-water type of emulsion. The emulsion's dispersed phase droplets deliver the drug to the gastrointestinal mucosa in the dissolved state promptly accessible for absorption. We could improve the bioavailability of many drugs when they are formulated in SEDDS forms. A self-emulsifying drug delivery system (SEDDS) is a drug delivery approach in which a drug is formulated as a mixture of oils, surfactants, and co-surfactants that spontaneously form an emulsion or micro-emulsion when mixed with an aqueous medium.

Methods

Diclofenac sodium was obtained as a gift sample from Bio Chemical & Synthetic Product Ltd., Hyderabad, India. PEG-6000, Tween-40 and used oils were of analytical grade and of Central Drug House (P) Ltd., and all other chemicals used were of analytical grade and were used without any type of further chemical up gradations. Phase diagram: Surfactant with co-surfactant were mixed in different proportions viz. 1:1, 1:4, 1:5, 5:1. 4:1; are known as SS (Solvent system).

Table 1: Solvent system design with Tween 20 and PEG 600

Sr. No.	Surfactant with co-surfactant	Solvent system code
1.	1:1	$SS1_{T20P600}$
2.	1:4	$SS2_{T20P600}$
3.	1:5	$SS3_{T20P600}$
4.	**5:1**	**$SS4_{T20P600}$**
5.	4:1	$SS5_{T20P600}$

Solubility study: (Patel, at.el., 2007) A pre-known number of vehicles that was pure or mixture of oil, surfactant or co-surfactant, were taken in sample bottle. An excess amount of model drug that is Diclofenac Sodium was mixed in sample bottle. Mixture of admixed were shaken with vertical shaker at room temperature (250C) for 2 hours the interval of 2 hours for total 12 hours. After equilibrium achieved of the mixture, sample bottles were centrifuged at 2000 rpm for 10 min., and un-dissolved drug molecules were separated by the means of filtration (Whatman filter paper). The samples were analyzed visually as well as through UV- Vis spectrophotometry in order to confirm concentration of the drug molecule in used solvent/solvent system.

Table 2: List of solvent used for solubility study.

Soyabean oil	Olive oil
Palm oil	Peanut oil
Corn oil	Cotton seed oil
PEG 400	PEG 600
Tween 20	Tween 40
Span 40	Span 20

Table 3: Observation of solubility study

Sr. No.	Solute+Solvent	Conditions
1	Diclofenac sodium + Soya-bean oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation
2	Diclofenac sodium + Palm oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation
3	Diclofenac sodium + Corn oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation
4	Diclofenac sodium + Olive oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation
5	Diclofenac sodium + Peanut oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation
6	Drug + Cotton seed oil	Tween 20, NTP, mild agitation
		Tween 40, NTP, mild agitation
		Span 20, NTP, mild agitation
		Span 40, NTP, mild agitation

Sr. No.	Solute+Solvent	Conditions
1	Diclofenac sodium + Soya-bean oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation
2	Diclofenac sodium + Palm oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation
3	Diclofenac sodium + Corn oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation
4	Diclofenac sodium + Olive oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation
5	Diclofenac sodium + Peanut oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation
6	Diclofenac sodium + Cotton seed oil	Tween 20, 45^{0}C, mild agitation
		Tween 40, 45^{0}C, mild agitation
		Span 20, 45^{0}C, mild agitation
		Span 40, 45^{0}C, mild agitation

The solutions were examined firstly through visually and with the help of turbidity meter. Based on both visual and turbidity solutions were categorized in four categories: • Transparent and easy in flow (TS) • Transparent and viscous in flow (TG) • Milky and easy in flow (ES) • Milky and viscous in flow (EG) Phase diagrams were prepared with the help of software (Chemix School 12.0). Point A was oil, point B was SS4 T20P600 and point C was distilled water. Granules preparation: By using tween as surfactant different formulation codes were designed and prepared with formulation abbreviation from SDT1 to SDT8. The SEDDS of diclofenac sodium were prepared by melting the surfactant mixture of tween-40 in co-solvents like PEG-600 by using oil like soyabean oil or Olic acid. During melting the temperature should be 70°C. The molten blend was prepared by using China dish. By using different ratio of ingredients. 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. Emulsion which was formed after application of the prepare formulations at supposed site of application were evaluated under dye test and dilution test for category of emulsion determination, creaming test, globules size and Ostwald ripening test for physical stability of prepared formulation. Tablet preparation: Dispensed all tabulated excipient in a tray and blended them with gental shakes. 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 send for full dry. After complete dry it was lubricated by using talcum (4%) and Mg. Stearate (2%) w/w then compressed as tablet. Result: Visual observation table in order to select the solvent system for preparation of SEDDS formulation of diclofenac sodium.

Table 4 : Observation of solubility study at NTP

Sr. No.	Solute+Solvent	Conditions	Observation	
			After 02 hours	After 12 hours
1	Diclofenac sodium + Soya-bean oil	Tween 20, NTP, mild agitation	TG	TG
		Tween 40, NTP, mild agitation	**TS**	**TS**
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	EG	EG
2	Diclofenac sodium + Palm oil	Tween 20, NTP, mild agitation	EG	EG
		Tween 40, NTP, mild agitation	EG	EG
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	**TG**	**TS**
3	Diclofenac sodium + Corn oil	Tween 20, NTP, mild agitation	EG	EG
		Tween 40, NTP, mild agitation	EG	EG
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	EG	EG
4	Diclofenac	Tween 20, NTP, mild agitation	EG	EG
	sodium + Olive oil	Tween 40, NTP, mild agitation	EG	EG
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	EG	EG
5	Diclofenac sodium + Peanut oil	Tween 20, NTP, mild agitation	EG	EG
		Tween 40, NTP, mild agitation	EG	EG
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	EG	EG
6	Drug + Cotton seed oil	Tween 20, NTP, mild agitation	EG	EG
		Tween 40, NTP, mild agitation	EG	EG
		Span 20, NTP, mild agitation	EG	EG
		Span 40, NTP, mild agitation	EG	EG

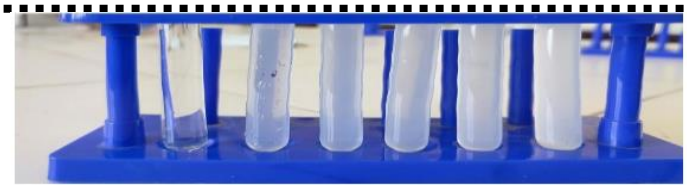

Figure 1: Observation of solubility study at NTP

Table 5: Observation of solubility study at modified conditions

Sr. No.	Solute+Solvent	Conditions	Observation	
			After 02 hours	After 12 hours
1	Diclofenac sodium + Soya-bean oil	Tween 20, 45^{0}C, mild agitation	TS	TG
		Tween 40, 45^{0}C, mild agitation	**TS**	**TG**
		Span 20, 45^{0}C, mild agitation	TS	TG
		Span 40, 45^{0}C, mild agitation	**TS**	**TG**
2	Diclofenac sodium + Palm oil	Tween 20, 45^{0}C, mild agitation	TG	TG
		Tween 40, 45^{0}C, mild agitation	**TS**	**TS**
		Span 20, 45^{0}C, mild agitation	SG	SG
		Span 40, 45^{0}C, mild agitation	SG	SG
3	Diclofenac sodium + Corn oil	Tween 20, 45^{0}C, mild agitation	SG	SG
		Tween 40, 45^{0}C, mild agitation	ES	ES
		Span 20, 45^{0}C, mild agitation	ES	ES
		Span 40, 45^{0}C, mild agitation	**TS**	**TG**
4	Diclofenac sodium + Olive oil	Tween 20, 45^{0}C, mild agitation	ES	ES
		Tween 40, 45^{0}C, mild agitation	ES	ES
		Span 20, 45^{0}C, mild agitation	ES	ES
		Span 40, 45^{0}C, mild agitation	ES	ES
5	Diclofenac	Tween 20, 45^{0}C, mild agitation	ES	ES
	sodium + Peanut oil	Tween 40, 45^{0}C, mild agitation	ES	ES
		Span 20, 45^{0}C, mild agitation	ES	ES
		Span 40, 45^{0}C, mild agitation	ES	ES
6	Diclofenac sodium + Cotton seed oil	Tween 20, 45^{0}C, mild agitation	ES	ES
		Tween 40, 45^{0}C, mild agitation	ES	ES
		Span 20, 45^{0}C, mild agitation	ES	ES
		Span 40, 45^{0}C, mild agitation	ES	ES

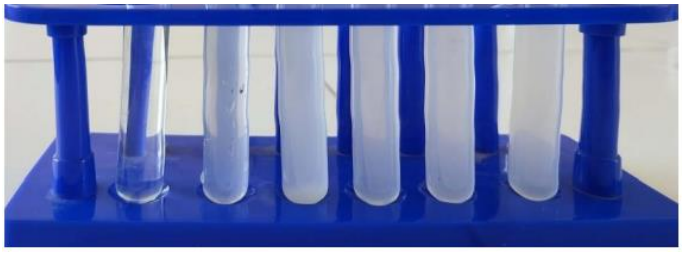

Figure 2: Observation of solubility study at modified conditions Based on the results of drug Solubilization potential solvent system SS4T40P600 was selected for further study. In order to prepare phase diagram further addition of designed component were a vortex blender. All successive addition was 5%w/w every time, mixing temperature was room temperature and second addition was only after complete dispersion of first added components. Soyabean oil was selected for further study, as soyabean oil shown a good solubility index with model drug. Phase diagram was prepared by blended the oil phase and SS in different ratio in %weight /weight units. Taken ratios were 1:1, 1:2, 1:4, 1:8 (Oil: SS4 T40P600).

Table 6.: Evaluation results of Emulsions

Formulation code	Dye test	Dilution test	Creaming/sedimentation*	Globule size range# (µm)	Ostwald ripening**
STD1	O/W	Diluted with water	16	6	9
STD2	O/W	Diluted with water	18	8	8
STD3	O/W	Diluted with water	14	6	7
STD4	O/W	Diluted with water	15	4	10
STD5	O/W	Diluted with water	17	3	12
STD6	O/W	Diluted with water	19	4	11
STD7	O/W	Diluted with water	11	5	10
STD8	O/W	Diluted with water	10	3	15

*Creaming / Sedimentation exceeds 20% after how much time (days). **flocculation increases size range of globules twice then that of their starting size after how much period of time (days). # Avg. globular size of 10 globules.

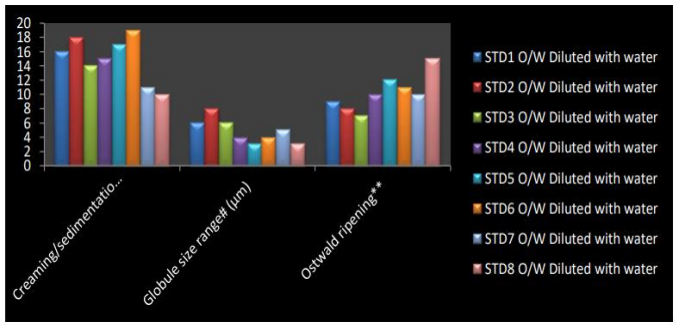

Figure 3: Evaluation results of Emulsions

Granules evaluated under following criteria:

Table 7: Granules evaluation results

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
SDT1	0.729±0.134	0.863±0.78	31.331±0.16	12.570±0.25	1.070±0.19
SDT2	0.730±0.32	0.842±0.23	30.377±0.25	13.410±0.23	1.080±0.22
SDT3	0.742±0.62	0.859±0.21	31.877±0.10	14.347±0.19	1.115±0.54
SDT4	0.754±0.12	0.857±0.36	26.505±0.19	11.482±0.69	1.142±0.35
SDT5	0.737±0.19	0.867±0.32	32.133±0.01	11.704±0.13	1.172±0.65
SDT6	0.746±0.39	0.856±0.23	31.437±0.21	12.218±0.29	1.237±0.27
SDT7	0.748±0.21	0.854±0.35	29.427±0.64	13.476±0.67	1.154±0.23
SDT8	0.745±0.45	0.863±0.67	26.346±0.35	12.062±0.45	1.144±0.012

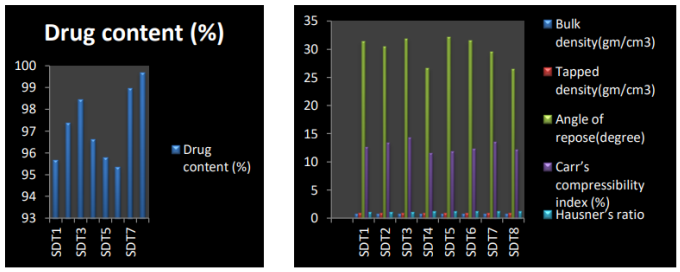

Figure 4: Granules evaluation results.

SEEDS tablets were evaluated under following criteria:

Formulation Code	Weight variation (mg) ±SD	Thickness (mm) ±SD	Hardness (kg/cm^2) ±SD	Friability (%)	Drug content (%)±SD	Disintegration Time (Minutes)
SDT1	398±1.15	5.22±0.030	6.09±0.200	0.46±0.32	95.66±2.41	8.43 ± 0.42
SDT2	401±0.71	5.28±0.021	5.13±0.115	0.35±0.25	97.36±3.46	7.52 ± 0.52
SDT3	394±1.46	5.25±0.030	6.25±0.103	0.69±0.62	98.43±1.25	7.53 ± 0.42
SDT4	395±0.86	5.09±0.064	6.15±0.123	0.36±0.71	96.62±0.95	9.12 ± 0.23
SDT5	389±0.46	5.17±0.030	5.33±0.115	0.63±0.09	95.76±1.61	8.45 ± 0.26
SDT6	401±2.10	5.18±0.041	6.40±0.115	0.44±0.03	95.33±0.66	9.15 ± 0.43
SDT7	400±0.17	5.18±0.050	5.64±0.110	0.21±0.07	98.96±1.61	10.26 ± 0.40
SDT8	397±0.66	5.24±0.052	6.85±0.100	0.12±0.12	99.67±0.64	6.16 ± 0.12

Table 8. Comparative data for evaluation of various properties of SEDDS tablets

Figure 5: SEDDS tablets evaluation results.

In vitro Drug Release and Release Kinetics

The release profile of formulation (SDT1-SDT8) along with in house developed SEDDS is displayed in figure 8.6 showed %CDR profile. The formulation SDT1 and SDT2 released 94.750±0.65 and 87.345±0.23 of drug within 120 min and achieve zero order kinetics. However the formulation SDT3,SDT4,SDT5, SDT6, and SDT8 showed release of drug up to 12 minutes but Formulation,SDT8 best modulated zero order release kinetics up to 110 minutes with maximum regression coefficient value of r2=0.9961; was optimized and compared for % CDR and release kinetics. The comparative profile of in house developed SEDDS Tablets with optimized formulation (SDT8) showed that the in-house developed SEDDS tablet released its major part of drug within 110 minutes.

Formulation Code	Zero Order(r^2)	Higuchi(r^2)	First Order(r^2)	Peppas "n" value
SDT1	0.9759±0.032	0.9623±0.021	0.5989±0.026	0.46±0.02
SDT2	0.9778±0.021	0.9762±0.001	0.5761±0.065	0.78±0.04
SDT3	0.9221±0.035	0.9932±0.008	0.6243±0.042	0.52±0.02
SDT4	0.9598±0.025	0.9901±0.010	0.6101±0.035	0.56±0.008
SDT5	0.9452±0.002	0.9854±0.015	0.6473±0.027	0.61±0.02
SDT6	0.9861±0.002	0.9695±0.018	0.7043±0.013	0.87±0.04
SDT7	0.9696±0.003	0.9701±0.042	0.7142±0.019	0.94±0.05
SDT8	0.9961±0.065	0.9501±0.034	0.7442±0.029	0.87±0.04

*n= 3

Table 9: Mathematical modeling and drug release kinetics of SEDDS tablets

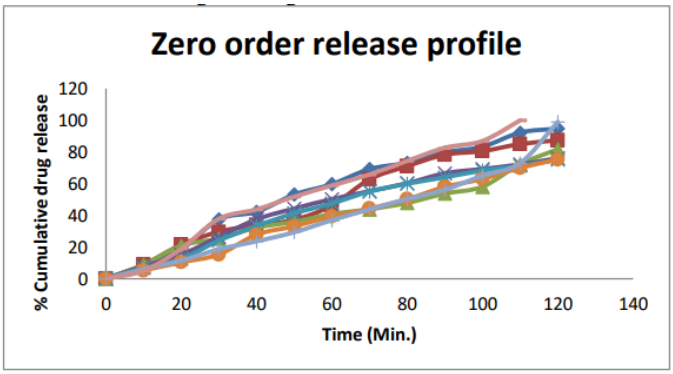

Figure 6: Zero order curve profile of prepared formulations

On the basis of the release kinetic the formulation SDT8 was found as the optimized formulation because it provides us the planned release kinetics i.e. zero order release with correlation coefficient (r2=0.9961) in the pattern of controlled release study. The % cumulative drug release 0 20 40 60 80 100 120 % Cumulative drug release 0 20 40 60 80 100 120 140 Time (Min.) Zero order release profile of the formulation SDT8 was found 99.66 in 110 minutes and thus it increases the absorption percentage of therapeutic agent.

SEM analysis

There is no indication of any type of keratolysis in applied area of cadaver skin part observe in SEM analysis. This indicates that increased penetration flux of

model drug was not due to any rupture in penetration barrier but only due to support opening of channels.

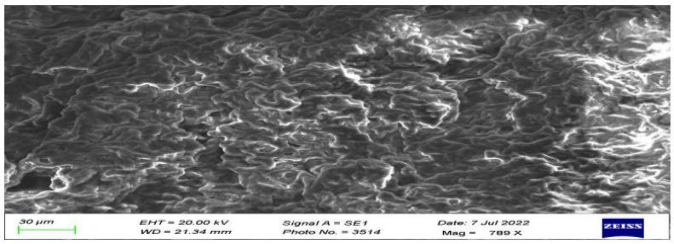

Figure 7: SEM picture of treated (STD8) cadaver skin.

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