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Dissolution Enhancement of Loratadine by Formulating Oleic Acid and Cremophor EL Based Self Emulsifying Drug Delivery System (SEDDS)

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ABSTRACT

For this experiment, Oleic Acid and Cremophor EL based Loratadine SEDDS were prepared. Different amount of solvent and surfactant were used to prepare SEDDS. After preparation of different formulations their dissolution studies were performed at 50-rpm, paddle method in which dissolution medium was maintained at 37°C (±0.5°C) temperature by using Dissolution Tester USP II. Three capsules from each formulation were used in each dissolution study and the release profile of Loratadine was monitored up to one hour. For the formulation development with fixed dose Loratadine (10 mg) and varying amounts of oleic Acid and Cremophor EL were used. In the experiment major determinant is found to be surfactant concentration. In all cases it is found that higher surfactant concentration increased the drug release. Other two determinant factors are amount of Oleic acid and percent drug loading. It was observed that without Cremophor EL, drug release from the formulation was slow. The rate and extent of drug release increased from the matrices with increasing the amount of Cremophor EL in the formulation.

INTRODUCTION

SEDDS (Shah *et al.,* 1994) are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs (R.N. *et al.,* 2004), which display dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. Typically SEDDS is formulated in liquid form. But to get some extra advantages along with the avoidance of some disadvantages it is usually converted into Solid Self-Emulsifying Drug delivery System (S-SEDDS). Oils can solubilize the lipophilic drug (Kommuru *et al.,* 2004) in a specific amount. It is the most important excipients because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long - chain trigly ceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS owing to their formulation and physiological advantages. Nonionic surfactants with high hydrophilic-lipophilic balance (HLB) values used in formulation of SEDDSs (e.g. Tween, Labrasol, Labrafac CM I, Cremophore etc.). The usual surfactant strength has a high HLB and Hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble Cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The addition of a drug to a SEDDS (Carvajal *et al.,* 1994) is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio.

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So, the design of an optimal SEDDS requires preformulation solubility and phase-diagram studies. In the case of prolonged SEDDS (Farah *et al.,* 1994), formulation is made by adding the polymer or gelling agent. According to Reiss, self-emulsification (Reiss *et al.,* 1975) occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion.

The free energy of the conventional emulsion is a direct function of the energy required a new surface between the oil and water phases. About 40% of new drug candidates are highly lipophilic (Serajuddin *et al.,* 1999),that means these drugs have poor aqueous solubility and exhibit a strong challenge to attain the attributes of modern drug delivery system because of their low bioavailability, high intrasubject/ intersubject variability and lack of dose proportionality. To meet this problem, Self- Emulsifying Drug Delivery System (SEDDS) (Catherine *et al.,* 2004), is a very effective way.

On the other hand, oral rout is the most favorable rout among all other routes and capsule dosage form is the most widely accepted solid dosage form because of low production cost, convenience of process control, high stability and reproducibility, better patient compliance etc. So, by considering these factors, the objective of this particular type of experiment is to development a solid Self-emulsifying drug delivery system capsule by using one of the poorly soluble drugs, Loratadine and ensuring the greater bioavailability than other system.

MATERIALS AND METHOD

Materials

Loratadine was provided by General Pharmaceuticals limited Dhaka, Bangladesh and Cremophor EL was of analytical-reagent grade and purchased from BASF, Germany. Oleic Acid was of analytical-reagent grade and was purchased from E. Merck, Darmstadt, Germany.

Loratin fast and Oradin tablet dosage forms were purchased from local drug store in Dhaka city after checking their manufacturing license numbers, batch numbers, production and expiry dates.

Method

Preparation of Standard Curve for Loratadine

HCl and distilled water were used as the media for preparing the standard curve. At the very beginning, 20mg of Loratadine was dissolved in 1000m1 of media in a 1000 m1 volumetric flask and labeled the flask as stock solution.

From this stock solution,1 ml, 2m1, 3m1, 4m1,5ml, 6m1, 7m1, 8ml, 9m1 and 10m1 were taken with volumetric pipettes and each time the withdrawn solution was taken in different volumetric flask and the volume of each of the solution was made up to 10m1 with media. After these, the absorbance of the solutions was measured by a UV-VIS Spectrophotometer of Shimadzu (UV mini-12401, SHIMADZU CORP. Kyoto, Japan) at 280 nm and the data were plotted against concentration.

Formulation of SEDDS

SEDDS were formulated by using Drug (Loratadine) and various types of Oils (Arachis Oil, Capmul PG 8, Miglyol 812, Neobee M-5, Oleic Acid, Soya bean Oil), Surfactant (Tween 80, Cremophor EL). At First, all the ingredients were weighted as per the formulation required and taken in the dry and clean vial. Then all the ingredients were mixed by using the vortex mixer for 5 minutes after closing the vial with the stopper. After that the mixer was heated on a water bath at 90° C temperature until it became a clear solution. This solution was then encapsulated properly by using Empty Gelatin Capsule Shell (Size#2).

The different formulations is shown in the table 1 below

Study of Appearance, stability and Duration for forming SEDDs

The duration of forming the SEDDS was actually the time required to get a clear solution of the content which consists drug, oils and surfactants. This time was recorded during heat was given. After forming the SEDDS, the contents were kept at room temperature for 24 hours and then the appearance was observed.

The duration was longest for the SEDDS containing Arachis oil, Neebeo M-5. Miglyol 812, and Soybean Oil and that were as long as nine and half hours. After that period the appearance of the SEDDS that was created was not so clear and a hazy, ointments like formulation were created for all the cases. Surfactant variation did not affect the appearance and duration of forming SEDDS after 24 hours this formulation became just like ointment with precipitation.

The SEDDS contain Oleic acid and Cremophor EL were formed only within one and half to three and half hour and the surfactant variation affect the duration greatly, i.e. Cremophor EL reduce the duration to almost half, The appearance of these SEDDS was clear and it was remain clear after 24 hours also.

Dissolution Studies

Dissolutions of the capsules were carried out by using USP Type **II** Dissolution Apparatus (ELECTROLAB, India). The amount of the drug in each capsule was 10mg (standard drug) which was added to 900m1 0.1N HCl as dissolution media. Under this circumstances a perfect sink condition was maintain to mimic dynamic situation in GIT.

The mixture was stirred at 50 Rotation per minute (RPM) at 37°C, 5m1 sample was withdrawn by using Plastic Syringe at predetermined times filtered and cotton buds were used to filter the sample. The duration of this analysis was 1 hour with the intervals 5, 10, 15, 20, 30, 45, and 60 minutes.

Each test was performed in triplicate. After withdrawn the sample the absorbance were measured by using the UV-VIS Spectrophotometer (SH1MADZU CORP, Kyoto, Japan) at 280 nm and the data were plotted after calculating average percent release. Same procedure was followed to get the percent release of drug from our different formulations.

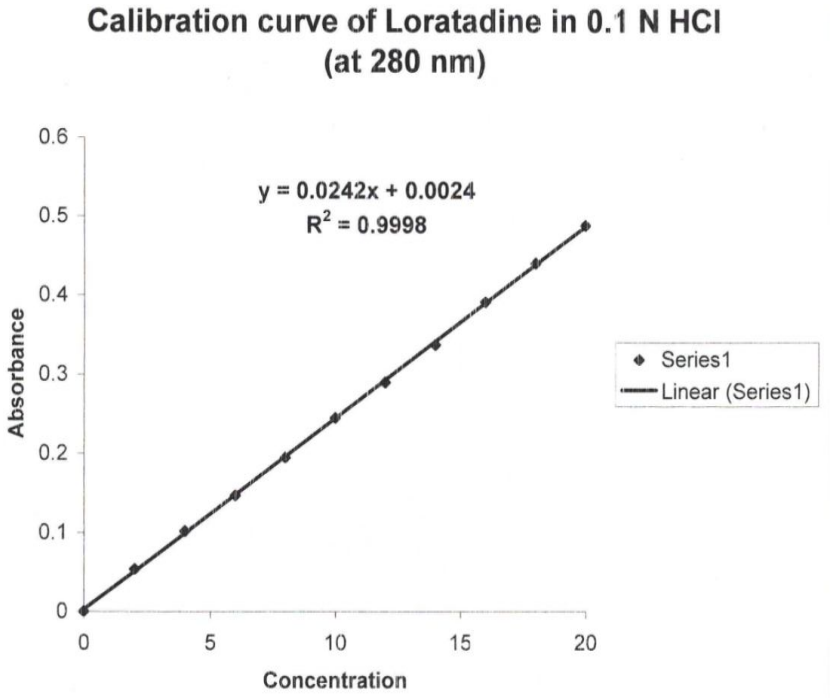
Table. 1:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loratadine	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Cremophor EL	400mg	600mg	800mg	400mg	600mg	800mg	400mg	600mg	800mg
Oleic Acid	400mg	600mg	800mg	600mg	800mg	400mg	800mg	400mg	600mg

RESULTS AND DISCUSSION

Data Standard Curve for Loratadine

Sample (ml)	Conc. (µg/ml)	Media (ml)	Absorbance (nm)
0	0	0	0
1	2	9	0.054
2	4	8	o.102
3	6	7	0.147
4	8	6	0.195
5	10	5	0.245
6	12	4	0.29
7	14	3	0.337
8	16	2	0.391
9	18	1	0.44
10	20	0	0.488



Data for percent Release of Loratadine from Various Formulation

Time (min)	% Drug Release from F1	% Drug Release from F2	% Drug Release from F3	% Drug Release from F4	% Drug Release from F5	% Drug Release from F6	% Drug Release from F7	% Drug Release from F8	% Drug Release from F9	Loratadine	Loratin fast	Oradin
0	0	0	0	0	0	0	0	0	0	0	0	0
5	30.00	92.55	52.81	92.18	40.37	8.36	64.67	50.01	68.55	4.48	83.57	62.74
10	49.01	75.63	56.64	93.81	54.53	21.82	74.62	56.98	136.99	5.52	86.21	74.12
15	59.41	75.67	59.36	94.71	61.93	39.37	84.86	66.48	92.56	5.57	87.86	78.00
20	65.00	83.68	64.03	99.91	69.77	53.28	86.90	77.28	107.14	10.10	89.52	75.59
25	78.00	100.00	77.96	97.08	87.27	65.57	89.93	80.46		15.76	93.52	76.63
30	88.00		88.19	99.68	94.03	93.50	91.25	86.33		20.82	97.04	86.03
45	95.00		92.15	101.71	103.02	99.92	96.21	96.68		31.74	99.24	86.81
60	101.00		99.56	102.45	107.41	101.49	97.78	102.39		32.66	100.95	98.78

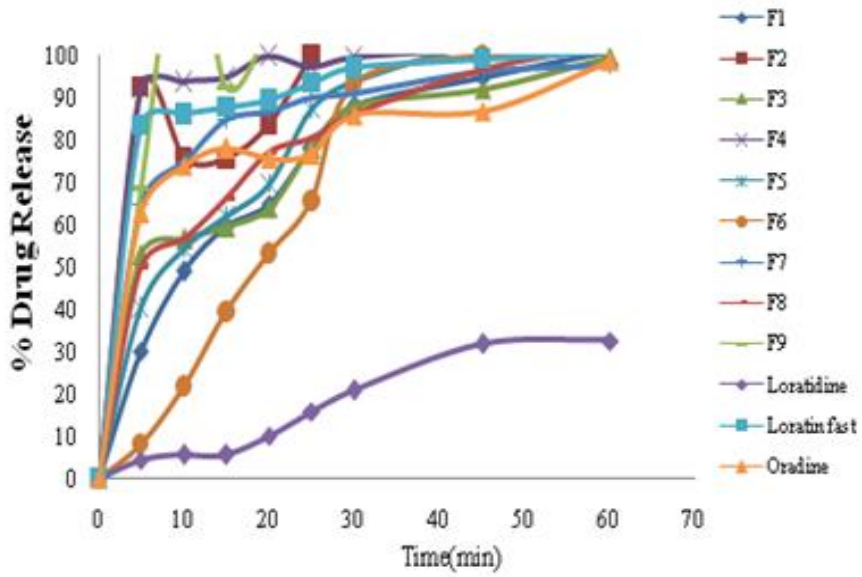


Fig: Percent Release of Loratadine from Various Formulation.

DISCUSSION

In the experimental design the percent release of the drug from formulation 2 is greater than the formulation 1.The figure for F2 was 100% at 25 minutes whereas it was 78% for formulation 1.The percent release of the drug is highest from the formulation 9 that was 107.14% at only 20 minutes whereas the percent release of the drug from standard Loratadine only 10.10% at 20 minutes. The percent release of the drug from two market products (Loratin Fast and Oradin) were 89.52% and 75.59% respectively both at 20 minutes.

CONCLUSION

An approach of development of SEDDS capsule however has been possible to establish through this study. The suitable choice of oil and surfactant has much more impact on this increment. Individually the Oleic acid gives the better result compare to others oil and Cremophor EL gives the better result compare to others surfactant. In case of combination these two oils together give better result than any other combination also.

Both Tween80 and Oleic Acid give better result but between these two surfactants, Cremophor EL is best to give steady result. Thus, this study provides a possible way by which liquid SEDDS can be converted into capsule.

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