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FORMULATION AND EVALUATION OF TABLET OF NICARDIPINE HCL AS A SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Nicardipine HCl is an oral calcium channel blocker used to treat hypertension and heart failure, however it has poor oral solubility, stability, and bioavailability. This study's goal was to create and test a solid self-emulsifying drug delivery system for nicardipine HCl tablets that would increase the medication's solubility, stability, and oral bioavailability while using the least amount of surfactant feasible. Several solid SEDDS (S-SEDDS) formulations were also made using T4 (tablet). Tablets were made utilizing the Direct Compressional method with an improved SEDDS composition. [T4] In vitro release was also nearly similar for tablets of SEDDS that is, 35.18 % and 92.67 in 5 min and 30 min respectively. Increasing the drug's oral bioavailability (now between 35 and 40 percent) is also a primary objective. In summary, our research showed that the Direct Compressional methodology might be a practical way to make solid SEDDS tablets. When more cosurfactant was added to the mixture than surfactant, the microemulsion quality dropped dramatically. Compared to the other formulations, the microemulsion produced by the T4 formulation is the most stable upon dilution and has the best microemulsion penetration.

KEYWORD: Nicardipine HCl, Direct Compressional technique, bioavailability & calcium channel Blockers.

INTRODUCTION

About 40% of novel candidate pharmaceuticals have low water solubility, and oral administration of these compounds is frequently accompanied by poor bioavailability, significant intra- and inter-individual variability, and a lack of dose proportionality.[1] "These issues are addressed using a variety of formulation strategies.[1] These include the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and solid dispersions. There has been a lot of interest in the creation of self-emulsifying drug delivery systems (SEDDS) to increase the oral bioavailability of lipophilic medicines recently.[2,3] A self-emulsifying oil formulation (SEOF), also known as a self-emulsifying dispersion system, can be created by combining natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and cosolvents / surfactants (SEDDS).[4] Self-emulsifying drug delivery systems (SEDDS) can be diluted in aqueous media, such as gastrointestinal (GI) fluids, to produce oil-in-water (o/w) emulsions, micro emulsions, and self-emulsifying emulsions. Drops of oil would swiftly pass through the

stomach and boost the drug's distribution throughout the GI tract, lowering the possibility of discomfort that may happen when significant volumes of medication come into prolonged contact with the intestinal wall. The fact that SEDDS include a significant interfacial space between the oil and water, which facilitates the drug's breakdown, gives them an additional benefit over regular oil solutions. SEDDS are formulations that are physically stable as opposed to emulsions, which are weak and metastable dispersion forms.

Among the techniques that have been shown to be successful in the formulation of medications that are only partially water soluble are micronization, solid dispersion, and cyclodextrin complexation".[5] While these techniques have sometimes been successful, they also have a number of disadvantages. The main problems with micronization are those related to chemical and thermal stability.

When medications are micronized using the traditional approach, they often deteriorate and lose bioactivity. It might be challenging to take tablets or capsules with a high dosage of active component because of the huge quantity of vehicles employed in solid dispersion. Supports are a major contributor to the high cost of manufacturing because of the specialized equipment and techniques needed for lyophilization or spray drying. The conventional solvent-based approach may be used, but it is challenging to manage very viscous precipitates. Complexes cannot be formed by cyclodextrins and drugs that are insoluble in water or organic solvents. This finding has led to a reconsideration of the formulation of these medications because it has been demonstrated that high-fat meals boost the oral bioavailability of drugs that are lipids with weak water solubility. Lipid suspensions, solutions, and emulsions have been utilized historically to increase oral bioavailability; however, self-micro emulsifying drug delivery systems (SEDDS) have lately attracted a lot of attention.[6]

Lipid solution, lipid emulsion, micro emulsion, and dry emulsion are a few examples of these lipid drug delivery methods. Self-emulsifying systems, and more specifically a classification system called the formulations classification system, have been developed to make sense of the plethora of systems available and the plethora of ways in which excipients may be combined to create lipid-based formulations (LFCS). This classification provides a framework for guiding regulatory authorities in their oversight of lipid formulations and their effects in vivo and encourages the adoption of a systematic and reasonable formulation approach to avoid "trial and error" iterations. Pouton first created LFCS in 2000, and it has only just been upgraded.[7] The LFCS divides lipid-based formulations into four types, each of which has unique traits and potential implications for how the medication will be diluted and metabolized in relation to the formulation's capacity to stop precipitation.

EXPERIMENTAL WORK

Table 1: Actual values of ingredients taken for SEDDS tablet.

Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Nicardipine HCl	20	20	20	20	20	20	20	20	20
Tween 80	6	6	6	12	12	12	18	18	18
PEG 400 (ml)	9	18	27	9	18	27	9	18	18
Carbopol	35.8	29.8	23.8	26.8	20.8	12.8	17.8	10.8	7.8
Chitosan	1.2	1.2	1.2	1.4	1.4	1.4	1.8	1.8	1.8
Polyvinylpyrrolidone	2	2	2	4	4	4	6	6	6
Microcrystalline cellulose	1	1	1	2	2	2	3	3	3
Magnesium stearate	0.7	0.7	0.7	1.4	1.4	1.4	2.1	2.1	2.1
Talc	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.3	0.3
Isopropyl Myristate(ml)	1	1	1	2	2	2	3	3	3
Colloidal silica	8	5	2	7	3	2	4	2	5
Total	85	85	85	85	85	85	85	85	85

EVALUATION PRECOMPRATIONAL PARAMETERS OF TABLETS

Bulk density: The mass of dry powder in a graduated cylinder is used to calculate the bulk density from the volume of the bulk material.[8]

Bulkdensity (ρ0) = weight of powder/ Bulk volume

Tapped density: Measuring powder is created by tapping a cylindrical measuring device mechanically.[8]

Tapped density (ρ t) = weight of powder/Tapped volume

Carr's index: The following equation, which takes the compressibility percentage of the powder into consideration, may be used to evaluate the strength of a powder bridge or arch. [8]

Carr's index = (tapped density − bulkdensity) / tapped density

When the tapped density (w/v) is decreased, the Carr's index is decreased, and the result is improved flow characteristics. These are some Carr's index extremes that serve as an example for demonstration purposes:

Hausner's ratio: Since powder flow properties are related to interparticle friction, predictions of these properties are possible.[8]

Hausner's ratio = tapped density /bulk density

Here are some examples of when Hausner's ratio begins to drop off:

Assuming a value of 1.25 or less, good flow is being generated (=20% Carr). while a value > 1.50 indicates low flow (=35% Carr),

Tablet Evaluation: The following analyses were performed on the final tablets:

***In-vitro* dissolution**

Utilizing USP type II equipment, the dissolving test was conducted. Approximately fifty rotations per minute were made by the head. A total of 900 ml of dissolving media with 0.02% Tween 20 in 0.1 N HCl at 37 0.5 ° C were used. 5 ml of the dissolving medium were taken out, filtered, and then refilled at 0, 5, 10, 15, 20, 25, and 30 minutes. If required, the obtained samples were diluted with dissolving liquid before being subjected to ultraviolet (UV) analysis at 254 nm for the presence of the medication. The dissolution tests were repeated three times, and the averages were recorded. Table 8.39 displays the outcomes;[9,10]

Weight variation

The weight of each tablet in a batch must be within the allowed range, and there should be no significant differences between any of the tablets. Twenty pills were used for the study of weight reduction. Twenty pills were picked at random and precisely weighed using a digital balance. We provide the data as the average of 20 rate for different.

Thickness[11]

Ten tablets were measured using a digital vernier caliper to establish their average thickness. The data is presented as the mean SD of 10 separate measurements..

Hardness[11]

The pads' hardness was measured using an Electolab durometer.

Friability[11]

The Roche crusher was used to determine how easily the pills broke. After being spun in a drum for 100 revolutions at a speed of 25 revolutions per minute (RPM), a sample of 10 tablets or tablets with a known weight (W0) is weighed again (W). By using the following formula, we were able to determine the percentage of friability from the amount of weight that was lost. Weight loss should not exceed 1% w / w without breaking any tablets.

Friability = [(Initial wt. – Final wt.) / final wt.]* 100

RESULTS AND DISCUSSION

Evaluation of Tablets

Table 9.3 displays the assessment criteria for lots T1 through T9 of tablets. The tablet form of Nicardipine HCl performed well across the board.

- **Evaluation of Precompressional Parameters**

The bulk density was determined to be between 0.365 and 0.3712 g/ml, whereas the tapped density was between 0.4010 and 0.4780 g/ml. The angle of repose was determined to be anywhere between 25.33 and 29.73Ø, while Carr's compressibility index ranged from 7.27% to 13.74%. This shows that the formulations have a desirable flow characteristic.

Table 2: Evaluation Precompressional parameters for SEDDS tablet of Nicardipine HCl.

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
T1	0.3712±0.11	0.4101±0.25	7.27±0.659	1.177±0.76	29.73± 0.41
T2	0.3803±0.5	0.4120±0.26	7.58±0.514	1.053± 0.60	25.33 ±0.63
T3	0.3843±0.15	0.4120±0.5	7.43±0.760	1.059±0.88	28.44 ±0.35
T4	0.376±0.20	0.4270±0.37	13.74±0.386	1.073±0.53	27.44 ±0.52
T5	0.355±0.17	0.4600±0.24	15.31±0.794	1.224±0.11	31.34± 0.13
T6	0.3810±0.45	0.4780±0.65	18.42±0.120	1.24±0.20	28.26 ±0.43
T7	0.3850±0.81	0.4384±0.33	10.88±0.30	1.113±0.21	27.27±0.42
T8	0.326±0.20	0.4340±0.37	13.54±0.386	1.063±0.53	27.64 ±0.52
T9	0.365±0.17	0.4360±0.24	15.61±0.794	1.244±0.11	31.94± 0.13

Table 3: Evaluation compressional parameters for SEDDS tablet of Nicardipine HCl.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
T1	85±0.1	2.3±0.2	3.12 ± 0.3	0.26±0.4
T2	84±0.5	2.8±0.5	3.10 ± 0.6	0.28±0.2
T3	84±0.9	3.8±0.8	3.16±0.5	0.14±0.6
T4	85±0.3	3.2±0.9	3.15±0.3	0.15±0.9
T5	85±0.5	4.1±0.5	3.11 ±0.2	0.30±0.4
T6	83±0.3	4.2±0.4	3.14 ± 0.8	0.17±0.3
T7	85±0.7	2.5±0.5	3.18 ± 0.9	0.10±0.8
T8	84±0.7	2.7±0.8	3.20 ± 0.1	0.24±0.6
T9	83±0.9	4.2±0.4	3.17 ± 0.2	0.21±0.2

Many different regulatory requirements and additional factors were used to assess each tablet formulation. Researchers examined the effects of various formulations on stability as well as properties including thickness, hardness, friability, weight fluctuation, active component content, and in vitro dissolution.

Table 4: *In vitro* dissolution study of SEDDS formulations.

Time (min)	%Drug released								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
5	31.84	34.23	30.84	35.18	33.84	37.23	34.23	31.84	34.84
10	40.71	42.40	43.71	50.84	47.71	48.40	46.40	42.71	45.71
15	66.69	60.72	61.69	68.27	69.69	62.72	69.72	63.69	66.69
20	70.78	73.37	78.78	80.34	70.78	71.37	79.37	74.78	77.78
25	80.12	81.14	82.12	92.16	80.12	83.14	81.14	85.12	88.12
30	84.54	87.32	85.54	92.67	87.54	84.32	84.32	86.54	89.54

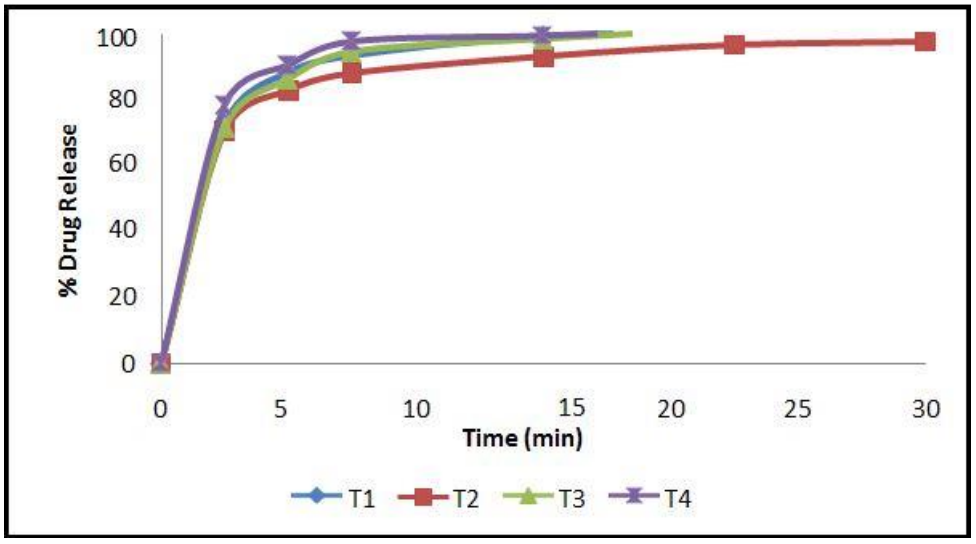

Figure (a): *In vitro* dissolution of batch T1 toT4.

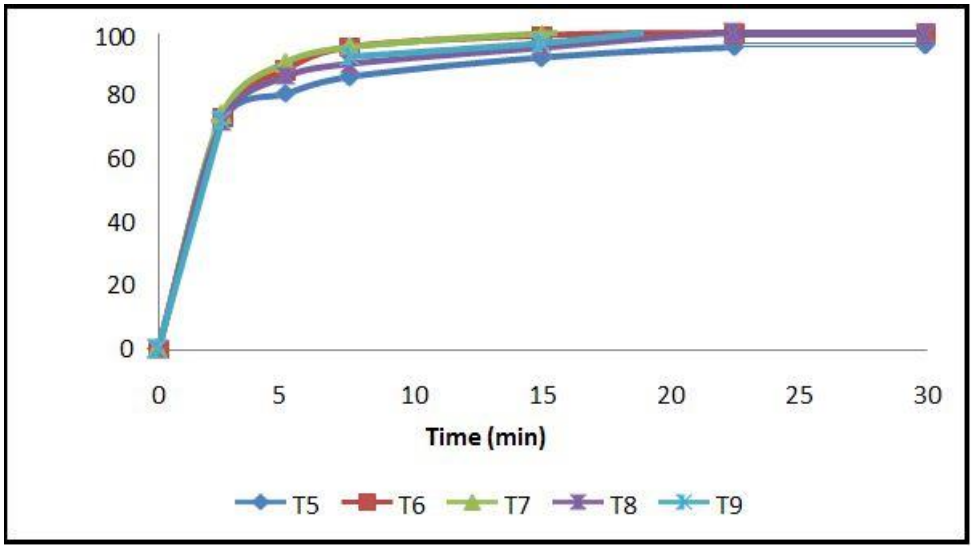

Figure (b): *In vitro* dissolution of batch T5 toT9.

CONCLUSION

- A greater Nicardipine HCl concentration may be solubilized and incorporated into SEDDS at a higher concentration if the SEDDS has a higher concentration of Surfactant.
- All formulations had pH values between 3.5 and 4.0, indicating that pH has no effect on stability. Therefore, it is fair to infer that the medicine does not diffuse in the exterior phase and is contained inside the body. Being the exterior phase, water's pH was reflected throughout the system. When exposed to an alkaline environment, nicardipine HCl becomes unstable. As can be seen, the pH ranges from acidic to neutral in these compositions.
- The T4 formulation was found to have a minimum average particle size of 9.15 nm in water.
- With a release rate of 92.67% in 30 minutes, the T4 formulation had the highest rate of all SEDDS pill batches tested. The SEDDS formulation of Nicardipine HCl was shown to be substantially more efficient in an in vitro research. After then, the T4 batch was taken out of circulation for more research and comparison
- The T4 formulation has the fastest release rate of any known formulation at any moment
- From the two-way ANOVA it can also be said that the change in time and in the compositions of various formulations.

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