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Formulation and *In Vitro* Evaluation of Halofantrine Solid Dispersions

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Keywords: Halofantrine , Crosspovidone , CCS, FTIR.

ABSTRACT

Halofantrine is a malaria medication. It has been demonstrated that it selectively blocks open and inactivated HERG channels, resulting in mild cardiotoxicity. It is a BCS class II medication with a longer half-life. To increase the physiological efficiency of Halofantrine solid dispersion, an oral disintegrating tablet including Crosspovidone, Mannitol, and SSG was developed. Halofantrine solid dispersions were created with various carriers in various drug-to-carrier ratios (1:1, 1:2 and 1:3). The solubility, melting point determination, drug content uniformity, and in vitro dissolution investigations of Halofantrine solid dispersions generated by solvent evaporation technique were described. FT-IR investigations and other analytical methods were used to characterise the solid state. Finally, when all formulations are compared, formulation (F3) comprising Halofantrine + Crosspovidone (1:3) yields the best outcomes. It was deemed to be the best formulation after 60 minutes of solvent evaporation and maximal drug release. Fast dissolving tablets are created from the optimum formulation by combining multiple disintegrants in varying doses. The before and post compression settings were investigated, and the findings were presented. All of the findings are within the allowed range. The manufactured tablets were tested in vitro for drug release using a 6.8pH buffers F3C6 formulation including CCS, which demonstrated 99.02% release of the drug in 20 minutes. The improved formulation is shown below. Kinetics of first order release.

INTRODUCTION

Micronization, surfactant use, and the creation of solid dispersions are common methods for increasing the solubility & absorption of poorly water-soluble medications.[1] Chiou & Riegelman [2] There are six forms of drug-carrier interactions in solid-state dispersions: simple eutectic mixes, solid solutions, glass solutions & glass suspensions, amorphous phases, & compound or complex formation. Solid dispersion usage on poorly water soluble pharmaceuticals have been intensively investigated in recent years for solubility enhancement.[3, 4, 5, 6, 7, &8.] A pharmaceutical product's bioavailability may be limited due to poor solubility behaviour.

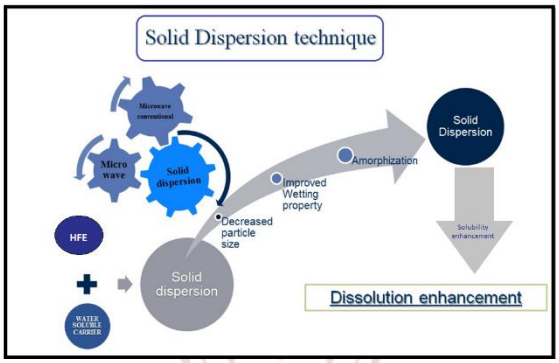

Figure No. 1. Solid dispersion technique

Previous research [9] has observed that freeing the drug from its delivery mechanism as a small or colloidal particle boosted the dissolving rate and bioavailability of a solid dispersion. Recent research, however, indicates that agglomeration is the rate-limiting step in a hydrophobic micro emulsion solution distributed.[10] This discovery contradicts the advantages of a solid dispersion approach. Early studies in our lab found that the role of the a carrier in the this compromising influence was significant [11]. This discovery contradicts the advantages of a solid dispersion approach. Early studies in our lab found that the role of a carrier in this compromising influence was significant.[12]

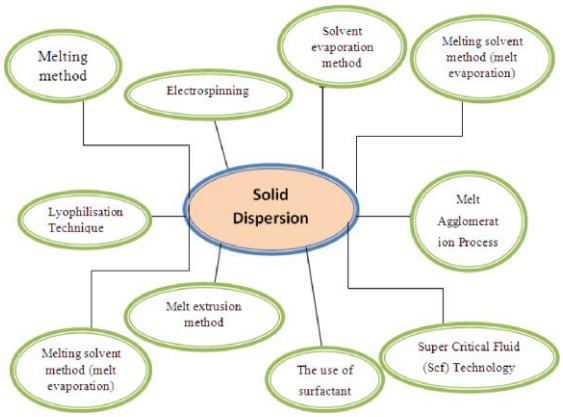

Figure No. 2 Solid Dispersion Techniques4

A polymer with a high glass transition temperature is preferred because it allows the essential glassy state to form. Furthermore, if the reached transition temperature of a solid dispersion is higher than that of the medication, it can inhibit intermolecular interaction at storage room temperature, reducing the chance of nucleation and crystal formation even further.[13, 14.]

Halofantrine is an antimalarial.[16] It is a member of the phenanthrene family of chemicals, which also contains quinine and lumefantrine. It appears to block heme molecule polymerisation (by the parasite enzyme "heme polymerase"), causing the parasite to be poisoned by its own waste.[17,18] Halofantrine has been demonstrated to selectively block both open and inactivated HERG channels, resulting in cardiotoxicity. It is a synthetic antimalarial medication that works as a blood schizonticide. It is efficient against multidrug resistant bacteria (including mefloquine resistant) Malaria caused by Plasmodium falciparum.[19,20] Halofantrine's mode of action may be similar to that of chloroquine, quinine, and mefloquine, in that it forms toxic complexes with ferritoporphyrin IX that destroy the parasite's membrane. The patients were given 500 mg of halofantrine hydrochloride at 0, 6, and 12 hours (total 1.5 g).

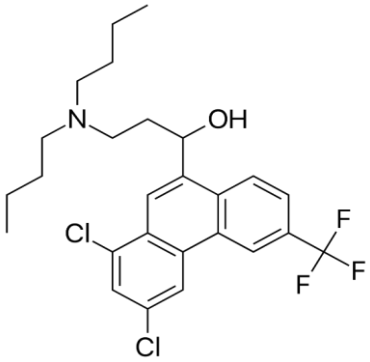

Figure No. 3 Structure of Halofantrine

With such a mean parasite clearance time of 52.7 h and a fever clearance time of 33.8 h, all patients responded to therapy. For HAL and BHAL, the following kinetic parameters (mean values) were determined: maximum plasma concentration (Cmax)=896 and 491 ng•ml1, respectively; time to achieve the Cmax (tmax)=15 and 56 h; clearance half-life (t1/2)=91 and 79 h; and mean residence time (MRT)=71 and 102 h. Depending on the medical response the plasma level of HAL and BHAL were sufficient for the treatment of mild p. falciparum in the 6 patients.

MATERIALS AND METHODOLOGY:

Halofantrine API was procured from B.M.R. Chemicals, Hyderabad and Mannitol, Cross Povidone, Methanol, PEG 4000 CCS, were procured from S.D Fine Chemicals.

PREPARATION OF SOLID DISPERSIONS OF HALOFANTRINE:

There are several carriers, which have been reported for the preparation of solid dispersions by using Mannitol, Cross povidone and SSG various methods of preparation.

a. Solvent evaporation

In solvent evaporation method, the drug and carriers weremixedin1:1,1:2 and 1:3 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed throughsieve#60. And now the obtained product was collected.

Table No. 1 Formulation of Solid Dispersions of Halofantrine

Formulation code	DRUG: POLYMER RATIO (HALOFANTRINE:CROSS POVIDONE)
F1	1:1
F2	1:2
F3	1:3
Formulation code	**Drug : polymer ratio (Halofantrine:Mannitol)**
F4	1:1
F5	1:2
F6	1:3

Formulation code	**Drug : Polymer ratio (Halofantrine :SSG)**
F7	1:1
F8	1:2
F9	1:3

FORMULATION OF HALOFANTRINE TABLETS: [29-31]

Equivalent weight of Halofantrine was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table.

All the ingredients were passed through # 40 mesh sieve separately. The drug and MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#40 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F3C1to F3C6.

Table No. 2 Formulation of Halofantrine Tablets

Ingredients (mg)	**F3C1**	**F3C2**	**F3C3**	**F3C4**	**F3C5**	**F3C6**
Halofantrine (weight equivalent to 5mg)	18	18	18	18	18	18
Aspartame	3	6	9	--	--	--
CCS	--	--	--	3	6	9
MCC	76	73	70	76	73	70
Mg.st	2	2	2	2	2	2
Talc	1	1	1	1	1	1
Total	100	100	100	100	100	100

EVALUATION OF TABLETS[29-34]

Post compression parameters

Weight variation test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated.

Tablet hardness

The hardness of a tablet indicates its strength. It is the amount of force needed to shatter a tablet by compressing it in the radial direction. The force is measured in kilogrammes, and a hardness of 3-5 kg/cm2 is regarded adequate for uncoated tablets. The hardness of ten pills from each formulation is measured using a Monsanto hardness tester, a Pfizer hardness tester, and so on. Excessive hardness lowers disintegration time substantially.

KINETICS OF DRUG RELEASE:

- **Zero Order Kinetic**

It describes the system in which the drug release rate is independent of its concentration.

$$Qt = Qo + Ko\ t$$

- **First Order Kinetic**

It describes the drug release from the systems in which the release rate is concentration dependent.

$$Log\ Qt = log\ Qo + kt/\ 2.303$$

- **PRE FORMULATION STUDIES**

a) Solubility studies: Solubility of Halofantrine was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration.

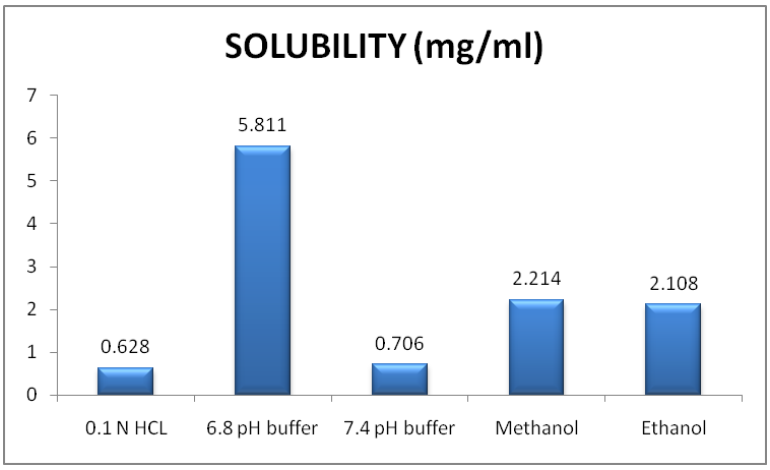

Figure No. 4 Solubility studies of Halofantrine

RESULTS AND DISCUSSION:

From the above conducted solubility studies in various buffers we can say that 6.8 pH buffer solution has more solubility when compared to other buffer solutions.

UV Scan Spectrum of Halofantrine: UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers.

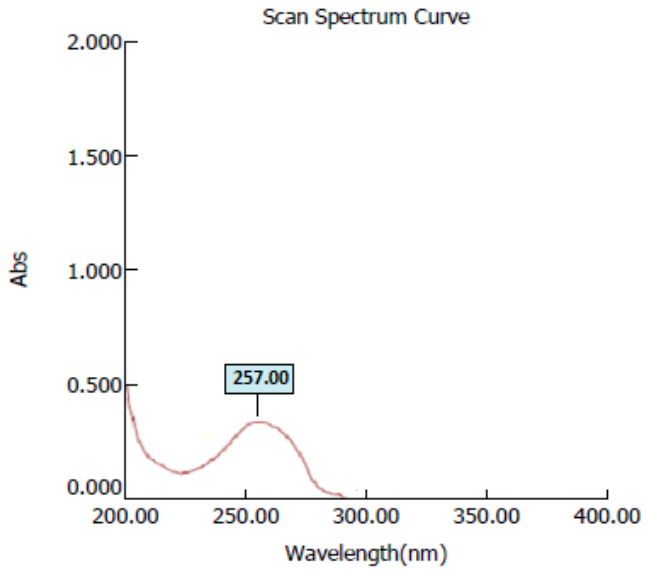

Figure No. 5 Uv Spectrum of Halofantrine

Discussion: Halofantrine at 10µg/ml was found to be 257 nm.

Calibration curve data of Halofantrine: 10mg of Halofantrine was taken in a10ml volumetric flask.To The solution was made up to the mark with 6.8pH buffer to give 1000 µg /ml concentration. From this Solution 1ml is diluted to10mlwith,6.8pH buffer to give 100 µg.

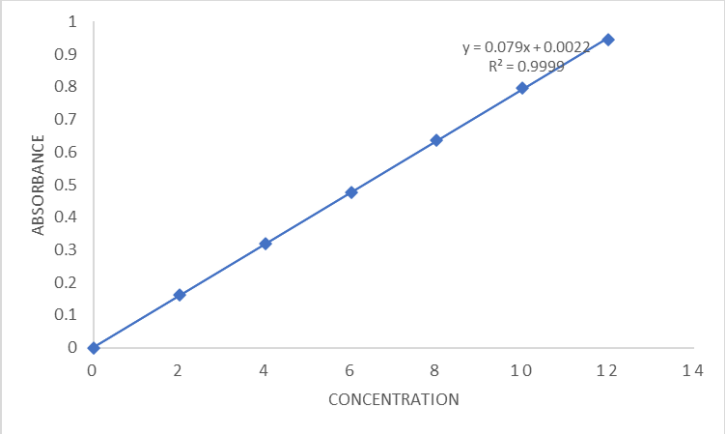

Figure No. 6 Calibration curve

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

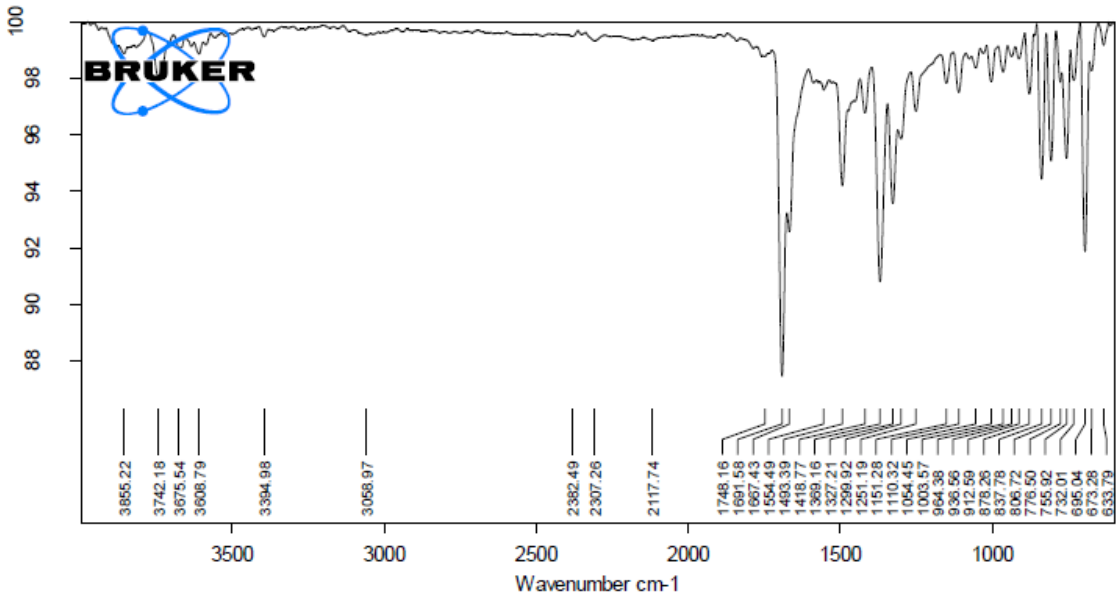

Figure No. 7 IR spectrum of pure Halofantrine

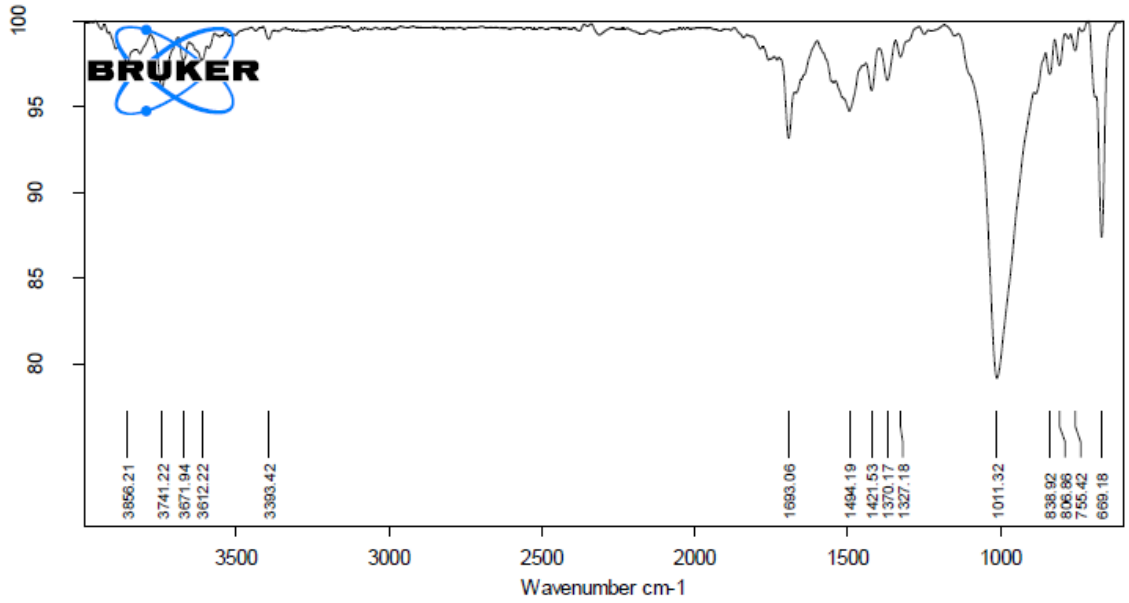

Figure No. 8 IR spectrum of Halofantrine Optimised Formulation

Percentage yield of solid dispersions

Table No. 3 Percentage yield of solid dispersions

Formulation code	Percentage yield
F1	91.64
F2	96.43
F3	92.54
F4	96.12
F5	90.25
F6	92.36
F7	95.64
F8	93.67
F9	96.43

Discussion: The Percentage yield of the formulated solid dispersions was found to be in the range of 90.25- 96.43% respectively.

Percentage drug content of solid dispersions

Table No. 4 Percentage drug content of solid dispersions

Formulation code	%Drug content
F1	96.12
F2	98.02
F3	96.34
F4	92.15
F5	90.36
F6	95.78
F7	91.67
F8	98.02
F9	95.61

Discussion: The percentage Drug content of the formulated solid dispersions was found to be in the rangeof90.36- 98.02% respectively.

***IN VITRO* DRUG RELEASE STUDIES OF SOLID DISPERSIONS:**

Table No. 5. *Invitro* drug release studies for formulations (F1-F9)

Time (Min)	Percentage drug release								
	Halofantrine : Crosspovidone			Halofantrine :Mannitol			Halofantrine : SSG		
	1:1 (F1)	1:2 (F2)	1:3 (F3)	1:1 (F4)	1:2 (F5)	1:3 (F6)	1:1 (F7)	1:2 (F8)	1:3 (F9)
0	0	0	0	0	0	0	0	0	0
5	45.42	53.26	59.62	37.53	41.44	50.21	43.27	48.56	55.66
10	52.16	59.63	66.35	43.92	48.02	57.12	49.52	55.33	62.67
15	55.85	62.98	70.03	47.36	51.48	60.51	53.17	58.81	65.97
30	65.32	73.09	79.32	56.62	60.23	71.02	62.38	68.62	75.53
45	74.19	82.32	88.56	65.43	69.04	80.36	71.02	77.58	84.82
60	83.26	91.42	97.12	74.56	78.45	89.02	80.24	86.28	93.94

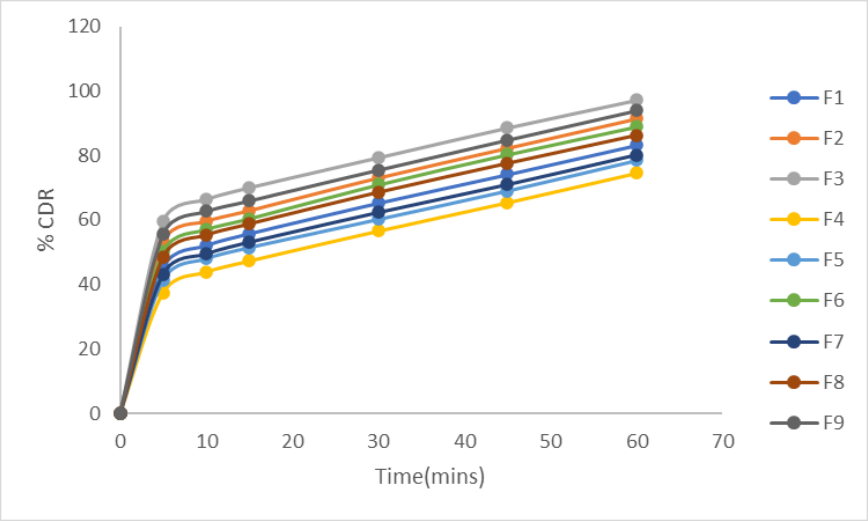

Figure No. 9 *In vitro* drug release studies

IN-VITRO DRUG RELEASE KINETICS STUDIES FOR BEST FORMULATION F3:

Zero order release kinetics studies:

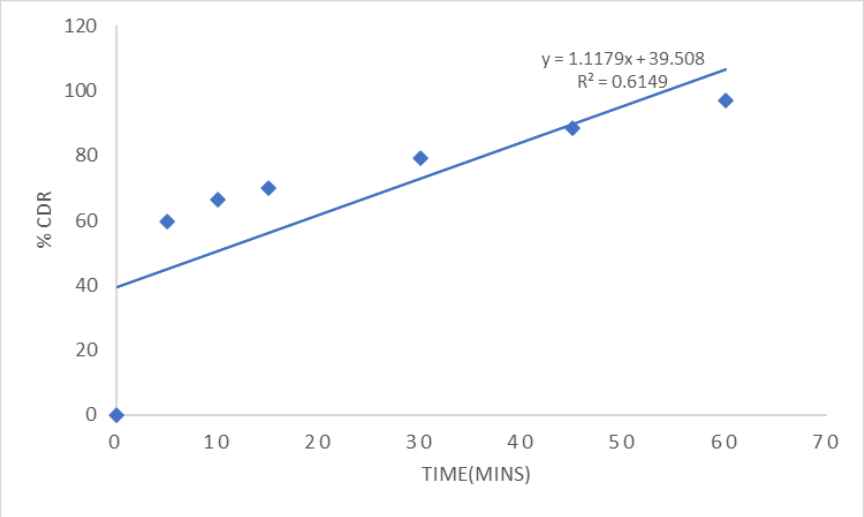

Figure No. 10 Zero order release profile for best formulation (F3)

First order release kinetics studies:

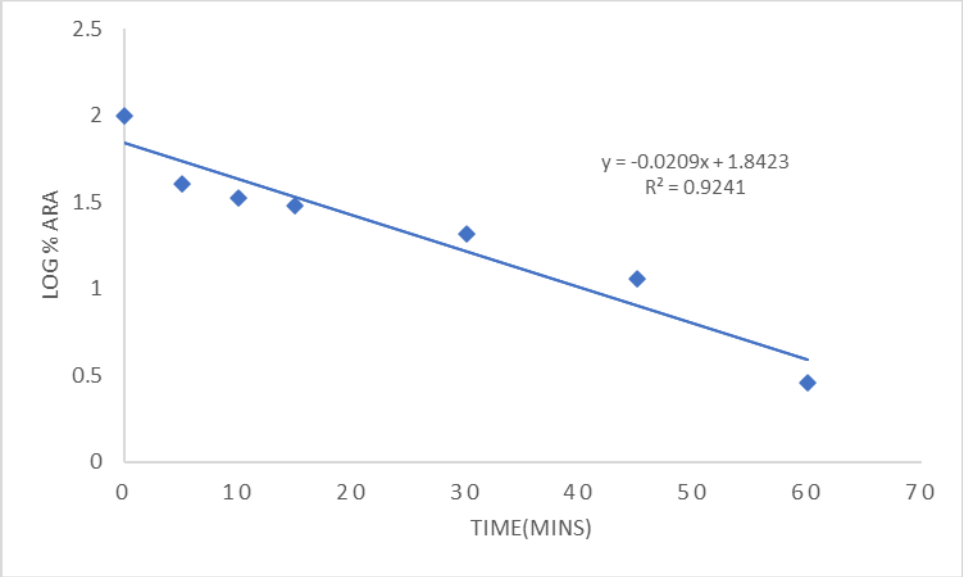

Figure No. 11 First order release profile for best formulation (F3)

Evaluation of Halofantrine Fast disintegrating Tablets:

Table No. 6: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD	Carr's index (mean±SD	Hausner's ratio (mean±SD)
F3C1	0.312	0.358	27.64	14.57	1.15
F3C2	0.315	0.359	26.48	16.49	1.16
F3C3	0.328	0.372	28.34	12.67	1.18
F3C4	0.334	0.379	30.12	11.56	1.13
F3C5	0.329	0.389	29.37	13.61	1.20
F3C6	0.326	0.386	27.68	15.29	1.17

Characterization of tablets

Post Compression parameters

Table No. 7 Post Compression parameters

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)	Drug Content (%)
F3C1	100.56	2.06	8.05	3.4	0.54	21	99.37
F3C2	99.54	2.11	8.10	3.6	0.19	25	97.68
F3C3	98.36	2.09	8.09	3.5	0.38	16	96.02
F3C4	100.45	2.13	8.00	3.3	0.62	29	99.34
F3C5	99.73	2.03	8.08	3.1	0.77	15	100.36
F3C6	101.26	2.16	8.15	3.2	0.93	21	98.55

Dissolution studies of the Tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table No. 8. % Cumulative drug release of formulations F3C1 – F3C6

Time (Min)	F3C1	F3C2	F3C3	F3C4	F3C5	F3C6
0	0	0	0	0	0	0
5	61.38	67.36	76.21	70.23	72.57	82.68
10	68.06	74.87	83.72	77.23	79.65	89.53
15	71.24	77.23	86.92	80.23	82.63	92.32
20	78.15	84.26	93.23	87.42	89.15	99.02
25	84.54	90.74	99.23	93.35	95.74	
30	91.85	97.32		100.02		

IN VITRO DRUG RELEASE OF F3C1-F3C6

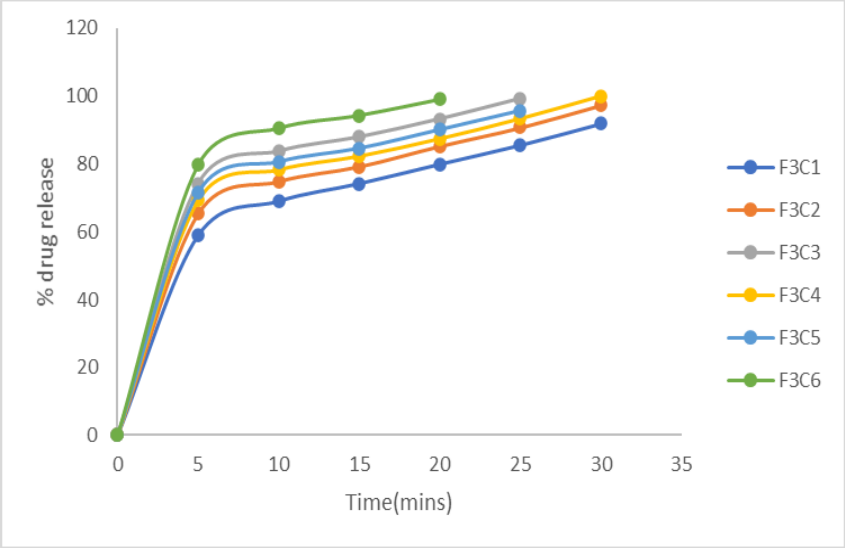

Figure No. 12 In vitro drug release of formulations F3C1-F3C6

DRUG RELEASE KINETICS:

ZERO ORDER PLOT OF (F3C6):

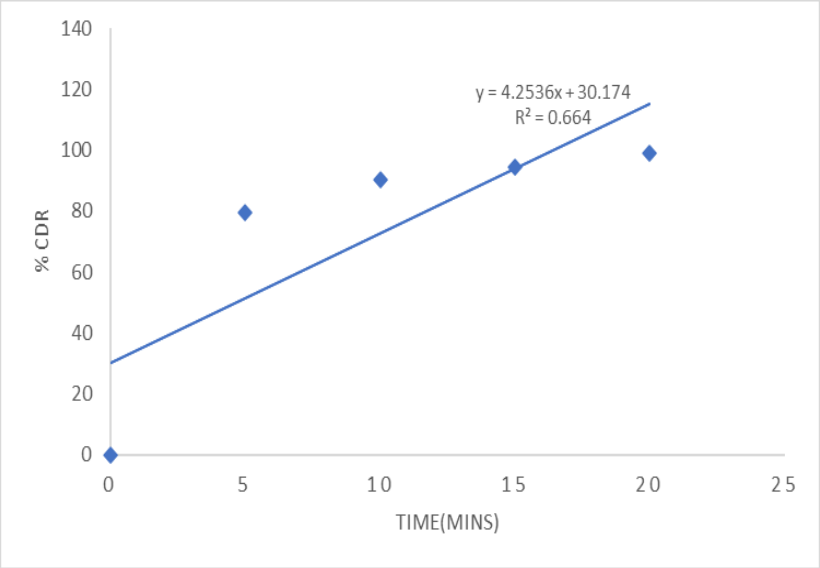

Figure No. 13. ZERO ORDER PLOT OF (F3C6)

FIRST ORDER PLOT OF (F3C6):

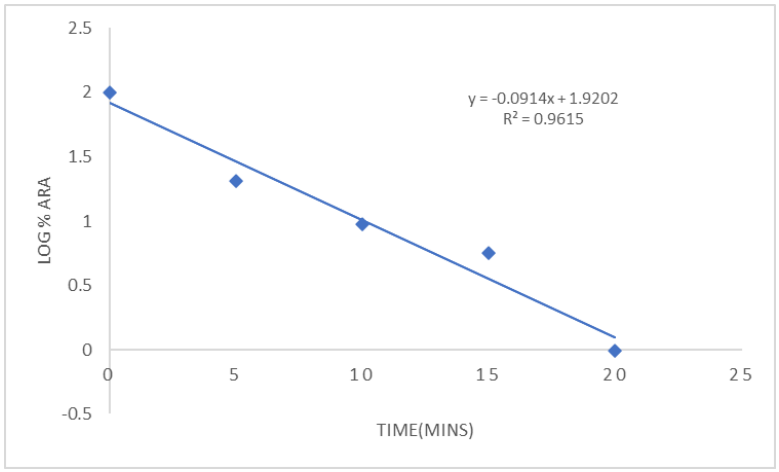

Figure No. 14. FIRST ORDER PLOT OF (F3C6)

SUMMARY:

The therapeutic effectiveness of a pharmacological product intended for oral administration is determined by its absorption via the gastro-intestinal tract. Dissolution is typically the rate-limiting phase in the gastro intestinal uptake of a medication from a solid dose form. Poorly soluble medications have been demonstrated to be unexpected and to absorb more slowly than those with better solubility. As a result, these medications pose significant obstacles for future development into bioavailable dose forms. As a result, it is critical to improve the water solubility, dissolution rate, and bioavailability of these medicines from their oral solid dose forms. Mannitol and Crosspovidone solid dispersion techniques have been utilised to enhance the dissolving characteristics and bioavailability of weakly water-soluble medicines. This research has shown The solid dispersion approach has the potential to significantly improve Halofantrine dissolving performance.

Halofantrine is an antimalarial and a BCS class II medication whose absolute bioavailability is limited.

As a result, a favourable formulation that can improve the solubility and dissolution rate of this model medicine may be beneficial. Hence, research were conducted to increase the solubility and thus dissolving rate, efficiency, and bioavailability of the weakly soluble medication Halofantrine utilising mannitol, Crosspovidone, and SSG.

The introductory section provided a quick overview of solid dispersions. Furthermore, in this chapter, an introduction to dissolving rate and several ways to improving solubility was explored, with a focus on solid dispersion technology. The goal and purpose were also explored.

With the comprehensive drug description of Halofantrine, drug profiles and excipient profiles were supplied, which defined their usage, contraindications, and adverse effects.

A review of the literature on the manufacture of solid dispersions using various medications and previous research work also by different methods.

The methodology, materials used, and experimental procedures used in the current inquiry were all thoroughly discussed. Later, all assessment parameters and the procedure of preparing physical mixes and solid dispersions of Halofantrine by solvent evaporation were detailed. Halofantrine solid dispersions were created with various carriers in various drug-to-carrier ratios (1:1, 1:2and1:3).

The solubility, melting point determination, drug content uniformity, entrapment efficiency, and in vitro dissolution investigations of Halofantrine solid dispersions made by solvent evaporation technique were described. FT-IR investigations and other analytical methods were used to characterise the solid state.

Finally, when all formulations (F1-F9) were compared, the formulation (F3) including Halofantrine+Crosspovidone (1:3) showed superior results by solvent evaporation technique at the end of 60 minutes with drug release of 97.12%, hence it was chosen as the best formulation.

The FDT tablets were created utilising multiple disintegrants in various concentrations based on the optimum formulation.

The before and post compression settings were investigated, and the findings were presented. All of the findings are within the allowed range.

The prepared tablets were tested for drug release in vitro using a 6.8pH buffer.

In 20 minutes, 99.02% of the medication is released from an F3C6 formulation including CCS. Firstorder release kinetics are used in the improved formulation.

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