Liquisolid Compacts of CinacalcetHCl with Improved Micromeritics and Biopharmaceutical Attributes

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Abstract

The aim of the research is to improve micromeritic properties and oral bioavailability CH by liquisolid technique.Cinacalcet hydrochloride (CH) is a calcimimetic drug approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD.) The major problem associated with CH is its poor aqueous solubility and low bioavailability (20-25 %). The objective of this research is to improve the micromeritic properties, dissolution rate and biopharmaceutical attributes of CH via liquisolid technique.CH liquisolid compacts were formulated using tween 80 as the non-volatile solvent, neusilin US2 as the carrier material, aerosil as the coating material. Fourier-transform infrared spectroscopy **(**FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction (P-XRD) study performed. Pharmacokinetic study was performed in albino rabbits for checking the enhancement potential of biopharmaceutical attributes of the selected liquisolid formulation.Liquisolid formulation exhibited improvement in micromeritic properties FT-IR and DSC confirmed no drug-excipient interaction. P-XRD study revealed presence of CH in porous carrier in dissolved state. The different R values and concentrations were found to have a marked effect on the dissolution

profile. Selected formulation F12 exhibited increased dissolution rate with disintegration in less than 3 min. Pharmacokinetic study for liquisolid formulation F12 showed 1.7 times improvement in oral bioavailability.Liquisolid formulation for CH can be considered a promising approach for the development of a stable and scalable solid dosage form with improved micromeritics and biopharmaceutical attributes.

Keywords: Pharmacokinetic study, Cytotoxicity study, Flowability and dissolution rate

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INTRODUCTION

The Drugs that are poorly water soluble have a slow dissolution rate [1]. The poor water solubility of drugs is a major challenge to the formulation of the oral pharmaceutical dosage forms [2]. It is the rate limiting step for the majority of the drug substances available in different dosage forms. Several approaches reported for solubility enhancement include solid dispersions [3], complexation with β- cyclodextrin[4], micronisation[5], spray-drying technique [6] and microwave[7] induced dissolution rate improvement.

Spirea*et al*. developed the liquisolid technique to increase the dissolution properties of water insoluble drugs [8]. In the liquisolid systems, lipophilic or water indissoluble drugs are dissolved or suspended in suitable water miscible non-volatile solvent which can be further converted into an acceptably flowing, compressible, non-adherent, dry looking powders [9]. This can be obtained by using porous carrier and coating material. Coating material should be a material possessing fine (0.01–5 µm in diameter) and highly absorptive particles, which contribute to covering the wet porous carrier particles and displaying a dry powder by adsorbing excess liquid to ensure good flowability of the created blend [10, 11]. This technique was

successfully used to augment the solubility and dissolution rate of several poorly water-soluble drugs such as naproxen [12], famotidine [13], carbamazepine [14], piroxicam[15], indomethacin [16], hydrocortisone[17] and prednisolone [18].

Cinacalcet hydrochloride (CH), a calcimimetic medication, is approved for the treatment of people with secondary hyperparathyroidism who are also receiving dialysis for chronic kidney disease (CKD) [19]. Additionally, CH is utilized to treat patients with parathyroid cancer who have hypocalcaemia. The major problem associated with its formulation and efficacy is its poor aqueous solubility and its low bioavailability (20-25%) [20]. The aim of this work is to improve the micromeritics, dissolution and oral bioavailability of CH via liquisolid technique. Tween 80 was used as the non volatilisable liquid vehicle. Neusilin US2 and aerosil were used as carrier and coating materials respectively to produce powders with acceptable flowing properties which can be compacted into tablets.

MATERIAL AND METHODS

Material

CH was received as gratis sample from Dr Reddy's Laboratories ltd, Hyderabad, India. Neusilin US2 and Fuzicalin were received as gift sample from Fuji chemical industries co Ltd, Mumbai, India. Microcrystalline cellulose (MCCPH102) and Tween 80 were gift sample from Abbes healthcare OPC Pvt Ltd, Mumbai, India. All other materials used were of analytical grade.

M**ethods**

Analytical Method:

A reported ultra-fast liquid chromatography method was used for the estimation of CH [21]. 10 mg of CH was dissolved in acetonitrile: TBHS (tetra butyl hydrogen sulphate solution) (50:50) to get 1000 µg/mL standard stock solution. Retention time for the chromatogram was determined. Calibration standards for CH were generated at nine levels by properly mixing and diluting with

mobile phase to get concentrations in the range of 100-100000 ng/mL. The calibration graph was created by plotting peak areas against respective concentrations.

Solubility Study

Solubility of CH in different non-volatile liquid vehicles *vis-a-vis* glycerol, tween 60, 80, Polyethylene glycol 300, 400, labrasol, captex 200P, captex 355EP/NF, labrafac, lauroglycol and span 20 was determined[22]. Solutions (saturated with CH) in the non-volatile liquids were shaken for 48 h at 25^{o} C then centrifuged, filtered and analyzed using the Ultrafast liquid chromatography (UFLC) method.

Determination of loading factor:

To figure out the liquid loading factor at each R value, 3 porous carriers were selected *vis-à-vis* Neusillin US2, Avicel PH102 and Fujacalin[23]. Aerosil was selected as coating for all the carriers. Liquid powder admixtures were prepared at 3 different ratios i.e. R = 10, 15 and 20. The carrier (Neusillin US2, Avicel PH 102, and Fujacalin) was added to non-volatile solvent followed by the coating substance (Aerosil 200) in the appropriate amount. The combination was mixed for 3 min and left overnight.

Angle of repose was used to evaluate flow properties of powder by placing them on a funnel. The powder was allowed to flow through the funnel and the height of powder heap was determined. A curve was constructed by taking angle of repose versus liquid composition. The maximum flowability was determined to be at a 25° angle of repose. Equation was used to get the loading factor (Lf) at each R value

$$Lf = \frac{Weight\ of\ the\ liquid\ corresponding\ to\ 25^{0}}{Weight\ of\ the\ carrier}$$

Preparation of Liquisolid Tablet

CH was dissolved in selected non-volatile solvent i.e. Tween 80 and vertex was done for 15 mins for complete solubilization of drug (Table 1). Then it was mixed with required quantity Neusilin US2 which acts as carrier in the formulation. Aerosil, cross povidone, talc were added and mixed for 10 min until freely flowable powder was formed. Utilizing flat, circular punches with a 12 mm diameter, the air-dried powder compositions were directly compressed into tablets (Minipress-II, Karnavati, Ahmedabad).

Characterization

Micromeritic properties of Liquisolid powders

According to protocol, the flow characteristics of the liquisolid powder formulations F1 to F12 were assessed. The formulations were assessed for the angle of repose, Hausner's ratio, and Carr's index [24]. Quality Control tests for liquisolid Tablets such as drug content, hardness, disintegration time, weight variation and friability test were carried out as per standard procedure for the evaluation of prepared liquisolid tablets [25].

***In vitro* Dissolution Test**

Selected formulation with disintegration time less than 10 mins i.e. F8, F11 and F12 were selected for *In vitro* dissolution study. Pure drug CH was also subjected to dissolution study. The study was carried out using United States pharmacopoeia (USP) type II paddle equipment with rpm 50 using 0.1 N HCl as medium. This study was performed for 2 h in 0.1 N HCL followed by phosphate buffer pH 6.8 upto 12 h. The samples were analyzed by UFLC. The dissolution data was used to determine parameters such as dissolution efficiency (%), mean dissolution time (min), Hixson Crowell cube root equation as per standard procedure [26].

FT-IR Study

It was performed using the Infrared spectrophotometer (IR affinity, Shimadzu). Samples of 2 mg were mixed with dry potassium bromide (KBr) powder and compressed into discs. The FT-IR of pure drug and selected liquisolid formulations were performed.

DSC Study

A DSC with a thermal analyser (DSC 60, Shimadzu) was used to conduct the study. All of the correctly weighed samples (2 mg) were placed in sealed aluminium pans before being scanned at a rate of 10°C/min from room temperature to 220°C.

P-XRD Study

Powder XRD (Multiflex, M/s. Rigaku, Tokyo, Japan) tests on pure drug CH and liquisolid formulation were carried out in the range of 2 to 70^0 2Ɵ angle.

Scanning electron microscopy (SEM) Study

By using SEM, Hitachi, Tokyo, Japan), the shape and surface of a liquisolid formulation were investigated. The platinum coating was applied after the sample had been attached to the carbon-coated metallic stub. For surface investigation using SEM in a high vacuum, coated samples were used.

Stability Study

Stability studies of formulation F12 was carried out at 40 ±2°C/75±5% RH for six months as per the (ICH) Q1A (R2) guidelines. The sample was collected and evaluated for drug content, disintegration time and dissolution at 30 min [27].

Pharmacokinetic study

12 no. of male rabbits (albino) of body weight (2 kg) were selected. The selected animals were divided into 2 groups (6 rabbits in each). Group 1 was administered with CH Liquisolid

compact i.e. formulation F12) i.e. test and group 2 with standard aqueous suspension of CH. All of the chosen animals received twice-daily feedings of sanitary food and clean water. The study was approved by institutional animal ethical committee (IAEC) of Roland Institute of Pharmaceutical Sciences with protocol number 95.

The dose for rabbit was calculated as follows:

Total dose in mg (in humans) × 0.07 (factor for each 1.5 kg weight of rabbit)

= (30×0.07 ×1.6)/1.5 = 2.24 mg of 1.6 kg rabbit ≅ 2.3 mg

2 mL of aqueous suspension of CH containing (1.15 mg/mL) and selected liquisolid formulation F12 (56 mg of liquisolid formulation equivalent to 2.3 mg of CH) were administered using Ryle's tube. Marginal ear vein was punctured by using needle no. 24 at regular intervals and 0.5 mL of blood was collected in eppendorf tube each time at 0 0.5, 2, 6, 12, 24 and 48 h. Various pharmacokinetic parameters such as Cmax, Tmax and area under the curve (AUC) were determined.

***In-vitro* Cytotoxicity Study**

In-vitro cytotoxicity study using MDA-MB (breast cancer cell line) were performed for pure drug solution and liquisolid formulation F12 at three different concentration levels *vis-a-vis* 100, 250 & 500 µg/mL. At each concentration level, two samples of 10 µL and 100 µL were inoculated on the culture plate. Simultaneously one placebo formulation was also subjected to the above study. A 96-well flat bottomed plate, with each well at a density of 1×10^4 cells was used for the cell plating and incubated for 24 h in the CO_2 incubator at 37°C. Once the cells were attached, three replicate of 10 µL and 100 µL of the three formulations at above mentioned concentration levels were directly added to plates. The cells were incubated in CO_2 incubator for 24 h at 37°C. The cytotoxicity following the above mentioned treatments was evaluated by 3-

[4,5-dimethylthiazole-2-yl]-3,5-diphenyltetrazolium bromide dye (MTT; Sigma,M2128) assay method. The acetic isopropanol was added in order to dissolve the formzan crystals. After solubilising, the absorbance was measured with EPOCH 2 (Biotek) at a wavelength of 590 nm [28].

RESULTS AND DISCUSSION

Analytical method: Reported UFLC method for estimation of CH was followed for analysis of samples. The mobile phase acetonitrile: TBHS (50:50), C_{18} column with a flow rate 1 mL/min was used for the analysis. The retention time was found to be 4.3 min. The linearity range for CH was 100 to 100000 ng/mL. The linearity range for CH in rabbit serum was also 100 to 100000 ng/mL.

Solubility Study:

CH exhibited highest solubility in tween 80 (51.83 mg/mL) followed by labrasol (37.75 mg/mL). It exhibited lesser solubility in all other solvents (**Figure 1)**. As the drug exhibited highest solubility in tween 80, further studies were carried out using Tween 80. The hydrophilic polyethylene oxide groups are responsible for higher solubilization of CH [29].

Liquid loading factor

Three porous carriers namely Neusillin US2, MCC PH 102 and Fujacalin were attempted to determine the liquid loading factor. The flowable liquid retention potential value in % w/w was 3.09, 0.029 and 0.349 for Neusillin US2, MCC PH102 and Fujacalin respectively for carrier to coating ratio of R = 20. Other formulations with R 10 and 15 showed lower liquid retention potential. High liquid retention potential value for Neusillin US2 can be attributed to its high specific surface area (300 m^2/g) and high adsorption capacity [30].

Preparation of Liquisolid Compact

The liquisolid powders were prepared by simple mixing technique. The method used for the preparation is scalable. CH was completely soluble in tween 80. As the proportion of neusillin US2 increased, the liquisolid formulation became flowable for processing into tablet dosage form.

Micromeritic properties of Liquisolid powders

Micromeritic evaluation of pure drug CH showed very poor flowability. All the liquisolid formulations with different R values showed that angle of repose, Carr's index and Hausner's ratio were suitable for tableting **(Table 2).** This improved flowability with liquisolidformulations can be ascribed to adsorption capacity and compressibility characteristics of neusilin US2 [31]. The improvement in flowability is also due to coating aerosol on the wet surface of porous carrier.

Quality Control tests for Liquisolid Tablets

Drug content of all formulation was more than 95 % ensuring uniform mixing of drug with excipients. Weight variation of all formulations was within the acceptable range of deviation i.e. ± 5% which ensures good flowability. Formulations F1 to F4 were rejected as these have low hardness and high friability which can be attributed to lower proportion of Neusillin US2 which is also responsible for imparting hardness or strength to the tablets. Formulation F5, F6 and F7 were rejected as these did not disintegrate within 15 min. Similarly formulation F9 and F10 were rejected as these did not disintegrate within 15 min. Finally formulation F8, F11 and F12 were selected for further studies as these passed all QC tests for tablets **(Table 3)**[25].

***In vitro* Dissolution Test**

Pure drug CH, liquisolid formulation F8, F11 and F12 were subjected to dissolution test for 2 h in 0.1 N HCl (**Figure 2).** It was observed that less than 15 % CH dissolved during 2 h of

dissolution study in 0.1 N HCl. Liquisolid formulation F12 showed nearly 100 % CH dissolution in 1 h. Q30 value for formulation F12 shows 30 times improvement in dissolution rate. Dissolution efficiency for formulation F12 is also highest at different time points i.e. 15, 30, 45 and 60 min. Lowest MDT for formulation F12 suggest better dissolution compared to pure drug and all other formulations. Higher correlation coefficient for Hixson Crowell cube root equation suggests change in surface area during dissolution **(Table 4)**[32].

FT-IR Study

FT-IR study of CH revealed absorption bands at 1517 cm-1 assigned to the CH3 group, absorption bands at 1338 cm-1 assigned to the CH2 group, absorption bands at 2909 cm-1 assigned to the NH group, absorption bands at 796 cm-1 assigned to the CF3 group, and absorption bands at 805 cm-1 assigned to the benzene group (F**igure 3)**. The CH and excipients were compatible with one another because the liquisolid formulation likewise displayed absorption bands in a related range.

DSC Study

A distinct endothermic peak caused by drug melting can be seen on the thermogram of pure CH (Tonset = 178.83 ^{0}C, Tmelting = 181.9 ^{0}C). The crystalline form of the CH is indicated by the strong endothermic peak and narrow melting range. Thermogram of neusilin US2 based liquisolid formulations exhibited absence of peak (**Figure 4)**. This can be attributed to the adsorption of solubilized drug onto porous carrier. Further the obtained results indicate that there was no positive evidence for the interaction between drug and excipient material.

P-XRD Study

` In **Figure 5,** the powder-XRD patterns of the pure medication CH revealed prominent peaks at scattered angles of 13.76, 15.85, 18.8, 21.17, 24.17, and 25.35 degrees. The crystalline peaks completely disappeared in the diffractogram of liquisolid formulation. Similar results are also reported for the liquisolid formulations of rosuvasatin[33]. This can be attributed to the adsorption of dissolved CH to the porous carrier. As the drug is in dissolved state (molecular state) so no peaks were observed. This observation was also evident in DSC study.

SEM

Liquisolid formulation F12 was studied for surface morphology using SEM. **Figure 6** depicts the presence of pores in the formulation in which drug solution is entrapped. The average size of pores was 98 ± 23 µm with nearly spherical shape.

Stability Study

Stability study for the selected liquisolid formulation showed no significant changes in drug content, disintegration time and drug release at 30 min at probability (P) < 0.05 level during 6 months of stability (**Table 5).** Hence the selected liquisolid formulation is suitable as per ICH guidelines.

Pharmacokinetic Study

The results of the pharmacokinetic study are depicted in **Table 6** and time Vs serum drug concentration curve **(Figure 7).** Lower Tmax for F12 suggests faster dissolution followed by faster absorption of CH in liquisolid formulation. Cmax was nearly 2 times more than that of pure drug signifying improved intensity of therapeutic action. AUC of F12 was 1.7 times more than that of pure CH indicating better extent of absorption and improvement in bioavailability[34].

***In-vitro* Cytotoxicity Study**

The cytotoxicity of formulations F12 was shown in figure 8as cell viability %. From the figure it was found that the concentration of CH in liquisolid formulation was not cytotoxic for MDA- MB (breast cancer cell line). Minimum viability was determined as 96% which indicates the safety of the incubated formulations. Placebo formulation did not exhibit any cytotoxicity on the cells suggesting the excipients are not cytotoxic.

CONCLUSION

Liquisolid formulations were prepared by using tween 80 as non-volatile solvent. Porous carrier neusillin US2 with coating material aerosoil with R = 20 has shown highest liquid retention potential. Liquisolid formulations exhibited desirable flowability for processing into tablet dosage form. Selected formulation F12 exhibited increased dissolution rate with disintegration in less than 3 min. Pharmacokinetic study for liquisolid formulation F12 showed 1.7 times improvement in oral bioavailability. Hence Liquisolid technique can be used successfully to improve dissolution rate and oral bioavailability of CH.

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Ethical Approval:

This research has passes institutional animal ethical committee (IAEC) clearance with number 926/PO/Re/S/06/CPCSEA/95.

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Conflict of Interest

The authors declare no conflict of interest

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List of Abbreviations

AUC = Area under the curve

CKD = Chronic kidney disease

CH = Cinacalcet hydrochloride

DSC = Differential scanning calorimetry

FT-IR = Fourier-transform infrared spectroscopy

IAEC = Institutional animal ethical committee

ICH = International council for harmonisation

MCC = Microcrystalline cellulose

KBr = Potassium bromide

P-XRD = Powder X-ray diffraction

P = Probability

SEM = Scanning electron microscopy

TBSH = Tetra butyl hydrogen sulphate solution

UFLC = Ultrafast liquid chromatography

USP = United States pharmacopoeia

Table 1, Composition of Liquisolid compacts of CinacalcetHCl

Formulation code	CH (mg)	Tween 80 (ml)	Tween 80 (mg)	Weight of liquid medication (mg) W	R	Lf	Quantity of carrier Q in mg (Q =W/Lf)	Quantity of Coating (q) in mg q = Q/R	Cross povidone (mg)	Talc (mg)	Tablet weight (mg)
F1	30	0.6	500	530	10	3.94	135	13.5	0	5	684
F2	30	0.6	500	530	10	3.94	135	13.5	5	5	689
F3	30	0.6	500	530	10	3.94	135	13.5	10	5	694
F4	30	0.6	500	530	10	3.94	135	13.5	15	5	699
F5	30	0.6	500	530	15	3.35	158	10.53	0	5	703
F6	30	0.6	500	530	15	3.35	158	10.53	5	5	708
F7	30	0.6	500	530	15	3.35	158	10.53	10	5	713
F8	30	0.6	500	530	15	3.35	158	10.53	15	5	718
F9	30	0.6	500	530	20	3.29	161	8.05	0	5	704
F10	30	0.6	500	530	20	3.29	161	8.05	5	5	709
F11	30	0.6	500	530	20	3.29	161	8.05	10	5	714

F12	30	0.6	500	530	20	3.29	161	8.05	15	5	719

CH = cinacalcetHCl, R = carrier and coating material ratio, Lf = loading factor

Table 2 Micromeritic properties of pure CH and its Liquisolid powder formulations

Formulation	Angle of repose(˚)	Carr's index (%)	Hausner's ratio
CH	42 ±2.1	28.5 ±1.42	1.6 ± 0.008
F1	24 ±1.2	18 ± 0.9	1.24 ± 0.06
F2	23 ±1.15	16 ±0.8	1.21 ± 0.06
F3	24 ±1.2	20 ±1	1.2 ±0.06
F4	20 ±1	17 ±0.85	1.23 ±0.06
F5	25 ±1.25	16 ±0.8	1.21 ±0.06
F6	24 ±1.2	18 ± 0.9	1.2 ±0.06
F7	23 ±1.15	15 ±0.75	1.21 ±0.06
F8	22 ±1.1	16 ±0.8	1.23 ±0.06
F9	25 ±1.25	17 ±0.85	1.22 ±0.06
F10	24 ±1.2	15 ±0.75	1.2 ±0.06
F11	22 ±1.1	16 ±0.8	1.21 ±0.06
F12	23 ±1.15	18 ± 0.9	1.22 ±0.06

*Mean ± SD, n = 6

Table 3, Quality Control tests for Liquisolid tablets of CH

Formulations	Drug content* (%)	Weight variation** (mg)	Friability** (%)	Hardness*** (Kg/cm^2)	Disintegration time*** (min)
F1	96 ± 4.8	683±34.15	3.4 ± 0.02	3.5 ± 0.175	28 ± 1.6
F2	97 ± 4.85	688±34.4	2.5±0.02	3.7±0.185	16±1.3
F3	98±4.9	693±34.65	3.7±0.03	3.8±0.19	14±1.2
F4	99±4.95	698±34.9	2.8±0.04	3.7±0.185	11±1.05
F5	96±4.8	703 ± 35.4	0.7±0.03	5.1±0.255	23±1.5
F6	97±4.85	708 ± 35.65	0.6±0.03	5.2±0.26	18±0.95
F7	99±4.95	713 ± 35.9	0.6±0.03	4.9±0.245	16±0.8
F8	98±4.9	718 ±36.15	0.7±0.03	5.2±0.26	9 ±0.6
F9	96±4.8	704 ± 35.35	0.5±0.02	5.8±0.29	29 ±1.51
F10	99±4.95	709 ± 35.6	0.6±0.03	5.9±0.295	16 ± 0.7
F11	96±4.8	714 ± 35.85	0.8±0.04	6.0±0.3	7±0.35
F12	97±4.85	719 ± 35.6	0.7±0.03	6.2±0.31	2.5 ±0.15

*Mean ± SD, n = 10, ** Mean ± SD, n = 20, ***Mean ± SD, n = 6

Table 4; *In-Vitro* release kinetic study

Parameters	CH	F8	F11	F12
Q30 (%)	1.5 ± 0.04	26 ± 0.2	35 ± 1.5	45 ± 1.2
DE15 (%)	1.2 ± 0.03	4.5 ± 0.5	16.2 ± 0.8	24 ± 1.3
DE30 (%)	1.7 ± 0.04	22.5 ±2.5	31.3 ± 1.3	42.2 ± 2.5
DE45 (%)	2.1 ± 0.05	42.2 ±3.6	53.2 ± 3.4	70.1 ± 3.4
DE60 (%)	5.4 ±0.09	51.3 ± 3.5	77.1 ± 4.2	95.2 ± 3.5
MDT (min)	45.67 ± 1.1	31.87 ±2.6	31.42 ± 3.1	27.87 ± 1.6
Hixson Crowell's (r^2)	0.834	0.967	0.998	0.998

Mean ± SD, n = 6

Table 5: Stability data of selected Liquisolid tablet (F12)

Time (months)	Drug Content(%w/w)	Disintegration time (min)	Drug release at 30 min (%)
1	97 ± 4.85	2.5 ± .03	45 ± 2.25
2	97 ± 4.85	2.6 ± 0.5	45 ± 2.25
3	96.5 ± 4.82	2.8 ± 0.4	44 ± 2.22
6	97.8 ± 3.56	2.5 ± 0.5	45 ± 3.5

Mean ± SD, n = 6

Table 6: Pharmacokinetic parameters

PK Parameters	Aqueous suspension of CH	Liquisolid tablet (F12)
Cmax (ng/ml)	5117.08 ± 36.5	9190.7 ± 45.2
Tmax (h)	6 ± 0.2	2 ± 0.1
AUC (ng.h/ml)	130563.11 ± 89.4	227395.86 ± 124.3

Mean ± SD, n = 6

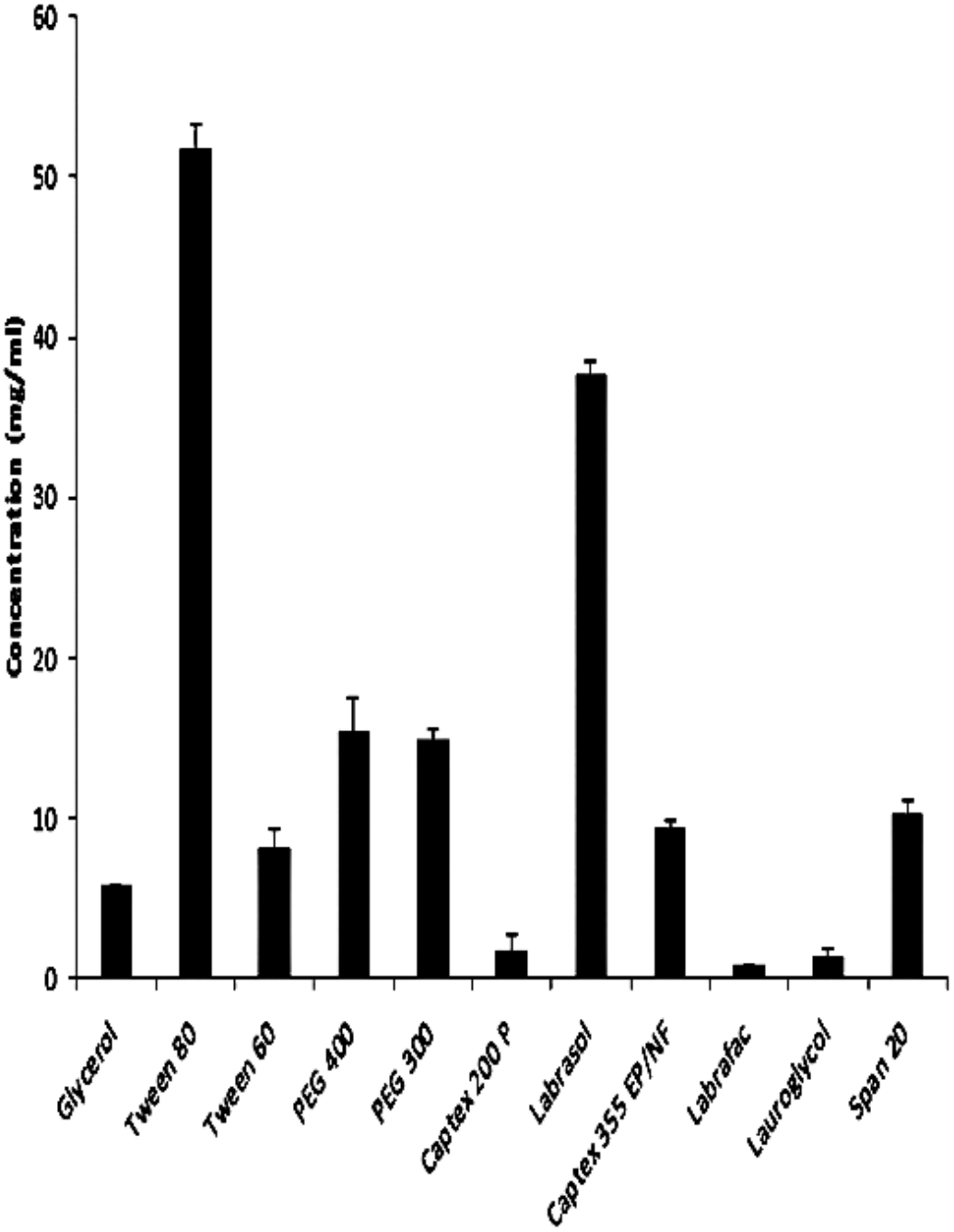
Concentration (mg/ml)
60
50
40
30
20
10
0
Glycerol
Tween 80
Tween 60
PEG 400
PEG 300
Captex 200 P
Labrasol
Captex 355 EP/NF
Labrafac
Lauroglycol
Span 20

Fig.1: Saturation solubility of CH in non-volatile solvents

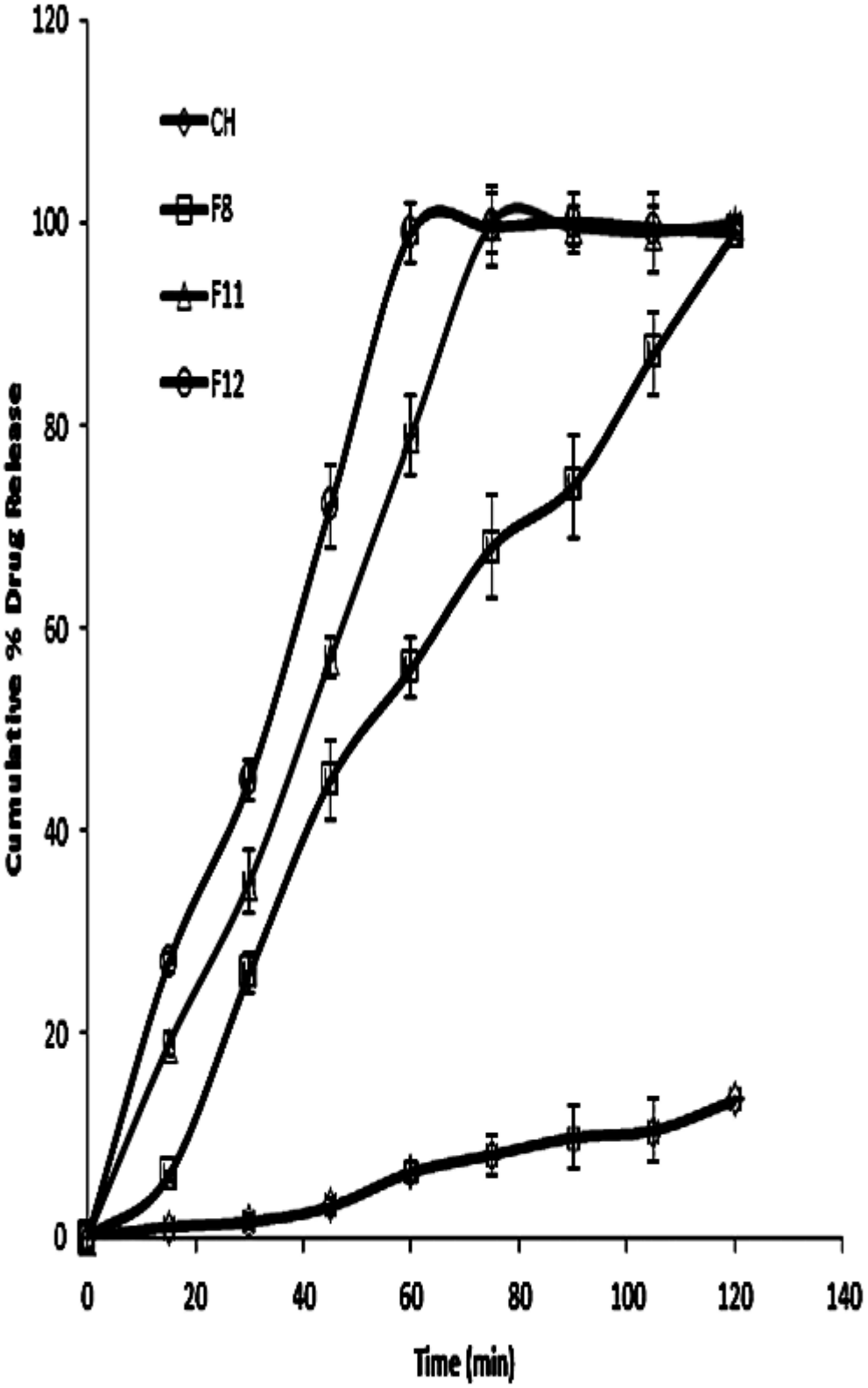
120
100
80
60
40
20
0
CH
F8
F11
F12
Cumulative % Drug Release
0
20
40
60
80
100
120
140
Time (min)

Fig.2: In-vitro dissolution profile for selected liquisolid formulations

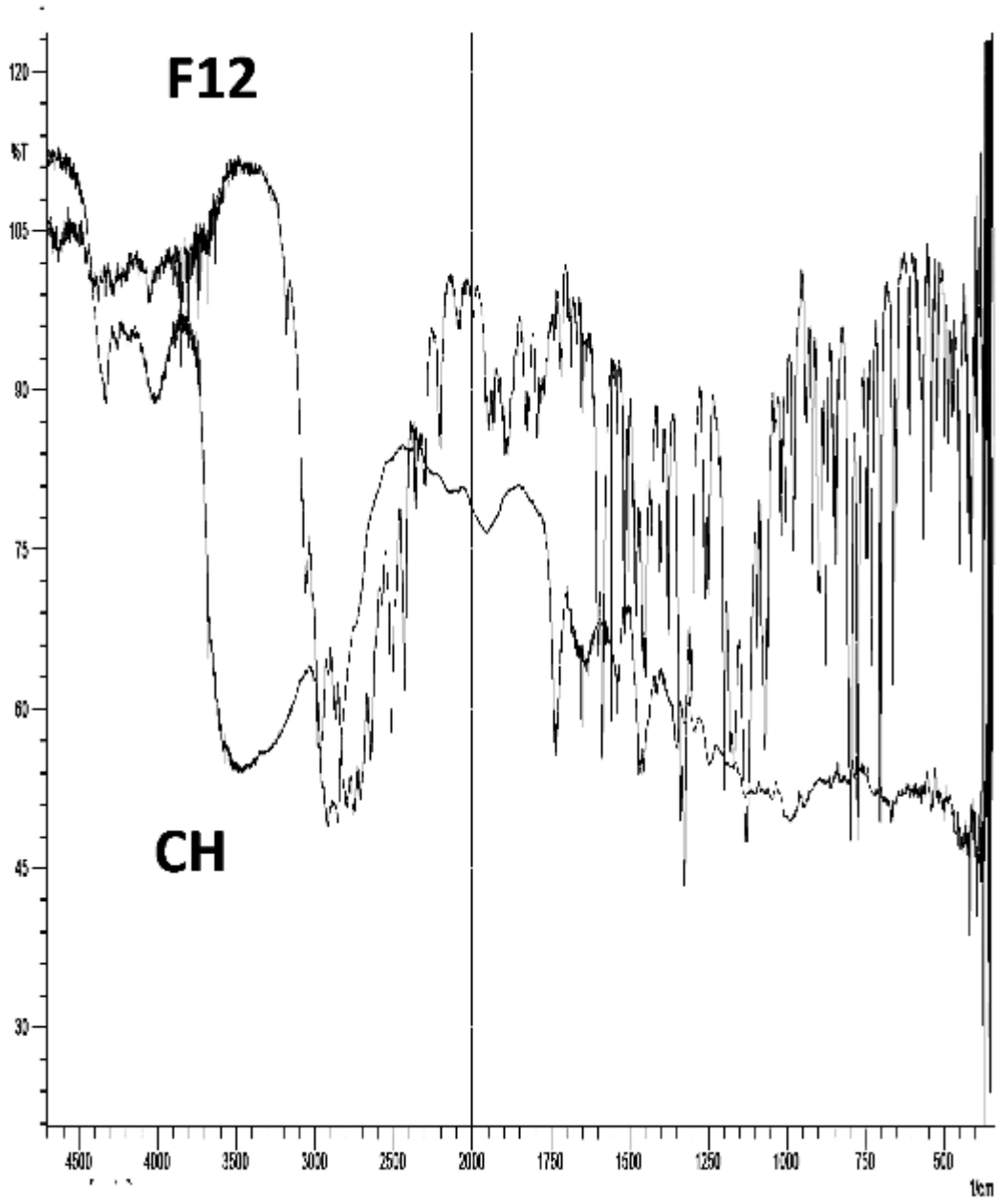

Fig. 3: FT-IR study for pure drug powder CH and selected liquisolid formulation (F12)

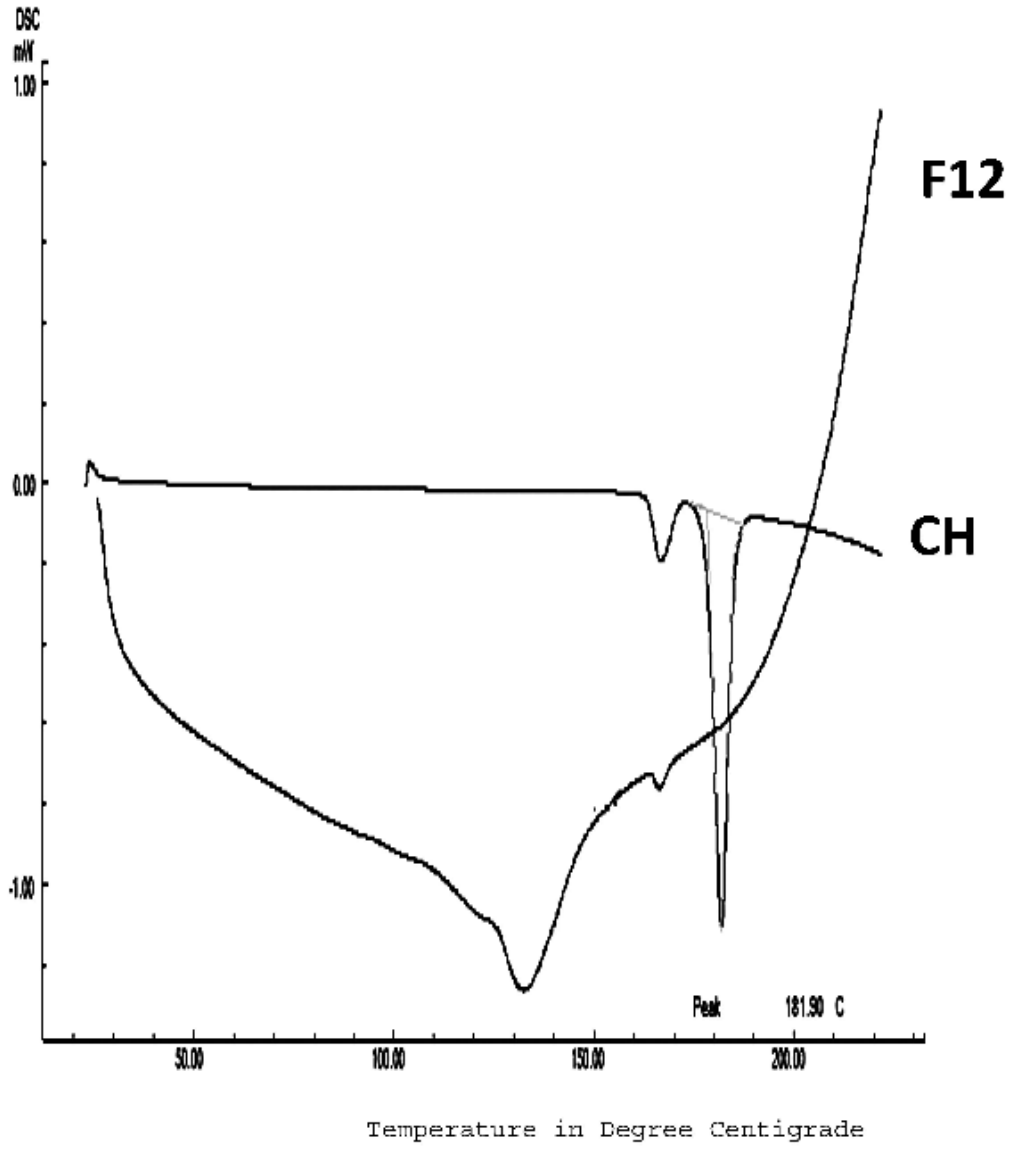
DSC
mW
1.00
0.00
-1.00
F12
CH
Peak 181.90 C
50.00
100.00
150.00
200.00
Temperature in Degree Centigrade

Fig.4: DSC thermogram for pure drug powder CH and selected liquisolid formulation (F12)

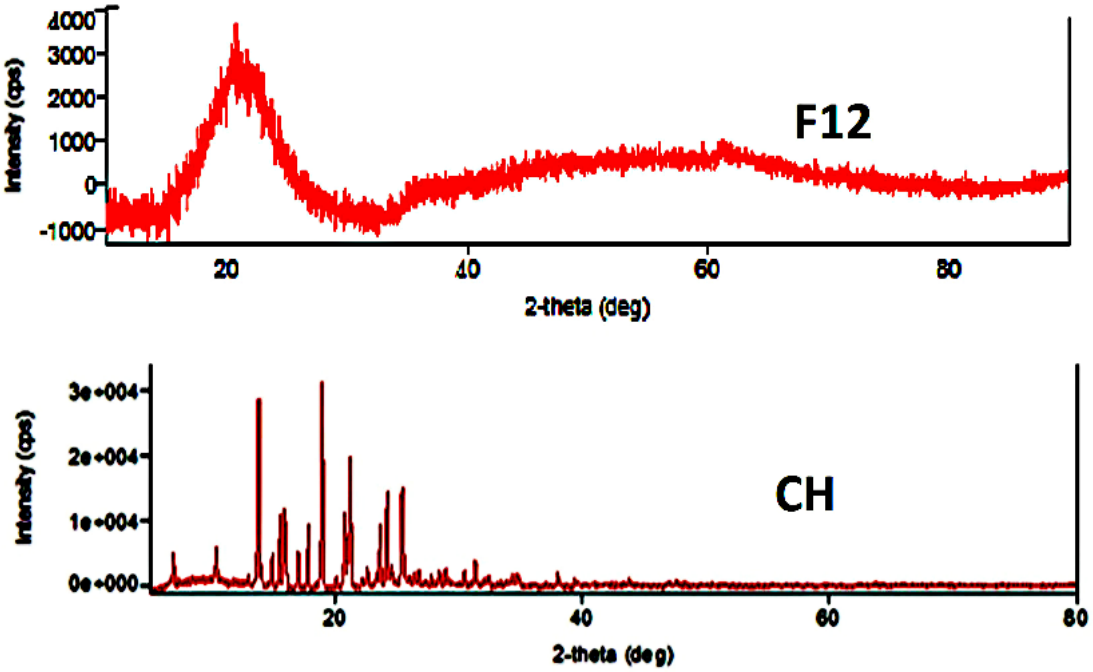

Fig.5: P-XRD for pure drug powder CH and selected liquisolid formulation (F12)

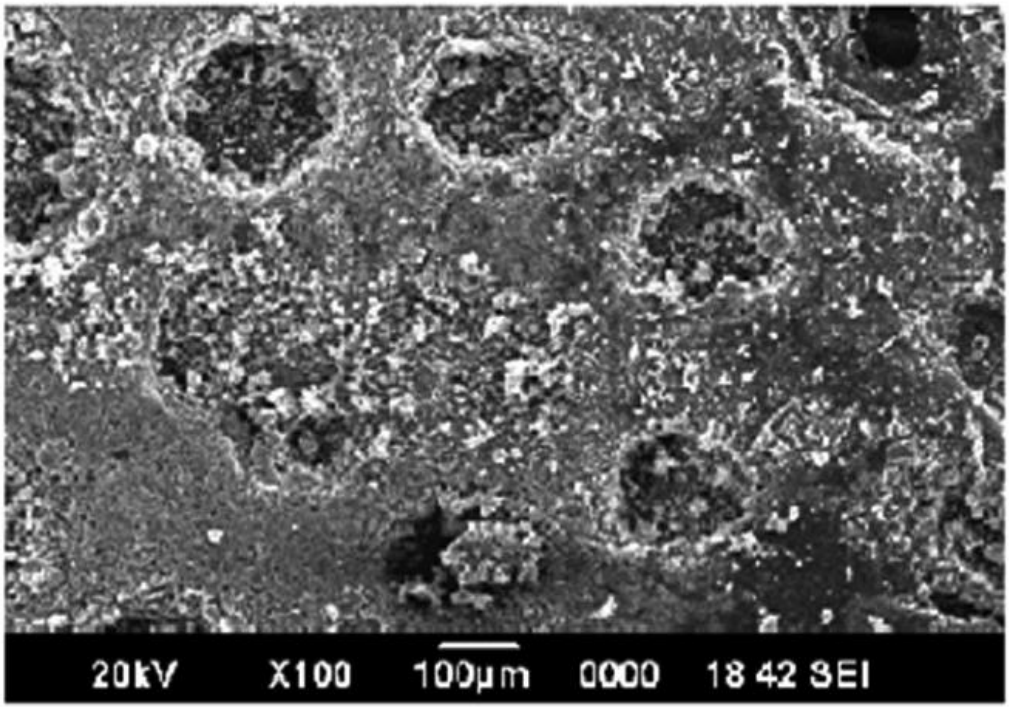

Fig.6: SEM for selected liquisolid formulation F12

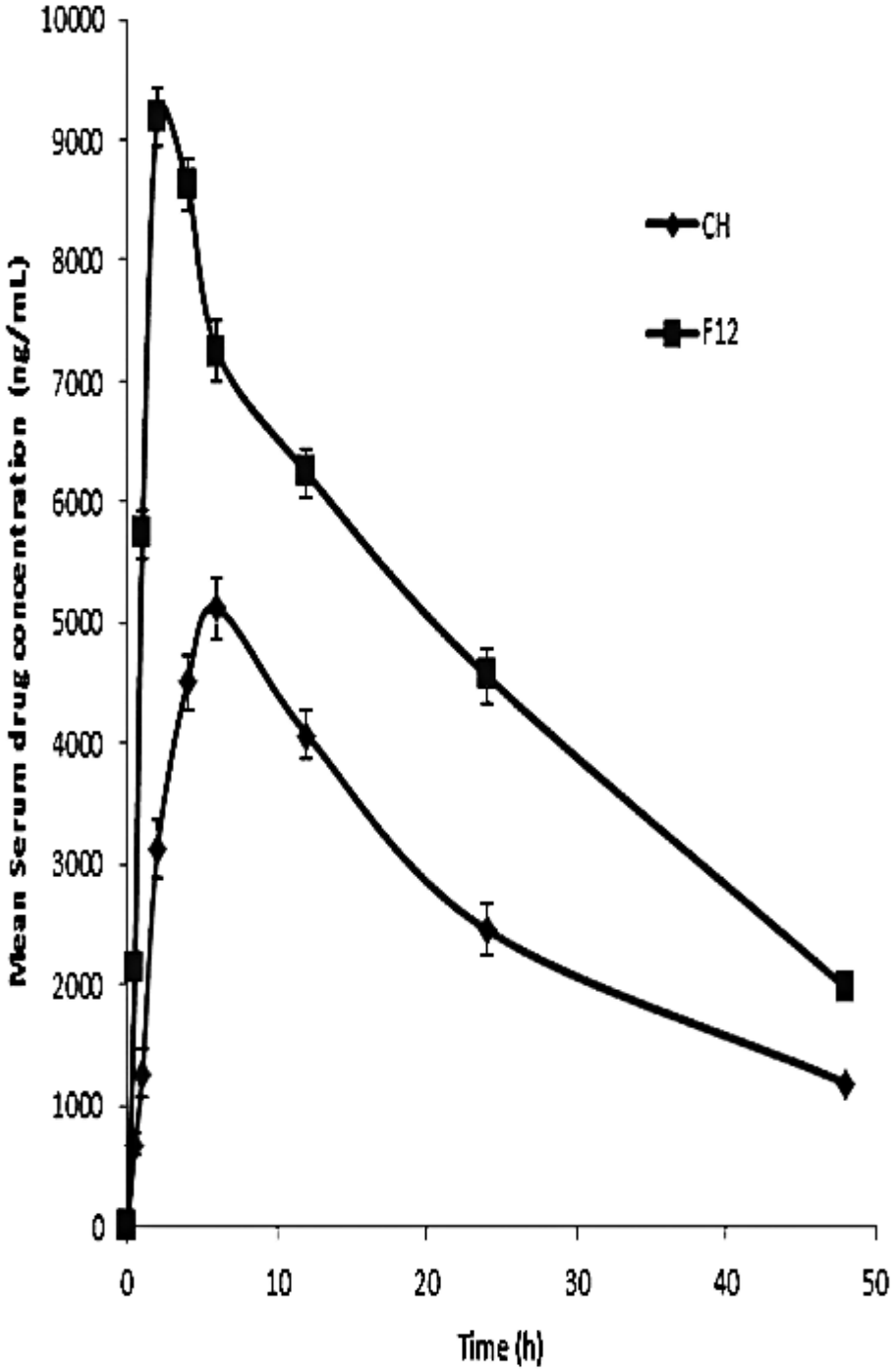
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Mean Serum drug concentration (ng/mL)
0
10
20
30
40
50
Time (h)
CH
F12

Fig. 7: Serum drug concentration versus Time curve for aqueous suspension of CH and F12

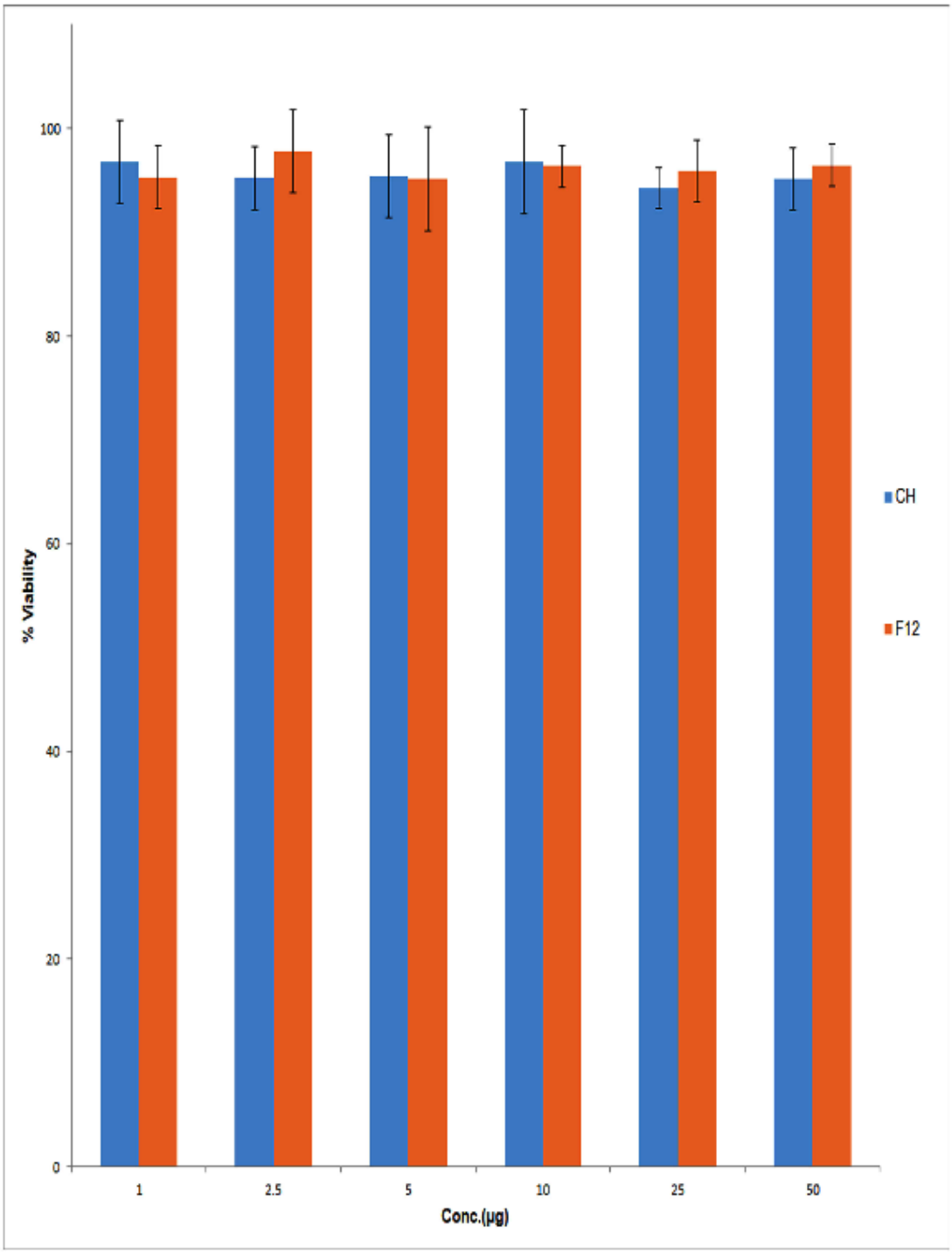

Fig 8: *In-Vitro* cytotoxicity study by MTT assay method