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Improvement of The Photostability of Nimodipine by Using Liquisolid Compacts Technique

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***Abstract*— Liquisolid compacts are one of the modern drug formulation techniques used for drug formulation for several objectives including protection against photosensitivity. This study evaluates the photoprotective effect of the liquisolid compact technique on a calcium channel blocker antihypertensive drug, nimodipine, which is considered a photosensitive drug model. Liquisolid compact tablets of nimodipine were prepared from; Avicel PH-102 as a carrier material, (colloidal silicon dioxide, Cab-O-sil, and titanium dioxide as coating materials), croscarmellose sodium (CSS), sodium starch glycolate (SSG), crospovidone (CP) as super disintegrants, and propylene glycol as the liquid vehicle. However, the ratio of carrier to coating materials was kept constant in all formulations at 35:1. This ratio was chosen after testing the ratios 15:1, 20:1, 25:1, 30:1 and 35:1. The feasibility of the prepared liquisolid systems was also evaluated for first; the pre-compression and post-compression characteristics. Second, the possible drug-excipients interaction using FT-IR. Third, the photostability of Nimodipine in pure form, conventional tablets, and in the prepared liquisolid tablets through irradiation with a light dose of 0.55 W/m2/h visible light, 50 W/m2/h UVA and 0.27 W/m2/h UVB for 12 h in order to estimate the effect of coating material type on Nimodipine stability especially in the prepared liquisolid formulations. The results showed that all of the prepared liquisolid tablets showed satisfactory properties regarding pre and post-compression properties. Interestingly, the FTIR spectra study ruled out any interaction between nimodipine and excipients in the prepared liquisolid tablets. Besides, all of the prepared liquisolid tablets had shown a superior drug dissolution profile compared to the conventional and direct compressed tablets. Finally, 92.43% of the drug remaining was found in the liquisolid formulation (F7) after 12 h photo-irradiation as compared to 65.48% drug remaining for the pure drug substance and 75.12% for directly compressed tablets indicating that liquisolid technique had significantly inhibited the photo-degradative effect of light in the prepared liquisolid formulations. It can be concluded that the liquisolid compacts technique is a promising approach for the improvement of photostability of this photosensitive Nimodipine with an acceptable stability as well as enhanced dissolution rate.**

***Keywords*— Liquisolid compact technique, Nimodipine, Photostability, enhanced dissolution**

I. INTRODUCTION

So far, many obstacles that faced the pharmaceutical industry, including photo-degradation of the active pharmaceutical ingredient besides low drug dissolution. Hence, ongoing efforts regarding these difficulties are focused on developing methods that are designed to protect the therapeutic moiety in its activity form against the light induced adverse stability effects. For light liable therapeutic compounds known as light sensitive or photosensitive [1], ultraviolet radiation region in the light, electromagnetic spectrum is the main cause of the unwanted photochemical changes. Nevertheless, artificial light sources, like fluorescent light, may also induce such alterations in these photosensitive drugs [2]. This degradation may happen during the handling, production, storage, distribution as well as the clinical use of their dosage forms products. The expected photosensitivity ultimately leads to undesirable effects such as dose reduction of the active drug that brings about the reduction in the efficacy, losing or changing of the active pharmaceutical ingredient/the excipients, as well as the liberation of undesirable by-products that could be toxic. This effect may exert a potential risk on patients who consume these degraded products. Thus, pharmaceutical preparations should be investigated for the possible existence of the photo-degradation products in order to ensure the safety, efficacy, and stability of the final commercial products [3-5].

Liquisolid compacts technology described by Spireas can be used to convert a liquid into a free flowing and easily compressible dry powder through simple physical mixing of a liquid form drug available as a suspension or solution in suitable non-volatile liquid vehicles, with selected excipients, "termed the carrier" and coating material. However, organic inert, preferably water-miscible and high boiling point solvents such as propylene glycol, liquid polyethylene glycols, or glycerin are the best suitable liquid vehicles for drugs to be formulated with this technique on one the hand. On the other hand, During this process, the liquid form drug is incorporated into a porous carrier material whereupon saturation of the carrier with liquid, a liquid layer is formed on the particle surface, which is readily adsorbed by the fine coating particles. Hence, a dry, free flowing and compressible powder is obtained [6]. This liquisolid compacts technologies a promising technique for the photo-protection of lightsensitive drugs. The principle behind such effect of the technique is based on the coating material's photoprotective property since they have a high refractive index and their capability to diffract light waves of different energies. In addition, to the photoprotective benefit, this technique is reported to be a well-known method for the dissolution enhancement of poorly water-soluble drugs [7]. According to Spireas model of liquid-solid, the carrier and coating powder can hold only a definite amount of the liquid while maintaining sufficient flowability and compactibility [8]. The idea of the role of liquisolid compact technique in the photostablization of drug products was first proposed by researcher Khames et al. the Photostability testing of drug substances, and formulated products is an integral part of the development process in industry to ensure their quality during the shelf -life period. It is carried out under standardized conditions to determine the extent to which the drug or the product undergoes an undesirable chemical change [9].

Nimodipine (NIM) is a dihydropyridine calcium channel blocker indicated for improving neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured congenital aneurysms [10]. However, according to the biopharmaceutical classification system (BSC), it belongs to class II "low solubility–high permeability" drugs. Its oral bioavailability is about (13%) after administration is about (13%) due to its low water solubility as well as extensive first-pass metabolism in the liver [11]. The available dosage forms of this drug are tablets and capsules of 30 mg dose in addition to intravenous infusion of 10 mg/50 ml concentration. Nimodipine is known to be light-sensitive. Therefore its I.V solution and capsules should be stored only in the manufacturer's light-protective container below 25°C [12]. UV light induces both oxidation of the dihydropyridine ring and modification of the nitro group in the original nimodipine molecule. These chemical alterations include and the aromatic nitro group of Nimodipine molecule to a nitroso group and/or oxidation of the dihydropyridine ring to a pyridine ring leading to manipulations in its activities or potency and generally, loss of its therapeutic action [13]. In order to override the low dissolution rate and the photo-liability formulation problems of Nimodipine, the aims of this study are to improve its photostability as well as enhancing its dissolution rate using liquisolid compacts technology.

II. Materials and Methods

A. Materials

Nimodipine Microcrystalline celullose (Avicel PH-102), Silicon Dioxide (Aerosil 200), Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate, Titanium dioxide, and Mg-stearate are obtained by Hangzhou Hyper Chemicals Limited, China. Propylene glycol (PG) was purchased from Fluka Chemicals AG, Switzerland. PEG-400 obtained from Avon chem, United Kingdom. Tween 80 were purchased from Thomas baker (chemicals) Pvt Ltd, India. Methanol supplied by Avantor performance materials. However, the following instruments were used in this study, tablets compression machine from Korsch EKO, Germany, Hardness tester form Stokes, Monsanto Co. Ltd., USA, Friabilator TAR 120 from Erweka, Germany. Fourier Transform Infrared System (FTIR- 8400 S) form Shimadzu, Japan, Copley Dissolution 8000 Tester from Copley Scientific, UK, HBO Mercury short-arc lamp 200 WATTAGE (High radiant power in the UV and the visible range, dosimeter to calculate the doses in the different UV bands and visible light Oriel Corp., U.S.A, temperature-controlled cooling unit, scanning spectrophotometer Sco tech, spuv-26, Germany.

B. Methods

1) Solubility Studies

Solubility studies of Nimodipine were carried out in PG, PEG 400, and Tween 80 to select the best non-volatile solvent for dissolving of Nimodipine in a liquid vehicle. Saturated solutions were prepared by adding an excess of Nimodipine to the vehicles and shaking using an isothermal shaker water bath at 25 ± 0.5 ^{0}C for 72 hr with constant vibration. Then, the samples were centrifuged at 3000 rpm for 20 min, followed by the collection of the supernatant layer of each sample that was subsequently filtered using a filter membrane (0.45 μm). After filtration, the samples diluted with methanol, and the solubility determined at λ max 238nm by using UV- visible spectrophotometer in a triplicate measurement, and mean reading is taken [14].

2) Use of A Mathematical Model to Design Liquisolid Systems

The formulation design of the proposed liquisolid systems in this study was done according to the mathematical model suggested by Spireas using propylene glycol (PG) as a liquid vehicle, Avicel PH-102 as a carrier material, Aerosil 200 as A coating material and sodium starch glycolate as super-disintegrant [8]. Firstly, the liquid loading factor (Lf) defines the ratio of the weight of liquid medication (W) to the weight of the carrier material (Q) in the formulation. This ratio can be correlated with the flow and the compression properties of the liquisolid system. The liquid loading factor (Lf) can be calculated using the following equation:

$$\mathbf{Lf = W / Q \text{ - - - - -(a)}}$$

Secondly, the excipient ratio (R-value) of the powder is defined as:

$$\mathbf{R = Q / q \text{ - - - - -(b)}}$$

Where R: Ratio of the weight of carrier (Q) and coating (q) materials present in the formulation.

It can also be calculated from the following equation:

L f = ΦCr + ΦCo (1/ R) - - - - -(c)

Where Φ Cr, Φ Co are the flowable liquid retention potentials (Φ – values) of Carrier (Avicel PH-102) and Aerosil 200, respectively. The flowable liquid retention potentials (Φ – values) of powder ingredients were used to calculate the required excipients quantities [15].

3) Preliminary Screening of Optimized R-Value, Drug Concentration, and Loading Factor

Different liquisolid systems were formulated according to the earlier mentioned equations (a, b and c), denoted LS1 to LS7 using the calculated R values 15, 20, 25, 30 and 35:1. The concentration of the drug in the liquid vehicle was 30% (w/w) in the first five formulations, while the concentration was set at 15% (w/w) in LS6 and 45% (w/w) in LS7. The composition of different liquisolid formulas with different R values are shown in table (1). Firstly, a mathematically calculated quantity of pure drug based on the formerly listed equations was weighed in a 20 ml beaker then the calculated weight of non-volatile solvent (PG) was added. The mixture was heated to 60 ºC in sonicator for 15 minutes until a liquid medications' homogenous solution was achieved. Subsequently, the obtained liquid medication (drug and solvent) was incorporated into the calculated quantity (Q) of the carrier material (Avicel PH-102) and (q) coat material (Aerosil 200) and were mixed thoroughly using a porcelain mortar and pestle. The resulted blend was mixed with super-disintegrant. F cylindrical finally, the final blend was lubricated with 1% magnesium stearate to be compressed into a cylindrical tablet using a single punch tablet machine of 6 and 8mm die size [16]. The optimized R-value, drug concentration, and Lf were determined according to the flow properties.

Table (1): Composition of different nimodipine liquisolid compact tablet formulas

Liquisolid System Material (mg)	LS1	LS2	LS 3	LS4	LS5	LS6	LS7
Nimodipine (NIM)	30	30	30	30	30	30	30
Drug concentration in PG (% w/w)	30%	30 %	30%	30 %	30 %	15%	45 %
Carrier : coating ratio (R)	15	20	25	30	35	35	35
Loading factor (Lf)	0.38	0.32	0.29	0.27	0.25	0.25	0.25
Liquid vehicle (PG) (mg)	70	70	70	70	70	170	33.6
Carrier (Q) Avicel PH-102	184.2	218.7	241.3	259.2	280	680	146.4
Coating material (q) Aerosil	12.2	10.93	9.65	8.64	8	19.4	4.18
Sodium starch glycolate SSG (5%)	14.82	16.48	17.54	18.39	19.4	45	10.8
Magnesium stearate (1%)	3.14	3.46	3.72	3.9	4	9.45	2.27
Total weight	314	346	372	390	412	954	230

4) Flow Properties of The Prepared Liquisolid Powder System

a) Determination of The Angle of Repose

For the prepared liquisolid system powder, the repose evaluation approach was considered for the assessing flow properties of the resulted powders. The repose angle was determined using the fixed funnel method through permitting the powder to flow throughout a glass funnel, passing freely onto a surface. The height and diameter of the resultant cone were eventually measured, and the angle of repose was calculated with the following equation:

tan (θ) = h/r - - - - - (d)

where: **h** is the height of the powder cone, and **r** is the powder of (17).

b) Determination of Compressibility Carr's Index and Hausner's Ratio

To estimate the compressibility of Carr's Index, the powder blends were poured into a measuring glass cylinder, the untapped volume (V_0) was determined, then the tapped volume (Vf) was measured after successive 100 tap cycles until the volume became constant. Carr's index was determined according to the following equation:

Carr's Index=(V_0-Vf)/V_0.100 - - - - - (e)

The Carr's index, closely related parameter; Hausner's ratio was calculated using the equation:

Hausner's Ratio= V_0/Vf - - - - -(f)

Where (V_0) untapped volume and (Vf) tapped volume. If the Hausner's ratio is less than 1.25, there is a good flow, while if Hausner's ratio is more than 1.25, there is a poor flow. However, the addition of the glidant can improve the flowability of the powder [18].

C. Formulation of the liquisolid tablet of nimodipine

After optimizing the formula, blends with optimum (R value, drug concentration, and Lf) were selected for further optimization by formulating to desirable tablets. Seven liquisolid systems batches of Nimodipine (denoted as F1 to F7) were prepared as listed in Table (2). Each batch's fifty tablets were compressed into cylindrical tablets, each containing 30 mg of the drug-using single punch tablet machine of 8mm die size [11]. The formulas (F1-F3) were prepared in order to investigate the impact of different types of super-disintegrants; croscarmellose (CSS), sodium starch glycolate (SSG), and crospovidone (CP) in the concentration of 5 % on the physical properties of the prepared tablets. The formulas (F4-F5) were prepared to investigate the impact of different types of carrier materials Avicel PH-101 and Avicel PH-200, on the physical properties of the prepared tablets. The formulas (F6-F7) were prepared in order to investigate the impact of different types of coating materials Cab-O-sil and titanium dioxide on the physical properties of the prepared tablets. The R-value was set at 35:1, and the concentration of drug in the liquid vehicle was 30% in all formulations.

Table (2): Composition of different Nimodipine liquisolid formulas

Formula No. / Material (mg)	F1	F2	F3	F4	F5	F6	F7	DCT
Nimodipine	30	30	30	30	30	30	30	30
PG	70	70	70	70	70	70	70	------
CSS	19.4 (5%)	-----	-----	------	-----	-----	-----	------
SSG	------	19.4 (5%)	-----	------	-----	-----	-----	------
CP	-----	------	19.4 (5%)	19.4 (5%)	19.4 (5%)	19.4 (5%)	19.4 (5%)	17 (5%)
Avicel PH-102	280	280	280	-----	----=	280	280	280
Avicel PH-101	-----	-----	-----	280	-----	-----	-----	-----
Avicel PH-200	----	-----	-----	------	280	-----	-----	-----
Aerosil 200	8	8	8	8	8			8
Cab-O-sil	-----	-----	------	-----	-----	8	------	-----
Titanium dioxide	-----	-----	------	------	------	------	8	------
Magnesium stearate (1%)	4	4	4	4	4	4	4	3.4
Total weight	412	412	412	412	412	412	412	338

D. Preparation of Directly Compressible Tablets of Nimodipine

A Nimodipine's conventional tablets formulation as directly compressed tablets (DCT), was prepared by utilizing the following components without the addition of any non-volatile liquid solvent; drug, carrier, coating material, super disintegrant, and lubricant. The preparation process involved mixing of the drug with Avicel PH-102 and Aerosil 200 (ratio of Avicel PH-102 to Aerosil 200 was set at 35:1) for 10 minutes. The resulted blend was subsequently mixed with crospovidone (as disintegrating agent) for 10 minutes, then magnesium stearate was added and mixed for 2 minutes. The obtained final mixture was directly compressed using a single punch-tableting machine 8mm die size [19].

E. Post-Compression Evaluation of Nimodipine Liquisolid Tablets:

1) Hardness Test

Three tablets were randomly selected from each tablet batch for hardness determination using a hardness tester apparatus (Monsanto). The mean of three determinations ± SD expressed as a force in kg/cm2 required to crush the tablets was recorded [20].

2) Friability Test

Friability test was performed using Roche friabilator apparatus in order to evaluate the effect of friction and shocks, which may often cause tablets to chip, cap or break. Ten tablets were initially weighed (W initial) and placed in the friabilator that was operated at up to 100 revolutions. The tablets were weighed again (W final). The percentage friability expressed as a percentage (%) was calculated using the underlying equation (g). Friability of tablets less than 1% are considered acceptable [21].

% Friability = {(W initial- W final) / W initial} x 100 % - - - - (g)

3) Content Uniformity Test

Ten randomly elected tablets from each batch were grounded in mortar into a fine powder then 30 mg of Nimodipine equivalent powder mass was transferred into a 100 ml volumetric flask. The volume was completed to 100 ml with methanol. The solution was sonicated with intermittent shacking for 1 hr of sonication then filtered., the solution was analyzed for drug content at λ max 238nm after the desired dilution, then the drug concentration was calculated by using methanol calibration curve equation [22].

4) In-Vitro Dissolution Studies of Nimodipine Liquisolid Tablets

The in-Vitro dissolution studies were carried out using USP apparatus type I at 50 rpm using a dissolution medium consist of 0.5 % SLS in water maintained at 37°C. At different time intervals, the drug was determined by measurement of its concentration in a solution using UV-Visible Spectrophotometer at 238nm. Then, the in-vitro drug release profile of all batches was compared with that of the conventional formulation and directly compressed tablets for drug release. The mean of six determinations was considered [23].

5) Photostability Testing

The photostability testing of drug substances and products is conducted according to ICH Q1B guideline. The drug substance and fifty tablets from each conventional and formulations of liquisolid compacts tablets of different coating materials (F5, F6 and F7) were irradiated to deliver a dose of 0.55 $W/m^2/h$ visible light, 50 $W/m^2/h$ UVA, and 0.27 $W/m^2/h$ UVB for 12 h at 15 cm distance from the light source as measured by the dosimeter representing 0.64 kJ/m^2 visible light, 6.47 kJ/ m^2 UVA and 0.04 kJ/ m^2 UVB for different time intervals (0, 0.5, 1, 2, 3, 4, 6, 8 and 12 h). All samples were irradiated in triplicate at 25°C using temperature-controlled cooling unit [9].

F. Fourier Transform Infrared Spectroscopy (FTIR)

This test was performed to identify any sign of complexation and interaction between Nimodipine and other excipients used in the preparation of liquisolid tablets. The samples were grounded and mixed with potassium bromide (KBr), and the spectrum was obtained within the interval of the wave number of 4000-400 cm^{-1} [24].

G. Statistical Analysis

The experiments' results were presented as a mean of triplicate samples ± standard deviation and analyzed with one-way analysis of variance (ANOVA) at the level of ($P < 0.05$).

III. Results and Discussion

The solubility of Nimodipine in various liquid vehicles listed in the table (3) shows that the solubility of Nimodipine was markedly increased in PG($P < 0.05$). This effect may probably be attributed to the low viscosity (48 mPa s) and molecular weight (76.1g/mol) of the utilized PG as compared to tween 80 that has high viscosity (425 mPa s) and molecular weight (1310 g/mol) besides, to the hydrogen bonding producing capability of the alcoholic PG attributed to its multiple hydroxyl groups. Accordingly, among the tested non-volatile solvents, PG could be a better choice as a

solvent for the formulated liquisolid systems of Nimodipine as more solubilizing vehicle [25, 26].

Table (3): Solubility of Nimodipine in various solvent

Solvents	Solubility (%w/w) [Mean ± S.D.*]
Propylene glycol (PG)	5.122 ± 0.0546
PEG 400	1.873 ± 0.1162
Tween 80	0.135 ± 0.0972

*S.D. Standard deviation from the mean. n=3

Furthermore, the estimated Carr's index, Hausner's ratio, and angle of repose parameters determining the flow properties of the prepared preliminary liquisolid systems were listed in the table (4). However, the required amounts of excipients for the formulation of the prepared liquisolid formulas of Nimodipine and the flowable liquid retention potentials (Φ-values) of the utilized powder excipients was calculated using **a, b,** and **c** equations. Flowable liquid retention potentials for Avicel PH-102 and Aerosil 200 in PG were (0.16, 3.33), respectively [27]. The powder flowability is a critically important to point "rate-limiting step" in the formulation of the liquisolid system. Otherwise, weight variation may occur. Obviously, according to Lf values reveled table (4), decreasing the liquid loading factors (Lf), has enhanced the powder flow. In addition, since it is hard to prepare a formulation with good flowability and compatibility when the loading factor is above 0.25, because fewer amounts of carrier and coating materials are used during preparation of these formulations, and excess liquid is not completely adsorbed, leading to the formation of agglomerates. A reasonable flow was achieved when the liquid load factors (Lf) equal to or lower than 0.25, which is in agreement with what was reported in the literatures [28]. Besides, it was found that there is a relationship between Lf and the flow properties of the prepared liquisolid system powder blends, liquisolid systems with low Lf values have better flow properties. This can be explained by the fact that the liquisolid systems with high Lf values contain high amounts of liquid and low powder excipients quantities according to the equation (Lf = W/Q). In contrast, the liquisolid systems with low Lf values contain high amounts of the carrier material (Avicel PH-102) and low liquid vehicle quantities. The R-value of 35:1 was the optimum one as revealed by data listed in the table (1).

Regarding the angle of repose and the flowability of the formula data listed in the table (4) reveals that the increase in the concentration of drug in the in the vehicle (LS6, LS5 and LS7) of inclining drug concentrations 15%, 30% and 45%, respectively, causes a reduction in the angle of repose and increase in the flowability of the formula. The angle of repose was (47.84) in the formula LS6 ~~as~~ compared to that formula LS5 and LS7, which equal to 33. This result can be explained by the too much liquid vehicle amount produced very soft and sticky compacts [29]. While the powder admixture of the formula LS6 was aggregated with some segregation noticed during powder mixing, the powders for the formulas LS5 and LS7 liquisolid formulations appeared as fine powder. According to the flow properties shown in table(4), the formula LS5 was chosen for further optimization through to liquisolid formulation as a tablet using R value equal to 35:1 and drug concentration of 30% in the liquid vehicle. The corresponding Lf value can be calculated using equation **(h)**. The appropriate quantities of Avicel PH-102 (Q) and Aerosil 200 (q) required to convert the required amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system were calculated using equations **a, b** and the following equation:

Lf =0.16 +3.31 (1/R) for PG ----- (h)

were 0.16 and 3.33 flowable liquid retention potentials (Φ-values) for Avicel PH-102 and Aerosil 200 or silica (cab-O-sil) in PG, respectively.

Table (4): Flow properties of the prepared liquisolid systems of nimodipine

Liquisolid System	Angle of Repose*	Type of Flow	Carr's Index*	Type of Flow	Hausner's Ratio*	Type of Flow
LS1	44.52 ± 0.48	Pass	25.64 ± 0.60	Pass	1.33 ± 0.004	Pass
LS2	43.89 ± 1.21	Pass	23.49 ± 0.84	Pass	1.33 ± 0.016	Pass
LS3	40.25 ± 1.32	Pass	25.45 ± 1.52	Pass	1.31 ± 0.028	Pass
LS4	39.63 ± 0.65	Fair	23.74 ± 0.31	Pass	1.28 ± 0.004	Pass
LS5	33.81 ± 0.94	Good	16.20 ± 0.41	Fair	1.22 ± 0.004	Fair
LS6	47.84 ± 0.90	Poor	28.32 ± 0.78	Poor	1.40 ± 0.012	Poor
LS7	33.10 ± 0.53	Good	16.80 ± 1.14	Fair	1.20 ± 0.028	Fair

*S.D. standard deviation from mean. n=3

The post-compression parameters values, like hardness, friability, and content uniformity listed in the table (5), have shown that the formulated liquisolid tablets measured hardness values within the range of 3.70 to 4.63 kg/cm^2. However, the percentage of friability was less than 1% for all formulations, ensouringg the formulated tablets' optimum mechanical stabilit. The percentage of drug content for all of the formulas was found in the range of 96.2-100.6%, which complies with the USP limits.

Table (5): Hardness, Friability and Content Uniformity Percentage of Nimodipine Liquisolid Tablets

Formula code	Hardness (Kg/cm^2) mean ± S.D, n=3	% Friability (w/w)	% Content Uniformity mean ± S.D, n=10
F1	4.63 ± 0.20	0.73	100.6±3.40
F2	3.83 ± 0.05	0.56	97.6 ±2.24
F3	4.21± 0.26	0.86	98.6 ±3.15
F4	3.70 ± 0.17	0.44	100.4±2.96
F5	4.36 ± 0.11	0.69	97.4±2.68
F6	3.92± 0.15	0.72	98.9 ± 2.37
F7	4.05 ± 0.07	0.29	97.8±2.59
DCT	4.29 ± 0.29	0.64	96.2±2.23

Interestingly, the dissolution profile of the different formulations Nimodipine liquisolid tablets and directly compressed tablets modeled in figure (1) reveals that the

tablets prepared with CP show a significantly faster dissolution ($p<0.05$) than the corresponding tablets prepared with CCS or SSG. This enhancement in dissolution can probably be attributed to the solid support's porous morphology that tends to absorb water by a 'wicking' mechanism when exposed to water without a considerable swelling. Thus, it may enhance the the hydrophobic drug's wettability with a little tendency to gel formation [30]. Besides, it can be concluded that formulas prepared with super-disintegrant CSS show the lowest dissolution behavior than CP and SSG, that may be attributed to the swelling nature of CCS, that is typically has a unique fiber shaped morphology. Besides, these individual fibers can act as hydrophilic channels to absorb water deeply into the system, lending to swell to the extent of more than 100% of their original diameter when exposed to water.

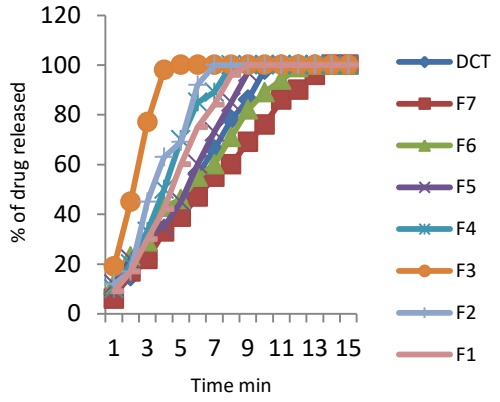

Figure (1): In-vitro dissolution profile of nimodipine liquisolid tablets and direct compressed tablets DCT (results are expressed as mean, n=6)

The resulted wetting caused a tremendous volume increase in their particle diameter could serve as an impediment for the drug to release [31].

Accordingly, a significant effect on dissolution with different microcrystalline cellulose type (Avicel) have been noticed within the prepared tablets ($p<0.05$). The formula prepared with Avicel PH-102 shows better dissolution properties compared to the formula prepared with Avicel PH-101 and 102. This due to the sensitivity of Avicel types to lubricant, which depends on the particle size. The Formula containing Avicel PH-102 with a mean particle size of 100µ has a surface area less than Avicel PH-101 " with a mean particle size of 50µ". Thus, the effect of hydrophobic lubricant on the coarse particles of Avicel PH-102 with a smaller envelop surface area is more prominent than that on the fine particles of Avicel PH-101 with a larger surface area [32].

Remarkably, the formula containing Aerosil 200 has shown a significantly higher percent release of Nimodipine ($p<0.05$) in comparison to the formula containing silica (Cab-O-sil), making it a better coating material as it facilitates the faster release of the drug than silica (Cab-O-sil). However, through comparing these two grades of silicon dioxide with particle sizes within the colloidal range, silica (Cab-O-Sil) has produced dispersions of the highest viscosity, while, Aerosil 200 has possessed a lower viscosity. It is hypothesized that the decrease in drug release rate seen with the silica (Cab-O-sil) is attributed to its tendency for viscous gel formation during the dissolution [33].

The directly compressed tablets of Nimodipine have shown the lowest dissolution properties as compared to lquisolid formulas, which can be explained by the fact that Nimodipine is already in solution in PG. Nevertheless, it is carried by the powder particles (Avicel PH-102 and Aerosil 200) at the same time. In accordance, it is reported that when the drug is formulated in the liquisolid system is completely dissolved in the liquid vehicle, is still in a solubilized state even when it is located in the powder substrate hence showing an improved/accelerated release rate due to its markedly increased wettability and surface availability to the dissolution medium [34].

The photostability tests results modeled in Figure (2) reveals that the liquisolid formulations of Nimodipine have produced an improved photostability as specified by the significant increase in the remaining drug percentage after exposure to different light energies for 12 h ($p < 0.05$) as compared to that of the individual "unformulated" active drug as well as the conventional product. The photo-stabilizing effect of liquisolid mixtures is related to the metal oxides, titanium dioxide, and silicon dioxide have been reported to be photoprotective because of their high refractive indices [9, 35]. Formula F7 prepared with titanium dioxide has shown the best photostability due to its high diffraction index, photocatalytic, and UV protective activities in addition to its high light scattering and incident-light reflection capabilities as compared to F5 and F6 formulas, which are prepared with Aerosil 200 and Cab-O-sil, respectively.

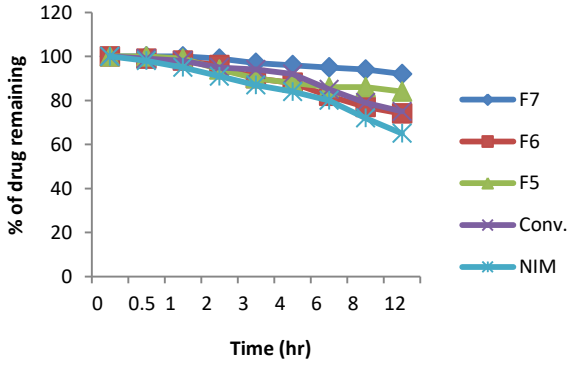

Figure (2): Effect of light on nimodipine stability in liquisolid formulations prepared with three different coating materials, conventional tablets, and pure nimodipine.

Furthermore, there is an observed correlation between the photo-stabilizing action of the liquisolid preparations and the coating materials' refractive indices. In this context, both silicone dioxides (Aerosil 200 and Cab-O-sil) have been reported to have a refractive index of 1.544 at visible wavelengths (632nm), while titanium dioxide has a refractive index of 2.496, under the same conditions at 25 ºC

[9]. The prepared tablet dosage form quality tests, hardness, friability, and content uniformity are listed in the table (5). Notably, all values are within the acceptable limits of USP values.

Finally, the FTIR spectra of pure Nimodipine drug shown in figure (3) revealing the major characteristic functional groups, which are (C-H stretching of benzene ring) at 3097 cm^{-1}, (NH stretching of aliphatic secondary amine) at 3298 cm^{-1}, (NH bending of aliphatic secondary amine) at 1647 cm^{-1}, (C-H asymmetric stretching of methyl) at 2981 cm^{1}, (C-H asymmetric stretching of methylene) at 2933 cm^{-1}, (carbonyl stretching of ester) at 1691 cm^{-1}, (C=C) stretching of benzene ring) at 1622 cm^{-1}, (C-H symmetric stretching of methyl) at 2899 cm^{-1}, (C-H symmetric stretching of methylene) at 2845cm^{-1}, 1523 cm^{-1} and 1496 cm^{-1}, (NO2 symmetric stretching) at 1309 cm^{-1} (NO_2 asymmetric stretching) at 1454 cm^{-1} in accordance with that reported in literature [13]. The prepared liquisolid tablets (F7) powder FTIR spectra shown in figure (4) have revealed the significant characteristics of Nimodipine functional groups present in the spectrum of pure drug. The broad peak belongs to the (OH-stretching of PG) is probably resulted from hydrogen bond formation between PG and the drug. This spectral alteration indicates that there is a potential drug–excipient compatibility between all components of prepared Nimodipine liquisolid tablets.

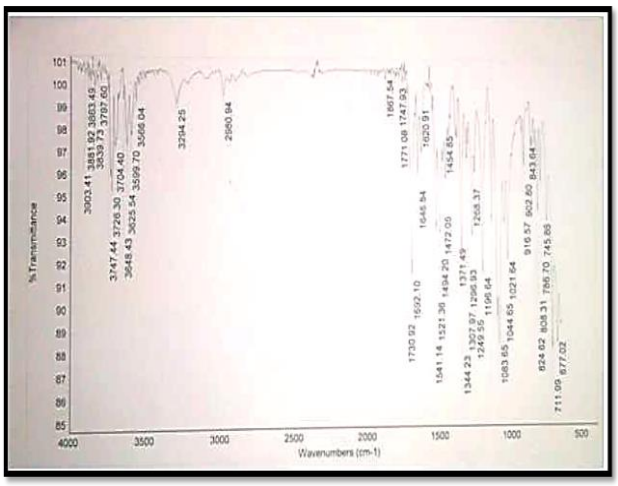

Figure 3: FTIR spectrum of pure nimodipine powder

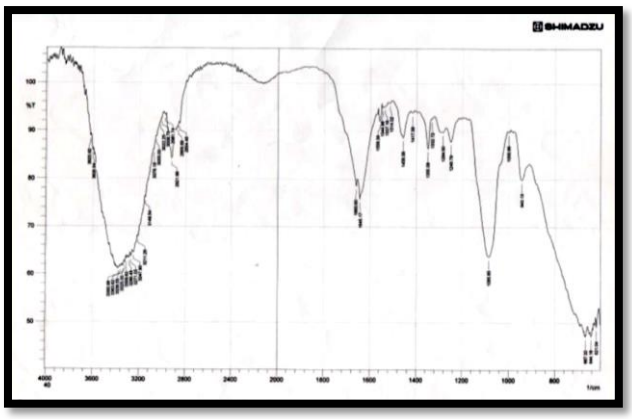

Figure 4: FTIR spectrum of nimodipine liquisolid formula

IV. Conclusion

In this study, a liquisolid compacts tablets of Nimodipine prepared at different coating materials, carriers, and super disintegrants in addition to carrier/coat ratios. The best proposed suitable carrier/coat ratio in the prepared liquisolid tablets is up to 35, resulting in satisfactory physicochemical properties. Among all of the used super-disintegrant, the formulations containing crospovidone as super disintegrant is fulfilling one with a satisfactory collection of parameters. While, among all of the used carriers, Avicel PH-102 was the best one as compared to the others. Finally, the degradative effect of light against Nimodipine is significantly inhibited with such type of liquisolid compacts technique type formulation. Such photoprotective effect of liquisolid formula is maintained by the incorporated coating materials due to their high refractive indices. Titanium oxide is the best photo-protectant as compared to the other used coating materials. Hence, it can be concluded that the liquisolid compacts technique is a promising approach for the improvement of photostability of the drug products that is sensitive to the light besides significantly increasing the drug dosage form dissolution rate.

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References

1. Giuseppina I., et al., (2017), "Photosensitive drugs: A review on their photoprotection by liposomes and cyclodextrins." *Drug delivery*, 24(2): 33-44.

2. Lindsay R S.., et al., (2013), "Effects of ultraviolet radiation, visible light, and infrared radiation on erythema and pigmentation: a review." *Photochemical & Photobiological Sciences*, 12 (1): 54-64.

3. Piechocki JT, Thoma K. (2006). Pharmaceutical photostability and stabilization technology. New York: CRC Press.

4. Tønnesen HH. (2004). Photostability of drugs and drug formulations. New York: CRC Press

5. Ioele G., De Luca M., Garofalo A., Ragno G., (2017) “Photosensitive drugs: a review on their photoprotection by liposomes and cyclodextrins,” DRUG DELIVERY, 24(2): 33–44.

6. Urvashi B. P., Shah C., Patel M. H. , (2018), "Liquisolid compacts: an effective approach towards enhancement of dissolution rate of poorly soluble drugs." *Pharma Science Monitor*, 9(2) : 115-121.

7. Mei L., et al., (2017) "Liquisolid technique and its applications in pharmaceutics." *Asian journal of pharmaceutical sciences*, 12(2): 115-123.

8. Spireas S., Bolton M., (1999), "Liquisolid systems and methods of preparing same". *US Patents*, 5(968) : 550.

9. Ayalasomayajula L. U., (2016), " Formulation and evaluation of atenolol orodispersible tablets by co-processed super-disintegration process." *Int J Adv Pharm*, (5) :46-51.

10. Daniele, T., et al., (2008), "Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies." *Clinical and experimental hypertension*, 30(8) : 744-766.

11. Yang, Z., et al., (2014), "Solid dispersion in the development of a nimodipine delayed-release tablet formulation." *Asian journal of pharmaceutical sciences*, 9(1): 35-41.

12. https://en.wikipedia.org/wiki/Nimodipine.

13. Yuki, K., et al., (2008), "Photochemical stabilities of some dihydropyridine calcium-channel blockers in powdered pharmaceutical tablets." *Journal of pharmaceutical and biomedical analysis* 47(3): 618-624.

14. Mowafaq M. G., Neamah A. J., (2017), "Formulation and characterization of nimodipine nanoemulsion as ampoule for oral route." *International Journal of Pharmaceutical Sciences and Research*, 8(2) : 591.

15. Elkordy A. A., Tan X. N., Essa E. A., (2013), "Spironolactone release from liquisolid formulations prepared with Capryol™ 90, Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles". *Eur J Pharm Biopharm*, (83) :203-23.

16. Karmarkar A. B., Gonjari I. D., Hosmani A. H., Dhabale P. N., Bhise S. B., (2009), "Dissolution rate enhancement of fenofibrate using liquisolid tablet technique". *Lat Am J Pharm*, (28) :219-25.

17. Varshosaz J., Minayian M., Ahmadi M., Ghassami E., (2016), "Enhancement of solubility and antidiabetic effects of Repaglinide using spray drying technique in STZ-induced diabetic rats." *Pharmaceutical Development and Technology*, 21(6) :1-10.

18. Lu M, Xing H, Yang T, Yu J, Yang Z, Sun Y, Ding P. Dissolution enhancement of tadalafil by liquisolid technique. Pharmaceutical Development and Technology. 2016;21(6) :1-13.

19. Fu J., et al., (2011), "Nimodipine (NM) tablets with high dissolution containing NM solid dispersions prepared by hot-melt extrusion." *Drug development and industrial pharmacy*, 37(8) :934-944.

20. Malke S, Shidhaye S, Kadam V., (2009), "Novel melt granulation using sugars for metoclopramide hydrochloride orally disintegrating tablet". *Asian J Pharm Clin Res,*(2) :68-72.

21. Bayrak Z., Tas C., Tasdemir U., Erol H., Ozkan C. K., Savaser A., et al., (2011), " Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation" *Eur J Pharm Biopharm*, (78) :499-505.

22. Neha D., Kirti P., (2019), "Formulation and evaluation of nimodipine tablet by liquisolid technique." *International journal of trend in scientific research and development*, (3):739-745.

23. Ahmed K., (2013), "Liquisolid technique: a promising alternative to conventional coating for improvement of drug photostability in solid dosage forms." *Expert opinion on drug delivery* 10(10): 1335-1343.

24. Kamal D., Kavita P., MV Ramana M. V., (2010), "Preparation, characterization and in vitro evaluation of aceclofenac solid dispersions." *ARS Pharm*, (51), :57-76.

25. Raymond C., Paul J., Sian C, (2009), "The Handbook of Pharmaceutical Excipients.", *Pharmaceutical Press and American Pharmacists Association*; p:592.

26. Khanfar M, Sheikh Salem M, Kaddour F. Preparation of sustained-release dosage form of Venlafaxine HCl using liquisolid technique. Pharmaceutical development and technology. 2014;19(1):103-115.

27. Karmarkar A. B., Gonjari I. D., Hosmani A. H., Dhabale P. N., Bhise S. B., (2009), "Dissolution rate enhancement of fenofibrate using liquisolid tablet technique. Part II: evaluation of in vitro dissolution profile comparison methods*". Lat Am J Pharm*; 28(4):538-543.

28. Singh S. K., Prakash D., Srinivasan K. K., Gowthamarajan K., (2011), "Liquisolid compacts of glimepiride: an approach to enhance the dissolution of poorly water-soluble drugs." *J Pharm Res*., 4(7):2263-2268.

29. Nokhodchi A., Aliakbar R., Desai S., Javadzadeh Y., (2010), "Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release.", *Colloids and Surfaces B: Biointerfaces*.;79(1):262-269.

30. Ehsan A. M., Al Hammad A. B., (2013), "Formulation and evaluation of rosuvastatin orodispersible tablets." *International Journal of Pharmacy and Pharmaceutical Science*; 5(2):339-346.

31. Rajesh Y. V., Rekha N. B., Newton A. M., (2010), "Role of type and concentration of super disintegrants on immediate-release tablets of Ezetimibe." *An International Journal of Advances in Pharmaceutical Sciences*.;1(2) :264-281.

32. Thoorens G., Krier F., Leclercq B., Carlin B., Evrard B., (2014), "Microcrystalline cellulose, a direct compression binder in a quality by design environment-A review.", *International Journal of Pharmaceutics*, 473(1):64-72.

33. Albertini B., Passerini N., González-Rodríguez M. L., Perissutti B., Rodriguez L., (2004), "Effect of Aerosil® on the properties of lipid controlled release microparticles.", *Journal of Controlled Release*.,100(2) :233-246.

34. Javadzadeh Y., Shariati H., Movahhed-Danesh E., Nokhodchi A., (2009), "Effect of some commercial grades of microcrystalline cellulose on flowability, compressibility, and dissolution profile of piroxicam liquisolid compacts." *Drug development and industrial pharmacy*; 35(2):243-51.

35. Antoniou C., Kosmadaki M. G., Stratigos A. J., et al., (2008), "Review article: sunscreens-what's important to know.", *J Eur Acad Dermatol Venereol*; (22):1110-18.