Research Article

Comparative Study between Liquisolid Compacts, Liquisolid Microsystem and Solid Dispersion Technology for the Preparation of Immediate Release Nicardipine Tablets

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Received: 07-01-2017; **Revised:** 28-02-2017; **Accepted:** 15-03-2017.

ABSTRACT

Liquisolid technology is a new concept for drug delivery that can improve dissolution of poorly soluble drugs. Nicardipine is class ll drug had low bioavailability mainly due to its poor dissolution. In this work, immediate release tablets of nicardipine had been prepared using liquisolid (F1-F11), liquisolid microsystem (MSF1-MSF6 and MSF10) and solid dispersion (SD1-SD6) technologies then comparing their pre-compression, post-compression and in-vitro dissolution profiles, in addition to X-ray, DSC and SEM analysis. It was found that optimum liquisolid formula (F10) and liquisolid microsystem (MSF3) showed significantly higher flowability, compressibility parameters and higher dissolution rate than solid dispersion formula (SD2) since the drug is in the solubilized form and completely in the amorphous state which provides greater surface area for drug dissolution. While the lowest dissolution rate was for the formula prepared by direct compression method and the marketed tablet. This study also showed that liquisolid microsystem compacts showed increase in drug loading capacity due to the presence of PVP and reducing the amount of additives significantly thus reducing the total weight of the tablet to more than half which improve patients compliance and economic feasibility.

Keywords: Nicardipine, liquisolid, microsystem, solid dispersion and immediate release.

INTRODUCTION

Oral drug delivery is considered as the most preferable route for chronic treatment of various diseases, due to its greater stability, flexibility in formulation, dosage accuracy, low cost of manufacturing, packaging and patient friendly administration.[1] Since most of the drugs are poorly water soluble and suffering from poor dissolution and it is worst if given in the form of solid dosage forms like tablets.[2]

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug such as micronization, adsorption onto high surface area carriers, lyophilisation, co-grinding, formulation of inclusion complexes, solubilisation by surfactants, solid dispersions, hydrotrophyand liquisolid technology .[3]

Liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution into dry, non-adherent, free-flowing and compactible powder mixturesthat can be compressed into tablet or filled in hard gelatin capsules. This technology has also been used to enhance the dissolution rate of poorly water soluble drugs. This can be achieved by blending the drug with selected carriers and coating materials using non volatile solvent.[4,5]

The selection of non-volatile solvent is a prime factor to be taken in consideration because the presentation of drug in solubilized state depends on the solvent capacity. However, improving patient compliance, economic feasibility, as well as improving drug effectiveness is the main goal for any drug development and industry. Therefore, looking for technology that may achieve such a goal is highly attractive. Involvement of micro system technology in the preparation of liquisolid compacts (named liquisolid micro system) is applied and evaluated in a comparative study with that prepared using conventional liquisolid technology and solid dispersion as well as direct compression in an attempt to improve loading capacity of the polymer and reduce the size of the final product, improve patient compliance with better effectiveness alternative to nicardipine marketed tablet.[6,7]

MATERIALS AND METHODS

Nicardipine was obtained from Aladdin Chemistry Co-Ltd, China. Other materials such as: aerosil 200, PVP, avicel PH 102, Magnesium stearate, Propylene glycol (PG), Tween 80, PEG 400 from Samara drug industry,Iraq.

Mathematical modeling

The concept of liquisolid system stands on two fundamental terms: the flowable (Φ- value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. Depending on the carrier/coating ratio (excipient ratio, R value) of the powder substrate an acceptable flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded.[8]

The liquid/carrier ratio is termed liquid loading factor Lf [w/w] and is defined as the weight ratio of the liquid

formulation (W) and the carrier material (Q) in the system.

Lf = W/Q------ equation (1)

'R' represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

R =Q/q------ equation (2)

Therefore, the optimum liquid loading factor (Lf) required to obtain acceptable flowing and compressible liquisolid systems are equal to either ΦLf or ΨLf, whichever represents the lower value. As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q) and coating (q) material required to convert a given amount of liquid formulation (W) into an acceptable flowing and compressible liquisolid system may be calculated as follows:

Q= W/Lf----- equation (3)

q = Q/R------- equation (4)

Preparation of liquisolid formulas

Nicardipine solubility was estimated (mg/100ml) in various non-volatile solvents (distilled water, 0.1 N HCl (pH 1.2), PG, PEG 400, Tween 80 and Methanol)measured by mean ± S.D. * is (0.00219 ± 0.0028,0.473 ± 0.0035,40.326± 0.271, 5.391 ± 0.193, 1.536 ± 0.214 and 2.217 ± 0.025) respectively. *S.D. standard deviation from mean, n=3.

Accordingly, propylene glycol (PG) was chosen as the best one. Then different powder blends (applying mathematical modeling) containing nicardipine 20 mg as active ingredient solubilized in PG and using Avicel PH 102 (as carrier), aerosil 200 (as coating material) and croscarmellose sodium (CCS) as super disintegrants were prepared according to steps shown in (figure 1). Where the resulting liquid medication (drug and solvent)added to the calculated quantity (Q) of the carrier material (Avicel PH 102) and mixed thoroughly in mortar and pestle. Different carrier: coating ratio (R-value) 15, 20, 25, 30, 35, 40 and 50 were used (table 2). Propylene glycol (PG), polyethylene glycol (PEG400), tween 80 or methanol were used as solvent.[9]

The following mixing process using a porcelain mortar and pestle were applied for all the preparation:

- The first stage; the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute the drug in the non-volatile solvent.
- The second stage; the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and was left standing for approximately 10 minutes to allow the drug solution to be absorbed on the carrier particles.
- In the third stage; the coating material was added with appropriate mixing for 1 minute with one rotation per second then the powder was scrapped off the mortar surfaces by means of an aluminum spatula, and mixed with CCS as superdisintegrant (3%w/w).

The prepared powder (F1-F11) formulas as shown in (tablet 1) were directly compressed in a single punch machine using Mg. stearate as a lubricant .[10,11]

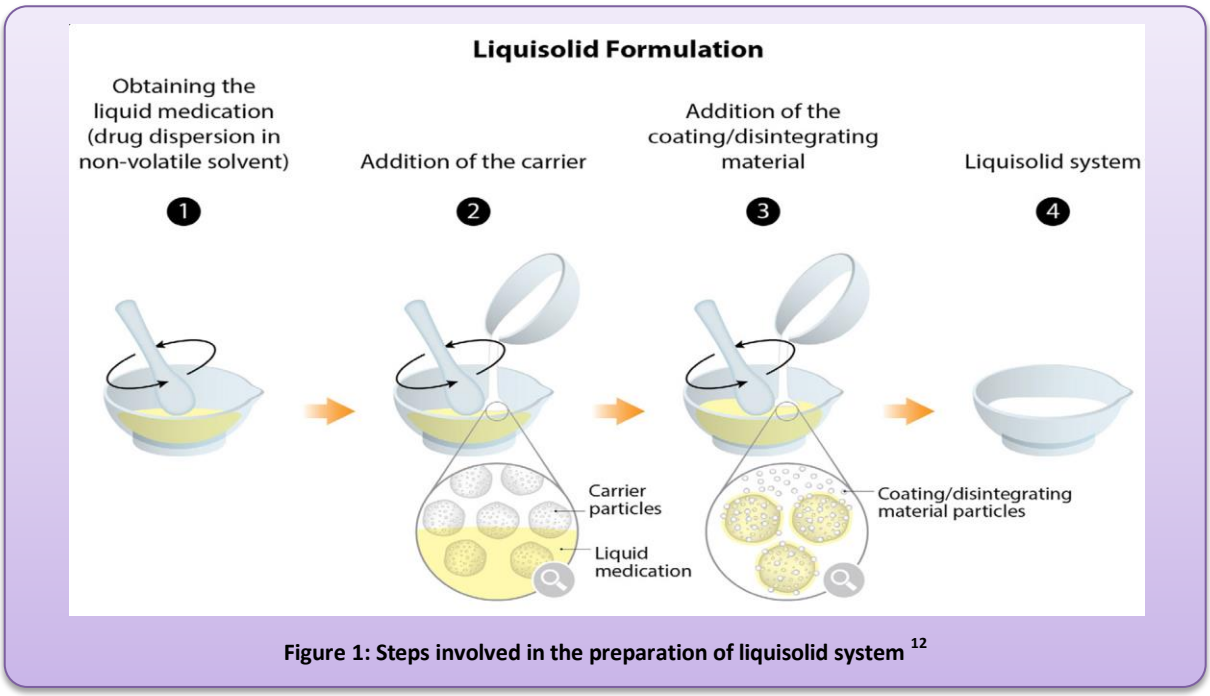


Figure 1: Steps involved in the preparation of liquisolid system [12]

Preparation of liquisolid micro system formulas

In an attempt to improve carrier capacity, microsystem liquisolid formulas (MSF1-MSF6 and MSF10) were prepared by dissolving 20 mg of nicardipine in different amount of PG to which additional additives were added including (PVP, PEG4000) in different proportion as shown in table 2 and the liquid solution obtained were added to the carrier (avicel PH102) placed in a mortar and the procedure proceed as previously mentioned. To the prepared microsystem powder, 3 % ccs was added and compressed into a single punch machine using Mg. stearate as a lubricant.[13, 14]

Table 1: Composition of different nicardipine liquisolid compact tablet and liquisolid microsystem formulas prepared by using propylene glycol (PG) liquid vehicles.

Preparation of liquisolid system									
LS code	Drug conc. (%)	(R ratio)	loading factor (Lf)	Liquid vehicle (mg) (PG)	Weight ratio (w) of liquid formulation	Carrier (Q) (mg)	Coating (q) (mg)	CCS (mg) 3 % w/w	Total weight (mg)
F_1	15	15	0.38	113.33	133.33	350.31	23.35	15.68	522.68
F_2	15	20	0.33	113.33	133.33	409.61	20.48	17.43	580.85
F_3	15	25	0.29	113.33	133.33	455.98	18.24	18.79	626.34
F_4	20	15	0.38	80	100	262.74	17.52	11.76	392.02
F_5	25	15	0.38	60	80	210.19	14.01	9.41	313.62
F_6	30	15	0.38	46.67	66.67	175.17	11.68	7.84	261.36
F_7	35	15	0.38	37.14	57.14	150.13	10.01	6.72	224.00
F_8	40	15	0.38	30	50	131.37	8.76	5.88	196.01
F_9	40	20	0.33	30	50	153.61	7.68	6.53	217.83
F_{10}	40	25	0.29	30	50	171.00	6.84	7.05	234.89
F_{11}	50	15	0.38	20	40	105.10	7.01	4.70	156.81
DCT	-	-	-	-		208.5	8	12.5	253
Preparation of liquisolid microsystem									
MSLS code	Drug conc. (%)	(R ratio)	loading factor (Lf)	Liquid vehicle (mg) (PG)	Carrier (Q) (mg)	Coating (q) (mg)	CCS (mg) 3 % w/w	Additives 12%	Total weight (mg)
MSF1	15	15	0.38	33.99	105.09	7.01	4.70	23.295PVP	194.09
MSF2	15	20	0.33	33.99	122.88	6.14	5.23	25.669PVP	213.91
MSF3	15	25	0.29	33.99	136.79	5.47	5.64	27.515PVP	229.41
MSF4	20	15	0.38	24.00	78.82	5.25	3.53	17.944PEG 4000	149.55
MSF5	20	20	0.33	24.00	92.16	4.61	3.92	19.726PEG 4000	164.42
MSF6	20	25	0.29	24.00	102.57	4.10	4.23	21.055 PEG 4000	175.95
MSF10	40	25	0.29	15.00	85.50	3.42	3.52	17.377 PVP	144.81

Preparation of solid dispersion tablets

Solid dispersion formulas (SD1-SD6) were prepared using solvent evaporation method by dissolving 20 mg of nicardipine in methanol to which carrier were added including (PVP, PEG4000) in different drug proportion (1:3), (1:5), (1:7) with continuous stirring then evaporated to get solid material which was pulverized and milled then diluent (avicel PH102) were added to solid dispersion powder and mixed together for a period of 10 minutes. The mixture was mixed with croscarmellose sodium (as disintegrating agent) for 10 minutes . Talc powder and Mg. stearate were added and mixed for 5 minutes as shown in (table 2).[15]

Table 2: Formulation of solid dispersion and solubility of nicardipine with different carriers (PVP & PEG 4000).

Solid dispersion	Carrier	Ratio of drug: carrier	Solubility in 0.1 N HCl ±standard deviation
SD1	PVP	1:3	0.983 ±0.034
SD2	PVP	1:5	1.151 ±0.019
SD3	PVP	1:7	1.029 ±0.017
SD4	PEG 4000	1:3	0.743 ±0.041
SD5	PEG 4000	1:5	0.811 ±0.037
SD6	PEG 4000	1:7	0.721 ±0.021

According to solubility result in 0.1N HCl, SD2 was selected as the best one and compressed on single punch tablet machine. Sufficient compression load was applied in order to produce tablets with the hardness of 5–7 Kg .[16]

Flowability and compressibility parameters evaluation

Various micrometrics' parameters studies including angle of repose, Carr's index and Hausner's ratio for liquisolid formula (F1-F11), liquisolid microsystem formulas (MSF1-MSF6 and MSF10), the selected formula of solid dispersion (SD2) and powder formula for direct compression were estimated.[17]

Post-compression parameters evaluation

The prepared tablets of liquisolid formulas, liquisolid microsystem formulas and selected solid dispersion SD2 tablets were evaluated applying the following tests:[18]

-Thickness test done by Vernier instrument (Copley, UK).

-Hardness test done bytablet hardness tester (Guoming, India).

-Friability test done by friabilator (Vanguard, USA)

-Weight variation test.[19]

- In-vitro dissolution test: [20]

In-vitro dissolution of the prepared tablets was performed using USP apparatus type II (paddle) at 37 ± 0.5°C in 900 ml dissolution medium (HCl solution pH1.2) at 50 rpm. Then, the withdrawn samples were filtered and analysed spectrophotometrically at λ max 240 nm. Each test was done in triplicate.

Variables affecting the dissolution profile of nicardipine from liquisolid, liquisolid microsystem tablets

A- Effect of drug concentration

Different concentrations of drug in liquid vehicle (15 %, 20 %, 25 %, 30 %, 35 % ,40% and 50%) for each formula (F1, F4, F5, F6, F7, F8 and F11) were used in preparing liquisolid tablet to assess the effect of drug concentration on the release of nicardipine in comparison to that prepared by directly compression (DCT) method. The same was applied for liquisolid microsystem formulas MSF3, MSF6 and MSF10 containing (15%, 20% and 40% of nicardipine).

B- Effect of carrier: coating ratio (R-ratio)

Formulas F8, F9 and F10 were prepared containing respectively different carrier: coating ratio(15:1,20:1,25:1) keeping drug concentration in liquid vehicle constant (40%).For liquisolid microsystem formulas; MSF1, MSF2 and MSF3 were prepared containing respectively different carrier: coating ratio (15:1,20:1,25:1) keeping drug concentration in liquid vehicle constant (15%). All these formulas were compared to tablets prepared by direct compression method.

C- Effect of superdisintegrants type

Formula 10 was re-prepared to contain croscarmellose, sodium starch glycolate and crosspovidone each one separately as superdisintegrant to study their effect on percent drug release.

D- Effect of superdisintegrant concentration

3%,5%,7% of croscarmellose sodium were used in order to choose the best concentration that gave the appropriate release of nicardipine from selected liquisolid tablet dosage form (F10).

E- Effect of liquid vehicles type

The selected formula (F10) prepared using PG as vehicle, is re-prepared using PEG400 and Tween 80 as vehicle to study the effect of liquid vehicle type on release of nicardipine from their tablets.

DSC, X-ray and scanning electron microscope analysis

For the selected formula (F10), selected liquisolid microsystem (MSF3), selected formula for solid dispersion (SD2) and powder formula for direct compression (DCT), in addition to pure drug and physical mixture of the components, the following analysis were applied; X-ray diffractometry (XRD) (Shimadzu 6000, Japan), DSC (DSC-6, shimadzu, Japan), and SEM (Tescanvegalll, Czech) .[21]

Statistical analysis

All data were presented as mean ± SD. Statistical analysis was performed by applying Graph Pad Prism Version 7 by choosing one-way ANOVA, followed by Tukeys test (pairwise comparisons) at 95% significance ($p<0.05$).

RESULT AND DISCUSSION

Pre-compression evaluation: Flowability and compressibility parameters evaluation

The powder flowability is critical point in preparation of solid dosage forms to ensure an acceptable content uniformity of drug dose.From theresult shown in table 3; the liquisolid formulas (F1-F11) showed reduction in the angle of repose, Carr's index and Hausner ratio which indicate acceptable flowability of the formula. Accordingly, these formulas (F1-F11) were used for further study. Formulas for liquisolid microsystem (MSF1, MSF2, MSF3, MSF5 and MSF6) showed better flowability and compressibility properties than the conventional liquisolid formula (F1-F11) this could be attributed to the presence of PVP that causes reduction in the weight of excipients added, while MSF4 showed a little increase in the angle of repose, Carr's index and Hausner ratio indicating less flowing property since this formula has different carrier: coating ratio. Good flowability is also obtained for solid dispersion selected formula (SD2) and powder prepared for direct compression (DCT).[22]

Post-compression parameters for the prepared tablets:

These tests applied for all tablets prepared by liquisolid system (F1-F11), all liquisolid microsystem formulas (MSF1-MSF6 and MSF10), selected solid dispersion formula SD2, and tablet prepared by direct compression method DCT, in comparison to marketed tablet. The results (table 3) showed that the friability and hardness test of all the prepared tablets lies within the acceptable limits according to B.P indicating that the tablets have acceptable toughness and with stand abrasion during handling, packaging and shipment .The compactness of tablet may be due to presence of avicel PH 102 molecularly dispersed in all prepared formulas and the nature of crystalline cellulose particles of avicel PH 102 that are held together by hydrogen bonding which when compressed are deformed plastically and a strong compact is formed due to the extremely excessive number of surfaces brought in contact during the plastic deformation and strong hydrogen bonds formed.[23]

The percentages of content uniformity for all nicardipine formulas arranged from 95.18 % to 101.17%. This complied with B.P. content uniformity specification.

All the prepared formulas gave acceptable disintegration time (3.19-7.61) min. due to presence of superdisintegrantcroscarmellose sodium (CCS) which accelerate disintegration of tablet by virtue of its ability to absorb larger amount of water when exposed to aqueous environment.Tablet prepared using liquisolid microsystem technique MSF3 was found to have shortest disintegration time (3.19 min.), this may be due to presence of PVP in its content which may inhibit precipitation of drug from the supersaturated solution around drug particles (crystal growth inhibition).While disintegration time of tablets prepared by direct compression (DCT) was 6.13 minutes which is closely to that of marketed tablet . It is obvious that optimum formula tablets prepared by liquisolid microsystem gave acceptable post-compression parameters with shortest disintegration time than that prepared by conventional liquisolid technology, solid dispersion and marketed tablet.[24]

In-vitro dissolution test

Variables affect drug dissolution profile of nicardipine from liquisolid formulas and liquisolid microsystem formulas.

A. Effect of drug concentration in liquid vehicle

Formulas prepared by conventional liquisolid system (F1, F4, F5,F6,F7,F8 and F11) containing different concentrations of nicardipine (15, 20, 25, 30,35, 40 and 50 %) respectively were used keeping carrier: coating ratio constant (15:1). The results demonstrate that increasing the concentration of drug in the liquid vehicle causes elevation in drug release rate in comparison to DCT.[25]

The same observed with liquisolid microsystem were MSF3, MSF6 and MSF10 containing nicardipine (15%, 20% and 40 %) keeping carrier: coating (R ratio) constant in comparison to direct compression tablet (DCT).Generally observed that the least percent of drug release was from tablet prepared by direct compression method ,While those prepared by liquisolid and liquisolid microsystem formulas showed significant higher percent drug release .However, higher percent drug release (85%) obtained from tablet prepared by liquisolid microsystem indicating higher loading capacity by this method.[26]

Table 3: Pre-and post-compression evaluation

Pre-compression evaluation: Flowability and compressibility parameters for powder blend of the prepared formulas for nicardipine						
Formula	**Angle of repose θ (degree)**	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Carr's index**	**Hausner ratio**	**Type of flow**
F1	43.26±0.514	0.418±0.01	0.491±0.03	1.17	14.868	good
F2	29.58±0.428	0.435±0.03	0.482±0.02	1.11	9.751	excellent
F3	33.83±0.516	0.407±0.03	0.484±0.04	1.19	15.909	good
F4	41.32±0.268	0.395±0.04	0.516±0.06	1.31	23.450	passable
F5	40.37±0.396	0.363±0.06	0.468±0.06	1.29	22.436	passable
F6	34.02±0.614	0.416±0.02	0.477±0.02	1.15	12.788	good
F7	43.71±0.357	0.365±0.04	0.475±0.04	1.30	23.158	passable
F8	31.42±0.273	0.424±0.05	0.482±0.01	1.14	12.033	good
F9	30.58±0.489	0.435±0.07	0.491±0.04	1.13	11.405	good
F10	27.69±0.413	0.431±0.02	0.476±0.03	1.10	9.454	excellent
F11	33.93±0.637	0.426±0.05	0.489±0.02	1.15	12.883	good
DCT	34.78±0.571	0.429±0.03	0.493±0.02	1.15	12.982	good
MSF1	32.92±0.428	0.424±0.03	0.481±0.01	1.13	11.850	good
MSF2	31.35±0.616	0.419±0.01	0.488±0.01	1.16	14.139	good
MSF3	33.27±.362	0.413±0.04	0.463±0.04	1.12	10.799	good
MSF4	36.72±0.329	0.438±0.01	0.531±0.03	1.21	17.514	fair
MSF5	31.39±0.489	0.429±0.05	0.482±0.01	1.12	10.996	good
MSF6	34.58±0.526	0.418±0.02	0.465±0.04	1.11	10.108	good
MSF10	29.71±0.528	0.431±0.01	0.476±0.21	1.10	9.454	excellent
SD2	33.64±0.384	0.423±0.01	0.471±0.02	1.11	10.191	good
Post compression evaluation						
Formula	**Hardness (Kg/cm^2)**		**Friability (%)**	**Weight variation**	**Drug content%**	**Disintegration time (min.)**
F1	5.24±0.02		0.39±0.01	99.35±0.01	98.92±0.03	5.44±0.03
F2	6.43±0.07		0.27±0.37	100.27±0.21	99.57±0.03	5.81±0.06
F3	4.16±0.01		0.64±0.47	99.23±0.52	99.84±0.01	5.54±0.42
F4	5.82±0.02		0.67±0.16	99.41±0.13	96.83±0.03	5.86±0.11
F5	4.32±0.09		0.71±0.03	98.22±0.35	99.45±0.01	5.29±0.01
F6	5.82±0.11		0.24±0.19	99.32. ±0.22	97.56±0.16	5.17±0.04
F7	5.91±0.8		0.51±0.05	100.53±23	99.34±0.02	5.59±0.12
F8	5.14±0.08		0.24±0.27	100.12±0.01	96.69±0.29	4.12±0.02
F9	5.73±0.07		0.35±0.28	99.32±0.01	99.55±0.38	4.23±0.14
F10	5.81±0.04		0.64±0.01	99.24±0.012	100.05±0.16	3.97±0.01
F11	4.73±0.12		0.14±0.02	99.18±0.23	99.49±0.06	5.37±0.01
DCT	4.97±0.08		0.18±0.63	99.58±0.01	96.73±0.42	6.31±0.01
MSF1	5.31±0.08		0.37±0.56	99.71±0.15	96.17±0.31	5.27±0.24
MSF2	5.48±0.08		0.23±0.51	99.83±0.01	97.51±0.26	5.41±0.16
MSF3	6.38±0.019		0.28±0.36	99.63±0.24	99.52±0.02	3.19±0.26
MSF4	5.85±0.03		0.32±0.67	99.73±0.16	98.95±0.01	6.57±0.01
MSF5	5.28±0.06		0.37±0.59	99.86±0.01	98.86±0.04	5.86±0.15
MSF6	5.83±0.03		0.21±0.03	99.81±0.02	98.23±0.028	5.06±0.03
MSF10	6.13±0.017		0.26±0.21	99.72±0.02	99.59±0.01	3.61±0.02
SD2	5.72±0.03		0.29±0.02	99.46±0.02	98.59±0.031	6.56±0.04
Marketed tablet	6.34±0.014		0.19±0.04	99.38±0.16	95.18±0.023	6.82±0.01

B. **Effect of carrier: coating (R-ratio):** To study the effect of R-ratio on drug release; F8, F9 and F10 (liquisolidformulas) were prepared containing different R-ratio keeping drug concentration constant.The result showed that upon increasingcarrier: coating ratio the drug release is increased since it increases drug wettability and surface area. The same result observed with liquisolid microsystem formula (MSF1, MSF2 and, MSF3) containing different R-ratio keeping drug concentration constant.All these results compared to drug release from DCT to reveal the effect of presence of carrier. Tablets prepared by liquisolid technology and liquisolid microsystem showed significantly higher drug release from that of tablet prepared by direct compression method (DCT), indicating higher surface area and revealed the effect of presence of carrier.[27]

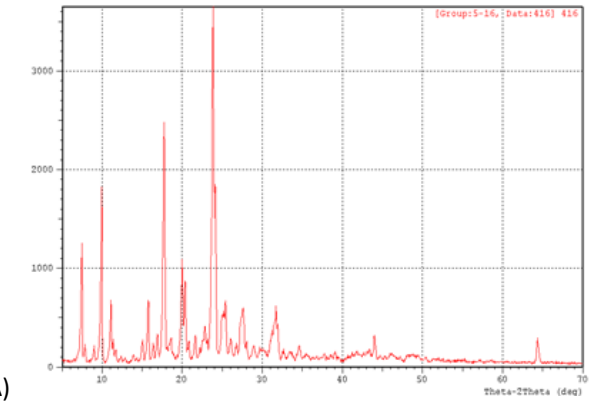
C. **Effect of disintegrant type on dissolution profile:** The result explained the effect of type of superdisintegrantmaterials added to liquisolid selected formula (F10) using croscarmellose sodium, sodium starch glycolate and crosspovidone. The percentage of drug released in the first 20 minutes were 83.58%,42.52% and 47.30% respectively in 0.1 N HCl (pH 1.2); which is significantly different. The highest release may be attributed to the nature and particle size of croscarmellose sodium.Which can uptake more water and causes faster disintegration.

D. **Effect of superdisintegrantconcentration on dissolution profile:** The result show the effect of concentration of croscarmellose sodium as (superdisintegrant materials) that is added to liquisolid selected formula (F10) in different concentration (3%,5%,7%). All formulas showed higher release than that from DCT (which contain 5 % CCS) this is attributed to presence of carrier (avicel PH 102) and liquid vehicle (PG) in liquisolid formulas that enhance drug release.Therefore, the role of carrier used in liquisolid is more predominate than other additives.[29]

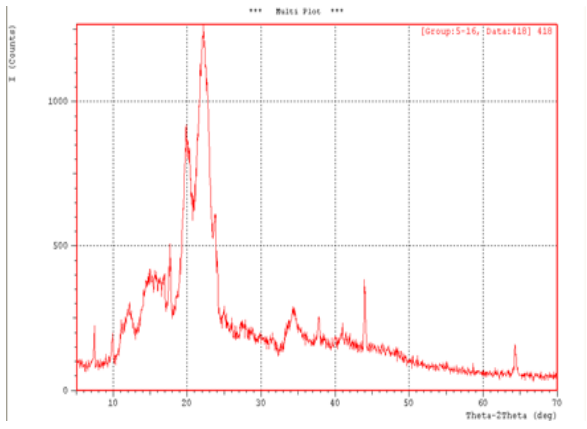
E. **Effect of liquid vehicles type:** Formula 10 (containing PG) is re-prepared using PEG 400 and Tween 80 each one separately as liquid vehicle. The release profile of nicardipine from F10 (PG) showed significant higher release that that prepared using another liquid vehicle. this is attributed to higher solubility of drug in PG than other two vehicles as previously presented in solubility of nicardipineSo, the drug will be completely in solution in F10 (PG) while it is partially dissolved in F10(PEG 400) and F10 (Tween80). All liquisolid formulasshowed higher drug release than that from DCT which reveals the role of liquid vehicle in addition to carrier in liquisolid formulas.[30]

X-ray diffractometry (XRD).

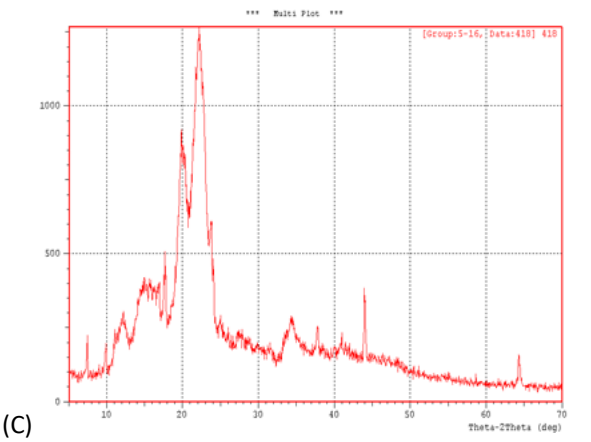
The X-ray diffractogram of pure nicardipine (figure2-A) exhibited several characteristics sharp and intense peaks suggested that the drug existed as crystalline state. The diffraction peaks for simple physical mixture of F10 content and DCT of nicardipine (Fig. 2 B and C) showed reduction in intensity of the characteristics peaks of nicardipine demonstrating that its crystalline structure remain unchanged after the physical mixing and direct compression. The X- ray diffraction patterns of F10 and MSF3 (Figure 2 D and E) showed disappearance of nicardipine characteristics peaks indicating that the drug loss its crystallinity upon the preparation of the two formulas. While X-ray for SD2 (Fig.2-F)shows less intensity peaks indicating a reduction in drug crystallinity. It is concluded that nicardipine in the three formulas was converted to the amorphous form which is more solubilized due to its absorption on the applied carrier.[21]



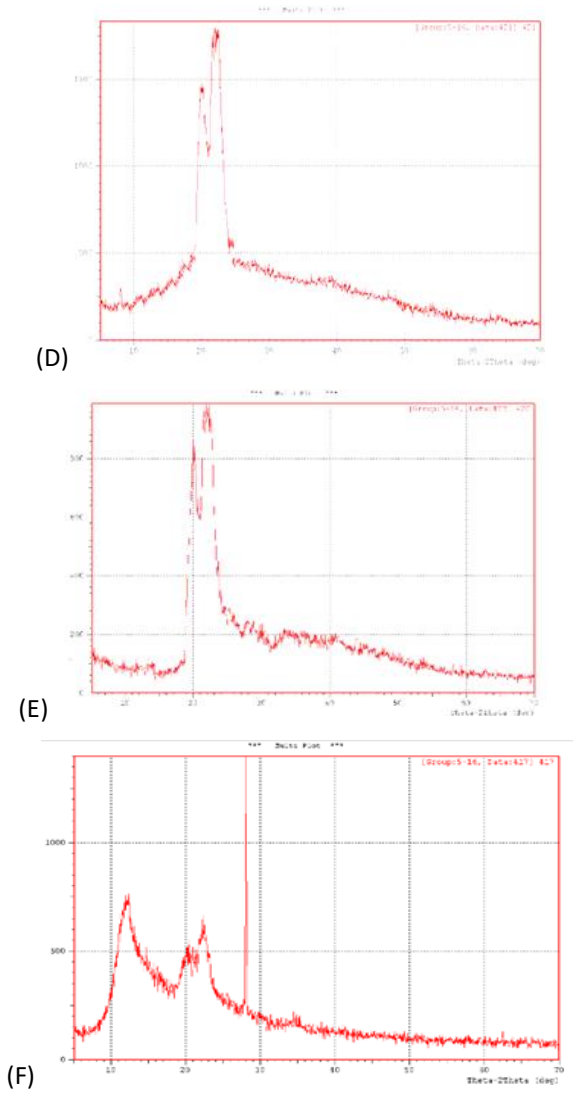
(A)



(B)



(C)



(D)

(E)

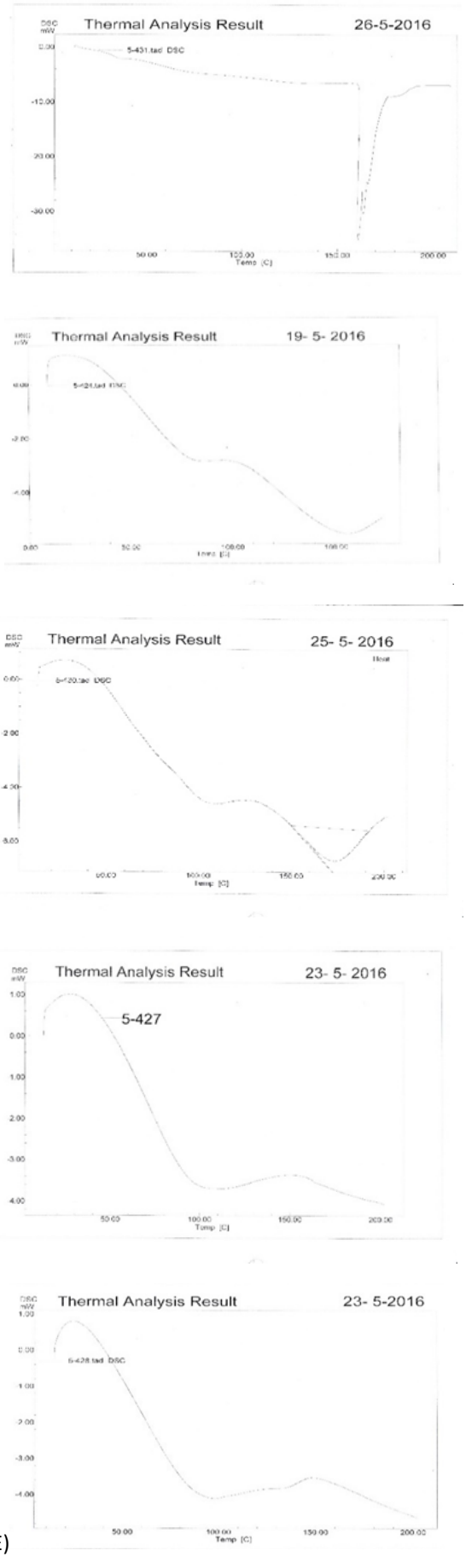
(F)

Figure 2: X-ray diffraction pattern of (A) pure powder of nicardipine,(B) simple physical mixture, (C) DCT powder , (D) selected liquisolid formula F10 ,(E) selected liquisolid microsystem formula MSF3 and (F) selected solid dispersion (SD2)

Differential scanning calorimetry (DSC)

DSC thermogram of pure nicardipine (Fig.3-A), demonstrating a sharp characteristic endothermic peak at 167.5 °C corresponding to its melting temperature. Such sharp endothermic peak shows that nicardipine used was in a pure crystalline state. DSC spectrum of physical mixture of F18 content and DCT (Fig.3-B and C) exhibited peak at 167°Cindicating that there is no interaction between the drug and excipients used in the formulations; and the drug is still in the crystalline form.

On the other hand, the DSC analysis for the selected liquisolidformula F10, selected liquisolid microsystem formula MSF3 and selected solid dispersion formula SD2 thermogram (Fig.3-D, E and F) respectively; showed complete disappearance of characteristic peak of nicardipine. This disappearance upon formulation undoubtedly indicates the formation of an amorphous solid form and it is in a good agreement with reported data which states that disappearance of drug melting point indicated drug amorphization.[29]



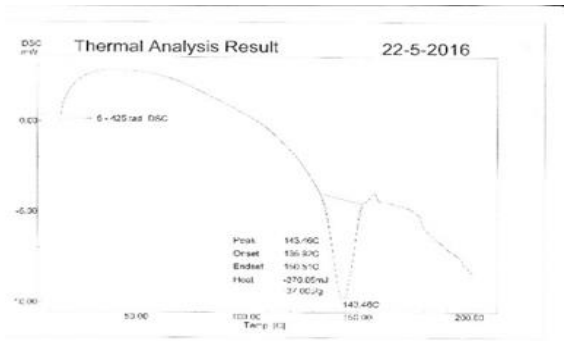
(A)

(B)

(C)

(D)

(E)

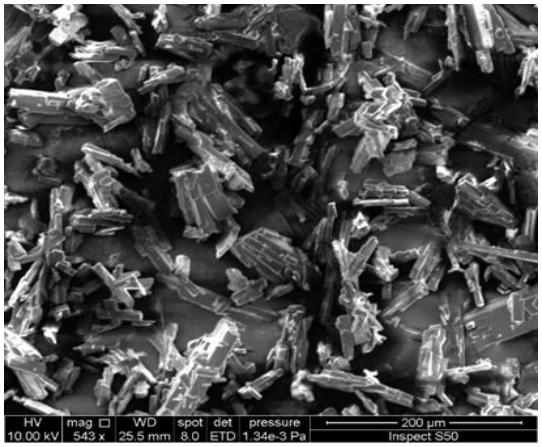


(F)

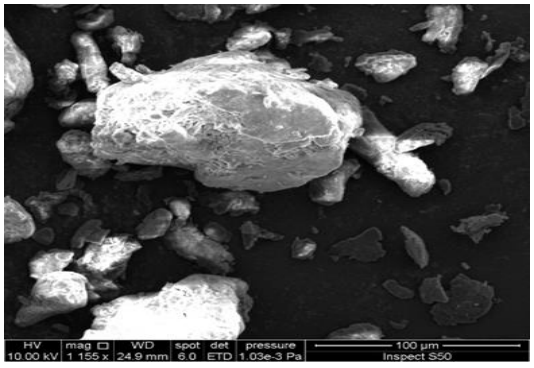
Figure 3: DSC thermal analysis of (A) pure nicardipine, (B) physical mixture of F18 content, (C) DCT formula, (D) selected liquisolid formula F10, (E) selected liquisolid microsystem formula MSF3 and (F) selected solid dispersion (SD2)

Scanning electron microscopy (SEM)

Morphological characteristics of pure powder of nicardipine, selected liquisolid formula F10, selected liquisolid microsystem formula MSF3 and selected solid dispersion formula SD2 were studied using SEM. The photomicrograph of the pure powder of nicardipine (figure 4-A) showed that the drug is crystalline in nature, as observed previously by DSC and XRD. The photomicrograph of selected liquisolid formula F10, selected liquisolid microsystem formula MSF3 and selected solid dispersion formula SD2 (Fig.4 B,C and D) showed complete change in nicardipine morphology to the (non-crystalline) amorphous form , although F10 and MSF3 showed more amorphous molecularly dispersed form.[21]



(A)



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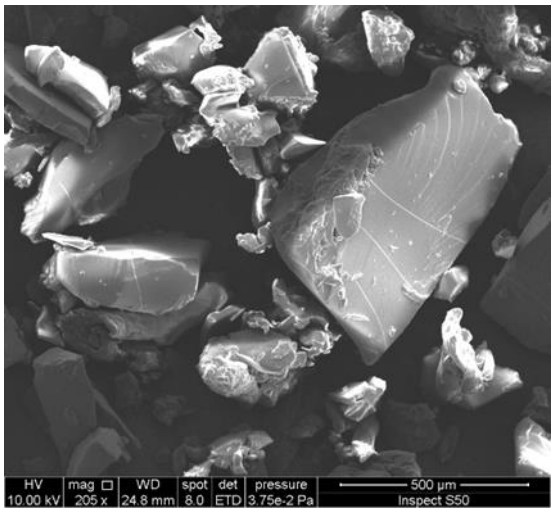
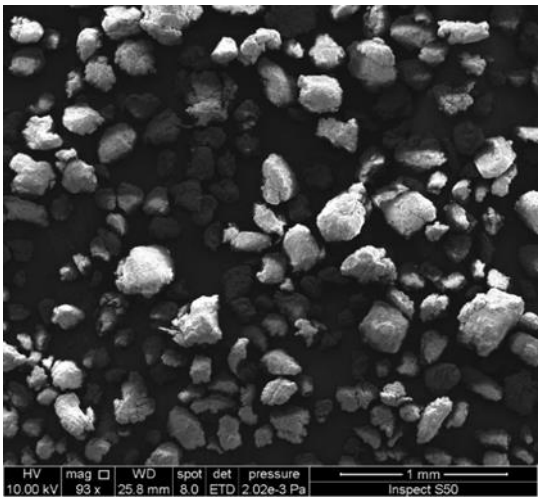


(C)



(D)

Figure 4: SEM analysis for of (A) pure nicardipine, (B) selected liquisolid formula F10, (C) selected liquisolid microsystem formula MSF3 and (D) selected solid dispersion (SD2)

Further comparative evaluation

Figure (5) showed comparison between the dissolution profile of drug from the selected liquisolid formula (F10), liquisolid microsystem formula MSF3 with the dissolution profile of drug from selected solid dispersion formula (SD2) and that prepared by direct compression as well as the marketed tablet (Nicardipino®, Ratiopharm, Spain),it was found that the percent of drug release after 90 minutes was 100 and 85 % respectively for F10 and MSF3 while it was 45 % and 30 % from marketed tablet and DCT. This significant difference is due to surface of drug available for dissolution in liquisolid and liquisolid microsystem formulas (F10 and MSF10) is related to its specific molecular surface which is observed from X-ray, DSC and SEM to be much greater than that of nicardipine particles released from tablet prepared by direct compression method and from the marketed tablet, as well as from that prepared by solid dispersion technology (SD2) .Therefore, the presence of carriers, liquid vehicles and other additives as well as the method of preparation of liquisolid formulas showed superiority over other technology in improving drug solubility as well as its

release profile and so it may improve drug absorption and bioavailability especially nicardipine had low bioavailability (35%) attributed mainly to its low solubility. All the prepared immediate release tablet of nicardipine gave acceptable flowability, compressibility, hardness, friability and uniform drug content .This study revealed that microsystem technology applied for preparation of liquisolid compacts for nicardipine (MSF10) change the drug and excipient to the amorphous form completely which is approved by SEM, X-ray and DSC analysis in addition to the presence of PVP and this causes increase in drug loading capacity of the carrier and consequently reduced the amount of excipients added leading to reduction in total tablet weight to more than half that of weight of F10 prepared by conventional liquid solid system.This will improve patient's compliance and economic feasibility. In addition, it increases drug solubility and give remarkable immediate release that may improve drug absorption and bioavailability.

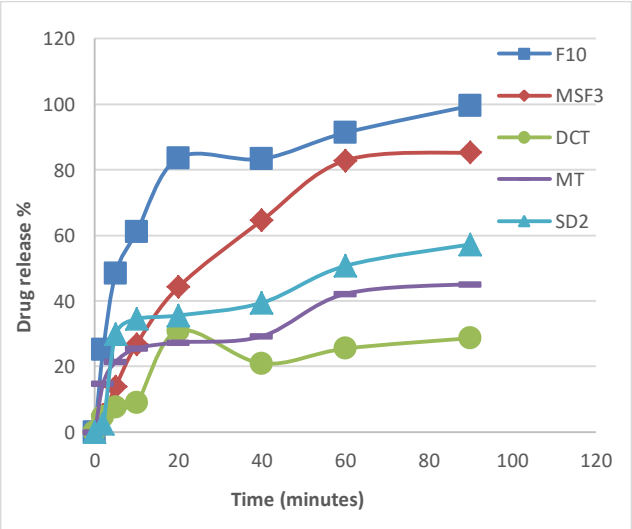


Figure 5: Dissolution profiles of nicardipine from the selected liquisolid formula F10, selected liquisolid microsystem formula MSF3, selected solid dispersion SD2, direct compression tablet formula (DCT) and marketed tablet (Nicardipino®,Ratiopharm,Spain) in 0.1N HCl (pH1.2), at 37 ºC.

CONCLUSION

The present study revealed that the application of liquisolid microsystem technology reduces significantly and markedly the total tablet weight and size through increasing the loading capacity of the polymer used and modification in the method of preparation that improve patient compliance and presents promising economic technology that may improve drug bioavailability through improving its solubility and release from the prepared formula leading to increase in drug effectiveness in comparison to liquisolid compact ,solid dispersion as well as directly compressed tablet and marketed nicardipine immediate release tablet.

Acknowledgments: The authors would like to thank Al-Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad-Iraq for its support in the present work.

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Source of Support: Nil, **Conflict of Interest:** None.