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Neusilin US2 based Liquisolid Compact technique for the enhancement of solubility and dissolution rate of Olmesartan: Box-Behnken design approach

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ABSTRACT: The therapeutic efficacy of an active ingredients are imperfect owing to the poor solubility and dissolution rate. Moreover, dissolution is the rate-limiting period towards the absorption and bioavailability of the active ingredients. Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) recommended for the therapy of high blood pressure as well as minimizes the chances of stroke, heart attack and kidney problems. Olmesartan medoxomil is a BCS class II molecule with only 26 % bioavailability. Hence, the current research work was focused on cost-effective Liquisolid technology for the improvement of solubility, dissolution rate and thereby achieving higher therapeutic efficacy. Liquisolid Compact is one of the best technique for improvement of solubility of potent hydrophobic molecules by utilizing non-volatile solvent. The solubility of olmesartan was estimated in several non-volatile solvents and tween 80 (95 mg/ml) was found to be best. The formed liquid medicaments were converted into the free-flowing powder blends for direct compression by the addition of carrier (Dibasic anhydrous calcium phosphate) and coating agent (Neusilin US2). The drug-excipients compatibilities were confirmed with FTIR. QbD design (Box-Behnken) was applied which comprised of independent factors (X1: DCP, X2: Neusilin US2, X3: CCS) and dependable factors were (Y1: Disintegration time, Y2: Dissolution release). The Design of expert software (DOE, Statease, Version 11) showed 12 batches which were evaluated for their flowing characteristics. The optimized batch F12 showed excellent flowing characteristics (Carr's index: 14, Angle of repose: 24.42), rapid disintegration time (2.07 min), *in-vitro* drug release (99.45%) and qualify under accelerated stability testing with minimal drug loss.

KEYWORDS: Olmesartan; solubility enhancement; Liquisolid; Box-Behnken design; neusilin US2.

1. INTRODUCTION

New therapeutic molecule designing and development processes resulted in the generation of highly lipophilic moiety. The high lipophilicity ensure the passage of active molecule through the gastrointestinal barrier to elicit the therapeutic response [1]. The therapeutic efficacy of any active ingredients are dependent on its solubility characteristics in the gastrointestinal tract. Plenty of newly developed molecules in the clinical trials and around 40% of approved molecules in the market are hydrophobic in nature and hence, indicated poor bioavailability [2]. The low aqueous solubility of a molecules showed minimal bioavailability and therefore require high dose or frequent administration leads to elicit the several adverse effects on the body [3]. The active pharmaceutical ingredients are categorized into class I-IV rely on their solubility and permeability characteristics under biopharmaceutical classification system (BCS) [4]. The BCS class II molecules possesses low solubility, hence these drugs require the appropriate solubility enhancement approach [5].

However, those compounds are unsuccessful in producing therapeutic efficacy due to the unmatched conditions of 'Lipinski's ''Rule of Five'' [6]. The molecule having less than 100 µg/ml are considered as poorly water soluble [7]. Moreover, as per the guidelines stated by the BCS, the active ingredient is measured as

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highly soluble when the uppermost therapeutic dose is soluble in 250 ml of the fluid at the pH range of 1-7.4 at 37 ± 0.5 ^{0}C, otherwise the therapeutic agent is poorly soluble [4] [8].

The high patient comfort, compliance, economic, safe, self-administration and no pain are provided by oral drug delivery system (ODDS). Additionally, ODDS provides greater surface area for the absorption, thus continues as most preferred drug delivery [9]. After oral administration, the active ingredients are soluble and dissolved in the GIT so that it is then reaches inside the plasma for initiation of therapeutic response. But, molecules showing poor solubility and dissolution in the GIT failed to explore the therapeutic response and required improvement [10]. Liquisolid Compact technique first applied by Spires for progress of solubility and dissolution rate of therapeutic compounds. This method is established by formulating liquid medication of the lipophilic moiety using non-volatile solvent. Additionally, liquid medicaments are converted into the freely flowing compressible powder by incorporating carrier and coating agents. The liquid load is adsorbed on the surface of carrier agents and adding coating agents improves the flowing characteristics of the powder. The Liquisolid Compact system describe the development of tablets for quick release by addition of superdisintegrants and lubricants [11-12]. The higher solubility and dissolution of poorly soluble active ingredients are achieved through enhancing the wettability of solid particles with non-volatile liquid, rising drug surface area [13].

The large number of population in the world are suffering with cardiovascular diseases and mortality rate is more than 18 million per year. Out of them, biggest reason for mortality is hypertension. The most widely used therapeutic categories for the treatment of hypertension are ACE inhibitors, ARA inhibitors, beta-blocking and calcium channel blocking agents respectively [14-15]. The most promising agents recommended during high blood pressure, stroke and cardiac failures are the ARB. ARB has typical action against angiotensin II and modulate the blood pressure by their prompt vasoconstriction mechanism. Moreover, these agents are highly effective and good tolerability in several persons [16].

Olmesartan medoxomil (OM) is an ARB widely utilized for the treatment of high blood pressure and also prevents the occurrence of stroke, heart failure and kidney problems. OM is also suggested over other antihypertensive agents for the controlling of type-2 diabetes associated nephropathy. OM is a prodrug which rapidly undergoes ester hydrolysis and generate olmesartan during its absorption in the GIT. The elimination half-life of OM is about 10-15 hrs. [17]. Quality by design (QbD) is a systematic pathway towards development of an pharmaceutical product with predefined objectives and ensuring quality in the finished products. The prime components involved in QbD designs are QTPP, CQA, CMA, CPP and RA, etc. [18].

Neusilin US2 is basically magnesium aluminometasilicate (MAS) is a synthetic material existed in amorphous form. It is versatile excipient utilized for direct compression and wet granulation technique. The biggest significance of greatest surface area and large adsorption capacity for water and oil make them unique. Moreover, it has high stability and extended shelf-life which attracts the manufacturers to incorporate in solid orals for superb adsorption efficiency.

2. RESULT AND DISCUSSION

2.1. Evaluation of preformulation studies

OM was evaluated for preliminary identification characteristics and observed as white powder. The melting point of OM was recorded in the range of 178-180 ^{0}C. The LOD of OM was found to be 0.38%.

2.2. Determination of solubility of OM

The OM tested practically insoluble in distilled water at room temperature. Solubility of OM was estimated in numerous non-volatile solvents and detected highly soluble in tween 80. The solubility of OM in tween 80 was 95 mg/ml, tween 20 was 77 mg/ml, span 20 was 23 mg/ml, PEG 400 was 38 mg/ml and in PG was 47 mg/ml.

2.3. Interaction studies

The powder sample was analyzed with FTIR and identified as pure sample of olmesartan. The FTIR spectrum showed sharp peak at 3678.25 cm^{-1} for the occurrence of O-H stretching, C=O stretching observed at 1741.72 cm^{-1}, C-H stretching at 1705.07 cm^{-1}, and C-N stretching at 1134.14 cm^{-1}. All the peaks confirmed the

identity of the compound olmesartan medoxomil. Moreover, the drug found to be compatible with dibasic calcium phosphate and neusilin US2 confirmed with unchanged band and peaks. The FTIR spectrum were depicted in **Fig. 1 to 3**.

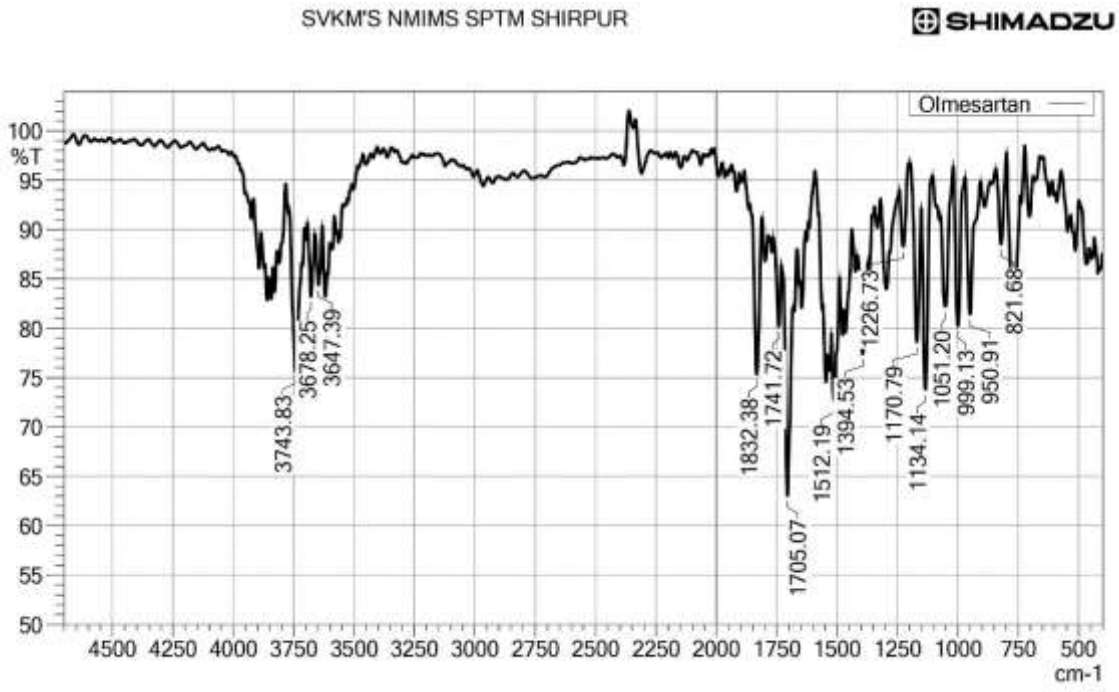

Fig. 1. FTIR of Olmesartan medoxomil

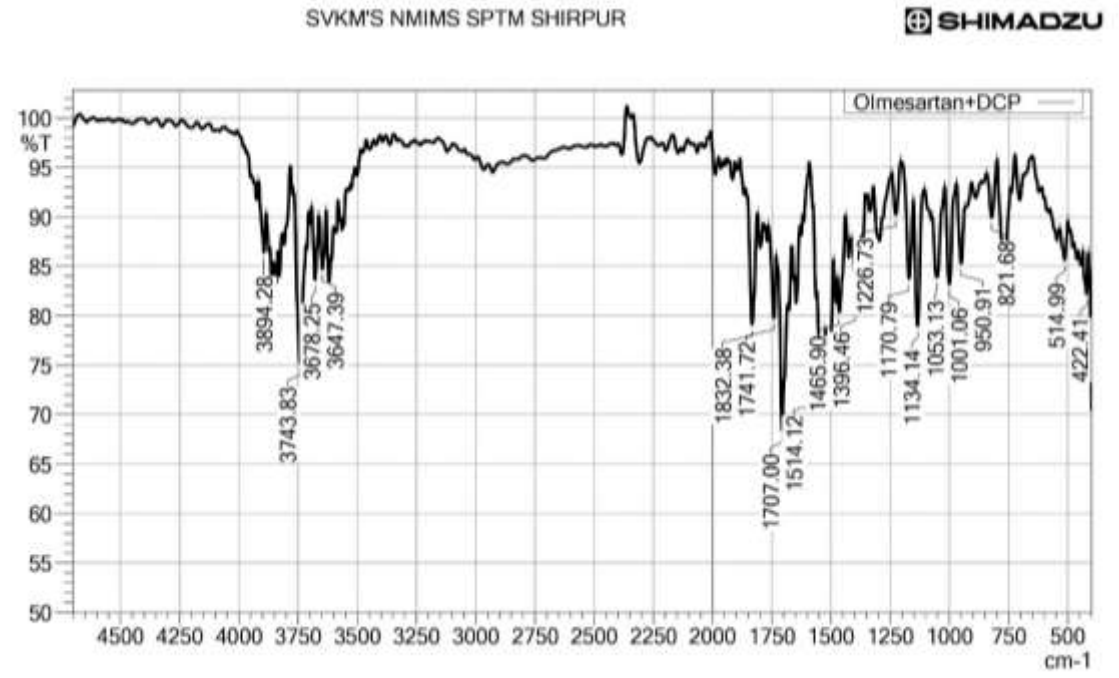

Fig. 2. FTIR Spectra of Olmesartan+DCP

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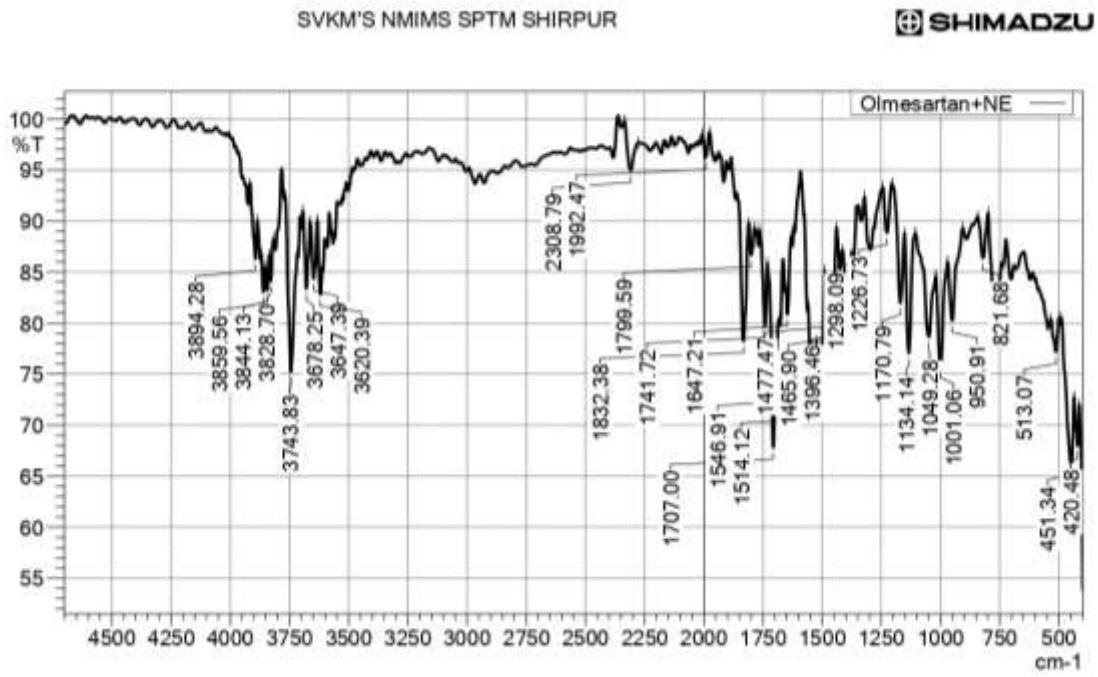

Fig. 3. FTIR Spectra of Olmesartan and Neusilin US2

2.4. Evaluation of powder blends for flowing characteristic

The rationale behind the determination of these flowing characteristics was to find out that powder blends were capable of flow from hopper to the dies and subsequent compression. Results indicated that coating agent neusilin US2 has excellent adsorption capacity compared with carrier agent. Neusilin US2 possesses extreme surface area and porosity as well as good compressibility which gives synergistic effect in direct compression process. All the batches were successfully passed in flowing characteristics. The consolidation index of powder blends were obtained in the range of 10.20 to 16.66% and angle of repose in the series of 18.59 to 27.04. The evaluation of flowing characteristics of powders was depicted in Table 1.

Table 1: The evaluation of flow characteristics of powder blends

Batch	Bulk density	Tapped density	Carr's index (%)	Angle of repose (θ)	Hausner's index
F1	0.43±0.05	0.50±0.09	14±0.05	24.52	1.16
F2	0.44±0.09	0.50±0.07	12±0.09	21.47	1.13
F3	0.42±0.07	0.50±0.03	16±0.07	26.37	1.19
F4	0.44±0.04	0.50±0.10	13.72±0.10	23.87	1.13
F5	0.44±0.08	0.49±0.08	10.20±0.12	18.59	1.11
F6	0.43±0.06	0.51±0.09	15.68±0.16	25.62	1.18
F7	0.43±0.05	0.50±0.05	14±0.08	24.52	1.16
F8	0.40±0.09	0.48±0.06	16.66±0.14	27.04	1.2
F9	0.44±0.04	0.50±0.08	12±0.16	21.56	1.13
F10	0.44±0.07	0.51±0.03	13.72±0.09	23.94	1.15
F11	0.42±0.05	0.50±0.05	16±0.12	24.44	1.19
F12	0.43±0.06	0.50±0.07	14±0.11	24.42	1.16

All value are n =3 ±SD.

2.5. Optimization

The design of expert software (Statease, USA, Version 11) was utilized for optimization analysis. The Box-Behnken design model was applied considering 3 independent and 2 dependent parameters. The BBD design predicted 12 runs and accordingly batches were formulated. The BBD was depicted in Table 2.

Table 2: Optimization study by BBD for Olmesartan medoxomil tablet

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:DCP	B:Neusilin US2	C:CCS	DT	Dissolution
		mg	mg	mg	min	%
11	1	170	60	12	2.09	99.18
12	2	170	80	12	2.07	99.51
5	3	160	70	7.5	2.14	98.74
6	4	180	70	7.5	2.15	98.68
4	5	180	80	9.75	2.11	98.49
2	6	180	60	9.75	2.11	98.53
3	7	160	80	9.75	2.11	98.51
1	8	160	60	9.75	2.12	98.56
10	9	170	80	7.5	2.14	98.34
8	10	180	70	12	2.08	99.31
9	11	170	60	7.5	2.15	98.45
7	12	160	70	12	2.07	99.45

DCP: Dibasic calcium phosphate, CCS: Cross carmellose sodium, DT: Disintegration time.

Moreover, optimization analysis also performed with ANOVA studies for their dependable parameters disintegration time (p-value: 0.0157) and dissolution release (p-value: 0.0279) was set up to be significant indicated with the help of p-value <0.05 designated in the Table 3 and 4.

Table 3: ANOVA for Quadratic model disintegration

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	0.0094	8	0.0012	20.12	0.0157
A-DCP	0.0000	1	0.0000	0.2143	0.6749
B-Neusilin US2	0.0002	1	0.0002	3.43	0.1612
C-CCS	0.0091	1	0.0091	156.21	0.0011
AB	0.0000	1	0.0000	0.4286	0.5594
AC	0.0000	1	0.0000	0.0000	1.0000
BC	0.0000	1	0.0000	0.4286	0.5594
A^2	0.0000	1	0.0000	0.0000	1.0000
B^2	0.0000	1	0.0000	0.2143	0.6749
C^2	0.0000	0			
Residual	0.0002	3	0.0001		
Cor Total	0.0096	11			

Table 4: ANOVA for Quadratic model dissolution

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	1.94	8	0.2423	13.45	0.0279
A-DCP	0.0078	1	0.0078	0.4338	0.5572
B-Neusilin US2	0.0021	1	0.0021	0.1173	0.7546
C-CCS	1.31	1	1.31	72.87	0.0034
AB	0.0000	1	0.0000	0.0014	0.9726
AC	0.0016	1	0.0016	0.0888	0.7851
BC	0.0484	1	0.0484	2.69	0.1997
A^2	0.2415	1	0.2415	13.41	0.0352
B^2	0.5460	1	0.5460	30.32	0.0118

C²	0.0000	0	
Residual	0.0540	3	0.0180
Cor Total	1.99	11	

The 3-D response surface graphs were showed in Fig. 4 and 5. The 2-D contour plots for dependable parameters were depicted in Fig. 6 and 7 respectively.

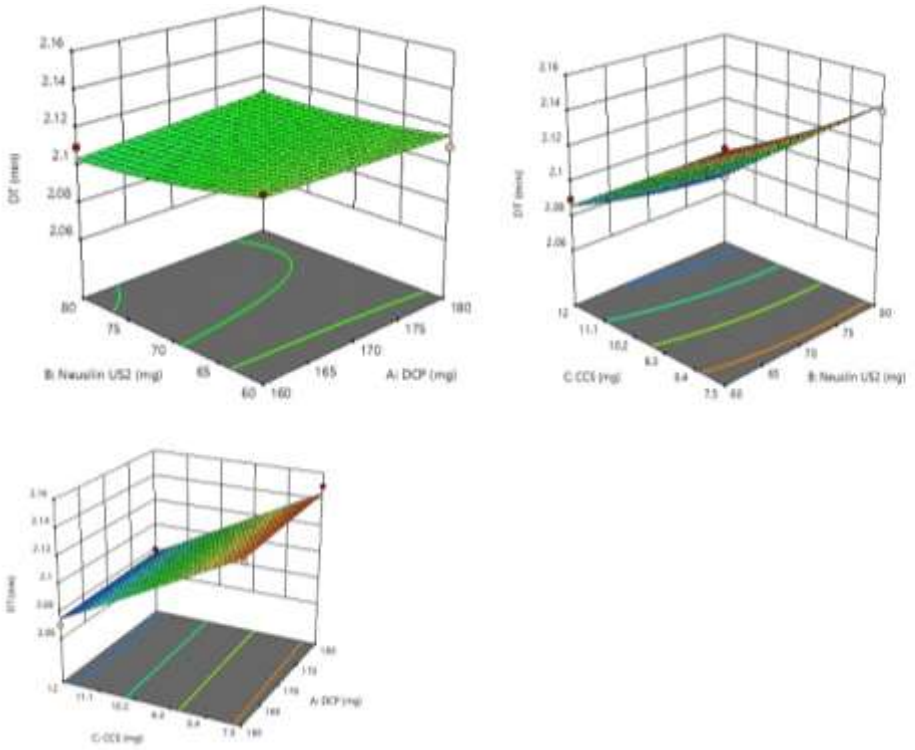

Fig. 4. 3-D Surface response surface graph for Disintegration time

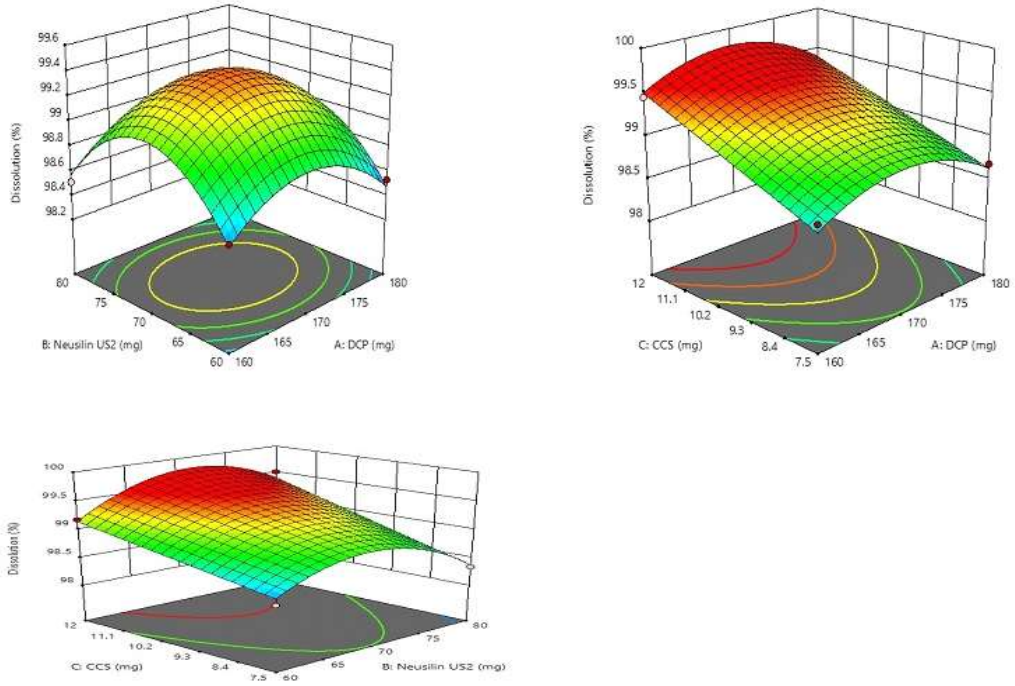

Fig. 5. 3-D Surface response graph for Dissolution

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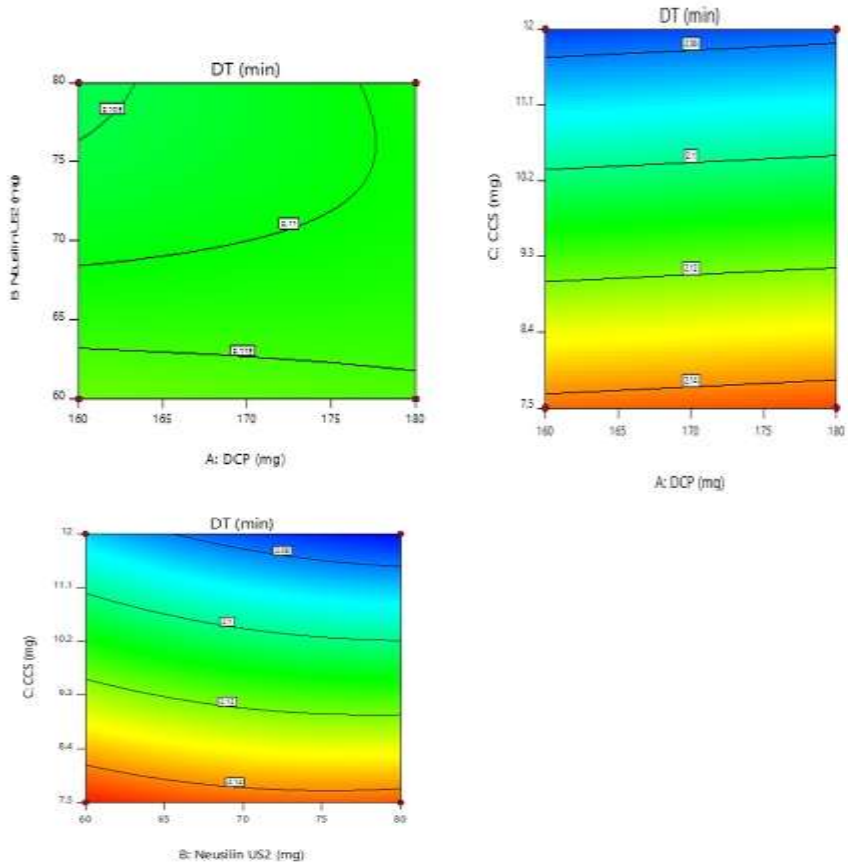

Fig. 6. 2-D Contour Plots for Disintegration time

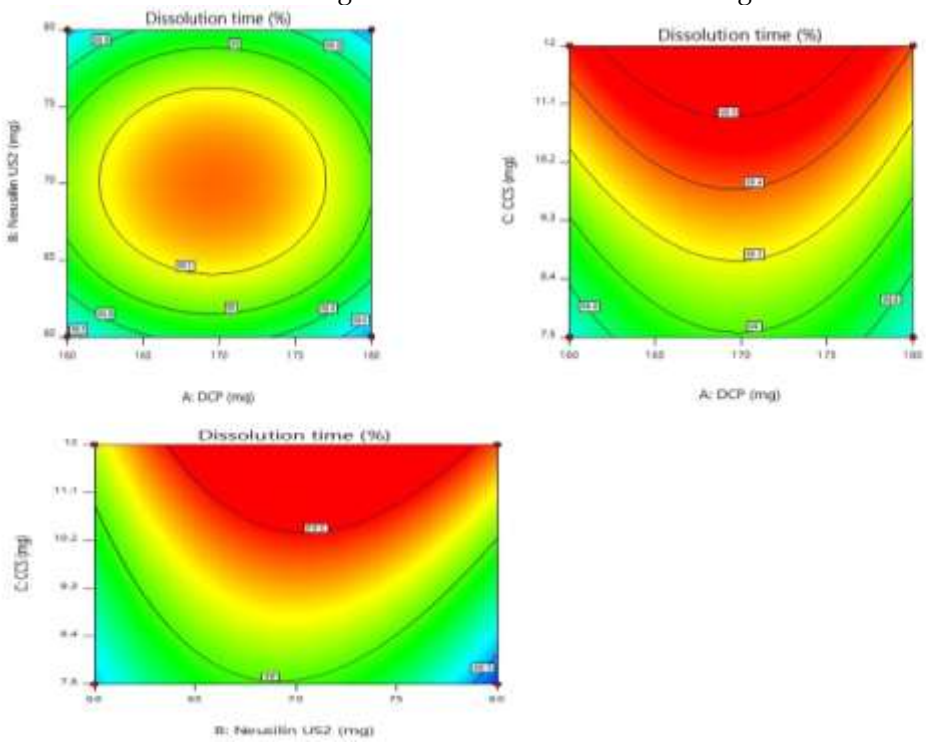

Fig. 7. 2-D Contour plots for dissolution

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The model equations for dependable parameters were written as follows.

For Disintegration time

DT = +2.11 +0.0012 A -0.0050 B - 0.0338+0.0025 AB +0.0000 AC -0.0025 BC +0.0000 A^2 +0.0025 B^2 +0.0000 C^2.

Dissolution = +99.39 -0.0313 A +0.0162 B +0.4050 C+ 0.0025 AB -0.0200 AC +0.1100 BC -0.3475 A^2 -0.5225 B^2+ 0.0000 C^2.

The quadratic polynomial equations comprised of plus sign showed synergistic effects and negative sign was antagonistic effects. The factors A, B, C were concentration of DCP, Neusilin US2 and CCS respectively. These factors have showed responses for their individual concentration. Whereas, AB, AC and BC showed combined effects on the dependable parameters. For disintegration time, concentration of DCP showed synergistic action and concentration of Neusilin US2 and CCS have antagonistic effects. In case of dissolution, concentration of DCP indicated antagonistic effects and synergistic effects were observed with Neusilin US2 and CCS.

The effects of 3 formulation factors were showed in 3-D surface response curve and contour plots showed effects of two parameters. The optimum concentration of DCP and Neusilin US2 required to get less disintegration time. The concentration of cross carmellose sodium have significant effect on the tablet disintegration time. The tablets with greater concentration resulted in prompt hydration and swelling, thereby rapid release were occurred. The contour plots indicated significance of two parameters on the disintegration and dissolution profile. The overall effects and optimum range for disintegration time with formulation factors and percent of drug dissolution range were predicted by the contour plots. The contour plots for disintegration time was 2.12 min and 99.2 % dissolution were showed.

2.6. Evaluation of post compression parameters of Tablets

The tablets prepared in the batches of F1 to F12 were subjected for their post compression evaluation parameters such as weight variation, hardness, friability, disintegration time, *in-vitro* dissolution release and content uniformity. All the prepared batches were qualify the weight variation test according to the limits prescribe in Indian Pharmacopoeia. The hardness was tested with Monsanto hardness tester and found in the series of 4.3 ±0.08 to 4. 6 ± 0.04 kg/cm^2. The friability was estimated using Roche friabilator and observed in the range of 0.47 to 0.68 %. Tablets of all batches were disintegrated at a time of 2.07 to 2.14 min. The content uniformity of all batches were observed in the range of 98.39 to 99.66%. The results were depicted in Table 5.

Table 5: The post compression evaluations of OM Tablets

Batch	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration (min)	Content uniformity (%)
F1	301±0.42	4.3±0.06	0.61±0.22	2.09±0.04	98.39±0.53
F2	321±0.57	4.4±0.11	0.53±0.15	2.07±0.08	99.47±0.30
F3	298±0.49	4.4±0.09	0.57±0.25	2.14±0.10	98.56±0.42
F4	319±0.64	4.5±0.06	0.51±0.18	2.15±0.09	98.94±0.78
F5	330±0.71	4.6±0.04	0.47±0.13	2.11±0.07	99.04±0.56
F6	309±0.34	4.3±0.08	0.59±0.20	2.11±0.06	99.23±0.51
F7	310±0.55	4.4±0.05	0.58±0.14	2.11±0.03	99.30±0.95
F8	290±0.68	4.3±0.12	0.56±0.17	2.12±0.08	99.34±0.46
F9	317±0.75	4.5±0.10	0.53±0.21	2.14±0.07	99.18±0.61
F10	322±0.32	4.4±0.07	0.56±0.10	2.08±0.10	99.58±0.39
F11	299±0.27	4.5 ±0.15	0.68±0.24	2.15±0.11	99.08±0.66
F12	300±0.50	4.4±0.05	0.56±0.15	2.07±0.08	99.65±0.54

All value are n =3 ±SD.

2.7. *In-vitro* dissolution studies of OM tablets

The *in-vitro* drug dissolution studies for OM tablets were performed with using USP type II dissolution apparatus using pH 6.8 phosphate buffer as dissolution media. The 3 tablets from each batch were placed in the dissolution apparatus and frequent sampling was carried out at an interval of 5 min. After withdrawing of 5 ml of sample from dissolution apparatus immediately add the pH 6.8 phosphate buffer to maintain the stock solution. The samples were diluted, filter through 0.45 µ filter paper (Whatman filter paper no. 41) and analyzed spectrophotometrically at 257 nm.

All the batches showed prompt release of OM due to the conversion of solid form of the drug in the liquid medication. The drug release from the F1 batch was found to be 99.18% after 30 min. whereas, the cumulative amount of 99.51% of OM was recored in F2 batch. The release rate was slighly more in the F2 batch comparatively with the F1 due to higher concentration of neusilin US2. Similarly, the cumulative percentage of drug released from the batches F3 to F6 were 98.74%, 98.68%, 98.49% and 98.53% respectively within 30 min except for F3 which was observed in 40 min due to less concentration of superdisintegrant compared with oher batches. Among all these batches the slight variations in the drug release was due to the composition and hardness of the tablets.

Similarly, F9 and F11 batches showed slower the drug dissolution comparatively with the other batches like F7, F8, F10 and F12. Moreover, the drug released in the batches of F7 to F12 observed as 98.51%, 98.56%, 98.34%, 99.31%, 98.45% and 99.45% respectively. The addition of neusilin US2 showed positive effects on the blending, disintegration and dissolution properties. Hence, the prompt release of OM was occurred in quick time. Due to this reason, Neusilin US2 is considered as one of the best adsorbent for liquisolid Compact technique. Moreover, sodium stearyl fumarate is an hydrophilic lubricant which doesnot retard the tablet disintegration and dissolution time as showed by magnesium stearate. The *in-vitro* dissolution profile of olmesartan was depicted in the Fig. 8 and 9 respectively.

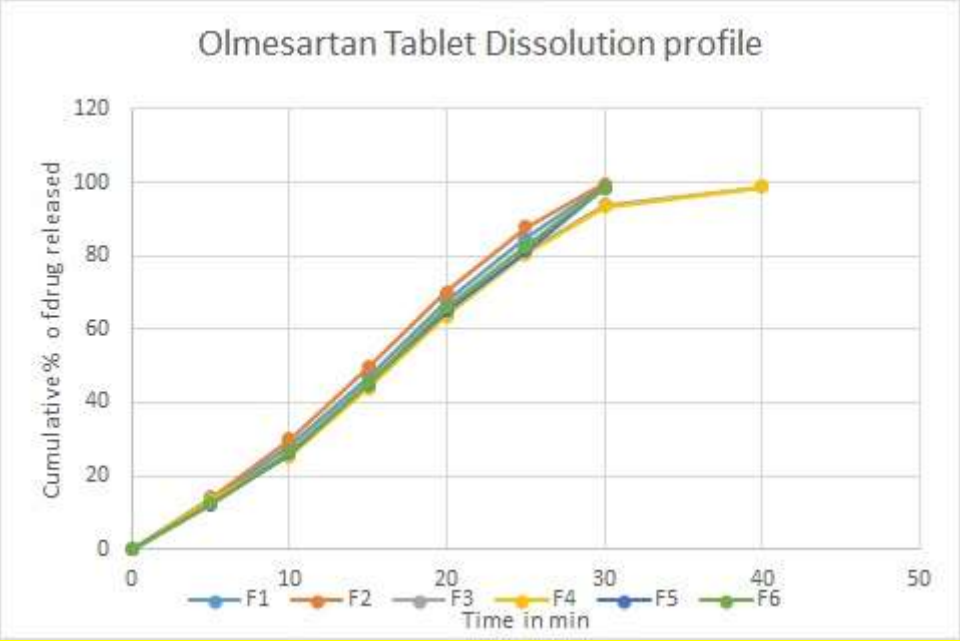

Fig. 8. In-vitro dissolution of F1 to F6. All values in n=3, ±SD.

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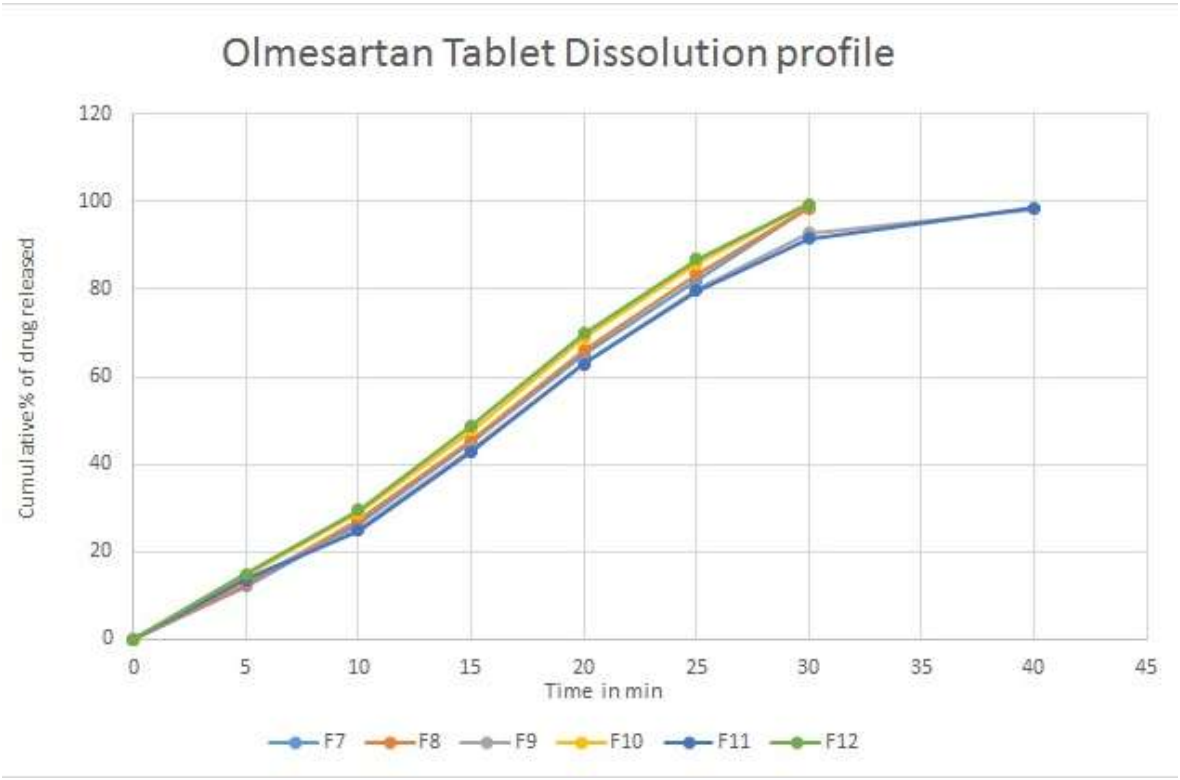

Fig. 9. In-vitro dissolution of F7 to F12. All values in n=3, ±SD.

2.8. Accelerated stability study

The optimized batch F12 was chosen on the basis of least disintegration time, higher dissolution release and minimal material with maximum effects. Further F12 tablets were subjected for accelerated stability study according to the ICH guidelines. The influence of humidity and high temperature on the prepared tablets were evaluated and result was depicted in Table 6.

Table 6: Stability study of an optimized batch F12

Parameters	After 1 month	After 2 month	After 3 month
Physical appearance	No change	No change	No change
Hardness(kg/cm²)	4.3±0.21	4.2±0.16	4.1±0.22
Friability (%)	0.60±0.19	0.64±0.30	0.70±0.24
Disintegration (min)	2.05±0.05	2.02±0.06	1.99±0.09
Drug content (%)	99.60 ±0.38	99.56±0.44	99.32±0.48

All value are n =3 ±SD.

3. CONCLUSION

Cardiovascular diseases including hypertension affects large number of population in the world and reported high mortality. Olmesartan medoxomil is recommended in the treatment of high blood pressure, cardiac failure, stroke and kidney problems. But, the versatile use is limited due to their less solubility and dissolution rate resulting in minimal absorption and bioavailability in the biological system. Liquisolid Compact technique was utilized for the enhancement of solubility and dissolution rate of OM. This technique offers simplicity, cost effective and mainly depends on the adsorption efficiency of coating agent (Neusilin US2). As the liquisolid Compact technique converted solid into the liquid medicament and reconverting into the solid powder was totally depends on the high adsorption efficacy of coating agent. Neusilin US2 possesses high surface area and porosity which makes them excellent adsorption tendency and incorporation of it improves the flowability and compressible characteristics. Due to this characteristics, total weight was not increased otherwise with other coating agent weight increases at high level in the development of tablets. Hence, Neusilin US2 was considered as best coating agent for liquisolid Compact technique. Moreover, QbD approach using BBD was provided the systematic development of formulation with minimal runs and hence, saved material as well as time. The randomization of different combinations with BBD always found useful in the identification of an optimized batch with best results.

4. MATERIALS AND METHODS

4.1. **Materials**

Olmesartan medoxomil and cross carmellose sodium was gifted by Ajanta Pharmaceuticals, Aurangabad. Dibasic calcium phosphate and sodium steraryl fumarate was supplied by Nitika Pharmaceuticals, Nagpur. Neusilin US2 (magnesium aluminometasilicate) was provided by Gangwal chemicals, Mumbai. All other chemicals are of analytic grade only.

4.2. **Methods**

4.2.1. Preformulation analysis

Olmesartan medoxomil was analyzed for melting point, loss on drying (LOD) and also for their organoleptic characteristics such as color and odor etc. [19].

4.2.2. Scrutiny of non-volatile solvent

An accurately weighed quantity of 20 mg of OM was allowed to dissolve in various non-volatile solvents such as polyethylene glycol 200 and 400, propylene glycol, tween 20 and 80, span 20, glycerin etc. The solvent which showed highest solubility was identified and further estimated saturation solubility by adding excess quantity of OM which was kept in orbital shaker incubator for about 48 h at 37^0 C. The solution was further diluted, filtered through 0.45 µm filter and estimated for drug content by UV visible spectrophotometer (Shimadzu, 1900 Japan) [20].

4.2.3. Determination of load factor

Load factor has great significance for adsorbing the quantity of liquid medicament on the surface of powders. Depending on the viscosity of non-volatile solvent, weight of carrier and coating agents were decided so as to form the powder blend freely flowable and compressible. The process determine the flowing potential of liquid (Φ) and compressible potential of liquid (¥). The excipient ratio (R) can be calculated by diving the quantity of carrier (Q) to the coating material (q). The liquid load factor was calculated from the following equations [21-22].

$$R = Q/q \quad \text{……..1}$$

$$Lf = \Phi_{ca} + \Phi_{co} \quad x\ 1/R \text{ ……2}$$

$$Q = W/L_f \quad \text{……..3}$$

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4.2.4. Interaction study

The identity of OM was confirmed by FTIR (IRAffinity-1s, Shimadzu) scanned under the ranges of 400 to 4000 cm^{-1}. Moreover, the compatibility was also checked between OM with carrier (DCP) and coating agent (Neusilin US2) [23].

4.2.5. Evaluation of powder blends

The powder blends were estimated for their flowing characteristics such as bulk density, tapped density, consolidation index, angle of repose and Hausner's ratio [24].

4.2.6. Optimization

QbD was useful in attaining the objective of developing the product deficient with any error and guards the materials as well as time. The critical quality attributes for designing Liquisolid Compact was the disintegration and dissolution time, whereas the independent parameters were variations of carrier and coating agents. The 3^2 Box-Behnken design (BBD) was applied and predicted 12 runs to find out the optimized batch [25].

4.2.7. Formulation of tablets from the powder blends

Accurately weighed quantity of the OM was transfer in the mortar succeeding adding of selected non-volatile solvents. To the liquid medicaments precalculated quantity of carrier agent's namely anhydrous dibasic calcium phosphate were added. Subsequently, the coating agent neusilin US2 was added to make the powder blends in their compressible form. Before compression, cross carmellose sodium (CCS), sodium steraryl fumarate (SSF) was added [26] and blended without any friction. The powder mass was subjected for compression and tablets were prepared on 12 station multi-tooling machine (Rimek mini press-II, Karnavati Engineering, Ahmadabad). The formulation constituents were depicted in Table 7 [27-28].

4.2.8. Weight variation test

The prepared tablets about 20 were unsystematically picked and accurately weighed. The mean weight of an individual tablets were recorded with standard derivations. The weight variation test passes within 2.5 % variations from the average tablets [29].

4.2.9. Hardness

The hardness of tablets from each batch was tested by Monsanto hardness tester [30].

4.2.10. Friability

The tablets from each batch were weighed accurately equivalent to 6.5 g and further kept in the Roche friabilator which was rotated at a speed of 25 rpm for 100 rotations. After rotation, tablets were collected and reweighed. The percentage of friabilator was calculated by deducting the weight of initial from final weight [31].

4.2.11**.** *Disintegration time*

The 6 tablets were unsystematically picked and placed in the disintegration test apparatus containing 900 ml of simulated gastric fluid at 37±0.5° C. The time required to pass all the particles from the sieve number 10 were recorded [32].

4.2.12. In-vitro dissolution

The dissolution study of OM tablets were performed with USP Dissolution apparatus II (Paddle) using pH 6.8 phosphate buffer. The paddle was allowed to rotate at a speed of 50 rpm, at 37±0.5° C. The samples were withdrawn at an interval of 5 minutes, diluted, filter through 0.45 µm membrane filter and analyzed spectrophotometrically at 257 nm [33].

4.2.13. *Content uniformity*

The prepared tablets about 10 were randomly selected and converted into the powder after crushing. The average weight of tablet containing a powder was taken and dissolved with pH 6.8 phosphate buffer. The solution was further diluted and filter through 0.45 µ membrane filter and analyzed spectrophotometrically at 257 nm [34].

4.2.14. Stability study

The stability study of an optimized formulation was carried out according to the ICH guidelines. The optimized batch was kept at 40^0 C and 75 % RH for about 3 months. The samples were withdrawn at an interval of one month and estimated for their physical appearance like any changes in color, texture and size of the tablets. Moreover, the drug content, disintegration and dissolution time were also assessed [35].

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