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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF NEBIVOLOL AND VALSARTAN

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ABSTRACT: Better patient compliance can be achieved using a combination of two drugs compared to a single drug. The main objective of the present research work has been done to prepare fast dissolving tablets of Nebivolol HCl (NEB) and Valsartan (VAL) using super disintegrating agents. **S**olid dispersions of VAL were prepared with Mannitol to improve the solubility and release behavior in dissolution fluid. Fast Dissolving tablets of NEB and VAL were formulated by employing the direct compression method. The prepared fast dissolving tablets were evaluated for various parameters like weight variation, hardness, friability, disintegration time, drug content, wetting time, *in-vitro* drug release, FTIR, DSC studies and short term stability studies. It was found that ratio 1:1 (VAL: Mannitol) shown satisfactory drug release compared to other prepared solid dispersion. Pre-formulation studies of both drugs were performed. The FTIR and DSC studies revealed that there is no chemical interaction with excipients. Percentage weight variation and drug content uniformity were found to be within the approved range of all the formulations. Evaluation parameters like hardness and friability indicated good mechanical resistance of the tablets for all the formulations. The *in-vitro* release studies showed that 99.6% of NEB and 99.5% VAL within 90 sec. Overall, in the formulations prepared by the direct compression method, F13, which contains 6% CCS as super disintegrants release 99% of (NEB and VAL) in 2 min was found to be the best formulation. The results concluded that fast dissolving tablets of NEB and VAL showing enhanced dissolution might lead to improved bioavailability and effective therapy for hypertension.

INTRODUCTION: Controlling blood pressure (BP) is an important health priority to reduce the serious health consequences associated with hypertension, such as heart failure, stroke, and end-stage renal failure. The vast majority of hypertensive patients will require at least two medications to achieve the recommended goals. The combined dosage form of two or more drugs has been proven useful in multiple therapies as they offer better patient compliance than a single drug.

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The fixed-dose combination of any two antihypertensive drugs (NEB and VAL) from different drug classes is typically more effective in reducing blood pressure than a dose increase of component monotherapy.

Recently, the NEB 5mg/d and VAL 80 mg/d is the only β-blocker combination approved by the US Food and Drug Administration (FDA) for the treatment of hypertension. NEB is a selective β_1 receptor antagonist used for the management of hypertension and angina pain. It reaches a mean peak plasma concentration approximately in 1.5 to 4 h post-oral administrations. VAL is an angiotensin II receptor antagonist and is widely used in the management of hypertension. VAL is rapidly absorbed after oral dose with a

bioavailability of about 23%. Peak plasma concentrations occur 2-4 h, and its plasma half-life is about 7.5 h and belongs from BCS class II drug.

The aim of present research work was undertaken to formulate fast dissolving tablets of NEB and VAL through its incorporation of an oral dosage form that is able to release NEB and VAL immediately. The main objective of this work was the formulation of fast dissolving tablets composed of two different classes of drugs by using a simple and easy-to-scale-up formulation strategy. Different drug compatible excipients were tried as fillers and binders. To achieve faster disintegration, Cross povidone (CP), Sodium starch glycolate (SSG), and Croscarmellose sodium (CCS) were used as super disintegrating agent [1, 2].

MATERIALS AND METHODS:

Materials: Nebivolol HCl and Valsartan were obtained as a gift sample from the Astron Research Centre, Ahmedabad, India. Crospovidone (CP), Sodium starch glycolate (SSG) and Croscarmellose sodium (CCS) were purchased from Astron chemicals, Ahmadabad, India. All other chemicals used were of suitable analytical grade.

Methods:

Preparation of Solid Dispersion of VAL: Solid dispersions were prepared by using different ratios of VAL and Mannitol. The weighed amount of drug and the carrier was dissolved in solvent (methanol). The mixture was mixed thoroughly and continuously until the solvent used was evaporated, and a semisolid mass was obtained. The completely dried mass was pulverized using a mortar and pestle and sifted through 60# to obtain a uniform particle size and stored in a desiccator at room temperature and evaluated [3, 4, 5].

Characterization of Solid Dispersion:

Drug Content: About 80 mg of drug equivalent of solid dispersion (theoretical) was weighed accurately and transferred to a 100 ml volumetric flask. Then the volume was makeup with 0.1 N HCl: Methanol (1:9) and shake for 10 min to ensure complete solubility of the drug. After that, the solution was filtered, and the filtrate was diluted suitably and assayed for drug content at 250 nm by using UV-Visible spectrophotometer (Shimadzu 1680, Japan)

***In-vitro* Dissolution Study of Solid Dispersion:** Solid dispersions were subjected to *in-vitro* dissolution. The dissolution test was carried out using the USP Paddle method [apparatus 2] (Electro Lab TDT‑06 T, Mumbai). The stirring rate was 50 RPM, and 900 ml of 0.1 N HCl (pH 1.2) was used as a dissolution medium at 37 ± 1 °C. Samples of 5 ml were collected at usual intervals of time, filtered and replaced with 5 ml of fresh dissolution medium. Dilutions were made and analyzed using a UV-visible spectrophotometer (Shimadzu 1680, Japan). The dissolution study was also performed for pure powder.

Fourier Transform Infrared Spectroscopy: The Fourier transform infrared spectrum of a moisture-free powdered sample of NEB HCl, and VAL was recorded on the IR spectrophotometer (FTIR 8400, Shimadzu, Kroyto, Japan) by potassium bromide (KBr) pellet method. The range of spectra was found to be 600 to 4000 cm^{-1}. The characteristic peaks of the different functional groups were recorded.

Differential Scanning Calorimetry: The possibility of any interaction between the drug and the carriers during the preparation of solid dispersion was assessed by carrying out the thermal analysis as well as its solid dispersions using DSC (DSC TA-60WS, Kroyoto, Japan). The weighed amount of the sample was first cooled to −10 °C and was held at that temperature for 1 min. The sample was then heated to 250 °C at a rate of 10 °C/min. The DSC thermograms of NEB HCl and VAL and its mixture were recorded.

Pre-compression Study of Powder Blend:

Bulk Density and Tapped Density: Weighed quantity of the powder (W), was carefully poured into the graduated cylinder, and the volume (V0) was measured. After that, by tapping 100 times manually, the volume was checked and calculated from the below equation.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_F$$

Compressibility Index (CI) / Carr's index: Compressibility index (CI) / Carr's index was calculated by using the following formula.

$$\%\ \text{Carr's index} = (\text{T.D.} - \text{B.D.} / \text{T.D.}) \times 100$$

Hausner's ratio: Hausner's ratio is a number that is correlated to the flowability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density / Bulk Density)

Angle of Repose: Angle of repose of powder was determined by the funnel method. Accurately weight powder was taken in the funnel. Height of the funnel was attuned in such a way the angle of the funnel just touched the apex of the powder. The powder blend was allowed to flow through the funnel freely on to the surface.

Diameter of the powder cone was measured, and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Formulation of Fast Dissolving Tablets: A Direct compression method was employed for the fabrication of Fast Dissolving tablets. An accurately weighed quantity of 5 mg NEB and solid dispersion of VAL (equivalent to 80 mg VAL) was mixed with superdisintegrants (Sodium starch glycolate, Cros-povidone, Croscarmellose Sodium), Avicel PH102 and Aspartame in geometrical dilution method as per formula in **Table 1**. Then Aerosil and Talc were added, mixed thoroughly, and compressed into tablets by using a Rotary punching machine (Hardik Engineering, Ahmedabad) to produce flat-faced tablets. The average tablet weight is 200 mg [6, 7, 8].

TABLE 1: FORMULATION OF FAST DISSOLVING TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Nebivolol HCl	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Valsartan (SD)	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160
SSG	4	8	12	16	20	-	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	4	8	12	16	20	-	-	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	-	-	-	-	4	8	12	16	20
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Avicel pH 102	22	18	14	10	6	22	18	14	10	6	22	18	14	10	6
Tablet weight	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

*Note: - All amounts are in mg. SD: Solid Dispersion

Post-compression Evaluation of Fast Dissolving Tablet:

Weight Variation Test: The twenty tablets were selected arbitrarily from every formulation and weighed independently to check for weight variable [9].

Uniformity of Thickness: Thickness was measure by Vernier caliper, and results will be recorded [10].

Hardness Test: The hardness of the tablets was determined using Monsanto type Hardness tester (Shivani Scientific Industries Pvt. Ltd., Mumbai.) It is expressed in Kg/cm^2. [11]

Friability Test: [12] The friability of tablets was determined by using Roche Friabilator (Electrolab, Mumbai, India). It is expressed in percentage (%). 6.5-gram weight equivalent tablets were initially weighed and transferred into friabilator. Variability of tablets less than 1% is considered acceptable.

Drug Content: Five tablets were randomly selected, accurately weighed, and the average weight per tablet calculated. The tablets were ground individually to a fine powder. Accurately weighed tablet, powder transferred to 100 ml volumetric flask. Add 0.1 N HCl: Methanol (1:9) up to the mark. After the solution was filtered, rejecting first few ml of the filtrate. 1 ml of filtrate was taken in a 10 ml volumetric flask and diluted up to the mark with 0.1 N HCl: Methanol (1:9) and analyzed spectrophotometrically at 250 nm and 282 nm for VAL and NEB HCl respectively [13, 14].

Wetting Time: A piece of tissue paper (12 × 10.75 cm^2) folded twice was placed in a Petri dish (internal diameter 9 cm) containing 10 ml of phosphate buffer solution (pH 6.8). A tablet was placed on the paper, and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected, and the average wetting was recorded [15, 16, 17].

***In-vitro* Dispersion Time:** It is determined by placing one tablet in a beaker containing 10 ml of

pH 6.8 phosphate buffer 37 ± 0.5 ºC, and the time required for complete dispersion was determined [18, 19].

***In-vitro* Disintegration Time:** The *in-vitro* disintegration time of a tablet was determined using the disintegration apparatus (Electro lab ED-2L, Mumbai). Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1 N HCl (pH 1.2) maintained at 37 ± 2 °C as the immersion liquid [20, 21].

***In-vitro* Dissolution Studies:** *In-vitro* release studies were carried out using tablet USP type II dissolution test apparatus (Electro Lab TDT-06 T, Mumbai). Tablets were added to the 900 ml of 0.1N HCl (pH 1.2) at 37 °C ± 0.5 °C, which was stirred with a rotating paddle at 75 rpm. Samples (2 ml) were collected at predetermined time intervals and replaced with an equal volume of fresh medium and analyzed with a UV-visible spectrophotometer at 250 nm and 282 nm wavelength for NEB HCl and VAL respectively [22, 23].

RESULTS AND DISCUSSION:

Solid Dispersions of VAL: All prepared solid dispersions have white color, odorless and free-flowing in nature, whereas pure drug had poor flow property. All solid dispersions of VAL with mannitol show higher solubility than a pure drug in 0.1N HCl and water. In ratio of 1:1 was exhibit more solubility than other prepared ratios. The solubility of VAL solid dispersion in the ratio of 1:1 was observed 11.26 mg/ml and 21.48 mg/ml compared to pure drug 0.013 and in 0.141 in 0.1 N HCl and water, respectively **Table 2**. *In-vitro* dissolution study showed that 1.1 ratios of solid dispersion had 74.2% drug release compare to pure drug 34.6% after 4 min.

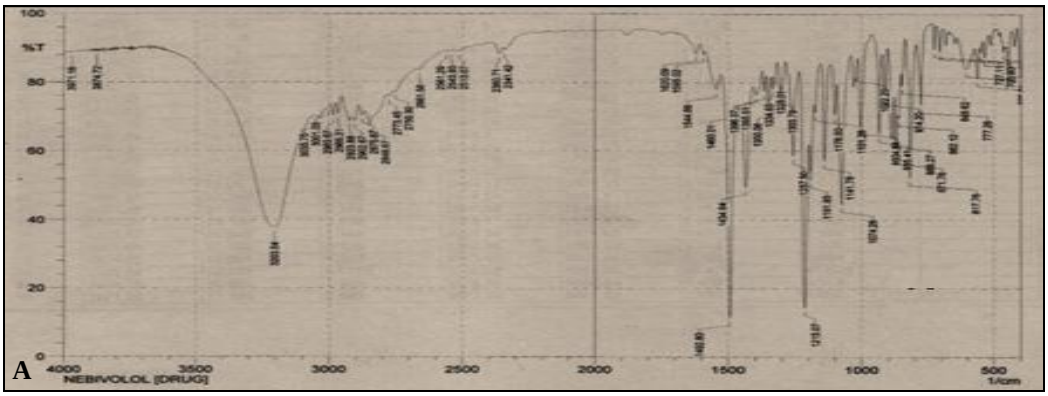
TABLE 2: DRUG CONTENT, SOLUBILITY AND DRUG RELEASE OF VAL SOLID DISPERSIONS

S. no.	Ratio of solid dispersion	Colour	% drug content (n=3)	Solubility in 0.1N HCl (mg/ml) (n=3)	Solubility in water (mg/ml) (n=3)	% Drug Release after 4 min (n=3)
1	Pure Drug	White	100	0.013 ± 0.005	0.141 ± 0.0009	34.6 ± 0.6
2	1:1	powder	96.8 ± 0.5	11.26 ± 0.8	21.48 ± 0.7	74.2 ± 0.5
3	1:2		98.2 ± 0.8	9.18 ± 0.5	18.49 ± 0.4	62.3 ± 0.7
4	1:3		95.6 ± 0.9	6.74 ± 0.9	14.34 ± 0.3	56.9 ± 0.8
5	1:4		97.7 ± 0.4	4.19 ± 0.4	12.47 ± 0.6	48.2 ± 0.5

Fourier Transforms Infrared Study: IR spectra of the NEB, VAL, and their tablet mixture were shown in **Fig. 1**. Interpretation data of FTIR of NEB, VAL, and their mixture with excipients are shown in **Table 3**. From **Fig. 1A** and **B** show that excipients do not interact with NEB since the observed peak of the pure drug was present in the mixture also. Therefore, NEB was found compatible with excipients. From **Fig. 1D** was shown boarding and extending of peaks compared to its pure form **Fig. 1C**. It was observed after the formation of solid dispersion of VAL with mannitol. Also, prepared tablet mixture was shown both drugs characteristic peaks.

TABLE 3: FTIR DATA OF NEB, VAL AND THEIR MIXTURE

Peaks	NEB	NEB + Mixture	VAL	VAL + Mixture
N-H	1595	1589	---	---
O-H	3203	3208	---	---
C-O	1101	1107	1604	1615
C=C	3003	2996	---	---
C-N	1303	1309	---	---
C-H	2923	2930	2962	2951
C=O	1595	---	1730	1725



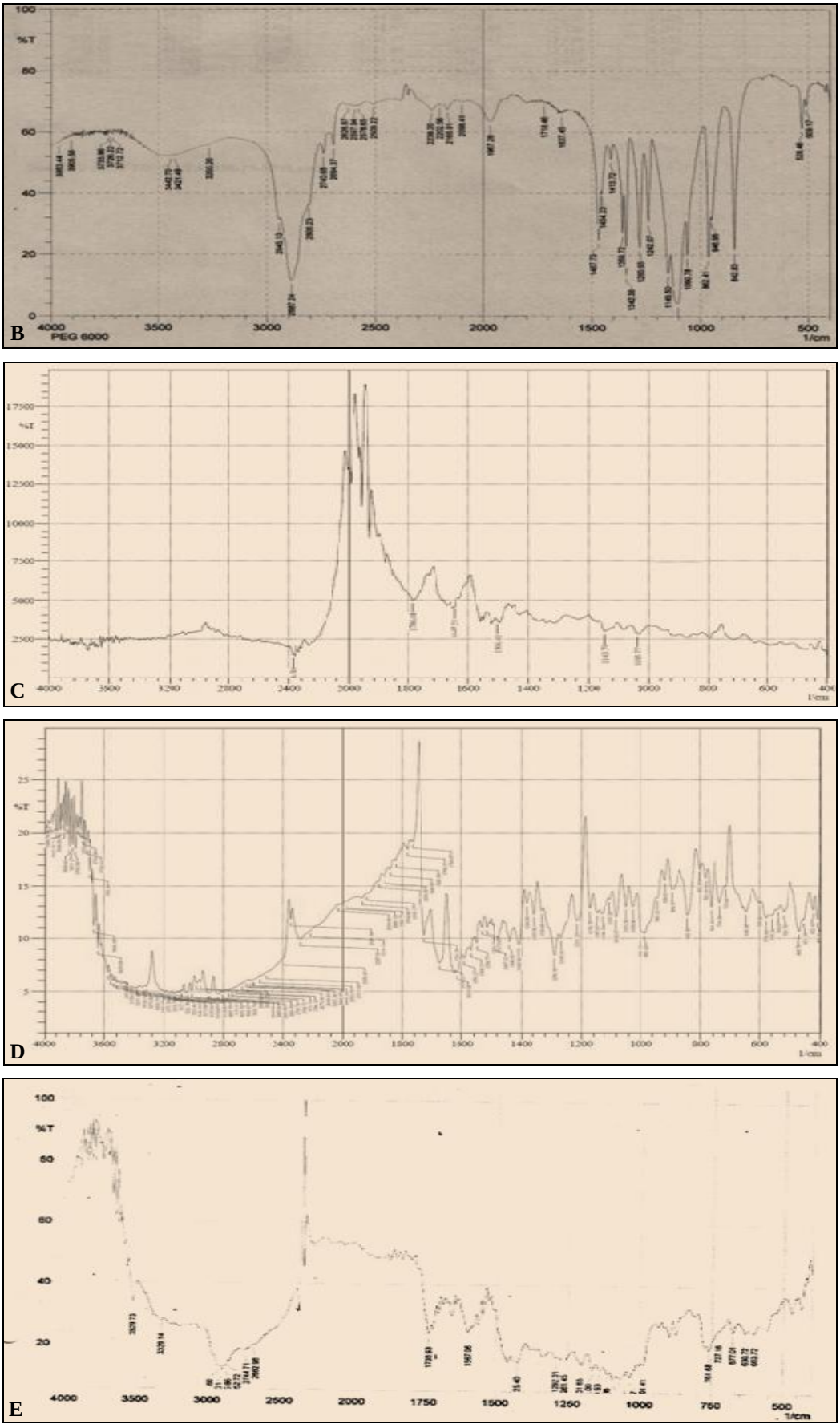


FIG. 1: (A) FTIR SPECTRA OF NEB (B) FTIR SPECTRA OF NEB + EXCIPIENTS (C) FTIR SPECTRA OF VAL (D) FTIR SPECTRA OF VAL+ EXCIPIENTS (E) FTIR SPECTRA OF VAL + NEB + EXCIPIENTS

DSC Study: Thermal behavior of NEB, VAL, Mannitol showed their endothermic peaks at 228.78 °C, 102.43 °C, and 161.3 °C, respectively **Fig. 2(A-C)**. The DSC curve of NEB and VAL was shown a sharp endothermic peak at corresponding to its melting, indicating its crystalline nature. Lack of melting peak of VAL (102.43 °C) in the thermogram **Fig. 2(D)** indicated that the crystallinity of the drug was reduced in solid dispersion. The amorphous state in comparison to crystalline form is a high-energy state and is expected to have a high absorptivity.

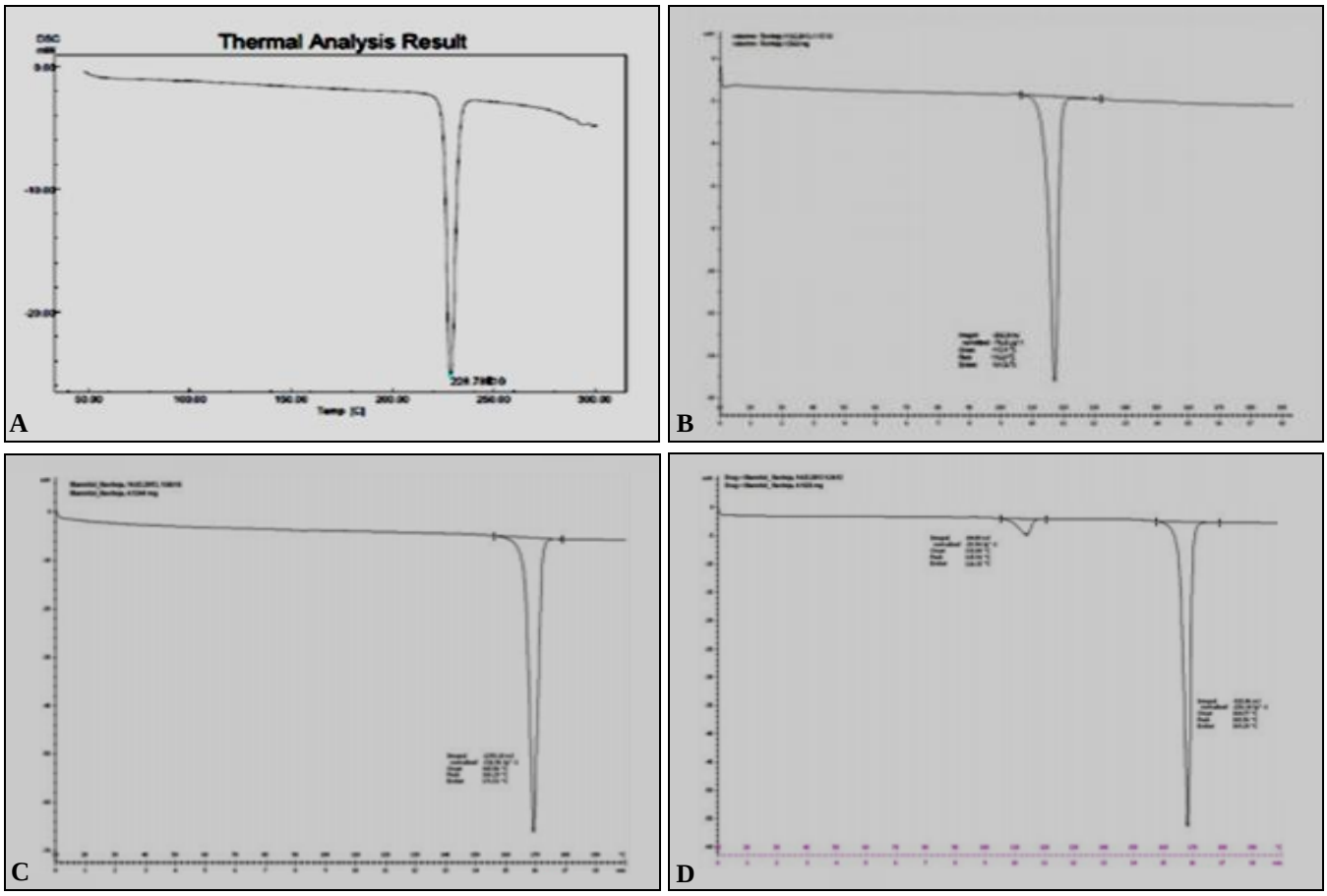


FIG. 2: (A) DSC OF NEB (B) DSC OF VAL (C) DSC OF MANNITOL (D) DSC OF VAL WITH MANNITOL

Pre-compression Parameter: Pre-compression parameter like bulk density, tap density, angle of repose, Hausner's ratio, and carr's index was measured **Table 4**.

TABLE 4: PRE-COMPRESSION PARAMETER

Formulations	Bulk Density (gm/ml) (n=3)	Tapped Bulk Density (gm/ml) (n=3)	Compressibility (%) (n=3)	Angle of Repose (θ)
F1	0.520 ± 0.04	0.655 ± 0.06	13.5 ± 0.2	26°56'
F2	0.525 ± 0.03	0.675 ± 0.07	15.0 ± 0.3	27°72'
F3	0.518 ± 0.02	0.671 ± 0.05	15.3 ± 0.3	25°60'
F4	0.530 ± 0.05	0.666 ± 0.08	18.9 ± 0.7	28°10'
F5	0.525 ± 0.07	0.675 ± 0.07	13.2 ± 0.5	29°38'
F6	0.515 ± 0.05	0.655 ± 0.06	14.0 ± 0.6	27°48'
F7	0.523 ± 0.04	0.653 ± 0.05	19.1 ± 0.8	25°89'
F8	0.535 ± 0.03	0.630 ± 0.04	12.5 ± 0.4	26°32'
F9	0.552 ± 0.02	0.663 ± 0.06	14.1 ± 0.3	30°12'
F10	0.531 ± 0.01	0.645 ± 0.05	11.4 ± 0.4	24°75'
F11	0.543 ± 0.05	0.652 ± 0.04	10.9 ± 0.5	22°45'
F12	0.535 ± 0.05	0.651 ± 0.06	11.6 ± 0.2	21°48'
F13	0.529 ± 0.04	0.668 ± 0.05	13.9 ± 0.1	25°11'
F14	0.541 ± 0.04	0.668 ± 0.06	12.7 ± 0.3	22°69'
F15	0.545 ± 0.06	0.653 ± 0.04	10.8 ± 0.4	23°28'

Post-compression Parameter: The direct compression technique was used for the preparation of tablets. Post-compression parameter like weight variation, thickness, hardness, friability, wetting time, disintegration time, and drug content was measured. The evaluated parameters were within an acceptable range for all the F1-F15 formulations. The values are indicated in **Table 4**. Formulation F1-F15 found within the weight variation limit. No, any tablet weight deviation found in all formulation. The thickness of F1-F15 batches found between 3.0 to 3.6 mm. The hardness of all batches F1-F15 found between 3.40 to 3.90 kg/cm^2. It means all bathes have good mechanical strength. Friability of F1-F15 batches found below 1%.

TABLE 4: WEIGHT VARIATION, THICKNESS, HARDNESS AND FRIABILITY OF FORMULATION F1-F15

Formulation Code	Weight Variation (mg) (n=3)	Thickness (mm) (n=3)	Hardness (kg/cm^3) (n=3)	Friability %
F1	200.6 ± 2.36	3.07 ± 0.02	3.40 ± 0.36	0.50
F2	200.4 ± 2.36	3.04 ± 0.03	3.76 ± 0.32	0.40
F3	200.5 ± 2.05	3.04 ± 0.02	3.86 ± 0.25	0.35
F4	200.2 ± 2.78	3.20 ± 0.06	3.67 ± 0.14	0.50
F5	200.0 ± 2.72	3.06 ± 0.08	3.96 ± 0.12	0.60
F6	200.3 ± 2.46	3.06 ± 0.03	3.84 ± 0.20	0.20
F7	200.7 ± 2.30	3.04 ± 0.03	3.77 ± 0.35	0.40
F8	200.2 ± 2.10	3.07 ± 0.01	3.54 ± 0.30	0.55
F9	200.8 ± 2.01	3.02 ± 0.05	3.88 ± 0.22	0.45
F10	200.1 ± 2.56	3.43 ± 0.03	3.53 ± 0.37	0.35
F11	200.7 ± 2.20	3.51 ± 0.02	3.90 ± 0.10	0.40
F12	200.1 ± 2.31	3.52 ± 0.03	3.79 ± 0.43	0.30
F13	200.6 ± 2.42	3.45 ± 0.02	3.39 ± 0.29	0.40
F14	200.0 ± 2.52	3.46 ± 0.02	3.46 ± 0.31	0.30
F15	200.4 ± 2.32	3.43 ± 0.01	3.81 ± 0.25	0.40

Wetting Time: Wetting time depends on the inner structure of the tablet. The results of the wetting time were shown in **Table 5**. It was found that as the concentration of superdisintigrating agents was increased and wetting time was reduce in all formulations. This is because of the ability of swelling and capacity of water absorption by super-disintegrating agents. Formulation F15 gave minimum wetting time, *i.e.*, 8 sec for super disintegrating agent as CCS.

***In-vitro* Dispersion Time:** The *in-vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion was observed in all formulations. The *in-vitro* dispersion data is tabulated in **Table 5**. Similarly, as wetting time, *in-vitro* dispersion time was decreased as the concentration of superdisintegrating agent was increased**.** Formulation F10-F15 gave minimum *in-vitro* dispersion time compare to other formu-lations. It happens due to the effect of croscarmellose sodium.

***In-vitro* Disintegration Time:** It was found that as the concentration of superdisintegrating agent was increased and disintegration time was reduced in all formulations. The internal structure of tablets that is pore size distribution, water penetration into tablets, and swelling of disintegration ingredients are suggested to be the mechanism of disintegration.

Drug Content: % Drug content of formulation F1-F15 found within the acceptable limit as per IP.

TABLE 5: POST COMPRESSION PARAMETERS OF FORMULATION F1-F15

Formulation code	Wetting Time (Sec) (n=3)	*In-vitro* Dispersion Time (Sec) (n=3)	*In-vitro* Disintegration time (Sec) (n=3)	% Drug Content	
				NEB HCl (n=3)	VAL (n=3)
F1	420 ± 20	388 ± 15	378 ± 18	98.5 ± 0.5	99.9 ± 0.1
F2	303 ± 15	249 ± 13	311 ± 21	97.9 ± 0.2	99.7 ± 0.2
F3	142 ± 2	109 ± 10	239 ± 17	99.7 ± 0.3	99.8 ± 0.4
F4	86 ± 5	64 ± 6	99 ± 8	96.6 ± 0.2	99.9 ± 0.2
F5	47 ± 2	37 ± 6	89 ± 8	97.2 ± 0.4	99.7 ± 0.6
F6	45 ± 6	42 ± 8	80 ± 10	101. ± 0.3	99.8 ± 0.2

F7	51 ± 10	38 ± 5	108 ± 13	99.5 ± 0.4	99.4 ± 0.3
F8	59 ± 6	48 ± 12	52 ± 16	99.9 ± 0.6	99.7 ± 0.2
F9	75 ± 2	59 ± 4	65 ± 8	99.5 ± 0.2	99.5 ± 0.2
F10	17 ± 1	14 ± 2	19 ± 7	98.9 ± 0.6	99.6 ± 0.1
F11	18 ± 2	12 ± 1	12 ± 3	93.5 ± 0.3	99.7 ± 0.3
F12	14 ± 4	7 ± 1	13 ± 4	101.5 ± 0.5	99.8 ± 0.2
F13	12 ± 2	7 ± 2	9 ± 2	96.6 ± 0.9	99.7 ± 0.3
F14	12 ± 3	7 ± 1	17 ± 7	98.3 ± 0.6	99.5 ± 0.5
F15	8 ± 1	10 ± 3	19 ± 4	97.7 ± 0.5	99.4 ± 0.8

***In-vitro* Dissolution Study:** The results of dissolution studies of fast dissolving tablets are shown in **Tables 6** and **7**. Dissolution results show that more than 85% drug released after 5 min from all batches. It can be seen from the results that the dissolution rate was increased by increasing the proportion of superdisintegrants from 4mg to 20mg. The order for the superdisintegrants to enhance the dissolution rate could be ranked as CCS > CP > SSG **Fig. 4**.

TABLE 6: % DRUG RELEASE OF NEB FROM FORMULATION F1-F15

Batch code	% Drug Release in seconds (n=3)						
	30	60	90	120	180	240	300
SSG: Superdisintegrant							
F1	21.3±0.26	39.8±0.10	70.6±0.32	84.5±0.11	89.4±0.25	91.5±0.10	92.4±0.30
F2	30.4±0.30	57.7±0.15	80.4±0.05	86.6±0.30	90.2±0.15	94.3±0.23	98.4±0.15
F3	36.5±0.20	59.6±0.30	89.4±0.15	95.6±0.15	97.5±0.30	99.4±0.20	-
F4	42.3±0.40	51.7±0.10	69.6±0.26	79.3±0.20	89.5±0.20	94.4±0.32	97.4±0.20
F5	58.6±0.26	67.4±0.11	81.4±0.15	90.6±0.20	95.4±0.40	99.5±0.28	-
Crospovidone: Superdisintegrant							
F6	60.5±0.10	79.7±0.20	85.5±0.15	96.5±0.20	98.4±0.20	99.5±0.20	-
F7	45.3±0.32	59.8±0.10	82.5±0.10	86.3±0.15	89.5±0.32	91.4±0.21	96.5±0.26
F8	55.8±0.10	78.8±0.26	89.5±0.28	93.4±0.11	95.5±0.20	98.3±0.10	-
F9	59.4±0.25	69.6±0.20	92.5±0.05	95.6±0.20	99.6±0.26	-	-
F10	45.6±0.23	57.8±0.98	75.5±0.32	89.5±0.20	99.5±0.20	-	-
Crosscarmellose sodium: Superdisintegrant							
F11	55.7±0.15	69.6±0.20	89.6±0.25	98.5±0.25	-	-	-
F12	39.3±0.32	75.8±0.10	90.4±0.20	99.5±0.15	-	-	-
F13	38.5±0.10	70.5±0.15	99.6±0.15	-	-	-	-
F14	40.8±0.20	68.7±0.15	82.5±0.20	93.4±0.25	99.6±0.11	-	-
F15	59.7±0.15	75.6±0.23	89.7±0.20	98.6±0.15	-	-	-

TABLE 7: % DRUG RELEASE OF VAL FROM FORMULATION F1-F15

Batch code	% Drug Release in seconds (n=3)						
	30	60	90	120	180	240	300
SSG: Superdisintegrant							
F1	25.5±0.15	49.4±0.25	72.5±0.26	81.6±0.30	88.5±0.25	92.4±0.20	93.6±0.25
F2	32.2±0.25	56.6±0.30	82.5±0.32	89.3±0.15	92.4±0.28	94.4±0.30	99.5±0.20
F3	39.4±0.20	60.6±0.26	90.6±0.26	94.4±0.25	96.4±0.26	99.5±0.32	-
F4	49.3±0.15	52.6±0.26	70.5±0.30	82.6±0.26	92.4±0.32	93.5±0.30	98.4±0.26
F5	54.7±0.26	69.3±0.15	82.4±0.15	92.5±0.30	94.5±0.35	99.5±0.25	-
Crospovidone: Superdisintegrant							
F6	61.5±0.17	80.6±0.25	86.3±0.25	97.3±0.25	98.3±0.20	99.5±0.30	-
F7	49.4±0.20	60.6±0.32	81.3±0.17	87.5±0.20	90.4±0.25	92.6±0.26	97.4±0.32
F8	54.5±0.32	80.4±0.41	90.4±0.20	92.7±0.26	94.4±0.35	99.3±0.15	-
F9	60.5±0.20	70.5±0.15	93.6±0.32	96.4±0.25	99.5±0.36	-	-
F10	49.5±0.26	59.5±0.20	78.7±0.28	90.5±0.25	99.6±0.30	-	-
Crosscarmellose sodium: Superdisintegrant							
F11	55.8±0.15	71.6±0.30	90.3±0.15	99.4±0.35	-	-	-
F12	41.5±0.25	78.4±0.11	91.4±0.37	99.4±0.30	-	-	-
F13	42.3±0.30	71.5±0.25	99.5±0.30	-	-	-	-
F14	41.5±0.49	72.6±0.26	86.5±0.32	92.4±0.26	99.4±0.43	-	-
F15	62.4±0.11	78.3±0.35	92.6±0.30	99.3±0.20	-	-	-

The mechanisms by which drug dissolution enhancement occurs from tablets are numerous such as improved wettability, increased effective surface area, loss of drug crystallinity, and solubilization effects associated with the carrier are probably responsible for their effect. It can be inferred from the results that batch containing CCS (F13) exhibited a higher dissolution rate (99% release after 90 sec) as compared to that of batch containing CP (F6-F10) and SSG (F1–F5). Formulation F13 exhibits faster dissolution than other formulations. F13 batch was selected as promising formulation because of higher drug release, fastest disintegration time (9 sec), and optimum wetting time (12 s).

CONCLUSION: The above results, it can be concluded that the FDT (Fast dissolving tablet) of VAL and NEB HCL showing the enhanced dissolution may lead to improved bioavailability and effective therapy using solid dispersion method. Based on the *in-vitro* disintegration time and dissolution studies, formulations F13 was found to be promising and showed a disintegration time of 9 sec, and drug release was 99.6% and 99.5% for NEB HCl and VAL respectively.

It was concluded that fast dissolving tablets of NEB HCl and VAL were successfully formulated by employing the direct compression method with the help of a solid dispersion approach.

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