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ORIGINAL ARTICLE

Formulation and Evaluation Fast Dissolving Tablet of Nortriptyline HCl and Citalopram HBr for Treatment of Severe Depression

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ABSTRACT
The main aim is to combine nortriptyline HCl 50 mg with the citalopram HBr 40 mg by direct compression since combination of these two drugs showed significant superiority over citalopram alone in the treatment. Both drugs were undergoing extensive first pass hepatic metabolism, fdt formulation overcomes these problem. Excipients used in formulation are cross-povidone, sodium starch glycolate as superdisintegrant and mannitol, microcrystalline cellulose, magnesium stearate, talc as remaining excipient. Direct compression is used because it can formulate fdt with limited steps, cheap, high dose can be easily accommodate. Various precompression and postcompression studies were performed. Among 9 batches, nc8 batch was found to be the optimised batch with drug release, hardness, disintegration time, thickness, weight variation, friability, drug content, wetting time and water absorption ratio 92.21 %, 3.2 kg/cm², 76 sec, 3 mm, 199.9±1.68 mg, 0.69%, 97.21%, 20±0.9 sec, 113±0.9 respectively.
Keywords: *fast dissolving tablet nortriptyline hcl, citalopram hbr, direct compression, sodium starch glycolate, cros-povidone.*

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INTRODUCTION

Tablets are unit dosage form which contains one or more medicament with suitable excipient. Compared to other dosage forms tablets have relatively low manufacturing cost, packaging, more stability, temper resistance etc. The wide acceptance of tablet is due to ability of tablet to satisfy biopharmaceutical, marketing, production and patient requirements. Tablets offer advantages such as they are convenient dosage forms, they can be formulate to release the therapeutic agent to particular site within GI tract, less number of side effects, more accurate dosing, it is easier to mask the taste of bitter drugs, generally inexpensive. Tablet can be formulated with one or more therapeutic agent even if there are chemical or physical incompatibilities by using different approaches. A wide range of tablets can be formulated which offers range of release rates, duration, clinical effect. The chemical, physical and microbiological stability of tablets is superior to any other dosage forms.[1]

"A solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."The excipients used for formulation of FDT mostly contain at least one superdisintegrants. Permealising agent, bulking agent, sweetener or flavoring agent, lubricant.[2]

Nortriptyline HCl either inhibit the reuptake of the neurotransmitter such as serotonin at the β-receptors. It causes the more selective inhibition of the noradrenaline, which causes the symptomatic relieve from the depression. TCA does not cause inhibition of the monoamine oxidase nor do they affect the dopamine reuptake. As like other TCA antidepressants it has the effects on the histamine receptors 5-HT receptors in addition to other receptors.[11, 13]

Nortriptyline HCl has the half-life of 26 hours and belongs to BCS class II. It shows the bioavailability upto 85% and Tmax of 8.5 hours. The mechanism of action of Citalopram HBr is to inhibit the uptake of serotonin (5-HT). The molecular target of the Citalopram HBr is the serotonin receptor and thus inhibit uptake of serotonin in synaptic cleft. [13]

It has less binding affinity to histamine, acetylcholine and norepinephrine receptors. TCA drugs have more binding affinity than Citalopram HBr. They even have less affinity for the dopamine, GABA, muscarinic and cholinergic receptors. [11-14]

Citalopram HBr has the half life of about 35 hours and belongs to BCS class II. It has the bioavailability 80%. Both drugs belongs to BCS class II and undergo extensive first pass hepatic metabolism so formulating fast dissolving tablet using both these drugs will give better therapeutic effect than conventional tablet.[12].

MATERIAL AND METHODS

Nortriptyline HCl obtained as a gift sample from Flemingo pharmaceuticals, Thane and Citalopram HBr is obtained as gift sample from Flemingo pharmaceuticals Ltd, Thane. Mannitol, microcrsyraline cellulose, sodium starch glycolate, cross-povidone, , lactose, magnesium stearate, talc, aspartame. (Research lab).

3. METHOD

The fast dissolving tablet containing Nortriptyline HCl and Citalopram HBr was prepared by the direct compression method using superdisintegrants such as sodium starch glycolate and cross-povidone.

The drug and superdisintegrants are weighed accurately and passed through the sieve #40 and transferred into polythene bag and mixed in polythene bag upto 3 min. Then add other excipients mannitol, microcrystalline cellulose, cros-povidone, sodium starch glycolate, magnesium stearate, talc to it. Add talc and magnesium stearate at the last and mix it thoroughly.

Finally all the batches were compressed under rotary tablet compression machine. (Make-CREATE INDUSTRIES, MODEL-LP8GMP).

Table 1: Formulation table of fdt of nortriptyline hcl and citalopram hbr.

Ingredients	**Batches (mg)**								
	NC1	**NC2**	**NC3**	**NC4**	**NC5**	**NC6**	**NC7**	**NC8**	**NC9**
NortriptylineHCl	50	50	50	50	50	50	50	50	50
Citalopram HBr	40	40	40	40	40	40	40	40	40
Mannitol	56	50	44	56	50	44	52	40	28
MCC	40	40	40	40	40	40	40	40	40
Cros-povidone	4	10	16	-	-	-	4	10	16
Sodium starch glycolate	-	-	-	4	10	16	4	10	16
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Aspartame	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	200	200	200	200	200	200	200	200	200

PRECOMPRESSION PARAMETERS OF POWDER BLEND: [5, 6, 8, 9]

The fast dissolving powder blend was evaluated for various precompression evaluation parameters. This includes Angle of repose, Bulk density, Tapped density, Hausner's ratio and compressibility index which are performed before the compression of tablet.

Identification test by U. V vis. Spectrophotometer [5, 6, 8, 9]

i. For Nortriptyline HCl:

Weigh accurately 50 mg of drug and transfer it volumetric flask and dissolve it with distilled and water and make up the remaining volume with the distilled water to produce 1000 µg/ml. Now take the 1 ml and dilute upto 100 ml in volumetric flask of 100 ml to produce 10 µg/ml. This was scanned on UV-Vis spectrophotometer between wavelength ranges of 200-400 nm against distilled water as blank solution. From the spectrum obtained absorption maxima was determined.

ii. For Citalopram HBr:

Weigh accurately 50 mg of drug and transfer it volumetric flask and dissolve it with distilled and water and make up the remaining volume with the distilled water to produce 1000 µg/ml. Now take the 1 ml and dilute upto 100 ml in volumetric flask of 100 ml to produce 100 µg/ml. This was scanned on UV-Vis spectrophotometer between wavelength ranges of 200-400 nm against distilled water as blank solution. From the spectrum obtained absorption maxima was determined.

Melting point determination: [8, 9]

Melting point of fast dissolving tablet of Nortriptyline and citalopram HCl was determined by the capillary method. For this small amount of sample was taken in capillary tube which is sealed at end having diameter of about 1mm. Then capillary tube is placed in the melting point apparatus and heating is started, the temperature at which the sample starts melting was noted.

Solubility**:** [8, 9]

Solubility was determined by taking 5 mg of sample in different solvents such as distilled water, methanol, acetone, ethanol and checks whether soluble or not.

FTIR spectroscopy of Nortriptyline HCl and Citalopram HBr: [8, 9]

The FTIR spectrum of both API's was obtained on FTIR spectrophotometer (Perkin Elmer) separately. The spectrum was obtained by the pressed pellet technique. Pellet was made by mixing sample of drug and KBr in the ratio 1:100 and pressed under pressure upto 10 tons. The prepared pellet was scanned on the FTIR spectrophotometer from 4000 to 400 at resolution 1 cm^{-1}.

PRE-COMPRESSION EVALUATION [5, 6, 8, 9]

Bulk density: [8, 9]

The bulk density depends upon various parameters such as particle size, size distribution, and tendency of particle adhesion. Bulk density determines affects hopper design and milling equipment its size in scale up from pilot to commercial plant.The bulk density calculated by following method.

A sample powder of about 2 gm was taken and transferred to measuring cylinder of 100 ml and and tapped 3 times and volume occupied by the powder was measured.

Bulk density was calculated by the following formula:

$$Bulk\ density = \frac{weight\ of\ powder}{volume}$$

Tapped density: [8, 9]

The same measuring cylinder can be used to determine tapped density. This measuring cylinder tapped for 300 times per min and open operated 500 times. Volume was noted as Va and then again tapped for 750 times and this volume is noted as Vb.

Difference between Va and Vb is calculated, if the difference between Va and Vb is greater than 2% then again tapped for 1250 times. Tapped density is determined by using following formula.

$$Tapped\ density = \frac{weight\ of\ powder}{tapped\ volume}$$

Compressibility index:[8, 9]

Carr's index or compressibility index is the ability of powder blend to compress under pressure and decrease its volume which depends upon powder blend tapped density and bulk density. It is also depends upon the flow rate of powder blend indirectly. It is determined by using the formula:

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's ratio: [8, 9]

It is one of the parameter to check flow of powder blender or granules. The value greater than 1.25 indicates the poor flow. The hausners ratio greater than 1.50 indicates poor flow where the addition of glidant or increasing its concentration is required. It is not indicative of the how easy the consolidation occurs in tablet. Since the some powder with high value of the hausner's ratio poor flow consolidates rapidly which is required for uniform filling and complements the tablet machine's speed.

Hausner's ratio calculated by the following formula:

$$Hausner'ratio = \frac{tapped\ density}{bulk\ density}$$

Angle of repose: [8, 9]

Angle of repose was determined using fixed funnel method. The fixed funnel method employ a funnel that was its tip at given height (2cm), above the graph paper that was placed on a flat surface. Granules or tablet blend were carefully poured through funnel until the apex of conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile. Angle of repose was calculated using the following equation.

$\theta = \tan^{-1}(h/r)$,

Where, θ = angle of repose.

h= height of the pile.

r= radius of the base of the pile.

POST-COMPRESSION EVALUATION [5, 6, 8, 9]

Weight variation: [8, 9]

Weight variation test is done to ensure the uniformity of weight of tablet in each batch. For this as per IP 20 tablets were taken randomly and respective weight is taken and average weight is calculated is nothing but individual weight.

Table 2: Limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
From 130 to 324	7.5%
>324	5%

Thickness:[8, 9]

Thickness of the tablets was measured using vernier caliper. 10 tablets were taken randomly and thickness was calculated. It should be controlled within ±5 % variation of standard value. It is expressed in mm.

Hardness:[8, 9]

Hardness is nothing but the strength of the tablet to withstand the mechanical shocks, to avoid capping abrasion of tablet during the manufacture, packaging and shipping. It is the crushing strength of tablet.

Friability:[8, 9]

Friability is the ability of tablet to withstand shock, abrasion during handling, shipping, transportation etc. Roche Friabilator is used to perform the friability test. For this 10 tablets were taken and weighed accurately and then placed in Roche Friabilator. The Friabilator was rotated four minutes (100 revolutions) 25 revolutions per min.

The tablets were weighed again and compared to the initial weight. % friability was calculated and must be under 1 %. More friable tablet will have the lack if elegance % less patient acceptance. It will create excess dirty areas in manufacturing especially in coating and packaging. Friability can also affect the weight variation and content uniformity of tablet.

$$\%\ friability = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times 100$$

Disintegration test: [8, 9]

The USP device is used to test the disintegration time. This includes 6 glass tubes that have 3 inch length open at top surface and 10 mesh screens is present at the bottom end.

To determine the disintegration time for tablet, one tablet is placed in each tube and basket is filled with 1 L of water with simulated intestinal fluid 37±2 ^{0}C.

Move the basket up and down and through a distance of 5-6 cm at frequency of 28-32 cycles/min.

In-vitro dissolution: [8, 9]

The immediate release tablets are subjected to the in-vitro dissolution testing by using the 6.8 N phosphate buffer dissolution media for 30 min. Dissolution test were carried out in the dissolution test apparatus using 900 ml buffer solution and which is maintained at 37±0.2 ^{0}C. The tablets were cylindrical basket which is rotated at 50 rpm speed. At regular time interval of 5 min such as 5min, 10min, 15min, 20min etc. 5ml solution was withdrawn and filtered through whatman filter paper and analyzed at UV spectrophotometer. Further the % drug release and drug release kinetics were calculated.eg. zero order, first order, higuchi model, Hixson crowell model, Kors meyer peppas model etc.

Dissolution determination is very important as it is directly affect the bioavailability of drug. It is important tool that gives information for bioequivalence determination. It is generally referred as the IVIVC.

Drug content: [8, 9]

10 tablets were powdered using mortar and pestle. 100mg of powder was taken and transfer to volumetric flask and dissolve with the 6.8N phosphate buffer to form 1000 ppm solution. Further it is diluted 100 times and analyzed spectrophotometrically and further calculations were done to measure the drug content.

Wetting time: [8, 9]

A petri dish containing 0.2 % w/v amaranth solution (10ml) taken. The tissue paper with diameter of 10cm was placed in the petri dish with amaranth solution. Now place the tablet on the wetted tissue paper and time required for complete wetting of tablet i.e. upto the top of tablet was measured.

Water absorption ratio:[8, 9]

A piece of tissue paper was folded twice at the middle and placed in petri dish containing 6.8 N phosphate buffer solutions. A tablet was selected randomly and weight of tablet was measured and then places this tablet in petri dish with phosphate buffer. After complete wetting of tablet, tablet was taken and weighed. The water absorption ratio of tablet calculated by the following formula:

$$r = 100 \times \frac{Wa - Wb}{Wb}$$

Where, r = water absorption ratio.
Wa = weight of the tablet after phosphate buffer absorption.
Wb = weight of tablet before phosphate buffer absorption.
Content Uniformity: [8, 9]
10 tablets were powdered using mortar and pestle. 100mg of powder was taken and transfer to volumetric flask and dissolve with the 6.8N phosphate buffer to form 1000 ppm solution. Further it is diluted 100 times and analyzed spectrophotometrically and further calculations were done to measure the drug content.

RESULTS AND DISCUSSION

Pre-formulation studies [8, 9]

The absorption maximum of Nortriptyline HCl was found to be 239 nm in distilled water taken as blank. The absorption maximum of the Citalopram HBr is found to be 239 nm in distilled water as blank.

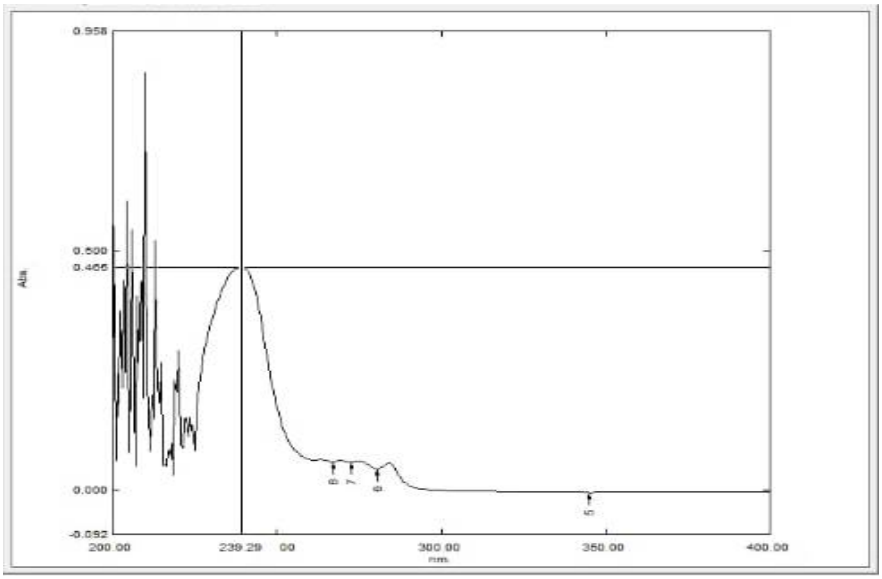

Figure 1: Absorption maxima of nortriptyline HCL

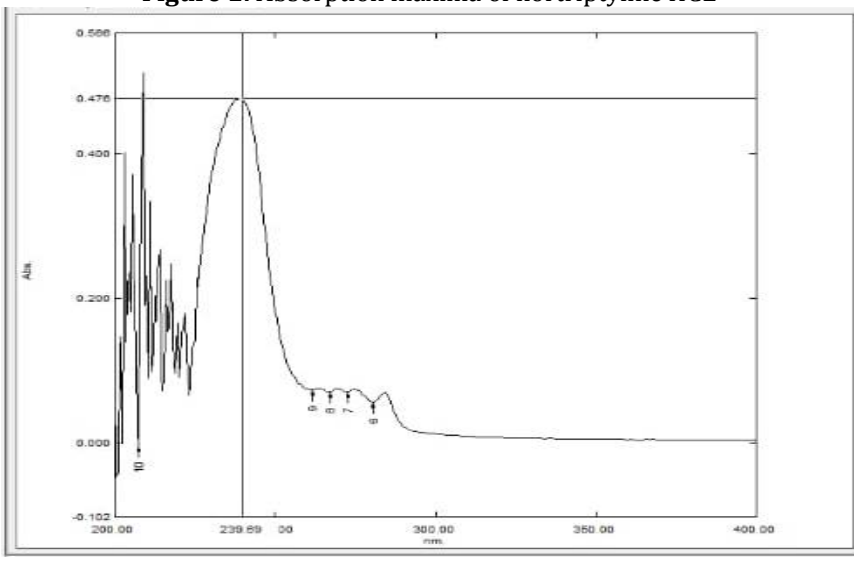

Figure 2: Absorption maxima of citalopram HBR

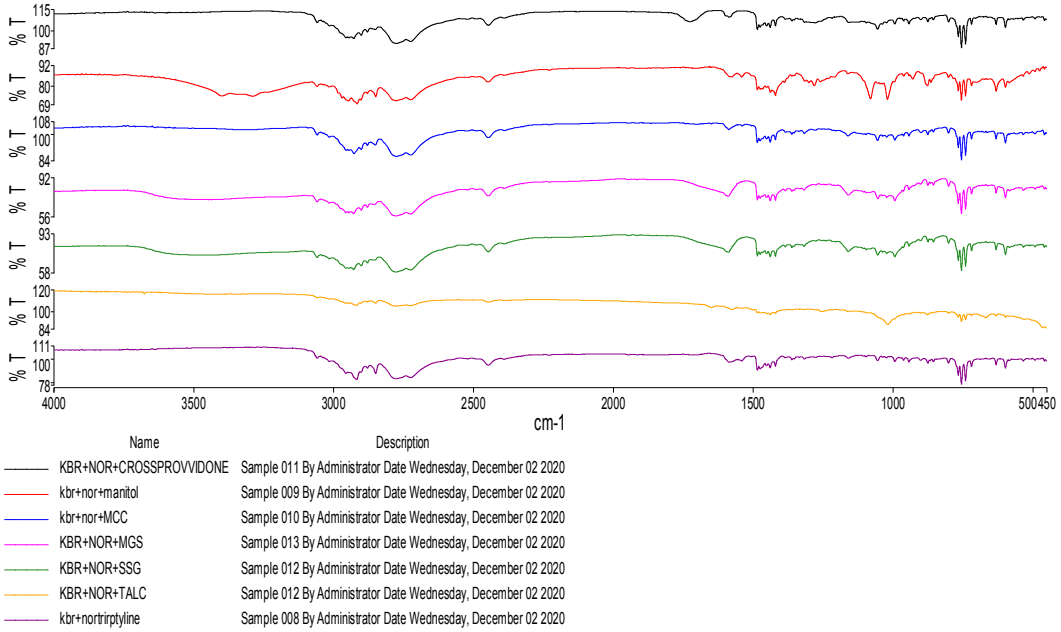

Figure 3: FTIR of nortriptyline HCL and excipient

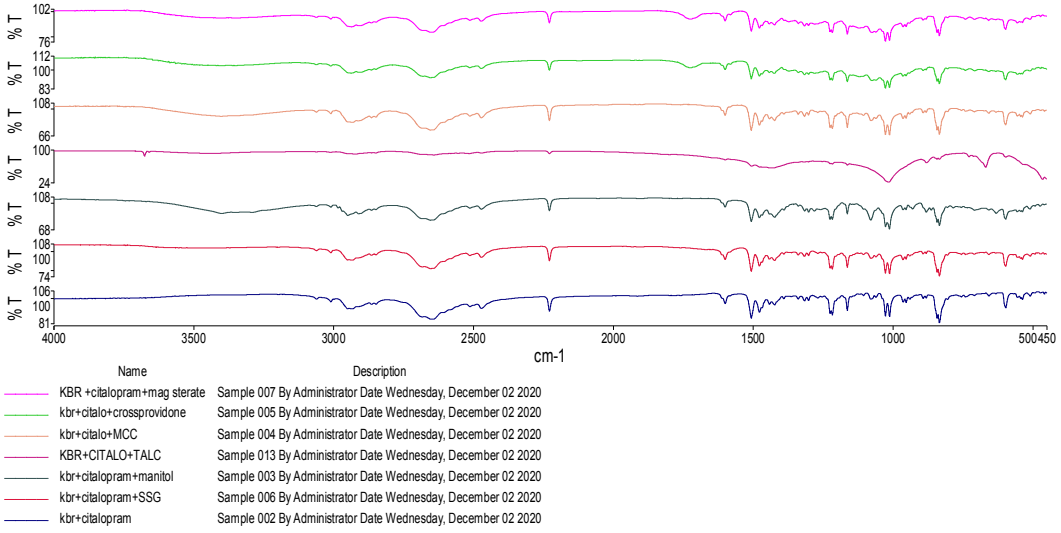

Figure 4: FTIR of citalopram HBR and excipient

Table 3: Preformulation study of nortriptyline hcl and citalopram HBR

Sr.no.	Parameter	Nortiptyline HCl	Citalopram HBr
1.	Identification by U.V. Vis spectrophotometer	239nm	239nm
2.	Melting point	217^{0}C-220^{0}C	182-188^{0}C
3.	Solubility	Freely soluble in ethanol (95%), sparingly soluble in water and methanol, practically insoluble in ether, in ether in benzene and in most solvents.	Sparingly soluble in water and soluble in ethanol.
4.	Compatibility studies	Compatible	Compatible

Pre-compression evaluation

The fast dissolving powder blend was evaluated for various precompression evaluation parameters. This includes Angle of repose, Bulk density, Tapped density, Hausner's ratio and compressibility index which are performed before the compression of tablet.

Table 4: Pre-compression evaluation of FDT of nortriptyline hcl and citalopram hbr

	Batches								
Parameter	**NC1**	**NC2**	**NC3**	**NC4**	**NC5**	**NC6**	**NC7**	**NC8**	**NC9**
Bulk density (gm/ml)	1.0712	1.0423	1.0565	1.0487	1.0623	1.0788	1.0491	1.0527	1.0629
Tapped Density(gm/ml)	1.2318	1.1882	1.1938	1.1955	1.2322	1.2406	1.1959	1.1895	1.2329
Carr's index (%)	13.03	12.27	11.50	12.27	13.78	13.04	12.27	11.50	13.78
Hausner's ratio	1.15	1.14	1.13	1.14	1.16	1.15	1.14	1.13	1.16
Angle of repose(degree)	24.4^0	23.5^0	21.8^0	22.5^0	24.2^0	24.7^0	23^0	$21^0.2^0$	22.8^0

Post-compression evaluation: [5, 6, 8, 9]

Various post compression evaluations were performed such as the weight variation, hardness, thickness, friability and uniformity of weight. The weight uniformity is indicative of the degree of uniformity of active drug. The thickness of the tablet is important aspect considered during packaging disintegration and dissolution of the tablet. Vernier caliper is used to measure the thickness of the tablet. Hardness is important as it maintains the integrity of the tablet during its transportation, storage, handling of the tablet. The friability of the tablet is measured by using the Roche Friabilator. Friability of the tablet must be less than 1%. Dissolution and drug content uniformity is measured as per USP guidelines.

Table 5:Results of post compression evaluation of FDT of nortriptyline HCL and citalopram HBR

Batches	**Weight variation**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Disintegration test (sec)**	**% Release(%)**	**drug content (%)**	**Wetting time (sec)**	**Water absorption ratio**
NC1	198.6±0.38	3	3.5	0.63	92	85.89	90.12	40±0.5	61±0.5
NC2	197.7±0.48	3	3.4	0.59	87	87.12	92.38	28±0.8	78±0.7
NC3	198.8±0.58	3	3.3	0.54	85	90.67	93.89	20±0.5	81±1.4
NC4	197.3±0.92	3	3.4	0.58	91	87.23	92.87	38±1.0	62±0.4
NC5	198.5±0.28	3	3.4	0.58	87	87.97	92.57	25±0.7	75±0.6
NC6	197.5±0.72	3	3.3	0.53	81	90.78	93.11	20±0.6	80±0.9
NC7	198.2±1.02	3	3.5	0.62	80	89.97	95.18	36±0.8	93±1.2
NC8	199.9±1.68	3	3.2	0.69	76	92.21	97.91	20±0.9	113±0.9
NC9	197.5±0.72	3	3.3	0.53	68	90.98	93.24	25±1.2	105±1.1

Table 6: Post compression evaluation fdt of nc8 (optimised batch)

Sr.no.	**Parameters**	**NC8**
1.	Uniformity of weight (gm)	199.9±1.68
2.	Thickness (mm)	3
3.	Hardness (kg/cm^2)	3.2
4.	Friability (%)	0.69
5.	Drug content	97.91
6.	% drug release	92.21

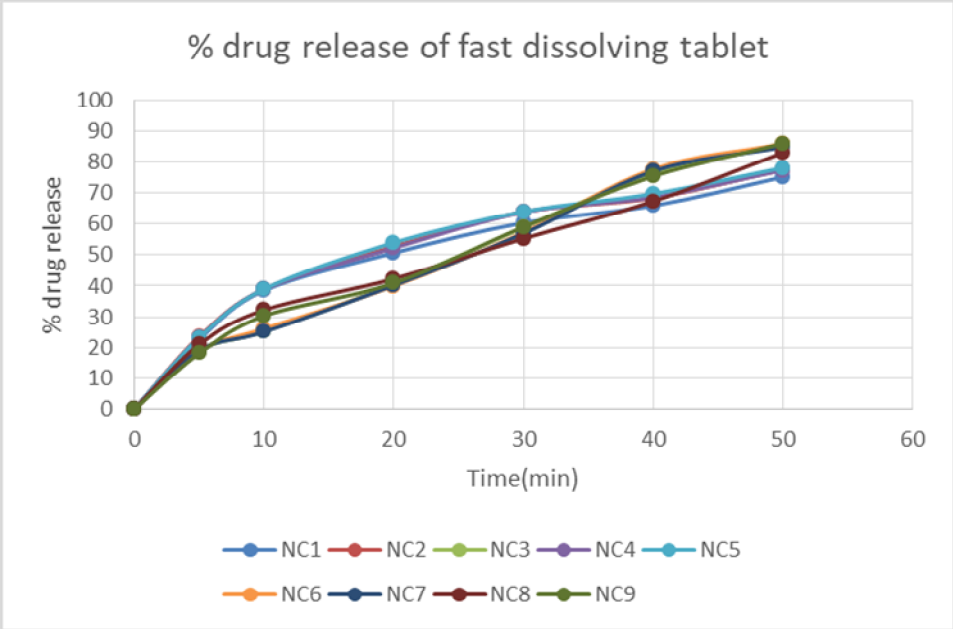

Figure5: Percentage drug release from FDT batches nc1 to nc9

Table 7: Drug release kinetics of optimized batch

Time (min)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
5	20.99	79.01	2.236	1.898	0.699	1.322	20.99	4.291	0.351
10	32.22	67.78	3.162	1.831	1.000	1.508	11.23	4.077	0.565
20	42.29	57.71	4.472	1.761	1.301	1.626	10.07	3.864	0.778
30	55.29	44.71	5.477	1.650	1.477	1.743	13	3.549	1.093
40	67.27	32.73	6.325	1.515	1.602	1.828	11.98	3.199	1.443
50	82.95	17.05	7.071	1.232	1.699	1.919	15.68	2.574	2.068
60	92.21	7.79	7.746	0.892	1.778	1.965	9.26	1.982	2.660

KINETIC MODEL

The batches NC1 to NC9 contain different superdisintegrants or the combinations of superdisintegrant. It was found that batches most of batches show higuchi drug release pattern.

CONCLUSION

The fast dissolving tablets of Nortriptyline HCl and Citalopram HBr were prepared by direct compression method which is one of the cheap and easy methods for preparation of the fast dissolving tablets. There are many batches were prepared to minimize the error and get the optimized batch. All preformulation parameters such as melting point, solubility, identification by UV spectrophotometer, compatibility by FTIR spectroscopy conducted and their results were found within limits. FTIR results and other compatibility study results show that the drug and excipients (superdisintegrant and other excipient) are compatible with each other to incorporate in the formulation. Precompression studies of the powder blend of the fast dissolving tablet were performed and all the values are found to be within acceptable limits of pharmacopoeia specification. The post compression parameter suggests that all the parameters such as Hardness, weight variation friability are within acceptable limit. In-vitro drug release study carried using 6.8N phosphate solution upto 1 hr and among all batches the dissolution of were performed and NC8 batch was found to be optimized batch. Drug release of optimized batch was found to be 92.21 % upto 1 hr. Therefore the fast dissolving tablet of Nortriptyline HCl and citalopram HBr can be used for treatment of severe depression.

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AUTHORS CONTRIBUTIONS
All authors contributed equally.

CONFLICT OF INTERESTS
Declare none.

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