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Formulation, Optimization and Evaluation of Taste-Masked Fast Dissolving Tablets of Amitriptyline and Mirtazapine

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ABSTRACT

Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablet. In the present study, an attempt has been made to prepare taste-masked fast dissolving tablets of two drugs, Amitriptyline and Mirtazapine using Primojel as and MCC as superdisintegrants and Camphor as subliming agent by direct compression technique. Both the drugs have bitter taste and pertaining to that patient compliance is less. Initially, the cation exchange resins Tulsion 335, Tulsion 339, Tulsion 344 were selected to prepare drug resin complex for masking the bitter taste of selected drugs. Finally, Tulsion 344 was used further for the study as this resin showed maximum drug loading. Six trial batches were prepared with each drug to find out the appropriate superdisintegrants. Based on the evaluation of trial batches, Primojel was selected for formulating the final batches by using Box-Behnken optimization tool. Concentration of superdisintegrants, Primojel & MCC and subliming agent Camphor were chosen as independent parameters and disintegration time (DT), % friability and % drug release were selected as dependent variables. The prepared tablets belong to trial batches and factorial batches were evaluated for pre-compression and post-compression parameters. The hardness of the tablets was in the range of 3.42-4.87 Kg/cm2 and 3.55-4.98 Kg/cm2 for Amitriptyline and Mirtazapine, respectively. The percentage friability of the tablets was less than one. Weight variation test results showed that the tablets were deviating from the average weight within the permissible limits of ±7.5 %. Drug content uniformity study results showed that uniform dispersion of the drug throughout the formulation i.e. 90.26%-99.97% for Amitriptyline and 92.82%-99.95% for Mirtazapine. An optimized batch was selected based on results obtained with ANOVA and evaluation parameters. Optimized batches of both the drugs showed better disintegrating character along with the rapid release (99.38±1.15% & 99.12±1.17%) for Amitriptyline and Mirtazapine, respectively, within 30 minutes. It was observed that there was no physical changes in the optimized formulations till the complete time period of stability. The drug content in the optimized formulations was found to be 99.05±1.12% (Aopt) and 99.11±1.11% (Mopt) at the end of three (03) months.

Keywords: *Fast dissolving drug delivery system, taste-masking, Tulsion 344, Amitriptyline, Mirtazapine, Box-Behnken design.*

INTRODUCTION

One of the major properties governing the patient compliance of the drug is its taste [1]. Oral administration of the bitter drug with an acceptable degree of palatability is a key issue for health care providers. To achieve better compliance and therapeutic value for the patient and more business and profits for the company main practical problem that confronts a pharmacist is to mask the unpleasant taste of the drug [2]. Major taste-masking efforts are required before acceptance of the drug for marketing. It is important at this point to introduce some basic concepts related to the taste masking of the drug. The basic concept behind the taste masking of any drug is based on the reduction of its solubility in the saliva so that the drug concentration in the saliva will be lower than that of the threshold value. The desire for improved palatability of formulations led to the development of various new technologies for taste abatement. Many of these technologies were successfully

commercialized [3]. Comforts of drug administration and patient compliance turned out to be an important consideration for the design of dosage forms. Amitriptyline is a tricyclic antidepressant (TCA), 3(10,11dihydro 5H dibenzo (a,b) cyclohetene-5-cylidene)-N,N-dimethylpropan-1-amine. It is the most widely used TCA and has at least equal efficacy against depression as the newer class of selective serotonin reuptake inhibitor (SSRI) according to a study from early 2001 [4]. As well as reducing depressive symptoms, these types of tricyclics also ease migraines, tension headaches, anxiety attacks and some schizophrenic symptoms. It is also known to reduce aggression and violent behaviour [5].

Mirtazapine is an atypical antidepressant having noradrenergic and specific serotonergic activity. It belongs to the chemical series called piperazinoazepines. It acts by blocking the histaminergic and muscarinic receptors and enhances serotonin neurotransmission at the 5-HT_1receptor. It is a tetracyclic antidepressant that is usually prescribed to patients suffering from major depression and anxiety. A large number of geriatric patients were reported to be receiving this medication [6-7]. The drug has bioavailability of 50% due to first-pass metabolism, high protein binding (80 %) and very high half-life (20–40 h) [6]. The aim of this study is to formulate, optimize and evaluate Amitriptyline and Mirtazapine fast dissolving tablets which will be absorbed from epigastric region and hence, the first pass metabolism is avoided.

MATERIAL AND METHODS

2.1 Materials

Amitriptyline and Mirtazapine were procured from Sigma Aldrich (Sigma Aldrich, Japan). Polyplasdone XL-10, Ac-di-Sol, Primojel from Simson Pharma limited, Mumbai, India. All the ingredients/chemicals were procured from various reputed companies.

2.2 Methods:

2.2.1 Determination of melting point

The melting points, of both the drugs i.e., Amitriptyline and Mirtazapine, were determined using open capillary method. The drug was packed into the capillary. The average of three values was taken as the melting point of the drug [8].

2.2.2 Compatibility study using FTIR technique

Drug-excipient compatibility study was carried out by FTIR (Shimadzu, Affinity- 1) spectroscopy. The mixture of drug and KBr (potassium bromide) was ground into fine powder using mortar pestle and then compressed into discs in a hydraulic press at a pressure of 75 kg/cm2. Each KBr disc was scanned 45 times at a resolution of 2 cm^{-1}. The characteristic peaks of both the standard drugs were recorded and compared with that obtained with individual formulation blend(s) [9].

2.2.3 Preparation of Taste masked polymeric complexes of the selected Drugs

2.2.3.1 Selection of Resin

For the acidic drugs anion exchange resins are used and for the basic drugs, cation exchange resins are used. Due to the basic nature of the drug & our requirement to mask the taste of drug along with optimum drug loading, the cation exchange resins Tulsion 335, Tulsion 339, Tulsion 344 were selected to prepare drug resin complex.

2.2.3.2 Preparation of drug-resin complex

The batch process was used to prepare the resinates. Drug: Resin ratios from 1:1 to 1:3 was prepared. An accurately weighed amount of activated resin particles was suspended in demineralised water for 30 min in a beaker containing 50ml of demineralised water to allow uniform swelling of polymer, after which the drug was added slowly under stirring conditions. The stirring was continued for 2 hrs. After allowing the particles to settle, the mixture was filtered into Whatman filter paper no. 41 and washed with 50ml of demineralised water to extract the free drug. With appropriate dilutions, the concentration of free drug in the filtrate was determined spectrophotometrically at λmax of each drug. The amount of drug bound to resin was determined by the difference between the original amount of selected drug and the amount of the collective filtrate [10-11].

2.2.3.3 Optimization of various parameters for maximum drug loading

2.2.3.3.1 Purification/Activation of Ion Exchange Resin

Tulsion 344, 1 gm placed on a whatman filter paper in a funnel, was washed with distilled water. The wet resin was activated with 1N HCl (100 ml), washed with purified water, and dried up overnight in a hot air oven at 50^0C before being placed in an airtight glass container. In the same way alkali activation of the Tulsion 344 using 1N NaOH was done. Tulsion 344 was also activated with combined treatment of 1N HCl and 1N NaOH solutions. The effect of resin activation on drug loading was studied.

2.2.3.3.2 Effect of Drug: Resin Ratio on Loading

Resinates were prepared using batch method. Drug: Resin ratios from 1:1 to 1:3 were prepared.

2.2.3.3.3 Effect of Soaking Time

For 10, 30, 40, 60, 90, and 120 minutes, selected resin was immersed in 25ml of deionised water. Selected drugs, Amitriptyline & Mirtazapine (in a 1:2 ratio) was accurately measured and applied to previously soaked resins. For 1 hour, the solutions were stirred. The mixtures were filtered using whatman filter paper no. 41, and the amount of free drug in the filtrate was measured spectrophotometrically at λmax of each drug [12-13].

2.2.3.3.4 Effect of pH

Accurately weighed quantity of Amitriptyline & Mirtazapine (as per 1:2 ratio) was added to selected resin that was soaked in 25 ml of solution of pH 2, 3, 4, 5, 6, 7 and 8 using standard solutions of hydrochloric acid and sodium hydroxide. The solutions were stirred for 1 hr. The mixtures were filtered using Whatman filter paper no. 41, and the amount of unbound drug in the filtrate was measured spectrophotometrically at λmax of each drug.

2.2.3.3.5 Effect of Stirring Time

For 30 minutes, selected resin was immersed in 25 ml of demineralised water. A precisely weighed quantity of selected drugs, (in a 1:2 ratio) was applied to the previously soaked resin. For 10, 30, 60, 90, 120, and 150 minutes, the solutions were stirred. The mixtures were filtered using Whatman filter paper no. 41, and the amount of unbound drug in the filtrate was measured spectrophotometrically at λmax of each drug [14-16].

2.2.3.4 Formulation development of Taste masked Fast disintegrating tablets

In the present work, taste masked fast disintegrating tablets of selected drugs i.e., Amitriptyline and Mirtazapine were prepared, and formulation factors were optimized using Box-Behnken design (BBD) to design a formulation with good strength with excellent fast disintegrating property.

2.2.3.4.1 Preparation of trial batches

Preliminary trial formulations of selected drugs were designed by sublimation method using three superdisintegrants (Polyplasdone XL-10, Ac-di-Sol, Primojel) in different ratios (5-10% w/w) along with Camphor (10-20% w/w) as subliming agent. Aerosil (lubricant) was added to impart the hardness to the tablets [17]. The formulation chart of trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine were shown in table 1 & 2. Trial batches were prepared to select out an appropriate superdisintegrant which will show rapid disintegration of the drug.

Table 1: Formulation chart for preliminary trial batches of taste masked fast dissolving tablets of Amitriptyline

Ingredients (mg)	**Formulation Code**					
	AT1	**AT2**	**AT3**	**AT4**	**AT5**	**AT6**
DRC (Eq. to 50 mg of Amitriptyline)	104.5	104.5	104.5	104.5	104.5	104.5
Polyplasdone XL-10	10	20	-	-	-	-
Ac-di-Sol	-	-	10	20	-	-
Primojel	-	-	-	-	10	20
Camphor	20	40	20	40	20	40
Starch	89.5	54.5	89.5	54.5	89.5	54.5
MCC	5	10	5	10	5	10
Mannitol	15	15	15	15	15	15
Aerosil	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4
Total	250	250	250	250	250	250

*DRC-Drug-resin complex

Table 2: Formulation chart for preliminary trial batches of taste masked fast dissolving tablets of Mirtazapine

Ingredients (mg)	Formulation Code					
	MT1	MT2	MT3	MT4	MT5	MT6
DRC (Eq. to 15 mg of Mirtazapine)	31.5	31.5	31.5	31.5	31.5	31.5
Primojel	10	20	-	-	-	-
Polyplasdone XL-10	-	-	10	20	-	-
Ac-di-Sol	-	-	-	-	10	20
Camphor	20	40	20	40	20	40
Starch	115.5	80.5	115.5	80.5	115.5	80.5
MCC	5	10	5	10	5	10
Mannitol	12	12	12	12	12	12
Aerosil	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4
Total	200	200	200	200	200	200

2.2.3.5 Pre-compression and post-compression studies

2.2.3.5.1 Pre-compression studies of trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine

Preliminary trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine were evaluated for Bulk density, Tapped density, Compressibility index (I), Hausner's Ratio and Angle of repose.

Bulk density- It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and its volume was noted. It is expressed in gm/ml as given by

$$Db = \frac{M}{Vo}$$

Where M=Mass of powder

Vo= Bulk volume of Powder

Tapped density- It is the ratio of total mass to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume and expressed in gm/ml as given by

$$Dt = \frac{M}{Vt}$$

Where, M=Mass of powder

Vt= Tapped volume of powder

Angle of repose- The frictional forces in a loose powder can be measured by the angle of repose (θ) confirmed as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

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

Where θ = angle of repose

h = height in cm

r = radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Compressibility index (I) - It indicated the ease with which a material could be induced to flow and expressed in percentage as given by

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt = tapped density of the powder.

Db = bulk density of the powder

Hausner's Ratio-For the determination of the Hausner ratio, the tapped bulk density (ρt) and aerated bulk density (ρa) of a powdery or granular substance are measured. The Hausner ratio is defined as follows:

$$H = \frac{\rho t}{\rho a}$$

2.2.3.5.2 Post-compression studies of trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine

Preliminary trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine were also evaluated for Weight variation, Hardness, Tablet Friability, Tablet Disintegration, Uniformity of dosage units, Wetting Time and *In-vitro* dissolution studies.

Weight variation

The twenty tablets were chosen at random from each formulation and weighted on a digital balance to calculate the average weight. Specific tablets were then weighed, and their weights were compared to an average weight.

Hardness

Tablet hardness was determined with the Hardness Tester (Pharma test GmbH, Hainburg, Germany) for 10 tablets (with known weight and thickness) of each batch; the average hardness and standard deviation were reported.

Tablet Friability

Friability of tablets was carried out using Roche friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a Friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture was recorded as the percentage weight loss. Friability should not more than 1%.

$$\% \text{ Friability} = 100\,(1 - W1/W2)$$

Where W1=Total weight of twenty tablets before friability

W2=Total weight of twenty tablets after friability

Tablet Disintegration

Disintegration of tablets was performed according to USP 36 using disintegration tester (Electrolab, India). A minimum of 6 tablets of each product were tested. One tablet of each product was placed in each of the six tubes of the basket. Then the apparatus was operated using 0.1N HCl maintained at 37±2°C as a disintegration medium.

Uniformity of dosage units

The uniformity of dosage units can be demonstrated either by content uniformity or weight variation according to USP 36. The content uniformity is based on the assay of the individual content of the drug substance in several individual dosage units to determine whether the individual content is within limits set. Five tablets of each drug were selected randomly and dissolved in 100 mL of 0.1N HCl, stirred for 60 min, and filtered. One ml of the filtrate was diluted to 100 mL with 0.1N HCl. Absorbance of these solution was measured at respective wavelength of selected drugs using 0.1N HCl as blank and drug content in respective samples was estimated [18].

Wetting Time

Five circular tissue papers were placed in a Petri dish of 10-cm diameter. Ten milliliters of water containing 0.5% eosin, a water-soluble dye, was added to the Petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch [19].

***In-vitro* Dissolution studies**

Dissolution test was carried out using USP type II dissolution test apparatus at 37±2°C and 50-rpm speed. Nine hundred milliliters of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 mL was withdrawn at specific time intervals and amount of drug released from DRC was determined [19].

2.2.3.6 Design of Experiment:

In a full factorial design, all the factors are studied in all the possible combinations, as it is most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. Design of experiment with the minimum number of experiments in preparing formulations with different variables comes to save time and costs. Methods used in experimental design include: mixture, factorial, combined, and response surface. The present work aimed at developing fast-disintegrating tablets of taste masked Amitriptyline and Mirtazapine by using optimization technique. Box-Behnken response surface methodology is most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. Based on preliminary trials, Primojel (5, 10 and 15%), MCC (5, 7.5 and 10%) and Camphor (10, 15and 20%) were selected as independent parameters. Formulations were generated by taking three factors at three level Box-Behnken design (BBD). The response surface methodology was applied to investigate the relative significance of the three variables, Primojel (X1), MCC (X2) & Camphor (X3) and their interaction on the responses i.e. disintegration time (Y1), % Friability (Y2) and percentage drug release (Y3) was studied. The statistical experimental design was generated, evaluated for the quality of fit of the model and the constant and regression coefficients were calculated. To graphically show the influence of each factor on the responses, the contour plots were generated using the Design-Expert® software (Version 13 Stat-Ease Inc. Minneapolis, USA) [20-23].

2.2.3.7 Preparation of Fast dissolving tablets of selected drugs

Fast dissolving tablets (FDT) of selected drugs, Amitriptyline and Mirtazapine were prepared by sublimation method according to the formulae given in table 3 & 4. Camphor as subliming agent. Aerosil was added to impart hardness to the tablet. All the ingredients were passed through #60 mesh separately, weighed and mixed in geometrical order. Then, lubricant and glidant (# 200 mesh) were added and mixed for further 5 min. The blend thus obtained was directly compressed using 7 mm flat round punches into tablets of 200 mg on a 10-station rotary tablet machine (Clit, Ahmedabad, India). The compressed tablets were then subjected to sublimation at 60° for six hours in hot air oven [24].

Table 3: Factorial design formulations of taste masked fast dissolving tablets of Amitriptyline

Ingredients (mg)	Formulation Code								
	Drug-Resin complex (Eq. to 50 mg of Amitriptyline)	Factor A	Factor B	Factor C	Other Excipients				
		Primojel	MCC	Camphor	Mannitol	Aerosil	Mg stearate	Starch	Total
AF1	104.5	12.5	12.5	37.5	15	2	4	62.0	250
AF2	104.5	37.5	18.75	25	15	2	4	43.25	250
AF3	104.5	12.5	18.75	25	15	2	4	68.25	250
AF4	104.5	37.5	12.5	37.5	15	2	4	37.0	250
AF5	104.5	25	18.75	37.5	15	2	4	43.25	250
AF6	104.5	25	25	50	15	2	4	24.5	250
AF7	104.5	12.5	18.75	50	15	2	4	43.25	250
AF8	104.5	25	25	25	15	2	4	49.5	250

AF9	104.5	25	12.5	50	15	2	4	37.0	250
AF10	104.5	12.5	25	37.5	15	2	4	49.5	250
AF11	104.5	37.5	18.75	50	15	2	4	18.25	250
AF12	104.5	25	12.5	25	15	2	4	62.0	250
AF13	104.5	37.5	25	37.5	15	2	4	24.5	250
AF14	104.5	25	18.75	37.5	15	2	4	43.25	250
AF15	104.5	25	18.75	37.5	15	2	4	43.25	250

Table 4: Factorial design formulations of taste masked fast dissolving tablets of Mirtazapine

Ingredients (mg)	**Formulation Code**								
	Drug-Resin complex (Eq. to 15 mg of Mirtazapine)	**Factor A**	**Factor B**	**Factor C**	**Other Excipients**				
		Primojel	**MCC**	**Camphor**	**Mannitol**	**Aerosil**	**Mg stearate**	**Starch**	**Total**
MF1	31.5	20	15	30	12	2	4	85.5	200
MF2	31.5	20	20	40	12	2	4	70.5	200
MF3	31.5	30	10	30	12	2	4	80.5	200
MF4	31.5	10	15	40	12	2	4	85.5	200
MF5	31.5	10	20	30	12	2	4	90.5	200
MF6	31.5	30	15	20	12	2	4	85.5	200
MF7	31.5	20	10	40	12	2	4	80.5	200
MF8	31.5	20	20	20	12	2	4	90.5	200
MF9	31.5	30	20	30	12	2	4	70.5	200
MF10	31.5	20	10	20	12	2	4	100.5	200
MF11	31.5	10	15	20	12	2	4	105.5	200
MF12	31.5	20	15	30	12	2	4	85.5	200
MF13	31.5	10	10	30	12	2	4	100.5	200
MF14	31.5	30	15	40	12	2	4	65.5	200
MF15	31.5	20	15	30	12	2	4	85.5	200

2.2.3.8 Pre-compression studies and post-compression studies of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine

The taste masked fast dissolving tablet blends were also evaluated for pre-compression and post-compression studies to determine their flow and compressibility.

Based on results obtained from factorial design and evaluation parameters, an optimized batch for both the drugs were selected. The formula obtained from optimization study was utilized further for the formulation of optimized batches which were further evaluated for post-compression parameters (Table 5).

Table 5: Formulation design of optimized batch of taste masked fast dissolving tablets of Amitriptyline

Ingredients (mg)	Formulation Code								
	Drug-Resin complex (Eq. to 50 mg of Amitriptyline & 15 mg of Mirtazapine)	Factor A	Factor B	Factor C	Other Excipients				
		Primojel	MCC	Camphor	Mannitol	Aerosil	Mg stearate	Starch	Total
Aopt	104.5	32.77	24.83	42.16	15	2	4	24.74	250
Mopt	31.5	28.50	19.56	37.41	12	2	4	65.03	200

*Aopt & Mopt=optimized batch of Amitriptyline & Mirtazapine

2.2.3.9 Evaluation of optimized batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine

The optimized formulations thus prepared were evaluated for post-compression parameters as mentioned in above section and stability testing.

2.2.3.10 Stability testing

Accelerated stability studies on the optimized promising formulations were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40°/75% RH for 3 months period (as per ICH guidelines). At interval of 1 month, the tablets were visually examined for any physical changes, changes in drug content and *in-vitro* drug release [25-26].

RESULTS AND DISCUSSION:

3.1 Determination of melting point

The melting points, of all the three drugs i.e., Amitriptyline and Mirtazapine, were determined using open capillary method. The melting point of Mirtazapine and Amitriptyline were compared with standards and depicted in table 6.

Table 6: Melting Point values of selected drugs

S. No.	Active Ingredients	Melting Point (^{0}C)	
		Observed value	Standard value
1.	Amitriptyline	198 ^{0}C	195-199 ^{0}C
2.	Mirtazapine	121 ^{0}C	119-123 ^{0}C

The observed melting point of both the drugs was in the standard range and thus, it was concluded that the drug samples were pure.

Compatibility study using FTIR technique:

Compatibility of both the drugs with the selected excipients was assessed by using FTIR spectroscopy. It was found that both the drugs were found compatible with the selected excipients. Following figures (Figure 1 & 2) are showing the FTIR spectra of pure drugs and formulation blends.

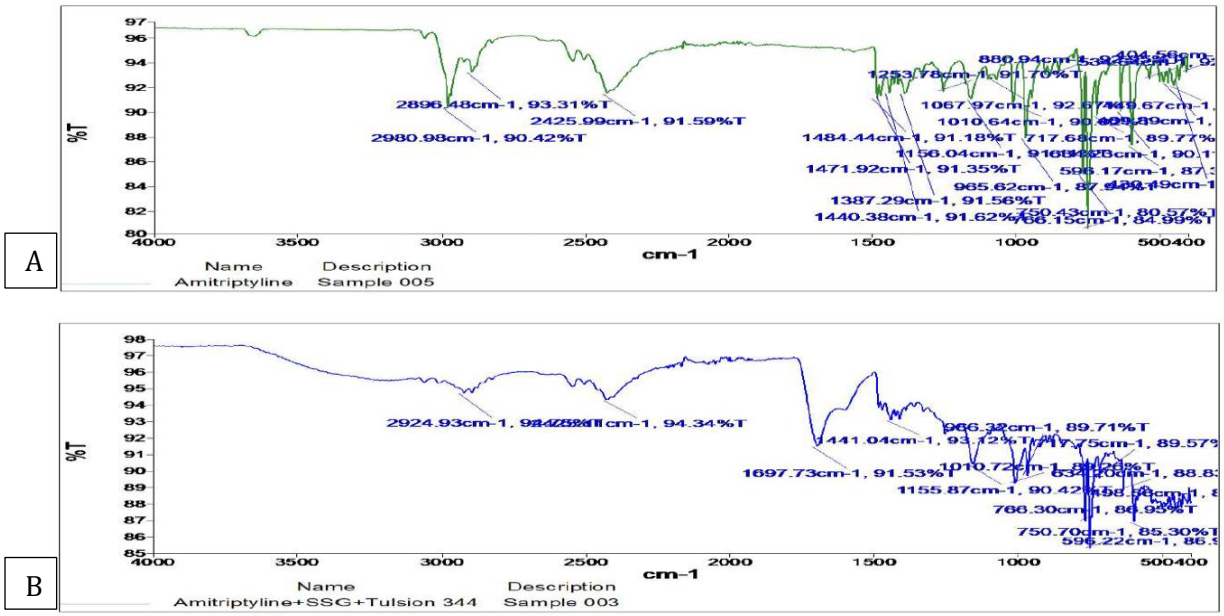

Figure 1: IR spectra of Amitriptyline, Pure drug (A) and Amitriptyline formulation blend (B)

The IR spectrum of Amitriptyline showed Asymmetric & symmetric CH_3 stretching at 2980.98, 2896.48 cm^{-1}, Asymmetric & symmetric CH_2 stretching at 2895.35, 2829.72 cm^{-1}, characteristic of HCl salt of tertiary amine at 2425.99 cm^{-1}, Nitro compound at 1253.78 cm^{-1}, C-H bending at 766.15 cm^{-1} and C6H6 (N) substitution at 750.43 cm^{-1}. While, the IR spectrum obtained with formulation blend represented Asymmetric & symmetric CH_3 stretching at 2924.93, 2788.22 cm^{-1}, Asymmetric & symmetric CH_2 stretching at 2852.31, 2721.24 cm^{-1}, Characteristic of HCl salt of tertiary amine at 2425.11 cm^{-1}, Nitro compound at 1155.7 cm^{-1}, C-H bending at 766.30 cm^{-1}, C6H6 (N) substitution at 750.70 cm^{-1}. From IR spectral data obtained with Amitriptyline with various excipients from formulation blend, it was observed that the peaks of Amitriptyline in combination with excipients were presenting the nearly similar value as that of pure drug, thus, confirmed the compatibility of pure drug with the selected excipients.

Similarly, FTIR spectra of Mirtazapine and its formulation blend were also constructed and represented in figure 2.

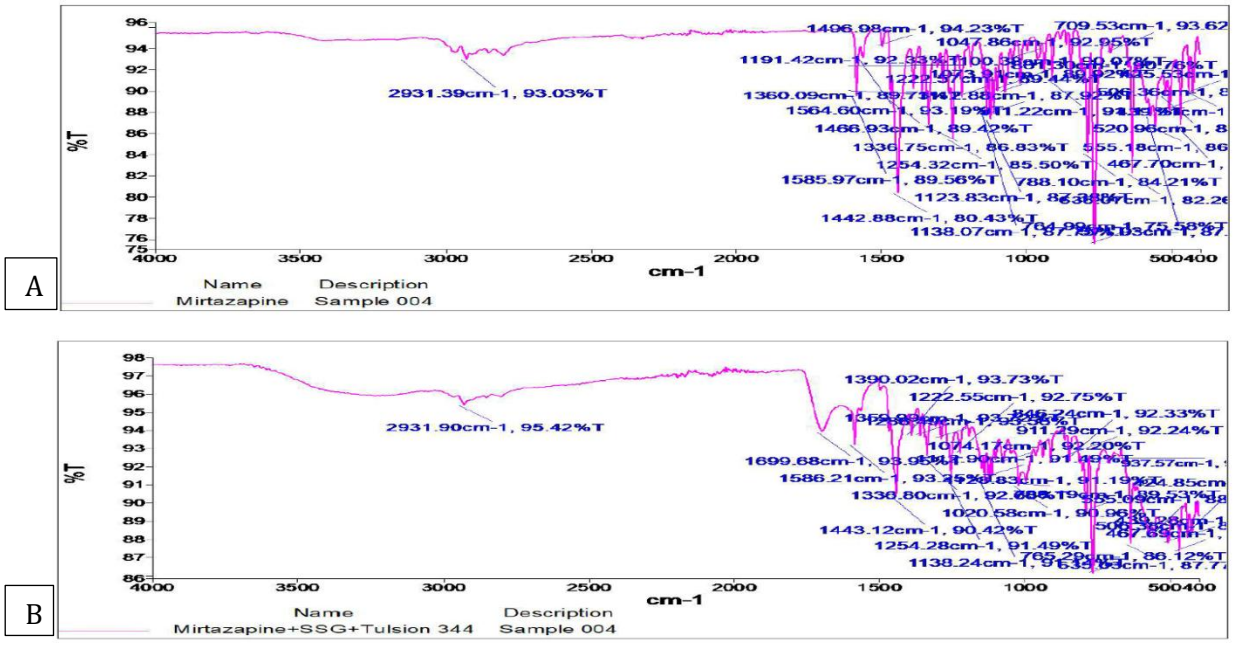

Figure 2: IR Spectrum of Mirtazapine, Pure drug (A) and Mirtazapine formulation blend (B)

The FTIR spectra of Mirtazapine pure drug has shown the C-H stretching of methyl gp at 2931.39 cm^{-1}, C-C stretching (Phenyl group) at 1585.97, 1564.60 cm^{-1}, Primary Aromatic amine at 1336.75-1288.62 cm^{-1}, Benzene ring C-H in plane bending at 1360.09-1073.91 cm^{-1} and Benzene ring C-H out plane bending at 764.99-635.07 cm^{-1}.

The FTIR spectra of Mirtazapine formulation blend reflected C-H stretching of methyl gp at 2931.90 cm^{-1}, C-C stretching (Phenyl group) at 1586.21, 1443.12 cm^{-1}, Primary Aromatic amine at 1336.80-1288.49 cm^{-1}, Benzene ring C-H in plane bending at 1359.99-1069.34 cm^{-1} and Benzene ring C-H out plane bending at 788.19-635.03 cm^{-1}.

It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and excipients. Existence of characteristics peaks of pure drugs i.e., Amitriptyline and Mirtazapine in the spectrum obtained with pure drug and selected excipients combination confirmed that there was no interaction between selected drugs and selected excipients.

Differential Scanning Calorimetry (DSC)

Drug and excipients compatibility was also checked by utilizing Differential Scanning Calorimetry.

Figure 3 showed the DSC of Amitriptyline which reflected a sharp endothermic peak at 198.37^{0}C and Amitriptyline has shown sharp peak at 196.59^{0}C in formulation blend, thus, confirmed the compatibility of the drug with the selected excipients. Similarly, Figure 4 demonstrated the DSC graph of Mirtazapine which showed sharp characteristic endothermic peak at 115ºC in pure state while the sharp peak exists at 114.96 ºC and this agrees with published results.

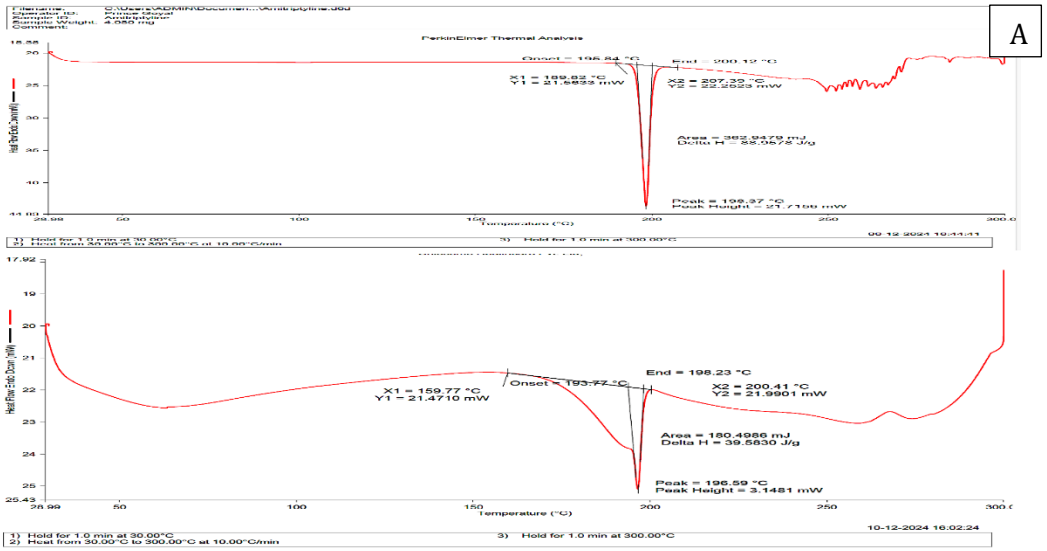

Figure 3: DSC spectra of Amitriptyline, Pure drug (A) and Amitriptyline formulation blend (B)

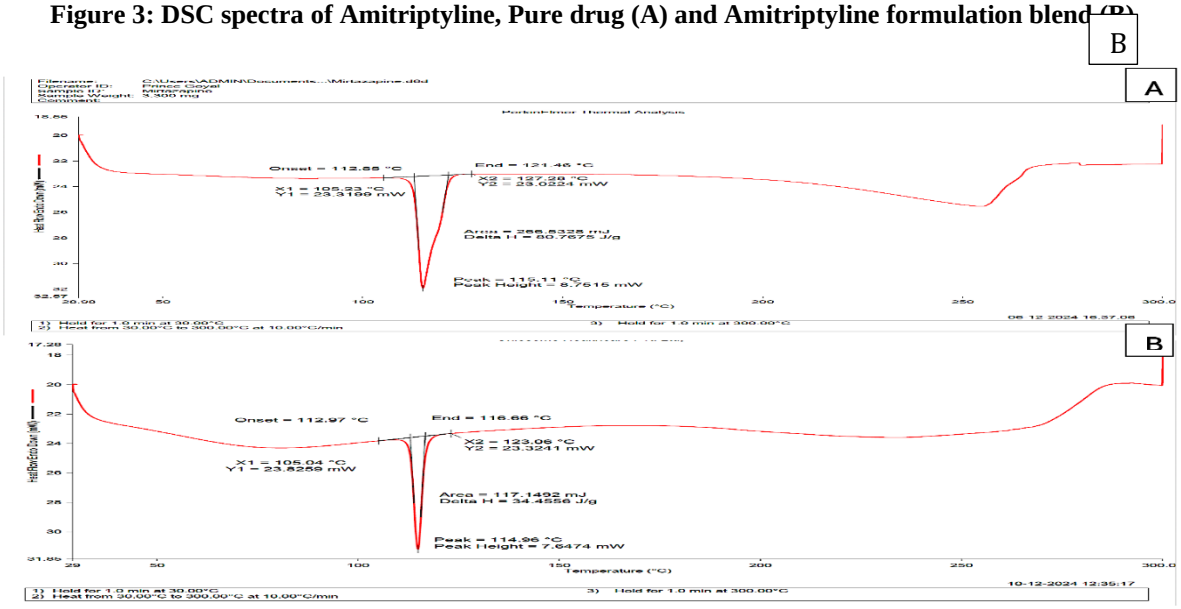

Figure 4: IR Spectrum of Mirtazapine, Pure drug (A) and Mirtazapine formulation blend (B)

This gives an indication that the drug has crystalline nature with high purity. Thus, it was confirmed that the selected drugs are compatible with the selected excipients.

Preparation of taste masked polymeric complexes of Amitriptyline and Mirtazapine

Drug-Resin complex (DRC)

Due to the basic nature of the drug & our requirement to mask the taste of drug along with optimum drug loading, the cation exchange resins like tulsion 335, tulsion 339, tulsion 344 were selected to prepare drug resin complex. Depending on the percentage of drug bound with the resin, a resin was selected. The results of percent drug loading in different resins were presented in figure 5A.

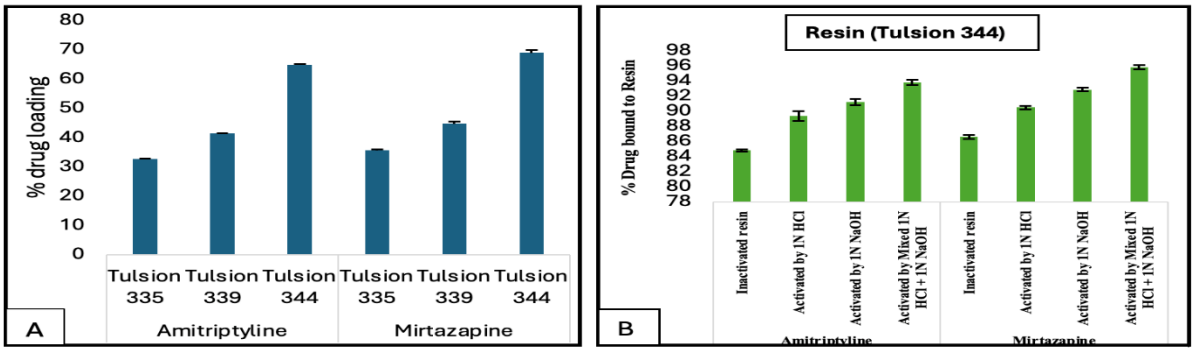

Figure 5: Percent drug loading with different resins (5A), Optimization of various parameters (5B)

Tulsion 344 is strong cation exchange resin and showed maximum drug loading of both the drugs i.e., Amitriptyline and Mirtazapine. It has fine particle size with high swelling efficiency made it suitable for batch process by providing more surface area for exchange of ions rather than column process. So, Tulsion 344 was selected for further optimization study.

Optimization of Various Parameters for Maximum Drug Loading

Combined acid and alkali treatment may purify the resin by removing adsorbed impurities associated with industrial scale manufacture and hence showed maximum drug loading upto 93.79±0.34% & 95.81±0.29% with Amitriptyline and Mirtazapine, respectively. Whereas inactivated resin showed 84.78±0.15% (with Amitriptyline) & 86.55±0.26% (with Mirtazapine). Resin activated with 1N HCl and 1N NaOH showed 89.34±0.65% & 90.48±0.22% drug loading of Amitriptyline, respectively and 91.17±0.44% & 92.83±0.21% drug loading of Mirtazapine, respectively (Figure 5B).

Effect of Drug: Resin Ratio

For the selection of the proper drug resin ratio, the ratio of the drug resin was varied, keeping the drug concentration as constant. The results showed that the drug resin in the ratio of 1:3 has shown maximum drug loading i.e., 96.52±0.48% with Amitriptyline and 98.34±0.77% with Mirtazapine (Figure 6A).

Effect of Soaking Time

Soaking resin accelerates and expands the ion exchange mechanism. The exchangeable groups are dormant and tangled in the resin matrix in non-soaked condition. Soaking causes swelling, which raises the surface area for the movement of exchangeable groups towards the outside. Soaking time of 30 min was optimized for maximum drug loading process showing 91.53±0.27% (Amitriptyline) and 93.79±0.88% (Mirtazapine) drug bound to resin. While soaking time of 10 mins was found to give 82.43±0.41% and 84.68±0.92%, 40 min. 91.85±0.55% & 93.94±0.17%, 60 min. 92.29±0.87% and 94.56±0.65%, 90 min. 93.81±0.44% and 95.98±0.15% drugs, Amitriptyline and Mirtazapine, respectively bound to resin (Figure 6B).

Effect of pH

The loading of Mirtazapine onto ion exchange resin is equilibrium process, which depends upon the presence of, cationic form of the drug in the solutions. The presence of cationic form of drug is influenced by pH of the solution, which therefore exerts an influence on loading efficiency. After activation with acid and alkali treatment, the exchangeable ion on the resin is H+. Relative selectivity of H+ is less than other ionic forms, and therefore it increases percent complexation. Maximum drug loading occurs at pH near neutral i.e., pH 7 shown 95.45±0.79% & 97.58±0.85% binding with Amitriptyline & Mirtazapine, respectively. This may be due to fact that the fraction of Amitriptyline (pKa- 9.4) and Mirtazapine (pKa- 7.1) protonation is less at acidic and basic pH and reduces interaction with resin at pH extremities (Figure 6C).

Effect of Mixing Time

The effect of mixing time on drug loading showed that, the percentage of drug bound to resin was found to increase as the mixing time increased. The results showed that maximum binding of 97.73±0.74% and 98.56±0.95% binding with Amitriptyline and Mirtazapine, respectively, occurred in approximately 2 hrs (Figure 6D).

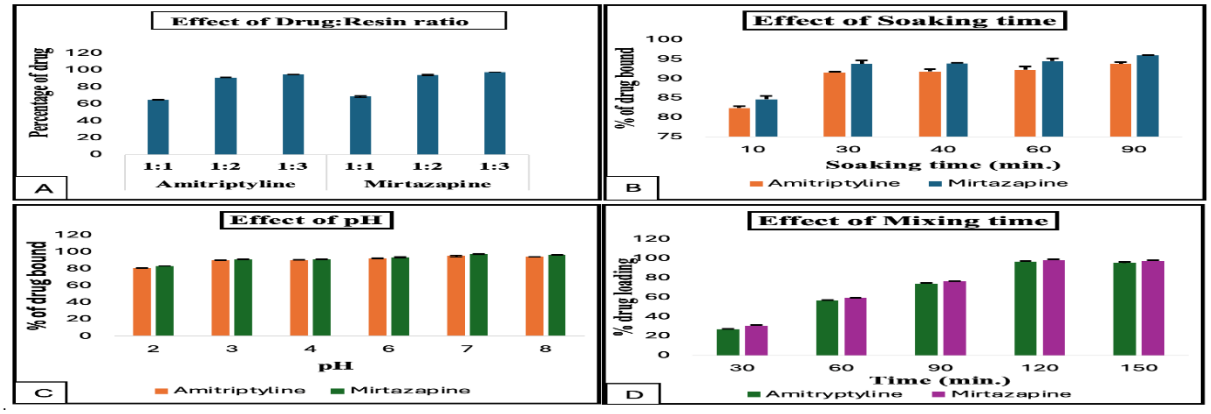

Figure 6: Effect of different parameters on drug loading; Effect of drug:Resin ratio (6A), Effect of Soaking time (6B), Effect of pH (6C) and Effect of Mixing time (6D)

Formulation development of Taste masked Fast disintegrating tablets

Initially, six trial batches were prepared with each drug and evaluated for pre-compression and post-compression parameters.

Pre-compression parameters:

The prepared trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine were evaluated for pre-compression parameters i.e., bulk density, tapped density, carr's index, hausner's ratio and angle of repose. The results were depicted in table 7-8. It was found that both the drugs have shown good flow property.

Table 7: Results of pre-compression parameters of taste masked fast dissolving tablets of Amitriptyline (trial batch: AT1-AT6)

Formulation code	Parameters				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (ɵ)
AT1	0.728	0.789	7.731	1.083	27.89
AT2	0.764	0.811	5.795	1.061	27.21
AT3	0.759	0.814	6.756	1.072	25.46
AT4	0.775	0.826	6.174	1.065	26.73
AT5	0.747	0.792	5.681	1.062	24.15
AT6	0.771	0.822	6.204	1.066	25.82

Table 8: Results of pre-compression parameters of taste masked fast dissolving tablets of Mirtazapine (trial batch: MT1-MT6)

Formulation code	Parameters				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (ɵ)
MT1	0.624	0.686	9.037	1.099	28.76

MT2	0.667	0.735	9.251	1.101	27.83
MT3	0.659	0.711	7.313	1.078	26.51
MT4	0.663	0.719	7.788	1.084	25.33
MT5	0.669	0.732	8.606	1.094	28.67
MT6	0.672	0.722	6.925	1.074	27.26

Post-compression parameters:

The prepared trial batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine were evaluated for post-compression parameters i.e., weight variation, hardness, friability, disintegration time, drug content and wetting time. Results were depicted in table 9-10.

Table 9: Results of post-compression parameters of taste masked fast dissolving tablets of Amitriptyline (trial batch: AT1-AT6)

Formulation code	**Parameters**					
	Weight variation	**Hardness (kg/cm^2)**	**Friability (%)**	**Disintegration time (DT, Sec.)**	**Drug content (%)**	**Wetting time (Sec.)**
AT1	Passed	3.67	0.325	129	98.16	58.7
AT2	Passed	3.69	0.442	81	99.12	42.8
AT3	Passed	3.65	0.317	115	98.38	51.5
AT4	Passed	3.61	0.439	69	99.25	35.9
AT5	Passed	3.66	0.383	102	98.56	45.6
AT6	Passed	3.65	0.465	56	99.12	32.8

Table 10: Results of post-compression parameters of taste masked fast dissolving tablets of Mirtazapine (trial batch: MT1-MT6)

Formulation code	**Parameters**					
	Weight variation	**Hardness (kg)**	**Friability (%)**	**Disintegration time (DT, Sec.)**	**Drug content (%)**	**Wetting time (Sec.)**
MT1	Passed	3.95	0.378	118	98.65	42.7
MT2	Passed	3.87	0.582	51	99.89	30.9
MT3	Passed	3.78	0.399	126	98.54	46.5
MT4	Passed	3.91	0.517	68	99.73	35.7
MT5	Passed	3.85	0.383	135	98.25	50.2
MT6	Passed	3.92	0.525	75	99.42	39.3

The fast-dissolving tablets have passed the weight variation test and % friability test, appreciable hardness and drug content, less disintegration time and wetting time which is desirable parameters for fast-disintegrating tablets.

***In-vitro* drug release**

The taste-masked fast disintegrating tablets of Amitriptyline and Mirtazapine were also evaluated for drug release characteristics. The taste-masked fast-dissolving tablets have shown more than 90% release at the end of 30 min., showing fast release from the formulation. The results were shown in figure 7.

Design of Experiment:

The effect of factors X1 and X2 is found to be statistically significant in nature. Response variables i.e., disintegration time, % Friability and % drug release were simultaneously optimized by desirability function using Design Expert software. This process allows the selection of most suitable level of factors to achieve desired level of responses.

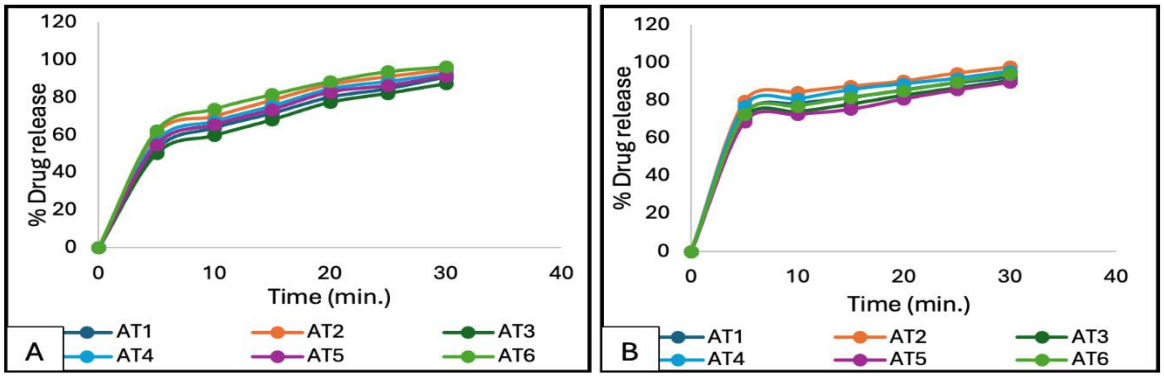

Figure 7: *In-vitro* dissolution study of taste masked fast dissolving tablets of Amitriptyline (trial batch: AT1-AT6) (A) and Mirtazapine (B)

The results of multiple linear regression analysis revealed that for obtaining desirable disintegration time (65.59 Sec. & 62.87 Sec.), %Friability (0.124% & 0.134%) and Drug release (99.28% & 99.05%) for Amitriptyline & Mirtazapine, respectively, the formulation should be prepared by using 32.77mg Primogel, 24.83mg MCC & 42.16mg Camphor and 28.50mg Primogel, 19.56mg MCC and 37.41mg Camphor for Amitriptyline & Mirtazapine, respectively.

Optimization of formulation parameters for the preparation of taste masked fast dissolving tablets of Amitriptyline

ANOVA technique was used to find out the significant models for all the three responses i.e., disintegration time, %friability and in-vitro dissolution by optimizing factor A (Primojel), factor B (MCC) and factor C (Camphor). ANOVA results were presented in table 11-13. Response surface and 3D graphs of taste-masked fast dissolving tablets of Amitriptyline were shown in figure 8.

Table 11: ANOVA for Quadratic model for Response 1: DT of taste masked fast dissolving tablets of Amitriptyline

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	7279.06	9	808.78	7.23	0.0211	significant
A-Primojel	1878.85	1	1878.85	16.79	0.0094	
B-MCC	3608.25	1	3608.25	32.24	0.0024	
C-Camphor	743.05	1	743.05	6.64	0.0496	
AB	362.90	1	362.90	3.24	0.1316	
AC	42.90	1	42.90	0.3833	0.5629	
BC	5.29	1	5.29	0.0473	0.8365	
A^2	56.40	1	56.40	0.5039	0.5095	

B^2	39.80	1	39.80	0.3556	0.5769	
C^2	589.30	1	589.30	5.27	0.0702	
Residual	559.61	5	111.92			
Lack of Fit	559.10	3	186.37	735.66	0.0014	significant
Pure Error	0.5067	2	0.2533			
Cor Total	7838.67	14				

Table 12: ANOVA for Quadratic model for Response 2: Friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.4455	9	0.0495	5.02	0.0453	significant
A-Primojel	0.1524	1	0.1524	15.44	0.0111	
B-MCC	0.2058	1	0.2058	20.85	0.0060	
C-Camphor	0.0342	1	0.0342	3.46	0.1218	
AB	0.0075	1	0.0075	0.7581	0.4237	
AC	0.0008	1	0.0008	0.0823	0.7857	
BC	9.000E-06	1	9.000E-06	0.0009	0.9771	
A^2	0.0043	1	0.0043	0.4389	0.5370	
B^2	0.0008	1	0.0008	0.0787	0.7904	
C^2	0.0423	1	0.0423	4.28	0.0933	
Residual	0.0493	5	0.0099			
Lack of Fit	0.0487	3	0.0162	51.89	0.0190	significant
Pure Error	0.0006	2	0.0003			
Cor Total	0.4948	14				

Table 13: ANOVA for Quadratic model Response 3: Drug release of taste masked fast dissolving tablets of Amitriptyline

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	85.53	9	9.50	5.55	0.0369	significant
A-Primojel	26.54	1	26.54	15.49	0.0110	
B-MCC	33.25	1	33.25	19.41	0.0070	

C-Camphor	13.99	1	13.99	8.17	0.0355	
AB	1.80	1	1.80	1.05	0.3528	
AC	0.0272	1	0.0272	0.0159	0.9046	
BC	0.8010	1	0.8010	0.4677	0.5244	
A^2	0.6462	1	0.6462	0.3773	0.5659	
B^2	0.3980	1	0.3980	0.2324	0.6501	
C^2	8.65	1	8.65	5.05	0.0745	
Residual	8.56	5	1.71			
Lack of Fit	7.64	3	2.55	5.51	0.1575	not significant
Pure Error	0.9249	2	0.4624			
Cor Total	94.09	14				

The Anova results revealed that p-values of all the three models was less than 0.0500 indicate model terms are significant.

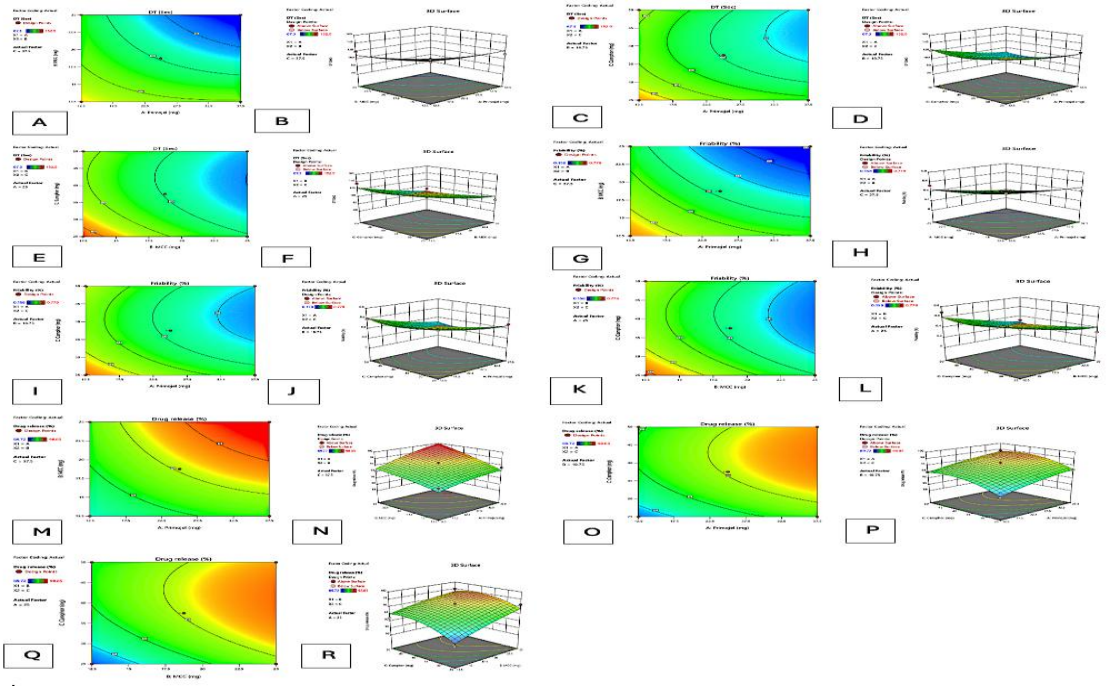

Figure 8: Response surface and 3D graphs of taste-masked fast dissolving tablets of Amitriptyline showing the effect of independent variables on dependent variables

From the above responses, it was observed that selected superdisintegrants, Primojel and MCC and subliming agent, Camphor had shown negative effect on responses, DT. As the this independent factor increased, the response, DT was decreased considerably, reflecting in graph moving from yellow to blue region. The selected superdisintegrants, Primojel and MCC and subliming agent, Camphor had shown negative effect on response, %Friability also. As the independent factors increases, the response, % friability was decreased considerably, reflecting in graph moving from yellow to blue region. In case of response 3, the selected independent factors had reflected positive effect on drug release. If the concentration of

independent factors increases, the drug release also increases in concentration dependent manner (Figure 8).

Optimization of formulation parameters for the preparation of taste masked fast dissolving tablets of Mirtazapine

The formulation parameters, Superdisintegrants and subliming agent were also optimized for formulating fast dissolving tablets of Mirtazapine. ANOVA results for optimization study of taste-masked fast dissolving tablets were represented in table 14-16. Response surface and 3D graphs of taste-masked fast dissolving tablets of Amitriptyline were shown in figure 9.

Table 14: ANOVA for Quadratic model for Response 1: DT of taste masked fast dissolving tablets of Mirtazapine

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	7033.61	9	781.51	6.49	0.0266	significant
A-Primojel	1943.76	1	1943.76	16.14	0.0101	
B-MCC	3248.18	1	3248.18	26.97	0.0035	
C-Camphor	727.71	1	727.71	6.04	0.0574	
AB	320.41	1	320.41	2.66	0.1638	
AC	55.50	1	55.50	0.4608	0.5274	
BC	0.2500	1	0.2500	0.0021	0.9654	
A^2	109.17	1	109.17	0.9063	0.3848	
B^2	53.67	1	53.67	0.4456	0.5340	
C^2	642.13	1	642.13	5.33	0.0690	
Residual	602.24	5	120.45			
Lack of Fit	588.56	3	196.19	28.68	0.0339	significant
Pure Error	13.68	2	6.84			
Cor Total	7635.85	14				

Table 15: ANOVA for Quadratic model for Response 2: Friability of taste masked fast dissolving tablets of Mirtazapine

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.3854	9	0.0428	12.00	0.0069	significant
A-Primojel	0.1969	1	0.1969	55.18	0.0007	
B-MCC	0.0950	1	0.0950	26.64	0.0036	
C-Camphor	0.0287	1	0.0287	8.04	0.0365	
AB	0.0133	1	0.0133	3.74	0.1110	
AC	1.000E-06	1	1.000E-06	0.0003	0.9873	

BC	0.0023	1	0.0023	0.6323	0.4626	
A^2	0.0116	1	0.0116	3.25	0.1315	
B^2	0.0150	1	0.0150	4.21	0.0956	
C^2	0.0296	1	0.0296	8.29	0.0346	
Residual	0.0178	5	0.0036			
Lack of Fit	0.0174	3	0.0058	24.01	0.0403	significant
Pure Error	0.0005	2	0.0002			
Cor Total	0.4032	14				

Table 16: ANOVA for Quadratic model for Response 3: Drug release of taste masked fast dissolving tablets of Mirtazapine

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	85.44	9	9.49	4.90	0.0473	significant
A-Primojel	27.45	1	27.45	14.18	0.0131	
B-MCC	30.46	1	30.46	15.74	0.0107	
C-Camphor	9.05	1	9.05	4.68	0.0829	
AB	1.06	1	1.06	0.5481	0.4924	
AC	0.0441	1	0.0441	0.0228	0.8859	
BC	1.40	1	1.40	0.7255	0.4332	
A^2	0.1483	1	0.1483	0.0766	0.7930	
B^2	0.6449	1	0.6449	0.3332	0.5888	
C^2	15.71	1	15.71	8.12	0.0359	
Residual	9.68	5	1.94			
Lack of Fit	9.61	3	3.20	100.04	0.0099	significant
Pure Error	0.0641	2	0.0320			
Cor Total	95.12	14				

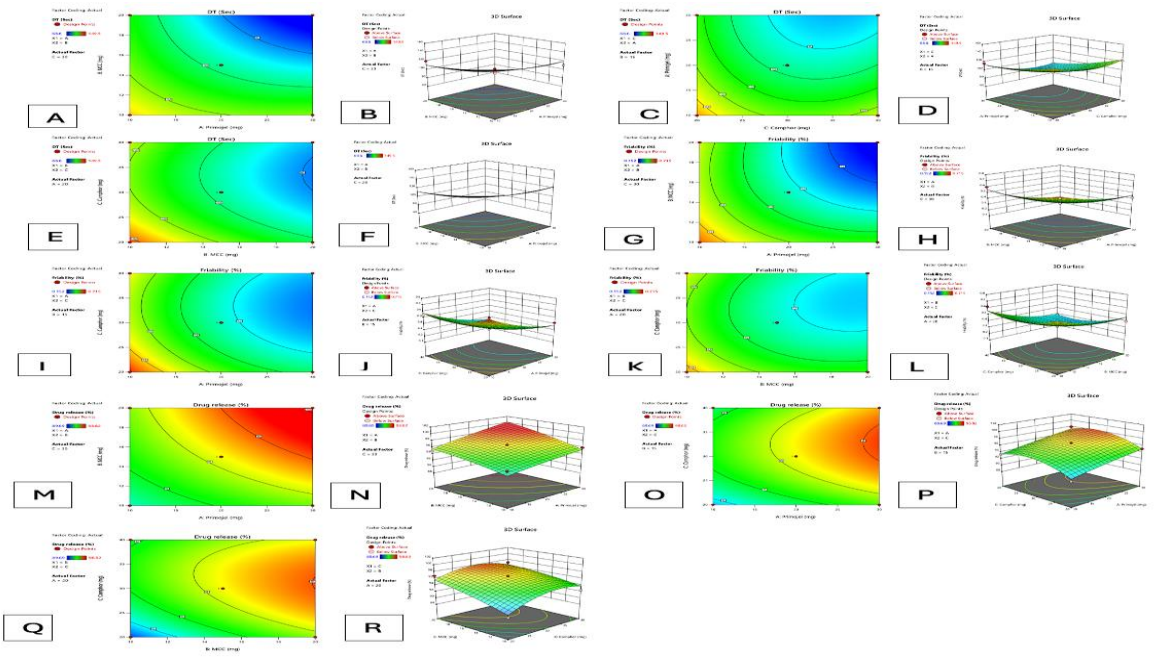

Figure 9: Response surface and 3D graphs of taste-masked fast dissolving tablets of Mirtazapine showing the effect of independent variables on dependent variables

From the above responses, it was observed that similar responses were found for taste-masked fast dissolving tablets of Mirtazapine as shown for Amitriptyline like, selected superdisintegrants, Primojel and MCC and subliming agent, Camphor had shown negative effect on responses, DT, % friability and drug release. As the this independent factor increased, the responses, DT and % friability were decreased considerably, reflecting in graph moving from yellow to blue region, while the response 3, drug release was increased in a dose-dependent manner. All the models were significant as p value was less than 0.5.

Evaluation of taste-masked Fast dissolving tablets of Amitriptyline and Mirtazapine

The finally prepared taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were also evaluated for pre-compression and post-compression parameters. Results were shown in following section.

1. **Precompression studies**

The taste masked fast dissolving tablet blends were also evaluated for pre-compression studies to determine their flow and compressibility. The results were presented in table 17-18.

Table 17: Micromeritic properties of tablet blends of taste-masked fast dissolving tablets of Amitriptyline

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
AF1	0.645	0.705	8.510	1.093	27.42
AF2	0.651	0.718	9.331	1.102	26.35
AF3	0.636	0.699	9.012	1.099	27.53
AF4	0.657	0.711	7.594	1.082	26.61
AF5	0.663	0.735	9.795	1.108	27.95
AF6	0.682	0.747	8.701	1.095	28.17
AF7	0.676	0.739	8.525	1.093	27.39
AF8	0.644	0.706	8.781	1.096	26.68

AF9	0.652	0.722	9.695	1.107	27.58
AF10	0.649	0.715	9.230	1.101	26.23
AF11	0.663	0.736	9.918	1.110	28.44
AF12	0.671	0.735	8.707	1.095	27.89
AF13	0.658	0.722	8.864	1.097	26.15
AF14	0.637	0.701	9.129	1.100	27.36
AF15	0.619	0.683	9.370	1.103	28.62

Table 18: Micromeritic (Pre-compression) properties of tablet blends of taste masked Fast dissolving tablets of Mirtazapine

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
MF1	0.632	0.695	9.064	1.099	27.52
MF2	0.675	0.745	9.395	1.103	28.37
MF3	0.691	0.759	8.959	1.098	27.45
MF4	0.634	0.699	9.298	1.102	26.72
MF5	0.679	0.742	8.490	1.092	28.15
MF6	0.628	0.692	9.248	1.101	27.81
MF7	0.647	0.712	9.129	1.100	28.38
MF8	0.671	0.737	8.955	1.098	27.29
MF9	0.682	0.751	9.187	1.101	26.77
MF10	0.673	0.732	8.060	1.087	27.11
MF11	0.661	0.729	9.327	1.102	28.49
MF12	0.658	0.731	9.986	1.110	27.53
MF13	0.694	0.763	9.043	1.099	28.91
MF14	0.662	0.725	8.689	1.095	27.44
MF15	0.669	0.741	9.716	1.107	27.15

2. Precompression studies

The prepared taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were also evaluated for post-compression parameters. The results were presented in table 19-20.

Table 19: Post-compression evaluation parameters tablet blends of taste masked Fast dissolving tablets of Amitriptyline

Formulation code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	DT (sec.)	Drug content (%)	Wetting time (Sec.)	*In-vitro* drug release (%)
AF1	249.1±1.12	3.82	0.611	126.3	94.36	60.3	93.27
AF2	250.1±1.11	4.09	0.486	116.4	96.92	52.8	94.69

AF3	250.2±1.18	3.58	0.727	138.6	92.87	65.9	90.64
AF4	248.4±1.15	4.13	0.415	112.8	97.51	50.1	95.33
AF5	249.2±1.11	4.22	0.398	99.6	98.43	48.9	96.82
AF6	250.5±1.14	4.55	0.219	79.5	99.91	39.5	97.94
AF7	247.9±1.19	3.88	0.583	121.5	94.72	57.5	93.85
AF8	249.3±1.13	4.38	0.311	92.1	98.92	45.3	96.59
AF9	248.6±1.16	3.67	0.693	135.7	93.58	62.8	92.86
AF10	250.3±1.12	3.95	0.527	118.9	96.69	54.3	94.11
AF11	251.5±1.17	4.41	0.285	86.2	99.11	42.7	97.57
AF12	252.7±1.18	3.42	0.779	152.9	90.26	73.5	89.72
AF13	249.5±1.15	4.87	0.158	67.3	99.97	36.8	98.85
AF14	250.2±1.12	4.32	0.363	98.6	98.75	46.2	96.13
AF15	251.1±1.18	4.28	0.376	99.2	97.54	48.4	95.46

Table 20: Post-compression evaluation parameters tablet blends of taste masked Fast dissolving tablets of Mirtazapine

Formulation code	**Weight variation**	**Hardness (Kg/cm^2)**	**Friability (%)**	**DT (sec.)**	**Drug content (%)**	**Wetting time (Sec.)**	***In-vitro* drug release (%)**
MF1	200.1±1.11	3.82	0.314	93.7	97.99	40.8	96.32
MF2	199.8±1.04	4.88	0.288	77.4	98.72	33.9	97.11
MF3	199.9±1.13	4.11	0.418	110.2	97.43	50.6	95.87
MF4	201.5±1.17	3.93	0.534	122.2	95.89	59.7	93.25
MF5	202.4±1.19	3.86	0.597	119.6	96.91	55.4	94.81
MF6	200.0±1.11	4.09	0.418	115.9	97.27	53.1	94.96
MF7	200.1±1.12	3.78	0.621	134.8	95.65	63.3	92.41
MF8	201.3±1.15	4.21	0.393	93.1	98.63	39.3	96.76
MF9	201.7±1.17	4.98	0.152	68.6	99.95	30.6	98.82
MF10	198.6±1.14	3.71	0.631	149.5	92.82	69.8	89.69
MF11	197.5±1.13	3.55	0.715	137.7	94.86	65.8	90.74
MF12	199.1±1.16	4.42	0.345	97.9	98.39	44.9	96.67
MF13	200.5±1.14	3.69	0.632	125.4	97.01	61.5	93.92
MF14	201.4±1.17	4.92	0.235	85.5	99.56	36.5	97.89
MF15	199.3±1.19	4.78	0.331	98.5	98.15	47.5	96.43

Selection of Optimized batch and Preparation & Evaluation of optimized batches of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine

Based on the results obtained from factorial design, an optimized batch was selected and formulated. The prepared optimized batches Aopt and Mopt were also evaluated for post-compression parameters and stability studies. The results of optimization study were depicted in figure 10. Predicted solution obtained from optimization study revealed that if Primojel, MCC and Camphor were used in the concentration 32.771, 24.838 and 42.164 mg then DT value as 65.599, % friability of 0.124 and drug release of 99.286 was obtained which is having desirability as 1, which is the maximum value. It reflects that the independent parameters showing good relation with dependent factors. In case of Mirtazapine taste-masked fast dissolving tablets, the Primojel, MCC and Camphor if used in the concentration of 28.507, 19.562 and 37.418 mg then DT, % friability and drug release were found to be 62.878 sec., 0.134% and 99.056% which reflected the desirability of 1.

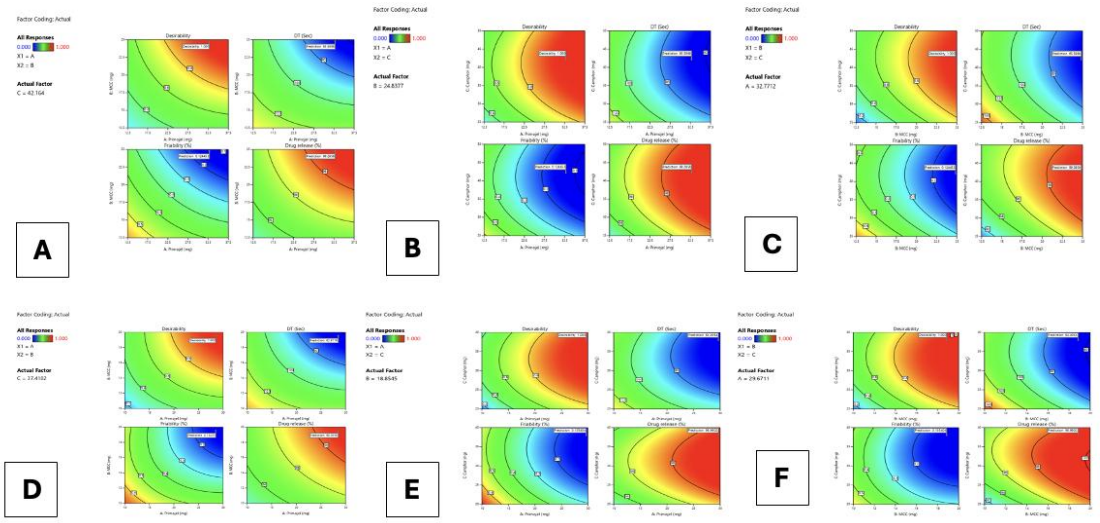

Figure 10: Desirability graph showing the optimized values of independent factors, Primojel and MCC (A); Primojel and Camphor (B); MCC and Camphor (C) to get desired response for taste-masked fast dissolving tablets of Amitriptyline. Desirability graph showing the optimized values of independent factors, Primojel and MCC (D); Primojel and Camphor (E); MCC and Camphor (F) to get desired response for taste-masked fast dissolving tablets of Mirtazapine

Formulation and Evaluation of optimized batches of taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine

Based on the above predicted solution obtained after optimization study, the optimized taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were formulated and evaluated for all the parameters as stated in above section. The optimized batches of taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were evaluated for post compression parameters and stability study. The results of these parameters were presented in table 21.

Table 21: Evaluation of taste masked fast dissolving tablets of Amitriptyline and Mirtazapine belong to optimized batch

3. Test	**4. Aopt (mean±S.D)**	**5. Mopt (mean±S.D)**
6. Weight variation test	**7.** 249.9±1.11	**8.** 200.1±1.16
9. Hardness (Kg/cm^2)	**10.** 4.79±1.16	**11.** 4.86±1.12
12. Friability (%)	**13.** 0.125±1.12	**14.** 0.134±1.11
15. Drug content (%)	**16.** 99.63±1.18	**17.** 99.91±1.15
18. Wetting time (Sec.)	**19.** 36.4±1.14	**20.** 31.5±1.13

21.	***In-vitro* disintegration time (Sec.)**	**22.**	65.65±1.17	**23.**	63.42±1.19
24.	***In-vitro* dissolution study (%)**	**25.**	99.38±1.15	**26.**	99.12±1.17

The percentage (%) drug release of optimized taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were depicted in figure 11.

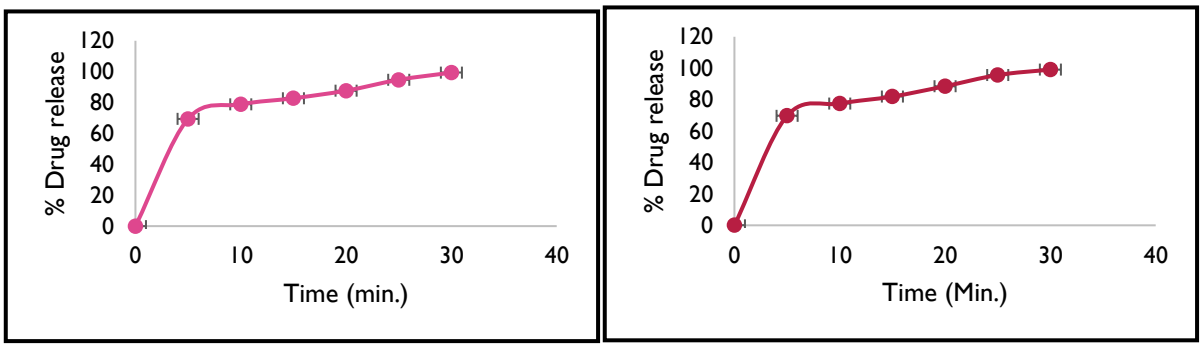

Figure 11: *In-vitro* drug release study of taste-masked fast dissolving tablets of Amitriptyline belong to optimized batch (Aopt) (A); taste-masked fast dissolving tablets of Mirtazapine belong to optimized batch (Mopt)

Stability study

The optimized formulations obtained with both drugs were kept at accelerated stability conditions were kept for 3 months and at an interval of one month, samples were withdrawn and analysed for any physical changes, drug content and *in-vitro* drug release. It was observed that there was no physical changes in the optimized formulations till the complete time period. The drug content in the optimized formulations was found to be 99.05±1.12% (Aopt) and 99.11±1.11% (Mopt) at the end of three (03) months. The results of percentage drug release at the storage of 0 day, 30 days, 60 days and 90 days from optimized formulations, Aopt and Mopt were depicted in figure 12.

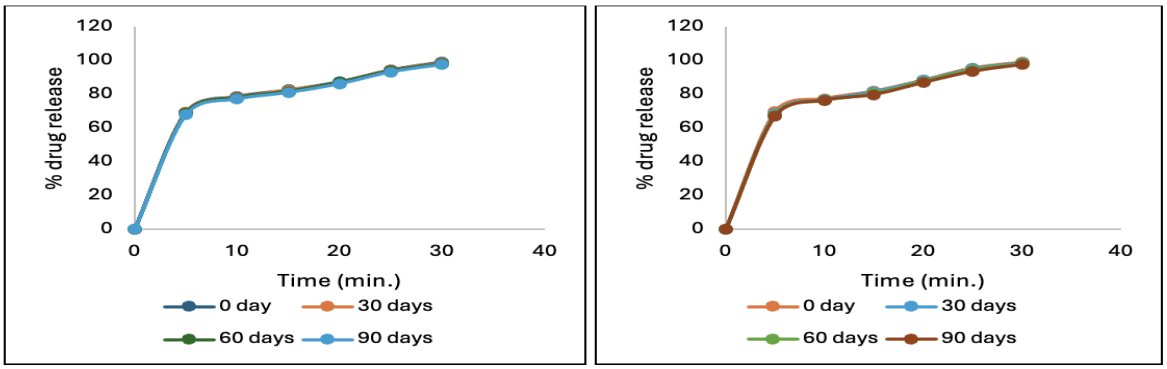

Figure 12: Effect of stability on *in-vitro* drug release from taste-masked fast dissolving tablets of optimized Amitriptyline batch (Aopt) and Mirtazapine optimized batch (Mopt) after the storage of 3 months

From the results it was observed that there was no considerable changes in the evaluation parameters of the optimized formulations Aopt & Mopt.

DISCUSSION

Taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine were prepared by a method employing Primojel as super-disintegrant and Camphor as subliming agent at different ratios. Tulsion 344 is strong cation exchange resin and showed maximum drug loading of both the drugs i.e., Amitriptyline and Mirtazapine. It has fine particle size with high swelling efficiency made it suitable for batch process by providing more surface area for exchange of ions rather than column process. So, Tulsion 344 was selected for masking the taste of Amitriptyline and Mirtazapine.

The flow properties of the powder mixture are important for the uniformity of mass of the tablets; the flow of the powder mixture was analyzed before compression to tablets. Low Hausner`s ratio (≤1.14), compressibility index (≤15) and angle of repose (≤ 29.00) values indicated fairly good flowability of the powder mixture.

Initially, six trial batches were prepared with different superdisintegrants to select an appropriate superdisintegrants for formulating fast dissolving tablets of selected drugs. Based on *in-vitro* results, Primojel was selected. A total of fifteen formulations were designed with both the drugs using Box-Behnken design and later on the prepared batches were evaluated for pre-compression and post-compression parameters.

ANOVA technique was used to find out the significant models for all the three responses i.e., disintegration time, %friability and in-vitro dissolution by optimizing factor A (Primojel), factor B (MCC) and factor C (Camphor). As the tablet powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation in the range from 247.9±1.19-252.7±1.18 mg (Amitriptyline) and 197.5±1.13-202.4±1.19 mg due to uniform die fill. Hardness, 3.67-4.55 kg/cm2 for Amitriptyline and 3.55-4.98 kg/cm2 and friability loss, 0.158 - 0.779 % for Amitriptyline and 0.152-0.715% for Mirtazapine indicated that tablets had good mechanical resistance. Drug content was found to be high (≥ 90 %) in all the tablet formulations. Wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the presence of a small amount of water, were found to be in the range of 39.5-73.5 sec. & 30.6-69.8 sec, for Amitriptyline & Mirtazapine, respectively (Tables 19 and 20).

The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. The faster disintegration of Primojel tablets may be attributed to its rapid capillary activity and pronounced hydration with low capacity for gel formation. Thus, these results suggest that disintegration times can be reduced by using a swelling and mechanical pressure creating disintegrant. Thus, wetting times of tablets with Primojel were found to be less. These results are consistent with disintegration test results. IR shows the drug interaction study, indicating that the drug was compatible with all the excipients (Figures 4 and 5).

The DSC of Amitriptyline which reflected a sharp endothermic peak at 198.37^0C and Amitriptyline has shown sharp peak at 196.59^0C in formulation blend, thus, confirmed the compatibility of the drug with the selected excipients. Similarly, the DSC graph of Mirtazapine which showed sharp characteristic endothermic peak at 115ºC in pure state while the sharp peak exists at 114.96 ºC and this agrees with published results. This gives an indication that the drug has crystalline nature with high purity (Figure 3 & 4). *In vitro* drug release studies were carried out in 0.1 N HCl and the dissolution profile is depicted in Figures 7 & 11.

Based on the results obtained from factorial design, an optimized batch was selected and formulated. The prepared optimized batches Aopt and Mopt were also evaluated for post-compression parameters and stability studies. The results of optimization study were depicted in figure 10. Predicted solution obtained from optimization study revealed that if Primojel, MCC and Camphor were used in the concentration 32.771, 24.838 and 42.164 mg then DT value as 65.599, % friability of 0.124 and drug release of 99.286 was obtained which is having desirability as 1, which is the maximum value. It reflects that the independent parameters showing good relationship with dependent factors. In case of Mirtazapine taste-masked fast dissolving tablets, the Primojel, MCC and Camphor if used in the concentration of 28.507, 19.562 and 37.418 mg then DT, % friability and drug release were found to be 62.878 sec., 0.134% and 99.056% which reflected the desirability of 1. The drug release from the optimized batches Aopt and Mopt was 99.38±1.15% 99.12±1.17% with Amitriptyline and Mirtazapine, respectively, at the end of 30 min. The optimized formulations obtained with both drugs were kept at accelerated stability conditions were kept for 3 months and at an interval of one month, samples were withdrawn and analyzed for any physical changes, drug content and *in-vitro* drug release. It was observed that there were no physical changes in the optimized formulations till the complete time-period. Thus, it can be concluded that the unpalatable taste of selected drugs can be masked by using Tulsion 344, and the addition of superdisintegrant and subliming agents is a promising approach to prepare taste-masked fast dissolving tablets of Amitriptyline and Mirtazapine.

CONCLUSION

The goal of this investigation has been achieved by preparing fast drug delivery technique of Amitriptyline and Mirtazapine with the aid of super disintegrating agents and a subliming material. The results of a Box-Behnken design revealed that the amount of camphor and superdisintegrants significantly affect the dependent variables, disintegration time, percentage friability and *in-vitro* dissolution. The optimized batch has shown promising results which are expected by a fast release formulation. A taste-masking technique was utilized to mask the bitter taste of both drugs and fast dissolution showed quick onset of action. It was thus concluded that by adopting a logical formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

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