Comparative study of different natural and synthetic Super disintegrants used in formulating the mouth dissolving tablets of Amitriptyline Hydrochloride drug for enhancing rapid Dissolution

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Abstract

Rapid disintegrating tablets (RDTs) have emerged as a promising oral drug delivery system particularly for pediatric, geriatric and dysphagic patients who have difficulty in swallowing conventional dosage forms. The present study was planned to formulate and evaluate mouth dissolving tablets of Amitriptyline Hydrochloride using various natural and synthetic superdisintegrants and to compare their effect on tablet performance and drug release characteristics. The synthetic superdisintegrants such as Croscarmellose Sodium, Sodium Starch Glycolate and Crospovidone were compared with natural superdisintegrants such as Locust Bean Gum, Mango Peel Pectin and Dehydrated Banana Powder.

Mouth dissolving tablets were prepared using direct compression method and evaluated for various pre compression and post compression parameters. The formulated formulations were evaluated for hardness, friability, weight variation, wetting time, disintegration time, drug content uniformity and in vitro drug release. All the formulations showed good pharmaceutical properties with hardness of 2.0–4.0 kg/cm2, friability less than 1% and weight variation within the pharmacopoeial limits. Drug content uniformity was found to be 98.54% to 101.23% indicating uniform distribution of Amitriptyline Hydrochloride throughout the tablet matrix.

The comparative evaluation showed that formulation with natural superdisintegrants showed fast disintegration of tablets and satisfactory drug release profiles. The drug release values of Locust Bean Gum, Mango Peel Pectin and Dehydrated Banana Powder were 99.81, 98.75 and 99.72% respectively. Crospovidone was found to be the best among synthetic superdisintegrants with nearly 99.80% of drug release within 5 minutes. Formulations of Sodium Starch Glycolate and Croscarmellose Sodium showed comparatively slower disintegration and dissolution characteristics.

Keywords: Rapid disintegrating tablets, Amitriptyline Hydrochloride, Natural Super-Disintegrants, Synthetic Super-Disintegrants.

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Introduction

Oral Drug Delivery System

ODDS is having high demand which is 60 to 70% in the pharma market due to its patient compliance, low price & ease of use [1]. Apart from that this delivery system has been altered by no. of factors like degradation by enzymes, Differences in GIT & other physiochemical characteristics. [2,3,4]. In the past 10 years new methods & nano systems are continuously evolving to increase permeability, site specific release & solubility are increasing [4].

Evolution of Oral Drug Delivery Strategies

Passive entry into the bloodstream occurs with conventional oral dose forms (e.g., tablets, capsules, suspensions, and liquids). However, the first pass effect and variable absorption limit the therapeutic effects of these drugs [5.6]. With the advancement in polymer chemistry release controlling formulations were developed like hydrophilic matrix system, osmotic pumps and pH sensitive coatings. These formulations help in maintaining steady plasma concentration as well as reducing the frequency of dosage and adverse effects [7,8].

Transport lipids such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers and self-emulsifying drug delivery systems (SEDDS) may be used to increase the bioavailability of hydrophobic drugs Mukherjee et al. [9,10]. Mucoadhesive compositions use the mechanism of polymer-mucosa binding. They could increase residence and absorption times [11].

Lipid-based Site-Specific and Colon-Targeted Delivery

Targeted drug delivery to the gastrointestinal tract (GIT) is a major advancement in the research of oral drug delivery systems (ODDS). [12]. The use of pH-responsive and time-controlled polymer coatings makes it possible to release therapeutic drugs at specific sites in the intestine, such as the colon. This is particularly useful in managing conditions like Crohn's disease and ulcerative colitis [13]. Natural and synthetic polymers like chitosan, alginate and different grades of Eudragit have been widely used to promote localized drug release while lowering systemic absorption and related side effects [14]. Biodegradable hydrogel systems are also promising carriers that can encapsulate bioactive compounds and release them in response to environmental stimuli such as microbial enzymatic activity or pH changes [15].

Challenges and Future Directions

Despite the tremendous progress in the research of oral drug delivery systems (ODDS), the clinical translation of successful ODDS is still hard. Some of the key challenges include stringent regulatory criteria, product stability in large-scale manufacturing, and formulation reproducibility. Precise and dynamic control over medication release can improve therapeutic effects by combining biosensor-based feedback systems with real-time monitoring tools [16]. Moreover, the application of machine learning approaches to predict in vivo absorption kinetics, optimize excipients and forecast dissolution properties is a valuable strategy for speeding up formulation design and development [17,18].

In the future, oral medication distribution is expected to be highly personalized, with smart polymers, digital therapies, and computational algorithms converging to provide formulations that are adaptive to the unique physiology of each patient. Next phase of oral delivery innovation will be more defined by green manufacturing technologies and sustainable biocompatible materials [19,20].

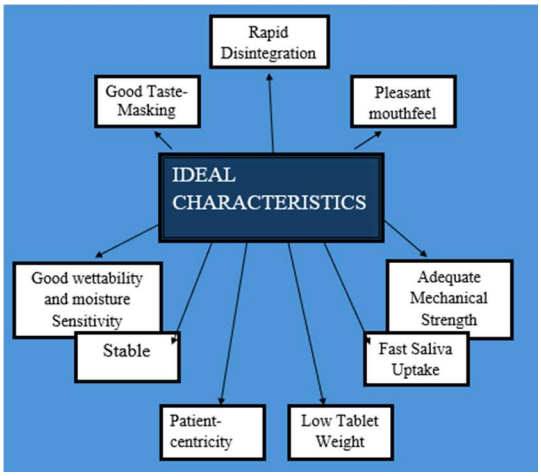


Figure no. 1 Ideal Characteristics of Mouth Dissolving Tablets

Amitriptyline Hydrochloride (Drug)

Amitriptyline hydrochloride is a tricyclic antidepressant (TCA). It belongs to Class I of Biopharmaceutics Classification System (BCS) due to its high intestinal permeability and good aqueous solubility. It is used for the treatment of major depressive disorder, neuropathic pain, migraine prevention and other anxiety related disorders. Amitriptyline hydrochloride has appropriate biopharmaceutical properties. This results in high systemic bioavailability and rapid absorption from the gastrointestinal tract after oral administration.

The therapeutic action of amitriptyline hydrochloride is thought to be mediated primarily by inhibition of the presynaptic uptake of the neurotransmitters norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT). The drug inhibits serotonin transporter (SERT) and norepinephrine transporter (NET), which results in increased synaptic concentration of serotonin and norepinephrine, and thus

improves neurotransmission in the central nervous system. This mechanism is mainly responsible for the analgesic activity in chronic neuropathic pain disorders and contributes to the antidepressant effect. Furthermore, amitriptyline hydrochloride exhibits antagonist activity at α adrenergic, muscarinic and histaminergic receptors which may affect its side effect and therapeutic profile. Amitriptyline Hydrochloride is still a model drug for the study of pharmaceutical formulation and drug delivery due to its known clinical efficacy and good absorption properties.

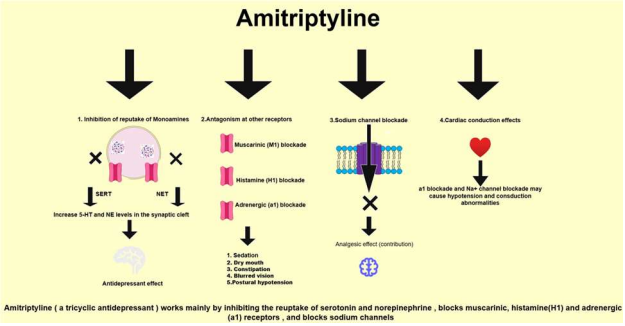


Figure no. 2 Mechanism of Action of Amitriptyline Hydrochloride

Material and methods

Materials

Amitriptyline HCl was obtained as a gift Sample from the Lozenges healthcare, Samba, Jammu & Kashmir, India. Croscarmellose Sodium, Sodium Starch Glycollate and Crospovidone, Locust bean Gum are taken from the Kiet Group of Institutions.

Method

Formulation of mouth Dissolving Tablets of Amitriptyline HCl by using Synthetic and Natural Super-Disintegrants.

Per tablet containing 25 mg of Amitriptyline HCl drug was prepared as per in the given table Lactose is used as a bulking agent, Microcrystalline cellulose was used as a direct compressible vehicle for direct Compression, Aspartame as a sweetening agent, Magnesium Stearate was used as a lubricating Agent, talc as diluent and lubricating agent. The synthetic super disintegrants (Croscarmellose Sodium, Sodium Starch Glycollate and Crospovidone) and natural super disintegrants (Locust Bean Gum, Mango peel pectin, Dehydrated Banana Powder) are used in different amounts for the comparison. All the excipients including drug are pass through the sieve (#80) for the proper mixing of all ingredients and keep the mixture in room temperature. the tablets were formulated with the direct compression technique; The mixture was compressed with the help of punching machine by using the 8mm round punch.

Experimental methodology

Preformulation Studies [21]

Preformulation studies are the first studies performed on drug substances prior to formulation development. These are used to check the Physicochemical characteristics of the novel multiple which can influence the preparation production and produce an accurate, safe and secure type of volume for a long time.

Preformulation is the first step to be taken. The logical production of an infinite amount of the drug portion. Analysis is described as the characterization of Physicochemical properties of a drug product alone and with excipients.

Solubility Study

Solubility study shows the solubility of Amitriptyline in different pH media (pH 1.2, 4.5 and 6.8)

API Physical Characterization

The Physical characterization of the medicine is calculated such as melting point and solubility.

Pre compression Parameters (Rheological properties) of the drug

Bulk mass, Carr's compression table, Carr's Compressibility Index, Angle of Repose and Hausner ratio were analyzed by sophisticated rheological instrument.

Bulk Density

The Apparent Bulk density ($\square_{\square}$)was determined using Graduated Cylinder, the mixture was poured in the cylinder. The weight of the blend and the bulk volume ($\square_{\square}$) were measured and the bulk density was calculated by using the formula

$$\square_{\square} = \frac{\square}{\square_{\square}}$$

Tapped density:

The know mass in the measuring cylinder was tapped for a fixed time. AND tapped density was determined by the formula The weight (M) of the blend and the minimum volume occupied in the cylinder (V_t) was measured

$$\square_{\square} = \frac{\square}{\square_{\square}}$$

Where, M= The weight of a dry mixture

Vb= The volume of bulk

Vt= The volume of tapping.

- **Carr's Compressibility Index:**

The granules have a remarkable feature of the Carr's compressibility index. Sometimes referred to as the index for carr's.

$$\square = \frac{\square_0 - \square_\square}{\square_\square} \times 100$$

- **Angle of Repose**

For the stand-alone and stand-alone funnel approaches, a funnel secured at its top, h, was suspended 2 cm above graphic paper mounted on a horizontal plane. The base of conical pile of which r is the radius.

$$\square = \tan -1 \frac{h}{\square}$$

Where, $\square$ = Angle of repose

h = Height of Pile

$\square$ = Radius of base of pile

- **Hausner's Ratio**

The Hausner ratio is an indirect measure of flowability. It is calculated by the following formula:

$$\text{Hausner Ratio} = \frac{\square_\square}{\square_\square}$$

Where $\square_\square$ = Tapped Density

$\square_\square$ = Bulk Density

Note- Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (> 1.25).

Recognition of the drug:

Identification of Drug pH

pH was determined with the help of pH paper. Drug is dissolved in the appropriate solvent and the pH paper is dipped in the solution. After the pH paper changes its color will match with the scale.

Calculation of the melting point

Temperature ranges from melting point of chemical's solid to liquid. The temperature of the compound changes from melted to solid at melting point. This is a physical property commonly used in drug identification.

Melting Point Apparatus- Method (by Capillary tube method)

Pick up a capillary tube.

The capillary tube was screened by a burner.

The capillary tube was pulled out by holding the tube by both ends and pushing in opposite directions, thereby screening the capillary tube on one extremity.

A small quantity of Amitriptyline has been placed on a sterile surface and the capillary tube was loaded with the compound.

A capillary tube (Veego /Macro scientific works) is connected to the melting point apparatus.

The samples were continuously observed as they began to melt and the temperature was determined using a thermometer. Gradual heating yielded the most reliable results.

Sample starts to fuse and ends up with complete fusion, it was recorded. We recorded the fusion spectrum.

Infra-Red Spectroscopic Method of Drug Identification [22]

Instrument Setup

Turn on the Shimizu FT-IR spectrophotometer and allow the IR source to warm up for at least 15 minutes until stable.

Make sure the sample compartment, ATR crystal or KBr pellet holder is clean and free of dust or previous residues.

Background Spectrum Acquisition

Background Scan before analysis of sample.

For ATR mode, keep the crystal clean, without any contents

Place a KBr blank pellet in the sample holder for the KBr pellet method.

Record the background spectrum from 4000 to 400 cm-1.

Sample Preparation:

Break off a tiny piece of the drug sample and make sure that it is dry and finely powdered.

KBr pellet method Accurately weigh about 1 mg of drug and mix well with 300 mg of dry potassium bromide. The ratio of drug to KBr should be 1:300.

Using a pellet press, press the mixture to form a transparent pellet.

Getting a Sample Spectrum

Place the prepared sample or pellet into the sample holder. • Scan the sample in the same conditions as the background.

Acquire the IR spectrum from 4000 to 400 cm-1 at the appropriate resolution.

iv. Processing of Spectrum

The instrument software automatically subtracts the background spectrum from the sample spectrum.

Smoothing and normalization of the spectrum, if necessary, without affecting characteristic peaks.

Identification of drugs

Compare the IR spectrum obtained for the sample with that of the authentic drug or with the official pharmacopeial spectrum.

Assign characteristic absorption bands to functional groups such as O–H, N–H, C=O, C–H and C–O.

Confirm identity by comparing the position and pattern of the major peaks.

Recordings

Save and print spectrum with sample name, date, scan range and instrument details.

Document observations and conclusions in the laboratory notebook or analytical report.
(Turn off the instrument after use as per laboratory guidelines.)

Amitriptyline standard curve: [23]
The drug concentration was determined spectrophotometrically by the calibration curve of Amitriptyline Hydrochloride. Amitriptyline Hydrochloride 10 mg was accurately weighed and transferred into 100 mL volumetric flask and dissolved in methanol to prepare stock solution. Working standard solutions of 2, 4, 6, 10 and 12 µg/mL were prepared from this stock solution by appropriate dilution with methanol.
The absorbance of each solution was measured at 239 nm on a UV-Visible spectrophotometer using methanol as blank. A graph was plotted between concentration and absorbance values. The calibration curve obtained was used for further quantitative analysis of the drug.

Media Preparation: [24]
Preparation of 0.1 N HCl solution Hydrochloric acid solution of 0.1 N was prepared by diluting the required amount of hydrochloric acid with distilled water and made up to 1000 mL. The pH of the prepared solution was checked by a digital pH meter.
Preparation of acetate buffer (pH 4.5) Acetate buffer (pH 4.5) was prepared by dissolving 2.99 g of sodium acetate trihydrate in distilled water and adding 1.6 mL of glacial acetic acid. The pH was adjusted to 4.5 and brought to a final volume of 1000 mL with distilled water.
Preparation of phosphate buffer (pH 6.8) Preparation of Phosphate buffer of pH 6.8 6.8 g of potassium dihydrogen phosphate was dissolved in distilled water. Sodium hydroxide was added slowly to bring the pH to 6.8 and the volume was brought to 1000 mL with distilled water.
Preparation of Saturated Solution of Drug: [24] Accurately weighed 25 mg of Amitriptyline Hydrochloride and transferred into a 500 mL volumetric flask. A small volume of selected medium was added and sonicated until the drug was completely dissolved. The volume was then made up with the same medium to obtain a clear stock solution. The prepared solution was filtered through a 0.45 µm PVDF syringe filter and the first part of the filtrate was discarded. From the stock solution, suitable aliquots were taken and diluted to get concentrations of 2, 4, 6 and 8 µg/mL. Separate sets of solutions were prepared in 0.1 N HCl, acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and distilled water.

The absorbance of each dilution was read at 239 nm against the corresponding blank medium. Absorbance was related to concentration and calibration plots were prepared and these plots were used for estimation of drug concentration in different studies.

Compatibility Study: [25,26]
Excipients are generally a substance used for the pharmaceutical active ingredient as a pharmacologically inactive ingredient. For compatibility testing, drugs and excipients were mixed separately (1:1) (1:1 gm). The glass flap has been closed and opened for one month and has been placed in the stabilising chamber at 25 °C/60% RH, 40 °C/75% RH and 60 °C. The trial was removed after a month and tested for color variations and odors. IR spectra is taken after one month and all shifts at high peaks are analyzed. This analysis was performed to find out such incompatibilities between ingredients.

Table no. 1: Result of Compatibility Studies

S. NO	Name of Excipients	Initial		25ºC+60 %RH (1M)		25ºC+60 %RH (1M)	
		Open	Close	Open	Close	Open	Close
1	Drug						
2	Croscarmellose Sodium						
3	Sodium Starch Glycollate						
4	Crospovidone						
5	Locust Bean Gum						
6	Mango Peel Pectin	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
7	Dehydrated Banana Powder	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
8	Microcrystalline	1 M	1 M	1 M	1 M	1 M	1 M

	Cellulose	onth	onth	onth	onth	onth	onth
9	Lactose	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
10	Magnesium Stearate	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
11	Drug+ Croscarmellose sodium	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
12	Drug + Sodium Starch Glycollate	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
13	Drug + Crospovidone	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
14	Drug + Locust Bean Gum	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
15	Drug + Mango Peel Pectin	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
16	Drug + Dehydrated Banana Powder	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
17	Drug + Water	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
18	Drug + Microcrystalline cellulose	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
19	Drug + Lactose	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
20	Drug + Magnesium Stearate	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month
21	Crospovidone + Locust Bean Gum	1 Month	1 Month	1 Month	1 Month	1 Month	1 Month

Table no. 2: Compositions of Tablets with proportion

Ingredients	**Rationale of Use**	**DC 0**	**DC 1**	**DC 2**	**DC 3**	**DC 4**	**DC 5**	**DC 6**	**DC 7**	**DC 8**	**DC 9**	**DC 10**	**DC 11**	**DC 12**	**DC 13**	**DC 14**	**DC 15**	**DC 16**	**DC 17**	**DC 18**
Amitriptyline Hydrochloride	API	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Lactose	Diluent	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103
Sodium Starch Glycolate	Synthetic Disintegrant	---	4	6	8	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cross-Carmellose Sodium	Synthetic Disintegrant	---	---	---	---	4	6	8	---	---	---	---	---	---	---	---	---	---	---	---
Crospovidone	Synthetic Disintegrant	---	---	---	---	---	---	---	4	6	8	---	---	---	---	---	---	---	---	---
Locust Bean Gum	Natural Disintegrant	---	---	---	---	---	---	---	---	---	---	4	6	8	---	---	---	---	---	---
Mango Peel Pectin	Natural Disintegrant	---	---	---	---	---	---	---	---	---	---	---	---	---	4	6	8	---	---	---
Dehydrated Banana Powder	Natural Disintegrant	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	4	6	8
Microcrystalline Cellulose	Filler	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Aspartame	Sweetener	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	Lubricant	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	Lubricant	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total Weight(mg)		**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Compression Parameter:

The lubricated blend was compressed in eight station rotatory punching machines at 8-12 rpm speed with the following specifications.
Punch Type-
Upper & Lower Punch-
Compress the tablets with an 8 mm round punch and evaluate all the in- process parameters.

Evaluation Parameters [26]
Precompression Parameters
Bulk Density
Tapped density
Hausner's ratio
Angle of repose
Carr's index
Calculation of Tablets
Post compression Parameters
Dimensions
Weight variation
Uniformity of Weight
Hardness
Disintegration
In vitro Dissolution
Friability
Stability studies
Dimensions
The size (diameter and thickness) of the tablet was measured with vernier calliper.
Weight fluctuations
The weight variance is determined by randomly selecting 20 pills and weighing them individually. Specification of changes in weight according to U.S.P.
Weight Consistency
The weight of all the tablets of each batch should be uniform and variation in weight within the permissible limits. Weight balance was used for checking weights to be less than ± 5 mg. Weight control is based on a sample of 20 tablets.
Hardness
The hardness was analysed with the help of Hardness Tester for the tablets by placing it in that and crushing / breaking power is determined. The hardness test was carried out on 6 tablets from each batch.
Friability Test
Friability tests are conducted to determine the ability of the tablets, to avoid wearing and tearing of the same in the packaging, handling and transportation. The friability of the tablets was determined by using the Roche friabilator. Roche weighed and spun 20 tablets of each formulation for 4 min at 25 rpm on the frying pad. The pills have been weighed out and taken away. % weight reduction was recalculated. Don't lose weight too quickly!
% weight reduction was calculated using the following equation:

$$\text{Friability (f)} = \left(1 - \frac{\square_0}{\square}\right) \times 100$$

Where, $\square_0$ is weight of the tablets before test

W is the weight of the tablet after test.

Disintegration Test.
The USP unit for the remaining fraction was composed of six glass tubes, 3" long, open at the top and 10" on the base of the basket rack. One tablet in each tube and one basket is placed in 37 ± 2 °C, in 1 litre of distilled water, so that tablets are below the surface of the liquid and come down not close to 2.5 cm from the bottom of the beaker.

In-vitro drug release studies [27]

The immediate release tablets are used for in-vitro drug release studies for direct drug delivery in pH 6.8 phosphate buffer for 30 minutes. Eight phase release tests were performed in an 8 steps dissolution test with a defined dissolution media volume at 37 ± 1 °C. The cylindrical basket rotates and keeps the tablets at 100 rpm. At each interval (2, 3, 5, 10, 15, 30, 35, 40 & 45 minutes), 5 ml of sample of the dissolving media shall be removed. At every time 5 ml of new medium shall be replaced. Samples were filtered 1 ml filtrate was diluted up to 10 ml.

Optimized factorial batch accelerated stability study [28]

Drug discovery stability tested of drug products are initiated and completed when the molecule or commercial product has been removed from the process.

Stability test is carried out according to ICH Q1C standards to find stability of medication and formulation stability.

The ICH Guidance Q1C formulations were the most satisfactory for stability testing (ICH Guidance of drug product).

Table no. 3: Stability Study Conditions

Type of Stability Study	Conditions
Accelerated Stability	40 ± 2°C and 75% ± 5% RH
In-between Stability	30 ± 2°C and 75% ± 5% RH
Real time Stability	25 ± 2°C and 75% ± 5% RH

The most suitable formulation for the aluminium packaging was preserved at ± 40 ± 2°C /75 ± 5% of RH for the first month.

A homogeneous formulation wrapped in aluminium foil was stored at room temperature and humidity.

Samples of in vitro release of drugs and percent drug content or test were analysed at end of tests.

Design of Experiment [29,30]

Systematic Design of Experiment (DOE) approach was used to optimize the formulation of Amitriptyline Hydrochloride mouth dissolving tablets prepared by direct compression method. The reason behind the use of DOE was to study the effect of selected formulation variables on critical quality attributes of the tablets and to identify an optimized formulation with the desired characteristics.

The experiment was designed by the Design Expert® software. Three independent variables related to super disintegrants were selected as independent factors. These were Crospovidone, Locust Bean Gum (LBG) and a combination of Crospovidone and Locust Bean Gum. Three levels for each factor were studied to study the effect of each factor on the formulation performance.

The prepared formulations were evaluated for selected response parameters like friability, disintegration time and in vitro drug release. The responses were selected as they are important to determine the quality and performance of mouth dissolving tablets.

The experimental design allowed for a systematic assessment of the individual and combined effects of the chosen formulation variables. The experimental runs yielded data which were further analyzed statistically to find out the significance of factors and optimised formulation.

Independent Variables and Their Levels

The formulation variables selected for optimization along with their coded and actual levels are presented in Table no. 4

Table no. 4: Independent Variables & their Levels

Sr. No.	Factor	Variable	Coded Level (-1)	Coded Level (0)	Coded Level (1)
1.	A	Crospovidone	4 mg	6 mg	8 mg
2.	B	Locust Bean Gum	4 mg	6 mg	8 mg
3.	C	Crospovidone + Locust bean Gum	4 mg	6 mg	8 mg

Response Parameters

The effect of formulation variables was studied on the following response parameters:

- Friability (%)

- Disintegration Time (min)

- *In vitro* Drug Release (%)

These responses were selected to evaluate the mechanical strength, disintegration behavior, and dissolution performance of the prepared mouth dissolving tablets.

Experimental Design Matrix

Based on the selected factors and levels, experimental runs were generated using Design Expert® software. The coded design matrix employed for the study is presented in Table 5.17

Table no. 5: Experimental Design Matrix

Std	Run	Factor 1 A: CROSPOVIDONE	Factor 2 B: Locust Bean Gum	Factor: 3 C: CP+ LBG	Response 1: Friability	Response 2: Disintegration Time min	Response 3 Invitro Drug Release %
11	1	0	-1	1			
2	2	1	-1	0			
13	3	0	0	0			
10	4	0	1	-1			
1	5	-1	-1	0			
9	6	0	-1	-1			
12	7	0	1	1			
7	8	-1	0	1			
8	9	1	0	1			
4	10	1	1	0			
6	11	1	0	-1			
5	12	-1	0	-1			
3	13	-1	1	0			

Statistical Analysis

Design Expert® software was used to analyze the experimental data obtained from all formulation batches. Statistical analysis was used to determine the effect of independent variables on the selected response parameters. Mathematical models were constructed to correlate formulation variables and responses. The developed models were analyzed for significance by analysis of variance (ANOVA) and optimized formulation was selected based on minimum disintegration time, acceptable friability and maximum drug release.

Preformulation Studies

Solubility Study:

Solubility studies of Amitriptyline at pH 1.2 and HPLC water at room temperature were performed and the result obtained as follows:

Table no. 6: Absorbance result of Amitriptyline

Conc. (ppm)	PH 1.2	Water
	Mean Absorbance	
0	0	0
2	0.128	0.132
4	0.256	0.391
6	0.384	0.389
8	0.512	0.517
10	0.640	0.648
12	0.768	0.773
Sample	0.576	0.547

API physical Characterization

The color and smell of Amitriptyline were Physically checked, etc. It has been discovered to be white powder, odorless and tasteless.

Rheological Properties of

Rheological properties of Amitriptyline like carr's index, tapping density, bulk density etc. were studied. The drugs are very poor with respect to the rest and flow angle (not passable) on the other hand compression of medication from the carr's index is very low. We provided the value of parameters evaluated in the below table.

Table no. 7: Result of rheological properties of Amitriptyline

No.	Factor	Value
1.	Bulk density	0.456 g/cm³
2.	Tapped density	0.54 g/cm³
3.	Carr's Index	17.42 %
4.	Angle of Repose	Passable
5.	Hausner's Ratio	1.354

Table no. 8: Result of Rheological Properties of Mixed Blend (Drug and Excipients)

Formulation Code	Angle of repose (θ)	Bulk density (g/ □□^{3})	Tapped Density (g/ □□^{3})	Hausner's Ratio	Compressibility Index (%)
□□$_0$	25.11	0.453	0.521	1.141	13.06
□□$_1$	24.12	0.451	0.543	1.193	14.67
□□$_2$	25.09	0.469	0.542	1.199	14.78
□□$_3$	23.32	0.425	0.512	1.208	14.87
□□$_4$	24.12	0.478	0.573	1.199	15.83
□□$_5$	24.23	0.473	0.531	1.193	17.56
□□$_6$	23.45	0.477	0.572	1.193	17.54
□□$_7$	24.33	0.463	0.562	1.203	13.78
□□$_8$	24.23	0.476	0.521	1.213	16.73
□□$_9$	25.33	0.454	0.573	1.202	15.53
□□$_{10}$	25.32	0.452	0.503	1.202	16.34
□□$_{11}$	24.43	0.421	0.532	1.204	17.23
□□$_{12}$	25.32	0.467	0.543	1.201	16.73
□□$_{13}$	25.32	0.459	0.514	1.194	17.26
□□$_{14}$	25.33	0.457	0.572	1.191	15.73
□□$_{15}$	24.33	0.479	0.512	1.182	15.62
□□$_{16}$	25.45	0.468	0.513	1.179	15.91
□□$_{17}$	25.22	0.466	0.552	1.196	16.52
□□$_{18}$	26.22	0.476	0.531	1.211	17.73

Comparative study of different natural and synthetic Super disintegrants used in formulating the mouth dissolving tablets of Amitriptyline Hydrochloride drug for enhancing rapid Dissolution

Identification of Drug
Identification of pH

The PH was determined with the help of PH paper, drug is dissolved in appropriate solvent and the PH paper is dipped in the solution, after the pH paper changes its color will match with the scale which is about 4.0 to 5.0 (Acidic).

Determination of the melting point:

The temperature was found with the help of a melting point apparatus, and it was found to have a range from 196 to 197°C, according to the normal Amitriptyline value temperatures.

Table no. 8: Melting point result of Amitriptyline

S.No.	Melting Point Apparatus
	Melting point Range (°C)
1	195-197
2	195-198
3	195-197
4	196-198

Identification by Infrared Spectroscopic Method:

Drug identification was carried out with the help of FTIR spectroscopy, and the values of the various functional groups in peaks are similar to the normal peak value.

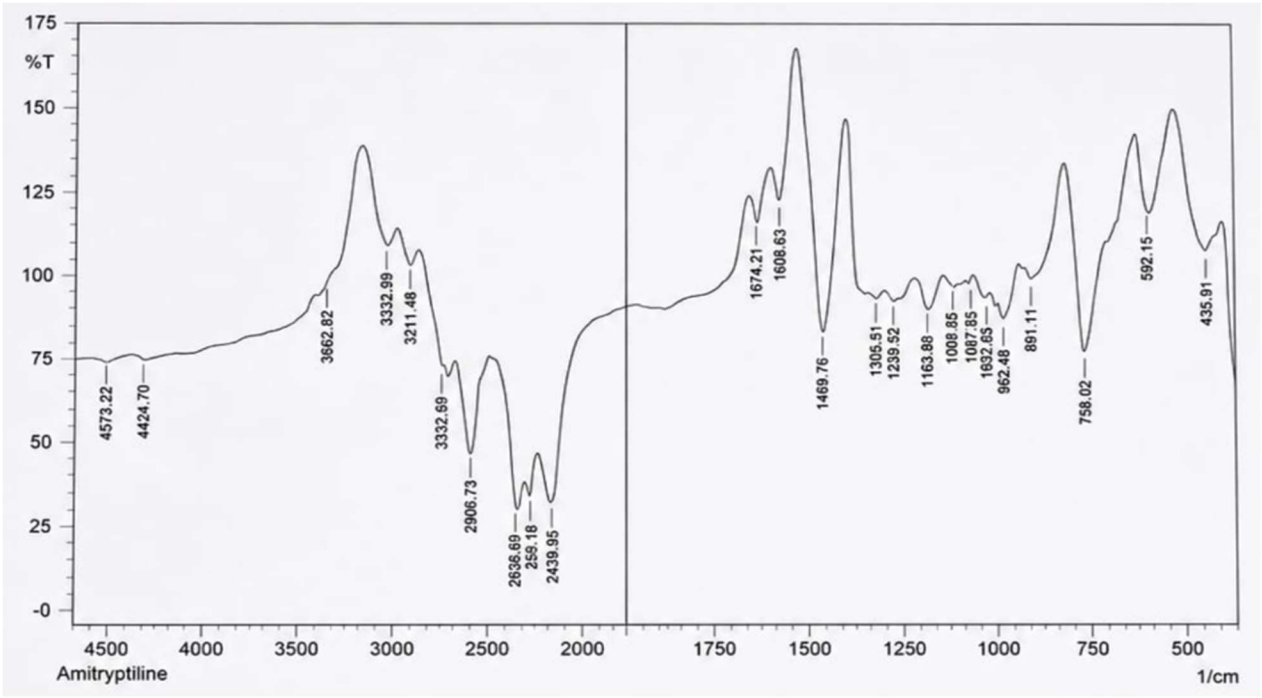


Figure no. 3 FTIR Spectra of Amitriptyline (API)

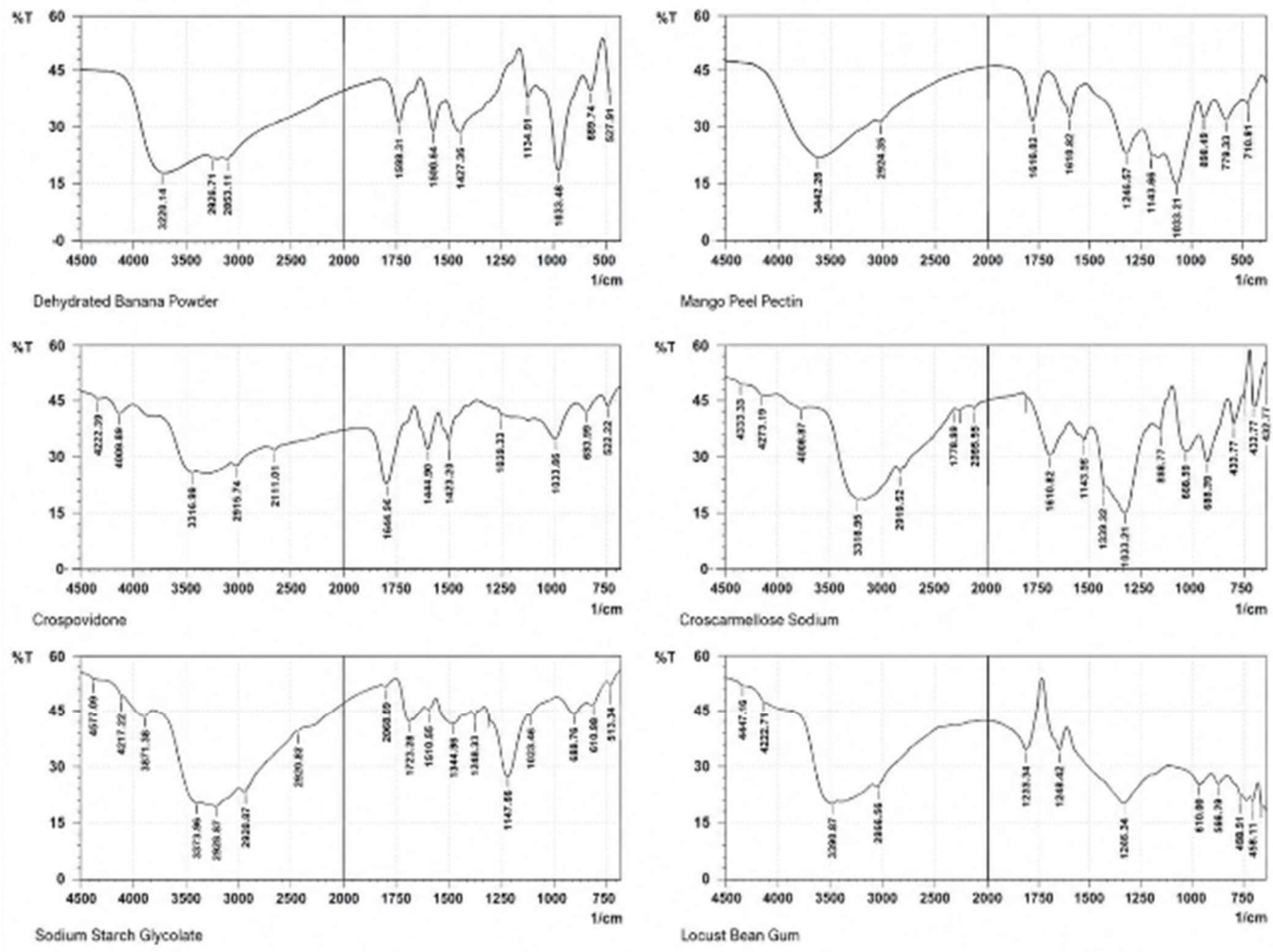


Figure no. 4 FTIR Spectra of Different Disintegrants

Standard curve

Table no. 9: Amitriptyline's standard 0.1 N HCL curve

SR. NO.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1.	0	0	0	0	0
2.	2	0.116	0.129	0.139	0.128
3.	4	0.241	0.259	0.268	0.256
4.	6	0.372	0.386	0.394	0.384
5.	8	0.498	0.514	0.524	0.512
6.	10	0.628	0.641	0.651	0.640
7.	12	0.752	0.783	0.769	0.768
Linear Equation			y = 0.0649x + 0.00112		
R2 value			0.9998		
Slope (m)			0.0649		
Intercept (c)			0.00112		

The Solution have been absorbed linearly, with increasing drug concentrations ranging from 2 to 12 µg/ml with 0.1N HCl. In this area, therefore, the drug followed beer legislation.

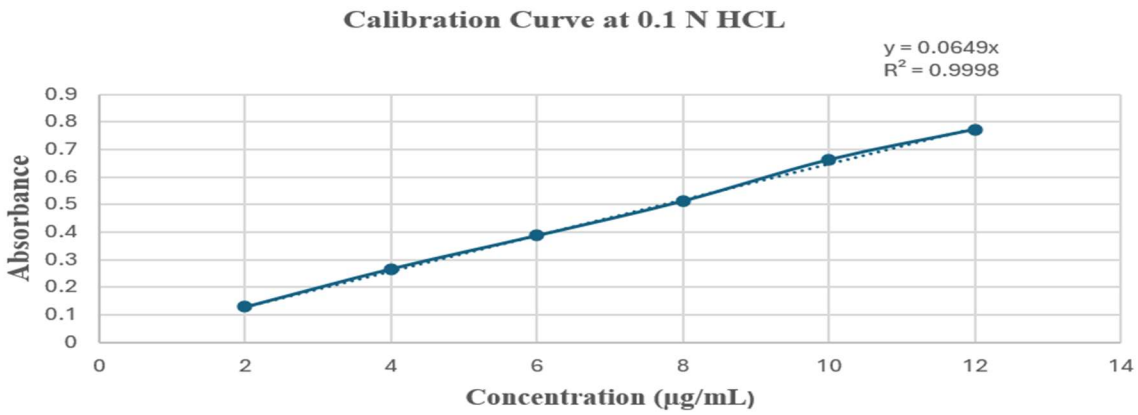


Figure no. 5 Amitriptyline standard 0.1 N HCl calibration curve (pH 1.2)

6.1 Compatibility Study:

Table no. 10: Result of Compatibility studies of Amitriptyline with Excipient.

S.No.	Name of the Excipients	Initial		25°C+60%RH(1M)		40°C+75%RH (1M)	
1.	Drug	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
2.	Croscarmellose Sodium	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
3.	Sodium starch Glycolate	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
6	Crospovidone	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
4.	Locust Bean Gum	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
5.	Mango Peel Pectin	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
6.	Dehydrated Banana Powder	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
7.	MCC	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
8.	Lactose	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
9.	Magnesium Stearate	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
10.	Drug + Croscarmellose sodiu	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
11.	Drug+ Sodium starch glycolat	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
12.	Drug + Crospovidone	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
13.	Drug + Locust Bean Gum	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
14.	Drug + Mango Peel Pectin	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
15.	Drug + Dehydrated Banana Powder	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
16.	Drug + Water	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
17.	Drug + MCC	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
18.	Drug + Lactose	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
19.	Drug + Magnesium Stearate	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
20.	Locust bean Gum + Crospovidone	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

Where comp.* is Compatible (means no modification). Results obtained for the compatibility studies with drug excipients show that the drug was compatible after three months with the relevant excipients being evaluated based on physical observation.

Preliminary Trials Evaluation:
Granules assessment:

For all the test batches, pre compression parameters were assessed, according to the specifications stated below. Table shows the findings of the rheological characteristics assessed in the trials.

Table no. 11: Results of Preliminary rheological Characteristics of Amitriptyline

Batch No.	B.D (gm/mol)	T.D (gm/mol)	% Compressibility	H.R.
F1	0.473	0.541	12.57	1.14
F2	0.432	0.513	15.79	1.19
F3	0.479	0.531	9.79	1.11
F4	0.511	0.579	11.74	1.13
F5	0.499	0.541	7.76	1.08
F6	0.487	0.535	8.97	1.10
F7	0.478	0.561	14.80	1.17
F8	0.497	0.573	13.26	1.15
F9	0.497	0.593	16.19	1.19
F10	0.492	0.549	10.38	1.12
F11	0.478	0.534	10.49	1.12
F12	0.503	0.593	15.18	1.18
F13	0.501	0.589	14.94	1.18
F14	0.499	0.578	13.67	1.16
F15	0.489	0.578	15.40	1.18
F16	0.478	0.548	12.77	1.15
F17	0.489	0.576	15.10	1.18
F18	0.502	0.544	7.72	1.08

By the direct compression technique tablets of batch F1 to F18 are obtained and results are from the granulate assessment. Almost all the batches have shown good results in flow and compression.

i. Evaluation of Tablet:

Medication content, Hardness, Friction and weight variation were tested in all trial batches according to the parameters described in section 5.4. The post compression parameters analyzed of all pre- test batches were not substantially more modified or different. Table 6.10 showed the results.

Table no. 12: Amitriptyline IR Tablet Assessment Parameters

Formulation Code	Weight Variation (mg)	Hardness Kg/ □□^{2}± SD	Thickness Kg/ □□^{2}± SD	Friability (%)	Drug Content (%) ±SD	Invitro Disintegration time (sec) ± SD	Water Absorption ratio (sec)	Wetting time (Sec)	% Drug Release
□□$_0$	199- 205 (within the IP limit of ±7.5 %)	4.1±0.310	3.70±0.009	0.41	99.18±0.70	241±0.70	81.01±0.70	60±0.260	97.74±1.23
□□$_1$		3.4± 0.321	3.70±0.021	0.52	99.73± 1.02	49.99± 0.85	79.3±0.59	27±0.207	98.43±1.21
□□$_2$		3.1±0. 324	3.72±0.121	0.50	98.73±0.67	38.42± 0.89	78.51±0.69	15±0.374	96.64±1.11
□□$_3$		3.2±0.209	3.71±0.041	0.58	99.57 ±0.79	39.25± 0.65	76.51±0.51	18±0.426	99.76±1.32
□□$_4$		3.3±0.391	3.70±0.021	0.67	99.95 ±0.98	35.19± 0.56	69.51±0.52	20±0.521	99.34±1.53
□□$_5$		3,2±0.532	3.70±0.021	0.60	99.89 ±0.79	33.19± 0.37	66.39±0.31	20±0.432	98.56±1.42
□□$_6$		3.5±0.532	3.70±0.032	0.58	99.94 ±0.85	31.19± 0.27	61.39±0.93	19±0.411	97.64±1.32
□□$_7$		3.4±0.543	3.72±0.021	0.71	99.67 ±0.85	31.15± 0.27	55.15±0.61	14±0.342	99.74±1.12
□□$_8$		3.7±0.453	3.71± 0.021	0.69	99.97 ±0.85	28.15± 0.24	67.43±0.53	13±0.226	97.67±1.22
□□$_9$		3.6±0.364	3.70±0.031	0.71	101.97 ±0.85	26.94± 0.24	60.48±0.61	09±0.338	98.86±1.34
□□$_{10}$		3.5±0.234	3.70±0.045	0.72	101.94±0.85	23.94± 0.43	59.67±0.73	12±0.524	97.85±1.34
□□$_{11}$		3.4±0.308	3.73±0.415	0.71	99.94± 0.85	20.94± 0.43	64.27±0.27	10±0.372	99.86±1.41
□□$_{12}$		3.7±0.375	3.43±0.023	0.70	100.87±0.85	19.94± 0.43	59.45±0.38	14±0.294	99.76±1.32
□□$_{13}$		3.5±0.381	354±0.032	0.70	100.49±0.85	18.95± 0.61	56.92±0.43	17±0.552	99.34±1.53
□□$_{14}$		3.4±0.321	3.52±0.023	0.65	99.89± 0.85	18.99± 0.47	53.73±0.72	12±0.226	98.56±1.42
□□$_{15}$		3.7±0.324	3.67±0.024	0.63	101.99±0.85	18.42± 0.49	51.64±0.84	11±0.227	98.64±1.22
□□$_{16}$		3.6±0.352	3.64±0.053	0.65	98.94± 0.85	17.42± 0.57	54.53±0.59	09±0.321	97.74±1.42
□□$_{17}$		3.5±0.325	3.67±0.061	0.68	99.94± 0.85	18.42± 0.49	52.94±0.49	10±0.321	98.76±1.32
□□$_{18}$		3.3±0.421	3.56±0.041	0.71	100 ± 0.85	19.29± 0.51	50.85±0.57	12±0.371	97.74±1.23

Table no. 13: Results of the trial research in Disintegration Time

Batch No.	Disintegration Time (sec)
F1	67
F2	56
F3	48
F4	66
F5	50
F6	40
F7	52
F8	51
F9	43
F10	32
F11	25
F12	19
F13	42
F14	46
F15	44
F16	50
F17	48
F18	54

Parameters such as Medication content, Hardness, Friability, thickness, weight variation and disintegration duration should be assessed between F1 AND F18 Batches. Among all batches, F

***In vitro* Drug Release study:**

Studies were conducted to evaluate drug release in-vitro for all preliminary batches. Parameters and conditions. Direct Compression is the best way to compress the tablets which has excellent flow and good compression characteristics. Table no. 13 Cumulative percentage of direct compression release of the medication (Batch F1 to F12). The cumulative percentage of the comparative drug release profile of preliminary studies is shown in figure no. 6

Table no. 14 Outcomes of the trial research in *In vitro* F1 to F18 Drug release

Time											**Trials**							
(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	34	35	34	39	38	35	47	50	54	48	57	54	45	46	45	42	40	43
10	36	39	40	43	47	44	54	57	69	59	65	68	55	59	60	46	44	48
15	42	51	53	58	58	55	62	64	77	64	68	74	58	62	67	47	48	52
20	46	54	55	60	62	64	68	75	83	71	77	79	63	67	68	60	58	64
25	48	57	57	61	65	66	75	81	85	76	80	84	65	70	74	61	65	69
30	50	59	60	61	71	72	83	87	89	84	86	87	69	73	80	63	66	70
35	52	605	61	65	74	77	90	92	90	88	94	91	73	75	81	66	69	73
40	55	62	65	70	81	83	93	95	96	93	96	96	77	78	83	70	74	78
45	56	65	66	73	81	84	95	97	98	97	99	99	78	80	85	71	76	79

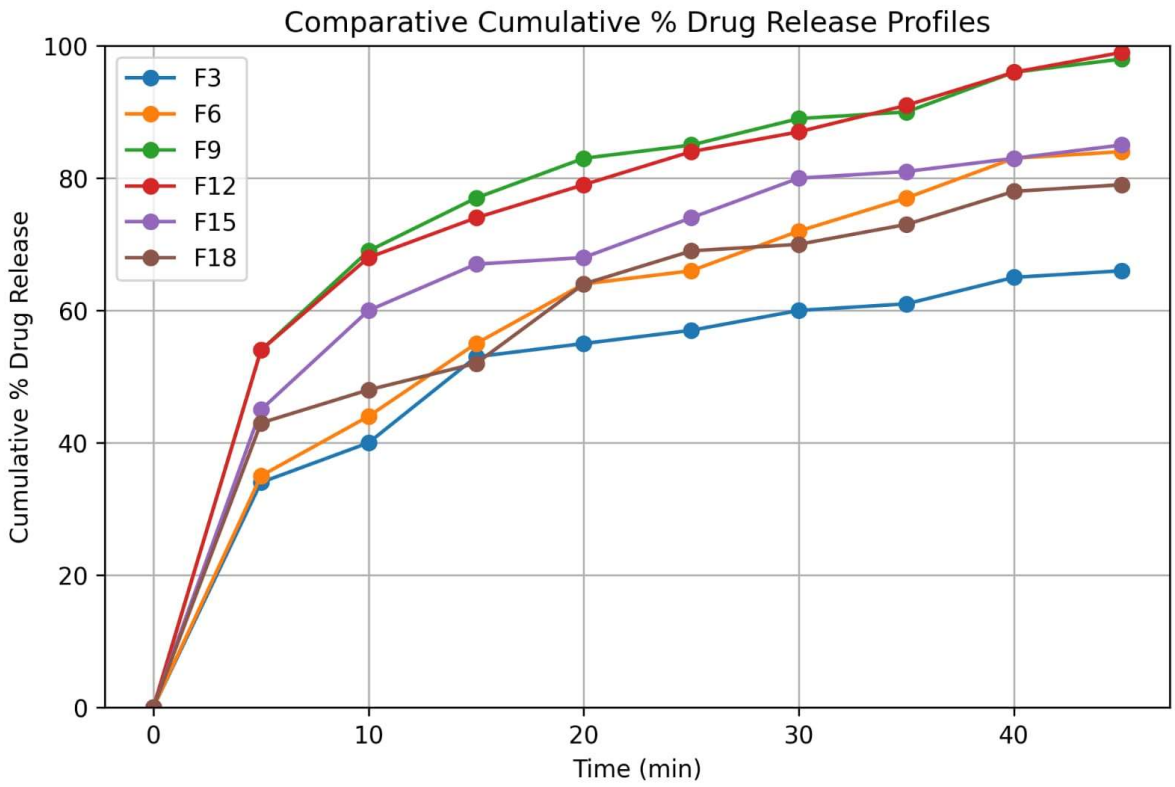


Figure no. 6: Direct Compression Trials Comparative Cumulative % drug release profiles

As shown in Table 14

• F1, F2, F3 formation contain 2%, 3% and 4% Sodium starch glycolate respectively in which F1 formulation disintegrants release 34% drug in 5 min and 56% in 45 minutes, F2 formulation disintegrants release 35% drug in 5 min and 65% in 45 minutes and F3 formulation disintegrants release 34% drug in 5 min and 66% in 45 minutes.

• F4, F5, F6 formation contains 2%, 3% and 4% Croscarmellose sodium respectively in which F4 formulation disintegrants releases 39% drug in 5 min and 73% in 45 minutes, F5 formulation disintegrants releases 38% drug in 5 min and 81% in 45 minutes and F6 formulation disintegrants releases 35% drug in 5 min and 84% in 45 minutes.

•F7, F8 and F9 formulation contain 2%, 3% and 4% Crospovidone respectively, in which F7 formulation disintegrants release 47% drug in 5 min and 95% in 45 minutes, F8 formulation disintegrants release 50% drug in 5 min and 97 % in 45 minutes and F9 formulation disintegrants release 54% drug in 5 min and 98% in 45 minutes.

• F10, F11, F12 formation contain 2%, 3% and 4% Locust Bean Gum respectively in which F10 formulation disintegrants release 48% drug in 5 min and 97% in 45 minutes, F11 formulation disintegrants release 57% drug in 5 min and 99% in 45 minutes and F12 formulation disintegrants release 54% drug in 5 min and 99% in 45 minutes

. • F13, F14, F15 formation contains 2%, 3% and 4% Mango peel Pectin respectively in which F13 formulation disintegrants release 45% drug in 5 min and 78% in 45 minutes, F14 formulation disintegrants release 46% drug in 5 min and 80% in 45 minutes and F15 formulation disintegrants release 45% drug in 5 min and 85% in 45 minutes.

• The F16, F17, F18 formation contains 2%, 3% and 4% Dehydrated Banana Powder respectively in which F16 formulation disintegrants releases 42% drug in 5 min and 71% in 45 minutes, F17 formulation disintegrants releases 40% drug in 5 min and 76% in 45 minutes and F18 formulation disintegrants releases 43% drug in 5 min and 79% in 45 minutes.

Accelerated Stability study of Optimized Product

Stability studies:

Accelerated stability studies: The aim of the accelerated stability research is to estimate the product life by rapidly increasing the rate of disintegration and ideally reducing the temperature.

Table no. 15 Various types of stability studies

Type of Stability	Conditions
Accelerated stability	40° ± 2°C and 75% ± 5% RH
Intermediate stability	30° ± 2°C and 75% ± 5% RH
Long-time stability	25° ± 2°C and 75% ± 5% RH

Stability Studies of Optimized Formulation (F10 -F18)

Tablet Optimization Tablet stability studies protocol Intermediate Release Amitriptyline (F1- F18) tablets were put in lined containers and kept under close wetness conditions at 45°C and 25°C temperature for 30 days The samples were analyzed for drug content after 30 days.

Storage condition and sampling schedule Optimized formulation was stored in stability chamber at room temperature (25°C ± a couple of °C/h ±5%) and accelerated stability (40°C ± 2°C/75% ±5%).

Samples were assessed in triplicate for medication content and plotted in forethought vs. time and time content vs. time graph.

Table no. 16: The *in vitro* release of drugs following an improved batch stability study (Percent drug release)

Time (min)	Initial	**After storage at** 40°C ± 2°C/75% ±5%	**After storage at** 25°C ± 2 °C/ 60 ±5%
0	0	0	0
5	82	80	79
10	87	86	85
15	90	89	87
20	93	92	90
25	95	94	91
30	95	94	93
35	96	95	93
40	98	97	95
45	98	98	97

Table no. 17: Optimized Formulation Stability Assessment for 1 month

Parameter	Description	*In vitro* drug release	% Assay or drug content
Initial	White to off white Color, biconvex, round shaped, plain on both sides	98	98.20
After storage at 40°C ± 2°C/75% ±5%		98	98.80
After storage at 25°C ± 2 °C/ 60 ±5%		97	97.00

Table no. 18: Optimized Batch Stability Study

Sampling Interval (Months)	% Assay		**Physical Appearance**
	40°C ± 2°C/75% ±5%	25°C ± 2 °C/ 60 ±5%	
0th	98.0	97.20	White to off White Color, round, biconvex, plain on both sides
1	99.0	98.48	

Optimization through Design of Experiment

Evaluation of Experimental Batches

All the formulations resulting from the Design of Experiment were successfully manufactured by direct compression and analysed for friability, disintegration time and in vitro drug release. The results of various trial runs proved that the variation in concentration and mix of super disintegrants greatly influenced tablet performance.

Table no. 19: Experimental Responses of DOE Batches

Comparative study of different natural and synthetic Super disintegrants used in formulating the mouth dissolving tablets of Amitriptyline Hydrochloride drug for enhancing rapid Dissolution

Formulation (T)	Response 1: Friability	Response 2: Disintegration Time min	Response 3 Invitro Drug Release %
T1	0.65	0.51	87.87
T2	0.68	0.48	87.73
T3	0.65	0.37	89.74
T4	0.54	0.18	96.73
T5	0.82	1.09	78.43
T6	0.79	0.59	81.12
T7	0.58	0.24	92.69
T8	0.56	0.32	95.54
T9	0.56	0.36	95.97
T10	0.76	0.52	90.13
T11	0.72	0.47	84.73
T12	0.73	0.35	89.27
T13	0.62	0.19	94.74

All batches' friability values stayed below the pharmacopeial limit of 1%, demonstrating the produced tablets' adequate mechanical strength. The findings imply that the integrity of tablets during handling and processing was not negatively impacted by the addition of super disintegrants.

The disintegration behaviour of the formulations changed noticeably. The slow disintegration of the pill was more in formulation T5 and the fastest disintegration was in formulation T13. These variations suggest that the type and concentration of super disintegrant had a significant effect on the disintegration process.
The drug release studies also indicated that the formulations were different. In general, the dissolution profiles were better for those batches with shorter disintegration times. Maximum drug release was observed in formulation T4. Formulations with lesser amounts of effective disintegrants showed slightly lower values of release.
The data comparison shows that Locust Bean Gum was very important in the quick disintegration of the tablets. Furthermore, the formulations containing small amount of Crospovidone and Locust Bean Gum performed better overall than the formulations containing Crospovidone alone. This behaviour may be due to swelling of Locust Bean Gum and fast penetration of liquid through Crospovidone.
The experimental results showed that the selected formulation factors directly affected the quality attributes of the tablets and were important in determining the overall performance of the mouth dissolving tablets.

Effect of Formulation Variables on Friability
Friability is an important quality attribute in the assessment of mechanical strength of a tablet and its resistance to handling, packing, shipping and storage. Mouth dissolving tablets require an optimum balance between rapid disintegration and sufficient mechanical integrity. If the tablets are too hard, they may show delayed breakdown. Tablets that are too fragile may chip or break on normal handling.
Friability values of all testing batches were found in the range of 0.54-0.87% which was within the permissible limit of no more than 1% as per pharmacopeial limit. The results showed that all formulations were having enough mechanical strength in spite of the presence of super disintegrants.
Among the developed formulations T8 batch showed lowest value of friability (0.54%) followed by T9 (0.56%) and T7 (0.58%). These formulations demonstrated better resistance to mechanical stress and abrasion. On the other hand, formulation T3 exhibited the maximum friability value (0.87%) but it was within the permissible limits.
The variation in friability observed in the formulations could be attributed to the variation in the type and concentration of super disintegrant used. The good integrity of tablets with suitable amounts of Locust Bean Gum may be due to the binding properties of the natural polymer. The locust bean gum may have improved adhesion of the particles during compression resulting in tablets with acceptable mechanical properties.
Comparison of the formulations indicated that inclusion of locust bean gum did not appear to adversely affect tablet strength. Formulations with Locust Bean Gum and a minute amount of Crospovidone also showed improved disintegration properties and acceptable friability values. The finding indicates that the selected super disintegrant method can be used to develop tablets with appropriate strength and fast disintegration behaviour.
General friability tests showed that all experimental batches had adequate mechanical integrity and were suitable

for further testing. The results indicated that the concentration of super disintegrant could be optimized without affecting the strength of the tablet.

Effect of Formulation Variables on Disintegration Time

The rate of dissolution after contact with saliva or a dissolving media is the disintegration time of a tablet and is an important parameter in the assessment of mouth dissolving tablets. The rapid disintegration is very important to ensure the quick availability of the drug and to enhance the convenience of the patients. The disintegration times of the experimental batches were found to be significantly different indicating the influence of the selected formulation factors on the tablet performance. Among the developed formulations, T12 took the longest time to fully disintegrate, while T13 showed the shortest disintegration time. This variance highlights the importance of careful selection and optimization of superdisintegrants in formulation development. From the comparison of the results, it was observed that formulations containing higher amounts of Locust Bean Gum dissolved faster than those with lesser quantities. The reason for this behaviour is that Locust Bean Gum can absorb water and swell when hydrated. The swelling process leads to a rapid breakdown of the compact mass due to stress on the tablet structure.

The study also showed that adding a small amount of Crospovidone in addition to Locust Bean Gum further improved tablet disintegration. Crospovidone speeds up the penetration of liquids through the matrix of the tablet by capillary action, hence, increasing the hydration of the polymer. Thus the process of disintegration of pill was more effective when both disintegrants were used together than when used separately. The disintegration time was shortened by Locust Bean Gum as the main factor, and the supporting disintegrating agent was Crospovidone according to the response pattern from the testing batches. Swelling and liquid uptake effects complement each other and were responsible for the improved tablet disintegration and formulation performance.

These results suggest that a fine optimization of the locust bean gum concentration is required for rapid disintegration. Finally, the addition of a small amount of Crospovidone can improve the system efficiency without affecting the tablet quality. The findings of the present study indicate that the method is applicable for the formulation of mouth dissolving tablets.

Effect of Formulation Variables on *In vitro* Drug Release

In vitro drug release studies were conducted to study the influence of formulation variables on the dissolution behaviour of Amitriptyline Hydrochloride oral dissolving tablets. The amount of drug available for absorption after tablet disintegration is reflected by drug release, which is a key parameter. Besides rapid dissolution, the ideal mouth dissolving tablet should give effective and reproducible delivery of the medicinal agent. The experimental formulations showed the percentage of drug release in the range of 78.43 to 96.73. Difference in dissolution profiles indicated that type and concentration of super disintegrant affected the release properties of produced tablets.

Among all the formulations the maximum drug release was observed in T4 (96.73%) followed by T8 (96.54%), T9 (95.97%) and T13 (94.74%). Moreover, these formulations showed relatively faster disintegration, implying a good correlation between drug release behaviour and tablet disintegration. The fast disintegration of tablet increased the surface area for disintegration and provided faster drug release into the dissolution liquid. Formulations with higher locust bean gum concentration often showed better dissolving performance. The quick hydration and swelling of the polymer aided in the effective disintegration of the tablet, increasing the surface of drug particles exposed to the dissolution liquid. This helped the dissolving properties of the compositions. The results also revealed that the incorporation of a small amount of crospovidone in locust bean gum enhanced the drug release. Locust bean gum caused swelling and dispersion of the tablet and crospovidone allowed rapid penetration of the medium of dissolution into the matrix of the tablet. All these mechanisms together resulted in efficient tablet disintegration and subsequent release of the drug.

On the other hand, the drug release values of formulations with longer disintegration times are usually smaller. This outcome suggests that the tablet's delayed disintegration could restrict the drug's availability for dissolution. Dissolution studies revealed that the optimization of super disintegrant concentration was essential to achieve desired release profile. Results showed that Locust Bean Gum is a good disintegrating agent and the inclusion of a small amount of Crospovidone to it improved the performance of the formulation further. The disintegration studies and the in vitro drug release results overall confirmed that the selected super disintegrant system has the potential to formulate mouth dissolving tablets with satisfactory dissolution behavior and rapid drug release.

Experimental batches prepared by the DOE study were evaluated statistically by Design Expert® software. The objective of this study was to study the effect of different concentration of superdisintegrants on the performance of Amitriptyline Hydrochloride mouth dissolving tablets and to find out the most influential factor on the selected responses.

The Analysis of Variance (ANOVA) was used to investigate the significance of the developed model and the contribution of each formulation variable. The generated model was evaluated by the statistical parameters like

F-value, p-value, coefficient of determination (R 2), adjusted R 2 and predicted R 2 . These parameters were used to check the reliability of the model and its applicability to prediction of formulation responses.

For drug release, the following polynomial equation was obtained:

Drug Release (%) = 89.59 + 0.0725A + 4.89B + 2.53C

where A means Crospovidone, B means Locust Bean Gum and C means combination of Crospovidone and Locust Bean Gum.

Regression coefficient comparison showed significant differences in the effect of formulation variables. The coefficient of Locust Bean Gum was significantly larger than that of Crospovidone, indicating that the changes in the concentration of Locust Bean Gum had a greater impact on the drug release. The positive coefficient value of the combination factor also indicated a positive contribution of both disintegrants towards formulation performance.

The ANOVA results supported the findings of the regression model. Among the factors studied, Locust Bean Gum was the most significant variable. Changes in its concentration gave rise to marked changes in the behaviour of tablet disintegration and dissolution. The crospovidone alone had a relatively small effect on the response. On evaluation of the formulation batches, the tablets with higher levels of Locust Bean Gum showed better results consistently. These formulations showed faster disintegration of the tablet and improved drug release as compared to the batches with lower concentration of the polymer. This may be due to the hydration and swelling properties of Locust Bean Gum which helps in the breakdown of the tablet matrix upon contact with the dissolution medium.

The combination batches also exhibited good performance. Crospovidone alone had a reduced effect but the combination of the two with locust bean gum increased the overall response. Crospovidone could promote rapid liquid penetration and thus could facilitate the hydration of the polymer, leading to a more effective disintegration of the tablet and better release of the drug.

The experimental observations and statistical results were in good agreement. The two methods identified Locust Bean Gum as the main factor responsible for the enhancement of tablet performance, while Crospovidone acted as a supporting component, which further improved the efficiency of the disintegration process. Statistical evaluation of data showed Locust Bean Gum as major super disintegrant in present formulation. The results also showed that the addition of a small amount of Crospovidone together with Locust Bean Gum gave an additional advantage and helped in the selection of the optimized formulation.

Build Information

File Version	25.0.0.0		
Study Type	Response Surface	**Subtype**	Randomized
Design Type	Box-Behnken	**Runs**	13
Design Model	Quadratic	**Blocks**	No Blocks
Build Time (ms)	1.0000		

Factors | Responses

Factors

Factor	Name	Units	Type	SubType	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	CROSPOVIDONE	mg	Numeric	Continuous	-1.0000	1.0000	-1 ↔ -1.00	+1 ↔ 1.00	0.0000	0.8165
B	LOCUST BEAN GUM	mg	Numeric	Continuous	-1.0000	1.0000	-1 ↔ -1.00	+1 ↔ 1.00	0.0000	0.8165
C	CP+LBG	mg	Numeric	Continuous	-1.0000	1.0000	-1 ↔ -1.00	+1 ↔ 1.00	0.0000	0.8165

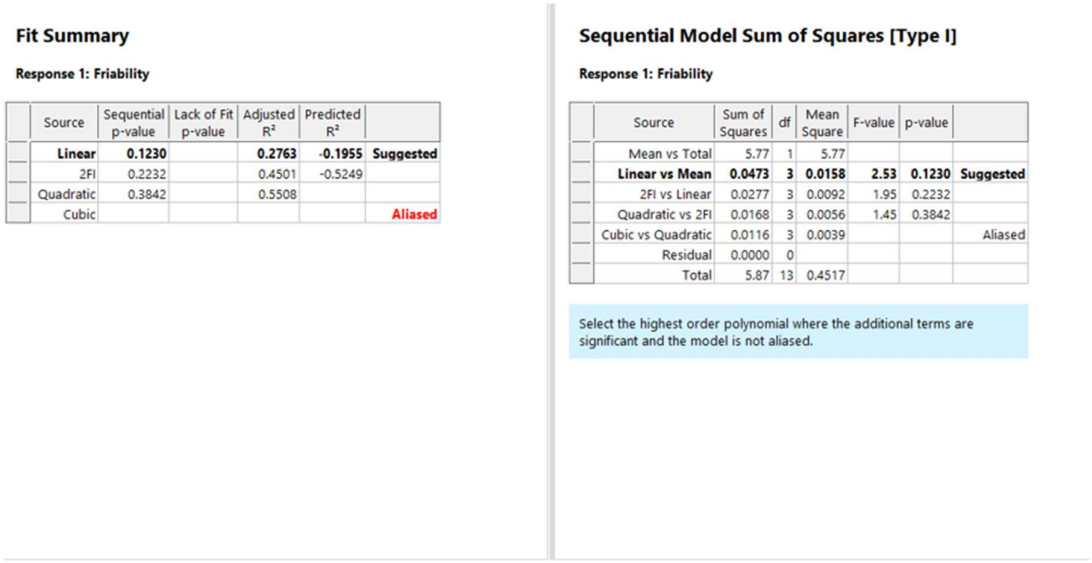
Figure no. 7: ANOVA Summary for Selected Responses

Response Surface and Contour Plot Analysis

Design Expert® software was employed to generate Graphical models to investigate the effect of formulation variables on the performance of tablets. The effect of variation in superdisintegrant concentrations on the measured responses were visually represented by response surface and contour plots.

The plots obtained for disintegration time showed a clear reduction in disintegration of the tablet with increase in the levels of Locust Bean Gum. The formulations containing higher concentrations of this polymer disintegrated faster than the formulations containing lower concentrations. This behavior might be related to the water absorption capacity of Locust Bean Gum and swelling within the tablet structure which results in faster breakdown

of the compact mass.
A different trend was observed for the formulations containing Crospovidone as the major component. Crospovidone was helpful in tablet disintegration, but the level of improvement was relatively lower than Locust Bean Gum. This observation suggests that the natural polymer had a greater effect on the response under the selected experimental conditions.
The drug release profiles showed a similar trend as found for the disintegration time. The products with fast tablet disintegration generally showed higher dissolution values. The release characteristics improved with increased concentrations of Locust Bean Gum and it was suggested that efficient disintegration of the tablets resulted in increased exposure of the drug to the dissolution medium.
The graphical models also revealed the advantage of combining both superdisintegrants. Several batches containing individual components were outperformed overall by formulations containing small amounts of Crospovidone together with Locust Bean Gum. The improvement may be due to rapid uptake of liquid by Crospovidone followed by swelling of Locust Bean Gum which causes effective tablet disintegration. The observed behavior in the response surface and contour plots was consistent with the experimental data and statistical analysis. In conclusion, the results indicated that Locust Bean Gum was the most influential variable on the performance of the formulation, whereas the inclusion of Crospovidone had a supportive role that further improved the tablet disintegration and drug release.



Fit Summary

Response 1: Friability

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	**0.1230**		**0.2763**	**-0.1955**	**Suggested**
2FI	0.2232		0.4501	-0.5249	
Quadratic	0.3842		0.5508		
Cubic					**Aliased**

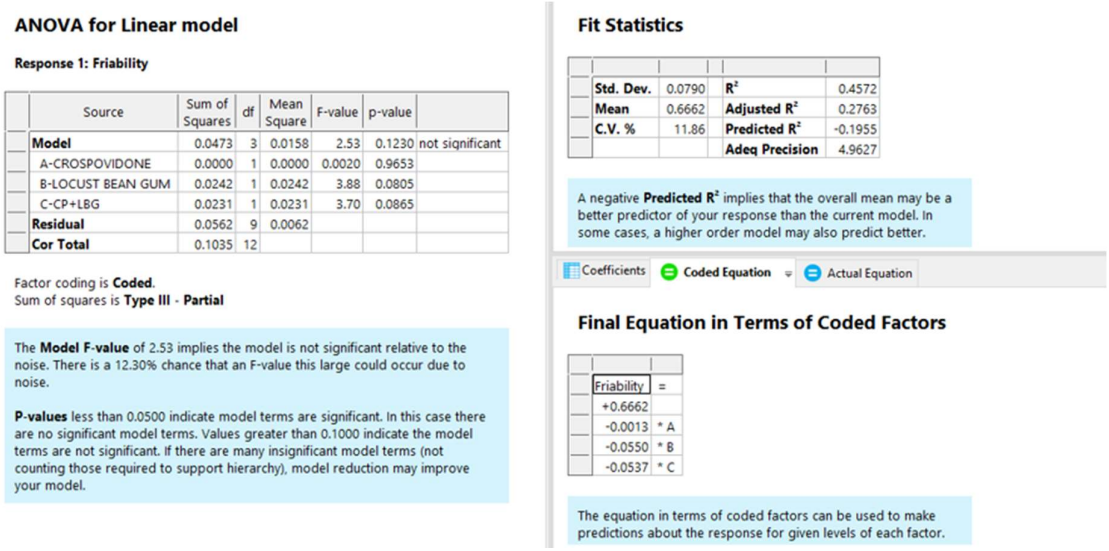
Sequential Model Sum of Squares [Type I]

Response 1: Friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Mean vs Total	5.77	1	5.77			
Linear vs Mean	**0.0473**	**3**	**0.0158**	**2.53**	**0.1230**	**Suggested**
2FI vs Linear	0.0277	3	0.0092	1.95	0.2232	
Quadratic vs 2FI	0.0168	3	0.0056	1.45	0.3842	
Cubic vs Quadratic	0.0116	3	0.0039			Aliased
Residual	0.0000	0				
Total	5.87	13	0.4517			

Select the highest order polynomial where the additional terms are significant and the model is not aliased.

Figure no. 8 Fit Summary (Response 1 – Friability)



ANOVA for Linear model

Response 1: Friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0473	3	0.0158	2.53	0.1230	not significant
A-CROSPOVIDONE	0.0000	1	0.0000	0.0020	0.9653	
B-LOCUST BEAN GUM	0.0242	1	0.0242	3.88	0.0805	
C-CP+LBG	0.0231	1	0.0231	3.70	0.0865	
Residual	0.0562	9	0.0062			
Cor Total	0.1035	12				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 2.53 implies the model is not significant relative to the noise. There is a 12.30% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.0790	**R^2**	0.4572
Mean	0.6662	**Adjusted R^2**	0.2763
C.V. %	11.86	**Predicted R^2**	-0.1955
		Adeq Precision	4.9627

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Coefficients | Coded Equation | Actual Equation

Final Equation in Terms of Coded Factors

Friability	=
+0.6662	
-0.0013	* A
-0.0550	* B
-0.0537	* C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor.

Figure no. 9: ANNOVA (Response 1 – Friability)

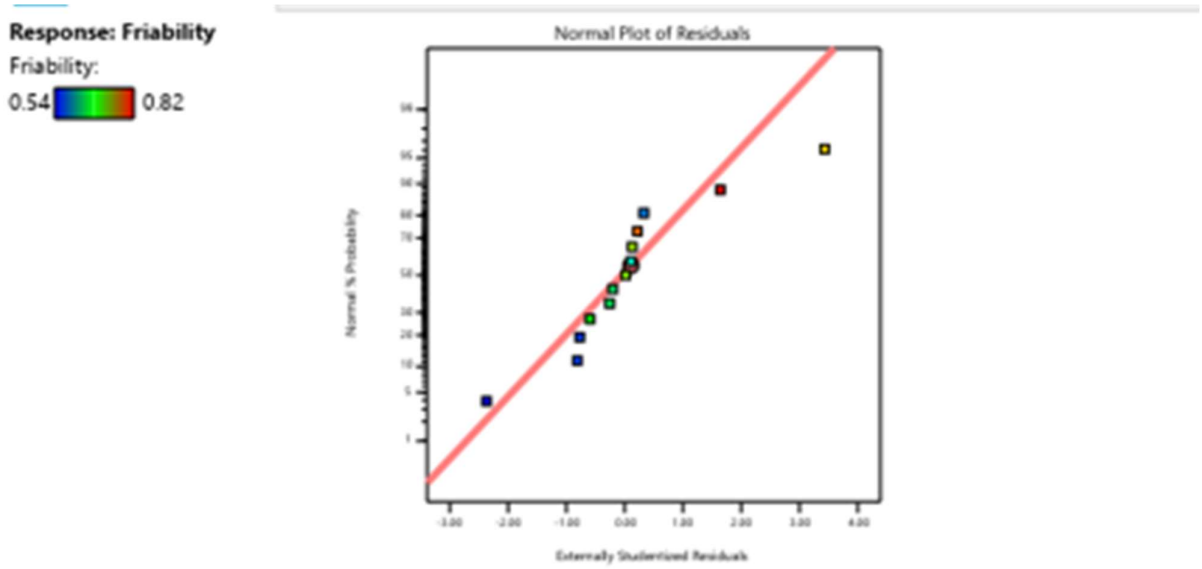


Figure no. 10: Contour Plot Graph (Response 1 – Friability)

Fit Summary

Response 2: Disintegration time

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.1251		0.2734	-0.1961	
2FI	**0.0942**		**0.5965**	**-0.0980**	**Suggested**
Quadratic	0.1682		0.8186		
Cubic					**Aliased**

Sequential Model Sum of Squares [Type I]

Response 2: Disintegration time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Mean vs Total	2.47	1	2.47			
Linear vs Mean	0.3014	3	0.1005	2.50	0.1251	
2FI vs Linear	**0.2274**	**3**	**0.0758**	**3.40**	**0.0942**	**Suggested**
Quadratic vs 2FI	0.1036	3	0.0345	3.45	0.1682	
Cubic vs Quadratic	0.0301	3	0.0100			Aliased
Residual	0.0000	0				
Total	3.14	13	0.2412			

Select the highest order polynomial where the additional terms are significant and the model is not aliased.

Figure no. 11: Fit Summary (Response 2- Disintegration time)

ANOVA for 2FI model

Response 2: Disintegration time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.5288	6	0.0881	3.96	0.0593	not significant
A-CROSPOVIDONE	0.0018	1	0.0018	0.0808	0.7858	
B-LOCUST BEAN GUM	0.2965	1	0.2965	13.31	0.0107	
C-CP+LBG	0.0032	1	0.0032	0.1437	0.7177	
AB	0.2209	1	0.2209	9.92	0.0198	
AC	0.0016	1	0.0016	0.0718	0.7977	
BC	0.0049	1	0.0049	0.2200	0.6556	
Residual	0.1337	6	0.0223			
Cor Total	0.6625	12				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 3.96 implies there is a 5.93% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.1493	**R^2**	0.7983
Mean	0.4362	**Adjusted R^2**	0.5965
C.V. %	34.22	**Predicted R^2**	-0.0980
		Adeq Precision	7.8067

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	0.4362	1	0.0414	0.3349	0.5374	
A-CROSPOVIDONE	-0.0150	1	0.0528	-0.1441	0.1141	1.0000
B-LOCUST BEAN GUM	-0.1925	1	0.0528	-0.3216	-0.0634	1.0000
C-CP+LBG	-0.0200	1	0.0528	-0.1491	0.1091	1.0000
AB	0.2350	1	0.0746	0.0524	0.4176	1.0000
AC	-0.0200	1	0.0746	-0.2026	0.1626	1.0000
BC	0.0350	1	0.0746	-0.1476	0.2176	1.0000

Figure no. 12: ANNOVA (Response 2- Disintegration time)

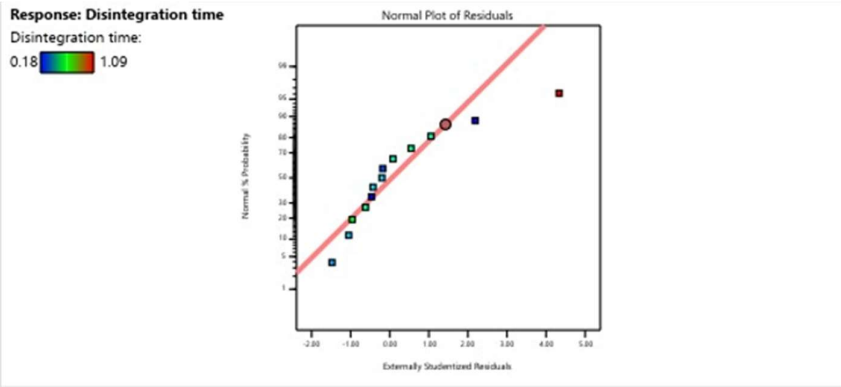


Figure no. 13: Contour plot graph (Response 2- Disintegration time)

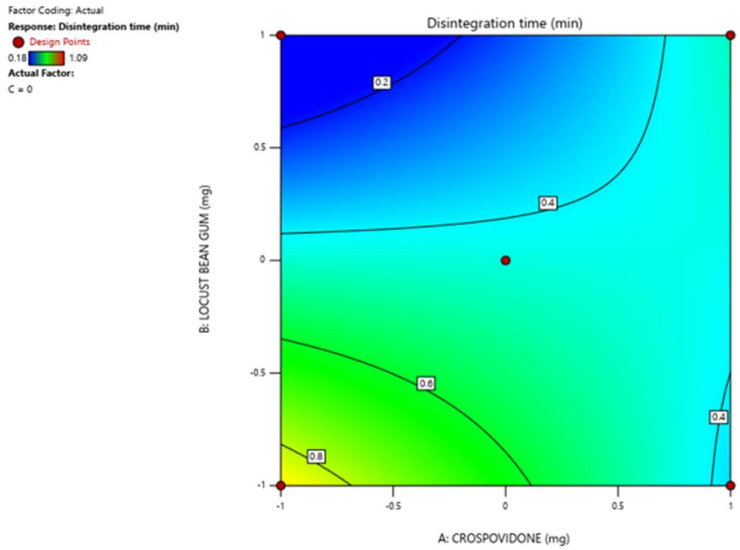


Figure no. 14: Model graph of disintegration time

Fit Summary

Response 3: In vitro drug release

	Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
	Linear	**0.0269**		**0.4963**	**0.1662**	**Suggested**
	2FI	0.1449		0.6735	0.0881	
	Quadratic	0.6114		0.6161		
	Cubic					**Aliased**

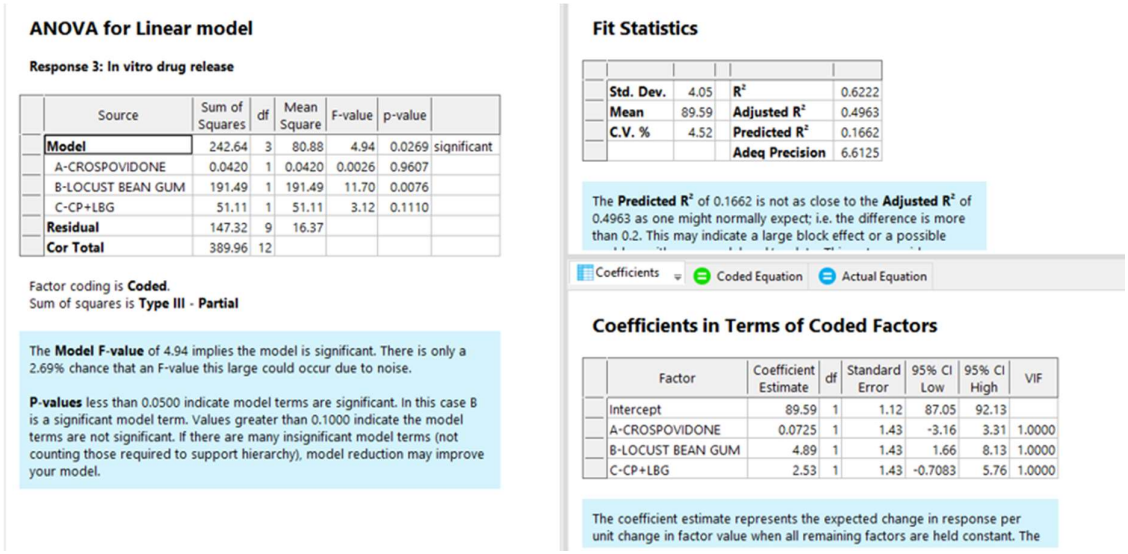
Sequential Model Sum of Squares [Type I]

Response 3: In vitro drug release

	Source	Sum of Squares	df	Mean Square	F-value	p-value	
	Mean vs Total	1.043E+05	1	1.043E+05			
	Linear vs Mean	**242.64**	**3**	**80.88**	**4.94**	**0.0269**	**Suggested**
	2FI vs Linear	83.65	3	27.88	2.63	0.1449	
	Quadratic vs 2FI	26.24	3	8.75	0.7009	0.6114	
	Cubic vs Quadratic	37.43	3	12.48			Aliased
	Residual	0.0000	0				
	Total	1.047E+05	13	8056.64			

Select the highest order polynomial where the additional terms are significant and the model is not aliased.

Figure no. 15: Fit summary (Response 3: In Vitro Drug Release).



ANOVA for Linear model

Response 3: In vitro drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	242.64	3	80.88	4.94	0.0269	significant
A-CROSPOVIDONE	0.0420	1	0.0420	0.0026	0.9607	
B-LOCUST BEAN GUM	191.49	1	191.49	11.70	0.0076	
C-CP+LBG	51.11	1	51.11	3.12	0.1110	
Residual	147.32	9	16.37			
Cor Total	389.96	12				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 4.94 implies the model is significant. There is only a 2.69% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	4.05	**R^2**	0.6222
Mean	89.59	**Adjusted R^2**	0.4963
C.V. %	4.52	**Predicted R^2**	0.1662
		Adeq Precision	6.6125

The **Predicted R^2** of 0.1662 is not as close to the **Adjusted R^2** of 0.4963 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	89.59	1	1.12	87.05	92.13	
A-CROSPOVIDONE	0.0725	1	1.43	-3.16	3.31	1.0000
B-LOCUST BEAN GUM	4.89	1	1.43	1.66	8.13	1.0000
C-CP+LBG	2.53	1	1.43	-0.7083	5.76	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The

Figure no. 16: ANNOVA (Response 3: In Vitro Drug Release).

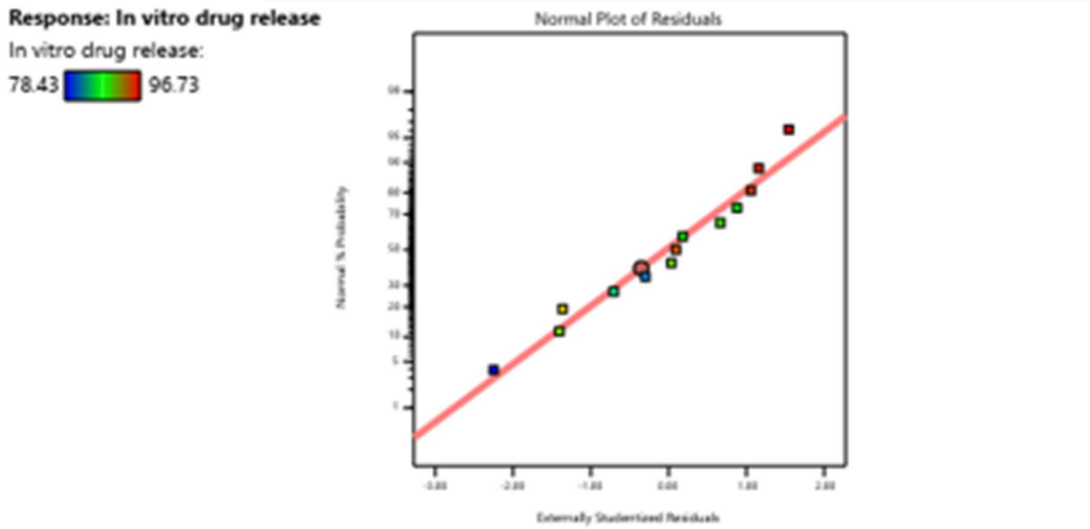


Figure no. 17: Contour Plot Graph (Response 3: In Vitro Drug Release).

Optimization and Selection of Optimized Formulation

The main aim of the optimization study was to find a formulation capable of rapid tablet disintegration while maintaining acceptable friability and maximum drug release. The combined effect of formulation factors on the selected solutions was evaluated by performing the optimization process using Design Expert® software. The best formulation was identified by comparing the trial results of each formulation batch. The best batch was selected based on improved dissolve properties, acceptable mechanical strength and shortest disintegration time. Formulations with relatively low drug release or delayed disintegration were not pursued further. The Locust Bean Gum formulations were better than Crospovidone alone in the evaluated batches. The results revealed that Locust Bean Gum was effective in enhancing tablet disintegration and dissolution behaviour. The optimization study also demonstrated that the performance of the formulation was further improved by the addition of a small amount of Crospovidone in addition to Locust Bean Gum. Locust bean gum decreased swelling and water retention, and crospovidone provided for fast liquid penetration into the tablet matrix. The synergistic effect of these mechanisms led to improved tablet disintegration and enhanced drug release. The best batch was selected according to the response values of evaluation and formulation F13. Among the trial batches, the formulation with the least disintegration time with high drug release and acceptable friability was found. The overall performance of the batch showed a good balance between mechanical strength and fast disintegration properties.

The optimization results showed that formulation with appropriate amount of Locust Bean Gum and less amount of Crospovidone can successfully improve the performance of mouth dissolving tablet. Thus, the selected optimized formulation was considered suitable for further characterization and validation studies.

Table no. 20: Optimized Formulation and Response Values

Sr. No.	Parameter	Optimized Batch
1.	Friability (%)	0.62
2.	Disintegration Time (min)	0.19
3.	Drug Release (%)	94.74

SUMMARY AND CONCLUSION

The present research has concluded that locust bean gum (LBG), a galactomanan polysaccharide, extracted from the seeds of the carob tree (Ceratonia siliqua) has a promising natural super disintegrant potential. Where Amitriptyline Hydrochloride – a BCS Class II drug with low aqueous solubility and pH dependent dissolution. LBG has been shown to promote quick disintegration of the tablet and drug release. The excellent disintegrating action of LBG can be attributed to its properties such as high swelling on hydration, high porosity and capillary action facilitating rapid draw of water into the core. All these combined action makes it a promising disintegrant and improves dissolution.

The compatibility studies once again proved the absence of any interactions between Amitriptyline Hydrochloride and the selected excipients by the IR spectroscopy. The IR spectra showed the characteristic peaks of pure drug substances unchanged. The determination of pure telmisartan melting point was estimated in range of 265-271 which is as per standard standards.

Of all the formulations, f8, a stable and effective Locust bean gum at optimum concentration, emerged as a very viable, eco-friendly alternative to synthetic super disintegrants used for immediate release of Amitriptyline Hydrochloride. Thus, this comparative study of natural and synthetic disintegrants and the reliability of natural disintegrants over synthetic paves the way for eco-friendly pharmaceutical formulations. Locust bean gum holds promise for developing fast dissolving oral dosage forms of poor soluble therapeutics. Design of Experiment approach provided systematic understanding on the effect of formulation variables on the performance of Amitriptyline Hydrochloride mouth dissolving tablets. The experimental results showed that the type and concentration of superdisintegrants directly affected the friability, disintegration time and drug release profile of the developed formulations.

The friability values obtained for all batches were within acceptable limits indicating that the selected formulation variables did not adversely affect the tablet strength. The prepared tablets were of adequate mechanical integrity to withstand normal handling and still maintain their fast disintegration characteristics.

There was a large difference in the time of disintegration between the experimental formulations. The results indicated that Locust Bean Gum had better efficiency in tablet disintegration than Crospovidone alone. Tablets with higher levels of Locust Bean Gum generally exhibited faster tablet breakup, possibly due to its hydration and swelling properties. Upon contact with the dissolution medium, the polymer absorbed water and swelled, which resulted in the disruption of the tablet matrix.

Dissolution study also showed similar trend. Formulations with faster disintegration also showed better drug release profiles. The faster tablet breakup improved available surface area for dissolution and hence accelerated drug release into the surrounding medium.

One important finding of the study was the beneficial interaction of Locust Bean Gum and Crospovidone. Locust Bean Gum was found to be major contributor towards tablet disintegration. Addition of small quantity of Crospovidone further improved formulation performance. This effect can be attributed to the difference in their mechanisms of action. Locust Bean Gum primarily swells, and Crospovidone increases liquid penetration via capillary action. These mechanisms together favoured rapid hydration and efficient disintegration of the tablets.

These findings were further supported by the response surface analysis and optimization studies. Graphical and statistical evaluation demonstrated that formulations with Locust Bean Gum alone or in combination with a limited amount of Crospovidone gave better results than formulations based mainly on Crospovidone. These observations highlight the importance of choosing the suitable super disintegrant system for formulation of effective mouth dissolving tablets.

In general, a clear correlation between the tablet performance and the formulation variables was established by the DOE study. The experimental data obtained was useful for optimization of formulation and to find out the suitable combination of superdisintegrants for rapid disintegration of tablets and improved drug release.

Conclusion

It was concluded that the mouth dissolving tablets of Amitriptyline Hydrochloride were formulated successfully by using different Synthetic and Natural Super Disintegrants and the formulations are compared successfully for better patient compliance and effective therapy.

Acknowledgements

Authors thank Lozenges Heathcare Pvt Ltd, Kiet School of Pharmacy for providing samples of Amitriptyline Hydrochloride, Locust bean gum, Mango peel pectin, Dehydrated banana powder, Crospovidone, sodium starch glycolate, Croscarmellose Sodium, Microcrystalline cellulose, Aspartame, Talc and Magnesium stearate.

Compliance with ethical standards

Conflicts of Interest

The authors declares that he has no conflict of interest.

Statement of human and animal rights

This article does not contain any studies with human and animal subjects performed by any of the authors.

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