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Design and Development of Propranolol HCl Fast Dissolving Tablets by Using Isolated Mucilage of *Salvia Hispanica* for the Treatment of Hypertension by Using DoE tools

Nandhini J[1], B. Anandhi[2], Soumya Stuti Patnaik[3], Rahul Lotan Shirole[4], Navinraj Dudhnath Mourya[5], Nahida Siddiqui[6], Jithin Mathew[7], V. R. Ravikkumar[8*], E. Karthikeyan[9]

[1]Department of Pharmaceutics, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Chennai - 602105, India
[2]The Erode College of Pharmacy, Erode, India
[3]Guru Nanak Institutions Technical Campus, India
[4]Department of Pharmacology, DCS's A.R.A. College of Pharmacy, Nagaon, Dhule (MS) India
[5]School of Pharmacy, Rai University, Gujarat, India
[6]CMR College of Pharmacy, Kandlakoya, Hyderabad, Telangana, India
[7]Department of Pharmacology, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Deralakatte, Paneer, Mangalore, Karnataka, India
[8]Dept. of Pharmacognosy, The Erode College of Pharmacy , Tamil Nadu Dr MGR Medical University Chennai, Perundurai Main Road, Veppampalayam, Erode-638112, Tamil Nadu, India
[9]Department of Pharmaceutical Chemistry, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Chennai-602105, Tamilnadu, India

***Correspondence Author:**
Prof. Dr. V. R. Ravikkumar,
Professor and Head, Dept. of Pharmacognosy, The Erode College of Pharmacy, Tamil Nadu Dr MGR Medical University Chennai, Perundurai Main Road, Veppampalayam, Erode-638112, Tamil Nadu, India
Orcid Id: 0000-0001-5549-8713

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Abstract The main issue with Hypertension therapy is quick commencement of effect. The creation of suitable dose forms may help address the issue of medications having a delayed beginning of effect. Oral Antihypertensive medication treatment is best suited for and has seen a rise in popularity with fast-disintegrating tablets. In terms of patient compliance, quick start of action, precise dosage, strong chemical stability, ease of self-administration, and compactness, they are superior to other traditional methods. As a popular hypertension medication, Propranolol HCl is a strong candidate for development into Fast Dissolving Tablets (FDTs). Because to first pass metabolism, it has a limited bioavailability. Therefore, the primary goal of the research was to create Propranolol HCl fast-dissolving tablets in order to increase the drug's bioavailability and dissolution rate. Microcrystalline cellulose used to make fast-dissolving Propranolol HCl tablets, together with varying concentrations of super disintegrates such as Chia Seed mucilage and sodium starch glycolate. Each batch was

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made by compressing it directly. Three formulation variables were combined, and the combined impact was examined using a 23 Full Factorial design. Here, the disintegration time is examined as a dependent parameter and the concentrations of chia seed mucilage, Sodium Starch Glycolate, and Microcrystalline Cellulose were considered as independent variables, X1, X2, and X3, respectively. The program Design Expert is used to depict the data.

Keywords *Salvia Hispanica*, Mucilage, Fast dissolving tablets, Hypertension

Introduction

Oral route of administration of therapeutic agents provides a convenient method of effectively achieving both local and systemic effects. Routes of drug administration that can be utilized in order to achieve systemic delivery of a drug include: parenteral, oral, buccal, transdermal, nasal and pulmonary, the best oral dosage form available in the market are tablets. Medication is delivered by the oral route in the form of tablet dosage and patient compliance is very convenient. Tablets are capable of delivering medication into the body on the principle of disintegration, dissolution and subsequent absorption. It requires time to enter the blood circulation. Oral drug delivery formulation and methods are generally focused on the following areas of gastrointestinal tract (GIT) [1]. Pediatric and geriatric patient have difficulty in swallowing tablets therefore fast dissolving tablets are a prefered dosage form. It is semisolid unit dosage form that contains disperses or disintegrates in less than 3 minutes in the mouth before swallowing, Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules and one important drawback of this dosage forms for some patients is the difficulty to swallow [2]. Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation and is moving rapidly.19 In recent years, polymers those are derived from plant origin have evoked tremendous interest because of their diverse pharmaceutical applications such as diluent, binder, disintegrate in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels, and bases in suppository [3].

The mucilage are preferred over the synthetic ones because they are biocompatible, cheap, and easily available than the synthetic. Mucilage are generally normal products of metabolism (physiological products), formed within the cell (intracellular formation). Mucilage is a thick, gluey substance produced by plants and some microorganism. Mucilage in plants plays a role in the storage of water and food [4].

Mucilage are polysaccharides hydrocolloids with sugar molecules linked with uronic acid, they are translucent amorphous substance and polymer of monosaccharides or mixed monosaccharides combines with uronic acid. On hydrolysis they yield mixture of sugar and uronic acid, since they contain hydrophilic molecules so they combine with water to form viscous solution, mucilage's are complex polysaccharides which consist of arabinose, galactose, rhamnose, and galacturonic acid [5].

Chia (*Salvia hispanica* L.) is a small seed that comes from an annual herbaceous plant, Salvia hispanica L. In recent years, usage of Chia seeds has tremendously grown due to their high nutritional and medicinal values. Chia was cultivated by Mesopotamian cultures, but then disappeared for centuries until the middle of the 20th century, when it was rediscovered. Chia seeds contain healthy ω-3 fatty acids, polyunsaturated fatty acids, dietary fiber, proteins, vitamins, and some minerals. Besides this, the seeds are an excellent source of polyphenols and antioxidants, such as caffeic acid, rosmarinic acid, myricetin, quercetin, and others. Today, chia has been analyzed in different areas of research. Researches around the world have been investigating the benefits of chia seeds in the medicinal, pharmaceutical, and food industry [6].

Material and Methods

Salvia hispanica were obtained from seller WELLNESS SOLUTION PVT. LTD.Pune-411057, Maharashtra (amazon market). India and Propranolol HCl was procured from Yarrow Chem, Products Mumbai. Lactose, acacia gum, Corn starch, talc and magnesium stearate were from Central Drug House (P) Ltd. & other chemicals purchased from Thermo Fisher Scientific

Figure 1: A. Extraction of mucilage, B. Isolated mucilage.

Indian Pvt. Ltd., Mumbai (AR Grade).

Methods

Isolation of Mucilage

The process begins with the selection of the plant's seed and fruit parts, followed by drying, grinding, and sieving of the seed powder. Next, it is heated in distilled water for complete dispersion, allowing for storage for 6–8 hours at room temperature. Next, it filters through double-layer muslin tissue, mixes the supernatant, adds twice the volume of acetone with continuous stirring, and finally washes the precipitated material in vacuum at 50–60 °C to obtain dry mucilage [7].

Mucilage % yield

Mucilage yield % was used to evaluate extraction efficiency. First, a known plant weight was extracted using a specified solvent. After extraction and filtering, mucilage was dried to constant weight [8]. Formula for calculating mucilage yield percentage:

% Yield= (Dried mucilage weight / weight of plant material)*100%

Determination of Swelling Index of Mucilage

A solubility research was carried out to ascertain the profile of mucilage's solubility in various solvents. Water, ethanol, methanol, and chloroform were among the solvents used to assess the solubility of the mucilage sample. According to the findings, mucilage was insoluble in chloroform and exhibited high solubility in water, moderate solubility in ethanol, and methanol [9].

Solubility of isolated mucilage's in various solvents

To establish their dissolving behaviour, the separated components were tested in different solvents. Individually, the separated components were tested for solubility in water, ethanol, methanol, chloroform, and others. Some materials dissolved well in polar solvents like water, ethanol, and methanol, whereas others dissolved better in non-polar solvents like chloroform. These results provide light on the separated materials' solubility, which is important for pharmaceutical, food, and other applications [11].

Identification test of isolated materials

Isolated mucilage powder was treated with 1% Ruthenium red solution and observed for any Color change. This test confirm mucilage present [12].

Preparation of Fast Dissolving Tablets by Direct Compression Method

To promote dissolve and patient compliance, direct compression was used to make fast-dissolving tablets. The recipe included active medicinal component, superdisintegrants, diluents, and sweeteners. The components were mixed evenly and compacted into tablets using a rotating tablet press. The tablets were tested for weight fluctuation, hardness, friability, disintegration time, and drug dissolving profile. The direct compression process for fast-dissolving tablets was easy, cost-effective, and repeatable, providing a formulation strategy for drug administration. The composition of each tablet is shown in Table 2 [13]

Experimental Design

Experimental design utilized in 2^3 factorial design

Table 1: 2^3Factorial design with upper & lower limits of all factors

3 Factors	2 Levels	
	-1	+1
Chia Seed Mucilage	5	15
Conc. of S.S.G.	6	12
Conc. of M.C.C.	20	40

Table 2: Formulae for the Preparation of Fast Dissolving Tablets as Per Experimental Design

Ingredients	Quantity in 'mg'							
	F1	F2	F3	F4	F5	F6	F7	F8
Propranolol HCl	20	20	20	20	20	20	20	20
Chia Seed Mucilage	15	15	5	15	5	5	15	5
S.S.G.	6	12	12	6	6	6	12	12
M.C.C.	40	20	20	20	40	20	40	40
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Mannitol	116	130	140	137	127	147	111	121
Total	200	200	200	200	200	200	200	200

in which three variables namely concentrations of Chia Seed mucilage, S.S.G and M.C.C. were kept at two levels. Main interactive influences were tested using statistical methods [11].

Evaluation of Fast Dissolving Tablets

Wetting Time

To find out how long it takes for the tablet to get wet, a piece of tissue paper folded twice was put in a small petri dish with 5 ml of distilled water inside it. The tablet was put on the paper, and the time it took for the tablet to get completely wet was recorded in seconds.

Study of In-vitro Dissolution

We tested Fast Dissolving pills in a USP XXIII type-II dissolution test device (Paddle type) with 900 ml of phosphate buffer pH 6.8 as the dissolution medium. The test was done at 50 rpm and 37±0.5°C. At set times, 5 ml of the samples were taken out using a syringe fitted with a pre-filter. The same amount of fresh breakdown medium was added to the volume that was taken out at each interval. After the samples were diluted properly, they were tested for drug release by measuring their absorbance at 288 nm with a UV-visible spectrophotometer. The determinations were made three times (n=3).

Disintegration Test

Saliva breaks down fast dissolving pills in the mouth, but there is not a lot of saliva in the mouth, and neither the USP nor the IP could find a tablet disintegration test that would work in real life. To find out how long it took the tablets to break down, a different method was used. A cylinder-shaped container was used, and a 10-mesh screen was put inside it so that only 2 ml of dissolving or breaking medium could go below the screen. Six milliliters of Sorenson's buffer (pH 6.8) were put into the jar so that four milliliters were below the sieve and two milliliters were above it. This was done to find out how long it took the particles to break down. After putting the tablet on the sieve, the whole thing was put on a shaker. This is how long it takes all the pieces to go through the screen. This is how long it takes the tablet to break up. The average number was found by picking six tablets at random from the group of samples [14].

Analysis of statistics

The gathered data were looked at using multiple regression analysis to fit polynomial equations and find out what the independent factors meant. An analysis of variance (ANOVA) test was used to see if the regression model and its results were statistically important. Response surface plots were made to find the best formulation settings and see how the interactions would affect the formulation. Experiments were used to validate the better version and make sure that the model's results were accurate and reliable [15-17].

Optimization and validation of formula of FDT Batch F-9

The Full Factorial design was made better with the help of Design Expert software version 13, and the formulation was proven to work. Fig 2-4 show the contour plots that were used to get the values needed to build a regression model that was used to find the best Optimized results.

Results and Discussion

Evaluation of Mucilage

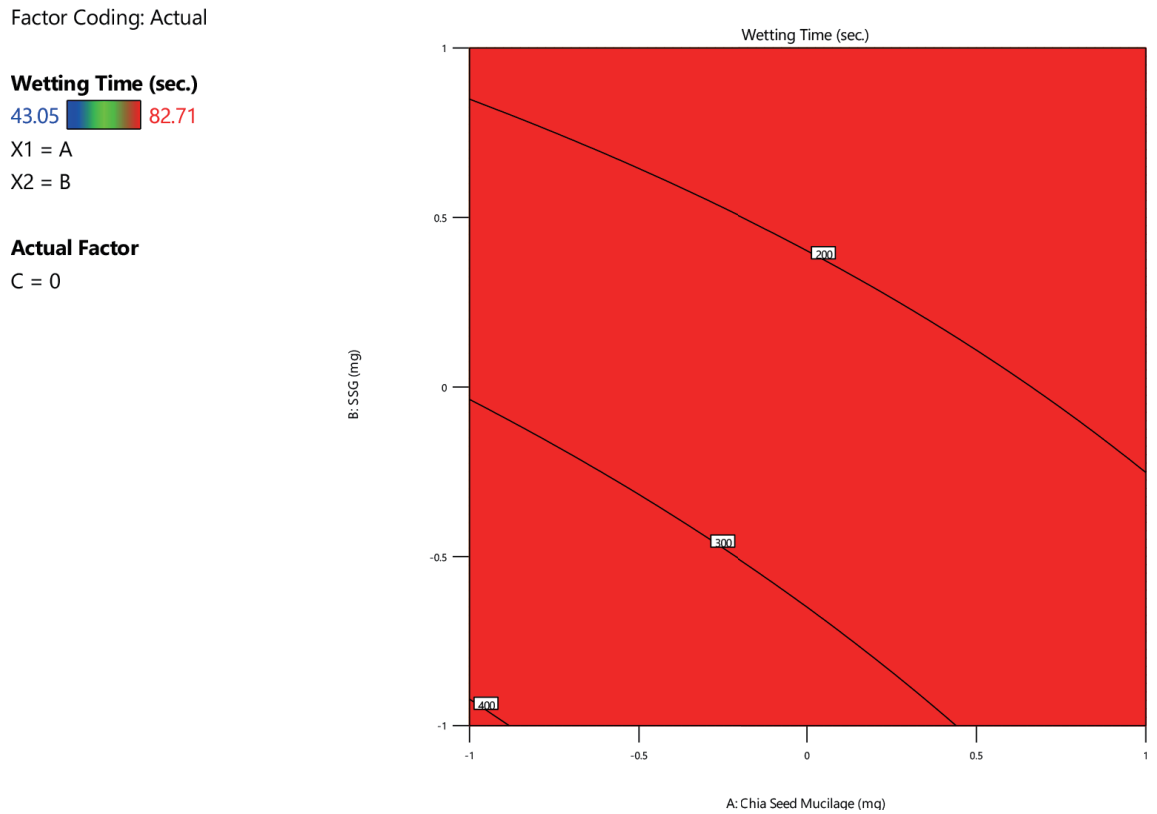

Figure 2: Contour plot for the wetting time

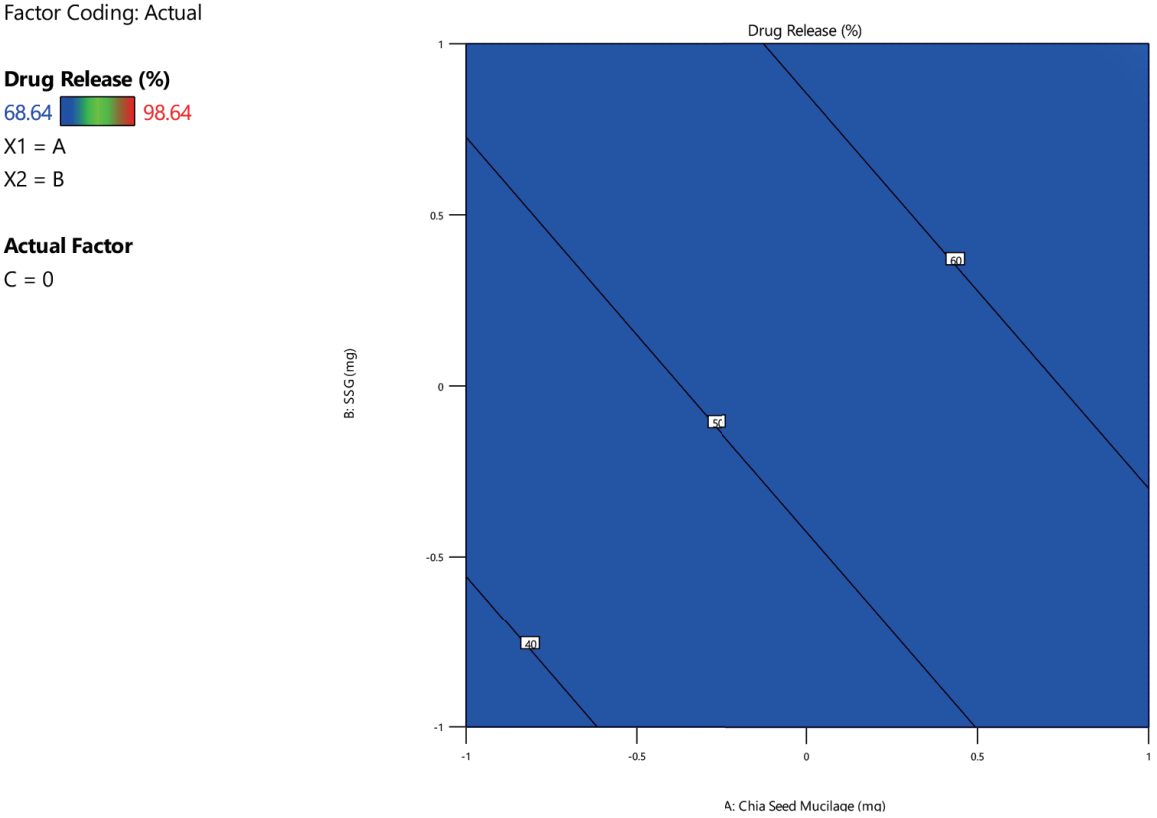

Figure 3: Contour plot for the Drug Release

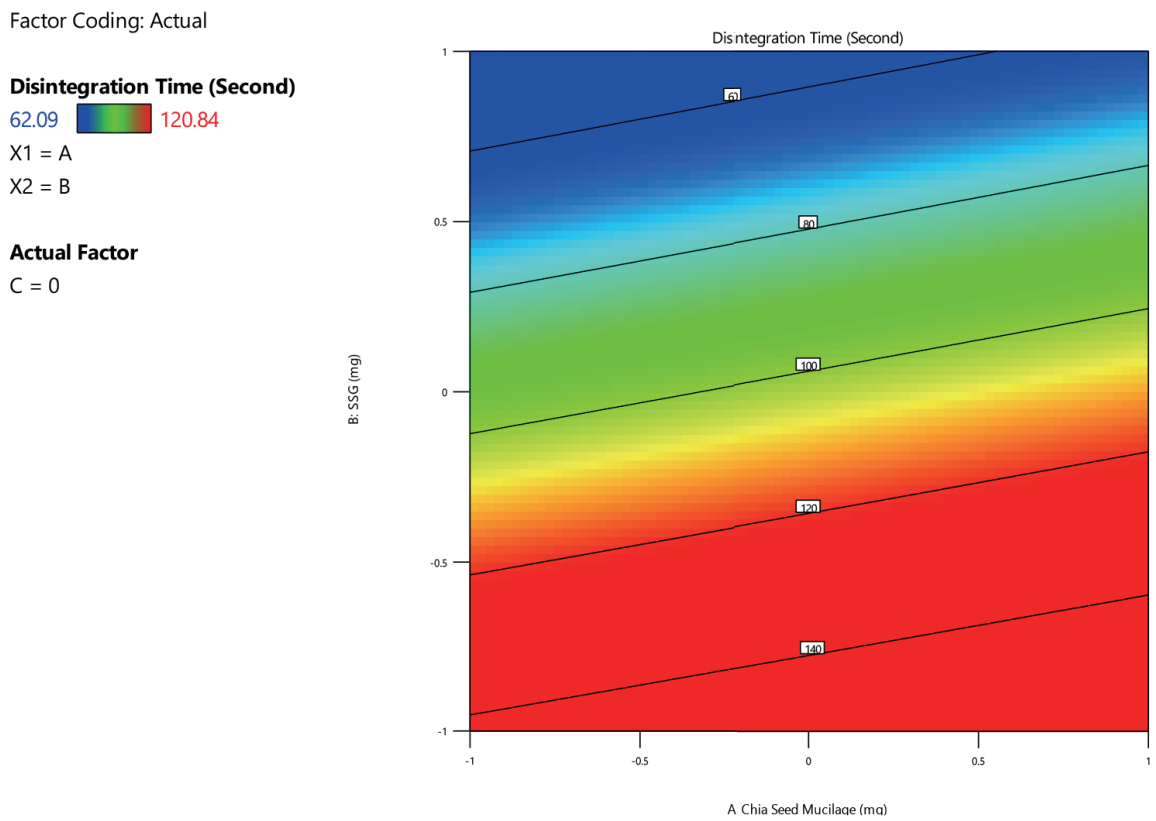

Figure 4: Contour plot for the Disintegration time

Table 3: Percent Yield of isolated materials.

Isolated Material	Quantity Used	Material Obtained (Yield)	% Yield (yield/quantity used*100)
Chia seed mucilage	200 gram	29.12 grams	14.56 %

Table 4: Solubility of isolated materials in various solvents.

Isolated material	Solvent	Solubility
Chia seed Mucilage	Water	Slightly soluble
	Hot water	Forms jelly like
	Ethanol	Insoluble

Table 5: Results for identification test of isolated materials.

Isolated Materials	Observation for Mucilage	Result
Chia Seed Mucilage	The solution turns pink color when treated with Ruthenium Red Solution.	Mucilage was present (+)

Isolated mucilage's was evaluated for their percentage yield and solubility study in different solvents, identification test of mucilage for confirmation and result are shown in Table 3-5.

In- vitro disintegration time

The in-vitro disintegration time was measured by the time taken to undergo complete disintegration.

Table 6: Result of data obtained from Experiment & DoE Study of FDT (Batch: 1-8)

Run	Independent Variable			Dependent Response		
	Factor-1 (A) Chia Seed Mucilage	Factor-2 (B) S.S.G.	Factor-3 (C) M.C.C.	Response-1 Wetting Time (Sec.)	Response-2 Drug Release (%)	Response-3 Disintegration Time (Sec.)
1	+1	-1	+1	43.05	80.66	62.09
2	+1	+1	-1	46.22	98.64	67.88
3	-1	+1	-1	48.26	72.43	69.14
4	+1	-1	-1	47.44	68.64	68.05
5	-1	-1	+1	50.65	75.24	73.845
6	-1	-1	-1	82.71	75.24	68.53
7	+1	+1	+1	76.94	85.43	120.84
8	-1	+1	+1	82.08	74.44	110.58

Table 7: Result of predicted Composition of Optimized Formulation by QbD Batch FDT (Batch-9)

Chia seed Mucilage	S.S.G.	M.C.C.	Wetting Time (Sec.)	Drug Release (%)	Disintegration Time (Sec.)	Desirability
15	10.42	13.61	45.84	97.76	63.49	0.860

Table 8: Results of Optimized Formulation of FDT (Batch-9)

Variables	Predicted Response	Observed Response	% Predicted Error (% PE)	Acceptance Criteria for % PE
Wetting Time (Sec.)	45.84	47.29	3.06	Less than 5.0 %
Drug Release (%)	97.76	99.28	1.53	Less than 5.0 %
Disintegration Time (Sec.)	63.49	64.81	2.03	Less than 5.0 %

Rapid disintegration within 3 minutes was observed in all the formulations. Disintegration time of all the formulations is checked and found within the range of 62.09 to120.84 sec.

Wetting time

Wetting time is closely related to the inner structure of the tablet. The wetting time of FDT prepared were found to be in the range of 43.05 to 76.94 sec.

In- vitro dissolution study

Cumulative % Drug release of Factorial Design Formulations F1-F8 at 30 min. were found to be in the range of 72.43 to 98.64%. From the result it reveals that the release rate was higher for formulations containing High level of chia seed mucilage and SSG compared with other Formulations batch containing Lower level, due to High concentration of Superdisintegrants in combination, shows various disintegration mechanism such as wicking and swelling etc.

Results of optimized formula by QbD for the preparation of the EM BT

Table No. 7 displays the statistical conclusions drawn from the model to demonstrate its best fit on there desirability value, which were based on a modified coded value that was produced when considering the optimal condition. You can see the improved formulation in Table No. 8 show the findings of an additional triplicate experiment that was conducted under different experimental conditions to compare

the anticipated results with the actual values of Wetting Time, Drug Release and Disintegration Time.

Conclusion

In present work, a fast disintegrating Propranolol HCl tablets were developed. Propranolol HCl was selected for this investigation because the absorption window of this drug is the upper part of small intestine Step by step studies were carried out to develop and optimize oral fast disintegrating tablet for Propranolol HCl using natural & semi synthetic superdisintegrants. Hence, finally it was concluded that the prepared optimized batch Fast dissolving tablets of Propranolol HCl might prove to be potential candidate for safe and effective fast disintegrating tablet dosage form by Formal Experimental Design method.

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Conflict of interest

Author declares that there are no conflict of interest.

Abbreviations

FDT= Fast Dissolving Tablet
SSG= Sodium Starch Glycolate
MCC= Microcrystalline Cellulose
DoE= Design of Expert

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