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Development And Characterization Of Mouth Dissolving Tablet Of Antineoplastic Agent – Erlotinib Hydrochloride

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Abstract: The focus of the present study is to develop and characterize mouth dissolving tablet of Erlotinib hydrochloride. Erlotinib Hydrochloride, a strong antineoplastic drug utilized in the treatment of numerous cancers, presents significant formulation difficulties due to its poor water solubility and unpleasant taste. This research focuses on the development and characterization of a mouth dissolving tablet (MDT) formulation of Erlotinib Hydrochloride aimed at raising patient compliance and therapeutic efficacy. The formulation employs a β-cyclodextrin inclusion complex established via the method of kneading to minimize the drug's unpleasantness and improve its solubility. The optimized complex, with a drug-to-β-cyclodextrin ratio of 1:2, was incorporated into MDTs using the direct compression technique. Comprehensive pre-compression evaluations, including measurements of bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose, were performed to ensure suitable powder flow. Post-compression parameters such as tablet weight variation, hardness, friability, disintegration time (goal <30 seconds), and in vitro dissolution (evaluated in phosphate buffer 7.4, pH 7.4) were subsequently examined. Characterization tests, including UV and FTIR analysis, confirmed the effective development of the inclusion complex without any chemical interaction between the drug and excipients. The optimized formulation exhibited rapid disintegration, satisfactory mechanical strength, and an enhanced dissolution profile compared to the pure drug, thereby demonstrating effective solubility improve and improved bioavailability. For mask the inedible taste of drug β-cyclodextrin inclusion complex prepared and additionally added the polymer Kyron T-314 that act as a taste masking agent and also super disintegrant. These findings suggest that the developed mouth dissolving tablet of Erlotinib Hydrochloride is a promising dosage form for cancer therapy, particularly for patients with swallowing difficulties. Future work will maybe involve scale-up studies and in vivo evaluation to further validate the clinical potential of this formulation.

***Key words*: Erlotinib Hydrochloride; β-cyclodextrin inclusion complex; Mouth Dissolving Tablet.**

I. INTRODUCTION

1.1 Introduction of Mouth Dissolving Tablet

During the last ten years, mouth dissolving drugs have gain recognition as a brand-new way of administering tablets, and they may be now considered one of the maximum commonly used dosages for pediatric patients, as well as the ones for geriatric patients with Parkinson's disorder or hand tremors, due to their ease of production and administration.

Oral contraceptives are typically administered thru a mouth-to-mouth route, with the purpose of preserving affected person compliance. Irrespective of age, humans with difficulty swallowing are not unusual.

It could be tough to swallow because of the dimensions or taste. Children who are bedridden, elderly, and pediatric sufferers may additionally face troubles with swallowing.

Dysphagia, that's characterized by using difficulty swallowing within the aged populace, is addressed thru mdt, making it an effective medicine shipping method for both juvenile and geriatric sufferers.
Tablets dissolving through the mouth dissolve in saliva hastily, and may be ate up without water, which is a great benefit over traditional dosages. Many mouth-dissolving tablet guidance technology have been developed due to the recognition and usefulness of the system.

- **Ideal properties of Mouth Dissolving Tablets:**
  - Requires no water for oral delivery and dissolves in seconds.
  - It needs to provide a pleasant mouthfeel.
  - It needs to carry satisfactory flavor masking properties.
  - The material should be hard enough to survive manufacturing and post-production handling.
  - Allow for heavy drug loading.
  - It needs to leave minimal or no remains in the mouth after disintegration.
  - Low sensitivity to surroundings conditions (such as temperature, humidity).

- **Advantages of Mouth Dissolving Tablets:**
  - Patients who are unable to swallow, those with renal failure or older adults, and those who refuse to do so (such as children, geriatrics, mental patients, elderly people) can be administered medication.
  - Maintaining patient confidentiality while confined to beds, journeying around, or having limited access to water.
  - Pregastric absorption optimizes bioavailability, lowered dose and improves clinical performance through minimizing the various side effects that may occur. The mouth-feeling design of the Mouth Dissolving Drug Delivery System changes people's attitudes towards drug.
  - The drug should be stable in both saliva and water. By quickly absorbing medication from the mouth, oratory cavity, and then passing it through the pharynx and stomach, can speed up the start-up period of action.
  - Dosing is more efficient and precise than that of liquid formulas.
  - Benefits of liquid medicine versus solid medicine.
  - New business opportunities arise from the creation of product lines, the extension of line production, lifecycle management, promotion of exclusive products, and patent extensions.

- **Limitation of Mouth Dissolving Tablets:**
  - If not appropriately developed, the tablets might create an undesirable flavor and/or gritty feeling in the tongue.
  - They often lack appropriate mechanical strength. As a result, it is necessary to use caution.

- **Difficulties with Existing Oral Dosage Form:**

1) The patient might be experiencing tremors, making it difficult to swallow powders and liquids. Dysphasia can result in gastrointestinal ulcers due to physical barriers and adhesion to the esophagus.

2) Swallowing solid dosage forms such as tablets and capsules can be problematic for young adults due to insufficient muscular and neurological system development, while elderly individuals may have dysphasia.

3) Since liquid medicinal products (suspension and emulsion) are placed in multi-dose containers, establishing homogeneity in the composition of each dosage may be problematic.

4) Buccal and sublingual formulation may irritate the oral mucosa, patients declined to take these drugs.

5) Product cost is the most important consideration, as parenteral formulations are the most expensive and cause discomfort.

- **Significance of MDTs:**

MDTs provide advantages in both solid and liquid form, along with specialized characteristics such as:

- Authentic dosing: Dosing units are precise, easy to transport and produce, possess strong physical and chemical stability, and are ideal for individuals in the ages of 5 years and older.
- Embellished Bioavailability: Drugs become more quickly absorbed by the mouth, throat, and stomach due to their higher absorption potential.
- Quick action: Quick disintegration causes the tablet to break down and become absorbed in the mouth.
- Patient acceptance: Patients are not required to drink water when taking the dose form.
- Ease of administration: Provides convenience for patients with swallowing difficulties, such as elderly, pediatric, mentally challenged, and bedridden individuals.
- Barrier free: The airways are not at risk of suffocating caused by physical obstruction when swallowed, leading to increased safety and compliance.

- Enhanced palatableness: Good mouth sensation is achieved, particularly in young patients, through the use of taste masking to prevent bitterness. This improves its palatability and comfort.
- Simple packaging: There is no need for a particular packaging. Push-through blisters can be utilized to package it.
- Business approach: New business prospective opportunities in differentiation of products, range expansion, originality and management of life cycles should be taken as part of the Business Avenue.
- Cost effective: The use of standard processing and packing equipment makes tablet production cost-effective.

Technique for Preparing Mouth Dissolving Tablets:

- Sublimation technology
- Moulding
- Lyophilization or Freeze-drying method
- Spray drying
- Mass extrusion
- Direct compression

Direct compression

Direct compression represents the most straightforward method for tablet production, characterized by its low manufacturing costs, conventional equipment, and reduced number of processing steps, making it a favorable option. Tablets produced through direct compression dissolve and disintegrate upon exposure to disintegrating agents, water-soluble excipients, and effervescent agents. The selection of appropriate disintegrant concentration and ratio is critical for achieving rapid dissolution. The advent of new compounds with enhanced disintegration efficiency and mechanical strength, even at reduced levels, facilitates the use of superdisintegrants. These super disintegrants, which improve compressibility and compatibility, do not compromise the mechanical strength of high-dose medication formulations, yet remain effective. Both the type and percentage of disintegrant are significant factors. Additional considerations include the particle size distribution, angle of contact, distribution of pore sizes, and absorption of water capacity. Research reveals that water-insoluble superdisintegrants, such as sodium starch glycolate and croscarmellose sodium, exhibit superior disintegration properties compared to slightly water-soluble agents like crosspovidone, due to their non-swelling nature. The formation of a viscous barrier in superdisintegrants that tend to swell can slightly impede disintegration. Provided the mechanical properties of the tablet are acceptable for its intended usage, there is no maximum limit to the amount of superdisintegrant. This ingredient functions as a self-contained superdisintegrant.

Patented Methods for the Preparation of MDTs:

1. Zydis technology
2. OraSolv technology
3. Durasolv technology
4. Wowtab technology
5. Flash tab technology
6. Flash dose technology
7. Oraquick technology
8. Shearform Technology
9. AdvaTab Technology
10. Nanocrystal technology

Materials and Methods:

Preparation of Cyclodextrin Inclusion Complexes Physical Mixture

Erlotinib Hydrochloride with β -CD in varied molar ratios (i.e. 1:1M, 1:1.5M, 1:2M and 1:2.5M) were mixed in a mortar for about one hour with consistent trituration, passed through sieve No. #80 and stored.

Kneading Method:

Erlotinib Hydrochloride and β-CD were tested in various molar ratios (e.g., 1:1M, 1:1.5M, 1:2M, and 1:2.5M). First, cyclodextrin is put to the mortar; then, a little bit of ethanol is added while mixing to produce a slurry consistency. The drug is then gradually integrated into the slurry, and the mixing procedure is repeated for an hour. The slurry is then air- dried at 25° Celsius for a duration of 24 hours, crushed, passed through filter No. 80, and stored.

Preparation of Erlotinib Hydrochloride – Cyclodextrin Inclusion Complexed Mouth Dissolving Tablets:

The most prominent batch from the kneading procedure with a 1:2M ratio of the inclusion complex of Erlotinib Hydrochloride – β – CD was converted into a mouth-dissolving tablet by direct compression method, comprising 25 mg of the drug. Erlotinib Hydrochloride – β-CD Complex, Crosspovidone, Sodium Starch Glycolate, Coprocessed Crosspovidone + MCC, Kyron T-314, Spray Dried Lactose, Aspartame, and Vanila Flavor were filtered through #80 sieves. Microcrystalline cellulose (Avicel pH-102) and Talc were filtered using #22 sieve. All of the components mentioned above were properly combined. Finally, a #80 sieve was used to mix the talc and magnesium stearate for 5 minutes. The drug and excipients were then crushed into a quick dissolving tablet using a single punch rotary tablet compression machine.

Erlotinib Hydrochloride was obtained from Dhamtec Pharma, Navi Mumbai, β – Cyclodextrin and Kyron T-314 from Lesar Chemicals, Ahemdabad, Spray Dried Lactose from Astron Research Centre, Ahemdabad, Magnesium Stearate and Talc from Chemdyes Corporation, Rajkot and vanilla flavor from Nutra Sweet, Mumbai.

Table 1 Formulation table of trial batches of mouth dissolving tablets

Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
ERL: β-CD Complex (1:2)	1:2	1:2	1:2	1:2	1:2	1:2	1:2	**1:2**	1:2
Sodium Starch Glycolate	2	6	10	-	-	-	-	-	-
Cross povidone	-	-	-	2	6	10	-	-	-
Coprocessed MCC+Crosspovidone (1:1)	-	-	-	-	-	-	2	**6**	10
Kyron T-314	25	25	25	25	25	25	25	**25**	25
Spray Dried Lactose	87	83	79	87	88	79	87	**83**	79
Magnesium stearate	4	4	4	4	4	4	4	**4**	4

Talc	4	4	4	4	4	4	4	**4**	4
Aspartame	2	2	2	2	2	2	2	**2**	2
Flavor	1	1	1	1	1	1	1	**1**	1

Table 2 Layout of factorial designs

3^2 Full Factorial Design		
Batch No.	**X_1 Amount of Co-processed MCC+Crosspovidone Ratio (mg)**	**X_2 Amount of Kyron (mg)**
F1	**-1**	**-1**
F2	**-1**	**0**
F3	**-1**	**+1**
F4	**0**	**-1**
F5	**0**	**0**
F6	**0**	**+1**
F7	**+1**	**-1**
F8	**+1**	**0**
F9	**+1**	**+1**

Translation of coded level in actual limit			
Independent variables	**Level**		
	Low (-1)	**Medium (0)**	**High (+1)**
Amount of Co-processed MCC+Crosspovidone Ratio (mg) X1	**4**	**6**	**8**
Amount of Kyron (mg) X2	**20**	**25**	**30**

All 9 batches were evaluated for the % drug release at 15 min. Hardness (kg/cm^2) (Y1) and Disintegration time (Sec) (Y2) to find out effect of the both parameters (X1, X2)

- **Independent variables**

  X1-Amount of Co-processed MCC+Crosspovidone Ratio (mg)

  X2-Amount of Kyron (mg)

- **Dependent variables**

  Y1- Hardness (kg/cm^2)

  Y2- Disintegration time (sec)

Table 3 Formulation table of factorial trial batch

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Erlotinib HCL and β-Cyclodextrin (DBC-1:2)	1:2	1:2	1:2	1:2	**1:2**	1:2	1:2	1:2	1:2
Co-processed MCC+Crosspovidone (1:1)	4	4	4	6	**6**	6	8	8	8
Kyron T-314	20	25	30	20	**25**	30	20	25	30
Spray dried Lactose	90	85	80	88	**83**	78	86	81	76
Magnesium Stearate	4	4	4	4	**4**	4	4	4	4
Talc	4	4	4	4	**4**	4	4	4	4
Aspartame	2	2	2	2	**2**	2	2	2	2
Vanila Flavor	1	1	1	1	**1**	1	1	1	1
Total weight of tablet	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

EVALUATION OF MOUTH DISSOLVING TABLETS:-

PRE COMPRESSION PARAMETERS:-

- **Bulk Density**:

A measured amount of powder was passed through sieve #18 and then placed in cylinders that were graduated. By pouring the powder into this graduated cylinder, they created an even and pure powder bed. By using graduation markers on the cylinder, the volume was measured directly in milliliters. This volume was known as the bulk volume, and the density of this bulk was calculated by following the formula.

Bulk density = Weight of powder / Bulk volume

- **Tapped Density**

Once the bulk volume had been measured, the same measuring cylinder was placed into the tap density equipment. The device was set up to discharge 300 taps of water per minute and run for 500 taps. Recording volume was done by using (Va) first and then tapping 750 times to record as (vb). Vb is the final tapped volume when the gap between Va and Vb is less than 2%. The tapped density is determined by the formula provided.

Tapped density = Weight of powder / Tapped volume

- **Flow properties:**

A material's flow properties are the product of various forces. There are several sorts of forces that can act between solid particles, including frictional forces, surface tension forces, mechanical forces caused by the interlocking of irregularly shaped particles, electrostatic forces, and cohesive or van der vaals forces. These forces may affect granule properties such particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy, and surface area.

- **Compressibility Index (CI):**

The relative flow rate, cohesion, and particle size distribution of the powder all have an indirect relationship with compressibility. Powders having compressibility values less than roughly 20% have been shown to have good flow characteristics. Tapped (ρ2) and Bulk (ρ1) density measurements help estimate a material's compressibility.

Carr's/ Compressibility index (%) = {(ρ2- ρ1) / ρ2} X 100

- **Hausner's Ratio:**

The relationship between the bulk volume and the tapped volume, or corresponding to the density of a sample. The flow properties of powders and granule are dependent on the ratio determined by Hausner. This can be determined by applying the formula that follows:

Hausner's ratio = Tapped density / Bulk density

Value < 1.25 indicate good flow (=20% Carr's index)

While > 1.50 indicate poor flow (=35% Carr's index)

If glidant is added, the flow can be enhanced from 1.25 to 1.5. Carr is a one-point index which does not reflect the speed or accessibility of consolidation. Despite poor flow due to high index, some materials consolidate rapidly for even filling on tablet machines, where power flows at nearly the same bulk density into the die and condenses quickly to near-tapped volume before being compressed.

POST COMPRESSION PARAMETERS:-

- **Weight Variation**

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per IP.

USP Average weight of tablet (mg)	**%Deviation**	**IP/BP Average weight of tablet (mg)**
80 or less	10%	130 or less
From 80 to 250	7.5%	From 130 to 324
250 or more	5%	More than 324

- **Hardness**

The hardness of the tablets will be tested with a Monsanto hardness tester. It is stated in kilograms per square centimeter. Three pills will be selected at random from each formulation, and the mean and standard deviation will be computed.

- **Friability**

Friability will be tested using a Roche-type Friabilator. Six tablets will be carefully weighed and placed in a tumbling contraption that circles at 25 rpm, falling the tablets six inches with each rotation. After 4 minutes, the tablets will be weighed, and the percentage loss calculated.

% loss = initial wt.-final wt. / initial wt. × 100

- **Thickness**

The thickness of three randomly selected tablets from each formulation will be measured in millimeters using a vernier caliper. The average value will be determined.

- **Drug Content**

Five tablets were chosen at random, and their average weight was computed. Tablets were ground in a glass mortar. One tablet us worth of powder was weighed and diluted in 100 ml of 7.4 pH phosphate buffer, which was then filtered and the drug content was measured spectrophotometrically at 247 nm using a UV spectrophotometer.

- **In-vitro drug release study**

Apparatus II paddle type, the USP dissolution test apparatus was utilized to investigate drug release from tablets. 900 ml of dissolution buffer with a pH of 7.4 was used, released at 37 ± 0.5 °C, with a spinning speed of 50 rpm, fresh medium was added to 5 ml samples collected at specified intervals. Using Whatmann

filter paper, the samples were subjected to an appropriate dilution and then examined by a UV spectrophotometer at 247 nm, with estimates of drug release made using a standard curve.

- **Stability Studies**

The improved batch's stability investigations were conducted in a stability chamber for one month at 40 degrees Celsius and 75% relative humidity (accelerated stability). After one month, the improved formulation was withdrawn and tested for drug content and in vitro release.

RESULTS & DISCUSSION

PRE FORMULATION STUDIES

Table 4. API Properties

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	White to off-white powder
2		Odour	Odorless
4	Flow Properties	Bulk density (g /ml)	0.38 ± 0.01
5		Tapped density (g /ml)	0.52 ± 0.01
6		Carr's index (%)	26.9 ± 0.02
7		Hausner's ratio	1.37 ± 0.01
8		Angle of repose (θ°)	42.1
9	Melting Point	224-228 °C	

DRUG POLYMER COMPATIBILITY STUDIES

The FT-IR spectra of Erlotinib Hydrochloride and Final Formulation were analyzed. All functional groups of Erlotinib Hydrochloride peaks were found in the formulation. That was indicate no drug-excipient interaction, implying that the excipients are compatible with the Erlotinib Hydrochloride. The FT-IR spectra of the erlotinib hcl and its formulation are presented in the figure below.

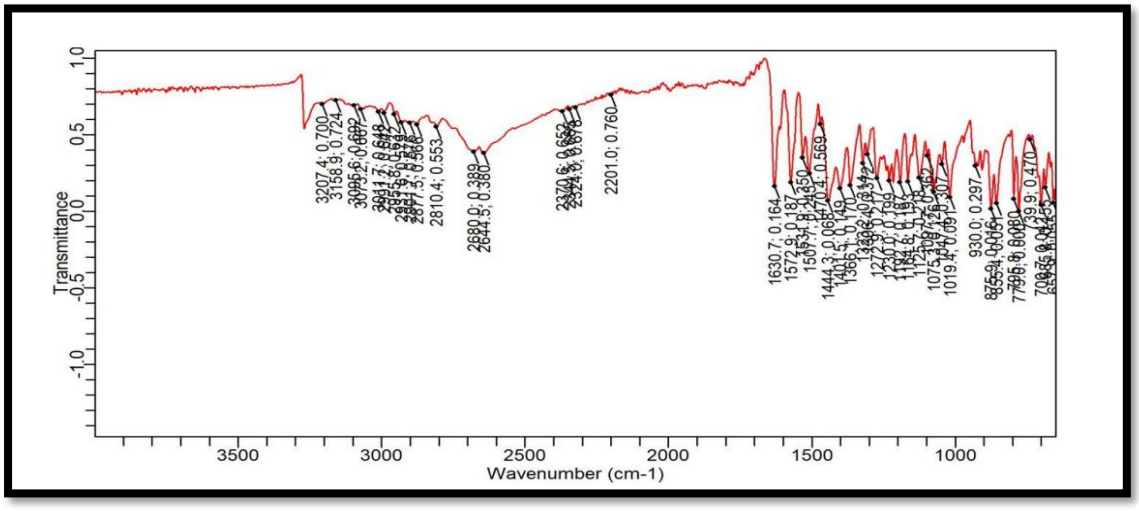


Figure 1 FTIR spectra of Erlotinib Hydrochloride

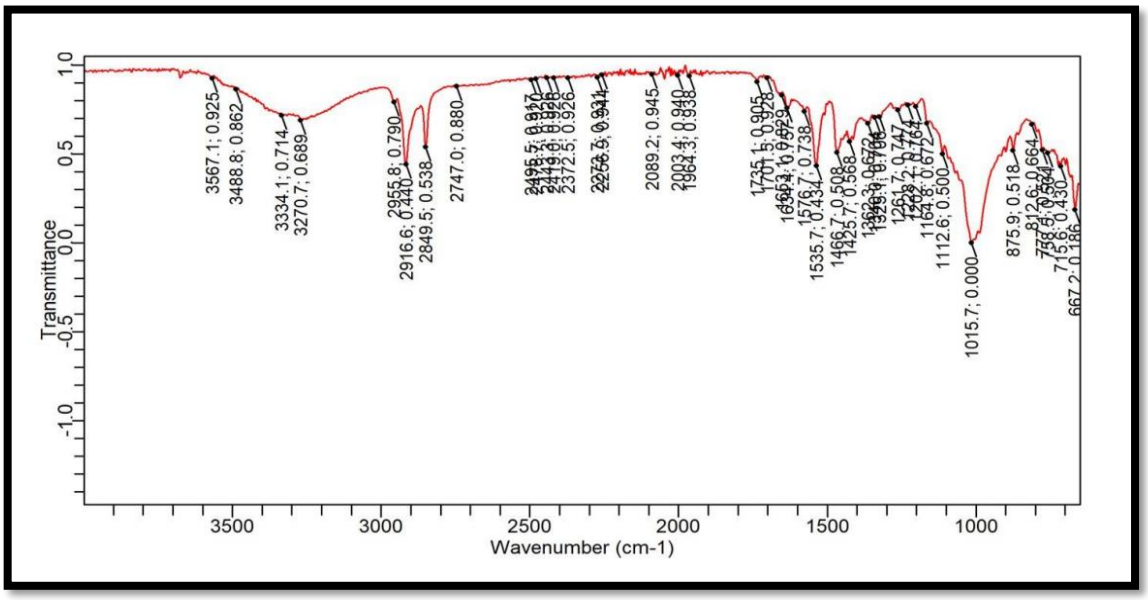


Figure 2 FTIR spectra of optimized formulation of Erlotinib Hydrochloride

Functional Groups	Standard Frequency (cm^{-1})	Erlotinib Hydrochloride Peak (cm^{-1})	Final Formulation Peak (cm^{-1})
N–H Stretching	3300 – 3500	3207.4	3334.1 – 3488.8
Aromatic C–H Stretching	3000 – 3100	2955.8 – 3095.6	2955.8
Ethynyl (C≡C) Stretching	2100 – 2260	2201.0	2256.9
C=O Stretching	1650 – 1750	1630.7	1653.1 – 1735.1
Aromatic Ring Vibrations	1400 – 1600	1401.5 – 1572.9	1425.7 – 1576.7

Conclusion: Based on the FTIR study findings presented above, it was concluded that all of the key functional groups of Erlotinib Hydrochloride were clearly identified in the final formulation, with no noteworthy alterations or disappearances. This demonstrates that there is no notable chemical interaction between the drug and the excipients, showing that Erlotinib is stable and compatible within the final formulation matrix.

DETERMINATION OF λmax AND CALIBRATION CURVE OF DRUG

Table 5 Standard calibration curve of erlotinib hydrochloride in phosphate buffer 7.4

Sr. No.	Concentration(µg/ml)	Absorbance at 247 nm (mean ± SD)
1	0	0
2	2	0.202±0.004
3	4	0.369±0.005
4	6	0.526±0.007
5	8	0.705±0.005
6	10	0.855±0.004

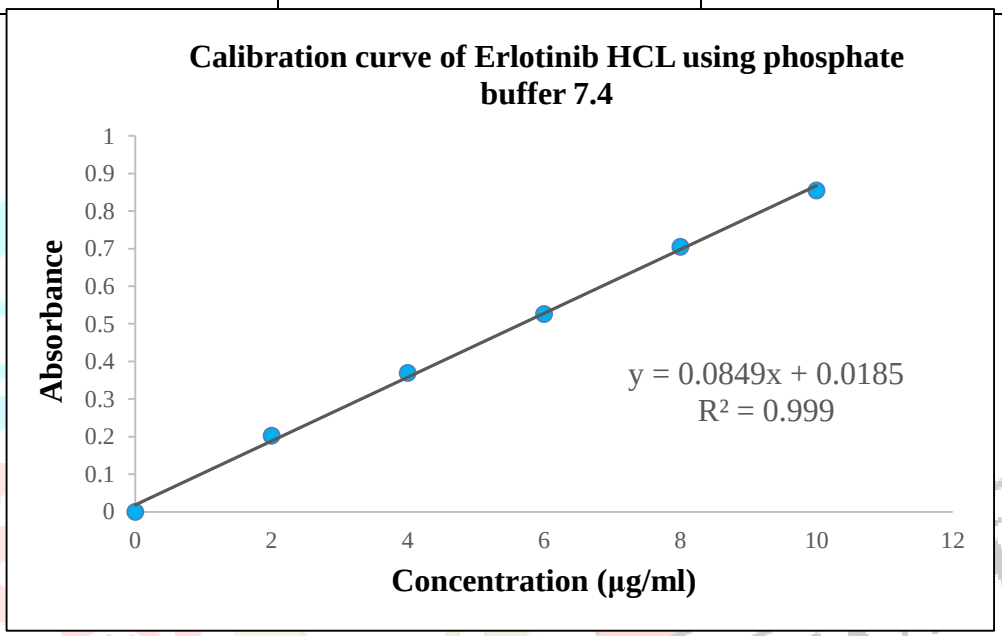


Figure 3 Calibration curve of erlotinib hydrochloride in phosphate buffer 7.4

Pre Compression Parameters:-

Powder blend of formulation T1-T9 checked for pre compression parameters like,

- ✓ **Bulk density**
- ✓ **Tapped density**
- ✓ **Compressibility index (CI) / Carr's index**
- ✓ **Hausner's ratio**
- ✓ **Angle of repose**

Table 6 Pre-Compression Parameters of Formulation T1-T9

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausner's ratio	Angle of Repose (θ)
T1	0.55 ± 0.03	0.63 ± 0.02	15.23 ± 0.05	1.16 ± 0.05	29.48 ± 0.4
T2	0.42 ± 0.02	0.49 ± 0.04	14.29 ± 0.04	1.17 ± 0.04	27.56 ± 0.3
T3	0.45 ± 0.04	0.51 ± 0.05	11.76 ± 0.06	1.15 ± 0.07	28.24 ± 0.3
T4	0.43 ± 0.05	0.53 ± 0.03	13.87 ± 0.02	1.17 ± 0.08	26.65 ± 0.2
T5	0.48 ± 0.02	0.56 ± 0.03	15.29 ± 0.04	1.16 ± 0.05	26.84 ± 0.1
T6	0.48 ± 0.03	0.55 ± 0.05	15.73 ± 0.05	1.21 ± 0.06	22.47 ± 0.1
T7	0.48 ± 0.05	0.54 ± 0.04	13.11 ± 0.08	1.15 ± 0.04	28.32 ± 0.3
T8	0.46 ± 0.04	0.50 ± 0.06	12.09 ± 0.07	1.16 ± 0.08	27.91 ± 0.3
T9	0.43 ± 0.06	0.49 ± 0.04	12.24 ± 0.05	1.17 ± 0.02	26.49 ± 0.2

Table 7 Post-Compression Parameters of Formulation T1-T9

Formulation	Weight variation (mg)	Hardness (Kg/cm2)	% Friability	Thickness (mm)
T1	201.2 ± 1.2	4.0 ± 0.1	0.85 ± 0.1	2.9 ± 0.10
T2	201.1 ± 1.1	4.2 ± 0.2	0.86 ± 0.2	3.0 ± 0.12
T3	199.3 ± 1.7	4.7 ± 0.4	0.95 ± 0.1	3.7 ± 0.15
T4	199.5 ± 1.3	4.1 ± 0.1	0.97 ± 0.3	2.9 ± 0.11
T5	203.1 ± 1.5	4.3 ± 0.5	0.85 ± 0.4	3.2 ± 0.14
T6	201.1 ± 1.7	4.9 ± 0.1	0.98 ± 0.5	3.9 ± 0.17
T7	199.3 ± 1.8	3.5 ± 0.2	0.80 ± 0.2	2.6 ± 0.11
T8	**200.1 ± 1.1**	**3.7 ± 0.1**	**0.57 ± 0.1**	**3.0 ± 0.12**
T9	201.2 ± 1.2	4.2 ± 0.5	0.77 ± 0.3	3.3 ± 0.13

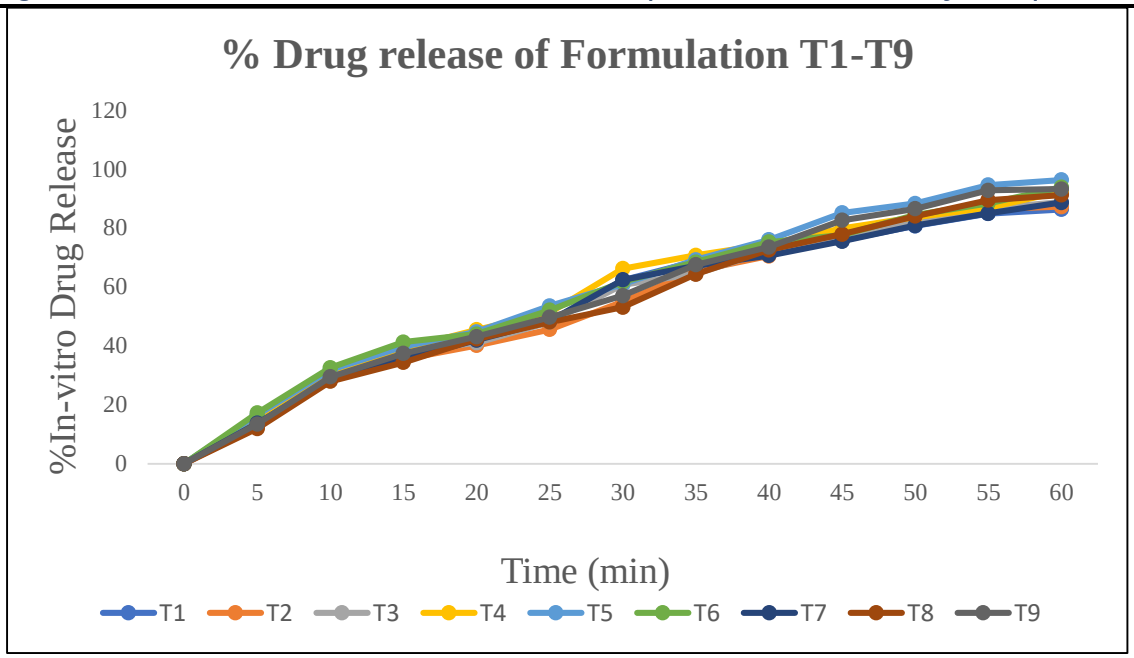
Table 8 Post Compression Parameters of Formulation T1-T9

Formulation	Disintegration Time (Sec)	Wetting Time (Sec)	Uniformity of Content
T1	45.15 ± 0.8	30.21 ± 0.8	97.72 ± 1.5
T2	42.35 ± 0.9	27.12 ± 0.9	98.34 ± 1.6
T3	50.42 ± 1.0	35.72 ± 1.0	98.23 ± 1.8
T4	48.10 ± 0.9	34.22 ± 0.9	98.72 ± 2.0
T5	45.30 ± 1.3	30.32 ± 1.2	98.99 ± 2.1
T6	50.70 ± 1.5	40.10 ± 1.7	98.59 ± 2.7
T7	36.22 ± 1.1	30.10 ± 1.3	98.21 ± 2.1
T8	**34.01 ± 1.7**	**27.24 ± 1.5**	**99.12 ± 1.6**
T9	36.10 ± 1.9	29.02 ± 1.7	98.92 ± 2.2

In-Vitro Drug Release

Table 9 % Drug release of T1 to T9 Formulations Tablets

Time (min)	T1	T2	T3	T4	T5	T6	T7	T8	T9
0	0	0	0	0	0	0	0	**0**	0
5	14.44	12.43	16.23	15.14	16.4	17.23	13.72	**11.93**	13.45
10	29.05	28.55	28.58	31.05	31.8	32.58	28.53	**27.97**	29.50
15	36.97	35.38	38.27	38.97	39.7	41.27	35.43	34.34	37.40
20	44.46	40.12	40.99	45.46	44.7	43.99	41.90	42.29	43.12
25	48.25	45.55	48.05	51.25	53.5	52.05	48.44	48.06	49.65
30	62.20	55.00	60.70	66.20	60.9	61.70	62.38	53.12	57.00
35	68.70	65.44	64.42	70.70	69.1	68.42	67.11	64.30	67.46
40	72.49	70.45	72.21	74.49	75.9	75.21	70.64	72.56	73.49
45	75.82	78.58	75.52	79.82	85.1	77.52	75.45	77.88	82.60
50	80.69	82.48	82.40	83.69	88.2	84.40	80.81	84.00	86.50
55	84.84	86.31	86.71	86.84	94.5	88.31	84.94	89.43	92.71
60	86.28	87.19	88.77	92.28	96.2	93.77	88.62	91.15	93.19



Evaluation of factorial batches

Powder blend of factorial batches F1-F9 checked for pre-compression parameters.

Observed results are mentioned in following table 15. From the below table it concluded that the all batches have a good flow property.

Table 10 Pre-compression Parameters of factorial batches F1-F9

Formulation Code	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Compressibility index (%)	Angle of Repose (□)
F1	0.46 ± 0.12	0.57 ± 0.16	22.41 ± 0.21	30.25 ± 0.23
F2	0.40 ± 0.10	0.51 ± 0.14	23.07 ± 0.20	28.79 ± 0.17
F3	0.43 ± 0.12	0.55 ± 0.18	20.00 ± 0.18	28.56 ± 0.15
F4	0.41 ± 0.18	0.54 ± 0.17	21.15 ± 0.24	29.00 ± 0.14
F5	0.45 ± 0.09	0.58 ± 0.10	22.03 ± 0.26	30.19 ± 0.18
F6	0.43 ± 0.10	0.56 ± 0.12	16.07 ± 0.12	29.67 ± 0.12
F7	0.39 ± 0.09	0.49 ± 0.18	20.40 ± 0.09	28.37 ± 0.20
F8	0.45 ± 0.16	0.50 ± 0.14	23.72 ± 0.24	30.62 ± 0.12
F9	0.43 ± 0.18	0.49 ± 0.10	20.37 ± 0.16	28.57 ± 0.18

Table 11 Post-Compression Parameters of factorial batches F1-F9

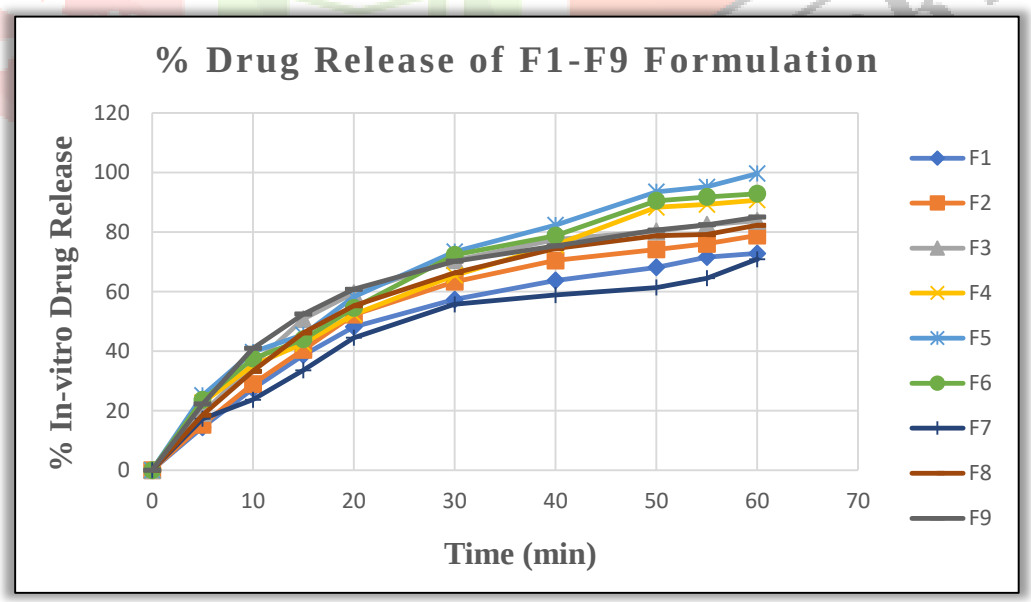
Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability %
F1	200.2±1.2	3.20±0.10	3.2±0.1	0.85±0.1
F2	200.2±1.2	3.25±0.11	2.9±0.3	0.78±0.2
F3	200.8±1.8	3.30±0.13	2.8±0.4	0.81±0.1
F4	199.2±1.1	3.25±0.10	3.3±0.2	0.85±0.3
F5	**200.2±1.3**	**3.00±0.17**	**3.6±0.1**	**0.54±0.4**
F6	201.8±1.4	3.28±0.13	2.7±0.3	0.65±0.2
F7	199.8±1.7	3.35±0.17	3.1±0.5	0.60±0.5
F8	200.1±1.6	3.25±0.20	2.8±0.4	0.69±0.4
F9	200.2±1.9	3.20±0.14	2.5±0.3	0.74±0.3

Table 12 Post-Compression Parameters of factorial batches F1-F9

Formulation Code	Disintegration Time (Sec)	Drug content %	Wetting Time (Sec)
F1	47.15 ± 0.8	95.72 ± 1.5	60.27 ± 0.8
F2	40.23 ± 1.2	96.96 ± 1.8	53.15 ± 1.2
F3	43.70 ± 1.5	95.24 ± 1.9	55.27 ± 1.3
F4	41.35 ± 1.2	96.91 ± 2.1	45.64 ± 1.4
F5	**30.12 ± 1.1**	**99.73 ± 1.2**	**25.34 ± 1.1**
F6	37.38 ± 1.7	98.12 ± 1.9	30.19 ± 1.4
F7	47.19 ± 1.9	95.68 ± 2.5	58.15 ± 1.7
F8	33.26 ± 1.4	97.61 ± 2.7	51.80 ± 1.9
F9	36.46 ± 1.4	96.80 ± 2.8	47.32 ± 0.9

Table 13 Drug release of factorial batches F1-F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	**0**	0	0	0	0	0	0	**0**	0
5	14.41± 0.5	15.25 ± 0.6	19.17 ± 0.8	22.65 ± 1.0	**25.12 ± 0.8**	23.62 ± 0.9	17.28 ± 1.1	18.50 ± 1.2	22.20 ± 1.4
10	27.34 ± 1.2	28.92 ± 1.3	35.34 ± 1.5	35.21 ± 1.4	**39.70 ± 1.1**	37.45 ± 1.0	23.65 ± 1.3	33.21 ± 1.4	40.91 ± 1.8
15	38.65 ± 1.4	40.41 ± 1.5	50.74 ± 1.7	42.60 ± 1.8	**45.46 ± 1.2**	43.92 ± 1.2	33.54 ± 1.7	46.12 ± 1.5	52.42 ± 2.0
20	48.14 ± 1.7	52.20 ± 1.6	59.45 ± 1.8	52.34 ± 2.1	**58.19 ± 1.4**	54.46 ± 1.4	44.44 ± 2.0	55.21 ± 1.7	60.74 ± 2.1
30	57.32 ± 2.0	63.30 ± 1.8	70.51 ± 2.0	65.41 ± 2.3	**73.41 ± 1.9**	72.34 ± 1.5	55.70 ± 2.1	66.32 ± 1.9	70.16 ± 2.3
40	63.72 ± 2.2	70.42 ± 2.0	77.42 ± 2.2	75.58 ± 2.4	**82.32 ± 2.0**	78.76 ± 1.7	58.84 ± 2.4	74.48 ± 2.0	75.33 ± 2.5
50	68.10 ± 2.4	74.12 ± 2.1	80.20 ± 2.3	88.28 ± 2.5	**93.52 ± 2.1**	90.49 ± 2.2	61.34 ± 2.5	78.71 ± 2.2	80.66 ± 2.6
55	71.54 ± 2.5	76.05 ± 2.4	82.42 ± 2.4	89.24 ± 2.6	**95.16 ± 2.4**	91.78 ± 2.4	64.45 ± 2.6	79.12 ± 2.4	82.41 ± 2.7
60	72.78 ± 2.7	78.82 ± 2.6	83.76 ± 2.5	90.71 ± 2.7	**99.65 ± 2.7**	92.86 ± 2.4	70.84 ± 2.7	82.26 ± 2.6	84.01 ± 2.8



Analysis of factorial design

The compiled results were analyzed using factorial design. For this purpose, Design Expert software was utilized. The factors and responses were input into the software, and the analysis was conducted based on the data presented in the table below.

Table 14 Factorial design layout

Batch code	Independent variable		Dependent Variables	
	X1	X2	Y1 (Hardness)	Y2 (Disintegration time)
F1	4	20	3.2	47.15
F2	4	25	2.9	40.23
F3	4	30	2.8	43.70
F4	6	20	3.3	41.35
F5	6	25	3.6	30.12
F6	6	30	2.7	37.38
F7	8	20	3.1	47.19
F8	8	25	2.8	33.26
F9	8	30	2.5	36.46

Translation of coded level in actual unit			
Independent variables	Real Value		
	Low (-1)	Medium (0)	High (+1)
Amount of Co-processed MCC+Crosspovidone Ratio (mg) X1	4	6	8
Amount of Kyron (mg) X2	20	25	30

ANOVA for Quadratic model
Response 2: Hardness (kg/cm^2)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.8603	5	0.1721	59.94	0.0033	*significant*
A-mcc+crosspovidone	0.3750	1	0.3750	130.65	0.0014	
B-kyron	0.2817	1	0.2817	98.13	0.0022	
AB	0.0025	1	0.0025	0.8710	0.4195	
A^2	0.2006	1	0.2006	69.87	0.0036	
B^2	0.0006	1	0.0006	0.1935	0.6897	
Residual	0.0086	3	0.0029			
Cor Total	0.8689	8				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 59.94 is indicative of the model's usefulness. The probability of obtaining an F-value of such magnitude due to noise is precisely 0.33 per cent.

Model terms are considered significant when their **P-value** is less than 0.0500. A, B, and A2 are crucial model terms in this scenario. Values above 0.01000 indicate that the model terms are not relevant. Model reduction can enhance your model when there are too many unimportant model terms, not counting those that support hierarchy.

Final Equation in Terms of Coded Factors

Hardness	=
-1.11389	
+1.01250	mcc+cross
+0.061667	kyron
+0.002500	mcc+cross * kyron
-0.079167	mcc+cross^2
-0.000667	kyron^2

Y = -1.11389+1.01250+0.061667+0.002500-0.079167-0.000667

It is possible to predict the response for specific levels of each factor by using an equation that reflects actual factors. The original units for each factor should contain the levels. Due to the fact that the coefficients are scaled to fit the units of each factor, and the intercept isn't located in center of the design space, it should be avoided from using this equation to determine the relative impact of every factor.

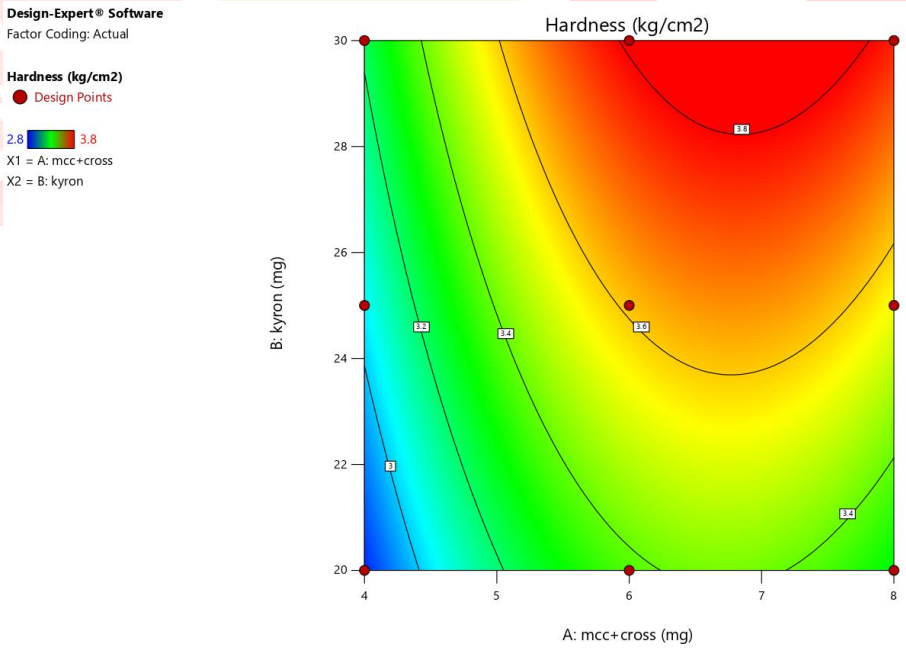


Figure 4 Contour plot for Hardness

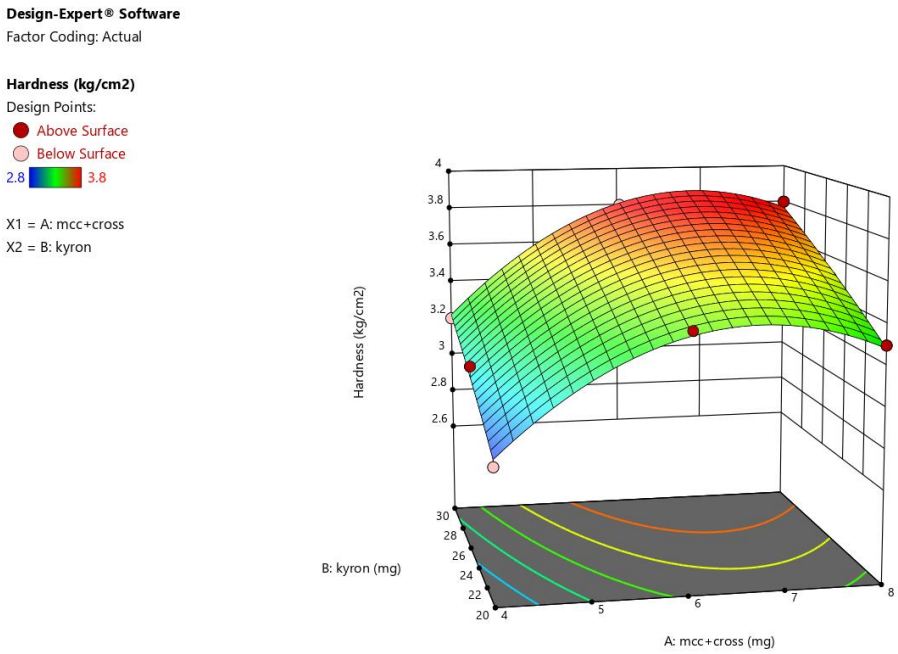


Figure 5 Surface plot for Hardness

ANOVA for Quadratic model

Response 2: Disintegration time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**270.20**	**5**	**54.04**	**17.04**	**0.0207**	***significant***
A-mcc+cross	**33.46**	**1**	**33.46**	**10.55**	**0.0476**	
B-kyron	**54.90**	**1**	**54.90**	**17.31**	**0.0253**	
AB	**13.25**	**1**	**13.25**	**4.18**	**0.1336**	
A^2	**50.97**	**1**	**50.97**	**16.07**	**0.0279**	
B^2	**117.61**	**1**	**117.61**	**37.08**	**0.0089**	
Residual	**9.52**	**3**	**3.17**			
Cor Total	**279.71**	**8**				

Factor coding is **Coded**.

Sum of squares is **Type III – Partial**

The **Model F-value** of 17.04 implies the existence of the model. A F-value of this magnitude is unlikely to occur because of noise, with a probability of 2.07%.

When model terms have a **P-value** less than 0.0500, they are typically considered to be significant. Significant models are characterized by the use of A, B.A2, and B2. When the model terms are less than 0.1000, they become insignificant. Model reduction can enhance your model when there are too many unimportant model terms, not counting those that support hierarchy.

Final Equation in Terms of Coded Factors

Disintegration time	=
+263.22444	
-11.77583	mcc+cross
-14.84967	kyron
-0.182000	mcc+cross * kyron
+1.26208	mcc+cross²
+0.306733	kyron²

Y = 263.22444-11.77583-14.84967-0.182000+1.26208+0.306733

The equation can be used to predict the response for specific levels of each factor using actual factors. Each factor should be listed in the original units with its levels. The relative impact of each factor cannot be determined by simply using this equation since the coefficients are scaled to fit the units of every factor and the intercept is not located in the center of the design space.

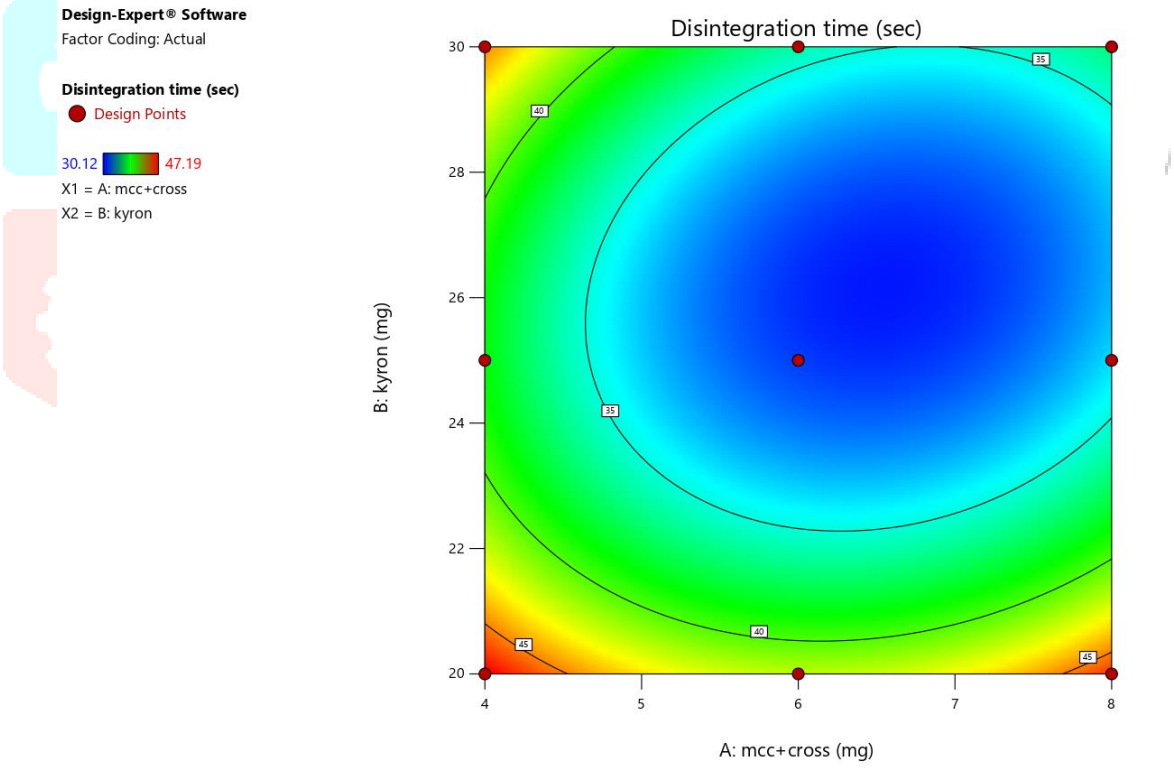


Figure 6 Contour plot for Disintegration time

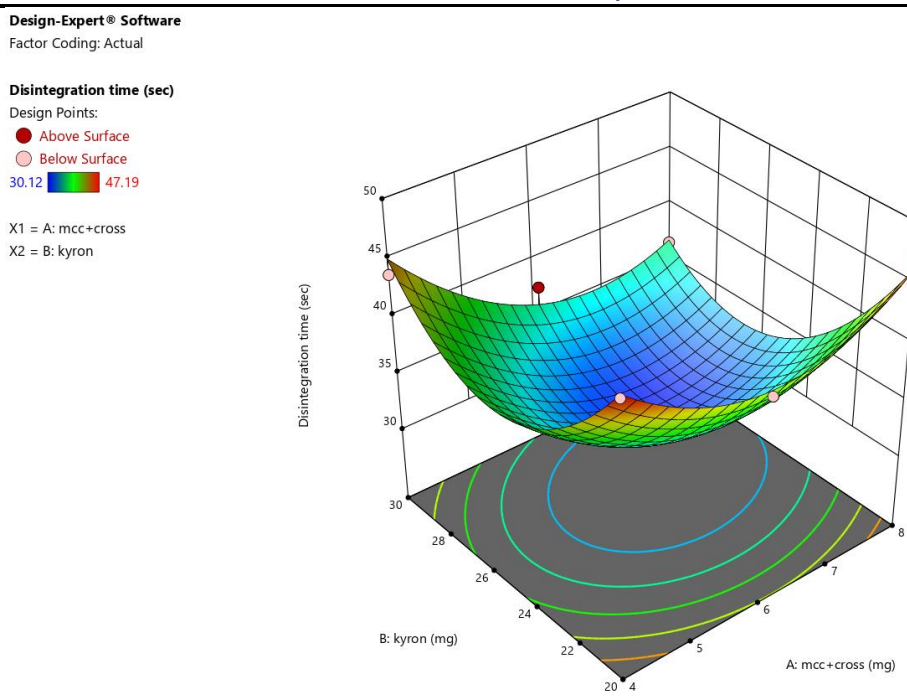


Figure 7 Surface plot for Disintegration time

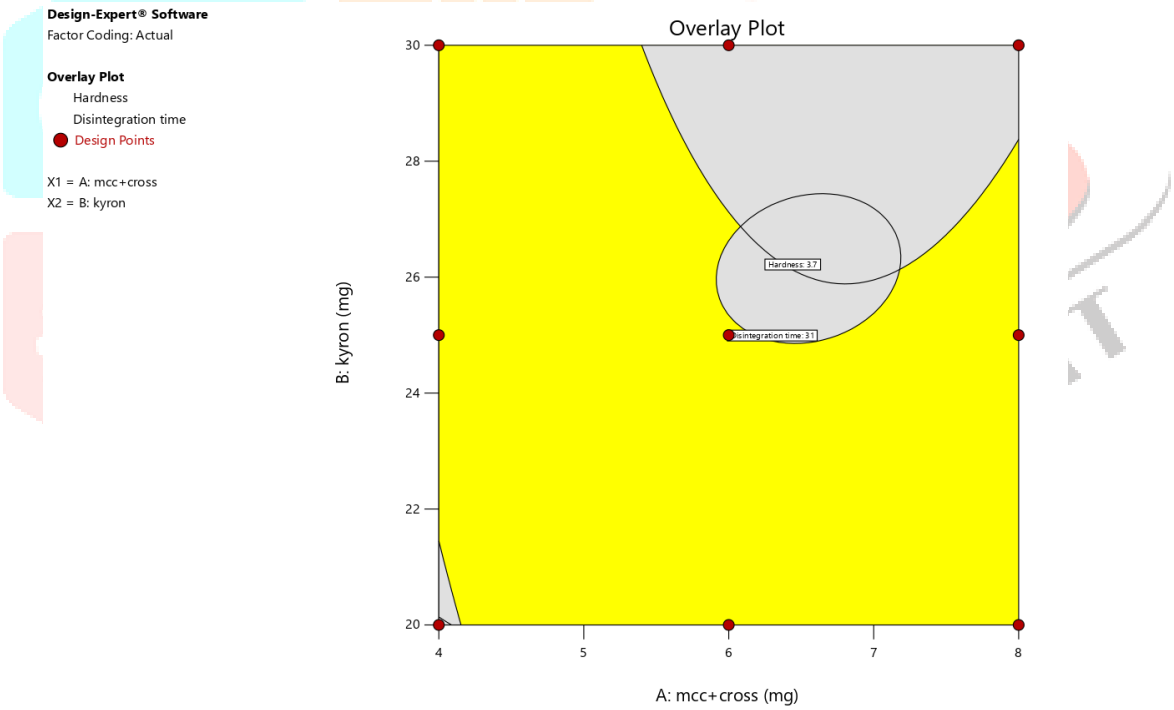


Figure 8 Overlay Plot

- **Validation of model**

Table 10 demonstrates how a checkpoint batch was created in accordance with the desirability function. The prediction was tested for accuracy using checkpoint batches C1 and C2, which were subjected to the same conditions. The required data was evaluated against the response data.

Compare the response variables of check point batch against the target response parameters. The expected versus observed bias was acceptable.

From the overlay plot shown in figure 12 that yellow region is the optimized region. Here batch C1 was seen in yellow region. So, it was concluded that Batch C1 is also considered as an optimized formulation.

Table 15 Check point batch

Batch	Amount of		Amount of Kyron (mg)	Hardness		
	MCC	Crosspovidone		Predicted	Observed	% Bias
C1	2.61	2.61	25.46	3.48	3.51	0.99
C2	3.47	3.47	28.55	3.81	3.80	1.00
Batch	**Amount of**		**Amount of Kyron (mg)**	**Disintegration time (sec)**		
	MCC	**Crosspovidone**		**Predicted**	**Observed**	**% Bias**
C1	2.61	2.61	25.46	32.69	32.72	0.99
C2	3.47	3.47	28.55	32.29	32.31	0.99

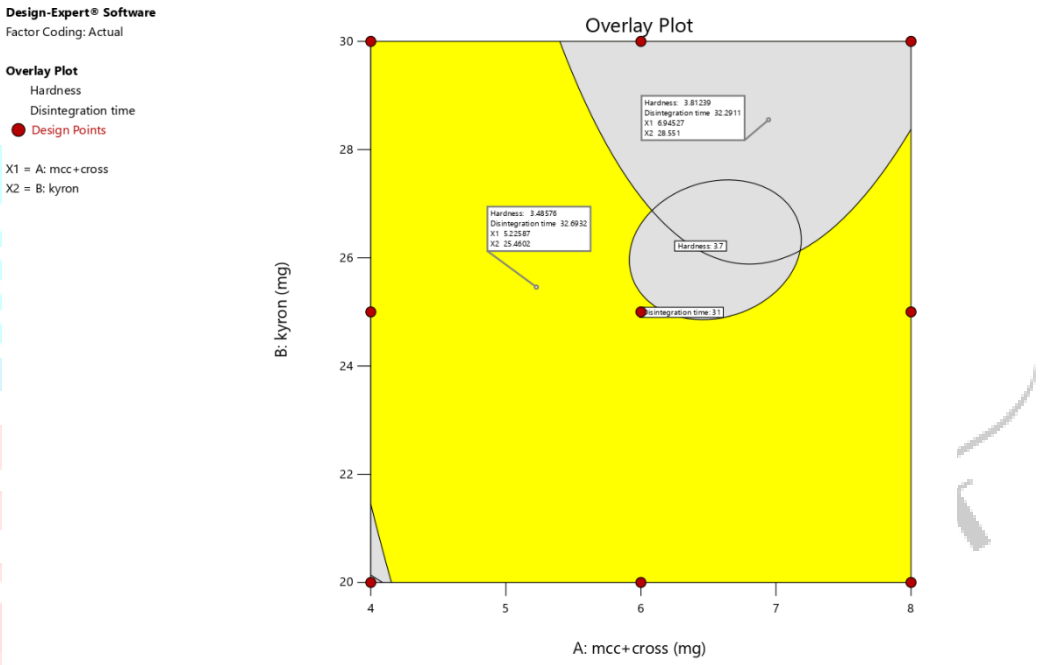


Figure 9 Overlay Plot for check point batch

- **Selection of Optimized batch**

Finally, optimized batch was taken from the overlay plot then complete analysis was done and finally loaded for stability study.

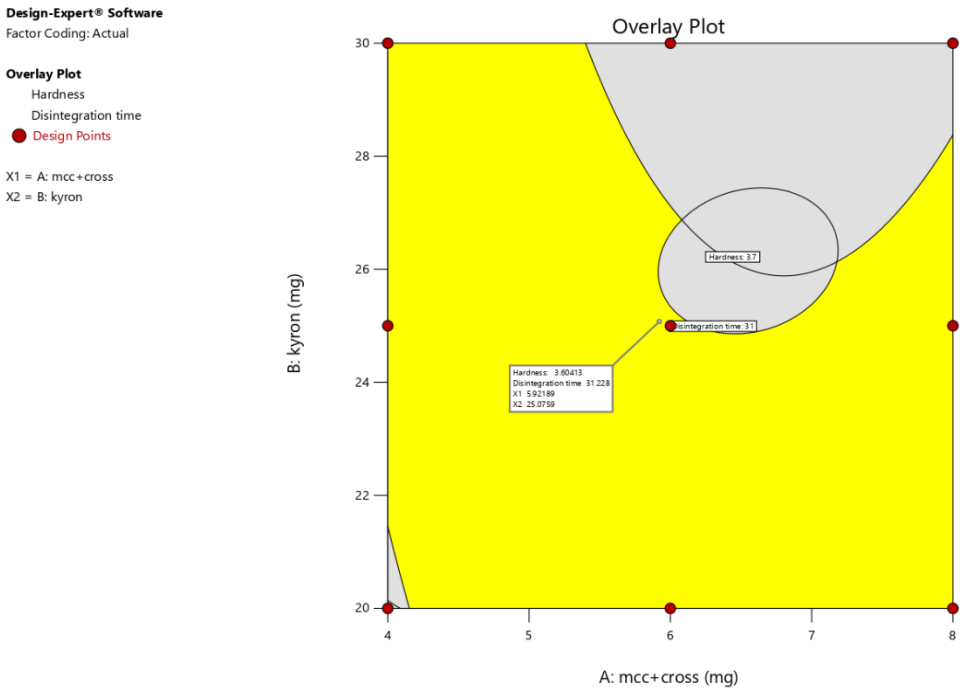


Figure 10 Overlay Plot for optimized batch

Composition of optimized batch O1

Ingredients (mg)	O1
Erlotinib HCl + β-Cyclodextrin	75
Co-processed MCC+Crosspovidone	5.92
Kyron T-314	25.07
Spray Dried Lactose	83.01
Magnesium Stearate	4.0
Talc	4.0
Aspartame	2.0
Vanila flavor	1.0
Total weight	200.0

Results of optimized batch O1

Evaluation Parameters	Results	
Weight variation (mg)	200.2 ± 1.3	
Thickness(mm)	3.0 ± 0.17	
Hardness(kg/cm2)	3.6 ± 0.1	
Friability (%)	0.54 ± 0.4	
Drug Content (%)	99.73 ± 1.2	
Wetting Time (sec)	25.34 ± 1.1	
Disintegration Time (sec)	30.12 ± 1.1	
% Drug Release	Time (min)	% Drug Release
	0.0	0.0
	5.0	25.12 ± 0.8
	10.0	39.70 ± 1.1
	15.0	45.46 ± 1.2
	20.0	58.19 ± 1.4
	30.0	73.41 ± 1.9

The optimized batch, O1, was developed and evaluated. Physical as well as chemical evaluations of the manufactured tablets revealed that they were satisfactory. The drug content of the tablets was considered to be enough due to their consistent distribution. Weight variation is also within permissible limits. Thickness was found to be uniform. Floating characteristics were also considered satisfactory. The drug release profile for one hour was 99.65%. Finally, optimized batch O1 was loaded to ensure stability for one month.

STABILITY STUDY

Stability tests favored batch O1, which produced superior results. The stability testing lasted one month in a chamber with temperatures of 40°C and a relative humidity of 75%. After a one-month interval, samples were extracted for examination. One hour later, the in-vitro drug release profile remained unchanged. The stability testing also found that the percentage of drug present was still within permissible limits. Additionally, the tablet's exterior remained unchanged.

Table 16 Results of stability study of batch O1

Batch	Time Period	Outer Appearance	Weight variation (mg)	% Drug Content	*In-vitro* drug release at 1 hr
O1	**Initial**	White tablet	200.13±0.50	99.73±1.2	99.65±2.7
	After 30 days	White tablet	200.3±1.05	98.81±0.54	98.36±0.57

CONCLUSION

The results of the study reveal that, the mouth dissolving tablet of erlotinib hydrochloride was prepared using cyclodextrin inclusion complex consisting β-CD, optimized ratio found out 1:2 and co-processed MCC+Crosspovidone ratio providing well-regulated release for 1 h. Trial batches T1-T9 batches pass the weight variation test. All batches have a good mechanical strength and hardness. Friability of T1-T9 found below 1 %. That means its passes the friability test. The formulation of erlotinib hydrochloride containing co-processed MCC+Crosspovidone as polymers shows desired drug release.

For taste masking of drug potassium polacrillin (Kyron T-314) was used and it's also used as Super disintegrant that helps to disintegrate tablet rapidly after contacting with saliva.

β-CD Complex and Kyron helps to mask the bitter taste of drug providing effective to pediatric, geriatric and bedridden patients.

Additional analysis of the formulation using 3^2 Factorial design. The co-processed MCC+Crosspovidone and Kyron were used as an independent variable to assess the impact of drug release after 1 hour. A check on F1-F9 factorial batches revealed that the weight variation and friability test were within the range. Consequently, also Tablets having good hardness. Thickness found uniform. Wetting time also found within limit. Drug content found between 94-98 % in all batches. Here co-processed MCC+Crosspovidone & Kyron both had significant effect on % drug release. Here % drug release was decreased with increasing the concentration of co-processed MCC+Crosspovidone & Kyron. From the factorial data optimized bath F5 was taken and analyze the ANOVA for responses like hardness and disintegration time. Both responses are significant for ANOVA. Contour plot and 3D surface plot of both included. Using check point batch analysis, validation of optimized formulation (C1&C2) was calculated, where C1 found optimized batch and this optimized batch was taken from the overlay plot as O1 then complete analysis was done and finally loaded for stability study. Formulation found stable during 1 month Stability study.

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