Research Article

Development and Evaluation of Levoamlodipine Fast Dissolving Tablet Using Microcrystalline Cellulose for the Treatment of Hypertension

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ABSTRACT

The present study focuses on the development and evaluation of a novel fast-dissolving tablet (FDT) of Levoamlodipine, an antihypertensive agent used in the management of high blood pressure. Levoamlodipine, a potent calcium channel blocker, has low oral bioavailability due to its poor water solubility and first-pass metabolism. To enhance its therapeutic efficacy and patient compliance, particularly in geriatric and pediatric populations who have difficulty swallowing conventional tablets, fast-dissolving tablets were formulated using the direct compression method. Microcrystalline Cellulose (MCC) was employed as a key diluent due to its excellent compressibility and disintegration properties. Various superdisintegrants like Sodium Starch Glycolate (SSG) and starch were incorporated to ensure rapid tablet disintegration in the oral cavity without the need for water. Other excipients such as magnesium stearate, talc, sucrose, and peppermint flavour were added to enhance palatability, flowability, and tablet stability. The prepared formulations were evaluated for pre-compression parameters (bulk density, tapped density, Carr's index, Hausner's ratio) and post-compression parameters (weight variation, hardness, friability, disintegration time, and in-vitro drug release). Among various formulations, the optimised batch exhibited rapid disintegration within 20 seconds and more than 85% drug release within 15 minutes, which meets pharmacopeial standards for FDTs. The UV spectrophotometric analysis at 237 nm confirmed the linearity and accuracy of drug content estimation in the phosphate buffer pH 6.8. The study concludes that Levoamlodipine FDTs using MCC are effective in enhancing patient compliance, ensuring quicker onset of action, and improving bioavailability for the treatment of hypertension. This novel approach provides a promising alternative to conventional tablets and supports the development of patient-friendly dosage forms in the management of chronic diseases like hypertension.

Keywords: Fast dissolving tablet, Levoamlodipine, Microcrystalline Cellulose.

INTRODUCTION

Drug Delivery System

Excellent platforms for ensuring regulated, repeatable medication delivery are biomaterials. Additionally, biomaterials are essential for improving or permitting the efficacy of both conventional small-molecule medications and other therapeutic classes, such as proteins and nucleic acids, that face delivery issues related to instability and inadequate tissue localisation. Drug delivery issues are discussed in this chapter, along with the evolution and application of various systems for delivering drugs made of biomaterials (DDSs) to address these issues[1]. The main facets of DDS development covered in this chapter, from fundamental studies to clinical implementations. Even though highly advanced, targeted, bioresponsive DDSs have only lately begun to fulfil their lofty potential, the ideas and methods being developed have their roots in long-standing historical motives. Therefore, in order to give a foundation for comprehending current biomaterial DDS design, a brief history of DDS from its inception to the present is first presented[2,3].

Drug Delivery Routes

Nasal, transdermal, parenteral, and oral, ophthalmic, intrathecal, vaginal, rectal, and pulmonary are common ways that conventional medications are delivered. Oral administration offers excellent patient compliance, and ~approximately 90% of current conventional drugs are administered via this route. Tens of billions of pills are consumed annually worldwide for aspirin alone. However, oral delivery faces difficulties connected to the severe conditions of the abdomen, intestines, and mouth, as well as inadequate transport through the intestinal epithelium layer of mucosa, which is covered in more detail later throughout this chapter (refer to the section "DDS Design to Overcome Biological Barriers")[4]. Additionally, oral medications undergo first-pass liver and intestinal enzyme metabolism following systemic absorption. This leads to drug breakdown at the time of initial delivery, which lowers the blood's unmodified drug concentration. Parenteral administration, which includes intravenous, subcutaneous, and intramuscular injections, accounts for almost 10 billion medication administrations annually worldwide (Kermode, 2004). Although the parenteral method guarantees that effective medication concentrations are quickly reached, injection site pain causes poor patient compliance. Additionally, oral medications undergo first-pass liver and intestinal enzyme metabolism following systemic absorption[5]. This leads to drug breakdown at the time of initial delivery, which lowers the blood's unmodified drug concentration. Parenteral administration is responsible for around 10 billion medication administrations each year. comprises intramuscular, subcutaneous, and intravenous injections globally. Although effective medication concentrations can be quickly reached by the parenteral

method, injection site pain makes patients less likely to comply. Although transdermal administration has a high patient adherence rate, it has historically only been used for tiny, lipophilic medications[6]. Because of their high epithelial surface area, which promotes quick drug efficacy, the Additionally interesting are vaginal, pulmonary, and nasal routes. Nevertheless, they are likewise restricted to tiny, lipophilic compounds because of difficulties in delivering drugs through the epithelial mucosa. DDS designs aim to improve medication efficacy and/or open up novel administration routes that circumvent negative side effects, deal with poor patient adherence, or get beyond biological barriers, as covered in the section "DDS to Overcome Biological Barriers[7,8]."

Choosing medications:

The optimal qualities of a medication that should be chosen

• Absence of bitterness

• A dosage of less than 20 milligrams

• molecular weight that is little to moderate

• Excellent stability in saliva and water

• partial non-ionisation in the mouth cavity's pH

• Capacity to permeate and divide into the GIT's uppermost layer (logp>1, or better yet,>2)

• The capacity of the mucosal tissue in the mouth to penetrate.

Tablet with Benefits That Dissolve Quickly:

- Fast-dispersing tablets are solid dose forms that have high drug loading and precise dosage (FDTs). They are also a fantastic substitute for conventional tablets and a suitable dose option for both paediatric and senior individuals[9].
- In the mouth, it absorbs quickly, works instantly, and melts when it meets saliva.
- Pregastric absorption changes the drugs' bioavailability, requiring lower dosages, which affects clinical reports and patient compliance.
- Because they may be taken anywhere, at any time, and disintegrate fast in the mouth, fast-dissolving tablets are perfect for those who are constantly on the go or who are conscientious but don't always have access to water. Patient compliance is enhanced as a result.
- They are particularly helpful for the elderly, young individuals, those who are resistant, and those who have dysphasia because of their solid unit dosage form, which makes them incredibly easy and practical to administer. Because there is no chance of a physical blockage obstructing the airways during swallowing, fast-dissolving pills are extremely safe and easy to use.
- Rapidly dissolving tablets have fewer leaves and vanish entirely in the tongue. This enhances the tablet's palatability and creates a pleasant mouthfeel.
- Fast-dissolving tablets are extremely stable because they are less vulnerable to environmental factors.
- Fast-dissolving pills are inexpensively priced because they come in simple blisters rather than elaborate, costly packaging[10,11].

Fast-dissolving medication delivery system concept:

Because of offers numerous benefits as well as excellent patient adherence in contrast to numerous alternative ways, the oral route is still the suggested administration method for the majority of medicinal substances that produce systemic effects. The majority of the drug delivery methods[12], Tablets and firm gelatin capsules, are currently available on the market. However, ingesting various dosage forms is a challenge for many patient groups, including the elderly, youngsters, intellectually impaired patients, patients who are recalcitrant, sick, or on decreased consumption of liquids or diets. Travellers and others with limited access to water are also impacted. The goal of the fast drug delivery system (FDDDS) concept was to increase patient compliance. When these dosage forms come into contact with saliva, they quickly dissolve and/or disintegrate to release the medicine, eliminating the need for water during administration. They are highly enticing to both because of this trait, paediatric and elderly patients[13]. All age groups frequently have trouble swallowing traditional tablets and capsules; however, those who are elderly and have dysphagia are most impacted[14].

The Fast Dissolving Drug Delivery System's Key Features

Easy administration for patients with swallowing difficulties, such as stroke sufferers, elderly people, bedridden people, and people with renal failure, and individuals with swallowing difficulties, including children, the elderly, and patients with mental health issues[15 16].

The dosage form can be swallowed without water; this is a really useful function for travellers who don't always have water at their fingertips. A rapid commencement of effect will result from the drug's rapid solubility and absorption[17].

Certain drugs are taken up by saliva as it passes down into the stomach from the mouth, throat, and oesophagus. The bioavailability of the drug is improved in specific circumstances. Because pre-gastric absorption reduces dosage, it can increase bioavailability and enhance clinical performance by lowering the undesired effects.

A pleasant mouthfeel can help patients, especially young ones, stop thinking of medicine as a bitter pill. By avoiding physical blockage, the oral administration of the standard formulation improves safety by removing the possibility of choking or asphyxia.

Novel business opportunities include product promotion, patent extensions, life cycle management, and distinctiveness. advantageous in situations requiring an extremely quick onset of effect, such as motion sickness, abrupt allergic reactions, or coughing[18].

The quick breakdown and disintegration of these tablets results in a higher bioavailability, especially for insoluble and hydrophobic medications. stability for an extended period of time since the medication stays in solid dose form until it is used. Consequently, it combines the benefits of solid dose forms for stability with liquid dosage forms for bioavailability[19,20].

MATERIALS AND METHODS

Levoamlodipine was obtained as a gift sample from New Delhi's Care Formulation Labs Pvt. Ltd., Narela. Microcrystalline Cellulose Synokem Pharmaceutical Ltd, Haridwar. Sodium starch glycolate, Starch, Talc, magnesium Stearate, sucralose and peppermint from BIT Meerut.

Preparation of Fast Dissolving Tablets of Levoamlodipine:

Levoamlodipine-containing fast-dissolving tablets were prepared using the direct compression technique. Using a mortar and pestle, a formulation containing 5 mg of levoamlodipine along with excipients such as microcrystalline cellulose (MCC), mannitol, crospovidone, sodium starch glycolate (SSG), and magnesium stearate was thoroughly mixed. Various concentrations and combinations of superdisintegrants like crospovidone and SSG were evaluated to optimise disintegration time and tablet performance.

All ingredients, except magnesium stearate, were precisely weighed and uniformly blended according to formulation specifications. The resulting powder blend was then passed through sieve number 60 to ensure uniform particle size and enhance powder flow properties[21].

After sieving, magnesium stearate was added to the blend and gently mixed for 5 minutes to avoid over-lubrication, which can affect tablet hardness and disintegration. The final blend was then subjected to tablet compression using a 9.5 mm flat punch with a break line on a rotary tablet punching machine with eight stations. Of these, four stations were equipped with dummy punches and the remaining four with die cavities to produce uniform tablets[22].

This method ensures the rapid disintegration of tablets in the oral cavity, facilitating the quick onset of action, especially beneficial for the treatment of hypertension[23,24].

Table 1: Composition of Azilsartan Medoxomil Fast Dissolving Tablets

Ingredients	Quantity for tablet (mg)						
	F1	F2	F3	F4	F5	F6	F7
Levoamlodipine	5	5	5	5	5	5	5
Microcrystalline Cellulose	60	60	60	60	60	60	60
Sodium Starch Glycolate	8	16	18	8	16	18	8
Starch	20	15	8	20	15	8	20
Magnesium Stearate	3	2	1	3	2	1	3
Talc	2	2	2	2	2	2	2
Sucarlose	50	48	40	50	48	40	50
Peppermint	2	2	2	2	2	2	2

Compressed tablet test variables:

Abrasion of tablets:

The tablet's crushing strength was measured using a Monsanto abrasion tester. The test tablets and the corresponding tablet value are held in place by the fixed and moving jaws of the Monsanto hardness test device. The force required to break the tablet was noted after the screw knob was turned forward until it did so. Three pills from every batch of formulations were randomly examined, and the mean result was captured[24].

Tablet Density:

Intentionally, five rapidly dispersed pills were used. Additionally, the typical Vernier calliper was used to measure thickness[25].

Friability:

The tablet's friability was used as a proxy for solidity estimation using a Roche Friability tester. After swallowing 20 tablets, they are meticulously weighed and put into the Friability tests. The individual who tested was operated at up to 100 rpm for four minutes at 25 times. The following formula calculates the percentage of mass friability damage

$$F = \text{Initial wt.} - \text{Final wt.}/\text{Initial wt} \times 100$$

Dispersion of Weight:

Several pill varieties are used in this process, which is weight-based. An electronic balance was used to weigh each of the twenty pills individually in grams. Then calculated the mean weight of the tablets and searched for differences in weight[26,27].

% weight deviation calculation:

% Variation = Individual wt. - Average wt./Average wt × 100

Wetting Time:

Inside the container, which holds 6 millilitres of water, is a tiny Petri dish with a diameter of 6.5 cm and a piece of tissue paper that has been folded twice. A tablet that had been previously weighed was put on tissue paper and left to absorb all of the water. The time of wetness was described as the duration required for water to thoroughly moisten the top surface of the tablet. The pill's moist weight comes next. The following formula was used to determine the ratio of water absorption (R)[28].

R = Wa-Wa/Wb X 100

Where,

Wb - Weight of tablet before wetting.

Wa - Weight of tablet after wetting.

Test of Disintegration:

The tablet investigation was conducted using the disintegration device. A one-litre beaker of water with a temperature setting of 37°C (2°F) was placed in a basket rack, and each of the six tubes in the basket contained a single pill. The device operated until the tablets were destroyed.

In Vitro Dissolution Studies:

An in vitro dissolution experiment was carried out using an Electro Lab Dissolve test unit spinning at 50 rpm. As the dissolving medium, 900 cc of pH 6.8 phosphate buffer was used at 2-minute intervals and filtered. The amount of medication dissolved was determined using a UV spectrophotometer (Shimadzu 1800, Japan) to measure the sample's absorbance at 252 nm, at Selegiline in phosphate buffer at pH 7.4 using the UV spectroscopy method. The medium that dissolves, which was maintained at 37.50 °C, was carefully taken out (5 ml). Throughout the experiment, the pace at which each formulation dissolves in vitro was determined using the following approach.

Dissolution parameters:

Utilised equipment: Electro lab.

Current temperature: 37± 0.50C

RPM: 50 rpm

Withdrawn volume: 5 ml for 5 min

λ max - 252nm

Release kinetic:

Zero order kinetics

It represents cumulative amount of drug release vs. time.

QT =K T

Where,

K = rate constant of zero order (conc/time)

Q= quantity of medication released in time T

T = time in hours

Plotting A straight line with slope (K_{0}) and intercept is produced by plotting concentration against time (at origin of axis).

First-order kinetics

It represents the cumulative % of drug release vs. time.

Log Q = Log*Q_{o} + - k * t / 2.303

Where,

Q_{0} = initial medication concentration

k = 1, rate constant of the first order

t-time

Higuchi kinetics

It represents the cumulative percentage of medication release against time squared.

Q = k * t ^ (1/2)

Where,

k = constant

time in hours

Korsmeyer and peppas model

It represents the log cumulative % drug release vs the log of time.

Mt / M = K t

Where,

K = constant (reveals structural and geometrical characteristics of devices)

Mr and M_{x} = absolute cumulative amount of drug release at time t and infinity

n = exponent (reveals release mechanism)

Stability studies:

Stability tests of the optimised formulation were carried out according to ICH recommendations. The proper formulation was tested for stability at 40°C and 75°RH for 90 days. Next, the product's in vitro release, colour, hardness, and disintegration time were evaluated.

RESULTS AND DISCUSSION

Preformulation Studies:

Solubility:

Levoamlodipine was examined for solubility in different solvents.

Table 2: Assessing a drug's solubility in different solvents

S. No.	Solvent	Descriptive Term
1	Phosphate Buffer (pH 6.8)	Moderate solubility
2	Water	Poor solubility
3	Ethanol	Good Solubility
4	Methanol	Very good Solubility
5	Acetone	Moderate Solublity
6	0.1N Hydrochloric Acid	Fair solubility in acidic medium

Standardisation of Drug:

UV Spectrophotometric Method for Levoamlodipine: The calibration curve for levoamlodipine at pH 6 in phosphate buffer in the table 3 is displayed. The amount of medicine was assessed using the UV method. The typical remedy for levoamlodipine, with a medium at a concentration of 0–7 g/ml, generated a straight-line relationship. Figure 1 displays the computed coefficient in a straight line for the phosphate buffer at pH 6.8.

Table 3: Standard calibration curve of Levoamlodipine in pH 6.8 phosphate buffer

S. No.	Conc. (µg/ml)	Abs. at 237nm
1	2	0.20
2	4	0.40
3	6	0.60
4	8	0.80
5	10	1.00
6	12	1.20
7	14	1.40

IR Spectra of Pure Drug:

The images under "IR Spectra of Pure Drugs" display the pure FTIR spectrum data of medications with different polymers used in formulation

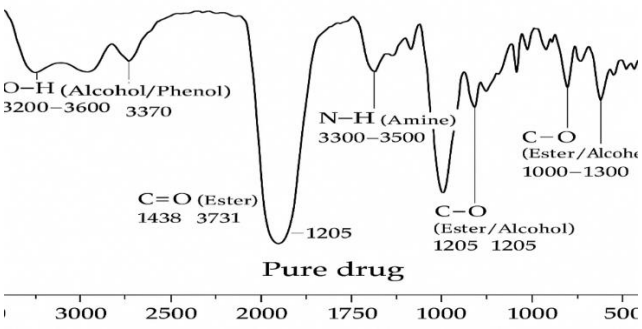

Figure 1: FTIR Spectrum of levoamlodipine

Talking about the FTIR spectrum

There was little to no evidence of a drug-polymer interaction in the formulation's IR spectra. Both medications' peaks and compositions were found to be identical. Since the drugs are unique zones of absorption that remained unchanged in the composition, this indicates that during formulation, the medication and the polymer did not interact[44 45].

Differential scanning calorimetry, or DSC:

Discussion: The DSC thermogram reveals the thermal behaviour of Levoamlodipine and its interaction with Microcrystalline Cellulose. Distinct endothermic peaks indicate phase transitions such as melting or decomposition. The sharp endothermic peak around 204.8°C corresponds to the melting point of pure Levoamlodipine. The presence of Microcrystalline Cellulose can shift or broaden peaks due to interaction or physical mixing. Additional peaks or shoulder transitions may reflect partial compatibility or altered crystallinity[46]. Lack of a major shift in Levoamlodipine's melting peak suggests no significant chemical interaction. Deviation in heat flow values indicates different thermal stability profiles in the mixture. Microcrystalline Cellulose remains thermally stable up to ~300°C, as no major events are observed below that. The thermogram confirms the preservation of Levoamlodipine's identity in the presence of the excipient. DSC is thus a valuable tool to assess compatibility, stability, and formulation feasibility in drug-excipient mixtures[47].

In Vitro Drug Release Studies:

Table 4: Studies of Release F1–F7

Time/Mins	% Release Drug						
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0.5	41.75±2.4	40.30±0.28	46.65±0.24	46.04±0.96	47.40±0.72	48.42±1.30	42.42±1.30
1	46.56±2.2	45.55±0.99	54.46±0.48	52.52±1.33	56.85±0.88	57.78±1.25	54.78±1.25
2	51.78±2.3	54.04±0.90	59.52±0.76	63.13±1.28	60.58±1.24	63.47±1.20	60.47±1.20
3	59.25±0.2	60.56±0.36	65.32±0.82	69.49±1.22	67.44±1.45	75.89±1.18	72.89±1.18
4	66.52±0.5	69.78±1.25	76.70±0.91	72.21±0.98	77.98±1.20	87.45±0.78	82.45±0.94
5	76.48±0.8	78.65±1.09	79.46±0.52	78.16±0.88	80.43±1.40	92.25±1.77	88.45±0.76
6	84.89±0.3	85.44±1.17	86.24±0.78	88.29±0.68	88.78±1.48	95.67±1.57	94.45±1.24
8	92.34±0.9	93.13±1.18	90.76±0.34	94.90±0.48	96.38±1.26	**98.96±0.82**	97.45±1.82

Point are expressed as the average ± standard deviation (n = 3).

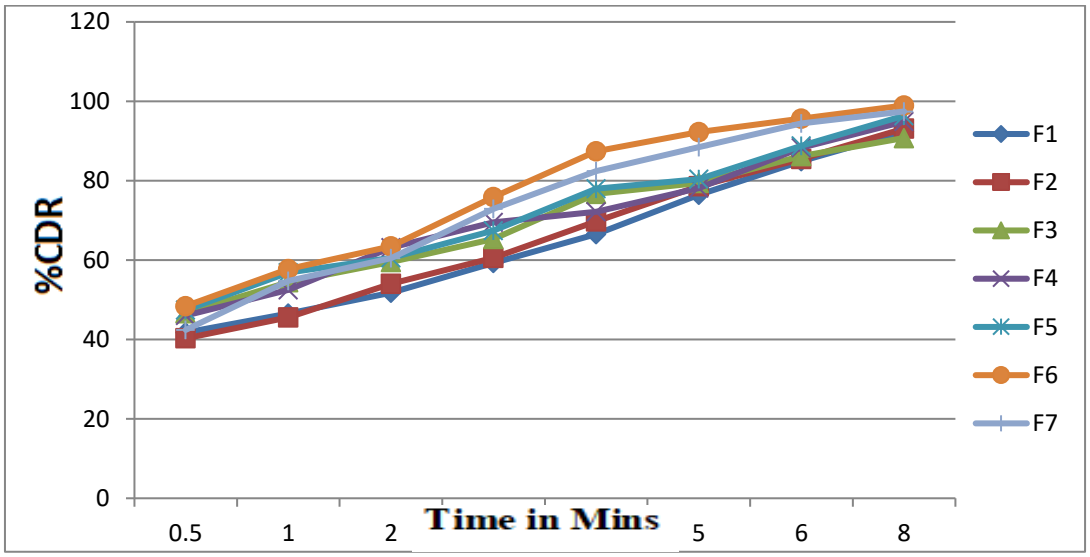

Figure 2: % Diagrammatic Representation of the Release Drug

Stability Studies:

Table 5: Data show the Stability data of the optimised formulation F4

Time (Days)	Storage Condition	Temperature & Humidity	Particle Size (µm)	Entrapment Efficiency (%)
0	Refrigerated	5 °C ± 3 °C / 60% RH	121.00	54.04
15	Refrigerated	5 °C ± 3 °C / 60% RH	121.00	54.04
30	Refrigerated	5 °C ± 3 °C / 60% RH	120.06	54.01
45	Refrigerated	5 °C ± 3 °C / 60% RH	119.34	51.11
60	Refrigerated	5 °C ± 3 °C / 60% RH	118.21	51.02
0	Room Temperature (Intermediate)	25 °C ± 2 °C / 60% RH	121.00	54.04
15	Room Temperature (Intermediate)	25 °C ± 2 °C / 60% RH	121.00	54.04
30	Room Temperature (Intermediate)	25 °C ± 2 °C / 60% RH	121.00	54.11
45	Room Temperature (Intermediate)	25 °C ± 2 °C / 60% RH	120.28	53.08
60	Room Temperature (Intermediate)	25 °C ± 2 °C / 60% RH	120.19	53.47
0	Accelerated	40 °C ± 2 °C / 75% RH	121.00	54.04
15	Accelerated	40 °C ± 2 °C / 75% RH	121.00	53.10
30	Accelerated	40 °C ± 2 °C / 75% RH	120.42	53.62
45	Accelerated	40 °C ± 2 °C / 75% RH	122.11	52.24
60	Accelerated	40 °C ± 2 °C / 75% RH	123.04	52.18

DISCUSSION

Formulations F1 through F7 have finished their drug release research in vitro. F6's pharmacological release time of 8 minutes for 98.96% of patients was shown to be the most efficacious when compared to another formulation.

The stability study of Formulation F6 was conducted under accelerated conditions under ICH guidelines (40 ±2 °C / 75 ±5% RH) for 90 days to evaluate the physical and chemical stability of the fast-dissolving levoamlodipine tablet. During the study period, minor variations were observed in key formulation parameters, including drug content, Disintegration time, tablet hardness, friability, and in vitro drug release. These variations remained within the acceptable pharmacopeial limits, reflecting that the formulation retained its integrity under stress conditions. Overall, the findings from the accelerated stability study suggest that Formulation F6 is robust, stable, and suitable for further development. Its consistent performance over the 90 days confirms the formulation's potential for long-term storage and commercial application

CONCLUSION

The present study focused on the creation and assessment of quick-dissolving tablets (FDTs) of Levoamlodipine using microcrystalline cellulose (MCC) to enhance patient compliance and rapid onset of action in hypertension therapy. Seven formulations (F1–F7) were prepared and

evaluated based on pre-compression, post-compression, and in vitro parameters, including hardness, consistency of Disintegration time, medication content, water absorption ratio, hardness, and medication release in vitro. Of all, Formulation F6 emerged as the optimised formulation. It exhibited superior characteristics: rapid disintegration time (under 15 seconds), high water absorption capacity, acceptable hardness and friability, and most notably, the highest drug release profile, achieving 98.96% drug release at 8 minutes**.** This indicates a fast and efficient drug release suitable for immediate therapeutic effect, crucial for managing acute hypertensive conditions. The stability study of F6 over 90 days under ICH conditions (40°C/75% RH) confirmed its robustness, with minimal deviations observed in physical and chemical parameters, thus validating its shelf life and formulation integrity.

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